0270-9139/86/0603-0495$02.00/0
HEPATOLOGY

Vol. 6, No. 3, pp. 495–501, 1986
Printed in U.S.A.

682
Put in CV

Adult Liver Transplantation: An Analysis of the Early Causes of Death in 40 Consecutive Cases

VALENTIN CUERVAS-MONS, A. JULIO MARTINEZ, ANDREW DEKKER, THOMAS E. STARZL AND DAVID H. VAN THIEL

Departments of Medicine, Pathology and Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261 and Servicio de Medicina Interna, Clinica Puerta de Hierro, Madrid, Spain 28035

One hundred twenty-nine adult patients who received an orthotopic liver transplantation and survived at least 24 hr after surgery were evaluated. During the period of follow-up, 48 of the 129 patients (37%) died. Only 40 of these 48 patients died at our institution and were included in this study. Seventeen of the 40 deaths (42.5%) occurred during the first month after orthotopic liver transplantation and 30 of the 40 deaths (75%) occurred during the first 60 days post-orthotopic liver transplantation. Death was related to infection in 21 cases (52.5%), to multiorgan failure in 8 (20%) and to uncontrollable rejection in 3 (7.6%). The remaining eight deaths (20%) were attributed to a variety of other causes. Eleven of the 21 deaths related to infection (52%) occurred during the first month after orthotopic liver transplantation. Bacterial sepsis was the leading cause of death and accounted for 17 of the 21 deaths (81%) in which infection was present at the time of death. The most frequently isolated bacteria were *Pseudomonas* and other enteric Gram-negative bacilli. Three patients had complete occlusion of the hepatic artery of the grafted liver. Six patients developed massive infarction of the liver despite patent vascular anastomoses. Histological signs of rejection were seen in 9 of the 31 patients autopsied (29%), but in only 3 of these (9.6%) was rejection the principal cause of death. The biliary anastomoses were patent in all 31 cases examined at autopsy.

Due to a variety of factors, including better initial selection of candidates for the procedure, refinements in the techniques of organ procurement and surgical grafting, the introduction of cyclosporine A and improvements in the pre- and postoperative management of such patients, the life expectancy of patients undergoing orthotopic liver transplantation (OLTx) has increased considerably in the last several years (1–4). As a result of these improvements and their effects upon patient survival, liver transplantation has become a widely practiced, albeit sophisticated and heroic, mode of therapy for individuals with otherwise terminal liver disease (3, 4). As survival following transplantation continues to improve, OLTx is being performed at more and more centers all over the world.

An analysis of the causes of death after OLTx, using cyclosporine A as the principal immunosuppressive drug, would appear therefore to be quite timely. It is hoped that this information will be useful to those centers which are performing the procedure presently and to those which are interested in starting a liver transplantation program in the near future.

PATIENTS AND METHODS

One hundred thirty-six consecutive adult patients who received an OLTx at the University of Pittsburgh between March, 1981 and July, 1984 were evaluated. Thirty-one of these patients received two successive transplants, and five received three. One patient who had received her first OLTx elsewhere, but who died at the University of Pittsburgh, was excluded from the analysis. Only patients who survived the immediate postoperative period (24 hr) were included in the study. Thus, seven patients who did not survive the required 24 hr after surgery were excluded from the analysis, leaving a total of 129 patients for evaluation. These excluded patients all died in the operating room or within several hours of leaving the operating room and were, for all practical purposes, "operative" deaths. Most (five) died of exsanguination, 1 died of a pulmonary embolus and 1 experienced an intraoperative cardiac arrest and could not be resuscitated.

The details of our patient selection method, surgical procedure, immunosuppressive regimen and supportive care have been described in detail previously (3–5). All OLTx recipients received comparble clinical management from the same medical and surgical teams.

