RENAL FAILURE IN CHILDREN WITH HEPATIC FAILURE UNDERGOING LIVER TRANSPLANTATION

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Renal failure in children with hepatic failure undergoing liver transplantation

Over a 3½ year period, 133 children with hepatic failure underwent orthotopic liver transplantation (OLT) at our center. Renal failure (creatinine clearance <20 ml/min/1.73 m²) was present in 19 (14.3%) of these children. In seven of the 19 children, renal failure was present before OLT, and in the other 12 after OLT. The causes of renal failure included hepatorenal syndrome in seven, postischemic acute tubular necrosis in five, severe prerenal azotemia in five, and cyclosporine nephrotoxicity in two. Eight other patients died of renal failure while awaiting emergency transplantation. Of the total of 31 deaths among 133 children who underwent OLT, nine occurred in the 19 patients with renal failure. Thus patients with OLT and renal failure had a significantly higher mortality than other patients with transplants ($P < 0.025$). Dialysis was not associated with improved survival. The majority of deaths in patients with renal failure were related to severe hemorrhage, thromboembolic events, and systemic fungal infections. Our experience suggests that renal failure is common in children with hepatic failure and is associated with reduced patient survival after OLT. (J PEDIATR 1986;108:393-398)

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Refinements in surgical technique and the introduction of cyclosporine immunosuppression have greatly improved survival of children undergoing orthotopic liver transplantation.[1-5] Over the past 3½ years, 173 liver transplants have been performed in 133 pediatric patients. Referral of this large number of patients to our center for OLT has provided a unique opportunity to study the late complications associated with severe liver failure in childhood. Specifically, we have found a high incidence of renal failure, which complicates the pre- and perioperative management of these patients and which may contribute to their mortality. In this report, we describe the occurrence of renal failure in children with hepatic failure undergoing OLT and highlight the influence of renal failure on patient survival.

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METHODS

Between June 1981 and December 1984, OLT was performed in 133 children at the Children's Hospital of Pittsburgh. Retrospective review of the clinical course in these patients was done to determine (1) the incidence and causes of renal failure, defined as GFR ≤20 ml/min/1.73 m²; and (2) the influence of renal failure and of dialysis on patient survival. We also examined the records of all 294 children with severe liver failure referred to our center for pretransplant evaluation, to determine the prevalence of renal failure in this patient population. Only specific clinical aspects of this larger group of patients that pertain

OLT	Orthotopic liver transplantation
HRS	Hepatorenal syndrome
ATN	Acute tubular necrosis
GFR	Glomerular filtration rate
FE_{NA^+}	Fractional excretion of sodium
BUN	Blood urea nitrogen
HPLC	High-performance liquid chromatography

Table I. Selected clinical features in 133 children undergoing orthotopic liver transplantation

Age (yr)	
Mean ± SD	6.1 ± 4.7
Range	0.7 to 18.0
Sex ratio (M/F)	1:1.1
Allografts received (n = 173)	
Single	98 (74%)
Two or more	35 (26%)
Follow-up (mo)	
Mean ± SD	12.5 ± 11.8
Range	1 to 42
One-year actuarial survival (%)	71:5
Overall survival	102 of 133 (76.7%)

to the persistence or development of renal failure after OLT are discussed.

In our study, the endogenous creatinine clearance was calculated from the mean of at least three serum creatinine values by the method of Schwartz et al.[6] The fractional excretion of sodium and its interpretation were determined by previously described methods.[7,8]

The clinical diagnosis of hepatorenal syndrome was established in patients with renal failure in the presence of severe hepatic failure by the absence of exposure to nephrotoxic medications, a normal urinary sediment, the presence of FE_{Na}^+ <1.0%, and a progressive and proportional rise in BUN and serum creatinine levels despite adequate blood volume expansion and blood pressure support through administration of blood, plasma, salt-poor albumin, and fluids.[9-12] In contrast to patients with HRS, those with postischemic acute tubular necrosis were identified by an abrupt decrease in urine output; abnormal urinary findings consisting of microhematuria, proteinuria, and granular or tubular casts; $FE_{Na}^+ \geq 2\%$; and a progressive rise in BUN and serum creatinine and potassium concentrations following a readily identifiable hypoxic-ischemic insult. In patients with prerenal azotemia, like those with HRS, results of urinalysis were normal and FE_{Na}^+ <1.0%. However, unlike most patients with HRS, the BUN to serum creatinine ratio was ≥20, and a prompt rise in central venous pressure and improved urine output and renal function followed circulatory volume expansion. Patients with cyclosporine toxicity were differentiated from other patients with renal failure by an indolent decrease in renal function despite normal results of urinalysis in the presence of blood trough cyclosporine levels >500 ng/ml (HPLC). Such patients were further identified by prompt renal functional recovery after appropriate reduction in cyclosporine dosage to maintain trough blood levels of 100 to 200 ng/ml.

