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PROTECTING THE KIDNEY IN LIVER TRANSPLANT CANDIDATES

* Practice-Based Recommendations from the American Society of Transplantation Liver and Intestine Community of Practice


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Abstract

Acute kidney injury (AKI) and chronic kidney disease (CKD) are common in patients awaiting liver transplantation, and both have a marked impact on the perioperative and long-term morbidity and mortality of liver transplant recipients. Therefore, we review the epidemiology of AKI and CKD in patients with end stage liver disease, highlight strategies to prevent and manage AKI, evaluate the changing liver transplant waiting list's impact on kidney function, delineate important considerations in simultaneous liver-kidney transplant selection, and project possible future transplant policy changes and outcomes. This review was assembled by experts in the field and endorsed by the American Society of Transplantation Liver and Intestinal Community of Practice and Board of Directors and provides practice-based recommendations for preservation of kidney function in patients with end stage liver disease.
Introduction

Kidney function is an important predictor of morbidity and mortality in patients with various chronic medical illnesses. In liver transplant (LT) candidates, kidney dysfunction is both common and associated with serious consequences, including increased mortality risk both pre- and post-LT. Post-LT kidney function is determined by at least three factors: (1) pre-transplant kidney injury, (2) perioperative damage and recovery in kidney function, and (3) post-transplant kidney injury; the first is addressed in this paper and the remaining two in our companion paper (1). Preservation of kidney function in patients with end-stage liver disease (ESLD) through prevention of acute kidney injury (AKI), accurate diagnosis of AKI and chronic kidney disease (CKD) and timely institution of therapy are critical determinants post-LT outcomes. We review the science and grade the available data on preserving pre-LT kidney function. All authors reviewed the data available and recommendations were graded according to the GRADE system (Supplemental Table 1) (2, 3).

Epidemiology, Pathophysiology, and Diagnosis of Acute and Chronic Kidney Disease in Patients with End-Stage Liver Disease

Kidney dysfunction is a common complication of liver cirrhosis, especially in patients with ascites. In patients with ESLD, this occurs in approximately 20% of hospitalized patients (4), and in over 50% of outpatients with decompensated cirrhosis (5). Most cases of kidney dysfunction in advanced cirrhosis are related to AKI. However, CKD is becoming more prevalent as increasing numbers of patients with chronic liver disease develop diabetes (6). Thus the spectrum of kidney dysfunction in cirrhosis is wide, ranging from AKI occurring over days to CKD occurring over months to years. Most causes of kidney dysfunction in advanced cirrhosis are related to functional hemodynamic changes resulting from cirrhosis and may reverse upon hemodynamic correction (4). Examples of these include volume depletion, resulting in pre-renal azotemia that is responsive to diuretic withdrawal and volume expansion, and kidney
dysfunction unresponsive to volume expansion, such as hepatorenal syndrome (HRS). Type 1 HRS (HRS-1) occurs over days, and type 2 HRS (HRS-2) is a less acute process, occurring over weeks to months. Kidney dysfunction related to structural disease (e.g. acute tubular necrosis (ATN), acute interstitial nephritis or glomerular diseases) is less reversible without disease specific therapies.

The major hemodynamic abnormality underlying functional kidney alterations in cirrhosis is splanchnic and systemic vasodilatation, which causes effective arterial under-filling. This leads to compensatory vasoconstrictor system activation (renin-angiotensin aldosterone and sympathetic nervous systems) and results in kidney vasoconstriction that first conserves sodium, then water and finally reduces kidney blood flow to a level that impairs glomerular filtration rate (GFR) (7). This decreased perfusion sets the stage for further kidney hemodynamic compromise from additional insults. The most common insult that precipitates kidney failure is bacterial infection (8). Bacterial products and the cytokines they induce have vasodilatory properties that promote further splanchnic and systemic vasodilatation, thereby worsening circulatory dysfunction. Bacterial products can also alter kidney peri-tubular microcirculation, directly inflict kidney damage, and cause oxidative stress (9, 10), which in turn affects cellular metabolism and induces apoptosis.

The definition of AKI in cirrhosis has recently undergone significant changes. Practically, patients with HRS-1 were previously not considered candidates for treatment unless their serum creatinine (Scr) reached ≥ 2.5mg/dL over a period of ≤ 2 weeks. However, data have emerged suggesting that smaller acute changes in Scr also negatively impact patient outcomes (11). This led to the development of various diagnostic criteria for acute renal failure: RIFLE or Risk, Injury, Failure, Loss of function and End-staged renal disease (ESRD) (12); Acute Kidney Injury Network (AKIN)(13); and Kidney Disease Improving Global Outcomes (KDIGO) (14). These various definitions of AKI have been proposed in the general population and are based on relative changes in Scr (rather than a threshold of Scr), urine output (UO) or initiation of renal
replacement therapy (RRT) (Table 1) (13, 15). In 2010, the Acute Dialysis Quality Initiative (ADQI) along with several members of the International Club of Ascites (ICA) recommended adaptation of the AKIN criteria to define AKI in patients with cirrhosis instead of the traditional definition using a fixed Scr cut-off value of greater than 1.5 mg/dL (Table 1)(16, 17). These criteria were adapted irrespective of the cause of AKI. As such, HRS-1 was categorized as a specific type of AKI. Since then, the use of AKIN criteria in predicting mortality has been validated in several studies of hospitalized patients with cirrhosis including those in the intensive care units (5, 18-20). Serum creatinine was chosen as the measure of kidney function despite its shortcomings because it is familiar and readily available to all clinicians. Calculated GFR in a population with a high prevalence of sarcopenia, such as in cirrhosis, can lead to a falsely increased GFR, and urine output can be misleading because of avid sodium and water retention that both increase the risk for inaccuracies. The same small change in Scr (≥0.3mg/dL) was adopted to define AKI in cirrhosis without staging (Supplementary Table 2).

