Causes of death after liver transplantation in children treated with cyclosporine and steroids

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Abstract: Two-hundred-and-twenty-seven children underwent orthotopic liver transplantation between March 1980 and March 1986. Seventy (31%) patients died during the study period. Four patients who died within 24 hours of the initial liver transplant and 5 patients who died outside of our institution were excluded from the analysis. Liver failure, related to either thrombosis of the hepatic artery, primary non-function of the graft or rejection accounted for 25 of the remaining 61 deaths. In 21 patients death was related to overwhelming sepsis while 7 patients died from excessive bleeding. Eight of the deaths were due to a miscellaneous group of causes. Twenty percent of the 150 patients who received a single liver transplant died compared to a death rate of 50% in patients who underwent three transplants. Eighty-five percent of the deaths occurred within 6 months after the initial liver transplant. Liver failure was the cause in the majority of the early deaths whereas the later deaths were more likely to be due to sepsis. This detailed analysis of the causes of death after pediatric liver transplantation in a large group of patients has revealed that advances in certain areas could lead to even better results.

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The first human orthotopic liver transplant was performed in Denver in March 1963 (1). However, the early results from Denver and Cambridge (2), the first two major centers performing liver transplants, were less than satisfactory with only about 25% of the patients surviving more than 1 yr (3). The deaths in the early post-operative period were related to technical complications and bleeding, overwhelming sepsis associated with high steroid administration and biliary complications (3, 4). There has been marked improvement in results in the last 7 yr, with 5-yr survival in the largest series approaching 70%. The reasons for these extremely encouraging results have included refinements in the operative technique (5), including the use of the veno venous bypass during the anhepatic phase (6), improvements in biliary reconstruction (7), improved methods of organ harvesting and preservation (8), and aggressive retransplantation (9). However, the major advance in liver transplantation has been the introduction of the immunosuppressive agent cyclosporine in 1978 (10). The use of cyclosporine in combination with steroids was introduced in March 1980 (11). The 1-yr survival rates for adults and children undergoing liver transplantation with this regimen have exceeded 70% (12). We have recently reported the complications and causes of death in adult liver transplantation in the cyclosporine era (13). The present report represents a retrospective analysis of the causes of death in pediatric liver transplantation using cyclosporine-steroid immunosuppression.

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Patients and methods

Two-hundred-and-twenty-seven pediatric patients who underwent orthotopic liver transplantation at the Children's Hospital of Pittsburgh between March 1980 and February 1986 were retrospectively evaluated. Sixty-three patients received two liver transplants, and 14 patients received three transplants. Only patients who survived the immediate post-operative period (24 h) after the first liver transplant were included in the study.

Our methods for patient selection, techniques for orthotopic liver transplantation, protocols for immunosuppressive management and post-operative care have been described in detail previously (3, 5, 14). All liver transplant recipients received

comparable clinical management and, in particular, all patients received combination cyclosporine and steroids after the transplant (11).

The age range of the 227 patients was 3 wk to 18 yr (mean 6.11 yr). The indications for liver transplantation in the 227 children are listed in Table 1. Nearly half of the patients had biliary atresia. Alpha-1-antitrypsin deficiency was the second most common indication for transplantation. Biliary atresia/hypoplasia and the hepatic-based inborn errors of metabolism accounted for 75% of the patients.

During the study period, 70 of the 227 patients died (31%). Four patients who died either during or within 24 h of the initial liver transplant were excluded. The causes of death in these 4 patients were: cardiac failure, uncontrolled bleeding, liver failure and septicemia. A further 5 patients who died outside of Pittsburgh were also excluded because there were insufficient details available to accurately determine the cause of death. The remaining 61 patients formed the basis for the analysis of the causes of death after pediatric liver transplantation. Complete autopsies were performed in 43 of the 61 patients and the cause of death in these patients was based upon clinical details as well as the autopsy findings. In the remaining 18 patients in whom an autopsy was not performed, the cause of death was determined using clinical criteria.

