CHAPTER 129

# Kidney Dysfunction After Liver Transplantation

*Phuong-Thu Pham, Theodore M. Sievers, and Phuong-Chi Pham*

**OBJECTIVES**

This chapter will:

1. Present the risk factors for early postoperative acute kidney injury after orthotopic liver transplantation (OLT), including pre-OLT, intraoperative factors, and post-OLT factors.
2. Present the factors affecting renal dysfunction in long-term survivors.
3. Suggest strategies to reduce risk factors.

Acute kidney injury (AKI) is common immediately after orthotopic liver transplantation (OLT), whereas chronic kidney disease (CKD) and end-stage renal disease (ESRD) increase in incidence with time. The cumulative risk of developing chronic renal failure post-OLT has been described to be approximately 8%, 14%, and 18% at 12, 36, and 60 months, respectively. Therefore identifying the risk factors for AKI or progressive CKD after OLT and developing strategies to either minimize the risks for AKI or retard the progression of CKD should be an integral part in the management of OLT recipients. Assessment of renal function pre- and post-OLT and an overview of the literature on the risk factors for early postoperative AKI and those affecting progressive CKD in long-term survivors are presented. Suggested therapeutic approaches to prevent, halt, or ameliorate renal dysfunction are also discussed.

## ASSESSMENT OF RENAL FUNCTION BEFORE AND AFTER LIVER TRANSPLANTATION

Although serum creatinine (SCr) is readily accessible in routine clinical practice, assessment of renal function in patients with liver cirrhosis based on serum creatinine (SCr) or creatinine-based equations overestimates true glomerular filtration rate (GFR), particularly in those with more severe renal dysfunction or more severe liver disease. In recent years, cystatin C (CystC) has been studied extensively as an alternative endogenous marker of kidney function in cirrhotic patients because it is independent of muscle mass. In a study comparing the performance of various creatinine (creat) and CystC-based GFR-predicting equations in OLT candidates (including CKD-EPI (creat), CKD-EPI (CystC), and CKD-EPI (creat-CystC) and the 4- and 6-variable Modification of Diet in Renal Disease (MDRD) and Hoek formulas), De Souza et al.[1] demonstrated that CystC-based had a better performance than creatinine-based equations, with CKD-EPI (CystC) equation showing the best performance regardless of the severity of ascites and in the presence of significant renal dysfunction defined as GFR less than 60 mL/min. In a small Japanese study of 14 cirrhotic patients, Adachi et al.[2] similarly demonstrated that CystC-based GFR-estimating equations had better performances compared with creatinine-based equations in terms of bias, precision, and accuracy. However, the superior performance of CystC over creatinine in cirrhotic patients with GFR less than 80 mL/min has not been demonstrated consistently.[3]

Similar to the cirrhotic population, CystC also has been suggested to be a more accurate filtration marker than creatinine among OLT recipients. In a study to evaluate whether the addition of CystC improves GFR estimation compared with various GFR estimating equations, Allen et al.[4] demonstrated that CystC-based equations had superior performance in GFR estimation compared with creatinine-based equations, whereas CKD-EPI (creat-CystC) outperformed those with either marker alone. A total of 586 iothalamate-measured GFR in 401 OLT recipients were available for analysis. Of the five GFR estimation equations examined, CKD-EPI (creat-CystC) was shown to have the highest coefficient of determination ($R^2$ of 0.83), followed by CKD-EPI (CystC) ($R^2$ of 0.78), MDRD-6 ($R^2$ of 0.77), and MDRD-4 and CKD-EPI (creat) ($R^2$ of 0.76 for both). Nonetheless, the CKD-EPI (creat-CystC) formula still underestimated measured GFR by approximately 12%, particularly in low GFR groups.

Although not yet readily available in many centers, CystC-based equations may enable clinicians to more accurately assess renal function in OLT candidates and recipients. However, CystC levels may be increased in high cell turnover states (such as hyperthyroidism, steroid use, and malignancy), advanced age, gender and ethnicity, fat mass, and diabetes, among others. Although more costly and complicated, traditional studies evaluating the renal

clearance of inulin or radioisotopes such as iothalamate remain the gold standard for evaluating renal function in patients with liver cirrhosis and in OLT recipients.

## RISK FACTORS FOR EARLY POSTOPERATIVE ACUTE KIDNEY INJURY AFTER ORTHOTOPIC LIVER TRANSPLANTATION

AKI has been reported to develop in 17% to 95% of OLT recipients, whereas severe AKI requiring perioperative renal replacement therapy occurred in 5% to 35% of patients.[5,6] The broad range in the incidence reported may be due to, in part, the lack of standardized definitions of AKI among studies. In one study consisting of 424 OLT recipients, AKI within the first 3 days after transplantation occurred in 52% of patients.[7] The former was defined as "50% increase in serum creatinine from preoperative baseline value or a 26.5 μmol/L increase from baseline within 48 hours without urine output."[7]

Although the risk factors for AKI are often multifactorial and difficult to establish, they can be linked to three distinct time frames in relation to the OLT: the pre-OLT, intraoperative, and post-OLT periods (discussed later in this chapter). Table 129.1 and Box 129.1 summarize suggested risk factors for early postoperative AKI and strategies to reduce risk factors.

### Pretransplantation Risk Factors

Pretransplantation renal dysfunction and hepatorenal syndrome (HRS) are well-established risk factors for posttransplantation AKI. Other suggested risk factors include higher serum bilirubin levels, hypoproteinemia, hypoalbuminemia, hyponatremia, viral hepatitis, high serum lactate levels, and severity of liver disease as reflected by the Child-Pugh or Model for End-stage Liver Disease (MELD) scores. The Organ Procurement and Transplantation Network recently has incorporated sodium into the MELD score. As of January 2016, the MELD-Na score is employed in the liver allocation system in the United States. Selected studies evaluating potential pretransplant risk factors for postoperative AKI and suggested pathogenic mechanisms are discussed.

#### *Hyponatremia*

The presence of hyponatremia, defined as a serum sodium level below 130 mEq/L at the time of transplantation, has been suggested to be associated with a high rate of complications after OLT, including neurologic disorders,

**TABLE 129.1**

**Risk Factors for Acute Kidney Injury in the Early Postorthotopic Liver Transplantation Period**

| RISK FACTORS | COMMENTS |
|---|---|
| **Pretransplantation Factors** | |
| • Pretransplantation renal dysfunction | • Bile cast-associated AKI is thought to be due to direct bile and bilirubin toxicity and tubular obstruction |
| • Hepatorenal syndrome | • Hypoalbuminemia may alter the pharmacokinetics of potentially nephrotoxic drugs, thereby increasing AKI risk |
| • High serum bilirubin levels | • High lactate levels may reflect hemodynamic instability or more severe liver disease, both of which may be associated with poor renal hemodynamics and AKI |
| • Hypoproteinemia | • Whether undiagnosed viral glomerulonephritis plays a role in the development of AKI is speculative |
| • Hypoalbuminemia | |
| • Hyponatremia | |
| • High serum lactate levels | |
| • Severity of liver disease as reflected by Child-Pugh or MELD scores | |
| • Viral hepatitis | |
| **Intraoperative Factors** | |
| • Hemodynamic instability during anesthesia induction and anhepatic phase | • The 2013 Cochrane database systematic review shows no reliable evidence that interventions during surgery provide a renoprotective effect |
| • Intraoperative bleeding and volume of transfused blood products | |
| • Standard surgical technique (with or without VVB) vs. piggyback technique (not consistently demonstrated, see comments) | |
| • Conventional risk factors (see text) | |
| **Postoperative Factors** | |
| • Acute tubular necrosis (ATN) | • Factors predisposing to ATN: ischemic or toxic insults (prolonged hypotension, sustained prerenal AKI, nephrotoxic drugs), sepsis |
| • Delayed liver graft function or primary nonfunction | • Reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radical released by donor liver with prolonged warm ischemia time may play a contributory role in the development of AKI |
| • Postreperfusion syndrome (ischemia-reperfusion injury) | • Drug-induced tubulointerstitial nephritis generally occurs in the setting of polypharmacy (e.g., simultaneous use of multiple antibiotics) |
| • Contrast nephropathy | • Intraabdominal hypertension from fluid accumulation, inflammation, bleed may lead to abdominal compartment syndrome with reduced renal perfusion and AKI |
| • Drug-induced tubulointerstitial nephritis | • Therapeutic drug monitoring of CNIs to minimize systemic overexposure |
| • Calcineurin inhibitor therapy | |
| • Prolonged use of dopamine or vasopressors | |
| • Perioperative volume of transfused blood products | |
| • Repeat laparotomy | |
| • Bacterial infection, sepsis | |
| • Intraabdominal hypertension | |
| • Donor liver with prolonged warm ischemia time | |

*AKI,* Acute kidney injury; *CNI,* calcineurin inhibitor; *MELD,* Model for End-stage Liver Disease; *VVB,* venovenous bypass.

