Liver Transplantation in Children

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Although liver transplantation is now accepted as the ideal therapy for end-stage liver disease, relatively few centers have gained a large experience in children, and good results have been elusive. Technical difficulty and a high incidence of graft failure are among the obstacles to success. At the University of California at Los Angeles, 39% of our liver transplants are in the patients who are younger than 18 years. We have analyzed our experience with 103 patients to emphasize factors important to a favorable outcome with the procedure. One hundred twenty-three transplants were performed in 103 children (mean age, 5.2 years; 48% younger than 3 years). No reduced-size grafts were used. Scrupulous attention to technical details of the vascular reconstruction, including frequent use of the supraceliac aorta of the recipient and interrupted suture techniques, ensured construction of sound hepatic artery and portal vein anastomoses at the first operation. Preoperative exchange transfusions were used if the prothrombin time was prolonged beyond 7 seconds, resulting in an average blood loss of only 3.3 volumes. Cyclosporine dosage was maintained in the high therapeutic range for the first 4 weeks, and anti-T-cell antibody (OKT3) was used for rejection (38%). Amphotericin prophylaxis was used for biliary atresia patients with multiple previous operations. Eighty-two of one hundred three patients (80%) are alive. There were no intraoperative deaths. Actuarial survival rates at 6 months, 1 year, and 5 years are 80%, 79%, and 77%, respectively. Survival of patients who underwent transplantation at age less than 1 year is 65% *versus* 85% at age more than 1 year ($p = 0.08$). Retransplantation was performed in 19 patients (18%), with a survival rate of 58%. Hepatic artery thrombosis, the most frequent technical complication, occurred in only 16 patients (13%). Survival rates of ABO identical-match *versus* nonidentical-match grafts were 96% and 60%, respectively ($p = 0.02$). Graft survival was only 47% if more than one steroid cycle was needed, compared to 75% survival with OKT3 treatment. Despite impairment of renal function (glomerular filtration rate [GFR] less than 80 cc/kg/min) in 54% of patients and hypertension requiring therapy in 27%, 90% of the children demonstrated enhancement of growth, development, and functional status. The following conclusions were made. (1) Pediatric liver transplantation is the treatment of choice for all types of end-stage liver disease and should be considered early. (2) Factors that enhance survival include technical precision, aggressive retransplantation, antifungal chemoprophylaxis and therapy, and judicious immunosuppression with use of OKT3 for rejection. (3) A successful pediatric liver transplantation program will offer dramatic functional rehabilitation and long-term physical and intellectual growth and development for patients with an otherwise fatal disease process.

ALTHOUGH CLINICAL LIVER transplantation was originally designed for and performed on children,[1] the experience with pediatric patients is far less than that which has accumulated for adults. Reasons for this are multifactoral and include shortage of small donors, lack of adequate experience in performing the procedures, and reluctance of some pediatricians and primary-care physicians to refer children with liver disease for transplantation.

Since the initiation of the the University of California at Los Angeles (UCLA) Liver Transplant Program in 1984, we have pursued actively the development and growth of a pediatric liver transplant unit. For nearly 5 years this represented the only major children's center in the West. At UCLA 39% of our liver transplants are performed in children younger than 18 years. We analyzed the cases of the first 103 transplant patients to emphasize factors important to a favorable outcome with the procedure.

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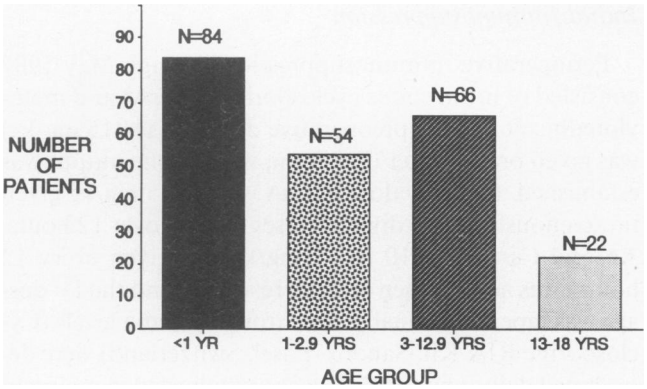


FIG. 1. Pediatric patients evaluated for OLT grouped by age.

Methods

Evaluation

Between January 1, 1984 and October 1, 1988, 225 children (135 female, 90 male) were evaluated for orthotopic liver transplantation (OLT). The age distribution is shown in Figure 1; of note 84 (37%) were 12 months old or younger. Of patients evaluated, 154 (68%) were accepted and placed on the active waiting list. Reasons for rejection were variable but most commonly reflected the extremes of pathology: either there was no clear indication for OLT or the patient was referred so late that multiple-organ failure developed. Diagnoses of patients evaluated and transplanted are shown in Figure 2.

The methods for evaluation and selection of children for liver transplantation have been described previously.[2] After evaluation patients are placed on the active waiting list if they suffer from end-stage liver disease resulting from any of the following conditions:

1. Biliary atresia with failure of a portoenterostomy.
2. Metabolic diseases associated with liver failure manifested by bleeding varices or abnormalities in hepatic synthetic function.
3. Cholestatic disorders that may not be an immediate threat to life but are responsible for an unacceptable lifestyle because of persistent jaundice, pruritus, fatigue, growth retardation, or inability to attend school.
4. Fulminant or subacute hepatic failure secondary to drugs, toxins, or hepatitis.
5. Primary liver tumors without extrahepatic spread.
6. Cirrhosis with a less predictable natural history but which is associated with bleeding varices uncontrollable by sclerotherapy or with impaired hepatocellular synthetic function.

