

## An Analysis of the Causes of Death After Pediatric Liver Transplantation

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REFINEMENTS in the techniques of organ procurement and surgical grafting and the introduction of cyclosporine (Cs) have led to improvements in results after orthotopic liver transplantation.<sup>1</sup> The 1-year survival rate after pediatric liver transplantation now exceeds 70%. This retrospective study represents an analysis of the causes of death after pediatric liver transplantation.

### PATIENTS AND METHODS

Two hundred twenty-seven patients underwent liver transplantation between March 1980 and February 1986 at the Children's Hospital in Pittsburgh. Sixty-three patients received two liver transplants, and 14 patients received three transplants. The age range of the patients was 3 weeks to 18 years (mean, 6.11 years). The etiology of the patients' liver disease is shown in Table 1. All patients were treated with a combination of Cs and prednisone.

Seventy of the 227 patients died during the study period. There were 31 males and 39 females with an age range of 5 months to 18 years (mean, 6.07 ± 0.6 years). The etiology of the liver disease of the patients who died is shown in Table 1.

Four patients who died in the immediate perioperative period (ie, intraoperative or within 24 hours) and five patients who died outside of Pittsburgh were excluded from the analysis. Forty-three of the remaining 61 patients who died were subjected to a postmortem examination. The cause of death in these patients was based on the available clinical information as well as the autopsy findings. The cause of death in the remaining 18 patients was based on the available clinical information only. Although the cause of death after liver transplantation was often multifactorial, an attempt was made, based on the available information, to identify the primary cause of death.

### RESULTS

Liver failure was the primary cause of death in 26 patients and was related to thrombosis of the hepatic artery in 11 patients, primary nonfunction of the graft in ten patients, and severe rejection in five patients. A further 21 patients died of overwhelming

sepsis. Opportunistic infections accounted for 15 of these deaths and included cytomegalovirus infection in four patients, varicella in two patients, aspergillosis in two patients, candida infection in two patients, pneumocystis and cryptococcus infection in one patient each, and a combination of viral and fungal infection in three patients. Excessive bleeding was the primary cause of death in a further seven patients and was related to intraoperative bleeding during exploratory laparotomy or liver retransplantation in four patients and rupture of a mycotic aneurysm in three patients. The miscellaneous causes of death included lymphoproliferative disease (two cases), recurrent hepatoma (one case), infarction of the small intestine (one case), cardiac failure in a patient who received a heart and liver transplant (one case), hyperkalemia in the postoperative period after a Nissen fundoplication (one case), and brain death due to an anomalous insertion of the superior vena cava into the infrarenal inferior vena cava (one case).

The time interval between the initial liver transplant and the death of the patient is shown in Table 2. Twenty-eight deaths occurred during the first month after the initial liver transplant. Liver failure was the primary cause of death in 20 of the 28 early deaths. All of the deaths due to primary

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**Table 1. Etiology of the Liver Diseases Encountered in 227 Patients Undergoing Liver Transplantation and in the 61 Deaths After Liver Transplantation**

Disease	Total	Deaths
Biliary atresia/hypoplasia		
Biliary atresia	107	33
Alagille's syndrome	13	6
Metabolic disorders		
$\alpha_1$ -Antitrypsin deficiency	30	6
Wilson's disease	6	2
Glycogen storage disease	5	2
Tyrosinemia	5	2
Other	2	
Cirrhosis		
Chronic active hepatitis	10	3
Other	16	
Familial cholestasis	10	4
Acute hepatic failure		
Fulminant hepatitis	3	3
Drug induced	2	2
Neonatal hepatitis	7	1
Miscellaneous	11	6

nonfunction of the graft occurred in the first month after the transplant. The deaths due to overwhelming sepsis, especially those due to viral infections, occurred after the first month. Eighty-five percent of the deaths occurred within 6 months of the initial liver transplant, and only three deaths occurred after the first year.

Thirty of the 150 patients who received a single liver transplant died during the study period. However, 24 of the 63 patients who

underwent liver retransplantation and seven of the 14 patients who received three liver transplants died.