The indications for transplantation in these 129 patients are shown in Table 1. The survival data for all patients have been updated to August, 1984. During the period of follow-up, 49 of the 129 patients have died (37%). Only 40 of these 48 patients died at the University of Pittsburgh and were included in this study. For 31 of the total 48 deaths (65%), autopsy reports were available, all from the University of Pittsburgh. Complete autopsies were performed in 21. Autopsy data excluding an examination of the brain, eyes and spinal cord were available in eight additional cases. In two cases, the autopsy was limited to the abdomen. In each of these 31 cases, the autopsy provided definitive data about the cause of death. In the remaining nine

Received September 23, 1985; accepted February 25, 1986.
This work was supported in part by grants from NIAMDD (Contract AA44225) and the Gastroenterology Medical Research Foundation of Southwestern Pennsylvania.
Dr. Cuervas-Mons was a recipient of a grant from the Fondo de Investigaciones Sanitarias de la Seguridad Social of Spain.
Address reprint requests to: David H. Van Thiel, M.D., University of Pittsburgh, School of Medicine, 1000J Scaife Hall, Pittsburgh, Pennsylvania 15261.

TABLE 1. Characteristics of the patients studied

Liver disease	Patients									p
	Total			Alive			Dead			
	n	Age (yr) Mean ± S.E.	M/F ratio	n	Age (yr) Mean ± S.E.	M/F ratio	n	Age (yr) Mean ± S.E.	M/F ratio	
Postnecrotic disease	36	32.5 ± 1.6	22/14	22	31.4 ± 2.0	13/9	14	34.3 ± 2.5	9/5	NS
Primary biliary cirrhosis	34	44.1 ± 0.9	0/34	24	41.2 ± 0.9	0/24	10	41.6 ± 1.9	0/10	NS
Sclerosing cholangitis	21	33.8 ± 1.9	12/4	15	35.8 ± 2.2	12/3	6	28.6 ± 3.2	5/1	NS
Hepatic malignancy[a]	15	32.1 ± 2.8	5/10	9	28.2 ± 2.6	3/6	6	37.8 ± 5.1	2/4	NS
α_1-Antitrypsin deficiency	5	40.4 ± 3.7	4/1	1	44	1/9	4	39.5 ± 4.5	3/1	
Wilson's disease	4	29.0 ± 4.4	2/2	3	32.0 ± 4.6	2/1	1	20	0/1	
Acute fulminant hepatic failure[b]	4	31.5 ± 2.4	3/1	1	37	1/0	3	28.5 ± 2.9	2/1	
Budd-Chiari's syndrome	3	33.0 ± 3.6	2/1	2	35.5 ± 4.5	2/0	1	28	0/1	
Secondary biliary cirrhosis	2	26.5 ± 4.6	1/1	1	32	1/0	1	22	0/1	
Caroli's disease	2	19	0/2	1	19	0/1	1	19	0/1	
Polycystic liver and kidney disease[c]	1	42	0/1	1	42	0/1				
Adenomas of the liver[d]	1	33	0/1	1	33	0/1				
Obstructive jaundice secondary to cryptococcus cholangitis	1	23	1/0				1	23	1/0	
Total	129	35.6 ± 0.9	57/72	81	36.4 ± 0.1	35/46	48	37.2 ± 1.4	22/26	

NS = not statistically significant.

[a] Including hepatocellular carcinoma (10 cases), fibrolamellar (3 cases), cholangiolar carcinoma (1 case) and hemangiosarcoma (1 case).

[b] Including two cases of toxic hepatitis (gold and methylethyl ketone, respectively) and two cases of viral non-A, non-B hepatitis.

[c] Kidney transplant also performed in this patient.

[d] This patient had had a previous hepatic trisegmentectomy.

cases in which autopsy was not performed, the cause of death had to be determined using clinical criteria.

Only one cause of death was identified for each patient studied. An infectious etiology was recognized as the cause of death if it was the major diagnosis established at autopsy or, in the cases in which no autopsy was performed, if infection was of primary importance in the patient's clinical management just prior to death. When a major infection coexisted with multiorgan failure or graft rejection, the cause of death was considered to be due to the infection, as the infection in such cases prohibited either more aggressive immunosuppression or retransplantation. A fungal infection was identified as the principal cause of death if it was demonstrated that tissue invasion had occurred and/or the fungal infection was the major clinical problem prior to the patient's death.