Of the 154 children accepted for OLT, 123 transplants were performed on 103 patients. Mean age of the transplant recipients was 5.2 years. Figure 3 shows the overall age distribution. Ten per cent of patients on the active waiting list died before transplantation. This was due to lack of suitable donors in approximately one half of cases and to progression of disease in the others.

Attempts were made to match donors to recipients of identical blood types. Upper and lower limits of body-weight ratio, donor to recipient, were 2.5 and 0.5, respectively. No reduced-size grafts were used in this series.

Techniques

The fundamental principles of donor retrieval, recipient hepatectomy, and liver grafting have been described extensively.[2-4] Several modifications of the procedure apply uniquely to children. The recipient hepatectomy in the patient with biliary atresia may be a formidable undertaking, particularly if the child has had several revisions of the portoenterostomy in attempts of salvage. In this setting, dense adhesions often bind the portal structures, duodenum, Roux-en-Y jejunal limb, and transverse colon

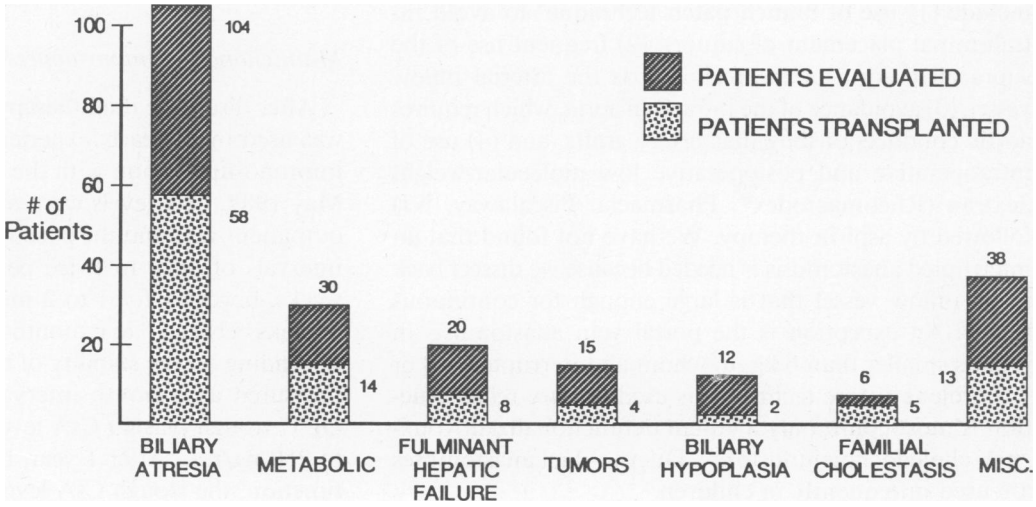


FIG. 2. Pediatric patients evaluated and number of transplants by diagnosis.

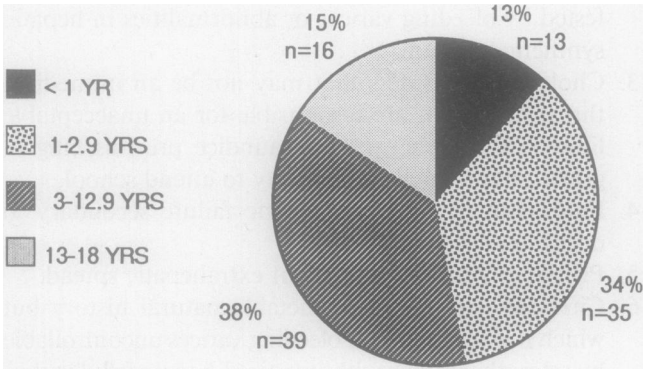


FIG. 3. Pediatric patients receiving OLT grouped by age.

into an unrecognizable and bloody tissue mass. To permit dissection without uncontrollable blood loss, unviolated tissue planes must be entered first. Thus dissection is begun with the posterolateral aspect of the right lobe of the liver, which usually is not scarred. In this plane, the transverse colon and second and third portions of the duodenum may be reflected down from the right lobe. Next the Roux-en-Y limb is identified at its point of entry through or above the transverse mesocolon and traced to the hilus of the liver. With the duodenum identified and separated, the limb is transected with a stapler and reflected inferiorly. This maneuver exposes the portal structures, which are easily identified lying below the divided limb. The conventional approach of hugging the undersurface of the liver to identify the components of the portal triad is bloodier and more prone to result in accidental enterotomies. Once the porta hepatis has been dissected, the portal vein is ligated very close to the liver, then divided to permit easy anterior access to the infrahepatic vena cava. Finally the suprahepatic vena cava is isolated.

The vascular anastomoses, particularly the hepatic artery, are most crucial for a satisfactory outcome. Important modifications that we have used to assure patency include (1) use of branch patch technique[4] to avoid intraluminal placement of sutures, (2) frequent use of the supraceliac aorta of the recipient as the arterial inflow vessel, (3) avoidance of the infrarenal aorta, which requires aortic conducts or long iliac artery grafts, and (4) use of intraoperative and postoperative low molecular-weight dextran (Rheomacrodex®, Pharmacia, Piscataway, NJ) followed by aspirin therapy. We have not found that an interrupted anastomosis is needed because we dissect back to an inflow vessel that is large enough for continuous suture. An exception is the portal vein anastomosis in infants smaller than 6 kg, in whom an interrupted 6-0 or 7-0 prolene suture technique is used. Biliary reconstruction is most commonly a 40-cm defunctionalized Roux-en-Y choledochojejunostomy. Duct-to-duct anastomoses are used infrequently in children.

