Renal Dysfunction After Liver Transplantation

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Overview

The reader will explore in this chapter current classification, staging, and management of postliver transplant renal dysfunction. Epidemiology, pathological mechanisms, and risk factors of posttransplant renal dysfunction will be discussed throughout the chapter giving evidences with a critical point of view. Preexisting renal dysfunction has seen an important raise with the introduction of the Model for End-Stage Liver Disease system for graft allocation, so prediction of posttransplant progression is becoming of major importance, primarily for a careful evaluation for the need of simultaneous liver-kidney transplant against liver transplant alone. Immunosuppressive drugs management in this context is still a matter of great debate in the current literature, often individualized by the clinician in light of the patient's personal characteristics, however, current recommendations will be summarized. General strategies to avoid progression of renal dysfunction will be also discussed, with specific attention for those that are more important in the liver transplant setting.

21.1 Introduction

Renal dysfunction is a crucial clinical issue in nonkidney solid organ transplantation, increasing morbidity, and hampering posttransplant survival. Acute kidney injury (AKI) and chronic kidney dysfunction (CKD) are frequently seen in patients with end-stage liver disease (ESLD) due to several factors like gastrointestinal

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bleeding, administration of potentially nephrotoxic drugs, hepatorenal syndrome, hyperbilirubinemia, and hypotension. The prevalence of patients who are transplanted with some degree of renal failure has further increased in the recent years after the introduction of the Model for End-Stage Liver Disease (MELD)-based allograft allocation system and the more frequent use of marginal grafts [1–3]. Furthermore, renal dysfunction may develop or be aggravated during LT and/or occur in the early and late postoperative course due to episodes of severe infections, acute rejections, and the use of nephrotoxic immunosuppressive drugs. Calcineurin inhibitors (CNI) have been associated with post-LT nephrotoxicity, and current treatment guidelines emphasize the importance of immunosuppression individualization to minimize renal damage while avoiding rejection [4]. However, their role in post-LT renal dysfunction may be overestimated, and other contributing etiologies should always be investigated.

As significant advances in the long-term outcome of LT have been achieved, the need to understand both the etiology and chronicity of renal dysfunction in the setting of LT has become essential to prevent correlated morbidity and mortality. Furthermore, in the era of donor shortage, it is indispensable to individuate those patients who will specifically benefit from simultaneous liver-kidney (SLK) transplantation, sparing those who will achieve full renal recovery after LT because of liver-related or purely hemodynamic damage.

The European Association for the Study of the Liver (EASL) currently recommends a continuous monitoring of renal function in LT recipients, which should be started immediately after LT, besides a continuous screening for and sufficient treatment of potential risk factors [5].

21.2 Definitions and Diagnosis

There is currently no consensus on the definition of AKI or CKD in the setting of LT. To address the need to define kidney dysfunction at the time of LT, both definitions in cirrhotic patients have been outlined by the International Ascites Club/Acute Dialysis Quality Initiative work group (Table 21.1) [6].

Table 21.1 Working party proposal for a revised classification system for renal dysfunction in patients with cirrhosis [6]

Diagnosis	Definition
AKI	Rise in SCr ≥50% from baseline or rise in SCr ≥0.3 mg/dL in <48 h. HRS type I is a specific form of AKI.
CKD	GFR <60 mL/min/1.73 m^2 for >3 months (calculated with the MDRD6 formula). HRS type II is a specific form of CKD.
Acute-on-chronic kidney disease	Rise in SCr ≥50% from baseline or rise in SCr ≥0.3 mg/dL in <48 h in a patient with cirrhosis whose GFR is <60 mL/min/1.73 m^2 for >3 months (calculated with the MDRD6 formula).

SCr Serum creatinine, *HRS* Hepatorenal syndrome, *AKI* Acute kidney injury, *GFR* Glomerular filtration rate, *CKD* Chronic kidney dysfunction, *MDRD6* 6-Parameter Modification of Diet in Renal Disease

The most frequent cause of renal dysfunction in ESLD patients is hepatorenal syndrome (HRS). As defined by the International Ascites Club, type I HRS is characterized by doubling of initial serum creatinine concentration, in the presence of cirrhosis with ascites, to >221.0 μmol/L (2.5 mg/dL) or a 50% reduction of initial 24-h creatinine clearance to <20 mL/min in less than 2 weeks; type II HRS is the milder form, associated with a more stable and slowly progressive form of functional renal failure [7, 8].