The histologic criteria used for rejection have been described in detail elsewhere (6–8). Briefly, early rejection consists of a portal and/or lobular mixed inflammatory infiltrate, disruption of the limiting plate and a characteristic bile duct cell injury, with occasional portal and central vein endothelitis. Late rejection is defined either as a vascular injury of the medium-sized hilar arteries which demonstrate subendothelial foam cells, fibrinoid necrosis and intimal hyperplasia or extensive periportal bridging fibrosis associated with disappearance of the interlobular bile ducts.

RESULTS

Cause of Death. The 40 adult subjects included in this study consisted of 24 females and 16 males. Their ages ranged from 18 to 52 years (33 ± 2 years; mean ± S.E.). The distribution of these 40 patients by age is shown in Figure 1. The overall mortality in this series was 37%. Because of small numbers and the many different causes of death possible, no differences were seen

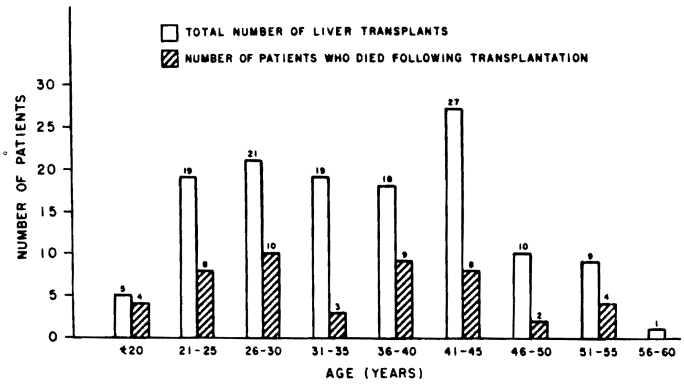

FIG. 1. Age distribution of the 40 adult patients who died after liver transplantation. *Open bars* represent number of patients having a transplant for each 5-year period. *Cross-hatched bars* represent number dying followng OLTx.

for the causes of deaths following OLTx in patients operated upon for different underlying diseases.

The principal causes of death identified in the 40 patients who died following transplantation and an initial 24-hr postsurgical period are listed in Table 2. Although only the primary cause of death is given for each case, other factors often contributed to a given patient's death. In fact, the cause of death in many cases was multifactorial. At times, it was difficult to determine which factor was the predominant factor responsible for a given patient's death. Generally, either the most prominent pathological event found at autopsy or the most important complication during their immediate preterminal clinical course, if an autopsy was not performed,

TABLE 2. Principal cause of death in the 40 consecutive adult patients studied who survived at least 24 hr but ultimately died after liver transplantation

Principle cause of death[a]	n	No	Yes	Cause of retransplantation
Infection[b]	21	12	9	Rejection (6) Thrombosis hepatic artery and massive hepatic infarction (3)
Multiorgan failure	8	4	4	Rejection (3) Thrombosis hepatic artery and massive hepatic infarction (1)
Rejection	3	2	1	Rejection
Massive GI bleeding	3	3	0	—
Massive CNS hemorrhage	2	1	1	Thrombosis hepatic artery and massive infarction
Massive pulmonary bleeding	1	0	1	Acute rejection
Pulmonary thromboembolism	1	0	1	Extensive hepatic coagulative, necrosis
Hyperkalemia	1	0	1	Thrombosis hepatic artery, massive hepatic infarction and CMV hepatitis
Total	40	22	18	

The abbreviations used are: GI = gastrointestinal; CNS = central nervous system; CMV = cytomegalovirus.

[a] Only the principal cause of death for each patient studied has been included. When a major infection coexisted with multiorgan failure (5 cases) or rejection (1 case), the cause of death was considered to be due to infection (see text).

[b] Including bacterial sepsis (13 cases), disseminated fungemia (2 cases), concomitant bacterial and fungal sepsis (4 cases), pulmonary fungemia (1 case) and disseminated herpes simplex virus infection (1 case).

was identified as the cause of death. As can be seen from Table 2, infection was the primary cause of death in 52.5% of the deaths, multiorgan failure accounted for 20% of the deaths and uncontrollable rejection and massive gastrointestinal bleeding each accounted for only 7.5% of the deaths. The remaining five deaths (12.5%) were attributed to a variety of causes, which included one case of massive pulmonary bleeding due to disseminated intravascular coagulation; one case of pulmonary thromboembolism, and one case each of cerebral hemorrhage and subarachnoidal hemorrhage. In one patient, no specific cause of death was identified at autopsy, and the death was attributed to a cardiac arrest which was thought to have occurred as a result of hyperkalemia.

