Renal Failure and Liver Transplantation

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In the United States, livers used for transplantation are allocated based on the model for end-stage liver disease system of scoring. Serum creatinine is one of the three variables in this system, and therefore patients undergoing liver transplantation frequently have renal insufficiency. In this report, we review the causes of renal insufficiency in the pretransplantation population and the impact of this insufficiency on survival while patients await liver transplantation. We then examine the impact of liver transplantation on renal function and the impact of renal failure at the time of transplantation on survival following transplantation. The role of simultaneous liver/kidney transplantation is also reviewed. Finally, post-liver transplantation renal function is reviewed, as is the impact of antirejection drugs on renal function.

Acute Kidney Injury and Chronic Kidney Disease in the Patient with Cirrhosis Awaiting Liver Transplantation

Renal insufficiency is common in patients awaiting liver transplantation, and the potential causes are shown in Table 1. One report found acute kidney injury (AKI) in 19% of hospitalized patients with cirrhosis, and among those patients AKI was prerenal in 68% and intrarenal in 32%.¹ About half of the patients with prerenal AKI had hepatorenal syndrome (HRS). Also shown in Table 1 are the intrinsic causes of renal disease in the population of patients with cirrhosis. With the epidemic of obesity and diabetes in the United States, increasing numbers of patients with nonalcoholic steatohepatitis also have diabetic nephropathy. The only form of AKI that clearly improves due to liver transplantation is HRS. All of the other forms of AKI follow an uncertain course depending on the etiology of the renal insufficiency. Successful treatment of hepatitis B and C can lead to resolution of the renal injury due to these infections.

Diabetic nephropathy may worsen posttransplantation due to the nephrotoxicity of calcineurin inhibitors and the effects of these drugs on blood pressure and glucose tolerance.

Effect of Renal Insufficiency on Pre- and Posttransplantation Survival and Outcomes

Patients with decreased glomerular filtration rates (GFRs) have an increase in mortality while waiting for liver transplantation. Hyponatremia, also thought to reflect kidney dysfunction, increases the risk of death for this group of patients as well.² Patients with renal dysfunction following liver transplantation have more prolonged hospital stays and are more likely to suffer from chronic kidney disease. In addition, the development of chronic kidney disease increases the risk of dying post-liver transplantation.³ A better understanding of the causes of AKI pretransplantation as well as better prediction metrics for reversibility of these processes before and after transplantation is needed to improve outcomes.

Management of HRS Pretransplantation, Effect of Liver Transplantation on Renal Function and Survival, and Role of Liver/Kidney Transplantation

HRS is common in the decompensated patient with cirrhosis and its development, especially HRS type 1, is associated with a high mortality. Use of albumin in patients undergoing large volume paracentesis and those with spontaneous bacterial peritonitis will reduce the incidence of HRS type 1, and the use of prophylactic antibiotics following a variceal bleed is likely to reduce the risk of developing HRS type 1. Several studies have shown that terlipressin, when used in combination with albumin, resolves HRS in approximately one third of patients (significantly better than placebo) and leads to an improvement in survival in those who respond.^{4,5} Patients who do not respond to terlipressin have a poor prognosis.

Abbreviations: AKI, acute kidney injury; CNI, calcineurin inhibitors; GFR, glomerular filtration rate; HRS, hepatorenal syndrome; mTOR, mammalian target of rapamycin; RRT, renal replacement therapy.

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TABLE 1: Causes of Renal Failure in Cirrhosis

AKI
Prerenal
Infection
Hypovolemia
HRS (types 1 and 2)*
Intrarenal
Acute tubular necrosis
Acute glomerulonephritis
Drug injury (contrast and antibiotics)
Chronic kidney disease
Diabetic nephropathy [†]
HCV-MPGN [‡] , [*]
HBV-MPGN [‡] , [*]
IgA nephropathy

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; IgA, immunoglobulin A; MPGN, membranoproliferative glomerulonephritis.

*Renal injury may resolve due to liver transplantation.