Initial Immunosuppression

Perioperative immunosuppression through May 1987 consisted of intravenous cyclosporine A (CsA) and methylprednisolone. The preoperative dose of CsA (15 mg/kg) was given orally. After operation, when urine output was established, the daily dose of CsA was 3 to 5 mg/kg given intravenously in two divided doses infused over 12 hours. An oral CsA dose (10 to 15 mg/kg/day given every 12 hours) was added when feeding resumed, and the IV dosage was tapered gradually. CsA trough plasma levels (Cyclosporine RIA-Kit, Sandoz, Basel, Switzerland) were determined daily, and the CsA dose was adjusted to maintain a therapeutic level between 200 and 300 ng/mL.

For the first five postoperative days, methylprednisolone was given in a rapidly decreasing dose, beginning at 20 to 30 mg/kg and tapering to 0.3 to 0.5 mg/kg. Maintenance oral prednisone later was substituted at this same dose.

In May 1987 initial immunosuppression with triple drug therapy was instituted. Intravenous azathioprine (1 to 2 mg/kg/day) administration was started on the first postoperative day and later converted to oral administration at the same dose. White blood cell count less than 4.0×10^3/mL, systemic sepsis, or pancreatitis were contraindications to starting azathioprine or continuing its use.

Between May 1987 and June 1988, patients were randomized into a trial using the monoclonal antibody OKT3 for rejection prophylaxis. Intravenous OKT3 was begun at 2.5 mg/day for children with body weights less than 30 kg or 5.0 mg for those greater than 30 kg. The first dose was given intraoperatively and then continued daily for 14 days. CD3+ cells in the peripheral blood were monitored, and the dose of OKT3 was increased if CD3 + percentage exceeded 10. During this trial methylprednisolone and azathioprine also were given as described above. CsA was begun on day 10 so that therapeutic levels would be achieved when OKT3 was stopped.

Maintenance Immunosuppression

After discharge dual therapy with CsA and prednisone was used in our early experience then replaced by triple immunosuppression with the addition of azathioprine in May 1987. CsA levels were monitored regularly at each outpatient visit and the dose was adjusted accordingly, at intervals of once to twice per week for the first 2 to 4 weeks, biweekly for 1 to 2 months, and once every 3 to 4 weeks between 3 to 6 months after discharge. Thereafter, depending on the stability of the patient, CsA levels were measured at 2-month intervals. For the first year after OLT, trough plasma CsA levels were maintained at 200 to 250 ng/mL. After 1 year, in patients with stable liver function, the trough CsA levels were allowed to fall to a

target of 140 to 160 ng/mL. Azathioprine was maintained at 1 mg/kg/day unless contraindications developed to preclude its use.

Treatment of Rejection

Episodes of rejection suspected on clinical grounds were confirmed in most cases by percutaneous liver biopsy. Initial treatment consisted of intravenous methylprednisolone at 30 mg/kg/day, tapering over 5 days to the maintenance dose. In patients failing to respond to the steroid cycle, a second liver biopsy was obtained whenever possible. High-dose steroids were restarted, or a decision was made to treat with antithymocyte globulin (until June 1985) or OKT3 (thereafter). The dose of ATG was 50 mg given over 10 to 14 days. OKT3 was administered and monitored as outlined above.

Postoperative Management

After OLT children were returned directly to the Pediatric Intensive Care Unit (PICU) under joint care of the pediatric intensivist, gastroenterologist, and transplant surgeon. Patients were monitored with cardioscope, central venous and arterial pressure lines, and pulse oximetry. Pulmonary artery catheters were used in patients with hemodynamic instability.

Initial ventilator setting include an FiO_2 of 1.0, tidal volume approximately 12 cc/kg, no positive end-expiratory pressure (PEEP), and a physiologic rate for age. Infants with body weights less than 8 kg were ventilated with pressure support at a pressure to give adequate chest excursion. The FiO_2 was weaned rapidly, and a PEEP of 3 to 4 cm H_2O was added if the FiO_2 could not be decreased to 0.40 or less. Patients were extubated within 12 to 36 hours after operation, with supplementation by oxygen hood or mask, depending on age.

Vasoactive or inotropic agents initiated in the operating room were continued in the PICU. In addition low-dose dopamine (2 mcg/kg/min) was used in patients with previously diminished renal function and in those who developed renal dysfunction after operation. Hypertension was controlled with a combination of sublingual nifedipine and intravenous hydralazine.

Initial fluid management in the PICU was largely dependent on the patient's volume status on return from surgery, with hypernatremia and fluid overload a common pattern. Most patients receive D_5W or D_5. 2NS with added potassium at limited volumes such that total fluid infusion was approximately 75% of calculated daily maintenance. Fresh frozen plasma was infused every 4 hours for 24 hours in patients transplanted through January 1987, but more recently was used only in patients with clinical bleeding. In the absence of significant bleeding, Dextran 40 was infused continuously for 7 days, then followed with daily low-dose aspirin. Hematocrit was maintained at 28% to 32%, with transfusion or phlebotomy and colloid replacement used as necessary. Coagulation studies were obtained daily. Hydrochloric acid (0.2 normal) is titrated to correct a base excess of 5 mmol/L (millimolar) or more, which occurs uniformly with a functioning graft.

All patients receive antibiotics for 48 to 72 hours after surgery. Ampicillin and cefotaxime was the standard regimen, with modifications made for pre-existing infections. If the donor had an infection, the recipient received a course of antibiotics appropriate for that infection. In addition all patients received oral nystatin and clotrimazole for fungal prophylaxis. Biliary atresia patients who had portoenterostomy revisions were treated prophylactically with low-dose amphotericin (0.3 mg/kg on alternate days) for 10 to 14 days.