**BOX 129.1**

**Strategies to Reduce Risk Factors**

**Pretransplantation**
- Risks and benefits of diuretics, lactulose, contrast dye exposure, nephrotoxic drugs, and NSAIDs should be weighed against the risk of precipitating HRS
- Use of plasma expanders in large-volume paracentesis is recommended (particularly in patients with severe hypoalbuminemia or ascites without peripheral edema)
  - In general, albumin is suggested to be more effective than artificial plasma expanders. Recommended dose: 1 g per kg body weight of 25% albumin (up to 100 g/day)
  - Albumin infusion in SBP may reduce HRS risk. Recommended dose: 1.5 g/kg at diagnosis of SBP and 1 g/kg IV 48 hours later

**Intraoperative**
- Control of bleeding during surgery
- Careful attention to fluid and electrolyte management
- Avoidance of hypotensive episodes

**Postoperative**
- Bleeding and infectious complications should be sought and treated aggressively
- Avoid use of contrast studies or nephrotoxic drugs if possible
- Manipulation of immunosuppression:
  - Early postoperative period: Consider antibody induction in patients with preexisting HRS or pretransplantation renal dysfunction (see also Table 129.6).
  - Late postoperative period: CNI minimization or withdrawal protocols (see Table 129.6)

*CNI,* calcineurin inhibitor; *HRS,* hepatorenal syndrome; *NSAIDs,* nonsteroidal antiinflammatory drugs; *SBP,* spontaneous bacterial peritonitis.

infectious complications, and AKI during the first month after transplantation.[8] It is well established that the presence of hyponatremia identifies a group of patients with cirrhosis who have severe impairment in circulatory function. The latter may act in concert with the intraoperative and perioperative hemodynamic changes to increase the risk of postoperative AKI.

In a single-center retrospective study consisting of 134 OLT recipients, AKI occurred in nearly half of patients (46.7%) in the postoperative period. Serum sodium was lower in the AKI compared with the non-AKI groups ($p = .02$). Viral hepatitis, longer warm ischemia time, and high levels of serum lactate were found to be risk factors for AKI, whereas a high MELD-Na score is a predictor for hemodialysis need.[9] A greater than eightfold increase in posttransplant hemodialysis need was observed among patients with a MELD-Na score *of at least* 22 (OR 8.4, 95% CI = 1.5–46.5). Among OLT recipients with viral liver disease, it is speculated that undiagnosed viral glomerulonephritis and superimposed hemodynamic instability may play a causative role in the development of AKI after OLT. In a small series of 30 OLT recipients with hepatitis C who underwent intraoperative kidney biopsy, membranoproliferative glomerulonephritis was found in 12, IgA nephropathy in 7, and mesangial glomerulonephritis in 6.[10]

## Hypoalbuminemia

A meta-analysis of observational clinical studies demonstrated that lower serum albumin was an independent predictor of AKI and death after AKI development.[11] The odds of AKI development in association with low serum albumin were more than doubled among the six studies of surgical or intensive care unit patients and nearly tripled among studies in other hospital settings. For every 10 g/L decrement in serum albumin, the odds of developing AKI increased by 134% (CI 1.74–3.14).

The mechanisms whereby low serum albumin increases the risk of postoperative AKI remain unclear. Nonetheless, it has been suggested that hypoalbuminemia modifies Starling's forces in the systemic capillaries and results in the reduction of GFR.[12] Hypoalbuminemia also has been suggested to alter the pharmacokinetics of potentially nephrotoxic drugs, thereby increasing the risk of AKI. In a prospective study consisting of 104 patients treated with intravenous amikacin for at least 36 hours, low serum albumin was found to be associated with amikacin accumulation in the plasma and an increased risk of nephrotoxicity.[13] It is speculated that specific ligand-binding properties of albumin may mediate renoprotection in patients treated with nephrotoxic drugs.

## Hyperbilirubinemia

The association between high serum bilirubin level and postoperative AKI has long been recognized. The spectrum of cholemic nephrosis ranges from proximal tubulopathy to bile cast nephropathy. In a clinicopathologic study of 44 jaundiced subjects (41 autopsies and 3 kidney biopsies), 18 had bile casts involving distal nephron segments and 6 had extension to proximal tubules. Eleven of 13 patients with HRS and all 10 with alcohol-related cirrhosis had tubular bile casts. A significant correlation was found between these casts and higher serum total and direct bilirubin levels ($p = .0001$ and $p = .003$, respectively). Furthermore, a trend toward higher serum creatinine, aspartate transaminase, and alanine transaminase levels were observed among patients with bile casts compared with those without. It is suggested that bile cast–associated AKI is due to direct bile and bilirubin toxicity and tubular obstruction analogous to that observed with myeloma or myoglobin casts.[14]

## Liver Disease Severity

In a retrospective study consisting of more than 600 recipients of liver-only transplants, Sanchez et al.[15] demonstrated that MELD scores greater than 21 were significant predictive indicators of the need for renal replacement therapy after OLT. The association between MELD score and severe AKI also was demonstrated by others. In a retrospective study consisting of 153 OLT recipients, hepatic encephalopathy, deceased donor liver transplant (compared with living donor transplant), MELD score, and intraoperative blood loss were found to be independent predictive factors for postoperative continuous renal replacement therapy.[16] A more favorable renal outcome was observed among OLT recipients with hepatocellular carcinoma (HCC) as the indication for OLT. The study findings suggest that liver disease severity as reflected by high MELD score portends a worse renal prognosis. OLT recipients with HCC generally had preserved liver function and a lower MELD score than OLT recipients with end-stage liver disease. Similarly, living donor liver transplant recipients had a lower MELD score and a lower incidence of AKI compared with their deceased donor transplant counterparts.

**TABLE 129.2**

**Predictive and Precipitating Factors for the Development of Hepatorenal Syndrome and Proposed Preventive Measures**

| PREDICTIVE AND PRECIPITATING FACTORS | PREVENTIVE MEASURES |
|---|---|
| **Predictive Factors**<br>• Hyponatremia < 133 mEq/L<br>• High MELD score<br>• Arterial hypotension (mean arterial pressure <85 mm Hg)<br>• Elevated neurohormones<br>  • Plasma renin activity<br>  • Aldosterone<br>  • Norepinephrine levels<br>• Poor cardiac output (<6.0 L/min)<br>• Elevated intrarenal resistive index<br>**Precipitating Factors**<br>• Infections (bacterial infection, predominantly SBP)<br>• Large volume paracentesis without albumin support<br>• Acute alcoholic hepatitis<br>• +/– Gastrointestinal (GI) bleed | • Albumin infusion at diagnosis of SBP<br>• SBP prophylaxis with quinolones<br>  • Short-term prophylaxis in acute GI bleed<br>  • Long-term prophylaxis in patients with history of SBP<br>• Albumin support with large volume paracentesis (>5 L)<br>• Pentoxifylline administration<br>• Proton pump inhibitors or low-dose Beta-blockers or both, where clinically indicated |

*SBP,* spontaneous bacterial peritonitis.

## Strategies to Reduce Pretransplantation Risk Factors

Every effort should be made to prevent or minimize the risk of developing pretransplantation AKI or HRS. Suggested predictive and precipitating factors for the development of HRS and proposed preventive measures are shown in Table 129.2.[17] The potential benefits of diuretics, lactulose, contrast dye exposure, nephrotoxic medications, and nonsteroidal antiinflammatory drugs must be balanced carefully against the risk of precipitating HRS. Large-volume paracentesis in patients with severe hypoalbuminemia or ascites without peripheral edema has been suggested to increase the risk for the development of acute volume depletion and potential HRS. In such cases, the use of plasma expanders has been advocated. In general, albumin has been suggested to be more effective than artificial plasma expanders in the prevention of circulatory dysfunction.[18] The recommended dose of albumin is 1 g per kg body weight of 25% albumin (up to 100 g/day). The use of albumin infusion in cirrhotic patients with spontaneous bacterial peritonitis (SBP) also has been suggested to reduce mortality and HRS risk, especially among those with renal dysfunction and hyperbilirubinemia at presentation. Albumin infusion at a dose of 1.5 g per kg body weight at diagnosis of SBP and 1 g/kg intravenously 48 hours later is recommended.

