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Pediatric Liver Transplantation With Cyclosporine and Steroids

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Although the first liver transplant in a human was performed in 1963, it was not until July 1967 that the first long-term survivor received a transplant. Dr Thomas Starzl successfully transplanted a liver into an 18-month-old girl with a hepatoma. She survived 13 months before succumbing to metastases of her original disease.[1] From 1963 until 1979, 170 patients were transplanted by Dr Starzl in Colorado, including 86 pediatric patients.[2] Conventional immunosuppression was used. From May 1981 until May 1983, 47 additional children received orthotopic liver transplants at Children's Hospital of Pittsburgh under Dr Starzl, using cyclosporine and steroids.[3] This report summarizes the experience of those 47 patients.

Patient Selection

After initial contact with the family or the referring physician, we received records of the patient's course, including biopsy material, for review. A brief hospital evaluation was then arranged to 1) confirm the diagnosis, 2) evaluate the severity of liver disease, 3) assure appropriate anatomy for transplant, and 4) provide education and support to the family.

Children considered for transplantation generally weighed 7 kg or more. Those with biliary atresia were considered if hepatoportoenterostomy had failed or if hepatic decompensation existed. Children with disorders of uncertain prognosis were considered active candidates when progressive hepatic decompensation occurred.

Immunosuppression

No systematic attempt at homologous leukocytic antibody (HLA) matching of donor and recipient was done. The same general guidelines for blood transfusions were used. ABO type-specific organs were usually used for transplant, because of the maximum cold ischemic time of 12 hours that can be subjected upon the harvested organ. In addition, the liver appears to be resistant to hyperacute rejection, as seen in renal transplants.[2]

Cyclosporine, a fungal extract with powerful immunosuppressive properties and minimal bone marrow toxicity, was administered to every patient immediately before surgery.[4] Oral cyclosporine was continued postoperatively until bilirubin and transaminases normalized. At that point, intravenous cyclosporine was tapered rapidly and discontinued. A burst of steroid was administered in the immediate postoperative period and rapidly tapered over 5 days to a baseline of 5 to 20 mg daily.

Results

In the 24-month period from May 1981 to May 1983, 47 children ranging in age from 7.5 months to 18 years received transplants. The smallest child weighed 7 kg. There were 20 males and 27 females. Thirty patients (64%) are surviving. Table 1 lists the diagnoses and outcome.

Sixty-four grafts were used in the 47 patients. Fifteen patients (32%) required retransplantation. Thirteen patients received two grafts and two patients received three grafts. Seven of the 15 patients (47%) with retransplants are surviving. Of the 64 grafts used, 38 (59%) survived or functioned normally at the time of the patient's death. Causes of graft failure included rejection (8), massive infarction with patent vessels (8), vascular accidents or thromboses (5), and infection (5).

Infection continues to be a major cause of morbidity and mortality, but is less serious than during the precyclosporine era. Before the use of cyclosporine, bacteremia and/or fungemia occurred with 70% of the grafts used.[5] In our experience, bacteremia (45%) and fungemia (6%) occurred with only 51% of the grafts used. In the 47 patients receiving transplants in Pittsburgh, enteric organisms predominated among the episodes of bacteremia. Enterococcus was the organism most frequently cultured from the blood, with *Escherichia coli* and *Pseudomonas* also seen. *Staphylococcus aureus* was usually cultured in relation to line-related bacteremia. *Candida* species often contaminated wounds

Table 1. Pediatric Indications for Liver Transplantation, May 1981 to May 1983.

Biliary atresia		19 (7)*
Metabolic conditions		13 (3)
α_1-Antitrypsin deficiency	8	
Glycogen storage disease I	1	
Hereditary tyrosinemia	1	
Wilson's disease	2	
Sea-blue histiocyte syndrome	1	
Biliary hypoplasia		3 (2)
Chronic active hepatitis		4 (2)
Familial cholestasis		5 (2)
Neonatal hepatitis		1
Biliary obstruction		1 (1)
Benign liver tumor		1
		47 (17)

*Deaths

and was related to repeated biliary-tract surgery. Cytomegalovirus has been cultured from urine, liver, and lung, and at least one graft was lost due to adenovirus infection.