CKD was also defined based on the National Kidney Foundation (NKF) definitions. Functionally, this allowed patients with acute deterioration of kidney function on a background of CKD to also be better defined.

More recently, the ICA (21) defined how baseline kidney function should be determined and outlined criteria for AKI progression, regression, and treatment response (Table 1). HRS-1 was renamed HRS-AKI, with removal of the Scr cut-off value of ≥2.5mg/dL, and was defined as development of ≥2 stage AKI (irrespective of final Scr) provided all the other HRS-1 diagnostic criteria are fulfilled. Once validated, these revised criteria will hopefully facilitate research collaborations, standardize study protocols, enable earlier therapeutic initiation, and reinvigorate pharmaceutical and academic investment into novel treatment strategies.

Although oliguria is not included in the current definition of AKI in patients with cirrhosis, UO has been found to be a sensitive and early marker for AKI in ICU patients and is associated with adverse outcomes (22-24).
Key Points and Recommendations:

- AKI, defined as an increase in baseline Scr of ≥0.3 mg/dL within 48 hours, is the preferred means to categorize acute kidney injury in patients with cirrhosis. 1B
- HRS-AKI is a subset of AKI in patients with cirrhosis. 1B
- More than half of patients with decompensated cirrhosis have at least some degree of kidney dysfunction. 1C

Prevention of AKI

Prevention of AKI is critical since it is associated with increased mortality in patients with cirrhosis (25) and is one of the most powerful predictors of post-LT survival. There are several, often co-existent, physiologic and clinical insults that can negatively impact kidney function (Table 2). More recently, the role of the gut microbiome translocation of bacteria or bacterial products and systemic pro-inflammatory responses have been increasingly recognized as an important contributor in the pathogenesis of organ dysfunction, including AKI and CKD (26). As such, long-term spontaneous bacterial peritonitis (SBP) prophylaxis with daily antibiotics (27-29), IV albumin use in patients with SBP (30, 31), prompt fluid replacement of gastrointestinal blood loss together with antibiotic prophylaxis for gastrointestinal bleeding (32, 33), and simultaneous administration of IV albumin with large volume paracentesis (>5L) (34) have all been shown to decrease the probability of HRS-AKI. Future interventional strategies may target altering the microbiome, preventing bacterial translocation, or abrogating pro-inflammatory responses. Although rare, abdominal compartment syndrome (defined as increased intra-abdominal pressure to >20 mmHg) usually from tense ascites may lead to AKI by increasing venous pressure and causing arterial vasoconstriction (35), which may improve following paracentesis with IV albumin (36, 37). Drugs may exert a direct nephrotoxic effect by several mechanisms: 1) direct kidney tubule toxicity (e.g. radiocontrast dye, aminoglycosides,
vancomycin, amphotericin B); 2) allergic interstitial injury [e.g. non-steroidal anti-inflammatory drugs (NSAIDs), beta-lactam antibiotics, diuretics]; and 3) intra-kidney blood flow impairment (e.g. radiocontrast dye, NSAIDs, renin-angiotensin-aldosterone system blockers)(38). In addition, changes in drug distribution due to volume overload and portal hypertension and altered pharmacokinetics due to changes in kidney and hepatic blood flow and function can clinically significantly modulate the concentration and half-life of medications and their metabolites.

**Key Points and Recommendations:**

- **AKI is best prevented in cirrhotic patients through utilization of SBP prophylaxis, IV albumin use in patients with SBP, antibiotic prophylaxis for gastrointestinal bleeding, and simultaneous administration of IV albumin with large volume paracentesis. 1A**

**Management of AKI**

Diagnosing the etiology of AKI is critical in determining therapy (Figure 1). Regardless of the AKI etiology, removing potential precipitating factors such as diuretics and optimizing volume status, should be initiated even before a cause of AKI is established (Table 3). Intravascular volume expansion is an important part of treatment but also part of establishing the AKI etiology. Patients in whom other causes of AKI have been ruled out should receive treatment for HRS with vasoconstrictors in combination with IV albumin (Table 3)(39-57). Meta-analyses have shown a correlation between vasoconstrictor therapy increasing mean arterial pressure (MAP), improvement in kidney function, and short-term survival benefit irrespective of the agent used (58, 59). Terlipressin is the most extensively studied and documented first-line therapy for HRS-AKI in countries with access. However, due to the unavailability of terlipressin in North America, midodrine in combination with octreotide (39,
43, 54), and in particular norepinephrine (49, 51, 54, 55) have also been shown to be beneficial in the treatment of HRS (40-42, 44-48, 50, 52, 53, 56) (Table 4). Unlike midodrine/octreotide (56), norepinephrine has been shown to be equivalent to terlipressin, although the expense of norepinephrine use, need for ICU monitoring, and the inferior quality of data continue to support terlipressin as the agent of choice in areas with access (60). The optimal duration of medical treatment is not well established, however in patients who failed to demonstrate improvement in Scr after day 4 are less likely to have HRS reversal (61) and an indication for treatment beyond 14 days has not been established. Increase in MAP ≥5 mmHg during treatment, baseline Scr <3 mg/dL, Child-Pugh score <13, lower MELD score, younger age, and bilirubin <10 mg/dL, have all been shown to be independent predictors of therapeutic response. Of note, recent data has compared infusion to bolus therapy with terlipressin and shown similar responses to both regimens with fewer side effects and a lower total daily dose needed in those receiving infusional therapy (62). Ideally those patients with response to therapy would be given priority for transplant to avoid the need for SLKT (63).