The time interval between the initial OLTx and the subsequent death of the patient was 46.4 ± 6.1 days (range = 4–296 days). The number of cases dying at a given time after OLTx is shown in Figure 2. As can be seen, 17 of the 40 deaths (42.5%) occurred during the first month after OLTx, and a full 30 of the 40 deaths (75%) occurred during the first 60 days posttransplantation. Among the 40 patients who died and were included in this study, 18 (45%) had had a second OLTx (Table 2). The cause of death in these 18 cases did not differ in terms of the principal causes of death or frequency of a given cause of death from those who received only a single transplant. Thus, the fact of a prior transplant did not appear to alter the cause of death but did enhance the risk of death, probably as a consequence of progressive debilitation that was either not improved or more usually worsened as result of the earlier failed transplant (Table 2).

Evidence of infection, often associated with septicemia, was present in 21 of the 40 patients (52.5%) who died in this series. The number of patients who died

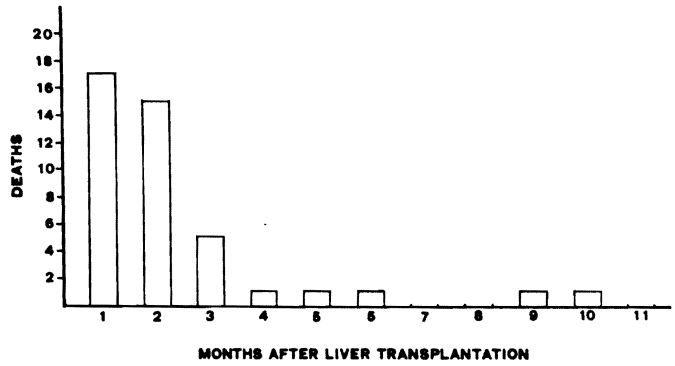

FIG. 2. Number of patients who subsequently died after liver transplantation, distributed as to time of death posttransplantation.

because of an infectious disease at specific time intervals after liver transplantation is shown in Table 3. Bacterial sepsis was the leading infectious cause of death and accounted for 17 of the 21 deaths (81%) in which infection was present at the time of death. In 4 of these 17 patients, bacterial sepsis coexisted with disseminated fungal infection, but the bacterial sepsis was considered to be the cause of death. At all time intervals studied (Table 3), bacterial sepsis was more prevalent than fungal sepsis. The latter tended to occur early rather than late following OLTx.

A wide range of pathogenic organisms was identified in the 21 patients. The organisms recovered in cultures obtained postmortem are identified in Table 4. The various microbiological agents which were isolated from these 21 patients prior to their death, but which were not identified in the postmortem cultures are not included in this table. The most frequently isolated bacteria were *Pseudomonas* sp. with other enteric Gram-neg-

TABLE 3. Number of patients who died because of an infectious disease after liver transplantation as a function of time posttransplantation

Types of infection	Months after liver transplantation			
	0–1	1–2	2–3	3–4
Bacterial sepsis	6	5	1	1
Concomitant bacterial and fungal sepsis	1	3	0	0
Invasive disseminated fungemia	2	0	0	0
Fungal pneumonia	1	0	0	0
Disseminated herpes simplex infection	1	0	0	0
Total	11	8	1	1
(%)[a]	(52%)	(38%)	(5%)	(5%)

[a] Per cent of total infectious disease-related deaths.