[†]Renal injury may resolve following successful treatment of the viral infection.

[‡]Renal injury may worsen following transplantation due to nephrotoxicity of antirejection medications.

FIGURE 1. Graph shows 180-day survival for HRS type 1 following use of albumin and terlipressin without (NR) or with (R) HRS reversal or liver transplantation (OLTx).⁶

Successful liver transplantation in patients with HRS type 1 dramatically improves survival (>90% at 90 days) compared with patients who do not undergo transplantation (mortality >90% at 90 days) (Fig. 1).⁶ Renal function also improves in most patients with HRS-1 following liver transplantation.⁷

Several studies have examined what factors predict the recovery of renal function post-liver transplantation. Consistently, the duration of renal replacement therapy (RRT) pre-transplantation is inversely associated with post-transplantation renal recovery. An analysis of the United Network for Organ Sharing database revealed that 70% of patients on RRT for <30 days were able to come off dialysis following liver transplantation, whereas that number fell to 11% if RRT exceeded 90 days.⁸ The United Network for Organ Sharing recommendations as to who should receive a simultaneous liver/kidney transplantation include: patients with end-stage renal disease, patients with chronic kidney disease with GFR ≤ 30 mL/minute, patients with AKI with creatinine ≥ 2.0 mg/dL and who are on dialysis ≥ 8 weeks, and lastly cirrhotics

TABLE 2: Nephrotoxicity of Agents Used Posttransplantation

Agent	Mechanism(s) of Nephrotoxicity
CNI (cyclosporine and tacrolimus)	Reversible afferent vasoconstriction leading to decreased renal blood flow and GFR Tubular defects in potassium secretion Phosphorous leak Irreversible interstitial fibrosis Worsening of hypertension, diabetes (indirect)
mTOR inhibitors (sirolimus and everolimus)	Worsening of proteinuria (direct podocyte toxicity) Accentuation of CNI toxicity via both hemodynamic effects and fibrosis
Trimethoprim	Decrease in creatinine secretion Na ⁺ channel blockade leading to impaired potassium secretion
Acyclovir	Crystal nephropathy

who have biopsy evidence of significant chronic renal injury.⁹ However, most centers in the United States do not follow these recommendations in patients with AKI. In addition, the data on the benefits of simultaneous liver/kidney transplantation are inconsistent.^{9,10} Given the lack of true discriminatory predictive parameters for recovery of renal function and the lack of definitive studies on the benefit of simultaneous liver/kidney transplantation, well-designed prospective studies are urgently needed to advance our understanding of these two issues.

Posttransplantation Renal Dysfunction and Effect of Drugs

Posttransplantation renal dysfunction is common and has adverse effects on the patient's quality of life and survival. Several drugs routinely given post-liver transplantation can contribute to renal dysfunction (Table 2). The calcineurin inhibitors (CNIs) tacrolimus and cyclosporine can cause a reversible decrease in renal blood flow and GFR. This reversible effect is caused by relative afferent glomerular vasoconstriction. This physiologic effect is somewhat concentration-related and is, for the most part, fully reversible. Use of CNIs can also be associated with progressive renal interstitial fibrosis and tubular dropout. This toxicity may be accelerated if there is underlying renal pathology. CNIs can also indirectly play a part in renal dysfunction by inducing hypertension and glucose dysregulation.¹¹

The mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus have been shown to prolong recovery from ischemia/reperfusion injury, possibly due to an inhibition of epithelial and endothelial growth factors. mTOR inhibitors, aside from their direct effects, accentuate CNI toxicity via unclear mechanisms. The combination of a CNI and mTOR inhibitor leads to a greater decrement in GFR than a CNI alone, and in animal models, increases CNI-associated renal fibrosis. Finally, mTOR inhibitors are associated with proteinuria and significant worsening of preexisting

proteinuria. This may be associated with direct podocyte toxicity or indirectly by impairing glomerular vascular repair. Patients with proteinuria should not be placed on an mTOR inhibitor except in extraordinary circumstances.¹²

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