### *Studies Evaluating the Renoprotective Effect of Terlipressin (Not Available in the United States or Canada)*

Terlipressin is a vasopressin analogue that can improve hemodynamics and GFRs in patients with HRS. In early studies, it demonstrated utility when used as a bridge to maintain renal function until liver transplantation.[19]

Results of the REVERSE study (a large, phase 3, multicenter, randomized, double-blind, placebo-controlled trial) demonstrated that terlipressin plus albumin was more effective than albumin alone in improving renal function in patients with cirrhosis and type 1 HRS. A significant decrease in SCr from baseline to end of treatment was observed among terlipressin- versus placebo-treated patients. SCr decreased by 1.1 mg/dL in the terlipressin compared with 0.6 mg/dL in the placebo-treated groups, respectively ($p < .001$). The incidence of confirmed HRS reversal was higher in the terlipressin versus the placebo group, although this did not achieve statistical significance (19.6% vs. 13.1%, $p = .22$).[20]

In a prospective, randomized, open-label study of 200 cirrhotic patients with SBP and bilirubin exceeding 4 mg/dL or creatinine exceeding 1 mg/dL, Salman et al.[21] demonstrated no significant difference in renal impairment or mortality among patients randomized to receive albumin (n = 50), terlipressin (n = 50), low-dose albumin + terlipressin (n = 50), or midodrine (n = 50). Renal impairment was defined as a more than 50% increase in blood urea nitrogen (BUN) or serum creatinine levels from the pretreatment values. Terlipressin alone or terlipressin in combination with low-dose albumin was associated with improvement in systemic, renal, and splanchnic hemodynamics. Terlipressin and albumin + terlipressin were associated with decreased cardiac output and portal flow, and increased systemic vascular resistance compared with albumin after 3 and 10 days. In contrast, no significant changes in heart rate, mean arterial pressure, cardiac output, or portal blood flow were observed in the midodrine group compared with the albumin group after 3 or 10 days. Furthermore, plasma renin activity, renal, and hepatic arteries resistive index were significantly higher in the midodrine group compared with the albumin group after 10 days. It was concluded that terlipressin and low-dose albumin + terlipressin may be a reasonable therapeutic alternative to standard-dose albumin in high-risk SBP patients. Further studies are needed.

## Intraoperative Risk Factors

Cross-clamping of the portal vein and inferior vena cava during the anhepatic phase (phase II) interrupts the venous return from the lower extremities and splanchnic bed and may result in decreased cardiac output and blood pressure, increased systemic vascular resistance, and reduced perfusion to vital organs. The latter may lead to renal hypoperfusion and potential ischemic kidney injury. Although venovenous bypass (VVB) has been shown to improve or restore normal hemodynamic physiology during

the anhepatic phase, the use of VVB has not been shown consistently to decrease the incidence of perioperative or early postoperative AKI.[22–23] In one single-center study, the degree of renal dysfunction (assessed by inulin clearance) measured at various perioperative periods (anesthesia induction, hepatectomy, anhepatic phase, biliary anastomosis, and 24 hours after surgery) was not significantly different between OLT recipients randomized to receive VVB support or no VVB support at any time point, with the exception of the anhepatic phase, which demonstrated a more marked renal function impairment in patients without VVB support. Nevertheless, renal function on postoperative day 7 and the need for hemodialysis/hemofiltration during the first week were similar in both groups. Multivariate analysis revealed that low mean arterial pressure at anesthesia induction was an independent risk factor for early postoperative severe AKI.[23] Cabezuelo et al.[24] showed that, compared with the standard surgical technique (with or without VVB), the piggyback technique significantly reduces the probability of AKI after liver transplantation. It is speculated that this is partly due to the reduction in retroperitoneal blood loss, because the piggyback technique does not require retrocaval dissection. In addition, it permits venous return to the heart during the anhepatic phase and avoids hemodynamic variation during inferior vena cava clamping. In a retrospective study conducted to evaluate the clinical outcome of three different surgical techniques, including retrohepatic caval resection (RCV) with VVB (RCV + VVB; n = 104), piggyback without VVB (PB-only; n = 174), Sakai et al.[25] similarly demonstrated a lower incidence of AKI ($p$ = .0001) and better patient and graft survival in the PB-only group. A small prospective randomized trial designed to compare the hepatic venous outflow and renal function between patients transplanted by the conventional (n = 15) or piggyback (n = 17) method showed a higher prevalence of severe AKI during the first 28 postoperative day among those transplanted using the conventional method with VVB (OR = 3.207, $p$ = .048).[26]

Although large, prospective clinical trials are lacking, it is conceivable that intraoperative risk factors for the development of perioperative and early postoperative AKI in OLT are similar to those in other surgical settings. These may include an anesthesia-induced decrease in effective blood volume, preexisting cardiovascular disease or severe cardiomyopathy, prolonged episode of hemodynamic instability or hypotension, severe intravascular volume depletion, use of drugs that can adversely affect intrarenal hemodynamics, older age, preexisting renal dysfunction, and diabetes mellitus. In this respect, hemodynamic instability associated with a prolonged anhepatic phase and major bleeding during hepatectomy potentially can predispose patients undergoing OLT to postoperative AKI.

## *Strategies to Reduce Intraoperative Risk Factors*

In a single-center study consisting of 40 living-donor liver transplant patients randomized to receive either hydroxyethyl starch (HES) or albumin intraoperatively and during the first 4 days post-OLT, Mukhtar et al.[27] demonstrated comparable renal outcomes and safety between the two treatment groups. However, in a subsequent retrospective study consisting of 174 patients who underwent OLT, Hand et al.[28] showed that administration of HES resulted in nearly threefold increase in AKI risk compared with albumin (adjusted OR 2.94, $p$ = .027). Propensity-matched analysis similarly demonstrated that HES-treated patients had increased odds (1.18) of developing AKI compared with their albumin-treated counterparts ($p$ = .044). Therefore the use of HES is not recommended in critically ill patients, including those with sepsis or severe liver disease because of increased mortality and risk of AKI requiring renal replacement. Whether use of the piggyback technique, as opposed to the standard surgical technique (with or without VVB), significantly reduces the probability of AKI after liver transplantation remains speculative. In recent years, most centers advocate the use of piggyback alone without VVB.

The 2013 Cochrane review showed a lack of a renoprotective effect of various pharmacologic agents and surgical techniques. The former includes dopamine and its analogues, diuretics, calcium channel blockers, ACE inhibitors, N-acetylcysteine, atrial natriuretic peptide, sodium bicarbonate, antioxidants, erythropoietin, and selected hydration fluids. It was concluded that there is no reliable evidence from the available literature to suggest that interventions during surgery can protect the kidneys from damage.[29]

## *Authors' Perspective*

Evidence-based intraoperative interventions to prevent or ameliorate AKI post-OLT are lacking. Nonetheless, control of bleeding during surgery, careful attention to management of fluid and electrolytes, and avoidance of hypotensive episodes may protect the kidneys from hemodynamically mediated ischemic injury.

## Postoperative Risk Factors

Factors that have been shown to cause or predispose OLT recipients to postoperative AKI, particularly acute tubular necrosis (ATN), include ischemic or toxic insult to the kidneys, prolonged hypotension, sepsis, sustained prerenal AKI, the use of nephrotoxic drugs, contrast nephropathy, delayed liver graft function or primary graft nonfunction, and postreperfusion syndrome or ischemia-reperfusion injury. It is suggested that reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radical released by donor livers with prolonged warm ischemia time play a contributory role in the development of AKI.[30] Other suggested predictive factors include prolonged treatment with dopamine or vasopressors, repeat laparotomy, intraabdominal hypertension, and perioperative volume of transfused blood products. The use of cyclosporine or tacrolimus in the posttransplantation period may exacerbate further renal dysfunction. Finally, polypharmacy, and specifically the use of multiple antibiotics, may contribute to postoperative AKI because of drug-induced tubulointerstitial nephritis.