Gastric pH was controlled with ranitidine and antacids. When total parenteral nutrition (TPN) was started on the first postoperative day, the ranitidine was given as a continuous infusion in the TPN.

Results

Survival

Of the 103 patients, 82 (80%) are alive to date. Survival of all patients according to age is shown in Figure 4. Survival for those younger than 1 year old was 65% *versus* 85% for those older than 1 year ($p = 0.08$). The overall 5-year actuarial survival rate is 77% (Fig. 5). Survival analysis among patients with biliary atresia, metabolic abnormalities, cirrhosis, and tumors shows the best prognosis for alpha-1-antitrypsin deficiency, with a 5-year survival rate of 95%. Patients with biliary atresia and tumors fared worse, with a 5-year survival rate of 71%.

Of the 21 deaths, four occurred within 10 days of transplantation as a result of brainstem herniation in patients with fulminant hepatic failure who never regained con-

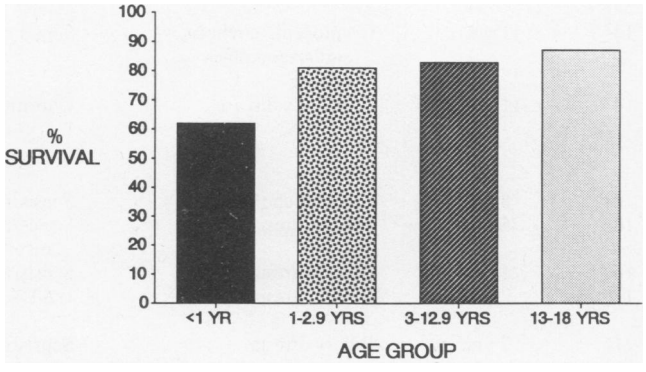


FIG. 4. Patient survival after OLT grouped by age.

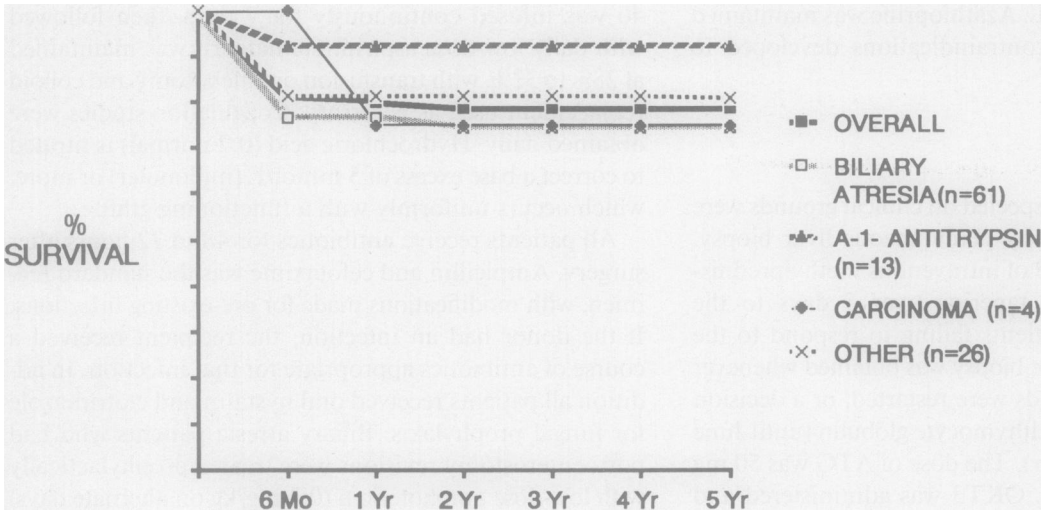


FIG. 5. Actuarial patient survival after OLT. Five-year overall survival of 77%. Kaplan–Meier method.

sciousness (two), bleeding and liver failure (one), and intrapulmonary bleeding (one). A detailed analysis of all causes of death is shown in Table 1.

There was a significant survival advantage when blood type matching was identical. In 82 transplants, an identical match was accomplished with a 96% survival rate. In con-

TABLE 1. *Death in 21 of 103 Patients*

OLT#	Age	Disease	Cause of Death	Time After Transplantation	Comment
10	4 yrs.	Biliary atresia	Bacterial sepsis	2.5 yrs.	Normal LFT
11	7 yrs.	Tyrosinemia w/hepatoma	Recurrent tumor	10 mos.	Tumor involved hepatic
16	8 mos.	Biliary atresia	Adenovirus infection	17 days	Retransplanted for suspected rejection
19	3 yrs.	Biliary atresia	Fungal sepsis	7 weeks	
23	12 yrs.	Biliary atresia	Fungal sepsis	25 days	Extensive previous biliary surgery (12 operations)
26	4 yrs.	Biliary atresia	Bacterial/fungal sepsis	4.5 mos.	Retransplant H.A.T.
31	2 yrs.	Fulminant hepatic failure	Brainstem herniation	10 days	Did not regain consciousness
48	14 mos.	Biliary atresia	Rejection	1 yr.	Noncompliance
51	14 yrs.	Alpha-1-antitrypsin	Ruptured splenic aneurysm	5 days	Normal LFT
75	10 mos.	Tyrosinemia	Intrapulmonary hemorrhage	2 days	
101	13 mos.	Biliary atresia	Sepsis	12 days	Retransplant
105	2 yrs.	Fulminant hepatic	Brainstem herniation	3 days	Did not regain consciousness
114	7 mos.	Biliary atresia	Respiratory failure	22 days	
123	2.5 yrs.	Biliary atresia	Sepsis/liver failure	12 days	Retransplant for primary nonfunction
134	11 yrs.	Cryptogenic cirrhosis w/ end-stage kidney disease	Sepsis	2 mos.	Kidney transplant not performed
143	11 yrs.	Gaucher's disease	Chronic rejection	3 mos.	Intracerebral bleed, after OLT #1 retransplant for rejection
161	8 yrs.	Familial cholestasis	Sepsis/intestinal infarction	2 mos.	Retransplant H.A.T.
163	5 mos.	Biliary atresia	Sepsis/respiratory insufficiency	1 mos.	
169	1 yrs.	Biliary atresia	Sepsis/liver failure	1 mos.	Retransplant
174	2 yrs.	Biliary atresia	HAT/sepsis	18 days	Died awaiting retransplant
216	2 yrs.	Biliary atresia	Sepsis/rejection	14 days	Retransplant