Other complications were numerous, and those occurring in the survivors are summarized in Table 2.[1] Two months served as a convenient marker for early and late complications, since most patients were discharged from the hospital at approximately that time. Hypertension was virtually universal in survivors, and generally responded to captopril. Rejection episodes occurred in more than two thirds of the survivors and was corrected with increased immunosuppression. Portal vein or hepatic artery thrombosis occurred in three patients, necessitating retransplantation. Late complications still included rejection as a major event. In addition, interstitial pneumonitis due to *Pneumocystis carinii* was seen in two patients. One patient developed intestinal obstruction from a lymphoproliferative disorder approximately 6 months posttransplant. This coincided with an acute rise in his Epstein-Barr virus (EBV) titer. The tumor was partially resected, and treatment consisted only of drastically reducing the immunosuppressive regimen. Although the patient developed chronic rejection, he has had no evidence of tumor recurrence 1 year after tumor resection. Increased immunosuppression has allowed better control of the rejection.

Thirteen children with various metabolic diseases received transplants. Eight children had α_1-antitrypsin deficiency. In all children in whom measured, α_1-antitrypsin levels became normal and the recipients assumed the protease inhibitor (Pi) type of the donor. There has been no evidence of regression or recurrence of the disease to date.[6,7] The child with type I glycogen storage disease required frequent daytime feedings and continuous nocturnal feedings before transplant. She received a transplant because of hepatic adenomata and progressive hepatic failure. Carbohydrate homeostasis 6 weeks postoperatively was normal, with the ability to withstand a 24-hour fast and brisk glycogenolysis in response to glucagon.[8] The patient with hereditary tyrosinemia was on a

Table 2. Number of Survivors Experiencing Major Complications.

Early (< 2 months)		Late (> 2 months)	
Hypertension (Seizures: 5)	29	Rejection (Chronic: 1)	7
Rejection	21	Portal vein obstruction	4
Life-threatening infection	8	Biliary anastomosis surgery	2
Biliary anastomosis surgery	5	Hypertension	2
Tracheostomy	4	Interstitial pneumonia	2
Vascular thrombosis (retransplant)	3	Lymphoproliferative disorder	1
Transient diabetes mellitus	2	Pseudotumor cerebri	1
		Recurrent metabolic disease	1

markedly restricted diet pretransplant and had developed a hepatoma. After successful hepatic transplantation, she maintained normal serum amino acids on a regular diet and has had no evidence of tumor recurrence. One of two patients who received transplants because of Wilson's disease survived, and has had normalization of serum ceruloplasmin and copper, has maintained normal hepatic copper, and has had increased urinary copper levels. In addition, central nervous system abnormalities consistent with Wilson's disease reversed over the 6 to 12 months posttransplant. The child with the sea-blue histiocyte syndrome had progressive neurologic deterioration, cirrhosis, and hepatoma. Despite successful hepatic transplantation and transient plateau of neurologic function, she has had recurrence of ceroid-like materials in the Kupffer cells of the transplanted liver and continued neurologic regression.[7]

Status of the 30 survivors as of May 1983 is listed in Table 3. Follow-up of these patients ranged from 5 to 28 months. All patients were clinically well. The average prednisone dose was 5 mg per day, or approximately 0.3 mg/kg per day. The mean cyclosporine dose was 15 mg/kg per day.

Table 3. Status of 30 Survivors of Transplant, May 1981 to May 1983.

Outcome	No.	Bilirubin (mg/dL)	Alanine Aminotransferase (IU/mL)
Excellent	27	0.2-1.1	12-100
Good	2	0.7-1.3	123-170
Fair	1	3.8	89

Linear growth was monitored before and after transplant. Twenty-four of the 30 survivors had been followed at least 6 months to obtain adequate growth data.[1] Two patients were mature at the time of transplant. Of the remaining 22 patients, all but 1 either exhibited accelerated growth velocity with catch-up growth or maintained normal growth velocity. The patient with the sea-blue histiocyte syndrome had no growth in the follow-up period, due to the use of high-dose steroid therapy to reverse rejection as well as possible recurrence of her original disease.