Statistical analyses were done only in patients who had transplants. A standard t test was used to compare renal function studies between dialyzed and nondialyzed patients with renal failure.[13] The influence of renal failure on survival among patients undergoing OLT was analyzed by the chi-square method with a Yates correction,[13] and the influence of dialysis on survival among patients with OLT and renal failure was assessed by the Fisher exact probability test.[13]

Table II. Frequency of renal failure in children referred for liver transplantation

	n	%
Frequency of renal failure (GFR ≤20 ml/min/1.73 m²)		
Among all patients evaluated for possible OLT	22 of 294	7.5
At time of admission for OLT	15 of 141	10.6
In patients with transplants	19 of 133	14.3
Renal failure before OLT	7 of 19	
Renal failure after OLT	12 of 19	

RESULTS

Selected clinical characteristics of the entire transplant population are shown in Table I. Although a wide spectrum of disorders accounted for the liver failure, biliary hypoplasia or atresia and metabolic disorders were the principal hepatic diagnoses in 59% of these patients. The diagnosis of liver failure was based on the presence of marked increases in the plasma concentration of bilirubin and hepatic transaminase and ammonia values, whereas plasma albumin and clotting factors were frequently reduced. The majority of patients had jaundice, variable degrees of ascites, edema, muscle wasting, epistaxis, or gastrointestinal hemorrhage associated with portal hypertension and disturbances in hemostasis, and hepatic encephalopathy. Other symptoms included anorexia and intermittent vomiting or diarrhea. Hypotension, often aggravated by orthostasis, was common, particularly in patients with ascites, even in the absence of overt gastrointestinal tract hemorrhage, abdominal paracentesis, conditions leading to dehydration, or diuretic agents used to limit the rate of edema formation. During a 12.5 ± 11.8 month (mean ± SD) follow-up period, the 1-year actuarial patient survival in this population was 71.5%, and the overall survival at the time of this analysis was 76.7% (102 of 133 patients). A complete report describing the preoperative, intraoperative, and postoperative care of this entire population is in preparation; thus we focus here specifically on the renal complications of OLT.

Among 294 patients referred for initial medical screening to determine their suitability for eventual OLT, 7.5% (22 of 294) had renal failure (Table II). However, of the

Table III. Clinical and corresponding nephropathologic diagnoses in 19 children with renal failure after liver transplantation

	Survival after OLT	Autopsy	Renal histopathologic findings
Hepatorenal syndrome (n = 7)	4	3	Enlarged, pale and edematous kidneys with normal architecture
Postischemic acute renal failure (n = 5)	0	5	Acute tubular necrosis, four; ATN, papillary necrosis, and multiple fungal abscesses, one
Prerenal azotemia (n = 5)	4	1	Preserved kidney size and normal architecture
Cyclosporine nephrotoxicity (n = 2)	2	—	—
Total (n = 19)	10	9	

141 patients who were subsequently admitted for OLT, 10.6% (15 of 141) had renal failure. Of these 15 patients, eight died of complications before a transplant could be performed. Thus, seven of the patients who actually received transplants had established renal failure at the time of OLT, and an additional 12 patients developed renal failure after OLT. Therefore, in the 133 patients who actually recieved liver replacement, the incidence of renal failure was 14.3% (19 of 133). The clinical and histopathologic findings in these 19 patients are shown in Table III.

In all patients with renal failure, urine output was <400 ml/m²/day, BUN 126 ± 53 mg/dl, and creatinine level 5.5 ± 3.3 mg/dl (mean ± SD). Dialysis (hemodialysis in eight and peritoneal dialysis in two) was utilized in 10 of these 19 patients. The main indications for dialysis were mixed hepatic/uremic encephalopathy, symptomatic fluid overload, electrolyte imbalance, and uremic pericarditis. Specific aspects of the dialytic therapy in these children will be described in a subsequent report. The mean BUN concentration in dialyzed patients was not significantly higher than that in nondialyzed patients (147 vs 104 mg/dl), but the GFR was significantly lower in patients receiving dialysis (17.5 vs 13.0 ml/min/1.73 m²; P <0.05).