HAT, hepatic artery thrombosis.

trast, of 16 compatible but unidentical matches and five incompatible grafts, survival was 55% and 60%, respectively (Fig. 6).

Complications

Technical complications most commonly appeared within 10 days of OLT. Hepatic arterial thrombosis (HAT) occurred most commonly and was seen in 16 of 123 cases (13%). Of these patients eight were younger than 2 years old; three required intraoperative revision of the anastomosis, and three received donor livers that required bench arterial reconstruction because of anomalies. None of these findings were significant ($p > 0.05$). The types of arterial reconstructions were variable and none had a significantly greater incidence of thrombosis. However use of the infrarenal recipient aorta for inflow with an aortic conduit or long iliac artery graft has been abandoned because of failure in two of four cases. Ten of sixteen patients with arterial thrombosis required retransplantation, six are currently alive without retransplant, and 13 of 16 are alive. Neither portal vein nor inferior vena cava (IVC) thrombosis was seen in this series. Two patients received superior mesenteric jump grafts for a thrombosed portal vein identified by pretransplant ultrasonography, and two patients with situs inversus had the donor infrahepatic vena cava oversewn because of a discontinuous IVC in the recipient.

Biliary tract complications were infrequent, occurring in only eight patients. The most common problem was a leak from the choledochojejunostomy in five (all requiring suture repair) and disruption in three requiring complete revision of the anastomosis. Late stenosis was seen in two patients who were treated with transhepatic balloon dilatation (Fig. 7). Intestinal perforation occurred in four patients with multiple revisions of the previous portoenterostomy. Of these three required diverting jejunostomy and one was repaired. Diagnosis was confirmed within 6 hours of perforation in all patients by the liberal use of a transtable lateral x-ray at first sign of abdominal distention (Fig. 8).

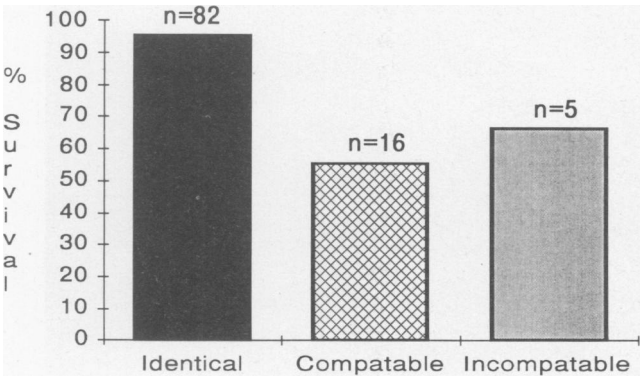


FIG. 6. First graft survival showing effects of ABO matching. Survival was 96%, 55%, and 60% for identical, compatible, and incompatible matches, respectively.

Renal Failure

Renal function was studied in 48 patients treated with cyclosporine for more than 1 year. True GFR was measured by plasma clearance of Indium-111-DPTA. Seventy-three per cent of patients had true GFR less than 70 mL/min/1.73 m^2, while 85% had true GFR less than 90 mL/min/1.73 m^2, the lower limit of normal GFR in children (Fig. 9). The mean true GFR of patients treated with cyclosporine for more than 24 months was lower ($p = 0.02$) than for patients treated between 12 to 24 months. Pediatric OLT patients with normal true GFR (more than 90 mL/min/1.73 m^2) had significantly lower HPLC plasma cyclosporine levels. Fifty per cent of patients with a true GFR less than or equal to 50 mL/min/1.73 m^2 had hypertension. There was no effect on true GFR of age, liver function, azathioprine use, or peritransplant treatment with other nephrotoxic drugs.