21.2.1 Renal Function Estimation

Currently, estimated glomerular filtration rate (eGFR) is the more appropriate way to stratify kidney function impairment, however, none of the creatinine-based formulas have been currently validated and they often lead to under and late intervention in the setting of ESLD and LT [9]. Additionally, waitlisted patients and LT recipients typically are more sarcopenic than other patients with CKD, besides the fact that creatinine can diffuse into the ascites yielding lowered serum concentrations. Therefore, serum creatinine almost certainly overestimates GFR. An iothalamate clearance is the only valid and clinically applicable method to evaluate true excretory kidney function in patients with severe liver disease; however, this method cannot be used routinely. Cystatin C, a protein generated at a constant rate by all body cells and freely filtered by the glomeruli and then catabolized by the tubular epithelial cells, has emerged as a better marker of kidney function in liver patients [10]. This protein is not eliminated by the liver and its serum concentration is independent of the splanchnic blood flow. A panel of predictive novel and traditional biomarkers (NGAL, kidney injury molecule 1, and others) are currently being studied to aid better and earlier identification of renal dysfunction in these patients.

21.3 Renal Dysfunction in Liver Transplant Candidates

The prevalence of renal dysfunction at the time of LT, defined as a serum creatinine level >1.5 mg/dL, ranges between 17% and 95% in recipients [11, 12]. This prevalence showed its highest values from 2002 to 2005, remaining essentially stable thereafter [13]. These observations are likely a result of the implementation of the MELD system for graft allocations, which includes creatinine as a predictor of short-term mortality, giving priority to those patients with poor kidney function. However, this did not lead to an increase in post-LT mortality or occurrence of severe CKD, likely due to the shorter waiting time and the increased likelihood of renal function recovery in these patients [14]. HRS is commonly incriminated as the cause of renal dysfunction at the time of LT [15]; however, other etiologies should be investigated because the prognosis and therapies differ considerably. Those patients at highest risk for post-LT severe renal dysfunction face significant function decline within the first year post-LT [9]. In this regard, the need to stratify liver candidates before transplant is extremely important to identify those patients at risk

of progressive renal disease, amenable to specific therapies, or to evaluate for combined liver-kidney transplant. On the contrary, some patients with preexisting renal dysfunction, especially if <12 weeks course, spontaneously recover or do not face significant post-LT worsening [16], therefore individuation of predictors of poor outcome should be of primary importance. Further, the risk of developing end-stage renal disease (ESRD) is not constant during the entire posttransplant period and different factors could interfere with renal function in the early versus late settings (Table 21.2) [16–20].

21.3.1 Liver Disease Etiology

Liver disease etiology can be also implied in renal dysfunction mechanism leading to either structural or functional impairment, with different impacts on recipient's survival. Among the most frequent transplant indications, patients with alcoholic liver disease (ALD) and nonalcoholic steatohepatitis (NASH) have the highest prevalence of renal failure at the time of LT than those with hepatitis C (HCV). Between these patients, those with ALD have more severe liver dysfunction at the time of LT [21]. Severity of liver disease has been reported to be closely associated with the

Table 21.2 Predicting early and late onset of ESRD from characteristics known at the time of transplant in patients with preexisting renal dysfunction [16–20]

Early ESRD onset	Late ESRD onset
Recipient characteristics: Age History of diabetes Coronary artery disease Serum creatinine[a] Long duration of kidney dysfunction History of dialysis (>12 weeks) Body mass index Bacterial infections Repeated use of nephrotoxic drugs Longer waiting time Alcoholic liver disease	History of diabetes Hepatitis C status African American race Serum creatinine[a] Serum albumin[a] Serum bilirubin[a]
Intraoperative characteristics: Standard technique versus piggyback technique Intraoperative large blood loss Intraoperative hemodynamic instability Higher blood transfusion requirement Primary graft nonfunction	
Donor characteristics: Liver donor risk index, in particular: • age • donation after circulatory death • cold ischemia time	