Comparison of survival in the 19 patients with renal failure with that in 114 patients with no renal failure (Table IV) showed significantly lower survival in the patients with renal failure complicating OLT (P <0.025). Survival was similar whether or not the patient received dialysis. In addition, dialysis was not associated with decreased survival when all patients with OLT were considered (Fisher exact probability test, P = 0.1). Among patients with renal failure following OLT, the highest survival rate occurred in patients with prerenal azotemia, followed by those patients with cyclosporine nephrotoxicity or HRS. None of the five patients with postischemic acute renal failure survived (Table III). Causes of death in the nine patients with renal failure after OLT included hemorrhage and infarction of the allograft in three, combined hemorrhage/infarction plus fungal infection in three, and rejection of the liver and hemorrhage in three.

Table IV. Effect of renal failure and of dialysis on survival in children undergoing liver transplantation

	n	%	P
Patient survival			
In patients with kidney failure (n = 19)	10	52.6	<0.025
In patients without kidney failure (n = 114)	92	80.7	
Effect of dialysis on survival in patients with kidney failure			
Survival in dialyzed patients (n = 10)	5	50.0	NS
Survival in nondialyzed patients (n = 9)	5	55.6	
Effect of dialysis on survival independent of renal failure			
Survival in dialyzed patients (n = 10)	5	50.0	NS
Survival in nondialyzed patients (n = 123)	97	78.9	

NS, not significant.

As shown in Table III, the clinical diagnoses were confirmed by renal histopathology in all nine patients with renal failure who died. At autopsy, the kidneys of patients who died with the clinical diagnosis of HRS were pale and markedly enlarged. Kidney weight and size were well above 100% for age in all three of these patients. There was jaundice of the renal parenchyma, and the tubules contained occasional bilirubin casts. The glomeruli appeared enlarged. Apart from minimal interstitial edema, no other abnormalities were noted. The renal findings were similar in one other patient who died of prerenal azotemia, except for a smaller kidney size and weight than in patients with

HRS. In patients with acute tubular necrosis typical tubular findings included dilation of the tubular lumen, degeneration or regeneration of the tubular epithelial cells, and absence of any significant interstitial lymphocyte infiltrates. One patient with postischemic ATN also had extensive papillary necrosis and multiple abscesses with *Aspergillus* and *Candida* organisms throughout the renal parenchyma. Two other patients had a minimal number of *Candida* organisms in the renal tubules or in glomeruli, without any clinical or microbiologic evidence to suggest systemic candidiasis.

DISCUSSION

Our data demonstrate that renal failure is an important complication in children with hepatic failure. Renal failure was present or developed in 14.3% of patients undergoing OLT. The incidence of renal failure (i.e., number of patients with renal failure/total number of cases of liver failure leading to consideration of OLT) was 7.5%, whereas the incidence of renal failure just before OLT was 10.6%. This increase in the incidence of renal failure reflected the further deterioration in hepatic function and general medical condition of the patients during the period between their previous evaluation and the time of actual transplantation. These figures provide only an estimate of the true incidence of renal failure in these patients, because our population is highly skewed by referral patterns and the availability of resources. Future prospective multicenter studies are necessary to determine the true incidence of renal failure in patients with hepatic failure being considered for OLT.

At our center, 4.1% (12 of 294) of the patients evaluated for transplantation and 5.3% (seven of 133) of patients undergoing transplantation had HRS. This represents the largest pediatric experience with HRS reported to date.[14-16] Although the clinical picture of this syndrome is somewhat indistinct and its pathogenesis is incompletely understood, the combination of clinical and laboratory findings used to define HRS in this study meet several criteria for its diagnosis.[9-12, 17, 18] Renal failure secondary to HRS resolved in four other patients after successful OLT, as previously reported in adults.[19] In these patients, in whom dialysis was required before OLT in all four and after OLT in three, renal function returned to normal levels 2 to 4 weeks after transplantation. Among the three patients with the clinical diagnosis of HRS who died after OLT, the relatively minor renal histopathologic findings were confirmatory.[20] Causes of death in these three patients were systemic candidiasis and aspergillosis, air embolism, and massive necrosis of the allograft, respectively. Hence, persistent hepatic dysfunction or sepsis after OLT may have prevented renal functional recovery in these patients.

The development of severe postoperative ATN and subsequent death in five patients was directly related to perioperative complications. The preexistence of HRS did not appear to predispose to the development of ATN, because it developed in none of the seven patients with HRS after OLT. Severe graft dysfunction, sepsis, and massive hemorrhage and hypotension combined to produce renal and systemic ischemia, which led to death in these patients. Thus, multisystem failure and not renal failure per se was directly responsible for patient deaths in this setting.

The single patient who died of prerenal azotemia after OLT developed systemic candidiasis, septic phlebitis, and gastrointestinal tract hemorrhage several days after a third OLT, which functioned well. In this patient, few abscesses containing *Candida* organisms were found within the renal parenchyma. These findings were considered to represent late histopathologic changes, because the initial urinalysis results, FE_{Na}^{+}, and clinical circumstances were compatible with prerenal azotemia secondary to low cardiac output.