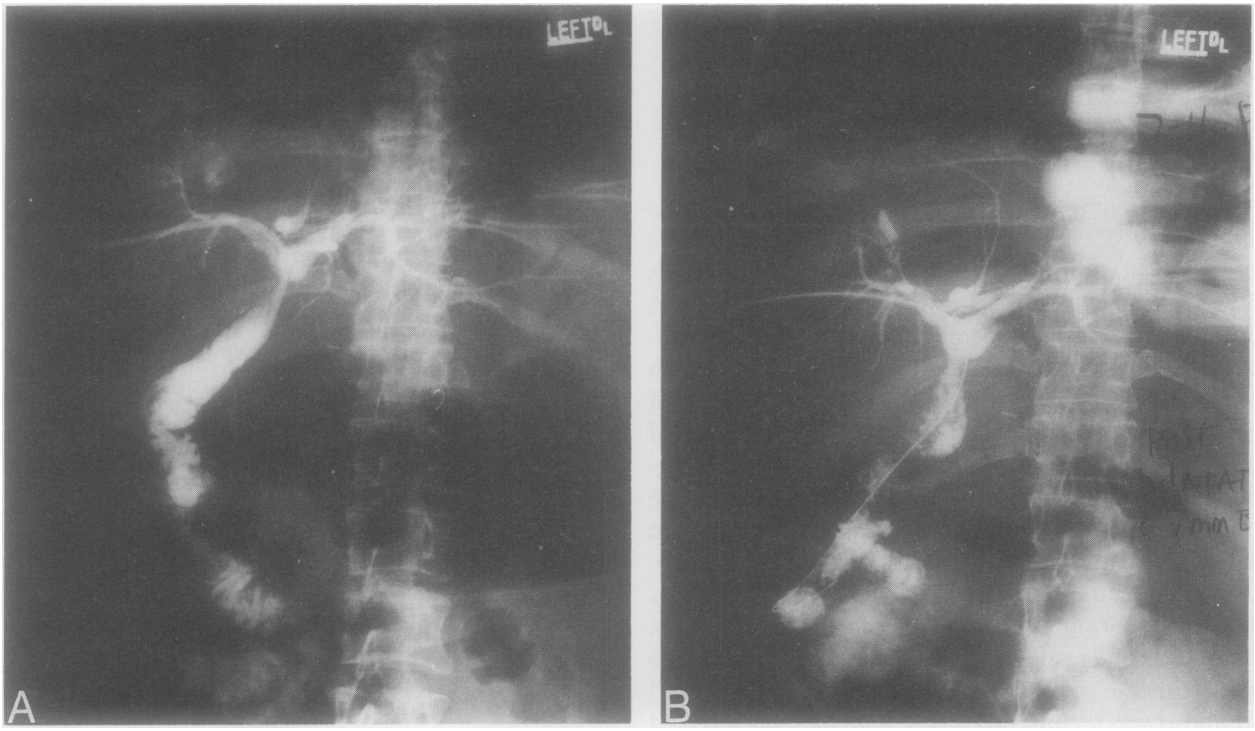
Rejection

Of 123 grafts initial immunosuppression was CsA and methylprednisolone (61 grafts); CsA, methylprednisolone and azathioprine (48); OKT3, methylprednisolone and azathioprine (12); and OKT3, methylprednisolone, azathioprine, and CsA (2 grafts). There was no difference in graft survival for initial dual or triple immunosuppression (32% and 33%, respectively). Of the 82 surviving patients, 52 are currently receiving triple maintenance therapy. The mean steroid dose is 0.24 ± 0.18 mg/kg, and the mean CsA dose is 13.5 ± 11.2 mg/kg. There is no significant difference in either steroid or CsA dose for patients on dual or triple immunosuppression.

Treatment of Rejection

A total of 94 grafts surviving more than 7 days required single or multiple steroid boluses for clinically suspected and/or biopsy-proved rejection. The first steroid bolus was unsuccessful in normalizing liver function in 38 grafts (40%). Ultimate graft survival rate was only 47% in this group, with a patient survival rate of 72%. Of these 38 grafts, 12 were treated with OKT3, 9 patients developed systemic sepsis following the steroid bolus, 5 had later biopsy evidence of vanishing bile duct syndrome, and 4 suffered a hyperacutelike rejection episode.

Of 13 patients requiring more than three steroid boluses, liver function eventually returned to normal in six. Four required retransplantation and three have chronically abnormal liver function.



FIGS. 7A and B. Biliary stricture before (A) and after (B) transhepatic balloon dilatation.