TABLE 4. Pathogenic organisms recovered in postmortem cultures in patients dying of an infectious disease after liver transplantation

Bacteria	
Pseudomonas	9
Enterobacter	2
Proteus morgagni	1
Escherichia coli	1
Klebsiella pneumoniae	1
Serratia marcescens	1
Citerobacter freundii	1
Streptococcus faecalis	1
Fungi	
Aspergillus fumigatus	5
Candida sp.	3
Viruses	
Cytomegalovirus	1
Herpes simplex	1

ative bacilli being second. Thus, infections due to *Pseudomonas* (*aeruginosa* and *maltophilia*) were present in 9 of the 17 cases (53%) in which a bacterial infection was the primary cause of death. The enteric bacilli isolated in the other six cases were: *Enterobacter* (2 cases); *Proteus morgagni* (1 case); *Eschericia coli* (1 case); *Klebsiella* (1 case), and *Serratia marcescens* (1 case). The principal sites of these bacterial infections were the lungs (pneumonia) in 7 cases (42%) and an intraabdominal site in 5 (29%). In five cases, the principal site of the infection could not be identified.

Disseminated fungal infection occurred in seven cases, and was the major cause of death in all seven. The etiologic agents isolated from these seven cases were *Aspergillus* (4 cases) and *Candida* sp. (3 cases). The specific sites of organ involvement in these cases of disseminated fungal infection are listed in Table 5. Disseminated fungal infection coexisted with bilateral fungal bronchopneumonia in 6 of these 7 cases.

Disseminated herpes simplex virus infection was the main cause of death in a single patient who required a second transplant 9 days after his initial transplanted organ failed. Following the second transplantation, he had poor respiratory and renal function and developed a right pleural effusion, sepsis and decerebrate posturing. At autopsy, a severe necrotizing herpes simplex infection involving the larynx, tracheobronchial tree, right lobe of the lung, the urinary bladder, colon and liver was found.

Pathological Findings in the Liver Allografts. The biliary anastomoses were patent in all 31 cases examined at autopsy. The various vascular anastomoses were intact and patent in 27 of the 31 patients studied (87%). Three patients had complete occlusion of the hepatic artery with resultant infarction of the grafted liver. Two of these three patients died because of infection (*Pseudomonas aeruginosa* septicemia and systemic candidiasis). The third patient had a streptokinase infusion started prior to death and died as a result of gastrointestinal bleeding from ulceration and rupture of esophageal varices. One additional patient was found to have mural thrombi at the hepatic artery and inferior vena caval anastomoses and a stenotic anastomosis of the portal vein. This patient also has an infarcted liver and died as a consequence of *Pseudomonas aeruginosa* sepsis.

The pathological findings present in the liver in these 31 patients are listed in Table 6. Histological evidence of rejection was present in 9 (29%), but in only 3 was the rejection process the principal cause of death. These three patients died on the 9th, 52nd and 159th post-OLTx day, respectively. Six patients developed massive infarction of the liver despite patent vascular anastomoses. Three of these died because of bacterial sepsis, and one died because of disseminated aspergillosis. No hepatic involvement of the sepsis process was evident in these four cases. In all six of these patients with massive hepatic infarction, hepatic failure was evident well before the death of the patient. All had had premorbid hypotension occurring as a response to their sepsis. In each case, hypotension management was limited because of pulmonary and renal complications and failure to respond to vasopressors. The time latency between the initial OLTx procedure and death in these patients was 18.8 ± 5.5 days. Focal necrosis and severe hepatic congestion with cholestasis was found in six patients. Massive ne-

TABLE 5. Organ involvement in seven patients who died after liver transplantation because of disseminated fungal infection

Organ involved	*Aspergillus*	*Candida* sp.
Brain	3	0
Thyroid	4	1
Heart	3	2
Lung	4	2
Liver	0	2
Spleen	0	2
Esophagus	1	1
Stomach	2	1
Duodenum	0	1
Colon	1	0
Peritoneum	1	1
Kidney	2	2
Urinary bladder	1	1

TABLE 6. Pathological findings of the liver allografts studied at autopsy in 31 patients who died after liver transplantation

	n	% having a second transplant
Massive infarction[a]	10	0
Rejection[b]	9	100
Focal necrosis and severe hepatic congestion	6	50
Chronic active hepatitis and cirrhosis[c]	1	0
Small hepatic infarcts	1	100
Cytomegalovirus hepatitis	1	0
Herpes simplex hepatitis	1	0
Minimal changes	2	50
Total	31	

[a] Six of these 10 patients had patent vascular anastomoses. Three patients had complete occlusion of the hepatic artery. Another patient had mural thrombi at the anastomoses of both the hepatic artery and inferior vena cava.