ESRD End-stage renal disease
[a]At the time of transplant

development of renal failure in cirrhotic patients [22, 23], which can partially explain the higher prevalence of renal failure in ALD patients undergoing LT. However, in these patients, the cause of kidney dysfunction is often functional due to HRS or recent infections [24]. Even though some authors do not agree and reported ALD as an independent risk factor for CKD after transplantation [25], recovery of renal function seems to be more common in ALD patients. Furthermore, renal failure in patients with ALD can be due to IgA nephropathy, which is known to be only partially reversible after abstinence [26]. Differently, in patients with ESLD due to NASH pretransplant, renal failure is more frequently due to parenchymal kidney disease secondary to the high prevalence of diabetes, hypertension, and other comorbidities related to metabolic syndrome [24]. This leads to a high percentage of nonrecovery of the kidney function after LT in such patients [27]. HCV-infected patients can present with concomitant CKD and membranoproliferative glomerulonephritis secondary to HCV cryoglobulinemic vasculitis, even though of rare occurrence [28]. Nevertheless, significant changes in HCV epidemiology are to be expected in the near future, since HCV infection will be virtually eradicated in the early stages of the infection, hopefully leading to a drastic reduction of correlated extrahepatic complications.

21.3.2 Acute Liver Failure

Accurate assessment of the severity of renal dysfunction in acute liver failure (ALF) is crucial because it strongly correlates with high morbidity and mortality [29, 30]. The prevalence of renal dysfunction in patients with ALF has been reported to vary from 38% to 79%, with two third of patients manifesting AKI and almost half requiring renal replacement therapy (RRT) in the immediate postoperative period [31–33]. Despite the high prevalence of severe dysfunction at the time of LT, only 21–26% show a GFR <60 mL/min/1.73 m^2 at 1 year thereafter. Post-LT renal recovery is similar to that observed in spontaneous survivors of ALF. A growing body of evidence supports a systemic inflammatory response to ALF, and the systemic inflammatory response syndrome (SIRS) is an independent predictor of AKI in ALF patients [32]; however, further studies are still required to define the underlying pathological mechanism. By 5 years posttransplant, the cumulative incidence of CKD is 35–42% [34, 35]. So that again renal dysfunction duration appears to be a key determinant of chronic renal impairment.

21.3.3 Living Versus Cadaveric Liver Donor

LT represents the standard of care for ESLD. However, measures applied to increase the donor pool imply different risks for post-LT renal dysfunction. In living donor liver transplant (LDLT), intraoperative complications are lower due to better surgical planning and grafts are usually of higher quality. Cold ischemia time is kept shorter and ischemic insults are lower. LDLT recipients therefore have a lower risk

for post-LT AKI than deceased donor LT (DDLT) [36]. However, operative risks for the donor need to be considered together with those of a partial graft, so that DDLT is still frequently preferred over LDLT in many countries.

On the other side, donation after cardiac death (DCD) has seen a rapid expansion in recent years representing 5–15% of liver allografts in the United States and the United Kingdom, respectively. Although DCD LT demonstrates satisfactory long-term outcomes, patient and graft survivals are worse than in donation after brain death (DBD). Moreover, DCD patients show greater morbidity with an increased incidence of ischemic complications than matched DBD patients, including AKI, with also greater frequency of RRT [37]. Importantly, peak perioperative aspartate aminotransferase, a surrogate marker of hepatic ischemia-reperfusion injury, demonstrated a strong relationship with AKI in this setting. The development of AKI after DCD LT has significant implications for morbidity and mortality, as highlighted by the longer duration of hospitalization, increased likelihood of CKD, and worse survival.

