Acute Kidney Injury After Liver Transplantation

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The incidence of postoperative renal insufficiency and acute kidney injury (AKI) in patients undergoing liver transplantation ranges from 20% up to 90% [1] and more than 80% of these episodes occur within the first 2 postoperative days. Earlier studies found that mortality at 30 days was 50% in patients who developed AKI and 29% in non-AKI patients [2]. AKI necessitating renal replacement therapy has been associated with mortality rates from 55 to 90% [3]. Risk factors for the development of AKI in these patients include preoperative renal dysfunction represented with a higher preoperative serum creatinine (SCrea), greater requirements for intraoperative blood transfusion, more frequent episodes of intraoperative hypotension, and other preexisting comorbidities [2].

AKI was traditionally defined as an acute reduction in glomerular filtration rate (GFR) sufficient to cause azotemia and multiple at times conflicting definitions existed in the literature that made comparisons of studies difficult. In 2004 the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group proposed a new classification scheme for AKI that includes separate criteria for SCrea/GFR and urine output [4]. These RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) criteria define AKI either by SCrea/GFR (increase of SCrea ≥3 times of the baseline or GFR decrease of 75% of the baseline, or SCrea ≥4 mg/dL) or by urine output (urine output <0.3 mL/h × 24 h or anuria × 12 h). A more recent definition by the Acute Kidney Injury Network (AKIN) proposes "An abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in SCrea of more than or equal to 0.3 mg/dL (≥26.4 μmol/L), a percentage increase in SCrea of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/h for more than 6 h)" [5] as a definition of AKI, reflecting the fact that even small changes of SCrea affect outcome for example after cardiac surgery.

Post-transplant AKI can be attributed to several causes (Table 31.1). Acute tubular necrosis (ATN) appears to be the major cause of AKI. Fraley et al. divided ATN into ischemic and nephrotoxic causes and attributed 52% of ATN to ischemia and 18% of ATN to nephrotoxic causes [6]. Other significant causes of postoperative ATN include contrast nephropathy, sepsis, and rarely rhabdomyolysis.

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Early diagnosis of AKI is of critical importance as only early intervention can potentially affect outcome. However SCrea is a very slow and insensitive marker that reflects renal function but not injury. It may take days after a renal injury for SCrea to increase and any intervention at this time would be too late. Furthermore, the decision when and how to start immunosuppression with nephrotoxic immunosuppressive often needs to be made before an increase of SCrea reveals substantial renal injury.

Recently novel biomarkers of renal injury have been discovered and tested as predictors of renal injury after liver transplantation. Of these neutrophil gelatinase-associated lipocalin (NGAL) is one of the most promising. NGAL is a 23 kD protein that can be detected in urine and blood within hours after renal injury and is a sensitive marker in multiple scenarios of kidney injury. After liver transplantation NGAL increases rapidly in blood and urine and can predict AKI with good sensitivity and specificity [7–9]. Further studies are required to confirm the clinical utility of this and other biomarkers.

In patients with ATN, muddy-brown casts are usually seen in the urinary sediment and an increased fractional excretion of sodium is evident. Treatment of ATN is usually supportive and there is no intervention that is able to prevent or ameliorate AKI [10]. However it is important to avoid further renal insults by maintaining blood pressure and renal perfusion and minimizing nephrotoxic drugs. Pharmacologic agents that may cause AKI are listed in Table 31.2.

AKI can usually not be attributed to a single cause and multiple renal insults are required to cause clinically overt AKI. Pre-existing renal insufficiency and hepato-renal syndrome, intra- and postoperative hypotension, hypovolemia, and vasopressor requirements possibly in conjunction with caval crossclamp (and renal venous obstruction) and the use of nephrotoxic drugs such as calcineurin inhibitors all contribute to renal injury and may precipitate AKI. Common postoperative causes of AKI are explained in more detail below.

