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Acute and Chronic Renal Failure in Liver Transplantation

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Abstract

We have performed a retrospective review of the incidence and etiologies of acute renal failure (ARF) in 105 adult patients receiving liver transplants. The prevalence of chronic renal failure was also determined. ARF occurred in 94.2% of these patients. Acute tubular necrosis was the leading cause of ARF and was associated with the highest mortality. Factors associated with increased mortality included: (1) peak serum creatinine >3 mg/dl, (2) multiple liver transplants and (3) the need for dialysis. Pretransplant renal failure did not increase mortality. Chronic renal failure developed in 83% of patients at latest follow-up (mean: 30.5 ± 7.9 months).

Keywords

Acute renal failure; Chronic renal failure; Liver transplantation; Ciclosporin nephrotoxicity; Dialysis; Acute tubular necrosis

Introduction

Since the introduction of ciclosporin, liver transplantation has become an effective treatment for end-stage liver disease with a 1-year survival now approximating 10% [1–3]. In the patient with severe liver disease, gastrointestinal hemorrhage, the administration of potentially nephrotoxic agents and a number of other insults may predispose to the development of acute renal failure (ARF) [4]. Hyperbilirubinemia, an ubiquitous finding in liver failure, may be directly nephrotoxic and may complicate matters by rendering patients exposed to other noxious influences more susceptible to the development of ARF [5]. Hypotension from massive blood loss complicated by the vascular instability, which often accompanies end-stage liver disease, provides a well-recognized clinical environment in which ischemic renal damage often occurs [6]. Postoperatively, infection, rejection, and volume overload or depletion in addition to ciclosporin toxicity make this period particularly troublesome with respect to the maintenance of normal renal function. Long-term patients require immunosuppression with ciclosporin to preserve liver function, but face the possibility of developing progressive renal insufficiency due to the nephrotoxicity associated with the chronic use of this drug [7,8].

Although renal function is, therefore, at jeopardy in each phase of liver transplantation, very little information is available which precisely identifies the etiology of ARF postoperatively or the contribution of ciclosporin to impaired renal function chronically. Most studies have been limited by small numbers of patients, and no study has specifically attempted to determine the precise etiology of ARF during the peri-operative period in adult patients. Likewise, although data have accumulated regarding the nephrotoxicity of ciclosporin in the heart transplant setting [7,8], a paucity of information is available on the renal consequences of

administering this drug on a chronic basis after liver transplantation. Transplantation of large numbers of patients with end-stage liver disease at the University of Pittsburgh has provided us with a unique opportunity to more fully characterize renal failure in this setting. Therefore, we have reviewed the charts of adult liver transplant patients during the perioperative period to evaluate the incidence, etiologies, and impact on survival of the development of ARF. In addition, we obtained long-term follow-up data on these patients to determine the prevalence of chronic renal failure after liver transplantation.

Patients and Methods

We reviewed the charts of 189 consecutive adult patients receiving orthotopic liver transplants at the University of Pittsburgh Health Center between December 1983 and August 1985. Sufficient information was available on 105 patients to allow their inclusion. Patients were excluded for the following reasons: (1) a portion of the charts was unavailable for review or, (2) the patient died within 72 h of transplantation. Each chart was reviewed by one of the authors for the occurrence and etiology of ARF in the postoperative period. The surgical procedures and immunosuppression schedules have been published elsewhere [2]. All patients were treated initially with prednisone 200 mg/day and ciclosporin 17.5 mg/kg/day. Both drugs were subsequently tapered to the minimum dose required to maintain graft function. Ciclosporin was measured by radioimmunoassay kit (Sandoz Laboratories).

Renal function was monitored by daily serum creatinine and BUN. Graft function was monitored with serial measurements of serum bilirubin, SGOT and alkaline phosphatase. Liver scans and nonenhanced CAT scans were obtained as clinically needed.

Etiologic Definitions

ARF was defined as a 50% or greater increase in postoperative serum creatinine (SCr) compared to pretransplant values. Pretransplant SCr was obtained within 24 h prior to surgery in all cases. When more than one potential insult was present, the insult considered to be the primary cause was used.