21.3.4 Evaluation for Simultaneous Liver-Kidney Transplant

Current guidelines recommend that patients with ESLD and with GFR <30 mL/min/1.73 m^2, or HRS requiring RRT more than 8–12 weeks, and patients with renal biopsy revealing more than 30% fibrosis and glomerulosclerosis benefit from receiving both liver and kidney grafts [38]. In these patients, acceptable survival rates have been demonstrated with maintenance of adequate renal function (CKD stages II and III) for up to 5 years. There is a debate regarding the need for combined liver-kidney transplantation in patients with GFR between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2. On the other hand, the benefit of allocating kidneys to SLK transplant candidates must be weighed against the loss of kidney grafts that would clearly benefit patients on chronic dialysis. Ideally, diagnostic kidney biopsies should be performed to determine the cause and reversibility of renal dysfunction, however, high complications rates are reported. Renal ultrasound should always be performed, to assess renal size and echogenicity, with bilateral small and echogenic kidneys indicating CKD [39]. This first-line analysis, combined with laboratory tests results, could guide selection of those patients to refer for biopsy, which should be reserved to those deemed to be at highest risk. Furthermore, transjugular route is preferred and considered safer.

21.4 Epidemiology and Etiology

21.4.1 Post-transplant Acute Kidney Injury

AKI is unfortunately a frequent complication with a reported incidences ranging from 12% to 95% after LT, varying in relation to the diagnostic methods, the definition criteria, along with the length of follow-up [12, 40, 41]. The prevalence of AKI

in the post-LT setting varies between 19% and 60%, with significant nonhemodynamic AKI complicating approximately 50% of liver transplants in the immediate postoperative period, with more frequent occurrence in those with hepatorenal syndrome at the time of transplantation. Among those with early onset of acute renal failure, 10–20% of long-term survivors develop permanent renal dysfunction or ESRD [18, 42]. The utility of serum neutrophil gelatinase-associated lipocalin (NGAL) is currently being validated as a surrogate for post-LT AKI, as it has been shown to predict AKI in all patients regardless of the pre-LT serum creatinine levels [43].

The predominant etiology of AKI in the immediate post-LT period is acute tubular necrosis (ATN). If patient has AKI associated with hemolytic anemia and thrombocytopenia, the differential diagnosis includes thrombotic microangiopathy (TMA), particularly when immunosuppression is tacrolimus based in the setting of a reduced von Willebrand factor-cleaving protease (ADAMTS13). The main risk factors for posttransplant AKI have been individuated in the presence of pretransplant renal dysfunction, hemodynamic instability in peri- and postoperative settings, and graft dysfunction.

21.4.2 Posttransplant Chronic Kidney Dysfunction

The majority of patients who survive the first 6 months after LT will present some degree of impairment in renal function, with a GFR <60 mL/min/1.73 m^2 in 50–60% and <30 mL/min/1.73 m^2 in 15–25% of subjects at 5 years [11]. GFR decline in patients with normal renal function before LT is maximal in the immediate post-LT, stabilizing by 9 months after LT. Thereafter, a decline greater than 30 mL/min/1.73 m^2 from baseline predicts the development of permanent renal dysfunction [19].

According to histopathological studies, only a subgroup of patients with post-LT CKD have evidence of CNI toxicity (16–48%), while diabetic (9–51%) and hypertensive (41–44%) nephropathies seem to be more prevalent [44–46].

21.4.3 Posttransplant Renal Replacement Therapy

The risk of ESRD requiring dialysis after LT reaches up to 5% per year, occurring more often in patients experiencing posttransplant complicated courses with events such as sepsis, primary nonfunction, and hepatic artery thrombosis, which are difficult to predict [47]. Severe or end-stage disease is expected in 10–20% of patients, requiring maintenance dialysis or even kidney transplantation of 5–9% within the first 10 years post-LT [11, 48]. Persistence of end-stage CKD is as high as 30% among LT recipients who were on pre-LT RRT for more than 3 months and received LT alone [49], so that the duration of pretransplant RRT is highly predictive of spontaneous posttransplant renal recovery.

The most frequent causes of post-LT renal dysfunction are listed in Table 21.3 [19, 50–52].

