Liver Transplantation in Children with Cystic Fibrosis: A Long-Term Longitudinal Review of a Single Center's Experience

By Jonathan A. Fridell, Geoffrey J. Bond, George V. Mazariegos, David M. Orenstein, Ashokkumar Jain, Rakesh Sindhi, Jonathan D. Finder, Ernesto Molmenti, and Jorge Reyes
Pittsburgh, Pennsylvania; Indianapolis, Indiana; and Baltimore, Maryland

Background: Improved long-term survival in cystic fibrosis (CF) has led to an increased incidence of extrapulmonary complications of this disease. Of these, end-stage liver disease is a significant cause of morbidity and mortality with liver transplantation being the only effective therapy.

Methods: Records of all CF pediatric liver transplant recipients were reviewed.

Results: Twelve children with CF were the recipients of 16 allografts. The 1- and 5-year survival was 91.6% and 75%, respectively. There were 5 deaths at a mean interval of 6.8 ± 6.3 years. All of these deaths were related to pulmonary disease. Pulmonary function improved or remained stable in 8 of 9 patients tested. Despite an 83% incidence of positive sputum cultures, there was only one early mortality related to pulmonary sepsis in the setting of primary liver allograft nonfunction.

Conclusions: Liver transplantation is acceptable treatment for children with CF and end-stage liver disease. Long-term survival is comparable to liver transplantation performed for other indications. Although posttransplant morbidity and mortality is related to lung disease, the authors speculate that as therapeutic improvements prolong the survival in CF, it is expected that longer survival after liver transplantation in this patient population may also be anticipated.
J Pediatr Surg 38:1152-1156.

INDEX WORDS: Pediatric liver transplantation, cystic fibrosis.

CYSTIC FIBROSIS (CF) is an inherited disorder that affects epithelial chloride transport and presents as a multisystem disease. The first signs and symptoms typically occur in early childhood. Because of improvements in pulmonary therapy, the predicted median survival rate for patients with CF in 2000 was 32.2 years.[1] As survival improves, more patients are living long enough to experience extrapulmonary complications.[2] The incidence of liver disease and cirrhosis associated with CF are 1% and 0.8%, respectively,[1] with an average age at onset of 7 years[3] and a reported peak incidence between the ages of 16 and 20 years.[4,5] The mean duration of survival after development of cirrhosis is 4.5 years. Approximately 20% of deaths after the diagnosis of cirrhosis result from liver complications and 33% from respiratory complications.[3]

From the Department of Pediatric Transplantation, Thomas E. Starzl Transplantation Institute, Children's Hospital of Pittsburgh and Antonio J. and Janet Palumbo Cystic Fibrosis Center, Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA; the Department of Surgery, Indiana University School of Medicine, Indianapolis, IN; and the Department of Surgery, The Johns Hopkins Hospital, Baltimore, MD.

Address reprint requests to Jorge Reyes, MD, Thomas E. Starzl Transplantation Institute, Children's Hospital of Pittsburgh, Room 7 North, 7950, 3705 Fifth Ave, Pittsburgh, PA 15213.

0022-3468/03/3808-0005$30.00/0
doi:10.1016/S0022-3468(03)00260-4

Liver transplantation is the procedure of choice for progressive, irreversible hepatic insufficiency. Outcomes after liver transplantation in children have improved significantly over the last 2 decades owing to improvements in operative technique, organ preservation, perioperative management, and advances in immunosuppressive medication protocols.[6,7] Preexisting pulmonary disease and the potential effect of immunosuppression on respiratory infections have led to reluctance in pursuing liver transplantation in the recipient with CF. Conversely, some patients have been referred for combined double lung and liver or heart/lung/liver multiorgan transplantation after irreversible deterioration of both organs.[8-11] In this report we review the encouraging results of 12 children who underwent transplant for CF-related liver disease.

MATERIALS AND METHODS

A total of 833 pediatric liver transplants were performed at the Children's Hospital of Pittsburgh between March 1981 and December 1998. Cyclosporine-based immunosuppression was used before November 1989 in 482 (57.8%) recipients, and the subsequent 351 (42.2%) recipients were treated with tacrolimus-based immunosuppression. All patients with CF who received a liver transplant during this period were reviewed. These patients were followed up until March 2002.