[b] Severe rejection (3 cases) and mild to moderate rejection (6 cases).

[c] This patient was HBsAg(+) before and after liver transplantation.

crosis, chronic hepatitis and cirrhosis were found in the liver of one patient who died 150 days posttransplantation because of an intraabdominal hemorrhage. This patient was HBsAg positive before and after OLTx surgery. Multiple small hepatic infarcts were seen in another patient who died of bacterial sepsis. One patient had severe cytomegalovirus hepatitis in the course of an overwhelming systemic cytomegalovirus infection, and a second patient died because of a disseminated herpes simplex virus infection, which included herpes simplex hepatitis. Minimal changes were found in the liver of the two other patients.

Neuropathologic Findings. The brain was available for study in 21 of the 31 cases which were autopsied (68%). Central pontine myelinolysis, which is a focal symmetrical demyelination with preservation of neurons and the majority of the axon cylinders located in the basis pontis near the tegmentum which is thought to occur as a consequence of electrolyte abnormalities and their rapid correction, was found in 6 of the 21 brains studied (29%). Three of these cases died because of disseminated fungemia (*Aspergillus* twice and *Candida* sp. once). The other three patients with central pontine myelinolysis died because of central nervous system hypoxia and multiorgan failure with widespread hepatic necrosis (2 cases) and *Pseudomonas* sepsis (1 case).

In the three cases of aspergillosis involving the brain, the infection took the form of necrotizing hemorrhagic infarcts. Miscellaneous neuropathological findings included the following: brain edema (4 cases); autolytic changes (4 cases); pituitary infarcts (3 cases), and one case of subarachnoid and intracerebral hemorrhage.

DISCUSSION

During the early years of liver transplantation, technical problems, mainly those related with the biliary tract anastomoses, were the major cause of recipient death and accounted for 39% of the 108 deaths in cases which were transplanted at the University of Colorado between 1963 and 1977 and have been reported previously (9). In contrast to this early series, technical problems accounted for only a minor percentage of the deaths in the present series. In fact, only 1 of the 129 patients (0.8%) who survived the first 24 hr after liver transplantation reported in the present series died as a result of a technical problem. Specifically, this patient died as a result of massive gastrointestinal hemorrhage occurring as a result of an arteriocholedochal fistula.

There are several reasons for this remarkable difference between these two series. These include improvements in the surgical procedure, the skill accrued in its performance, a better preoperative evaluation and patient selection and earlier treatment of technical problems, once they are recognized. Until 1976, cholecystoduodenostomy was the main type of the biliary anastomoses performed at the University of Colorado. With this type of biliary anastomoses, repeated bacterial contamination of the biliary tree, with cholangitis and consequent infection and death of the recipient was common (1–3, 9, 10). During these early years of clinical liver transplantation, most of the biliary tract complication were either unrecognized until late in the clinical course or at autopsy. This failure to recognize biliary tract sepsis in the earlier series was due principally to the many technical difficulties encountered by the physicians caring for the patients in establishing a specific diagnosis of biliary tract sepsis in such complexly ill patients (9, 10). Currently, biliary tract complications (particularly infection) are the initial diagnostic consideration in a liver transplant recipient who has an abnormal postoperative course. In fact, the transplant team at the University of Pittsburgh uses cholangiography as the initial step in the evaluation of any liver transplant patient who demonstrates an abnormal postoperative course. The current practice of creating a choledochocholedochostomy as the biliary anastomosis using a T-tube stent and the ready availability of the resultant percutaneous limb of the stent makes cholangiography possible in the evaluation of all such patients. As a consequence, an earlier and more accurate diagnosis of biliary tree complications can be made and earlier surgical intervention, if it is required, can be accomplished. Furthermore, in selected patients, therapeutic interventional radiologic techniques, such as dilatation of a biliary tract stricture, biliary stent removal and restoration of lumenal patency of an obstructed T-tube can be achieved rather easily. In the first 96 adult patients undergoing liver transplantation at the University of Pittsburgh, a biliary complication was diagnosed in 44 by cholangiography. These included 8 cases of obstruction, 24 cases of anastomotic biliary leak and 12 cases of assorted T-tube problems (11).