The term ischemic acute tubular necrosis (ATN) was applied if a 50% or greater rise in SCr occurred within 24 h after an identifiable hypotensive period. The urinalysis was required to be consistent with the diagnosis of ATN.

Aminoglycoside-induced ATN was defined as ARF occurring after at least 7 days of aminoglycoside administration. Trough levels were usually elevated and urinalyses were consistent with ATN.

Severe volume depletion as the cause for ATN was determined to be the etiology of ARF when the central venous pressure was severely depressed for prolonged periods of time and weight loss was documented. The SCr, which had risen initially sufficiently to satisfy the criteria for ARF, did not decline after volume repletion or reduction of ciclosporin dosage. Urinalyses were consistent with ATN.

Ciclosporin toxicity was determined to be the sole etiology of ARF if SCr fell to baseline following a reduction in ciclosporin dosage in the absence of other corrective measures.

Hepatorenal syndrome (HRS) was considered to be present prior to transplantation in the absence of other causes of ARF when the following criteria were met: (1) severe liver failure at the time of liver transplantation, (2) urinary sodium < 10 mEq/1, (3) absence of detectable volume depletion, and (4) urinary osmolality of 400 mosm/kg or greater. In addition, these patients were required to have oliguria and a slowly progressive rise in SCr.

Allergic interstitial nephritis was diagnosed in 1 patient taking trimethoprim-sulfa. Eosinophilia, skin rash and eosinophiluria were present and SCr fell to baseline after discontinuation of the drug.

Prerenal azotemia was diagnosed in patients with evidence for volume depletion (weight loss, low central venous pressures, etc.) in which SCr returned to baseline values after volume repletion. Urinalyses were required to have a benign appearance with high specific gravity. Although most would not apply the term ARF to these patients in clinical practice, a significant rise in SCr is often called ARF [9].

Statistical Analyses

All values presented are expressed as means $\pm$ SD. Student's t test or analysis of variance were used where appropriate to determine significant differences between means. Contingency table analyses were also employed to analyze some of the data. Multivariate analysis was performed using discriminant analysis techniques [10]. Life table analyses were carried out using standard methods [11].

Results

Demographic Data

Of the 105 patients included in this review, 43 (41%) were male and 62 (59%) were female. The mean age of all patients was 39.2 ± 9.9 years with ages ranging between 18 and 57 years. There was no significant differences in age between men and women. The commonest causes of liver failure in this group of 105 patients with ARF were: (1) primary biliary cirrhosis (30 patients, 28.6%), (2) sclerosing cholangitis (27 patients, 25.7%) and (3) chronic active hepatitis (23 patients, 21.9%). Other diagnoses included: Budd-Chiari syndrome, Wilson's disease, gold hepatotoxicity, hepatoma, alcoholic liver disease, α -1-antitrypsin disease, non-A, non-B hepatitis, hemochromatosis and polycystic liver and kidney disease. The incidences of these latter diseases varied between 1 and 5.7%.

ARF during the Perioperative Period

During the postoperative period, 99 (94.3%) of the 105 patients developed ARF. The mean pretransplant SCr in patients developing renal failure was 0.92 ± 0.62 mg/dl and peak SCr was 2.71 ± 1.4 mg/dl ($p < 0.0001$). There was no significant difference between pretransplant SCr in patients who developed ARF and those who did not. Renal failure was mild (peak SCr < 1 mg/dl) in 36 patients (36.4%), moderate in 24 patients (24.2%, peak SCr 2–3 mg/dl) and severe in 39 patients (39.4%, peak SCr 3–7.7 mg/dl). Ten of the patients in the latter group required dialysis.