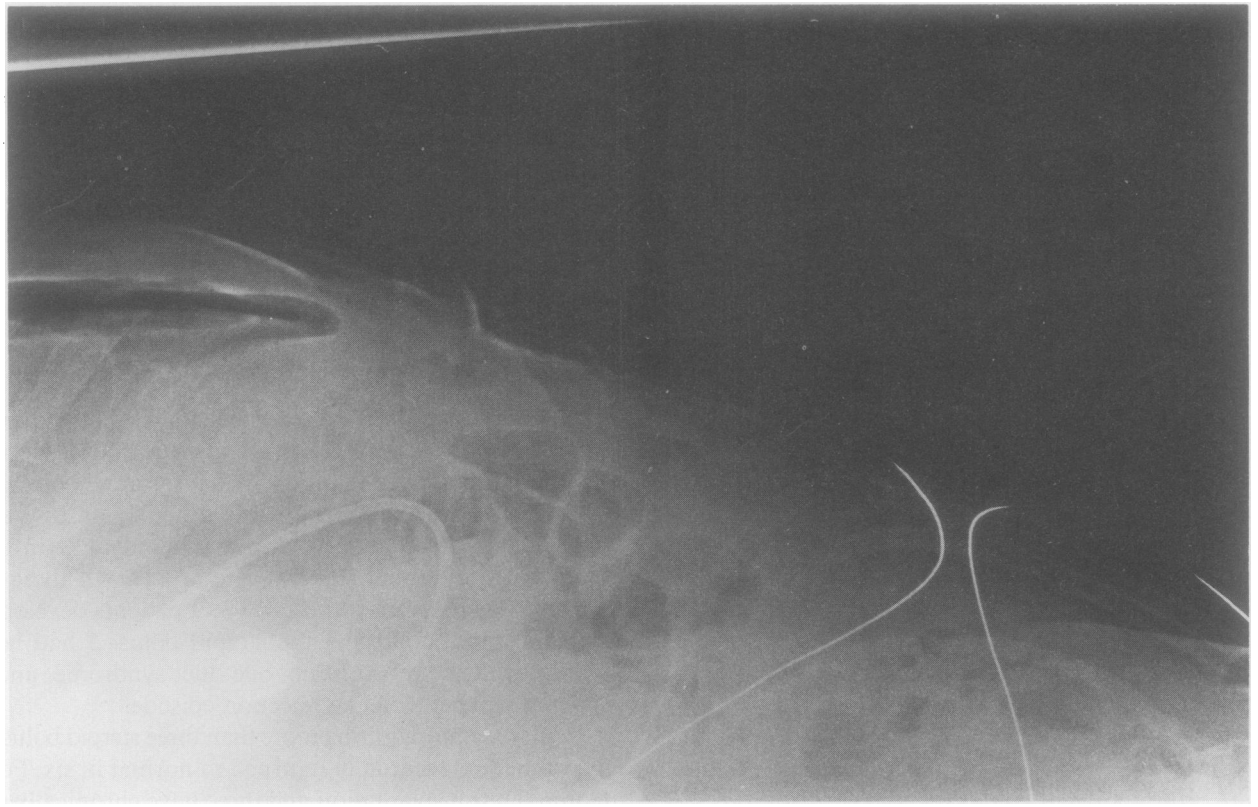


FIG. 8. Transtable lateral abdominal x-ray showing free intraperitoneal air in a patient with intestinal perforation.

Twelve patients received prophylactic OKT3. Early rejection was prevented in two patients, but there was no effect on the occurrence of late rejection. Five patients required later treatment with OKT3 for rejection, and normal liver function was achieved in four of them.

OKT3 was used to treat 43 episodes of rejection in 39 patients. Two patients received two courses of OKT3, and one patient was treated on three occasions. There was a 79% success rate in reversing rejection with OKT3.

Current Graft Function

Liver function was graded in the 82 survivors according to serum transaminases and serum bilirubin. Seventy-eight per cent had normal transaminases and bilirubin, 12% had elevated transaminases (more than 200 mg/dL) and normal bilirubin, and 10% had both elevated transaminases and bilirubin.

Retransplantation

Retransplantation was performed 21 times in 19 patients (18%), with a survival rate of 58%, and two patients received a third liver. Indications for retransplantation were HAT, rejection, primary nonfunction, and ischemia (Table 2).

Survival of patients retransplanted for HAT, rejection, primary nonfunction, and ischemia were 82%, 43%, 0%, and 100%, respectively.

TABLE 2. *Retransplantation*

OLT#	Indication	Outcome
16	Rejection	Dead
21	Rejection	Alive
25	Chronic rejection	Alive
26	HAT	Dead
36	#1 HAT #2 HAT	Alive
79	HAT	Alive
80	HAT	Alive
91	Ischemia	Alive
101	Primary NF	Dead
116	HAT	Alive
123	Primary NF	Dead
128	HAT	Alive
143	Chronic Rejection	Dead
161	HAT	Dead
162	HAT	Alive
169	Rejection	Dead
186	HAT	Alive
203	#1 HAT #2 Chronic rejection	Alive
216	Rejection	Dead

HAT, hepatic artery thrombosis.
NF, nonfunction.

Discussion

Human orthotopic liver transplantation has its foundations in the treatment of children, and the first successful human OLT was performed in a 19-month-old child with hepatocellular carcinoma in 1967.[5] This operation, although only successful in the short term, represented a pioneering effort and defined a new field of endeavor. One-year survival rates before 1980 were 30% to 40%,[6] but with the clinical use of cyclosporine and improved technical, anesthetic, and postoperative care, the 1-year survival rate is now 70% in most centers. Because of the improved results, the National Institutes of Health convened a consensus conference in 1983 and concluded that liver transplantation should be considered as the definitive therapy for various forms of end-stage liver in both adults and children.[7]

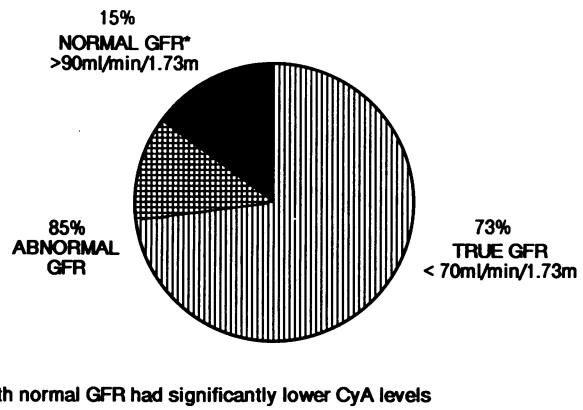


FIG. 9. True GFR measurements in patients receiving CsA for more than 1 year. Normal GFR in 15% of patients.

Although pediatric experience continues to increase, most liver transplants in this country are in adults. Fewer than 12 centers performing OLT have transplanted large numbers of children. We report a consecutive series of 123 pediatric liver transplants, which represents approximately 39% of our total liver transplant experience through December 1988.

Biliary atresia is the most common indication for pediatric liver transplantation and was the diagnosis in 47% of our patients. The surgical treatment of 'uncorrectable' biliary atresia was introduced in 1959 with description of the hepatoenterostomy operation by Kasai and Suzuki.[8] Portoenterostomy remains the preferred initial procedure in patients with extrahepatic biliary atresia, and it should be performed within 8 to 10 weeks of life for optimal results.[9] Even when bile drainage is successful, many patients will develop progressive cholestasis and cirrhosis. We believe that patients with failure of the first portoenterostomy should be referred for OLT, rather than undergo repeated attempts to achieve drainage, unless a clear mechanical obstruction can be demonstrated before operation. Not only have subsequent attempts at correction of a failed Kasai procedure been uniformly unsuccessful[10,11] but these reoperations increase the technical

hazards of liver transplantation substantially. Such patients have greater blood loss and risk of infections after OLT, and they accounted for all four cases of bowel perforation in this series. Survival after OLT in biliary atresia patients is usually less than that for childhood metabolic diseases, with rates of 64% to 75% reported.[12,13] This is the consequence of technical difficulties following previous operations, smaller size of patients, and more advanced portal hypertension and synthetic failure.