## *Strategies to Reduce Postoperative Risk Factors*

Bleeding and infectious complications in the perioperative period should be sought and treated aggressively. The use of contrast studies or nephrotoxic drugs should be minimized or avoided.

Therapeutic approaches in the postoperative period should be modified in patients with preexisting HRS or pretransplantation renal dysfunction. The cornerstone of postoperative immunosuppression in liver transplantation involves the use of calcineurin inhibitors (CNIs). The nephrotoxicity associated with CNI therapy has acute and chronic effects with associated histopathologic changes.[31] Tacrolimus appears to have less nephrotoxicity

than cyclosporine A.[32] Genetic polymorphisms of CYP3A5 and ABCB1 may play a role in CNI nephrotoxicity.[33] Systemic overexposure to CNIs is a recognized risk factor for the development of acute and chronic nephrotoxicity. To address this, immunosuppressive regimens have been developed in an attempt to provide immunoprotection while minimizing or eliminating the use of CNIs to avoid the associated acute and chronic nephrotoxicity. The use of CNI-sparing protocols to reduce postoperative AKI has met with variable results. The following section presents an overview of the literature and the authors' perspective on the use of various immunosuppressive strategies to prevent postoperative AKI.

## CNI-Sparing Protocols in the Immediate Postoperative Period

**POLYCLONAL INDUCTION THERAPY.** In a retrospective analysis consisting of 298 OLT recipients, Tchervenkov et al.[34] demonstrated that thymoglobulin induction was associated with a lower SCr at 6 months and a higher rejection-free graft survival rate at 1-year compared with no-thymoglobulin induction group, and its use allowed delayed introduction of CNI (mean 9.5 vs. 6.3 days, respectively, $p < .001$). The median baseline SCr for thymoglobulin and no-thymoglobulin induction groups were 0.97 and 0.95 mg/dL, respectively ($p$ = NS). Corresponding SCr at 6 months posttransplant were 1.39 versus 1.56 mg/dL, respectively ($p = .14$). Soliman et al.[35] similarly demonstrated that antithymocyte globulin (ATG) induction and delayed introduction of CNI (started on the evening of the third day of ATG administration, n = 262) had a salutary effect on renal function compared with CNI initiation in the immediate post-OLT period (no-ATG group, n = 129). SCr at transplantation was similar between the two groups. At 1-year follow-up renal function was significantly better in the ATG compared with the no-ATG groups (GFR were 81 mL/min vs. 75 mL/min, respectively, $p = .02$). Furthermore, ATG compared with no-ATG induction was associated with a more favorable rejection rate (14.5% vs. 31.8%, respectively, $p = .0008$). Five-year patient survival and adverse effects were comparable between the two treatment groups.

**MONOCLONAL INDUCTION THERAPY.** In a Canadian multicenter, randomized trial consisting of 148 OLT recipients randomized to receive either induction therapy with daclizumab and delayed introduction of low-dose tacrolimus (Tac) on postoperative day 4 to 6 (Tac trough level 4–8 ng/mL) or standard Tac dosing regimen (target trough level 10–15 ng/mL for the first month, and 4–8 ng/mL thereafter), significant improvement in eGFR was observed among daclizumab induction and delayed low-dose Tac compared with standard dose Tac group at 1- and 6-month follow-up. All patients received mycophenolate mofetil (MMF) and corticosteroid maintenance therapy. Baseline eGFRs by MDRD were comparable between the two treatment arms. The eGFRs by MDRD for the daclizumab induction versus standard Tac groups at 1- and 6-month follow-up were 86.8 versus 70.1 mL/min/1.73 $m^2$ at 1 month, $p < .001$, and 75.4 versus 69.5 mL/min/1.73 $m^2$, $p = .038$, respectively.[36] The findings were validated in the European multicenter, prospective, randomized, open-label trial (The ReSpECT Study). Adult patients with SCr of 200 µmol/L or less undergoing primary OLT were randomized to either group A (standard dose Tac with target trough levels >10 ng/mL + corticosteroids, n = 183), group B (MMF 2 g/day, reduced-dose Tac with target trough levels ≤8 ng/mL + corticosteroids; n = 170), or group C (daclizumab induction, MMF, reduced-dose Tac delayed until the fifth day posttransplant + corticosteroids, n = 172). At 52 weeks posttransplant, daclizumab induction, MMF, corticosteroids, and delayed reduced-dose Tac (group C) were found to be associated with less renal function impairment than standard-dose Tac and corticosteroids immunosuppression (group A) without compromising efficacy and tolerability. In contrast, the immediate introduction of reduced-dose Tac in combination of MMF and corticosteroid (group B) offered no beneficial effect on renal function compared with standard-dose Tac and corticosteroid regimen (group A). AKI requiring dialysis was less frequent in group C versus group A (4.2% vs. 9.9%; $p = .037$).[37]

In contrast to the Canadian and ReSpECT study findings, a French multicenter trial failed to demonstrate that daclizumab induction and delayed administration of Tac (post-OLT day 5) offered a beneficial effect on renal function compared with standard Tac (postoperative day 0) among OLT recipients with baseline creatinine of 180 µmol/L or less. Patients were randomized in a 1:1 ratio to receive either delayed Tac, daclizumab, MMF, and steroids (delayed Tac, n = 98) or standard Tac (post-OLT day 0), MMF, and steroids (standard Tac, n = 101). There were no significant differences in the mean eGFRs between the two treatment arms at 6, 12, and 24 months. Biopsy-proven acute rejection rates, and patient and graft survival rates were comparable between the two groups.[38] However, in the current study tacrolimus dosing was similar between the "delayed Tac" and "standard Tac" groups, whereas in the Canadian and ReSpECT trials delayed reduced-dose Tac was used. Delayed administration of CNI and CNI-dose reduction may be essential to preserve renal function.

In conclusion, the literature overview suggests that daclizumab induction in combination with delayed low-dose tacrolimus and MMF preserves early renal function after OLT without compromising immunoprotection. However, daclizumab was withdrawn from the European and U.S. markets. Currently, the monoclonal anti-IL2 receptor blocker basiliximab is used for induction therapy after solid organ transplantation.

## Mycophenolate Mofetil and Early CNI-Minimization Protocol

In a multicenter randomized study consisting of 195 adults undergoing primary deceased donor liver transplantation, patients randomized to receive reduced-dose Tac in combination with MMF (experimental arm, n = 95) had a lower incidence of renal dysfunction and acute rejection compared with those receiving standard-dose Tac (control arm, n = 100). All patients received corticosteroids. At 48 weeks post-OLT renal dysfunction occurred in 24% and 42% of patients in experimental and control groups, respectively (HR = 0.49; 95% CI: [0.29–0.81]; $p = .004$), and acute graft rejection occurred in 30% and 46% of patients, respectively (HR = 0.59, $p = .024$). The study was stopped after 195 patients had been enrolled because of slow recruitment rates and significant between-group differences in acute rejection rates. It was concluded that reduced-dose Tac in combination with MMF could replace full-dose Tac in adult liver transplantation.[39]

## De Novo Use of Sirolimus (or mTOR Inhibitors) in CNI-Minimization Protocol

A phase II international multicenter, prospective, open-label, active-controlled randomized trial demonstrated that de novo

sirolimus (loading dose: 15 mg, initial dose: 5 mg titrated to a trough of 4–11 ng/mL) in combination with reduced-dose Tac (trough: 3–7 ng/mL) after liver transplantation was associated with a significantly higher incidence of graft loss, death and sepsis, and a trend toward higher rate of hepatic artery and portal vein thrombosis compared with standard-dose Tac (trough: 7–5 ng/mL).[40] Interim analysis mandated termination of the study after 21 months. This has led the FDA to issue a black box warning for de novo use of sirolimus in the immediate or early posttransplant period.