The addition of newer noninvasive diagnostic imaging modalities (CT and ultrasound) as well as nuclear scintigraphy and other more invasive radiologic tests (angiography) play important roles in the diagnosis of anastomotic technical problems. Moreover, the existence of a very active organ procurement program has made liver retransplantation possible in cases that are not otherwise salvageable. As a result, early retransplanta-

tion in patients with hepatic artery thrombosis is accomplished as soon as possible following diagnosis, thereby avoiding the otherwise fatal outcome of such patients experienced in earlier series.

Transplanted tissues are subject to quite variable degrees of rejection. In the earlier series of deaths reported following liver transplantation, rejection was not considered to be a major problem (1, 2, 7, 8). This difference in results between previous series and the one currently being reported may be due, at least in part, to the fact that in the earlier series only autopsy samples of liver were available for study. As a result, it was thought that immunosuppressive c rtreatment was responsible for many of these deaths (9, 10). Since the introduction of cyclosporine A, a marked reduction in the incidence of acute liver graft rejection episodes has been noted as compared to that experienced with earlier forms of immunosuppressive therapy (3). Thus, it might be thought that early graft rejection no longer occurs or is not an important problem in the clinical management of liver transplant recipients. For example, only 3 of the 40 patients (7.5%) analyzed in the present study died as a direct effect of uncontrolled liver graft rejection. This low percentage of death caused directly by graft rejection does not mean, however that rejection is not an important problem in these patients. On the contrary, liver allograft rejection is a frequent and important problem experienced by such patients, but because of organ availability, severe rejection when it occurs can be managed aggressively with retransplantation in most cases.

Although the true incidence of liver rejection is difficult to ascertain, the rate of liver allograft rejection in a recent series without serial protocol liver graft biopsies was reported to be at least 37% (6). The actual incidence of liver allograft rejection is probably much greater. In this series, liver biosies were performed only when clinically indicated. Thus in this series, the incidence of rejection was calculated with the assumption that rejection had not occurred in those patients in which specimens were not available for examination (6). Obviously, this assumption may not be true in all cases as has been demonstrated when protocol biopsies have been obtained (7, 8).

Obviously, the primary treatment for liver allograft rejection is increased immunosuppression. The criteria for early retransplantation for uncontrollable liver graft rejection have been published elsewhere (12). Briefly, early retransplantation is attempted if, in the first month after grafting, the bilirubin level persists above 10 mg per dl, with or without an associated elevation of the transaminases, and it is unresponsive to two full courses of standard antirejection therapy. Any patient, regardless of serum bilirubin level, whose liver function deteriorates rapidly whenever the steroid dosage is reduced to acceptable maintenance levels (approximately 20 to 30 mg daily) or any patient who requires frequent intravenous bolus injections of steroids in an attempt to control rising transaminase levels is also a candidate for early retransplantation. Using these criteria, liver graft rejection was considered to be uncontrollable with standard immunosuppressive regimens in 14 of our first 93 consecutive adult patients (15%) (unpublished data), with 11 of these 14 patients (79%) being treated with early retransplantation. The remaining three died before a new liver was available for retransplantation. All 14 of these patients presumably would have died if early retransplantation had not been performed. Therefore, as early retransplantation appears to be the only chance for survival for such critically ill patients, we believe that the current tendency to ascribe most of the mortality following liver transplantation to factors other than rejection (2, 3, 9, 10, 13, 14) may not be entirely correct.