Mild and moderate cyclosporine nephrotoxicity is common in patients undergoing OLT,[21] no doubt caused by the high doses of cyclosporine utilized, as reflected in high blood concentrations of this drug. However, severe nephrotoxicity developed in only two of our patients. In one, renal function improved only after temporary discontinuation of cyclosporine and substitution of azathioprine; in the other, renal function improved after cyclosporine dosage adjustment. Hepatic function remains good in both patients.

Survival in our patients with renal failure after OLT was significantly lower than in patients who did not have severe renal dysfunction ($P < 0.025$). Systemic infection and hemorrhagic disorders, along with the severity of the underlying primary disorder or level of surgical success, greatly influence survival in patients with acute renal failure following trauma or major surgery.[22-25] Dialysis has been reported to improve survival in such patients by improving recovery from bacterial infections and by decreasing the risks associated with hemorrhage from gastritis and gastrointestinal tract ulcers or from the cardiopulmonary consequences of fluid overload and electrolyte disturbances.[24, 26, 27] Death in most of our patients with combined liver and renal failure resulted from such causes as bleeding from varices, thromboembolic events, systemic fungal infections, and chemical disturbances resulting from severe hepatic failure. Hence it is not surprising that dialysis, although effective in controlling fluid and biochemical abnormalities, failed to improve survival in our patients. In at least one patient who died of severe gastrointestinal tract hemorrhage while undergoing hemodialysis with low doses of heparin, the dialysis proce-

dure may have directly contributed to death. Thus our experience suggests that dialytic therapy may be helpful in the life support of patients with HRS awaiting OLT, but it provides little or no benefit in the patient in whom ATN is included in multisystem failure after OLT.

The method we used to calculate GFR in our patients relies on the assumption that height and muscle mass are proportional.[6] Inasmuch as muscle mass is reduced in most children with chronic liver failure, this method likely overestimates true GFR. Hence we believe that the renal failure in our patients was more severe than gauged by the calculated GFR. Despite significant differences in GFR between dialyzed and nondialyzed patients with OLT and renal failure, there was no difference in the survival rate of these two groups. This suggests that mortality was influenced more by the development of renal failure and associated morbidity in other organs than by complications arising from the dialysis procedure.

Although it is difficult to determine how renal failure affects survival in patients with severe liver failure or after OLT, there is little doubt that medical management becomes much more complicated in the presence of severe renal dysfunction. It is imperative that measures be taken to reduce the occurrence of renal failure in such patients, particularly because dialysis does not appear to decrease mortality in this setting. In patients with severe liver failure, it is mandatory that medical measures be taken to avoid hypovolemia or electrolyte imbalance, to decrease the risk of functional renal failure or HRS.[9, 10, 14-18] If there is doubt about the adequacy of circulatory volume, diuretic agents and paracentesis should be discontinued and a trial of blood, plasma, or colloid infusion should be instituted, with central venous pressure or pulmonary arterial wedge pressure monitoring. Such therapy may be helpful in excluding prerenal azotemia in a patient in whom acute oliguria develops, with elevation in BUN and serum creatinine concentrations. However, repeated and excessive attempts at blood volume expansion should be avoided in the absence of clinical response, because volume overload and acute pulmonary edema may supervene. In some patients, hypotension and increased susceptibility to acute renal failure may be related to factors other than simple circulatory inadequacy.[28] For example, bile acids can produce vasodilation by blunting the effect of vasoactive agents, thereby reducing total peripheral resistance and decreasing ventricular afterload while simultaneously increasing renal sympathetic vasoconstriction and consequently reducing renal blood flow and GFR.

Periodic urinalysis and monitoring of renal function by regular monitoring of BUN, serum creatinine, and electrolytes are essential in patients with severe liver failure, particularly in those with ascites or in those receiving large doses of diuretic agents. When renal failure supervenes, a low-protein, high-carbohydrate diet, aggressive treatment of infections, and gastrointestinal tract purging to limit urea and ammonia production are often helpful in decreasing encephalopathic symptoms. Whenever possible, hepatotoxic and nephrotoxic medications should be avoided, drug dosages should be modified, and drug blood levels should be monitored. Guidelines are available for drug usage in such a setting.[29, 30]

Our experience suggests that renal failure is common in children with hepatic failure and is associated with reduced patient survival after liver transplantation. Dialysis in patients with hepatic failure is hazardous and not effective in reducing overall mortality. Dialysis therefore should be considered mainly in patients with acute, reversible obstructive jaundice or in others in whom there is hope of reversing the hepatobiliary disorder by surgical procedures or by OLT.[31]

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