Transjugular intrahepatic portosystemic shunt (TIPS) has been shown to improve kidney function in small studies of patients with HRS (64-66). However, TIPS is contraindicated in patients with severe hepatic dysfunction, defined as serum bilirubin >5 mg/dL, a high MELD score, significant kidney dysfunction, cardiac failure or clinically significant hepatic encephalopathy.

The initiation of RRT should be made on clinical grounds, including hyperkalemia, oliguria with volume overload, metabolic acidosis, refractory hyponatremia not responding to medical management, and diuretic resistance/intolerance. Optimal timing for RRT indication has not been studied in patients with cirrhosis; however, data from AKI studies in critically ill patients without liver disease suggests that early RRT initiation and maintenance of negative fluid balance in those with volume overload may improve survival (67-71). In patients receiving RRT, continuous RRT allows for the slower correction of serum sodium and provides greater cardiovascular stability compared to standard hemodialysis (72, 73).
Although initial small studies on albumin dialysis using the Molecular Adsorbent Recirculating System (MARS) documented a survival benefit compared to standard medical therapy (74), a more recent multicenter study (RELIEF trial) failed to reproduce this benefit at 28-days, despite biochemical improvement (75).

**Key Points and Recommendations:**

- **Diuretic withdrawal and volume replacement are essential to determine etiology of AKI.** 1A
- **Terlipressin is the first line therapy for HRS-AKI in countries with access to this medication.** 1A

**Impact of AKI Treatment on Patient Survival and Kidney Function Post-LT**

The cumulative rates of stage 4 or 5 CKD and ESRD 10-years post-LT have been shown to be 18% and 25%, respectively (76). Although these high rates may be partially attributable to long-term calcineurin inhibitor (CNI) use, diabetes and hypertension (reviewed elsewhere), the most important predictor of CKD post-LT is pre-transplant kidney function. The development and duration of AKI pre-transplant not only reduces post-LT kidney function long-term but also increases mortality (77-86). Reversal of HRS-1 with vasoconstrictors pre-LT has been associated with improved post-LT outcomes (8, 87, 88). At the present time, specific pre-LT predictors of CKD development post-LT are lacking.

**Key Points and Recommendations see Table 3.**

**Evolution in the Composition of the Liver Transplant Waitlist**

The composition of the LT waitlist in the United States (US) and Europe is being transformed by three events that are increasing the rate of pre-transplant and post-transplant AKI and CKD. First is the decades-long obesity epidemic, with resulting parallel increase in the...
prevalence of non-alcoholic steatohepatitis (NASH). Second is the development of highly effective and well-tolerated direct acting antiviral (DAA) agents for hepatitis C virus (HCV) infection. Third is adoption of the MELD score, which includes Scr as the most heavily weighted value in MELD based organ allocation.

In addition to the contribution of ESLD to kidney dysfunction, some causes of cirrhosis have disease specific kidney injury mechanisms. Hepatitis C virus (HCV), for example, is associated with membranoproliferative glomerulonephritis and type 2 cryoglobulinemia. Reversal of kidney dysfunction is not an inevitable consequence of HCV eradication, even for cryoglobulinemia (89). Similar to HCV infection, NASH is independently associated with CKD (90, 91), and alcoholic liver disease, which is associated with IgA nephropathy.

Liver disease secondary to HCV infection continues to be the most common indication for LT, affecting ~one third of LT recipients (92). NASH is the third most common indication for LT in the US and the second most common reason for being waitlisted (93). Although this may still be an underestimate of NASH frequency, since it does not account for the likely high prevalence of NASH among the 10% of recipients with "cryptogenic" cirrhosis (93).

Although the number of patients with HCV infection in need of LT is projected to rise in the coming decade (92), the rate of increase is a small fraction of that occurring for NASH (93). The frequency of HCV patients needing LT will also be affected by the advent of well-tolerated DAAs; recent clinical trials of DAAs have demonstrated safety and efficacy even in patients with decompensated cirrhosis (94). In addition, HCV viremia has been associated with an increased risk of CKD and ESRD (95); although data are lacking, one would expect improved renal outcomes after virologic cure.

Based on these well-established trends in the US LT waitlist composition, it is highly probable that NASH and HCV will comprise well over half of transplant activity for at least the next decade. Although the association of NASH with pre- and post-LT CKD is likely related to the relatively high prevalence of diabetes and hypertension, NASH is predictive of CKD independent...
of other factors (90, 96). As both of these diseases are independently predictive of pre- and post-LT CKD, the rise in NASH frequency and the continued high prevalence of HCV as top indications for LT will almost certainly result in increased rates of CKD pre- and post-LT.

