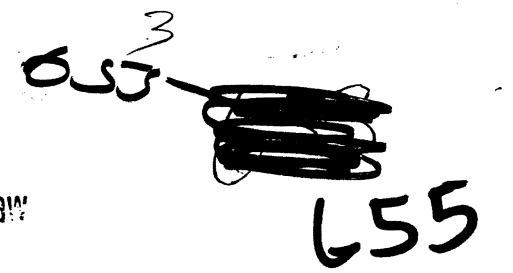

5 Pediatric Hepatology: A Three-Year Experience with Pediatric Liver Transplantation with Cyclosporine and Steroids

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INTRODUCTION

The first liver transplant in a human was performed by Dr. Thomas Starzl on March 1, 1963.[1] That patient died, as did the next four patients over the next seven months. Attempts by other surgeons in the United States and around the world also failed, until a moratorium on clinical trials was called, lasting until 1966. Not until July 23, 1967, was the first successful liver transplant in a human performed—again by Dr. Starzl. The patient was an 18-month-old girl with a hepatocellular carcinoma. She survived 13 months before succumbing to metastases from her original disease.[2] During the 1960s and 1970s, the pace of liver transplantation was slow but steady as the techniques of surgical and medical care were refined.[3]

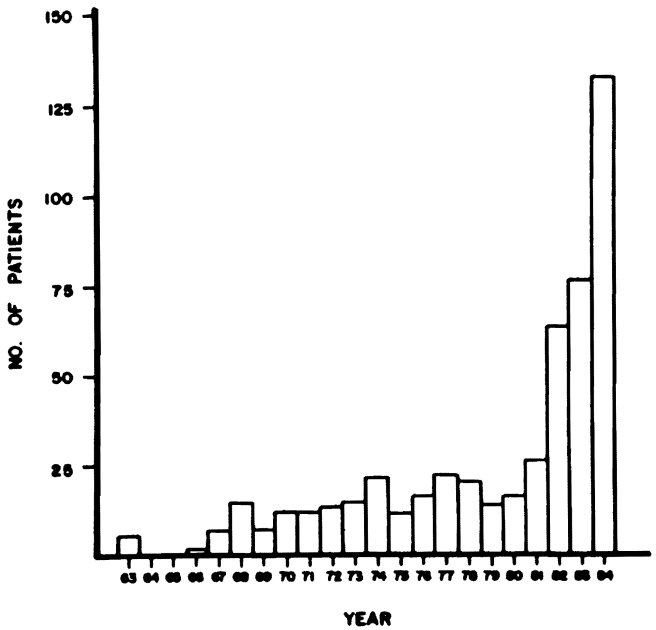

FIGURE 5.1. Number of liver transplants (children and adults) performed by Dr. Thomas Starzl and/or associates per year. 1981 to 1984 represents the Pittsburgh experience.

In 1968, Roy Calne and Roger Williams of Cambridge University and University of London, respectively, embarked on another successful liver transplant program and added additional cases for study.[4] However, it was not until the advent in 1979 of a new immunosuppressive agent, cyclosporine, that the number of cases as well as the number of survivors began to climb. From 1963 to 1979, 170 patients had livers transplanted in Denver by Dr. Starzl.[3] From 1981 to the end of 1984, the effort in Pittsburgh exceeded the entire Denver experience (Figure 5.1). Because of the pioneering work by Dr. Starzl and others and because of the improved survival rate due in part to the use of cyclosporine, other centers in the United States and around the world are establishing liver transplant facilities.

This chapter summarizes the experience with pediatric liver transplantation at the Children's Hospital of Pittsburgh from May 1981 through May 1984.

HARVESTING AND GRAFTING

A brief review of donor harvesting and organ grafting is presented only to maintain continuity. Details of these techniques can be found in other references.[3] Ideally, the donor is brain-dead, with a stable cardiovascular system during external support. Donors are usually accident victims.