Causes of death

Although there were usually many factors which contributed to the death of the liver transplant pediatric patient, only one cause of death was ascribed to each patient. Thrombosis of the hepatic artery was determined by either ultrasound or angiography, or both, and confirmed at autopsy in the autopsied patients. The histological criteria used for rejection have been documented previously (15, 16). In brief, early rejection consisted of a portal and/or a lobular mixed inflammatory infiltrate, disruption of the limiting plate, a characteristic bile duct injury and occasional portal vein endothelitis. Chronic rejection consisted of either a vascular injury of the medium-sized hilar arteries with subendothelial foam cells, fibrinoid necrosis and intimal hyperplasia, or periportal bridging fibrosis associated with disappearance of the interlobular bile ducts. Primary non-function of the graft refers to those transplants which did not function at all despite patency of all vessels and no evidence of rejection. These patients had progressive elevation of the bilirubin and transaminases, severe coagulopathy, hypoglycemia, renal failure and encephalopathy. Infection was recognized as the cause of death if it was the major diagnosis established at autopsy, or if completely documented infection was the major factor in the patient's clinical deterioration just prior to death. The etiology of the infection was determined either by appropriate cultures and stains or histologically.

Results

A cause of death could be accurately determined in 61 of the 70 patients who died during the study period. There were 26 males and 35 females and the age range was 7 months to 18 yr (mean 6.07 ± 0.6 yr). The indications for liver transplantation in the 61 patients who died are listed in Table 1. The majority of the patients who died were transplanted for biliary atresia/hypoplasia, but this diagnosis represents the most common indication for transplantation in the entire pediatric group (12). Twenty-seven and 23% of the patients with biliary atresia/hypoplasia and metabolic disorders, respectively, died during the study period. The death rates in patients with cirrhosis and neonatal hepatitis were low. All the patients who were transplanted for acute hepatic failure died.

Liver failure

The causes of death in the 61 patients who died after liver transplantation are shown in Table 2. Liver failure was the primary cause of death in 25 patients. In 11 patients the liver failure was due

Table 1. Etiology of the liver diseases encountered in 227 patients undergoing liver transplantation and in the 70 deaths after liver transplantation

		Total	Deaths
(1)	Biliary atresia/hypoplasia		
	Biliary atresia	107	32†††*
	Alagilles syndrome	13	7
(2)	Metabolic Disorders		
	Alpha-1-antitrypsin deficiency	30	6
	Wilsons disease	6	2
	Glycogen storage disease	5	2
	Tyrosinemia	5	2*
	Other	2	2
(3)	Cirrhosis		
	Chronic active hepatitis	10	3
	Other	16	
(4)	Familial cholestasis	10	4
(5)	Acute hepatic failure		
	Fulminant hepatitis	3	3
	Drug-induced	2	2
(6)	Neonatal hepatitis	7	10*
(7)	Miscellaneous	11	6
		227	70

† Died within 24 hours after the transplant.
* Died outside of Pittsburgh.

Table 2. Causes of death after pediatric liver transplantation

Liver failure:	
Hepatic artery thrombosis	11
Primary non-function	9
Severe rejection	5
Infection:	
Viral	6
Bacterial	8
Fungal	6
Other	1
Bleeding:	
Intra-operative	4
Ruptured mycotic aneurysm	3
Miscellaneous:	
Lymphoproliferative disease (2)	8
Recurrent hepatoma (1)	
Small intestine infarction (1)	
Cardiac failure after cardiac transplant (1)	
Hyerkalemia (1)	
Post-operative brain death (2)	
	61

to thrombosis of the hepatic artery. One of these patients developed a clostridial infection in the liver and died in the operating room during an exploratory laparotomy. A 2nd patient with a thrombosed hepatic artery developed a bile-stained hepatic abscess and also had mild rejection. In 2 other patients, thrombosis of the artery was complicated by massive varicela hemorrhage in 1 and disseminated sepsis in the other. Occlusion of the hepatic artery was thought to be due to kinking of the artery and intense vasospasm in 2 patients.