The Figure demonstrates the improved survival of pediatric patients at Children's Hospital of Pittsburgh when cyclosporine and steroids were used, as compared to overall survival in children during the precyclosporine era. In addition, from May 1983 until December 11, 1983, 19 additional patients received transplants. Two patients remain in the hospital at the time of this presentation. Two of the remaining 17 patients have died. The others have been discharged and are at home. These 15 patients represent an 88% survival rate since May 1983. Also, the retransplantation rate was only 18%.

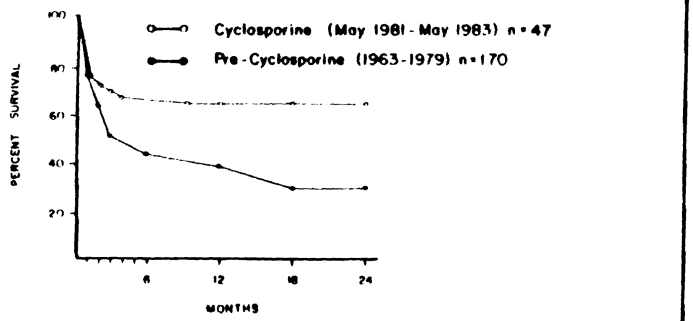

Figure. Survival rate of transplant patients at Children's Hospital of Pittsburgh. Closed circles represent patient survival before the use of cyclosporine. Open circles represent survival rate with cyclosporine and low-dose steroids.

Conclusions

Orthotopic liver transplantation with cyclosporine and steroid therapy is effective therapy for children with end-stage liver disease. Overall, survival rates have doubled with the advent of cyclosporine, as well as with improved surgical technique and medical care. In addition, early recognition of graft failure and aggressive retransplantation have contributed to improved patient survival.

Although cyclosporine is a potent immunosuppressant, its marrow-sparing character has contributed to fewer episodes of bacteremia and fungemia. This, too, has been a major factor in improved survival. While enteric and fungal infections remain serious problems, protozoal and viral infections with *Pneumocystis*, cytomegalovirus, and adenovirus also represent potentially life-threatening diseases.

Hypertension occurred in all but one survivor, and may be related to cyclosporine use.[9] Although the mechanism of the hypertension is unknown, it may be mediated via the renin-angiotensin system.[10] The lymphoproliferative disorder appears to occur with EBV infection, as described with other transplant patients.[11] The successful management of these patients may involve not immunosuppressing the patient any further with chemotherapy, but rather lowering the immune suppressive regimen to allow natural host defenses to combat the EBV infection.[12]

Liver transplantation provides a unique opportunity to intervene in metabolic disorders that previously were lethal. While transplantation is not recommended

as primary therapy for type I glycogen storage disease and Wilson's disease, it remains another option for potential cure when medical therapy fails.

Liver transplantation in children remains a challenging and demanding procedure, but the survival rate is constantly improving. Improvement in lifestyle is uniform. Psychosocial issues have been monitored closely, and preliminary data suggest considerable improvement in physical, language, and gross motor function. Children unable to participate in school before the transplant are now participating on a regular basis. In addition, improvement in health allowed lifting of restrictions to permit age-appropriate activities.[13] Because children often have newfound energy and become impulsive, parents sometimes require counseling to deal with the "loss" of a placid, docile, ill child and the sudden acquisition of an active, rambunctious one.

Overall, orthotopic liver transplantation represents a major advancement in the therapy of end-stage liver disease.

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Discussion

DR ANDERSEN: What do you think causes the hypertension problems in transplants? Is it cyclosporine?

DR ZITELLI: I believe that cyclosporine is related, but I am not sure of the exact mechanism. It may be mediated through the angiotensin system. We have found that captopril is the best agent for controlling hypertension.

DR VAN THIEL: In heart transplants in adults, cyclosporine dramatically increases peripheral resistance. Captopril seems to be the only drug that touches the hypertension. Vascular volume and cardiac output remain stable. Cyclosporine seems to affect peripheral vessels.

DR WHITINGTON: We have treated several children with propranolol. We just titrated them until we got a reduction in the heart rate.

DR ZITELLI: We also have used propranolol, but have found that many children will maintain hypertension despite large doses.

DR POLEY: How would you rate the potential risk for the development of non-A, non-B hepatitis after so many blood transfusions?