RESULTS

Twelve children with CF were the recipients of 16 liver allografts (Table 1). The mean follow-up was 8.7 ±

Table 1. Demographics and Preoperative Body Mass Indices of 12 Children Who Underwent Liver Transplantation for Cystic Fibrosis

Patient No.	Sex	TAC/CyA	Age at Transplantation (yr)	Diagnosis	Associated Conditions	BMI (Kg/M^2)	Percentile
1	M	TAC	6.87	CF	GIB	18.79	>90
2	M	TAC	14.77	CF	GIB, MI	15.30	<3
3	M	TAC	12.45	CF	GIB	19.27	<75, >50
4	M	TAC	13.65	CF	GIB	16.88	<25, >10
5	M	TAC	14.94	CF/BA	GIB	17.26	<25, >10
6	M	TAC	9.05	CF	GIB	15.83	<50, >25
7	M	TAC	15.08	CF		22.81	<75, >50
8	M	TAC	9.79	CF	GIB	14.40	<10, >3
9	F	CsA	13.35	CF	GIB, MI	13.09	<3
10	F	CsA	2.29	CF		(Weight 16.76 Kg)	>90
11	M	CsA	3.27	CF/BA		15.21	<25, >10
12	M	CsA	8.68	CF		15.20	<25, >10

Abbreviations: BMI, body mass index; BA, biliary atresia; TAC, tacrolimus; CsA, cyclosporine A; GIB, gastrointestinal bleeding; MI, meconium ileus.

4.7 years (range, 0.07 to 15.7 years). There were 10 boys (83%) and 2 girls (17%) with a mean age at transplant of 10.3 ± 4.5 years. Eight of twelve (66%) received tacrolimus-based immunosuppression, and 4 of 12 (33%) received cyclosporine-based immunosuppression. All of these patients had end-stage liver disease. Two patients had meconium ileus at birth. All patients had ascites and splenomegaly, and 8 patients (75%) had gastrointestinal bleeding, which required sclerotherapy in 7. The majority of patients in this group were wasted and malnourished. Eleven of the 12 patients had pancreatic insufficiency requiring oral pancreatic enzyme supplementation. Body mass indices were less than the 50th percentile for age in 8 of 12 patients including 7 that were less than the 25th percentile and 2 that were less than the third percentile (Table 1).

All liver transplants were cadaveric whole-organ grafts, with the exception of a cutdown left lobe graft used for the retransplantation of patient 1. Biliary reconstruction was performed using a roux-en-Y choledochojejunostomy in all cases. The primary liver pathology in 10 patients was CF-related liver disease. Two patients had biliary atresia in addition to CF-related liver disease (patients 5 and 11). The diagnosis of CF was not established until 3 years after transplantation for biliary atresia for patient 11. The mean time to extubation postoperatively was 6 days (range, 7 hours to 26 days) and the mean length of intensive care unit (ICU) stay was 12 days (range, 1 to 30 days, the majority were less than one week).

Two patients (patient 3 and patient 12) were lost to follow-up 6.5 and 10.6 years after transplantation respectively. Three patients required a second transplant for primary nonfunction (patient 1) or for hepatic artery thrombosis (patients 4 and 11). Patient 11 required a third allograft for chronic rejection nearly 14 years after his initial transplant (Fig 1B).

There were 5 deaths with a mean interval from initial transplant of 6.8 ± 6.3 years (range, 0.07 to 15.72 years). Patient 1 underwent retransplant for primary allograft nonfunction and subsequently died of systemic sepsis with disseminated candidiasis and aspergillosis. Despite negative sputum cultures, there was evidence of pulmonary candida and aspergillus on postmortem examination. With this exception, all other patients survived for at least 2 years after transplantation. The 1- and 5-year patient survival after liver transplantation in these patients was 91.6% and 75%, respectively with 2 additional patients dying 10.5 and 15.7 years after transplantation