The etiologies of ARF are listed in table 1. Ischemic ATN was the leading cause of ARF followed by cyclosporin toxicity. ATN resulted in nearly half of the cases of ARF (44.8%). Patients without a specific cause for ARF comprised 21.9% of patients but developed only a mild increase in SCr. One of the patients with aminoglycoside-induced ATN received both liver and kidney transplants for polycystic liver and kidney disease. For all patients, neither the mean nor peak cyclosporin levels correlated with the occurrence of ARF or peak SCr. Cyclosporin toxicity was probably underdiagnosed in this study since many of the patients not so classified experienced a fall in SCr when the dosage was decreased. Hepatorenal syndrome was diagnosed prior to transplantation; SCr continued to rise postoperatively and began to fall only after 8.0 ± 4.1 days. Oliguria was predominantly found in patients with ischemic ATN (32/34, 94%) and volume depletion-induced ATN. Oliguria was much less common in the other groups: aminoglycoside ATN (2/11, 18.2%), HRS (2/4, 50%), and allergic interstitial nephritis (1/1, 100%). The remaining patients were nonoliguric.

Mortality

Twenty patients died during the initial transplant admission. Relevant data are provided in tables 1 and 2. Autopsies were available on 13 of these patients. Histologic examination of the kidneys revealed vacuolization of tubular cells in all except 2 patients. Tubular cell dropout and mitotic figures were found in all patients with ATN. There was no evidence of interstitial fibrosis in any case. Three patients with ATN and sepsis were found to have small renal infarctions. Gram-negative sepsis was the immediate cause of death in 12 of the 20 patients but was also a major contributor to the deaths of 4 additional patients. The latter patients died of (1) a ruptured aortic anastomosis, (2) subarachnoid hemorrhage, (3) liver failure and (4) pulmonary hemorrhage. Although liver failure was the proximate cause of death in only 1 patient in this series, liver failure due to transplant rejection was a major complication in 16 others. The mean total bilirubin when SCr was at peak in survivors and nonsurvivors was 5.6 ± 5.7 and 11.1 ± 6.6 mg/dl, respectively ($p = 0.0041$). There was no difference in pre-transplant total bilirubin between survivors and nonsurvivors.

Discriminant analysis was performed, searching for the combination of factors which would best predict survival and the need for dialysis. The following variables were considered: (1) age, (2) sex, (3) pretransplant SCr, (4) peak SCr, (5) pretransplant BUN, (6) peak BUN, (7) pretransplant bilirubin, (8) bilirubin at peak SCr, (9) mean ciclosporin level prior to rise in SCr, (10) peak ciclosporin level prior to the initial rise in SCr, (11) duration of hospitalization, (12) etiology of liver disease, (13) etiology of ARF and (14) the need for dialysis. Only two factors, when combined, increased the accuracy of predicting patient survival. They were (1) the need for dialysis and (2) the etiology of ARF. Peak SCr was found to be the only important variable in predicting the need for dialysis. The influence of these variables and those which did not affect survival are considered below.

Pretransplant Renal Function and Perioperative Survival

Pretransplant SCr had no significant influence upon perioperative mortality (figure 1). Sixty-five of eighty-four patients with pretransplant SCr less than 1.1 mg/dl survived, as did 15 of 16 patients with values 1.1–2.5 mg/dl and 5 of 5 patients with values greater than 2.5 mg/dl. Although patients with the most severe pretransplant renal impairment appeared to have improved survival, there was no significant difference as a function of pretransplant SCr ($p = 0.1677$).

Degree of Renal Failure as a Predictor of Survival

Figure 2 displays the relationship of peak SCr to mortality. Among the 33 patients with a peak level < 1.7 mg/dl, 1 patient expired, yielding a mortality rate for that group of 3%. For patients with a peak SCr of 1.7–3 mg/dl, 2 of 30 patients expired (mortality rate of 6.7%). For patients with peak SCr between 3 and 4.3 mg/dl, mortality was 33.3% with 9 of 27 patients dying. Of the 10 patients with peak creatinine between 4.3 and 5.6 mg/dl, 4 (40%) expired. Two of the three patients with peak SCr between 5.6 and 6.9 mg/dl expired and both patients with peak creatinine of 6.9 mg/dl or greater died. A SCr greater than 3.0 mg/dl, therefore, carried a significant risk of death ($p < 0.0001$).