**Implications of AKI Etiology on Mortality Risk of MELD Score**

The near ubiquitous presence of kidney hypoperfusion/ischemia in cirrhosis, with subsequent low fractional excretion of sodium, can make the diagnosis of ATN difficult. Robust data regarding the reversibility of AKI in patients with cirrhosis were generated in a prospective study of 562 patients with cirrhosis and AKI (97). The authors observed that HRS was less common than prerenal or infection-associated kidney injury. Of the nearly 500 patients in whom a diagnosis could be made, the most common precipitating causes of AKI were: infection (46%), prerenal (32%), HRS (13%), and parenchymal (9%) kidney disease. Approximately 80% of AKI in patients with cirrhosis is secondary to a treatable precipitating cause, and it has been estimated that 10-20% of patients with cirrhosis who develop AKI have an element of ATN.

The curvilinear association with increasing MELD score and waitlist mortality, coupled with the direct relationship of MELD score with likelihood of undergoing LT, raises the possibility that treating AKI in patients on the waitlist may improve short-term mortality but decrease the short-term likelihood of LT. The net effect of longer waitlist time, with associated increased waitlist mortality, together with longer duration of kidney dysfunction is difficult to calculate and has not been modelled. Perhaps in part for this reason, survival following HRS is primarily dependent on reversal of hepatic failure with less significant survival improvement following HRS reversal (52, 98). Instead, treating AKI, other than HRS-1, in waitlisted patients presumes reversibility of AKI and a net benefit of successful treatment.
When weighing the relative merits of a specific organ offer, it is important to consider that a MELD score contributed to by AKI differentially impacts 90-day mortality dependent on the AKI etiology (97). Differential weighting of Scr according to AKI etiology could, in theory, be utilized to reduce waitlist mortality, which might be accomplished by utilizing delta Scr instead of absolute Scr values (99).

Key Points and Recommendations:

- The increased prevalence of NASH, advent of DAA therapy for HCV infection, and MELD based organ allocation have changed the LT waiting list (1A), and likely increased the prevalence of CKD pre- and post-LT. 1C
- The etiology of kidney dysfunction in patients with ESLD alters its impact on prognosis. 1B

Considerations for SLKT

Since the introduction of the MELD score to assign priority for donor allocation, the proportion of LT recipients that undergo simultaneous liver-kidney transplantation (SLKT) has tripled.(http://srtr.transplant.hrsa.gov/annual_reports/) The increase in SLKT frequency is a reflection of: 1) the increasing frequency of ESRD among LT recipients and 2) the high priority for LT assigned to patients with kidney dysfunction. In addition to MELD based allocation increasing the risk for AKI and CKD pre-LT, the MELD at transplant is increasing nationwide (93). As a result, kidney dysfunction has almost become a requirement for patients to advance to the top of waitlist (100). Thus, at the time of LT, a high percentage of ESLD patients have significant AKI with or without CKD with variable improvement after LT (77, 101-105). It is well known that recipients with AKI that results in prolonged dialysis post-LT have reduced survival (106). It is therefore no surprise that SLKT utilization has increased (107). This would be acceptable if kidney allografts were readily available, but there is already a severe kidney
allograft shortage for patients with isolated ESRD who also have high waitlist mortality. Furthermore, the addition of a kidney transplant to the LT procedure adds significant operative time, potential morbidity, and marked cost.

Ideally, patients with HRS-AKI with a favourable response to vasoconstrictor therapy and intravenous albumin would receive prioritization for transplant with a liver only to facilitate a single organ transplant before irreversible kidney dysfunction occurred (63). Alternatively, MELD coefficients could be changed to decrease the weight of kidney dysfunction in the MELD score. However, because changes to MELD have proven difficult, the creation of stringent criteria to access SLKT has been proposed. In 2008, a United Network for Organ Sharing (UNOS) consensus conference evaluated allocation of kidneys to LT candidates with kidney dysfunction (108). Several agreed-upon parameters predicting non-recovery of native kidney function post-LT included (108): 1) CKD with estimated (MDRD equation) GFR ≤30 mL/min; 2) CKD on kidney biopsy (defined as >30% glomerulosclerosis and/or 30% fibrosis); 3) AKI with Scr ≥2.0 mg/dL and dialysis ≥8 weeks; 4) special consideration to patients with comorbidities (e.g. hypertension and diabetes) and to patients >65 years old; and 5) metabolic kidney disease (e.g. hyperoxaluria, atypical haemolytic uremic syndrome, methylmalonic aciduria). Conversely, not meeting these UNOS criteria implies an expectation of native kidney function recovery to acceptable levels after LT alone. However, the UNOS criteria are not official Organ Procurement and Transplantation Network (OPTN) policy, and as a result the current allocation system allows listing for SLKT based on subjective clinical judgment, with the UNOS criteria serving as a guideline. A recent survey of US transplant centers showed that AKI leading to dialysis for a minimum of 4 weeks and CKD (defined mainly by GFR<30 mL/min) were minimum criteria used by most centers to recommend SLKT (109). However, because adherence to this guidance is not mandatory, SLKT selection criteria continue to vary dramatically across the United States (109). Unfortunately, neither center nor national
guidelines predict kidney recovery with a high level of certainty (77, 108, 110, 111). Other predictors, such as kidney ultrasound, measured GFR (iothalamate, iohexol) and kidney biopsy, may be too subjective, inaccurate, invasive, and costly for universal clinical implementation for SLKT selection.