When a donor is found, a team is sent to the donor's hospital and preparations made for harvesting. With respiratory and circulatory support for the donor, a midline incision is made and structures entering and exiting the liver are skeletonized. The liver is flushed in situ with a cold electrolyte solution, the cadaver is exsanguinated, and the liver is removed. It is placed in a sterile plastic bag, packed in slushed ice, and immediately transported. Notably, the procedure may be altered to accommodate harvesting the kidneys as well as the heart. Time is of the essence; the maximum cold ischemia time is only 8–12 h.[3]

While the donor organ is being harvested, another surgical team is preparing the recipient for transplantation. The recipient's hepatectomy may be difficult in the face of multiple previous abdominal operations, coagulation abnormalities, and massive collateral vessels. The structures surrounding the liver are skeletonized while the donor liver is en route. The timing of the recipient's surgery is coordinated with the harvesting team, so that on the organ's arrival the transplant may proceed with minimal delay.

The vessels and bile duct are clamped and transected. The liver is removed and the donor organ placed for grafting. The vascular anastomoses are completed and the biliary anastomosis performed. A bile duct to a Roux limb of jejunum is used in most children, especially those with biliary atresia. Whenever possible, a duct-to-duct anastomosis is performed.

IMMUNOSUPPRESSION

Constraints of cold ischemia time do not allow systematic HLA matching between the donor and recipient. In general, the donor and recipient are matched according to size and ABO blood group. In part, this is permitted because the liver appears to be resistant to hyperacute rejection despite the presence of preformed antibody.[5]

TABLE 5.1. Major Side Effects of Cyclosporine

Nephrotoxicity	Skin flushing
Hepatotoxicity	Breast fibroadenomata
Hirsutism	Pseudolymphoma
Tremor	Infection
Seizures	Hypertension
Gingival hyperplasia	

Previous immune suppression regimens included prednisone, azothiaprine, cyclophosphamide, antilymphocyte globulin, and thoracic duct drainage. Each of these regimens was attended by numerous complications, including bone-marrow suppression and infection. In addition, massive doses of steroids were often required to keep rejection in check, and these doses were associated with complications such as Cushingoid features, hypertension, and linear growth retardation.

Calne first reported the use of a new immunosuppressant, cyclosporine, in humans in 1978.[6] A fungal extract discovered by scientists at the Sandoz Laboratories in Switzerland, cyclosporine was noted to be a powerful immunosuppressant but had little or no bone-marrow suppression.[7] Cyclosporine selectively and reversibly affected T-cell function. As with any drug, however, cyclosporine has its own attendant toxicities (Table 5.1). Each of the effects, including the pseudolymphoma, is believed to be reversible by lowering the dose or temporarily stopping the drug.[8]

Intravenous cyclosporine is given immediately preoperatively, and maintained postoperatively at an initial dose of 6 mg/kg/day. Oral cyclosporine is also given when the patient is able to take medication enterally, and is overlapped with intravenous cyclosporine. A burst of steroids is given in the perioperative period and is rapidly weaned over 4–5 days to a baseline daily dose of 20 mg of prednisone. When liver functions normalize, the intravenous cyclosporine is weaned. As liver functions stabilize, the prednisone dose is gradually reduced to a minimum of 2.5–5 mg/day. On this regimen, most children have been able to grow and develop with little or no long-term steroid complications.

Rejection may be manifested clinically by fever, malaise, vague abdominal pain, hepatomegaly, and ascites, accompanied by a rise in bilirubin, transaminases, alkaline phosphatase, and gamma glutamyl transpeptidase. Rejection can be confused with ischemic injury, biliary obstruction, cholangitis, viral hepatitis, or drug toxicity. It is treated with boluses of steroids as well as adjustments in the cyclosporine dose.

EVALUATIONS AND TRANSPLANTS (PITTSBURGH, 1981–1984)

In a 36-month period from May 1981 to May 1984, 90 pediatric patients underwent liver transplantation. This is the single largest experience in pediatric liver transplantation. The process began when a family or physician contacted us about a potential candidate. Records were sent to us for review, and if the patient appeared to be a candidate, the family was asked to come to Pittsburgh for a formal evaluation. Two hundred and nine patients were evaluated for transplant. The evaluation centered on confirming the diagnosis, assessing the severity and progression of the patient's liver disease, evaluating anatomical suitability for transplantation, and educating the family.