While in our experience, technical problems and rejection have become lesser problems as the primary cause of death in liver transplant recipients, infection has become the *major* cause of mortality experienced by these patients. Thus in the present series, evidence of major infection, severe enough to have been responsible for the patient's death, was present in 52.5% of the cases. By far, bacterial sepsis and disseminated fungal infection were the most common cause of death in this series with *Pseudomonas*, other Gram-negative enteric bacilli, *Aspergillus* and *Candida* sp. being the most common pathogenic organisms being isolated. Although problems of surgical technique have played a historical role in the pathogenesis of these infections complicating liver transplantation, presently the basis for most is linked to the use of immunosuppressive agents either to treat or prevent rejection (15–17). Thus, we believe the risk of further attempts to rescue a severely injured or rejecting primary graft with additional immunotherapy and possible infection must be weighed against the risk of reoperation. In our opinion, failure to respond rapidly to intensified immunosuppression is an indication for retransplantation which should be attempted early rather than late in order to avoid unnecessary infections which are associated directly with enhanced immunosuppression. The vast majority of such infections, both bacterial and fungal, are recognized well before death. Moreover, most are treated with antibiotics selected on the basis of culture and sensitivity results. However, renal failure often limits the amounts used. Perhaps the routine use of liver graft biopsy, the only reliable means for detecting graft rejection (7, 8, 18) in cases with negative findings at cholangiography, would result in a more accurate and timely diagnosis of graft rejection, decrease the amount of immunosuppressive drugs being administered to the patient in the vain hope of treating rejection when it is not present, and hopefully result, therefore, in a lower death rate.

REFERENCES

1. Starzl TE, Koep LJ, Halgrimson CH, et al. Fifteen years of clinical liver transplantation. Gastroenterology 1979; 77:375–388.
2. Starzl TE, Koep LJ, Halgrimson CG, et al. Liver transplantation 1978. Transplant Proc 1979; 11:240–246.
3. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982; 2:614–636.
4. Van Thiel DH, Schade RR, Starzl TE, et al. Liver transplantation in adults. Hepatology 1982; 2:637–640.
5. Van Thiel DH, Schade RR, Gavaler JS, et al. Medical aspects of liver transplantation. Hepatology 1984; 4:79S–83S.
6. Demetris AJ, Lasky S, Van Thiel DH, et al. Pathology of hepatic transplantation: a review of 62 adult allograft recipients immuno-

suppressed with cyclosporin/steroid regimen. Am J Pathol 1985; 118:151-161.
7. Snover DC, Sibley RK, Freese DK, et al. Orthotopic liver transplantation: a pathologic study of 63 serial liver biopsies from 17 patients with special reference to the diagnostic features and natural history of rejection. Hepatology 1984; 6:1212-1222.
8. Eggiak HF, Hofstee N, Gips CH, et al. Histopathology of serial liver biopsies from liver transplant recipents. Am J Pathol 1984; 114:18-31.
9. Fennell RH, Roddy HJ. Liver transplantation. The pathologist's perspective. Pathol Ann 1979; 14:155-180.
10. Roddy H, Putman CW, Fennell RH Jr. Pathology of liver transplantation. Transplantation 1976; 22:625-630.
11. Zajko AB, Campbell WL, Bron KM, et al. Cholangiography and interventional biliary radiology in adult liver transplantation. Am J Radiol 1985; 14:127-133.
12. Shaw BW Jr, Gordon RD, Iwatsuki S, et al. Hepatic retransplantation. Transplant Proc 1985; 17:264-271.
13. Calne RY, McMaster P, Portmans B, et al. Observations on preservation, bile drainage and rejection in 64 human orthotopic liver allografts. Ann Surg 1977; 186:282-290.
14. Williams R, Smith M, Shilkin K, et al. Liver transplantation in man, the frequency of rejection, biliary tract complications and recurrence of malignancy based on an analysis of 26 cases. Gastroenterology 1973; 64:1026-1048.
15. Schroter GP, Hoelscher M, Putnam OW, et al. Fungas infection after liver transplantation. Ann Surg 1977; 186:115-122.
16. Dummer JS, Hardy A, Poorsattas A, et al. Infections in kidney, heart and liver transplant recipients on cyclosporin. Transplantation 1983; 36:259-267.
17. Wajszczuk CP, Drummer JS, Ho M, et al. Fungal infections in liver transplant recipient. Transplantation 1985; 40:347-353.
18. Dominguez R, Cuervas-Mons V, Van Thiel DH, et al. Radiologic techniques in the evaluation of liver allograft rejections. Gastrointestinal Radiol 1986 (in press).