Ultimately, dissemination of appropriate, mandatory selection strategies is needed. Recently, the OPTN/UNOS Kidney Transplantation Committee in collaboration with the Liver Intestine Transplant Committee proposed more specific SLKT medical eligibility criteria with a safety net for LT only allograft recipients with a continued need for kidney transplantation. Specifically, pre-LT patients with CKD would need documentation of dialysis or GFR ≤35 mL/min, and patients with AKI would need GFR ≤25 mL/min for ≥6 consecutive weeks prior to SLKT listing (112). For patients who do not meet these criteria but have non-recovery of kidney function post-LT alone, kidney transplant waitlist prioritization has been proposed. Prioritization would occur after OPTN review verifies GFR ≤20 mL/min or continued dialysis 60-365 days post-LT. If accepted, these criteria will provide greater stringency for SLKT allocation and will facilitate kidney transplant in LT recipients with persistent kidney dysfunction after liver only transplantation. Fortunately, a similar policy supporting stringent criteria for SLKT allocation and the potential for a safety net of kidney allograft allocation in LT recipients without renal recovery has been proposed in Canada (113).

Even with specific clinical criteria for SLKT allocation, pre-operative biomarker assessment would ideally allow more accurate kidney allograft allocation (Table 5) (110). Recent data has demonstrated that biomarkers can more appropriately classify, quantitate, and prognosticate kidney dysfunction (18, 114, 115). The majority of these markers, such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), are elevated in acute tubular injury, contrast nephrotoxicity, or peri-operative kidney injury but may also be markers of kidney disease progression (116). Pre-LT other plasma protein profiles [osteopontin, tissue inhibitor of metalloproteinas-1 (TIMP-1)] in conjunction with clinical
variables (age, diabetes) might be able to better predict post-LT kidney function recovery, but need clinical decision algorithm testing for SLKT vs. LT alone (117). Furthermore, pre-LT biomarker assessment may facilitate early post-LT institution of kidney sparing immunosuppression regimens. While these data require further validation, future studies should test the utility of serum and urine biomarkers as serial measures to guide management, including the decision to perform a SLKT or to implement nephro-protective strategies. This might have a greater potential to assist individualized therapeutic and organ utilization strategies if combined with immunologic risk assessment biomarkers.

Key Points and Recommendations:

- Predicting which patients have irreversible kidney failure requiring SLKT versus reversible kidney failure, requiring LT alone, by commonly utilized current criteria is suboptimal. 1C
- National criteria for SLKT allocation combined with a “safety net” of kidney transplant prioritization for LT alone recipients with post-operative kidney failure could improve kidney organ allocation in the ESLD population. 1D
- Pre-operative biomarkers of kidney recovery that would allow more specificity in decision-making for SLKT versus LT alone have the potential to improve kidney organ allocation in the ESLD population. 1C

Looking to the Future

An essential step in optimizing post-LT GFR is better understanding and management of pre-LT kidney dysfunction. When attempting to determine a goal minimum GFR post-LT to aim for, recent data indicate that the relation between post-LT kidney function and subsequent mortality may be accurately quantified. In a large single-center study, a >30% reduction in eGFR

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between 3 and 12 months post-LT was associated with increased mortality (OR=2.6; p<0.001) (118). In a separate study, a GFR of 15-29 mL/min had a HR= 2.7 (p<0.01), and a GFR <15 mL/min had a HR=5.5 (p<0.01) (119) for mortality.

CNI nephrotoxicity remains a major contributor to kidney injury following LT. Future CNI mitigation strategies may include individualized management of immunosuppression. For example, genetic polymorphisms such as cytochrome P450 34A, ATP-binding cassette subfamily B-1, and nitric oxide synthase 3 have been linked to susceptibility to CNI toxicity (120-122) and could be tested pre-transplant to plan for post-transplant immunosuppression. Further validation of these and other associations accompanied by functional confirmation may inform personalized application of immunosuppression. For more information on optimizing post-liver transplant renal function please see our companion paper (1).

On the policy level, the best information must shape future allocation decisions. SLKT utilization and equitable/appropriate access to kidney transplantation via a ‘safety net’ is likely to remain contentious but a consensus is urgently needed. In order to maximize post-LT survival outcome, an optimal policy regarding SLKT would aim for a post-LT GFR target of >60 mL/min in the maximum number of organ recipients. In addition, introduction of novel therapeutic agents would require adaptation of the organ allocation policy. For example, while future therapy for HRS may restore Scr, whether the corresponding reduction in the MELD score is commensurate with mortality benefits, based on the kidney functional recovery must be studied. Ultimately, promoting timely organ allocation and preventing pre- and post-operative morbidity and mortality would require prospective multicentre data collaborations and accurate risk assessment tools to inform data-driven interventions and rational policy development addressing all stakeholders in LT.

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Key Points and Recommendations:

- The relationship between functional impairment of the kidney and subsequent mortality may be quantitatively assessed, with GFR<60 mL/min portending higher mortality risk. 2C. Future research to mitigate kidney injury in the pre- and post-LT periods is needed to achieve optimal post-LT kidney function.
- Future organ allocation policy must incorporate best available scientific data and adopt rational approaches to optimize pre- and post-transplant outcome of all organ transplant patients (i.e., liver alone, kidney alone and SLKT). 2C

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Figure Legend

Figure 1: Algorithm for management of AKI.
Supporting Information

Additional Supporting Information may be found in the online version of this article

Table S1: The GRADE System: Rating Quality of Evidence and Strength of Recommendations

Table S2: Proposed IAC-ADQI diagnostic criteria for kidney dysfunction in cirrhosis [adapted from reference

References:


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Table 1: Definition and Staging of Acute Kidney Injury. [Adapted from Nadim et al.(123)]