Table 5.2 lists the indications for transplantation and the outcome. Biliary atresia accounted for 43% of the patients transplanted, with various metabolic disorders (24%) comprising the next largest group. Twenty-three patients died post transplantation with a minimum of a 6-month follow-up, giving a 74% survival rate.

COMPLICATIONS

The surgery and postoperative period are fraught with complications.[9] Table 5.3 summarizes the primary and secondary causes of death in 23 patients. Rejection and its complications as well as infection (including overwhelming varicella in 1 patient) were leading causes of death. Vascular complications, including thrombosed hepatic arteries or preexisting anomalies such as absent portal vein or anomalous venous drainage of the upper body, led to deaths in another 5 patients. Intracranial hemorrhage or cerebral edema led to the death of 3 more patients.

TABLE 5.2. Indications for Liver Transplantation

Biliary atresia*		39(10)#
Biliary hypoplasia		9(3)
Familial cholestasis		7(2)
Hepatitis		5(2)
Neonatal hepatitis		3(0)
Metabolic disorders		22(4)
A_1AT	15(3)	
Tyrosinemia	2(0)	
Glycogen storage disease I	1(0)	
Sea blue histiocyte	1(0)	
Hypercholesterolemia*	1(0)	
Wilson's disease	2(1)	
Biliary obstruction		1(1)
Benign tumor		1(0)
Idiopathic cirrhosis		1(0)
Acute hepatic failure		2(1)
		90(23)

*1 auxiliary transplant.
#() represents number of deaths.
*Combined heart-liver transplant.

Myocardial infarction occurred in a patient with Alagille's syndrome with a partially corrected pulmonary stenosis. Hepatic infarction (with patent vessels) led to graft loss and patient death in 5 other patients. This may have been due to ischemic injury during harvesting or during surgery in the patients lost shortly

TABLE 5.3. Major Factors in the 23 Deaths

	Primary	*Secondary*
Rejection	4	2
Vascular anomalies, preoperative	2	1
Vascular complications, surgical	4	1
Infection	4	5
Massive liver infarction with patent vessels	early 3 late 2	
Cerebrovascular accident/edema	3	
Myocardial infarction	1	1

TABLE 5.4. Early (First Two Months) Complications among the 67 Survivors

Hypertension (seizures 7)	66*
Rejection	46
Major infection	19
Biliary tract (surgical)	7
Prolonged tracheostomy	7
Vascular thrombosis (retransplant 5)	8
Renal failure (dialysis)	3
Diabetes mellitus (transient)	2
Myocardial infarction	2

*Numbers represent patients rather than episodes.

after transplant, but little explanation can be offered for 2 patients who had sudden infarction 10 and 11 days after the transplant.

Complications among the survivors can be divided into early (less than 2 months) and late (more than 2 months), using 2 months as a convenient dividing point. Most patients are usually discharged from the hospital by 2 months posttransplant. Table 5.4 lists the early onset complications in the 67 survivors.

Hypertension was an almost universal phenomenon occurring immediately posttransplant and often required multiple drug therapy for control. Seven patients had hypertensive encephalopathy with seizures. Fortunately, none has sustained serious permanent sequelae. Although the mechanism of the hypertension is unknown, it is suspected that cyclosporine may be in part responsible through its stimulation of the renin-angiotensin system. Rejection also occurred frequently, but was usually able to be controlled with bursts of steroids and alteration of cyclosporine doses.

Major life-threatening infections occurred in 19 patients. Gram-negative organisms were most frequently cultured, although the *Staphylococcus* as well as *Candida sp* and cytomegalovirus also caused significant morbidity.

Late complications (Table 5.5) included rejection as the most commonly occurring among the survivors. Surgical complications such as portal vein obstruction occurred in 4 patients. In two patients who had a portocaval shunt prior to transplantation the portal veins were thrombosed posttransplantation. Interstitial

TABLE 5.5. Late (After Two Months) Complications among the 67 Survivors

Rejection	22*
Portal vein obstruction	4
Biliary tract (surgical)	2
Hypertension	2
Interstitial pneumonitis	5
Lymphoma	2
Pseudotumor cerebri	1
Recurrent storage disease	1
Major infection	1

*Numbers represent patients rather than episodes.

pneumonitis with presumed *Pneumocystis carinii* occurred in 5 patients, usually about 3–4 months posttransplant. Two patients developed a lymphoproliferative disorder after a primary Epstein-Barr virus infection. One patient presented with intestinal obstruction,[8] while the other presented with marked tonsillar hypertrophy and airway obstruction. Both patients had resection of the tumor (patient No. 1 had only a partial resection), and cyclosporine was lowered. Neither patient has had evidence of recurrence of the tumor.