Table 21.3 Post-LT renal dysfunction causes [19, 50–52]

AKI	CKD	RRT
ATN caused by: • renal ischemia secondary to hypovolemia or sepsis in the peri- and postoperative period • use of nephrotoxic drugs	• CNI toxicity • hypertensive vascular changes • Membranoproliferative glomerulonephritis • IgA nephropathy • diabetic nephropathy • proliferative glomerulonephritis with crescents • ATN	• preexisting diabetes mellitus • major surgical infection • time spent on the transplantation list • coronary artery disease • graft primary nonfunction • duration of pretransplant RRT

AKI Acute kidney injury, *CKD* Chronic kidney dysfunction, RRT Renal replacement therapy, ATN Acute tubular necrosis, CNI Calcineurin inhibitors

21.4.4 Immunosuppressive Drugs

CNI represent the backbone of immunosuppression after LT with tacrolimus being superior to cyclosporine in terms of safety [53]. Initial oral dose of 0.15 mg/kg are routinely administered to obtain whole blood trough levels between 10 and 20 ng/mL to avoid rejection episodes. However, with such a regimen, possible toxic effects like renal dysfunction, arterial hypertension, or new-onset diabetes after transplantation (NODAT) are more likely to occur, contributing to long-term mortality. FK506 levels correlate well with the incidence of renal toxicity, with reduced dose regimens showing improved kidney function at 1 year after LT compared to standard regimens [54]. Therefore, therapeutic monitoring of whole blood FK506 levels is useful for minimizing the risks of renal dysfunction in LT recipients [55].

The acute nephrotoxicity of CNI is characterized by vasoconstriction of the afferent arteriole leading to a reversible "preglomerular" renal failure [56]. It is a dose-dependent phenomenon with little difference between cyclosporine and tacrolimus, accentuated by parenteral administration of these drugs.

CNI chronic nephrotoxicity depends on the duration of the vasoconstriction of the afferent arteriole, which may lead to interstitial fibrosis, tubular atrophy, and glomerular fibrosis until damage is no longer reversible. The nephrotoxic effects of chronic administration of cyclosporine are similar to those due to tacrolimus [57].

The mammalian target of rapamycin inhibitors (mTORi)—everolimus and sirolimus—have been associated with a significantly higher incidence of proteinuria compared with CNI in solid organ transplants. The exact mechanism from which mTORi affect glomerular permeability is not well characterized, but recent evidences suggest that mTOR inhibition induces proximal tubular epithelial cell dysfunction and reduces receptor-mediated albumin uptake through an angiotensin II-dependent mechanism. Moreover, it was speculated that at least part of the increase of proteinuria in late conversion studies could be explained by

hemodynamic changes secondary to CNI withdrawal. Calcineurin inhibitors are known to exert antiproteinuric effects, partly by increasing the resistance of the afferent arteriole and thus reducing intraglomerular pressure [58].

21.5 Prognosis

Preexisting renal dysfunction, whichever is the underlying etiology, is generally associated with inferior short- and long-term patient survival, increased costs, post-transplant sepsis, longer intensive care unit stays, and the need for dialysis. Regardless of pretransplant status, renal dysfunction after LT is a marker of poor outcome, with almost 7% of deaths after LT being directly attributed to kidney failure solely [59]. Both AKI episodes and CKD contribute directly and indirectly to substantial morbidity and mortality, especially for those subjects at higher risk for severe impairment (58%, 5-year survival) [60]. The 28-day and 1-year mortality rates for LT recipients who develop AKI are markedly increased to 16% and 26% versus 0% and 4% in those who do not [2, 61]. CKD has become one of the leading causes of morbidity and death after LT [59, 60], besides being a strong independent cardiovascular risk factor. The development of ESRD after LT increases patient mortality more than 40% [62], with the highest risk for those patients receiving RRT started postoperatively. Dialysis may be a stronger predictor of death than the MELD score in LT recipients with preexisting renal dysfunction [11].