## DISCUSSION

This retrospective study analyses the cause of death after pediatric liver transplantation. Liver failure was the most common cause of death after pediatric liver transplantation and was related to thrombosis of the hepatic artery, primary nonfunction of the graft, and severe rejection. Thrombosis of the hepatic artery continues to be a problem after pediatric liver transplantation. The etiology is probably multifactorial, and further research is needed before the problem is resolved. Improvements in assessing the quality of the liver in the donor, in the technique of harvesting the donor liver, and in the storage of the donor liver may decrease the incidence of primary nonfunction of the graft.

The phenomenon of accelerated rejection of the liver is being recognized increasingly and may account for some of the patients previously labeled as primary nonfunction of the graft and thrombosis of the hepatic artery. Again, further research is needed to fully understand and correctly treat this immunologic phenomenon and thus prevent some of the fatal complications. The introduction of Cs has been a major factor in the improvement of the results after liver transplantation.<sup>2</sup> However, management of rejection still constitutes a major problem. Too little immunosuppression results in a greater incidence of rejection, whereas overimmunosuppression increases the risk of opportunistic infections. Thus, the introduction of new, selective immunosuppressive agents would prevent rejection without the risk of overwhelming sepsis.

There is a growing realization that liver retransplantation in patients with primary technical failures or hepatic rejection is feasible, thus further reducing the numbers of patients dying posttransplant.<sup>3</sup> However, the lack of suitable pediatric donors continues to be a limiting factor. The use of partially

**Table 2. Time Interval Between the Initial Liver Transplant and the Death of the Patient**

Complication	Interval (mo)				
	0-1	1-3	3-6	6-12	>12
Liver Failure					
Primary nonfunction	10				
Hepatic artery thrombosis	8	1	1	1	
Rejection	2	2	1		
Sepsis					
Viral		6	2	1	
Bacterial	2	1	2		
Fungal	2		1		1
Other	1			2	
Bleeding	1	5			1
Miscellaneous	2	2		2	1

liver retransplantation and some patients who received three livers died.

## DISCUSSION

This retrospective study analyses the causes of pediatric liver transplantation. The most common cause of pediatric liver transplantation and thrombosis of the hepatic artery, nonfunction of the graft, and rejection. Thrombosis of the hepatic artery is to be a problem after pediatric transplantation. The etiology is probably bacterial, and further research is needed to resolve the problem. In assessing the quality of the liver, in the technique of harvest, and in the storage of the liver, may decrease the incidence of rejection of the graft.

Phenon of accelerated rejection of liver recognized increasingly and for some of the patients previous primary nonfunction of the thrombosis of the hepatic artery. research is needed to fully correctly treat this immunorejection and thus prevent some of complications. The introduction of a major factor in the improvement of results after liver transplantation. Management of rejection still continues a problem. Too little immunorejection in a greater incidence of overimmunosuppression in the presence of opportunistic infections. Introduction of new, selective immunoreagents would prevent rejection of overwhelming sepsis. Following realization that liver rejection in patients with primary biliary or hepatic rejection is feared, reducing the numbers of liver transplants. However, the pediatric donors continues to be a factor. The use of partially

resectomized adult livers may help to alleviate this problem. However, liver retransplantation was associated with an increased mortality. Twenty percent of the patients who received one liver transplant died compared with 50% of the patients who received three livers. It is important to identify those patients with the best chance for survival so as not to waste organs. In patients with a failure of three or more organ system liver transplantation or retransplantation the prognosis is extremely poor, with a survival rate of less than 20%.<sup>4</sup>

Opportunistic infection is always a concern with immunosuppressed patients, particularly when the dose has been increased to treat episodes of rejection.<sup>5</sup> Fungal infections, in particular, are associated with a high mortality. Fungal infections have been shown to be related to the use of high-dose steroids for

suspected or proved rejection, heavy perioperative blood loss, and prolonged stay in the intensive care unit.

The majority of the deaths after liver transplantation occurred soon after the transplant. Eighty-five percent of the deaths occurred within 6 months posttransplant, whereas only three patients who survived longer than 1 year posttransplant died.

This retrospective analysis has identified liver failure due to primary graft nonfunction, hepatic artery thrombosis and rejection, and overwhelming sepsis, in particular, opportunistic infections, as the major causes of deaths after pediatric liver transplantation. Thus, it would appear that despite the already superior results after pediatric liver transplantation, further technical and immunologic improvements could lead to even better survival.

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