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<th>AKI Definition</th>
<th>AKI Stage</th>
<th>AKI Stage</th>
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<tr>
<td></td>
<td>Serum Creatinine Criteria</td>
<td>Urine Output Criteria</td>
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<tr>
<td>AKIN (2007) (13)</td>
<td>Increase Scr ≥ 0.3 mg/dL (26.5 μmol/L) within 48 hours; or increase Scr ≥1.5x baseline within 48 hours; or UO &lt;0.5 mL/kg/h x 6 hrs</td>
<td>Increase ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 hrs or ≥1.5-2x baseline</td>
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<td></td>
<td>Baseline Scr is first Scr measured</td>
<td>Increase ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 hrs or ≥1.5-2x baseline</td>
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<td>KDIGO (2012) (14)</td>
<td>Increase Scr ≥0.3 mg/dL (26.5 μmol/L) within 48 h; or increase Scr ≥1.5 x baseline, which is known or presumed to have occurred within the prior 7 days; or UO &lt;0.5 mL/kg/h for 6 hr</td>
<td>Increase ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 hrs or ≥1.5-2x baseline</td>
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<tr>
<td></td>
<td>Unknown baseline Scr estimation based on the MDRD formula, assuming a normal GFR of approximately 75 to 100 mL/min/1.73 m²</td>
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<td>ADQI (2010) (16, 17) AKI in cirrhosis</td>
<td>Increase Scr ≥0.3 mg/dL (26.5 μmol/L) within 48 hours; or increase Scr ≥1.5 x baseline</td>
<td>Increase ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 hrs or</td>
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<td></td>
<td>HRS-1 is a specific form of AKI</td>
<td>≥1.5-2x baseline</td>
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<td>ICA (2015) (21) AKI in Cirrhosis</td>
<td>Increase Scr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or increase Scr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days</td>
<td>Increase ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 hrs or ≥1.5-2x baseline</td>
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Scr within 3 months can be used as baseline. In patients with more than one Scr value, value closest to hospital admission should be used. In patients without previous Scr, Scr on admission should be used.

acute rise >0.5 mg/dL (44 μmol/L) or on RRT

Table 2. Prevention of AKI in patients with cirrhosis

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Preventive Strategies</th>
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<tr>
<td>Hepatorenal syndrome development</td>
<td>• Antibiotic prophylaxis following GI bleeding x 7 days. 1A</td>
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<tr>
<td></td>
<td>• Albumin infusion during large volume paracentesis (&gt;5L, 6-8 gm/L of ascitic fluid removed). 1A</td>
</tr>
<tr>
<td></td>
<td>• Secondary &amp; primary SBP prophylaxis with daily antibiotics, preferably norfloxacin. 1B</td>
</tr>
<tr>
<td></td>
<td>• Early recognition and treatment of SBP with antibiotics and IV albumin at the dose of 1.5 g/kg of body weight at the time of diagnosis of SBP and 1 g/kg of body weight on the third day of treatment. 1B</td>
</tr>
<tr>
<td></td>
<td>• Judicious use of diuretics.</td>
</tr>
<tr>
<td></td>
<td>• Avoid dehydration with lactulose use.</td>
</tr>
<tr>
<td>Exposure to nephrotoxic medications (ex: NSAIDs, aminogyclosides, amphotericin, vancomycin)</td>
<td>• Close monitoring of drug toxicity and early recognition of drug-induced AKI and discontinuation of offending agent if possible. 1A</td>
</tr>
<tr>
<td></td>
<td>• Use lipid formulations of amphotericin B rather than conventional formulations of amphotericin B. 2A</td>
</tr>
<tr>
<td></td>
<td>• Use azole antifungal agents and/or the echinocandins rather than conventional amphotericin B, if equal therapeutic efficacy can be assumed. 1A</td>
</tr>
<tr>
<td></td>
<td>• Avoid nephrotoxic medications whenever possible.</td>
</tr>
<tr>
<td>Radio-contrast exposure</td>
<td>• Consider alternative imaging methods or avoidance of IV contrast if possible.</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury, AKIN, Acute Kidney Injury Network; ADQI, Acute Dialysis Quality Initiative; hr, hour; hrs, hours; ICA, International Club of Ascites; KDIGO, Kidney Disease Improving Global Outcomes; kg, kilogram; min, minute, RRT, renal replacement therapy; Scr, serum creatinine; UO, urine output
• Use low or iso-osmolar agents with lowest volume possible. 1B

• Optimize fluid status prior to administration of IV contrast with IV normal saline or IV bicarbonate. 1A

• Consider N-acetylcysteine use in combination with IV hydration. 2D

Hemodynamic instability

• Increase mean arterial pressure in setting of shock to >65 mmHg. 1C

• Use of protocol-based management of hemodynamic and oxygenation parameters. 2C

• Optimal fluid resuscitation with crystalloids or colloids. 2B

• Vasopressors in patients with persistent hypotension (1C), consider norepinephrine as first line. 2D

GI: gastrointestinal; SBP: spontaneous bacterial peritonitis; NSAID: nonsteroidal anti-inflammatory drug