Table 31.1 Causes of postoperative renal failure in liver transplantation

Acute tubular necrosis	Calcineurin inhibitor toxicity	Other
Ischemic	Tacrolimus	Abdominal compartment syndrome
Nephrotoxicity	Cyclosporine A	Hemolytic uremic syndrome
Nephropathy		Thrombotic thrombocytopenic purpura
Sepsis		Infection
Rhabdomyolysis		

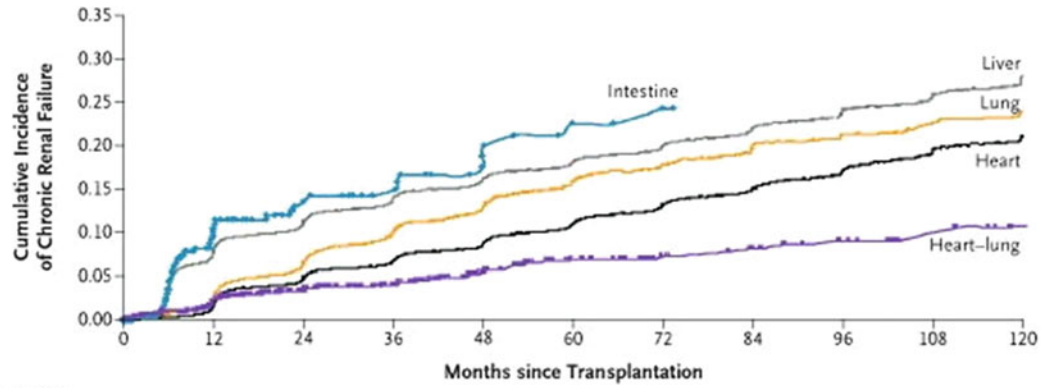
Calcineurin Inhibitors

Both tacrolimus and cyclosporine A contribute to the development of chronic renal failure in the post-transplant period in liver transplantation patients and the use of both tacrolimus or

Table 31.2 Agents associated with renal failure

Pre-renal hemodynamic changes	Acute tubular necrosis	Acute interstitial nephritis
Cyclosporin	Aminoglycosides	Penicillins
Tacrolimus	Amphotericin B	Cephalosporins
Radiocontrast agents	Cisplatin	Sulfonamides
Amphotericin B	Cephalosporins	Rifampin
ACE inhibitors	Radiocontrast agents	NSAIDs
ACE receptor blockers		COX-2 inhibitors
NSAIDs		Interferon
COX-2 inhibitors		Interleukin-2

From Coffman TM. Renal failure caused by therapeutic agents. In: Greenberg A, editor. Primer on kidney diseases. San Diego: Academic; 1998. p. 260–5



No. at Risk											
Heart–lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36,849	28,495	24,041	19,508	15,724	12,564	9844	7345	5292	3614	2261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1136	745	468	258	133

Fig. 31.1 Cumulative incidence of chronic renal failure among 69,321 persons who received nonrenal organ transplants in the United States between January 1, 1990, and December 31, 2000. (with permission: [17] Ojo AO et al. N Engl J Med 2003;349:931–940)

cyclosporine has been associated with acute increases in creatinine due to changes in renal hemodynamics [11]. Nonprogressive and dose-dependent renal dysfunction may be observed with elevations in SCrea levels paralleling the elevations of serum levels of the calcineurin inhibitor. Lowering the dose of calcineurin inhibitors may ameliorate deteriorating renal function. In addition, there have been a number of studies suggesting that chronic nephrotoxicity may be alleviated by the use of rapamycin as the primary immunosuppressive agent instead of calcineurin inhibitors [11, 12]. Late changes of calcineurin inhibitor use include renal tubular atrophy and renal interstitial fibrosis [13, 14] that may lead to irreversible renal failure requiring hemodialysis. Strategies to reduce the dose of calcineurin inhibitors by using alternate forms of immunosuppression have been attempted. Induction of tolerance in liver transplantation where calcineurin inhibitors are slowly weaned to very low doses may significantly diminish or eliminate the renal toxicity related to these agents while still providing adequate immunosuppression [15].