### De Novo Use of Belatacept and CNI Avoidance

Belatacept is a selective costimulation blockade agent developed to provide effective immunosuppression while avoiding the nephrotoxic effects associated with the use of calcineurin inhibitors. Results of phase III clinical trials in kidney transplantation demonstrated that belatacept-based immunosuppression was associated with significant improvement in eGFR and patient and graft survival at 7-year follow-up compared with cyclosporine-based immunosuppression.[41] Phase II clinical trials in OLT recipients similarly demonstrated a salutary effect of belatacept compared with Tac-based immunosuppression on renal function. A total of 260 patients were randomized to receive: (1) basiliximab + belatacept high dose [HD] + MMF, (2) belatacept HD + MMF, (3) belatacept low dose (LD) + MMF, or (4) Tac + MMF, or (5) Tac alone. All patients received corticosteroids. At 6-month follow-up, a higher proportion of patients in the belatacept-treated group met the composite end point of acute rejection, graft loss, and death compared with the Tac-treated group (42%–48% vs. 15%–38%, respectively). Mean calculated GFR was 15 to 34 mL/min higher in the belatacept-treated patients at 1 year. However, follow-up beyond 12 months revealed an increase in mortality rate and graft loss in high-dose belatacept-treated groups, necessitating early termination of the study.[42] This has prompted the FDA to issue a black box warning for belatacept use in liver transplantation.

### Authors' Perspective on the Use of Immunosuppressive Strategies to Prevent Postoperative AKI

In OLT candidates with pretransplant HRS or renal dysfunction, polyclonal or monoclonal induction and delayed introduction of reduced-dose CNI (in combination with MMF and steroid maintenance therapy) have a salutary effect on renal function while providing adequate immunosuppression. Although MMF and early CNI-minimization without induction therapy confer a beneficial effect on renal function, such regimen is not without increased risk of acute rejection. Manipulation of immunosuppressive therapy to avoid nephrotoxicity should be tailored to each individual patient. Belatacept and de novo sirolimus use should be avoided in OLT recipients.

## FACTORS AFFECTING RENAL DYSFUNCTION IN LONG-TERM SURVIVORS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

Commonly suggested risk factors for the development of progressive CKD or ESRD in long-term survivors of OLT include CNI nephrotoxicity, pre-OLT HRS, preexisting renal dysfunction, duration of AKI before transplant, development of hypertension, and diabetes mellitus (before or after transplantation). Other suggested risk factors are shown in Table 129.3.[43–47] HCV infection has variably been shown to be associated with an increased risk for development of CKD. In patients undergoing transplantation for chronic hepatitis C, disease recurrence has been reported to accompany the development of HCV-associated cryoglobulinemia, leading to irreversible kidney failure. The advent of the interferon-free protease inhibitor-based regimen may improve overall and renal outcomes in OLT recipients with chronic hepatitis C. In OLT recipients with pretransplant renal dysfunction, diabetes mellitus, and type 2 HRS have been suggested to be

**TABLE 129.3**

**Factors Affecting Renal Dysfunction in Long-Term Survivors and General Management of Chronic Kidney Disease**

| RISK FACTORS | CKD MANAGEMENT |
|---|---|
| • Pretransplantation HRS<br>• Pretransplantation renal dysfunction<br>• Duration of renal dysfunction in the pretransplant period<br>• Dialysis requirement in the pre- and posttransplantation period<br>• Postoperative AKI<br>• Chronic CNI nephrotoxicity<br>• Use of nephrotoxic drugs<br>• Diabetes mellitus (preexisting or posttransplantation diabetes mellitus [a.k.a. new onset diabetes after transplantation])<br>• Hypertension<br>• Hepatitis C infection* (particularly if associated with posttransplant alcohol use)<br>• Older age<br>• Diabetes mellitus and type 2 HRS are associated with CKD progression (limited data) | **KDIGO 2012 Guidelines for CKD**<br>1. Hypertension<br>• Treat BP to ≤140/90 mm Hg for either diabetic or nondiabetic with CKD and albuminuria <30 mg/24 hr (or equivalent).<br>• Treat BP to ≤130/80 mm Hg for either diabetic or nondiabetic with CKD and albuminuria >30 mg/24 hr (or equivalent).<br>• Use an ACEI or ARB in diabetic adults with CKD and urine albumin excretion (UAE) ≥30 mg/24 hr (or equivalent).<br>• Use an ACEI or ARB in nondiabetic adults with CKD and UAE ≥30 mg/24 hr (or equivalent) in whom treatment with BP-lowering drugs is indicated.<br>2. Diabetes<br>• Maintain hemoglobin A1C ~7% as safely tolerated<br>3. Metabolic acidosis<br>• Oral bicarbonate supplement to keep serum $HCO_3^-$ ≥22 to 27 mEq/L unless contraindicated |

*ACEI,* angiotensin converting enzyme inhibitor; *AKI,* Acute kidney injury; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CKD,* chronic kidney disease; *CNI,* calcineurin inhibitor; *KDIGO,* Kidney Disease Improving Global Outcomes.
*Whether successful treatment of chronic hepatitis C with the newer Direct-Acting Antiviral agents alters renal outcome remains to be studied.

associated with CKD progression after liver transplantation, whereas co-existing diabetes and stages 3 and 4 CKD increase ESRD risk.[48] Therefore it is suggested that pretransplant diabetes status should be incorporated into future guidelines for simultaneous liver-kidney transplantation.[48] Careful selection of candidates for dual organ transplantation avoids added renal-related complications after liver transplantation.

## Strategies to Reduce Risk Factors in Long-Term Survivors

Selected studies evaluating the use of CNI-sparing protocols to prevent, ameliorate, or retard the progression of CKD are discussed. In addition to manipulation of immunosuppressive therapy, blood pressure control and aggressive management of comorbid conditions such as diabetes mellitus and dyslipidemia are recommended. Statins have been shown to be safe and effective in treating hypercholesterolemia after liver transplantation. Nonetheless, close monitoring of liver function tests after statin therapy is mandatory. Table 129.3 summarizes the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the management of hypertension, diabetes, and acidosis in CKD patients in the nontransplant setting. Studies in OLT recipients are lacking.

### *Mammalian Target of Rapamycin Inhibitors and CNI-Sparing Protocols Early After Liver Transplantation (1 to 3 Months Post-OLT)*

In the prospective, open-label, multicenter Spare the Nephron Liver trial, CNI to sirolimus (SRL) conversion therapy 4 to 12 weeks post-OLT was found to be associated with significantly greater renal function improvement from baseline compared with CNI maintenance immunosuppression. At a median follow-up of 519 days after randomization, the mean percentage change in GFR was 19.7 ± 40.6 for the SRL + MMF group (n = 148) compared with 1.2 ± 39.9 for the CNI + MMF group (n = 145), $p = .0012$. The incidence of biopsy-proven acute rejection was significantly greater in the SRL-based (12.2%) compared with the CNI-based treatment group (4.1%, $p = .02$). Graft loss (including death) occurred in 3.4% of the SRL and in 8.3% of the CNI-treated patients ($p = .04$). Malignancy-related deaths were less frequent with SRL-based group. Study withdrawal because of adverse events occurred in 34.2% of the SRL and in 24.1% of the CNI-treated patients ($p = .06$). It was concluded that SRL + MMF combination therapy is an option for liver transplant recipients who can benefit from improved renal function but is associated with an increased risk of rejection.[49]

A 3-year extension study of a prospective, multicenter, open-label trial demonstrated a durable renal benefit and lower acute rejection rates among patients randomized to start everolimus in conjunction with reduced tacrolimus exposure at 1-month post-OLT compared with those remaining on standard tacrolimus immunosuppression.[50] The study consisted of 282 de novo liver transplant patients who were randomized at day 30 to receive either (1) everolimus + reduced exposure Tac (EVR + Reduced Tac), or (2) everolimus + tacrolimus elimination (Tac elimination), or (3) standard exposure tacrolimus (Tac Control). All patients received steroids for at least 6 months per local practice. From randomization to month 36, mean eGFR rate decreased by 7.0 ± 31.3 mL/min in the EVR + Reduced Tac group, and 15.5 ± 22.7 mL/min in the Tac Control group ($p = .005$). Acute rejection occurred in 4.8% of patients in the EVR + Reduced Tac and in 9.2% of the Tac Control group ($p = .076$). Rates of adverse events, serious adverse events, and discontinuation because adverse events were similar in both groups. Randomization to Tac elimination was terminated prematurely because of a higher rate of biopsy-proven acute rejection during Tac withdrawal.