IV: intravenous

Table 3. Management of Acute Kidney Injury

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Comments</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| IV Fluids | Crystalloid or colloids | • Diarrhea or over-diuresis requires crystalloids. 1A  
• Gastrointestinal bleeding needs packed red blood cells if hemoglobin is <7g/dL. 1A  
• IV fluids should be administered carefully due to risk of volume overload. 1C  
• IV medication concentration or conversion to oral medication when possible. 1C |

| RRT | Hemodialysis or continuous renal replacement therapy | • RRT should be initiated in patients with worsening AKI, fluid overload despite diuretic therapy or problematic acid-base status. 1D |

| Terlipressin* | Vasopressin analogue | • HRS1 patients need resuscitation with IV albumin (initially 1 g albumin/kg for two days, up to a maximum of 100 g/day, followed by 20 to 40 g/day) in combination with a vasoconstrictor (1A), preferentially terlipressin. 1A  
• In countries where terlipressin is not available, norepinephrine can be used as an initial therapy in ICU patients or as an alternative in patients in whom midodrine + octreotide has failed. 1C |

0.5–1.0 mg q4-6h, increased on day 4-2 mg IV q4-6 h**, if Scr has not decreased by >30% from baseline following fluid resuscitation

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IV infusion of terlipressin is an alternative to bolus dosing with similar efficacy and fewer side effects.

| Midodrine + Octreotide* | Alpha-adrenergic agonist (midodrine)  
|                        | Somatostatin analogue (octreotide)  
| 7.5 mg orally TID with increase to 12.5-15 mg TID to increase MAP by 15 mm Hg + octreotide SQ 100 μg TID, titrated to 200 μg TID on day 2, if renal function has not improved*** |

- We recommend TIPS in patients with HRS1 with lower MELDs. 1C
- Artificial liver support therapies for HRS should be limited to research only. 2D

| Norepinephrine* | Alpha-adrenergic agonist  
|                 | 0.5–3.0 mg/h continuous IV infusion to increase MAP by 10 mm Hg.  

| Transjugular intrahepatic portosystemic shunt (TIPS) | Decreases portal hypertension with subsequent decrease in vasoconstrictory mediators (vasopressin, norepinephrine, endothelin and angiotensin II) leading to improved cardiac output and GFR. |

| Albumin dialysis | Dialyzing blood against albumin containing solution across a highly permeable high-flux membrane. Blood-bound toxins are cleared by diffusion and taken up by binding sites of the albumin dialysate |

*Given in combination with intravenous albumin (initial dose 1 g/kg followed by 20 to 40 g/d)

** In Europe continuous infusion rather than an intermittent doses of terlipressin is used as lower doses can be used with similar results and less side effects.

***The doses quoted for midodrine were initially reported in a study of 5 patients. There is no absolute rule to raise the MAP by 15 mmHg, but rather the MAP has to be raised to an adequate level to provide renal perfusion. The use of subcutaneous octreotide is an alternative to continuous infusion.
Table 4. Results of Studies Using Vasoconstrictor Therapy in Patients with Type-1 Hepatorenal Syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Patients</th>
<th>Patients with Type-1 HRS</th>
<th>Treatment</th>
<th>Albumin</th>
<th>HRS Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angeli (39)</td>
<td>1999</td>
<td>Retrospective</td>
<td>5</td>
<td>100%</td>
<td>Midodrine + Octreotide</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td>Dopamine</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Colle (40)</td>
<td>2002</td>
<td>Retrospective</td>
<td>11</td>
<td>100%</td>
<td>Terlipressin</td>
<td>+ / -</td>
<td>60%</td>
</tr>
<tr>
<td>Halimi (41)</td>
<td>2002</td>
<td>Retrospective, multicenter</td>
<td>18</td>
<td>89%</td>
<td>Terlipressin</td>
<td>-</td>
<td>72%</td>
</tr>
<tr>
<td>Moreau (42)</td>
<td>2002</td>
<td>Retrospective, multicenter</td>
<td>99</td>
<td>100%</td>
<td>Terlipressin</td>
<td>+</td>
<td>58%</td>
</tr>
<tr>
<td>Esrailian (43)</td>
<td>2007</td>
<td>Retrospective</td>
<td>60</td>
<td>100%</td>
<td>Midodrine + Octreotide</td>
<td>-</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td></td>
<td>No treatment</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Uriz (44)</td>
<td>2000</td>
<td>Prospective</td>
<td>9</td>
<td>67%</td>
<td>Terlipressin</td>
<td>+</td>
<td>77%</td>
</tr>
<tr>
<td>Mulkay (45)</td>
<td>2001</td>
<td>Prospective</td>
<td>12</td>
<td>100%</td>
<td>Terlipressin</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Ortega (46)</td>
<td>2002</td>
<td>Prospective</td>
<td>13</td>
<td>76%</td>
<td>Terlipressin</td>
<td>+</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td>Terlipressin</td>
<td>-</td>
<td>25%</td>
</tr>
<tr>
<td>Duvoux (47)</td>
<td>2002</td>
<td>Prospective</td>
<td>12</td>
<td>100%</td>
<td>Norepinephrine</td>
<td>+</td>
<td>83%</td>
</tr>
<tr>
<td>Solanki (48)</td>
<td>2003</td>
<td>Randomized</td>
<td>12</td>
<td>100%</td>
<td>Terlipressin</td>
<td>+</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td></td>
<td>Placebo</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Alessandria (49)</td>
<td>2007</td>
<td>Randomized</td>
<td>12</td>
<td>41%</td>
<td>Terlipressin</td>
<td>+</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td>Norepinephrine</td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>Neri (50)</td>
<td>2008</td>
<td>Randomized, Multicenter</td>
<td>26</td>
<td>100%</td>
<td>Terlipressin</td>
<td>+</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26</td>
<td></td>
<td>Placebo</td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>Sharma (51)</td>
<td>2008</td>
<td>Randomized</td>
<td>20</td>
<td>100%</td>
<td>Terlipressin</td>
<td>+</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td></td>
<td>Norepinephrine</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Sanyal (52)</td>
<td>2008</td>
<td>Randomized</td>
<td>56</td>
<td>100%</td>
<td>Terlipressin</td>
<td>+</td>
<td>34%</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Design</td>
<td>Multicenter</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>-----------------</td>
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<td>---------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin-Lahi</td>
<td>2008</td>
<td>Randomized, Multicenter</td>
<td>23</td>
<td>56%</td>
<td>Terlipressin + 44%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh</td>
<td>2012</td>
<td>Randomized</td>
<td>23</td>
<td>100%</td>
<td>Terlipressin + 39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavallin (124)</td>
<td>2015</td>
<td>Randomized</td>
<td>27</td>
<td>92%</td>
<td>Terlipressin + 70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavallin (62)</td>
<td>2016</td>
<td>Randomized</td>
<td>39</td>
<td>100%</td>
<td>Terlipressin Infusion + 56%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyer (57)</td>
<td>2016</td>
<td>Randomized</td>
<td>97</td>
<td>100%</td>
<td>Terlipressin + 24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>99</td>
<td></td>
<td>Placebo + 15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 5: Biomarkers of Acute and Chronic Kidney Injury in Patients with Cirrhosis and Post-Liver Transplant.