While infections remain a major complication of the transplant procedure, the bone marrow-sparing qualities of cyclosporine may be helpful in limiting life-threatening infections. Table 5.6 compares the number of episodes of bacteremia and fungemia per graft in the precyclosporine era with the first 24 months of our own experience using cyclosporine. The number of episodes of bacteremia is less using cyclosporine. Fungal infections, however, may be slightly greater, although the number of episodes is quite small. While other factors such as differing surgical or medical regimens were not controlled in this superficial evaluation, it appears that cyclosporine may offer a protective advantage against bacteremia compared with previous immune suppression regimens.

METABOLIC DISORDERS

Liver transplantation provides a unique opportunity to study the systemic effects of hepatic-based metabolic disease.[10] In the

TABLE 5.6 Bacteremia/Fungemia (No. of Episodes per Graft)

Pre CYA (3/63–11/74)		*Post CYA (5/81–5/83*	
Bacteremia	69/102 (67%)	Bacteremia	29/64 (45%)
Fungemia	3/102 (3%)	Fungemia	4/64 (6%)
Total	71/102 (70%)	Total	33/64 (51%)

precyclosporine era, patients with metabolic disorders had a clear survival advantage,[11] but more recently the difference in survival between patients with biliary atresia, who historically had a poorer outcome, and children with metabolic disorders has narrowed significantly. Currently, the overall survival rate for all 90 patients is 74%. Transplanted patients with biliary atresia have a 74% overall survival rate, while patients with metabolic diseases have an 82% survival rate.

Fifteen patients with alpha-1-antitrypsin deficiency were transplanted. Fourteen patients were examined postoperatively. All 14 patients had normalized serum alpha-1-antitrypsin levels and all assumed the Pi type of the donor. In addition, on examination of the transplanted liver in all 15 patients, no PAS positive, diastase-resistant granules were noted. Clinically, no patient has had any evidence of disease consistent with alpha-1-antitrypsin deficiency.[12]

Two patients with Wilson's disease were transplanted. One survived. He was a 13-year-old boy who failed medical management and progressed to hepatic failure, renal failure, and coma. He had typical neurological findings of Wilson's disease with bradykinesia and cogwheel rigidity. After successful transplantation, liver function was normal and the hepatorenal syndrome resolved. Serum copper and ceruloplasmin normalized, although urinary copper excretion remained high. The boy's neurological function returned to normal over the year posttransplant. Return of neurological function has been also reported in other patients with Wilson's disease after successful transplantation.[13]

Two patients with tyrosinemia and hepatoma were successfully transplanted without evidence of recurrence of their original disease or tumor. In both cases, the tumor was entirely confined to the liver. Shortly after transplantation, both patients maintained normal serum amino acids while on a regular diet, and are now leading virtually normal lives.[14]

A teenage girl with glycogen storage disease, type I, had a history of profound hypoglycemia requiring portocaval shunting and continuous nighttime feedings. She developed progressive hepatic failure due to hemorrhage into hepatic adenomata. She underwent successful liver transplantation, and postoperatively was able to maintain a normal serum glucose during a 24-h fast. In addition, a brisk glycogenolytic response was demonstrated to parenteral glucagon administration.[15] Glucose homeostasis has remained normal during a 3-year follow-up. However, this patient's portal vein was thrombosed posttransplantation, and she required a distal splenorenal shunt to control portal hypertension. In addition, she has had problems with serious infections including *Pneumocystis carinii* pneumonia and *Candida torulopsis* meningitis.