21.6 Management

21.6.1 Immediate Postoperative Period [54, 58, 63–66]

Nephroprotective strategies during LT follow general surgical practice guidelines, such as maintenance of intravascular volume and mean arterial pressure. Renal function estimation at the time of LT may help guiding modifications of immunosuppression regimens. For LT recipients at high risk for post-LT renal dysfunction, early introduction of mycophenolate mofetil (MMF) and progressive CNI reduction to values of about 25–50% of the therapeutic range used during monotherapy protocol should be considered, aiming to its complete progressive suspension. As a matter of facts, acute nephrotoxicity from CNI has been shown to be reversible at dose reduction or drug discontinuation. However, rejection episodes are more common in these patients, even with late onset, especially in those with history of previous episodes. Alternatively, the association of sirolimus with tacrolimus has also been recommended, aiming again to tacrolimus suspension. This association, however, is not possible with cyclosporine since it can potentiate its long-term nephrotoxic effect by augmenting transforming growth factor-β. A preemptive strategy using antibody induction therapy with interleukin-2 receptor antagonists and delayed reduced dose tacrolimus has also shown lower nephrotoxic rates. In the rare eventuality of TMA occurrence, plasmapheresis may be necessary together with discontinuation or exchange of CNI.

21.6.2 Perioperative Use of Terlipressin [67]

Although not studied prospectively, treatment of HRS before transplantation with vasoconstrictors may improve outcome after transplantation. Furthermore, terlipressin may have a role in reducing portal hypertension during LT, lowering venous congestion, blood loss, and maintaining arterial blood pressure perioperatively. Terlipressin may also help preventing renal dysfunction after LT, improving renal perfusion, besides improvement of graft function. Anyway, terlipressin should be used for a short duration. Potential higher risk of hepatic artery thrombosis should be kept in mind and intensive perioperative monitoring for cardiac arrhythmias is required during its usage. Therefore, perioperative terlipressin should only be considered in patients at high risk of renal dysfunction or in patients who have just recovered from HRS and refractory ascites.

21.6.3 Long-Term Management [58, 63–65]

Despite evidence of using mTORi and MMF early after LT to minimize CNI nephrotoxicity, this strategy does not seem to apply as well later after LT. There is no substantial evidence that tapering or elimination of CNI in favor of other immunosuppressive drugs improves renal function when performed >1 year after post-LT renal dysfunction onset. If conversion from CNI to mTORi is attempted, it should be followed by close monitoring of renal function and urinary protein losses. If pathological proteinuria occurs, removal of the mTORi reduces proteinuria to near preconversion levels. Blood glucose and blood pressure should be monitored on a regular basis and alterations should be treated aggressively based on goals for patients not receiving transplants. Furthermore, if patient show unexplained kidney dysfunction, BK virus should be checked in blood and urine and, if positive, kidney biopsy should be considered before starting specific treatment. Patients who develop ESRD may be candidates for kidney transplant and should be referred for evaluation.

21.6.4 General Prevention and Treatment of CKD [63, 64]

Besides transplant population-specific management, LT recipients should be managed also according to basic measures applied to the general population. Key recommendations made by the Kidney Disease Improving Global Outcomes (KDIGO) regarding management of chronic renal dysfunction, relevant to liver transplant recipients, are summarized in Table 21.4 [63, 64].

Tips

- Patients awaiting liver transplant should be screened for potential risk factors for renal dysfunction, which should be considered, together with transplant variables, to estimate posttransplant risk.
- Renal function monitoring should be started immediately after transplant.

Table 21.4 KDIGO recommendations for the management of CKD in LT recipients [63, 64]