A 3-year extension study of the PROTECT trial (n = 81) showed a renal benefit among patients treated with everolimus-based CNI-free immunosuppression compared with their CNI-based treated counterparts.[51–52] All patients received basiliximab induction and CNI with or without steroid based on individual center practice. At 4 weeks posttransplant patients were randomized to either (1) start everolimus and discontinue CNI therapy or (2) to continue their current CNI-based regimen. MMF use per center practice was allowed by study protocol. After 3 years, the eGFR was approximately 10 mL/min higher in CNI-free compared with CNI continuation groups. The difference in the unadjusted and adjusted eGFR between the treatment groups did not achieve statistical significance using the Cockcroft-Gault formula ($p = .082$) but attained significance in favor of CNI-free regimen based on the Nankivell formula ($p = .028$). Biopsy-proven acute rejection, graft loss, death, and adverse events leading to drug discontinuation were comparable between the two treatment groups. Five-year follow-up data showed a sustained renal benefit of CNI-free regimen. Patients treated with EVR-based CNI-free immunosuppression had a significantly higher eGFR compared with their CNI-based treated counterparts, irrespective of the formula used (i.e., Cockcroft-Gault, MDRD4 or Nankivell formula). The adjusted mean eGFRs using the Cockcroft-Gault formula were 87.5 mL/min in the EVR group and 75.1 mL/min in the CNI group ($p = .031$). The 5-year patient and graft outcomes were comparable between the two treatment groups. The findings of the PROTECT study suggest that preemptive early conversion of OLT recipients from CNI to everolimus is safe and effective and may preserve renal function compared with CNI continuation. Nonetheless, per study protocol patients should remain rejection free for at least 4 weeks to be eligible for complete CNI withdrawal 8 weeks after the introduction of EVR.

### *Mammalian Target of Rapamycin Inhibitors and CNI Minimization or Withdrawal After the First 6 to 12 Posttransplant Months*

**CNI TO SIROLIMUS CONVERSION.** A large prospective, open-label, randomized trial designed to evaluate the renal benefit of CNI to SRL conversion *at least* 6 months after liver transplantation showed no benefit 1 year after conversion from CNI- to SRL-based immunosuppression.[53] A total of 607 OLT recipients who had been on CNI maintenance immunosuppression for 6 to 144 months posttransplant were randomized in a 2:1 ratio to abrupt conversion (<24 hours) from CNI to SRL (n = 393) or CNI continuation for up to 6 years (n = 214). Mean baseline GFR were 66.5 mL/min in both groups. At 12 months postrandomization, the SRL conversion group showed no significant improvement in Cockcroft-Gault GFR compared with the CNI-continuation group (eGFR changes from baseline were −4.45 ± 1.12 vs. −3.07 ± 1.36 mL/min, respectively, $p = .34$). Furthermore, SRL conversion was associated with higher rates of biopsy-confirmed acute rejection ($p = .02$) and discontinuation ($p < .001$), primarily for adverse events. It was concluded that liver transplantation patients showed no demonstrable

benefit 1 year after conversion from CNI- to SRL-based immunosuppression. Nonetheless, it is speculated that a substantial proportion of patients had extended CNI exposure and may have incurred irreversible nephrotoxic effect before SRL conversion therapy (mean time from transplantation to randomization was 4.0 years for the SLR-conversion and 3.8 years for the CNI-continuation group).

**CNI TO EVEROLIMUS CONVERSION.** In a prospective, randomized, multicenter study consisting of 145 OLT recipients with CNI-related renal dysfunction (eGFR 20–60 mL/min), initiation of EVR in combination with CNI reduction or discontinuation 1 to 5 years after liver transplantation (n = 72) showed no renal beneficial effect compared with continuation of standard-CNI exposure (controls, n = 73).[54] The primary end point of 8 mL/min difference in the change in creatinine clearance compared with controls was not met. Biopsy-proven acute rejection were similar (1.4%) in both groups. At month 6, 80% of the patients who had converted to EVR had discontinued CNI. Among patients who continued EVR, the mean increase in CrCl was 2.1 and 3.8 mL/min at months 6 and 12, respectively, versus 2.4 and 3.5 mL/min in controls. It is speculated that the high frequency of CNI dose reductions in controls (77% of patients) and the relatively long mean time posttransplant (>3 years) contributed to the small difference in CrCl. Notably, study drug discontinuation and adverse events occurred more frequent in EVR-treated patients.

In a retrospective study of 240 stable OLT recipients, late EVR conversion (mean time from transplantation to the introduction of EVR 4.9 ± 5.2 years) resulted in a small but statistically significant improvement in eGFR at month 12. The Cockcroft-Gault eGFR was 64.2 ± 30.0 mL/min on day 0 and 68.4 ± 32.5 mL/min at month 12 ($p$ = .007). Among patients with baseline serum creatinine levels ≥130 μmol/L, the eGFR values were 44.3 ± 15.7 mL/minute on day 0 and 53.7 ± 26.0 mL/minute at month 12 ($p$ = .003). Although the incidence of mild or moderate biopsy-proven acute rejection was low at 1.6%, EVR discontinuation resulting from adverse events occurred in 12.9% of the patients.[55]

In a multicenter, retrospective study of 477 OLT recipients, Bilbao et al.[56] demonstrated that improvement in renal function was higher in patients who underwent early CNI to SRL conversion therapy (defined as <1-year post-OLT) compared with their late conversion counterparts (>1-year post-OLT). The most common indications for conversion therapy included renal dysfunction (32.6% of patients), prevention of HCC recurrence (20.8%), management of HCC recurrence (7.9%), and de novo malignancy (29.7% of patients). Patients with renal dysfunction at baseline showed an eGFR increase of 10.9 mL at 3 months after SRL initiation ($p$ < .001), and 6.8 mL at 12 months ($p$ < .01), whereas no change in eGFR was observed among those who were converted more than 1-year post-OLT. Adverse events were the primary reason for discontinuation in 11.2% of cases. The study findings suggest that early conversion therapy is associated with better renal function recovery.

In a small series of 21 OLT recipients with chronic renal dysfunction (defined as creatinine ≥1.5 mg/dL) initiation of EVR at a mean of 62.4 ± 36.6 months after liver transplantation was associated with an improvement of renal function without an increase in rejection risk. CNI was discontinued after target levels of EVR were reached. During the study period, CNI was withdrawn completely in 20 patients. Rejection was not detected in any case. However, de novo proteinuria occurred in 8 patients. Notably, two of eight patients had more than 3 g/L proteinuria. The Cockcroft-Gault eGFR at 30, 90, 180, and 360 days were 58.64 ± 16.50 ($p$ = .013 with respect to basal values), 59.49 ± 13.27 ($p$ = .028), 59.82 ± 16.83 ($p$ = .124), and 64.46 ± 16.79 mL/min, respectively ($p$ = .025).[57]

**MYCOPHENOLATE MOFETIL– AND CNI-SPARING PROTOCOLS.** In a prospective, multicenter, randomized study, Pageaux et al.[58] demonstrated that introduction of MMF in conjunction with *at least* 50% CNI dose reduction in patients with chronic CNI-related renal dysfunction (SCr >140 μmol/L and <300 μ) was associated with a significant increase in creatinine clearance at 12-month follow-up (from 42.6 ± 10.9 mL/min to 51.7 ± 13.8 mL/min, n = 27). In contrast, no improvement in eGFR was observed among controls (no MMF, CNI dose reduction allowed but not below 75% of initial dose, n = 29). No rejection episode was observed in either group. The median time since transplantation was more than 5 years for both groups.

In a prospective, randomized study of 90 OLT recipients who were *at least* 1-year post-OLT (range 12 to 199 months), Beckebaum et al.[59] similarly demonstrated that MMF followed by CNI dose reduction (target trough levels 2–4 ng/mL for Tac and 25–50 ng/mL for cyclosporine) significantly improved renal function compared with continuation of maintenance CNI dose (control group) over a 1-year follow-up period. In the MMF group (n = 60), the calculated glomerular filtration rate (cGFR) significantly increased from 39.9 ± 10.1 to 49.2 ± 11.9 mL/min over a 12-month follow-up period, and no allograft rejection occurred. In contrast, no improvement in renal function was observed in the control group (cGFR at baseline and at 12 months were 41.3 ± 13.2 mL/min vs. 38.7 ± 11.2 mL/min, respectively, n = 30).