Homozygous familial hypercholesterolemia ravaged the heart of a 6-year-old Texas girl. During evaluation for her hypercholesterolemia, which ranged more than 1000 mg/dl, she had two myocardial infarctions requiring two separate double bypass operations and placement of an artificial mitral valve. A combined heart and liver transplant was performed.[16] Postoperatively, cholesterols fell to the 200–250 mg/dl range and plateaued at approximately 300 mg/dl. In this case, replacement both of the morphologically normal liver with a subcellular metabolic defect and of the damaged target organ, the heart, has allowed this patient to lead a virtually normal life.

The sea-blue histiocyte syndrome is a poorly understood, progressive degenerative neurological disorder characterized by the accumulation of ceroid-like material in macrophages in the liver and bone marrow. The marrow demonstrates a nonspecific sea blue histiocyte. Liver disease progresses to cirrhosis, and in our patient a hepatoma was also found at transplantation. Neurological deterioration temporarily plateaued after transplantation, but storage material accumulated in the transplanted organ again and neurological function again worsened. It appears that the metabolic defect in this disorder is not hepatocyte-based, and liver transplantation may not be indicated.[10,17]

Overall, previously fatal hepatic-based metabolic disorders are potentially curable with liver transplantation. Long-term follow-up of these patients, however, is imperative to assure no recurrence of the original disease, although none is expected. In addition, patients and families will continue to require genetic counseling since their offspring may still be at risk for these inheritable disorders.

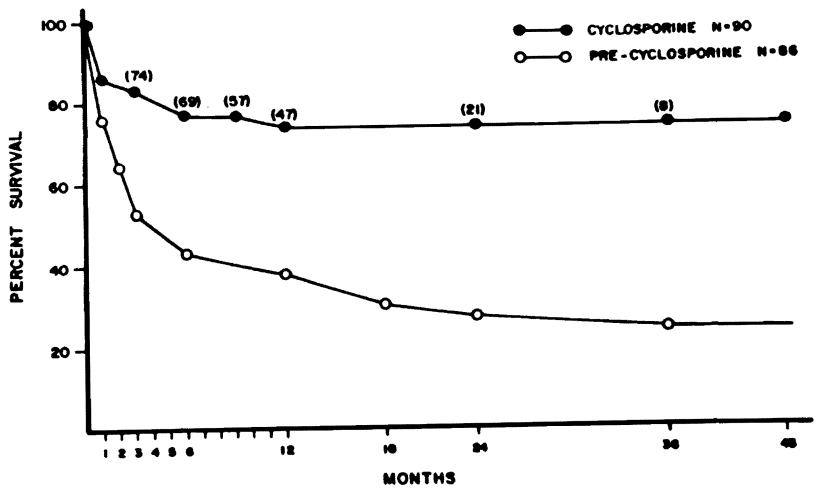

FIGURE 5.2. Comparison of survival of pediatric patients with cyclosporine and steriods transplanted in Pittsburgh (closed circles) with pediatric patients transplanted in Denver under conventional immunosuppression (open circles).

FOLLOW-UP

The pediatric survival rate under cyclosporine and steroids is compared in Figure 5.2 with the survival rate in the precyclosporine era. With improved surgical technique and medical management as well as the advent of cyclosporine, the current survival rates are over 74%.

Graft function as of March 1985 is summarized in Table 5.7. Patients with poor graft function are awaiting retransplantation.

TABLE 5.7. Graft Function in the 67 Survivors

	No.	*Bilirubin (mg/dl)*
Excellent	65	0.1–1.4
Poor	2	16–45

The quality of life for these patients is excellent postdischarge. More than 80% of the patients with growth potential will either exhibit catch-up growth or maintain a normal growth velocity. These patients have had fewer hospitalizations posttransplant compared with the pretransplant period and are able to attend school in appropriate age grades. Children are described by their parents as happier and more outgoing, and the physical stigmata of chronic liver disease are removed. There are still fears, however, of rejection and malignancy. Psychological adjustments for parents, patients, and siblings to the new "state of the family" may be difficult, and at times may lead to the vulnerable-child syndrome and sibling jealousy.

Liver transplantation is arduous and at times frustrating. It requires a massive team effort from every level of the hospital staff. With close cooperation and careful coordination, however, a successful and rewarding program can be established.

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