Etiology of ARF and Survival

Survival during the initial transplant admission was significantly influenced by the etiologic classification of renal failure (table 1, $p = 0.0085$). Patients with hypotension-induced ATN experienced the greatest mortality with 14 of 34 patients (41.2%) expiring during the initial transplant admission. Three of eleven patients (27.3%) with aminoglycoside-induced ATN died as did 1 of 2 patients with volume depletion-induced ATN. The overall mortality for patients with ATN was 39%.

The remaining etiologic groups demonstrated relatively low mortality rates. Within this group, patients with HRS had the greatest mortality with 1 of 4 patients (25%) expiring. Patients in the unknown group experienced low mortality with only one death in 23 patients (4.4%). The remaining etiologic groups experienced no deaths.

Dialysis as a Determinant of Perioperative Survival

The most significant predictor of death during the perioperative period was the need for dialysis. ARF requiring hemodialysis occurred in 10 patients or 10.1% of those with ARF. Five (14.7%) of the 34 patients with hypotension-induced ATN were dialyzed, as were 2 (18.2%) of the 11 with aminoglycoside-induced ATN and 1 of the 2 patients with volume depletion-induced ATN. One of the two remaining patients had HRS and the etiology of the ARF in the other patient was unknown. Of the 10 patients who were dialyzed, only 1 survived the initial transplant admission (i.e., 90% mortality rate). Ten (11.2%) of the eighty-nine patients who were not dialyzed died. Of the 20 patients who did not survive, 10 were dialyzed.

Number of Transplants as a Determinant of Survival

Multiple liver transplants were performed in 20 of the 105 patients. Mortality was directly related to the number of liver transplants. For solitary transplants, the mortality rate was 9.4% (8/85), for two transplants: 56.3% (9/16), and for three transplants: 75% (3/4), $p < 0.0005$. The need for dialysis was also directly related to the number of transplants: 1.2% (1/85) for solitary transplants, 31.3% (5/16) for two and 75% (3/4) for three transplants, $p < 0.0001$.

Renal Function during Long-Term Follow-up

Eighty-five patients survived the initial admission for liver transplantation. Mean follow-up in the survivors was 30.4 ± 9.9 months. Mean SCr for all survivors was 1.94 ± 0.94 mg/dl. Twelve patients died during the follow-up period and no patient was lost to follow-up. The causes of death included liver failure [8], metastatic carcinoma [1], probable myocardial infarction [1], pulmonary embolus [1] and unknown in 1 patient.

Mean pretransplant, discharge, and latest follow-up values of SCr for all survivors by etiology of ARF are presented in figure 3. Mean SCr at latest follow-up was greater than pretransplant and discharge values in all etiologic groups except HRS. Renal function at latest follow-up was relatively well preserved in patients with prerenal azotemia (1.7 ± 0.3), HRS (1.53 ± 0.5) and no ARF (1.38 ± 0.26) during the postoperative period.

Patients with an unknown etiology of ARF during the postoperative period developed moderate renal insufficiency with latest follow-up SCr of 2.24 ± 1.75 mg/dl. One patient, a 38-year-old male with alcoholic cirrhosis, has started chronic hemodialysis 18 months after transplantation. Since a renal biopsy was not performed, the precise etiology of his progressive chronic renal failure could not be documented.

Serum creatinine varied at each routine monthly clinic visit for all patients but tended to fall when ciclosporin dosage was reduced. Neither the daily ciclosporin dose at latest follow-up (355 ± 172.7 mg/day, 5.5 ± 3.3 mg/kg/day) nor the absolute ciclosporin level (mean: 476.9 ± 222 ng/ml) correlated with SCr at latest follow-up. There was no significant difference in mean ciclosporin dosage between etiologic groups either as regards liver failure or ARF.

At latest follow-up, 14 of the 85 surviving patients (16.5%) retained normal renal function defined as SCr less than 1.7 mg/dl. Figure 4 presents the life table analysis for the development of chronic renal failure. The greatest decline in renal function occurred during the first 18 months after transplantation. At 6 months, 1 year and 18 months after transplantation, the

probability of retaining normal renal function was 64.3, 48.5 and 39.7%, respectively. By the 39th month it was 22.67%.