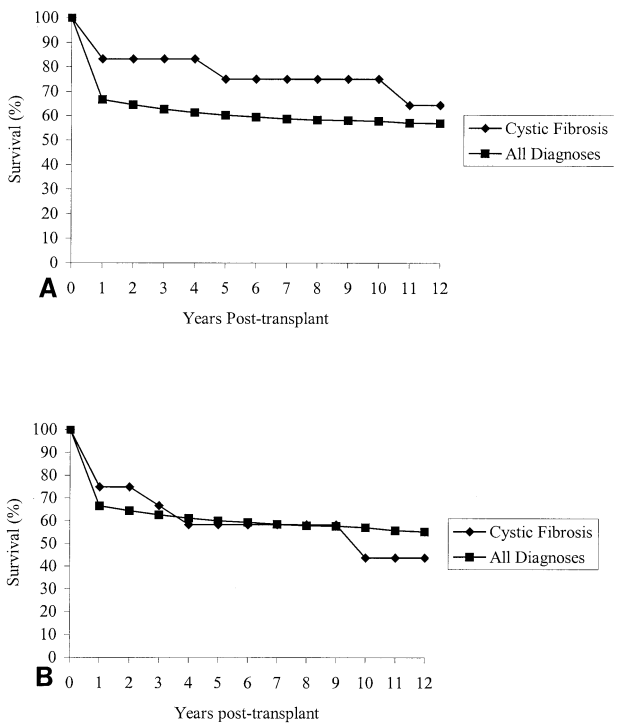

Fig 1. Kaplan-Meier survival curves comparing survival (A) and graft survival (B) in children with cystic fibrosis undergoing liver transplantation to all 833 liver transplant recipients at our center.

Table 2. Pulmonary Function Tests in Patients Undergoing Liver Transplantation for Cystic Fibrosis

	Pretransplant		Posttransplant		
Patient No.	FVC (% Pred)	FEV1 (% Pred)	FVC (% Pred)	FEV1 (% Pred)	Months Posttransplant
1	—	—	—	—	
2	86	70	94	82	2
3	74	73	90	71	19
4	53	51	73	60	132
5	82	84	99	97	2
6	89	94	90	94	68
7	69	57	81	85	2
8	95	83	82	47	29
9	87	84	95	95	16
10	—	—	—	—	
11	—	—	98	96	95
12	68	64	100	100	157
Mean	78.1	73.3	90.2	82.7	52.2
SD	13.2	14.2	8.94	17.93	

respectively, (Fig 1A). One of the 4 patients who died more than 16 years posttransplant was listed for a lung transplant at another center at the time of her death.

Of the 12 patients who underwent transplant, pre- and posttransplant pulmonary function test results were available before and after transplantation (mean of 52 months posttransplantation; range, 2 to 157 months) in 9 cases (Table 2). Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) went from a mean of 78% of predicted and 73% of predicted pretransplant to 90% of predicted and 83% of predicted posttransplant, respectively. There was no significant decompensation in pulmonary function perioperatively. In fact, pulmonary function improved or remained unchanged in 8 of these 9 children after transplant.

Sputum cultures pre- and posttransplant were analyzed (Table 3). Seven of the 12 patients (58%) had documented positive sputum cultures before transplantation including 4 with *Pseudomonas aeruginosa*, 3 with *Staphylococcus aureus*, one with *Candida albicans*, and 2 with *Burkholderia cepacia.* There were 10 documented positive sputum cultures postoperatively (83%) with *Pseudomonas* being the most common and with 1 positive sputum culture for *Aspergillus* that responded to antifungal therapy with amphotericin B (patient 2).

Table 3. Sputum Cultures Before and After Liver Transplantation in 12 Patients With Cystic Fibrosis

Patient No.	Sputum Preoperative	Sputum Postoperative
1	*Pseudomonas*	*Pseudomonas*
2		*Pseudomonas, Aspergillus*
3		*Pseudomonas*
4	*Staphylococcus, Pseudomonas*	*Staphylococcus, Pseudomonas*
5	*Staphylococcus*	*Staphylococcus*
6	*Staphylococcus/ Streptococcus, Diptheroids, Candida*	*Staphylococcus/ Streptococcus, Candida*
7	*B cepacia, Staphylococcus, Pseudomonas*	
8	*B Cepacia*	*B Cepacia*
9	*Pseudomonas*	*Pseudomonas*
10		
11		*Staphylococcus, Pseudomonas*
12		*Pseudomonas*

DISCUSSION

The liver disease associated with CF is considered to result from bile ductule plugging with inspissated secretions resulting in the pathognomonic focal biliary cirrhosis seen in these patients.[12,13] Two of the patients in this series were diagnosed also as having biliary atresia before transplantation and had undergone Kasai procedures. Review of pathology confirmed the prior diagnosis of extrahepatic biliary atresia, although the hepatectomy specimens had the characteristic changes of CF with focal biliary cirrhosis, regenerative nodules, and bile duct proliferation. There was more extensive inflammation than usually is found with biliary atresia. The unusual finding of biliary atresia in a patient with CF-related liver disease also has been reported by Mack et al[14] in one of 8 patients undergoing liver transplantation for CF.

The primary consequence of liver disease in CF is portal hypertension with massive splenomegaly, hypersplenism, varices, and ascites. Although individual complications of CF liver disease can be managed temporarily without transplantation, and there is some improvement with bile acid therapy, liver transplantation remains the only curative treatment for liver failure.