Although MMF in conjunction with CNI-sparing protocol has a beneficial renal effect, such protocol is not without its attendant risk of rejection. In a systematic review and meta-analysis of eight randomized controlled trials in which MMF in combination with low-dose CNI or CNI elimination was compared with normal-dose CNI regimens without MMF, Goralczyk et al.[60] demonstrated that MMF in conjunction with CNI sparing improved renal function with a mean increase in GFR of 8.27 mL/min. The renal beneficial effect was found to be more pronounced in the three trials that included patients with moderately severe renal dysfunction (mean eGFR 39.9 ± 10.1 in one study, eGFR 42.6 ± 10.9 mL/min in one study, and eGFR 49.9 ± 11.5 mL/min in one study).[58–59,61] In six trials, patients not previously on MMF were started on MMF in combination with CNI dose reduction or elimination (MMF conversion trials), whereas in two trials MMF was started de novo in combination with low-dose tacrolimus. In the MMF conversion trials, most patients underwent MMF conversion more than 5 years post-OLT. Notably, although MMF conversion in conjunction with CNI sparing improved renal function, CNI minimization or elimination was not without adverse outcomes. In five trials, patients in the MMF conversion group experienced a nearly fivefold increase in acute rejection risk (RR 4.96, CI 1.75–14.07). Two conversion trials were terminated early because of unacceptable acute rejection rate and/or graft loss associated with CNI elimination. In two other trials, one third of patients in the CNI elimination group were restarted on CNI at the end of the study period. The findings of the meta-analysis suggest that the renal benefit of CNI to MMF conversion in OLT patients with severe renal dysfunction should be weighed against the risk of rejection.

Tables 129.4 and 129.5 summarize studies evaluating the safety and efficacy of various CNI-sparing protocols in the early and late posttransplantation periods. The former is

**TABLE 129.4**

**Studies Evaluating the Safety and Efficacy of CNI Minimization or Withdrawal Protocols in the Early Postorthotopic Liver Transplantation Period (the First 3 Months Posttransplant)**

| STUDY DESIGN | STUDY PROTOCOL | RESULTS | COMMENTS | REFERENCES |
|---|---|---|---|---|
| Spare the Nephron Liver Trial<br>Prospective, randomized, multicenter study (n = 293) | Randomization at 4–12 weeks post-OLT to:<br>• CNI maintenance vs. CNI to SRL conversion (CNI + MMF vs. SRL + MMF) | Median f/u 519 days after randomization:<br>SRL + MMF (n = 148) was associated with a significantly greater renal function improvement compared with CNI + MMF (n = 145);<br>$p = .0012$ | • Biopsy-proven AR greater in SRL + MMF group; $p = .02$<br>• Study withdrawal because of adverse events higher in SRL + MMF group<br>• Malignancy-related death less frequent in SRL + MMF group | 49 |
| Prospective, randomized, multicenter study<br>n = 282 in the 3-year extension study | Randomization at 1-month post-OLT:<br>EVR initiation + reduced-Tac or<br>EVR + Tac elimination or standard Tac exposure | From randomization to month 36:<br>Significant improvement in eGFR in the EVR + reduced-Tac compared with standard Tac group; $p = .005$ | No difference in AR between EVR + reduced Tac and standard Tac<br>Tac elimination group terminated prematurely because of high AR rates | 50 |
| The PROTECT Trial<br>Prospective, randomized, controlled study<br>n = 81 in the 3-year extension study | All patients received basiliximab.<br>Randomization at 4 weeks post-OLT to:<br>Start EVR and discontinue CNI or<br>CNI continuation | • After 3 years, eGFR was approximately 10 mL/min higher in CNI-free compared with CNI continuation group<br>• 5-yr follow-up data showed sustained renal benefit of CNI-free regimen | 5-yr patient and graft survival outcomes comparable between the two treatment groups | 51,52 |

*CNI,* calcineurin inhibitor; *EVR,* everolimus; *f/u,* follow-up; *MMF,* mycophenolate mofetil; *OLT,* orthotopic liver transplantation.

defined arbitrarily as the first 1 to 3 months post-OLT and the latter as more than 6 to 12 months posttransplantation.

### *Authors' Perspective on Various Immunosuppressive Strategies to Prevent, Halt, or Ameliorate CNI Nephrotoxicity in Long-Term Survivors*

Early CNI dose reduction in combination with MMF is safe and effective and may confer long-term renal benefit, whereas early CNI withdrawal may increase rejection risk. The American Society of Transplantation Liver and Intestine Community of Practice expert panel emphasizes that CNI therapy typically is required to prevent rejection in the first postoperative year but can be reduced during that time period to improve renal function.[62] In patients with established renal dysfunction resulting from chronic CNI nephrotoxicity, early (arbitrarily defined as within the first posttransplant year) CNI dose reduction in a regimen consisting of an mTOR inhibitor appears to be more effective than late CNI dose reduction in improving or slowing the progression of renal dysfunction. In contrast, late CNI dose reduction in a regimen consisting of MMF may ameliorate renal function, albeit without rejection risk. CNI minimization or withdrawal probably should be considered only in patients with no prior rejection episodes and in those with minimal CNI requirement before withdrawal. Manipulation of immunosuppressive therapy in the face of moderately severe or severe chronic kidney disease (defined as CKD stage 3b to 4) may be futile, and the added risks of acute rejection should be carefully weighed against the benefits. Various immunosuppressive strategies to improve renal function after liver transplantation are summarized in Table 129.6 and Fig. 129.1.

## CONCLUSION

AKI is common after OLT, whereas CKD and ESRD increase in incidence in long-term survivors who often have excellent function of their allograft. Identifying the risk factors for renal dysfunction and developing strategies to prevent, halt, or ameliorate renal function should be an integral part of management of OLT candidates and recipients. Volume re-expansion is recommended after large-volume paracentesis. In general, albumin has been suggested to be more effective than artificial plasma expanders in the prevention of circulatory dysfunction. Hydroxyethyl starch should be avoided in patients with severe liver disease and in OLT recipients because of increased mortality and AKI risk. Evidence-based intraoperative medical or surgical interventions to prevent or ameliorate AKI post-OLT are lacking. Nonetheless, control of bleeding during surgery, careful attention to management of fluid and electrolytes, and avoidance of hypotensive episodes may protect the kidneys from hemodynamically mediated ischemic injury. Therapeutic approaches in the postoperative period should be modified in patients with preexisting HRS or pretransplantation renal dysfunction. The use of IL-2 receptor blocker or antilymphocyte preparations in conjunction with delayed and reduced CNI exposure may preserve early renal function. Although nonnephrotoxic, belatacept and de novo sirolimus use after liver transplantation are associated with increased mortality and graft loss and their use should be avoided. Early CNI reduction in conjunction with adjunctive therapy with an antimetabolite may improve renal function in the long term without increased rejection risk or graft loss. In contrast, complete CNI withdrawal particularly within the first posttransplant year may be associated with unacceptable acute

**TABLE 129.5**

**Studies Evaluating the Safety and Efficacy of CNI Minimization or Withdrawal Protocols in the Late Postorthotopic Liver Transplantation Period (More Than 6 to 12 Months Posttransplantation)**