DR VAN THIEL: It is probably appropriate for me to talk about it because children receive 5000 mL as the upper limit of transfusion, which is a pitifully small amount of blood in adults. The average liver transplant in adults requires about 40 units of blood. We have used as much as 160 units of blood in a single transplant, and the record in the United States is 268 units. To my knowledge, no one has ever made the diagnosis of non-A, non-B hepatitis after a liver transplant, and that tells you that things are so hectic in those first 3 months that it's impossible to make that diagnosis until a serologic marker is available.

DR ERLINGER: We were told before that in children with biliary atresia, transplantation was considered only when the earlier operation failed. Is that still the policy?

DR ZITELLI: Yes, when the Kasai procedure has failed or the patient develops other life-threatening progressive hepatic decompensation.

DR VAN THIEL: In a comparable disease in adults, sclerosing cholangitis, in which many of these same manipulations in the porta hepatis occur, prior surgery clearly extracts a cost in survivorship as a result of liver transplantation. In fact, sclerosing cholangitis carries the worst prognosis for survival in an adult who is to have a liver transplant. This is because of the multiple surgical procedures in the porta hepatis, sepsis related to those operations, and the massive collaterals that develop in the adhesions in and around the porta hepatis.

DR ALTMAN: The Kasai procedure certainly will stand or fall on its own merits. But extrapolating from sclerosing cholangitis to biliary atresia in children is imprecise, and the Kasai operation will relieve jaundice and allow growth and development in certain patients.

DR ZITELLI: I think the problem of transplantation in biliary atresia is such that we have not yet reached the stage of recommending liver transplantation as a primary mode of surgical therapy for biliary atresia.

DR BUSTAMANTE: Given the number of patients who can be helped by this procedure, how do you justify cost?

DR ZITELLI: That is very difficult, particularly with children. We would like to determine whether liver transplantation, despite the tremendous cost, is in fact a cheaper way to handle chronic liver disease than trying to support the patient over a period of time and ultimately have the patient die. We know, for example, that hospital treatment for gastrointestinal bleeding may cost $50,000 and the patients often have repeated gastrointestinal hemorrhages. We are comparing pretransplant and posttransplant costs to see if it is less expensive to perform transplants in these patients.

Management of Neonatal Cholestasis: A Summary

Philip Sunshine, MD

During this conference, we reviewed the various factors that relate t and focused on those that occur primarily in the neonatal period.

The major problem that currently confronts physicians caring appears to be that of cholestasis associated with the use of parente While this form of nutritional support is paramount for the surviv with gastrointestinal catastrophes, malformations, or immature f approach to solving the complication of cholestasis has continued even though we have devoted a great deal of time and effort to the u of this entity. In patients who require total parenteral nutrition (TP than 2 weeks, the incidence of cholestasis begins to increase signif in some cases, even though the TPN is discontinued, patients go c chronic liver disease and liver failure.[1] Apparently, many etiolog involved in producing this entity, and these have been addressed b The various factors that have been incriminated in the developn associated cholestasis are listed in Table 1.

Table 1. Factors That May Be Involved in the Developmen Parenteral Nutrition (TPN)-Associated Cholestasis.

Immature hepatic synthesis of bile acids
Immature hepatic excretory function
Elaboration of aberrant bile acids
Lack of enteral stimulation
Decreased activity of gastrointestinal hormones
Adverse effect of amino acids or their metabolites on canalicula
Amino acid imbalance
Decreased concentration of certain amino acids (cysteine, taurin
Oroticaciduria
Sepsis
Cholangitis
Decreased concentration of fat-soluble vitamins
Increased concentrations of copper in liver
Agents that interfere with sodium-coupled ion transport (furose

Blitzer[2,3] has illustrated the effects of various amino acids c uptake in isolated rat hepatocytes and also referred to the eff inhibitors of the sodium-coupled ion transport of bile acid upta co-workers[4] have demonstrated, at least in laboratory animals, and possibly tryptophan metabolites are major culprits in initiati picture. In addition, we are encountering an increasing number cholelithiasis who are receiving TPN, and possibly the same f to the production of gallstones are involved in the production c Similarly, patients with cystic fibrosis who require TPN dev readily, illustrating that secretion of bile acids can be altered sodium-dependent pumps are not operating well.