<table>
<thead>
<tr>
<th>BIOMARKER</th>
<th>Site of Origin</th>
<th>Source</th>
<th>Renal Injury in Cirrhosis?</th>
<th>Renal Injury in Liver Transplant Recipients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL (or lipocalin-2) (115, 125-130)</td>
<td>Activated Neutrophils, Renal Tubule</td>
<td>Serum, Urine</td>
<td>AKI</td>
<td>AKI</td>
</tr>
<tr>
<td>Cystatin-C (114, 131-136)</td>
<td>All Nucleated Cells</td>
<td>Serum, Plasma</td>
<td>AKI/CKD</td>
<td>AKI/CKD</td>
</tr>
<tr>
<td>Kidney injury molecule-1 (127, 137)</td>
<td>Renal Tubule</td>
<td>Serum, Urine, Tissue</td>
<td>AKI</td>
<td>-</td>
</tr>
<tr>
<td>Interleukin 8, 18 (126, 127, 129, 137)</td>
<td>Macrophages, Epithelium</td>
<td>Urine</td>
<td>AKI</td>
<td>AKI</td>
</tr>
<tr>
<td>Apolipoprotein AI, H, CIII (114, 138)</td>
<td>Hepatocyte, Enterocyte</td>
<td>Serum</td>
<td>-</td>
<td>CKD</td>
</tr>
<tr>
<td>Alpha-1, Beta-2 microglobulin (114, 139)</td>
<td>Alpha-1 (Liver); Beta-2 (all nucleated cells)</td>
<td>Serum</td>
<td>CKD</td>
<td>CKD</td>
</tr>
<tr>
<td>Tissue Inhibitor of metalloproteinase-1 (117)</td>
<td>Renal Tubule, Many Tissues</td>
<td>Plasma</td>
<td>AKI</td>
<td>-</td>
</tr>
<tr>
<td>Toll-like Receptor 4 (140)</td>
<td>Macrophages, Dendritic Cells, Fibroblasts</td>
<td>Urine</td>
<td>AKI</td>
<td>-</td>
</tr>
<tr>
<td>Trefoil Factor 3 (114, 141)</td>
<td>Enterocyte, Epithelium</td>
<td></td>
<td>AKI</td>
<td>CKD</td>
</tr>
<tr>
<td>Transforming growth factor beta-1 (142, 143)</td>
<td>Lymphocytes, Myeloid Cells</td>
<td>Urine</td>
<td>CKD</td>
<td>CKD</td>
</tr>
<tr>
<td>L-Fatty acid binding protein 1 (114, 117, 127, 130)</td>
<td>Hepatocyte, Enterocyte</td>
<td>Urine</td>
<td>AKI</td>
<td>AKI/CKD</td>
</tr>
<tr>
<td>Prostaglandin D2 synthase (144, 145)</td>
<td>Mast Cells</td>
<td>Serum, Plasma, Urine</td>
<td>CKD</td>
<td>CKD</td>
</tr>
<tr>
<td>Osteopontin (117, 141)</td>
<td>Fibroblasts, osteoblasts, most immune cells, muscle, endothelium, kidney</td>
<td>Serum, Plasma, Urine</td>
<td>AKI</td>
<td>-</td>
</tr>
</tbody>
</table>
Fig. 1. Algorithm for management of AKI

Pre-Renal (pre-renal azotemia, HRS)
  - Discontinue diuretics
  - Workup sepsis

Renal (GN, ATN, AIN)
  - Discontinue nephrotoxins
  - Workup sepsis

Post-renal (BPH, ACS)
  - Post-void residual
  - Foley placement
  - Renal ultrasound
  - Bladder pressure
  - Paracentesis for tense ascites

Clinically volume depleted (overdriuresis, diarrhea)
- Crystalloid and/or 5% albumin
- 25% albumin 1g/kg in first 24 hrs (≤150 g)

Assess AKI evolution at 48h

Resolution
- Surveillance

Persistence/Progression
- Hepatorenal Syndrome
- ATN
- Vasocommodator + Albumin

No improvement in kidney function
- Consider renal replacement therapy

Improvement in kidney function
- Stop therapy after complete response or for a maximum of 14 days or development of complications