Hypertension and hyperkalemia were common complications during the follow-up period. We could document a prior history of hypertension in 10 of the 85 patients surviving the initial admission for transplantation. During the follow-up period, 50 developed hypertension for the first time. Spontaneous hyperkalemia occurred in 23 patients at some time during the follow-up period. Thirteen were taking a β -blocker or angiotensin-converting enzyme inhibitor for hypertension. However, the hyperkalemia was probably not due to chronic renal failure per se since mean SCr values of patients with and without hyperkalemia were 2.04 ± 1.39 and 1.84 ± 0.61 mg/dl, respectively ($p = 0.42$).

Discussion

The major findings obtained in this study provide the following new information (1) ARF is a common complication of orthotopic liver transplantation. (2) The etiology of ARF is a major determinant of patient survival. The commonest and most serious cause of ARF is ATN related to prolonged ischemia associated with sepsis. (3) Pretransplant renal impairment did not result in greater risk of death. (4) Renal failure severe enough to require dialysis was almost universally fatal. (5) Chronic renal failure, probably due to ciclosporin, is also a common complication.

Only one previous study, by Ellis et al. [12] in children, has systematically determined the etiology of ARF after liver transplantation. These workers found that, of the 19 patients studied, HRS (7 patients) was the most common cause of ARF. We found that HRS was much less common in the adults (3.8%) and that ATN, of all causes, comprised fully 50% of patients with ARF.

Previous information on the incidence of ARF in the adult during liver transplantation derives from a limited number of relative small studies [12–17]. The incidence has been reported to be as low as 21% and as high as 73%. The major cause of these differing incidence figures appears to be variations in the criteria for ARF utilized in the various studies. Iwatsuki et al. [13] reported upon the incidence of ARF in 135 patients; 71 adults and 64 children. Acute renal failure was defined as the development of a BUN of 50 mg/dl or a SCr of 2 mg/dl. ARF occurred in 15 of 71 adults (21%) and 14 of 64 children (22%). Powell-Jackson et al. [14] reported a 53% incidence in 27 patients, using a SCr value exceeding $200 \mu\text{M}$ (2.3 mg/dl) as their criterion. In a preliminary communication, Danovitch et al. [15] reported an incidence of 66% for adults (37 children, 36 adults), using a 100% rise in SCr over pretransplant values as the basis for the diagnosis. Williams et al. [16] reported that 21 of 29 patients (73%) developed either acute or chronic renal failure defined as a 50% increase in SCr over the upper limits of normal for their laboratory.

In our series of patients, mortality was related to peak SCr, the need for dialysis, and the number of liver transplants. Although none of the previous studies of ARF in liver transplantation commented upon the influence of increasing numbers of transplants on survival, there is evidence which verifies this association [17,18].

Most previous studies confirm our observation that the need for dialysis is a grave prognostic indicator. Ellis et al. [12] further suggested that the dialysis procedure itself may increase the risk of death due to heparin-related hemorrhagic complications and the risk of hypotension. We could not verify this thesis since only 1 patient in our series experienced massive hemorrhage shortly after dialysis, which was due to rupture of the hepatic artery anastomotic site. This patient received no heparin during dialysis. None of the studies of ARF in liver transplantation has demonstrated a beneficial effect of dialysis on survival [12–15], nor is there

evidence that early and aggressive dialysis in any other clinical setting is effective in reducing mortality [19,20].

There is growing evidence that ciclosporin given chronically results in chronic renal failure [7,8,21–23]. While the pathogenesis of this form of nephrotoxicity is not well understood, the noxious effects of ciclosporin form a spectrum from an acute reduction in glomerular filtration rate which is usually reversible, to a chronic irreversible form characterized by interstitial fibrosis [7,22,23]. Increased renal vascular resistance may play a major role in the acute form and alterations in the levels of vasoconstrictor prostaglandins may have pathophysiologic importance [7,24–26].