Hypertension	• All hypertensive adults with CKD should be treated with BP-lowering drugs with the goal of – ≤140 mmHg systolic and ≤ 90 mmHg diastolic, if urine albumin excretion <30 mg/24 h – ≤130 mmHg systolic and ≤ 80 mmHg diastolic, if urine albumin excretion ≥30 mg/24 h • ACE-I or ARB therapy should be used in both diabetic and nondiabetic adults with CKD and urine albumin excretion >30 mg/24 h
NODAT	• Steroid-free regimens, use of induction therapy, and switching of CNI from tacrolimus to cyclosporine can reduce the risk of NODAT • Goals in regard to glycemic control should be the same as that of general population
Metabolic syndrome, dyslipidemia, and obesity	• Switching from cyclosporine to tacrolimus is associated with improved lipid profile • Sirolimus and everolimus can cause significant hyperlipidemia specially when used in combination with cyclosporine • Caloric restriction and weight management may improve metabolic syndrome and obesity • HMG-CoA inhibitors are considered as first-line agents to treat dyslipidemia, whereas patients with normal cholesterol and isolated hypertriglyceridemia might benefit more from omega 3 fish oil
Diet	• Lower salt intake of <2 g/day of sodium in adults, unless contraindicated • Lower protein intake of 0.8 g/kg/day in adults with or without diabetes and CKD with GFR <30 mL/min/1.73 m^2 at risk of progression • Avoid low protein intake in patients with malnutrition or at risk for malnutrition
Acidosis	• In patients with CKD and serum bicarbonate concentrations <22 mmol/L, oral bicarbonate supplementation can be given to maintain serum bicarbonate within the normal range, unless contraindicated
Diagnostic imaging	• All patients with GFR <60 mL/min/1.73 m^2 undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed according to the KDIGO clinical practice guideline for AKI including: – Avoidance of high-osmolar agents – Use of lowest possible radiocontrast dose – Withdrawal of potentially nephrotoxic agents before and after the procedure – Adequate hydration with saline before, during, and after the procedure – Measurement of GFR 48–96 h after the procedure • Avoid gadolinium-containing contrast media in people with GFR <15 mL/min/1.73 m^2 unless there is no alternative appropriate test • Patients with GFR <30 mL/min/1.73 m^2 who require gadolinium-containing contrast media should be preferentially offered a macrocyclic chelate preparation

KDIGO Kidney Disease Improving Global Outcomes, *CKD* Chronic kidney dysfunction, *BP* Blood pressure, *ACE-I* Angiotensin-converting enzyme inhibitor, *ARB* Angiotensin II receptor blocker, *NODAT* New-onset diabetes after transplantation, *AKI* Acute kidney injury

- Immunosuppressive protocols should be planned also considering short- and long-term expected renal function.
- For LT recipients at high risk for posttransplant renal dysfunction, early management should be applied.
- Antibody induction therapy with interleukin-2 receptor antagonists and delayed reduced CNI dose should be considered. Furthermore, early introduction of mycophenolate mofetil or mTORi with progressive reduction/suspension of CNI should be applied for renal function preservation.
- If pathological proteinuria occurs, removal of the mTORi reduces proteinuria to near preconversion levels.
- Besides specific management, common renal protection strategies should also be applied to transplanted patients. Primarily, blood glucose and blood pressure should be regularly monitored and alterations should be treated aggressively.
- Patients who develop ESRD may be candidates for kidney transplant and should be referred for evaluation.

Key Points

- Post-LT renal dysfunction is one of the main concerns in the liver transplant population and is associated with significant morbidity and mortality.
- Kidney function estimation is currently based on creatinine-based formulas which are inaccurate in determining true severity of renal dysfunction in these patients. Alternative biomarkers are currently being studied.
- The pathophysiology of post-LT renal dysfunction is multifactorial, and numerous risk factors have been identified. Immunosuppressive drugs are surely involved, however, other factors must be investigated and managed as early as possible.
- Preexisting renal dysfunction must be weighted in light of transplant-related variables and patient's features to predict posttransplant progression to end-stage disease.
- New antivirals for treating HCV will reduce the need for liver transplantation in HCV-positive patients, whereas the transplants performed for NASH-related cirrhosis are expected to rise, and this may have an impact on posttransplant renal dysfunction epidemiology.
- Evaluation for the need of simultaneous liver-kidney transplant against liver transplant alone is crucial to gain maximal benefit while avoiding graft wasting.
- Common renal protection strategies, applied to the general population, need to be studied in light of recipients' specific features to reduce even more the risk and improve outcome of post-LT renal function.
- Multidisciplinary collaboration between liver transplant specialists and nephrologists is mandatory and should start before waitlisting and continued over the long-term posttransplant follow-up.

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