| STUDY DESIGN | STUDY PROTOCOL | RESULTS | COMMENTS | REFERENCE |
|---|---|---|---|---|
| Prospective, randomized n = 607 | Month 6–144 post-OLT, 2:1 randomization<br>• Abrupt conversion (<24 hr) from CNI to SRL (n = 393) or<br>• CNI continuation (n = 214) | At month 12 post randomization<br>• No significant improvement in eGFR in the SRL conversion compared with the CNI-continuation group ($p$ = .34) | • SRL conversion was associated with higher AR rates and discontinuation because of adverse events | 53 |
| Prospective, randomized, multicenter n = 145 | Month 12 to 60 post-OLT eGFR 20–60 mL/min at enrollment<br>• Start EVR + CNI reduction/elimination or<br>• Standard CNI exposure | At month 6 postrandomization:<br>• No significant difference in eGFR between the two treatment groups | • AR rates similar in both groups<br>• Drug-discontinuation and adverse events more frequent in EVR-treated groups | 54 |
| Retrospective, multicenter study n = 240 | Mean time from liver transplantation to CNI to EVR conversion: 4.9 ± 5.2 years | • EVR conversion resulted in a small but statistically significant improvement in eGFR at month 12, $p$ = .007 | • Biopsy-proven AR rates: 1.6%<br>• EVR discontinuation because of adverse events: 12.9% | 55 |
| Retrospective, multicenter study n = 477 | Indications for CNI to SRL conversion:<br>• Renal dysfunction (32.6%)<br>• Prevention of HCC recurrence (20.8%) Management of HCC recurrence (7.9%)<br>• De novo malignancy (29.7%)<br>• Others | • Improvement in eGFR higher in early conversion (< 1 year post-OLT)<br>• Patients with renal dysfunction at baseline showed significant improvement in eGFR at 12 months with early (<1 year) but not late conversion (>1 year) | • SRL discontinuation because of adverse events 11.2% | 56 |
| Prospective study n = 21 | • Mean time from transplantation to EVR initiation: 62 months<br>• Inclusion: creatinine ≥1.5 mg/dL | • Significant improvement in CrCl at 30, 90, and 360 days compared with baseline values in EVR-treated patients | • De novo proteinuria developed in 8 patients (2 with proteinuria >3 g/L)<br>• No AR | 57 |
| Prospective, randomized, multicenter n = 56 | Median time since OLT >5 years SCr >140 and <300 μmol/L at enrollment<br>Start MMF + ≥50% CNI dose reduction<br>Control: no MMF + standard CNI | • Significant improvement in eGFR at 12 months in MMF-treated patients but not in controls | • No AR | 58 |
| Prospective, randomized n = 90 | Time from OLT to enrollment ≥1 year<br>• MMF + stepwise CNI reduction<br>• Control: CNI continuation | • Significant improvement in eGFR over a 1-year follow-up period in MMF + CNI dose reduction group but not in controls | • No AR in either group | 59 |
| Systematic review and meta-analysis of eight randomized controlled trials | MMF in conjunction with CNI dose reduction or elimination | MMF in conjunction with CNI sparing improved renal function with a mean increase in GFR of 8.27 mL/min | • In five trials, MMF conversion group had a nearly fivefold increase in AR risk<br>• Two trials terminated because of unacceptable AR rates with CNI elimination | 60 |

*AR,* acute rejection; *CNI,* calcineurin inhibitor; *eGFR,* estimated glomerular filtration rate; *EVR,* everolimus; *MMF,* mycophenolate mofetil; *OLT,* orthotopic liver transplantation; *SRL,* sirolimus.

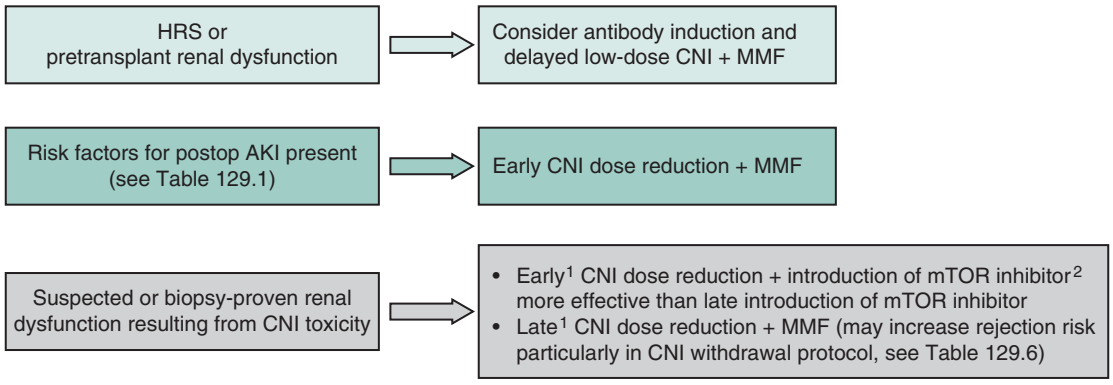
rejection rates and graft loss. At the authors' institution, early CNI-sparing strategies are employed in OLT candidates with pretransplant HRS or renal dysfunction. The former includes monoclonal or polyclonal antibody induction and delayed and reduced CNI exposure in a triple regimen consisting of CNI, mycophenolate mofetil, and steroids. CNI generally is introduced on postoperative day 2 or 3 at the discretion of the treating physician. The use of contrast studies or nephrotoxic drugs should be minimized or avoided. Although early transplantation of patients with baseline renal dysfunction may improve renal outcome after transplantation, the duration of AKI in the pretransplantation period continues to be prolonged despite adoption of the MELD score for the allocation of liver (designed to prioritize patients with renal dysfunction). Therefore careful selection of candidates for combined kidney-liver transplantation avoids added renal-related complications after liver transplantation.

**TABLE 129.6**

**Immunosuppressive Strategies to Improve Renal Function**

| | COMMENTS / AUTHORS' PERSPECTIVES |
|---|---|
| Immediate postoperative period<br>• Monoclonal or polyclonal antibody induction in conjunction with delayed low-dose tacrolimus and MMF preserves early renal function after OLT without compromising immunoprotection | • Currently available antibody induction agents:<br>  • Polyclonal antibody: thymoglobulin<br>  • Monoclonal antibody: basiliximab<br>  • Early CNI minimization + MMF without induction may improve renal function but without increased acute rejection risk<br>  • Belatacept and de novo sirolimus use should be avoided (FDA black box warning) |
| Early postoperative period (defined as <12 mo)<br>• Early preemptive CNI dose reduction + MMF is safe and effective, whereas complete early CNI withdrawal may increase rejection risk<br>• CNI therapy typically is required in the first posttransplant year but can be reduced during that time period to improve renal function (AST Liver and Intestine Community of Practice expert panel)<br>• In patients with established renal dysfunction resulting from CNI nephrotoxicity, early CNI dose reduction in a regimen consisting of mTOR inhibitor is more effective than late CNI dose reduction | • Modification of immunosuppressive therapy should be tailored to each individual patient |
| Late postoperative period (defined as ≥12 mo)<br>Late CNI dose reduction in a regimen consisting of MMF may ameliorate renal function albeit not without rejection risk | • CNI minimization or withdrawal probably should be considered only in patients with no prior rejection episodes and in those with minimal CNI requirement before withdrawal<br>• Manipulation of immunosuppressive therapy in CKD stages 3b-4 may be futile. The added risk of rejection should be weighed against benefits<br>• Modification of immunosuppressive therapy should be individually tailored |

*CKD,* Chronic kidney disease; *CNI,* calcineurin inhibitor; *FDA,* Food and Drug Administration; *MMF,* mycophenolate mofetil; *mTOR,* mammalian Target of Rapamycin.




[1]Early vs. Late (<12 months vs. ≥12 months)
[2]mTOR inhibitor not recommended in patients with preexisting proteinuria ≥500 mg/day

**FIGURE 129.1** Suggested renal-sparing immunosuppressive protocols after orthotopic liver transplantation.

## Key Points

1. Pretransplant renal dysfunction and preexisting hepatorenal syndrome are well-established risk factors for posttransplant AKI. The potential benefits of diuretics, lactulose, contrast dye exposure, or nephrotoxic medications must be balanced carefully against the risk of precipitating AKI or hepatorenal syndrome.
2. In large volume paracentesis, albumin infusion at a dose of 1 g per kg body weight up to 100 g/day is recommended. In the setting of SBP, albumin infusion at a dose of 1.5 g/kg at diagnosis of SBP and 1 g/kg IV 48 hours later is recommended.
3. Intraoperative risk factors for the development of perioperative acute kidney injury are likely similar to those in nontransplant surgical settings. Aggressive control of intraoperative bleeding, management of fluid and electrolyte abnormalities,

and avoidance of hypotensive episodes are imperative in the perioperative period.
4. Posttransplant AKI is likely multifactorial and may include ischemic or toxic insult to the kidneys, prolonged hypotension, sepsis, sustained prerenal acute kidney injury, and the use of calcineurin inhibitors or other nephrotoxic drugs. Bleeding and infectious complications should be treated promptly and aggressively.
5. Monoclonal or polyclonal antibody induction and delayed and reduced CNI exposure in a regimen consisting of an antimetabolite adjunctive therapy may improve renal function without increased rejection risk or graft loss. The use of calcineurin inhibitor–sparing protocols in patients with preexisting hepatorenal syndrome or pretransplant renal dysfunction should be individually tailored.
6. Complete CNI withdrawal particularly within the first posttransplant year may be associated with unacceptable acute rejection rates and graft loss.
7. Manipulation of immunosuppressive therapy such as calcineurin inhibitor minimization or withdrawal in the face of severe acute kidney injury may be futile. The added risks of acute rejection should be weighed carefully against the benefits.
8. Belatacept and de novo sirolimus use after transplantation should be avoided because of increased mortality risk and graft loss.

## Key References

A complete reference list can be found online at ExpertConsult.com.

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