Careful monitoring of calcineurin inhibitor levels is essential to avoid major toxicity. And decreasing doses when supra-therapeutic levels are observed may lessen the incidence of chronic renal failure. Other supportive treatments include strict control of blood pressure, control of hyperlipidemia, and control of post-transplant diabetes mellitus [16]. Often, however, renal failure is unrelenting and renal replacement therapy is necessary. Liver transplantation has the second highest incidence of renal failure requiring renal replacement therapy of solid non-renal transplants (after intestinal transplants). Twelve, 36 and 60 months after liver transplantations 8.0%, 13.9%, and 18.1%, respectively, developed chronic renal failure (Fig. 31.1). Chronic renal failure after non-renal solid organ transplantation is associated with a 4.55 times higher risk of death compared to patients with no chronic renal failure [17]. Therefore preventing chronic renal failure by reducing calcineurin inhibitors to the lowest possible dose and avoiding other injuries is paramount to ensure long-term success of the transplant.

Thrombotic Thrombocytopenic Purpura: Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) have been described in patients after liver transplantation

and are often attributed to immunosuppressive drugs. Both cyclosporine A and tacrolimus have been associated with TTP-HUS [18–22]. HUS is characterized by fever, microangiopathic hemolytic anemia and thrombocytopenia. In TTP, these symptoms are accompanied by neurologic changes and acute renal failure. TTP-HUS may be associated with malignant hypertension and subsequent arteriolar injury. The diagnosis is usually made on clinical grounds alone but may be confirmed by renal biopsy. Plasmapheresis has been successfully used with or without holding the toxic drug however usually changing immunosuppression is required to treat this condition.

Abdominal Compartment Syndrome

Increased intra-abdominal pressure is a contributing factor to AKI after liver transplantation. Progressive and abrupt increases in intra-abdominal pressure reduce cardiac output, contribute increased inspiratory pressures when ventilated and decreases in splanchnic, hepatic, and renal perfusion. These changes are collectively referred to as "abdominal compartment syndrome" [23–25]. Biancofiore et al. [26], using urinary bladder manometry, has shown that up to 32% of patients undergoing liver transplantation have intra-abdominal pressures greater than 25 mmHg. This elevation in intra-abdominal pressure was associated with renal failure, lower filtration gradient, and prolonged ventilation in the post-transplant period and may exacerbate renal injury to a degree that renal replacement therapy is necessary. Increased intra-abdominal pressure may also impede blood flow to the liver and graft function [27]. Frequent measurements of intra-abdominal pressure and possibly re-exploration if the intra-abdominal pressure is sustained high may help alleviate this problem.

Infectious Complications

Postoperative infections can progress to sepsis and septic shock and cause substantial renal injury that may progress to renal failure requiring renal replacement therapy. Specific infection that cause direct renal injury are often caused by viruses. Epstein-Barr virus (EBV) has been reported to cause renal failure in patients after liver transplantation [28]. If detected, appropriate antiviral therapy should be initiated. Post-transplant lymphoproliferative disorder (PTLD) may occur secondary to EBV and has been shown in autopsy studies to infiltrate the kidney [29]. Although there has not been a clear correlation between renal infiltration in PTLD and renal failure, this should be considered in the differential diagnosis of AKI.

There have been case reports of JC and BK polyoma viruses causing hemorrhagic cystitis and renal failure in bone marrow transplant recipients [30] and renal allograft recipients [31–33]. No reports of these viruses causing renal failure in liver transplant patients have been sited, however, these viruses have been found in the urine of liver transplant patients [34] and should be considered when other causes are not found.

Summary

Renal failure after liver transplantation is a serious and life-threatening complication. Early identification of high-risk patients is essential to minimize the development of this problem. Early diagnosis of renal dysfunction and optimal medical management postoperatively in the intensive care unit is required to ameliorate further renal injury. If irreversible renal failure develops, renal replacement therapy with hemodialysis may be required and possible renal transplantation should also be considered if ARF is not reversible.

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