Nine patients died from liver failure resulting directly from primary non-function of the graft. Six of these patients underwent retransplantation for primary non-function of the initial transplant. Five of these 6 patients died between 1 and 3 d after the retransplant from irreversible brain damage and 1 patient had a cardiac arrest during the retransplant. The remaining 3 patients died while awaiting retransplantation.

Liver failure caused by severe rejection accounted for 5 deaths. All 5 patients experienced multiple complications, usually septic in nature. One patient had severe rejection accompanied by cytomegalovirus pneumonia and candida peritonitis. Another patient had rejection and cytomegalovirus hepatitis. One patient with severe chronic rejection developed overwhelming E coli sepsis. The remaining 2 patients with severe rejection also had generalized sepsis.

Infection

Overwhelming sepsis, which most often represents a complication of over-immunosuppression, accounted for 21 deaths in this study. In most patients the sepsis was due to multiple organisms (i.e., mixed bacterial, viral, fungal). However, in 8 patients the major component was of bacterial origin. In 4 of these 8 patients, the sepsis was related to a perforation of the small bowel, necrosis of the small bowel, a leak from the Roux-en-Y anastomosis, and a perforation of the colon, respectively. The last-mentioned patient also had cytomegalovirus hepatitis and candida peritonitis. Two patients had staphylococcal septicemia, which was complicated by staphylococcal endocarditis in 1. Another patient, with a patent hepatic artery, developed a hepatic abscess and also had a cytomegalovirus pneumonia.

Predominantly viral infections accounted for 6 deaths. Four patients had disseminated cytomegalovirus infection with significant cytomegalovirus hepatitis. Two patients developed disseminated varicella infection 4 and 12 months after the liver transplant.

Six patients died as a result of overwhelming fungal infection. Three of these patients had disseminated candida sepsis and 2 patients had disseminated aspergillus. One of the latter patients developed the aspergillus soon after retransplantation for chronic rejection. The remaining patient had both disseminated aspergillus and candida sepsis, accompanied by cytomegalovirus hepatitis.

One patient with chronic rejection developed pneumocystis infection 9 months after the transplant and died.

Bleeding

Severe hemorrhage was the cause of death in 7 patients. In 3 of these, hemorrhage was due to rupture of a mycotic aneurysm. In 1 of the latter patients the mycotic aneurysm was situated at the anastomotic site of an iliac graft to the aorta. Two patients with intraperitoneal sepsis died from uncontrollable bleeding during exploratory laparotomy. Another patient exsanguinated during an exploratory laparotomy, as a result of an abscess eroding into the portal vein. The remaining patient died from bleeding during retransplantation for chronic rejection.

Miscellaneous

The miscellaneous causes of death included lymphoproliferative disease (2 cases), recurrent hepatoma (1 case), infarction of the small intestine due to an internal hernia (1 case), cardiac failure in a patient who received a combined heart and liver transplant (1 case), and hyperkalemia in the post-operative period after a Nissen fundoplication (1

case). Another patient, with an anomalous insertion of the superior vena cava into the infra-renal vena cava, was found to be brain-dead postoperatively, probably due to occlusion of the venous drainage of the upper extremity when the lower vena cava along with its anomalous superior vena caval insertion was clamped during the transplant procedure. One other patient, with evidence of brain-death preoperatively remained so after the liver transplant.

Time interval between transplant and death

The time interval between the initial liver transplant and the death of the patient, and its relationship to the causes of death, are shown in Fig. 1. Twenty-eight of the deaths occurred within the 1st month after the initial liver transplant and 85% of the deaths occurred within 6 months. Only 3 of the deaths occurred after the 1st yr following the first transplant.