Although the recipient hepatectomy in children may be an easier technical procedure than in adults, the infant with biliary atresia and multiple revisional operations represents a formidable challenge. Technical considerations include approach to the recipient hepatectomy and meticulous construction of vascular and biliary anastomoses. Our HAT incidence of 13% and biliary complication rate of 8% are comparable to recent reports of HAT rates of 7.4% to 33%[14-16] and biliary complications of 5% to 20%[14,17] in pediatric patients. Hepatic arterial thrombosis is a devastating complication, and at our institution, virtually all cases have occurred in the pediatric population. Hepatic arterial thrombosis must be suspected at the first sign of liver dysfunction, even in the early postoperative period. The definitive diagnosis is made with Doppler ultrasound examination or with angiography. Retransplantation is always required for early HAT, although 25% of our patients in which HAT occurred more than 2 weeks after operation are well but receiving long-term antibiotics with functioning grafts.

There is no role for expectant management of biliary complications because undrained bile collections become infected and uncorrected leaks often heal with strictures. Aggressive surgical and radiologic intervention with anastomotic repair or stenting is required and was performed in all eight of the biliary leaks that occurred in this series.

The immunosuppressive regimen used in children at UCLA has undergone several modifications since 1984. Currently triple induction and maintenance immunosuppression with cyclosporine A, corticosteroids, and azathioprine is used. Acute allograft rejection, occurring in approximately 70% of patients, usually can be treated successfully. Two corticosteroid boluses of 30 mg/kg were used as the initial treatment of acute allograft rejection and were successful in normalizing liver function in 60% of grafts treated. Partial or nonresponders receive repeated boluses. Based on our experience, we found that failure to control rejection with two to three steroid cycles is an indication for OKT3. The successful use of OKT3 for steroid-resistant rejection, as prophylaxis, and as first-line treatment of rejection has been reported by several centers.[18-22] The largest experience has been with treatment of rejection. Gordon et al.[22] reported the use of OKT3 to treat acute rejection in 130 OLTs. They found significantly lower retransplantation rates and improved 1-year graft survival as compared to historical controls who were transplanted under cyclosporine and steroids, with steroid or ALG treatment for acute rejection. Cosimi[23] reported a randomized trial comparing OKT3 and steroids in the treatment of rejection that had failed one or two boluses of methylprednisolone. The success of reversing rejection was 73% with OKT3 *versus* 23% for the steroids. We currently reserve OKT3 for treatment of rejection in patients who do not respond to steroid boluses or as first-line immunosuppression for patients with renal failure when cyclosporine is contraindicated. Measurement of the percentage of CD3+ cells is used to guide OKT3 therapy. Our results demonstrate the effectiveness of OKT3, with a 79% success rate in reversing steroid-resistant rejection.

Chronic use of immunosuppression in the child is fraught with serious complications. Infection occurred in two thirds of these patients and contributed to death in 62%. *De novo* malignancy was seen in only one child and responded to decrease in the cyclosporine dosage plus chemotherapy. Renal dysfunction is of significant concern and is measurable as a decrease of GFR after 1 year. These problems underscore the need for close monitoring of immunosuppression and development of less toxic drugs. Future improvements in immunosuppression lie in the identification of markers that predict rejection reliably and in the development of new agents with a better therapeutic index.

Analysis of the causes of death in this series (Table 1) shows that sepsis was a major or contributing factor in 13 of the 21 deaths (62%), a figure similar to the 65% rate reported by Andrews.[24] Causes of death among the subgroup of ABO unidentical patients is similar to that of the entire series, with sepsis being a major factor in 67% of the deaths among the ABO unidentical patients. No positive influence was seen on positive cross-match or HLA matching. It is probable that these patients fared worse because of their generally poorer preoperative condition.

Eighty-six per cent of all deaths occurred within 5 months of transplantation and only one death occurred more than 1 year after transplantation. Long-term survival has been excellent, with a 77% 5-year survival rate. These results are comparable to the 73%[24] and 86% rates[25] reported at 3 years and 2 years, respectively, by other centers.

As stated, no reduced-size liver grafts were used in this series. There have been deaths of patients on our waiting list that, in some cases, were due to lack of a suitable donor, but the rate is a relatively low 10%, which is comparable to the 4%[26] and 14%[27] rates reported by groups active in the transplantation of reduced-size grafts. As the activity of centers performing pediatric OLTs increase and donors become more scarce, the need for reduced-size liver transplantation undoubtedly will increase.

The experience reported herein supports the current

concept that OLT is the treatment of choice for end-stage liver disease in children. The procedure can be performed with acceptable morbidity and mortality rates, and excellent quality of life may be anticipated for most patients. Currently all of our school-age survivors are able to attend school. A survival rate of 77% at 5 years for a disease process that would otherwise be uniformly fatal gives families a renewed hope that their children will be able to lead normal lives. Improved results are anticipated with greater availability of donor organs, earlier transplantation of patients on the waiting list, and development of more specific, less toxic immunosuppression.

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