There was initial reluctance to proceed with transplantation in this patient population because of concerns about pulmonary decompensation after transplantation

Table 4. Literature Review of Isolated Liver Transplantation in Children with Cystic Fibrosis

Study	Year	No.	Deaths	Retransplants	Comments
Cox et al[22]	1987	1	1		Intracranial bleed (48 days).
Mieles et al[23]	1989	4	0	1 (HAT)	
Cox[24]	1990	5	3		
Revell et al[25]	1993	1	0		
Noble-Jamieson et al[16]	1994	5	0		
Mack et al[14]	1995	8	3		1 year 75%, one late death.
Noble Jamieson et al[17]	1996	9	0	1 (GCH)	
Noble-Jamieson et al[15]	1996	12	1		
Couetil et al[10]	1997	4	1		
Chavez-Cartaya et al[18]	1999	21	2	1 (HAT)	Adults and children
Molmenti et al[26]	2001	9	4		Pulmonary complications accounted for 3 deaths.
Milkiewicz et al[11]	2002	12	0		Adults and children.

Abbreviations: GCH, giant cell hepatitis; HAT, hepatic artery thrombosis.

and the risks of developing pulmonary infections while on immunosuppression. Several investigators have reported results suggesting that patients with CF tolerate transplantation well, with most patients showing stable or initial improvement in pulmonary function.[11,14-18] There have been very few deaths resulting from pulmonary infections in the immediate postoperative period (Table 4). Our patients followed this pattern as well, with a reasonably brief period to extubation and short intensive care stays in most patients. Despite an 83% incidence of positive sputum cultures posttransplant, there was only one perioperative mortality related to pulmonary sepsis. This patient (patient 1) had a difficult postoperative course with primary nonfunction of the initial allograft requiring urgent retransplantation. This, in turn, led to systemic sepsis with candidiasis and aspergillosis, presumably of pulmonary origin. However, 55% of the remaining 11 patients had documented positive sputum cultures before transplantation, including 2 with *B cepacia* and underwent transplantation without complication related to these organisms. This suggests that technical complications and poor graft function are very poorly tolerated in this susceptible patient population because of their underlying extraabdominal pathology.

There was no significant deterioration in pulmonary function tests in those studied. In fact, most patients had improved pulmonary function, possibly secondary to decreased airway inflammation attributable to cyclosporine and tacrolimus or owing to decreased intraabdominal pressure after the relief of portal hypertension with resulting decompression of the spleen and elimination of ascites.

All of the biliary anastamoses in this series were constructed using a roux-en-Y choledochojejunostomy. Patients with CF undergoing liver transplantation frequently have biliary anastamotic strictures. The biliary complication rate in this series was low, further supporting the contention of several investigators that the recipients' common bile duct should not be used for the biliary reconstruction.[10,15,18]

The 1-year survival rate for liver transplantation in this series was 91.6% with one early death after retransplantation from primary graft nonfunction. There were 4 additional deaths related to late pulmonary complications, 2 of them greater than 10 years posttransplant, for a 5-year survival rate of 75% and an overall long-term survival rate of 58.4% posttransplant. The patient and graft survival after liver transplant in this groups is comparable with that of liver transplants performed for other indications without associated lung disease (Fig 1A and B). Recurrent liver disease related to cystic fibrosis has not been encountered on any posttransplant liver biopsies, and CF-related liver disease was not responsible for any of the mortalities or graft losses in these children.

We recently reviewed the mortality rate beyond the first post transplant year for all pediatric liver transplants at our institution.[19] We found that only 3.58% of patients who survived beyond the first year subsequently died with a mean follow-up of 9.2 $\pm$ 2.4. The higher late mortality rate of the CF patients likely reflects the natural history of the underlying disease. Interestingly, reference to our adult population suggests that survival after liver transplantation in adult CF patients does not share the same encouraging results that we have found in the pediatric population, with a significantly decreased survival rate.[20,21] Therefore, liver transplantation should be considered early in the course of liver failure in children with CF.

Liver transplantation is acceptable treatment for children with CF and end-stage liver disease. Long-term survival is comparable with that of liver transplantation performed for other indications with no associated lung disease. Although morbidity and mortality are related to lung disease posttransplant, we speculate that because therapeutic improvements in pulmonary management have prolonged the survival in cystic fibrosis, it is expected that longer survival after liver transplantation in this patient population will be realized.

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