The majority of the early deaths were due to liver failure and the late deaths were more likely to be due to sepsis. Liver failure was the primary cause of death in 18 of the 28 patients who died within the 1st month after transplant. All of the deaths due to primary non-function of the graft occurred within the 1st month and all but 4 of the deaths due to liver failure occurred within the first 3 months. Overwhelming sepsis tended to be the primary etiology of the later deaths. The time interval between the transplant and death in patients who had disseminated viral infections was greater than 1 month. Similarly, 6 of the 7 deaths due to bleeding occurred after the 1st month.

Retransplantation and death

Thirty of the 150 patients who received a single liver transplant died during the study period. This compares with death rates of 38% and 50% in patients who received two and three transplants, respectively.

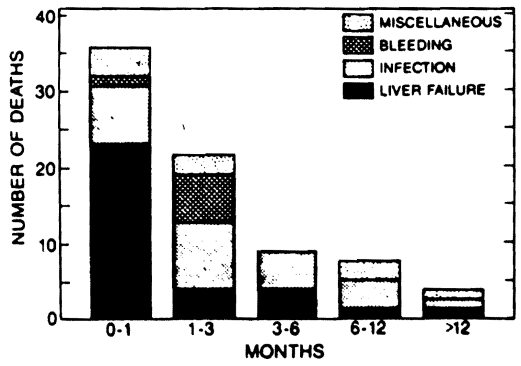

Fig. 1. The relationship of the causes of death to the time interval between the initial liver transplant and the eventual death of the patient.

Discussion

This report represents the first detailed analysis of the causes of death in the largest consecutive group of pediatric liver transplants during the cyclosporine era. Seventy of the 227 pediatric patients who underwent liver transplantation died during the study period. The primary causes of death in the 61 patients available for analysis included: liver failure, overwhelming sepsis, excessive bleeding, and a miscellaneous category of various etiologies.

Thrombosis of the hepatic artery accounted for 11 of the deaths due to liver failure. It is a devastating complication leading to death or necessitating retransplantation, and the incidence after liver transplantation has been reported to range from 3.7% to 10.7% (17). The presentation of hepatic artery thrombosis is varied and may mimic other complications; patients present with a fever, elevated transaminases, fulminant hepatic necrosis, necrosis of the bile duct with leakage of bile, and relapsing bacteremia singly or in any combination. In many patients, urgent retransplantation is required. However, a significant number of patients can survive for somewhat prolonged periods with a dearterialized graft. The mortality rate, even with retransplantation, is approximately 37.5% in children (18). The etiological factors which lead to hepatic artery thrombosis remain unresolved. Some of the factors which may play a role include technical problems, immunological phenomena and overzealous correction of the coagulopathy.

Nine of the deaths due to liver failure were related to primary non-function of the graft. The underlying factors leading to primary graft non-function include instability of the donor, inadequate preservation, prolonged cold ischemia, and prolonged warm ischemia. However, the relative contribution and importance of each of these factors remains undetermined and the ability to predict graft function after transplantation using standard criteria relating to these factors is still impossible (19). Patients present with progressive elevation of the bilirubin and transaminases, severe coagulopathy, hypoglycemia, renal failure, and encephalopathy. The majority of these patients require urgent retransplantation. However, there still exists a significant mortality even with retransplantation.

Retransplantation is the treatment of choice in the majority of patients with hepatic artery thrombosis and primary graft non-function. However, the lack of suitable pediatric donors continues to

be a significant deterrent to further improvement in the survival results. The use of partially hepatectomized grafts from adult donors may be a solution (20), and requires further evaluation.

Severe rejection unresponsive to therapy and leading to liver failure and death is not commonly seen, and accounted for only 5 deaths in this series. However, many deaths are indirectly related to rejection; overwhelming sepsis, which represented a major cause of death in this study, is clearly a complication of over-immunosuppression in patients with proven or suspected rejection.