Hypertension and hyperkalemia were also common complications of chronic ciclosporin therapy, as has been reported elsewhere [7,8,24]. While the etiology of the hypertension in these patients is not clear, it seems most likely to be the result of the drug, although it may be related to the alterations in renal function. Furthermore, the mechanism by which ciclosporin causes hypertension is unclear but could, in part, be the result of a drug-induced increase in peripheral vascular resistance [7]. There is evidence that the suppressed renin and aldosterone secretion rates often found in patients taking ciclosporin may represent a direct effect of the drug [27].

Liver transplantation with ciclosporin has clearly become the only method of preserving the lives of many desperately ill patients with end-stage liver disease. The very success of ciclosporin in preventing rejection and the deaths of these patients has allowed us to consider the effects of this drug over long periods of time. Strategies for reducing the chronic nephrotoxicity of ciclosporin are currently in evolution and the management of the patients in this study reflects the maturation of knowledge that is being acquired in the use of this agent.

Methods currently being practiced include: (1) attempts at reducing ciclosporin dosage to the absolute minimum required to prevent rejection while using only ciclosporine and prednisone, (2) reducing ciclosporin dosage by adding azathioprine and (3) developing new immunosuppressant agents without nephrotoxicity. Iwatsuki et al. [13] and Klintmalm et al. [28] have both suggested that the high incidence of chronic renal failure during the first 12–18 months after transplantation is directly related to high ciclosporine doses using during the early posttransplantation period. The relative reduction in the incidence of new patients developing chronic renal failure after 20 months in our study would support this hypothesis. The addition of azathioprine and subsequent reduction in ciclosporin was instituted in some patients at this center during this study and may further preserve renal function. Finally, new agents under investigation, used in combination with ciclosporin or alone, may further reduce the risk of acute and chronic ciclosporin nephrotoxicity [29].

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Fig. 1.
Pretransplant SCr values plotted versus percent survival in liver transplant recipients.

Fig. 2.
Percent survival in patients with mild, moderate, and severe ARF. Patients are categorized to the level of their peak SCr values.

Fig. 3.

Mean SCr values in the pretransplant period, at discharge, and at latest follow-up for patients categorized according to the etiology of their ARF. ISC = Ischemic ATN; AMI = aminoglycoside-induced ATN; VD = volume depletion-induced ATN; CYA = ciclosporin toxicity; PR = prerenal azotemia; NARF = no ARF; UNK = unknown; HPR = HRS; AIN = allergic interstitial nephritis.

Fig. 4.
The proportion of patients with normal SCr plotted vs. increasing time postliver transplantation. The values 85, 41, and 5 indicate the number of patients remaining in the study at the times noted.

Table 1

Etiology of ARF

Etiology	Number of patients	SCr, mg/dl		Deaths
		pre-Tx	peak	
Ischemic ATN	34 (32.4)	1.05 ± 0.78	3.27 ± 1.13	14 (41.2)
Aminoglycoside ATN	11 (10.5)	1.15 ± 0.73	3.97 ± 2.0	3 (27.3)
Volume depletion-induced ATN	2 (1.9)	0.75 ± 0.21	2.55 ± 1.6	1 (50)
Ciclosporine toxicity	17 (16.2)	0.78 ± 0.27	2.8 ± 1.4	0
Prerenal azotemia	7 (6.7)	0.74 ± 0.28	1.56 ± 0.8	0
HRS	4 (3.8)	1.9 ± 0.4	3.5 ± 2.1	1 (25)
Allergic interstitial nephritis	1 (1)	0.9	5.1	0
Unknown	23 (21.9)	0.74 ± 3.1	1.99 ± 0.79	1 (4.4)
No ARF	6 (5.7)	0.67 ± 0.34	1.18 ± 0.29	0
Total	105 (100)			20 (19)

Figures in parentheses represent percentage.

Table 2

Causes of death in patients with ARF following liver transplantation

Causes of death	Number of patients
Sepsis (12/12) ^a	12
Respiratory failure (aspiration) ^a	1
Subarachnoid hemorrhage	1
Rejection alone	1
Pulmonary hemorrhage ^a	1
Pulmonary embolus	1
Ruptured hepatic artery anastomosis ^a	1
Cardiac tamponade	1
Gastrointestinal hemorrhage ^a	1

^a Liver failure due to rejection contributed to death.