Opportunistic infections are always a major concern in immunosuppressed patients, particularly when the doses of the immunosuppressive agents have been increased to treat episodes of rejection. Bacterial infections are usually concentrated in the 1st and, to a lesser extent, in the 2nd and 3rd months after transplantation. Intra-abdominal and intra-thoracic infections, in the form of intra-peritoneal abscesses, intra-hepatic abscesses and pneumonia, predominate. A significant number of deaths due to bacterial infections were related to spontaneous bowel perforations and anastomotic leaks.

Fungal infections present a special problem after liver transplantation and are associated with a high degree of morbidity and mortality (21). Most infections are due to candida, but patients occasionally acquire aspergillus, cryptococcus and nocardia infections. Risk factors associated with fungal infections include the use of high-dose steroids for proven or suspected rejection episodes, heavy perioperative blood loss, prolonged stay in the intensive care unit, intensive and prolonged antibiotic therapy and surgery of the gastrointestinal tract. There was only 1 death due to Pneumocystis carnii and it occurred in a patient with chronic rejection 8 months after the transplant.

Disseminated viral infections due to cytomegalovirus and varicella accounted for 6 deaths in this series. Two other patients developed lymphoproliferative disorders related to Epstein-Barr virus. A significant number of the other deaths were associated with localized viral infection in the form of hepatitis and pneumonia. Cytomegalovirus hepatitis in the presence of rejection previously presented a particularly disturbing combination, since the therapeutic approach is completely different for these two complications. In the former a reduction of immunosuppression is indicated, whereas an increase in immunosuppression is required to control rejection. However, with the recent advent of DHPG (ganciclovir) therapy this problem can be managed much more easily.

It is well-established that retransplantation has significantly reduced the number of patients dying after liver transplantation (9). However, in this study retransplantation was associated with an increased mortality. The mortality rate in patients who received a single liver transplant was 20%, compared to 50% in patients who underwent three transplants. These findings are not surprising or completely unexpected in this particular study, since the pediatric patients undergoing retransplantation had multiple complications and were often moribund and a majority were emergent because of the etiology. This is in contrast to adults where the same complications may not be as devastating as in small children. Also the etiology of chronic rejection is more common in adults and gives much better results with retransplantation. Adult patients do not have to wait as long for a new liver as small children.

The extremely high mortality of third transplant recipients has important implications. It raises the question whether pediatric liver grafts, which are in short supply, should be wasted in these patients or should be used preferentially in first transplant recipients. The policy in Pittsburgh is to consider each case on its own merits.

The results after liver transplantation have improved dramatically in recent years with 1-yr survival rates exceeding 70% in children (3). However, this detailed analysis of the causes of death after pediatric liver transplantation in a large group of patients has revealed that advances in certain areas could lead to even better results. Improvements in the selection and management of the donor and in organ preservation should reduce the incidence of primary graft non-function. New preservation fluids are under investigation at the present time (22). New and more selective immunosuppressive agents with less toxicity would prevent or treat rejection episodes without compromising the recipient, and thus diminish the complications associated with over-immunosuppression, including opportunistic infections and lymphoproliferative disorders (23).

Further study of the pathogenesis and etiology of hepatic artery thrombosis is needed and should result in a reduction of the incidence of this major and devastating complication. The problem of viral infections, in particular cytomegalovirus infections, may become easier to manage in the future with the introduction of new antiviral agents i.e., ganciclovir. Many children who require urgent retransplantation often deteriorate while awaiting a suitable pediatric donor. The use of partially hepatectomized adult livers would make it possible to retransplant these patients under more optimal circumstances and thus improve the results after retransplantation.

In summary, this study has defined specific prob-

lematic areas and complications of orthotopic liver transplantation which are responsible for mortality in pediatric patients. Careful evaluation and study of these individual negative factors will allow even further improvement in these already superior results.

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