Management of Renal Failure in End-Stage Liver Disease: A Critical Appraisal

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Renal failure is a late consequence of end-stage liver disease (ESLD). Even with liver transplantation, pretransplant renal impairment remains a strong predictor of posttransplant mortality. This review seeks to summarize and critically appraise common therapies used in this setting, including pharmacologic agents, procedures (transjugular intrahepatic portosystemic shunt, renal replacement therapy), and simultaneous liver-kidney transplantation. More experimental extracorporeal modalities, e.g., albumin dialysis or bioartificial livers, will not be discussed. A brief discussion on the definition and pathophysiologic underpinnings of renal failure in ESLD will be held at the beginning to lay the groundwork for the main section.

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Overview of Renal Failure in End-Stage Liver Disease

ASSESSING RENAL FAILURE

Glomerular filtration rate (GFR) is the standard surrogate for renal function. The first challenge in defining renal failure in end-stage liver disease (ESLD) is accurately assessing GFR. The classic biomarker, serum creatinine (SCr), is inversely but nonlinearly correlated with GFR. Because of the unavailability of methods to monitor dynamic GFR changes, SCr increase remains the only practical way to diagnose acute kidney injury (AKI). It thus forms the basis to the updated International Club of Ascites’ AKI definition: an increase in SCr of ≥0.3 mg/dL within 48 hours or ≥50% from baseline within 7 days.(1)

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function for ≥3 months. Impaired kidney function is traditionally defined as GFR < 60 mL/minute in most transplant trials. However, the degree of albuminuria (urine albumin-creatinine ratio ≥300 mg/g and 30 mg/g for macro and microalbuminuria, respectively) has been incorporated into the new CKD staging system because of its recognition as an important predictor of CKD progression and disease-specific mortality in the general population independent of GFR levels.(2) GFR is usually estimated using biomarkers as single time-points (Table 1). These equations, derived from and validated in ambulatory CKD patients without liver disease, are frequently inaccurate in the ESLD populations (reviewed in depth by Davenport et al.(3)). Newer estimating equations incorporating the measurement of serum cystatin C seem to have the best overall performance. However, all guidelines are still based on SCr and SCr-derived equations. Current consensus opinion is that the better-performing 6-variable Modified Diet in Renal Disease (MDRD6) formula(4-6,8,9) be used for clinical and research purposes. Previously CKD staging has been on the basis of GFR category (≥90,
Inulin urinary clearance
Iothalamate/iohexol clearance (serum tracer disappearance)
Creatinine-based methods
Single Scr measurement
Scr-based equations:
Cockcroft-Gault, MDRD4
Scr-based equation: MDRD6
24-hour creatinine clearance
Other methods
Serum cystatin C-based equations

60-89, 30-59, 15-29, and <15 mL/minute corresponding to stages 1, 2, 3, 4, and 5, respectively. The most recent Kidney Disease Improving Global Outcomes (KDIGO) 2012 practice guidelines have recommended staging CKD on 2 dimensions: GFR category and level of albuminuria. Although this terminology is commonly used to describe patients before and after liver transplantation (LT), caution must be taken:

1. These categories were established to stratify risk of death and progression to end-stage renal disease (ESRD) in general CKD patients, whereas in pre-LT patients these outcomes are more likely driven by liver disease-related pathologies, hence CKD staging does not necessarily confer more information beyond GFR alone.

2. Staging does not imply anything about underlying etiology or reversibility, a fact also emphasized by the KDIGO 2012 practice guidelines.

ETIOLOGIES OF RENAL FAILURE

Renal failure in ESLD is commonly characterized as AKI and CKD. However, the overlap between the two can be substantial (Fig. 1). AKI, especially if severe or recurrent, can result in an irreversible loss of kidney function toward progressive CKD. Similarly, preexisting CKD also predisposes a patient to AKI episodes. Managing either therefore requires familiarity with both entities.

AKI is typically classified as having prerenal, intrinsic, or postrenal etiologies. In ESLD, prerenal and intrinsic etiologies predominate, and the main conundrum is frequently deciding between type 1 hepatorenal syndrome (HRS) and acute tubular necrosis (ATN). The diagnostic criteria for type 1 HRS are the following in a patient with diagnosed cirrhosis and ascites:

1. AKI meeting the International Ascites Club definition (see preceding section).
2. No response after 2 consecutive days of diuretic withdrawal and 1 g/kg albumin infusion.
3. Absence of shock or nephrotoxin use.
4. No macroscopic signs of structural kidney injury, defined as significant proteinuria (>500 mg/day), hematuria (>50 red blood cells per high-power field), or renal ultrasonography abnormality.

Traditionally, type 1 HRS is considered a “functional” renal dysfunction in which no renal parenchymal damage is sustained. Two multicenter European and North American cohorts called this paradigm into question. Urinary neutrophil gelatinase-associated lipocalin (NGAL), an immune-related protein secreted into the urine within 2 hours of AKI, was measured in 272 patients with AKI in ESLD. Although prerenal...
azotemia and ATN were associated with the lowest and highest levels of urinary NGAL, respectively, HRS landed in the middle, and HRS triggered by infection had somewhat higher NGAL levels than HRS without. These findings suggest that there is likely a spectrum of structural damage underlying type 1 HRS, either from renal ischemia or from sepsis-induced inflammation, and that the duration of ongoing ischemic and septic insult will determine the extent and reversibility of the renal damage.

CKD is defined as evidence of impaired kidney function for ≥3 months. Biopsy studies illustrate the diversity of possible pathologies and the relative indiscrimination of clinical and urinary sediment findings (Fig. 1). In kidney biopsies undertaken in 55 patients with mostly nonviral ESLD, all specimens showed glomerular and tubular lesions. Though limited by a high selection bias, this study still highlights processes in ESLD, including bacterial antigen translocation and decreased hepatic immunoglobulin A (IgA) clearance, which can result in immune complex-mediated renal lesions. Two studies with less selection bias reported on protocol peri-LT renal biopsies in 8 children and 30 hepatitis C–positive adults:

although 33%-50% of these patients had no clinical or laboratory evidence of renal disease, the majority (83%-100%) had glomerular lesions with immune complex deposition on biopsy. The extent to which they contribute to the burden of kidney disease in LT candidates and how they should be managed remains unknown.

**PATHOPHYSIOLOGY OF RENAL IMPAIRMENT IN END-STAGE LIVER DISEASE**

Underlying renal impairment in ESLD are circulatory dysfunction and impaired renal autoregulation. Circulatory dysfunction, arising from splanchnic vasodilation, shunts blood volume away from baroreceptor sites to increase activities of the sympathetic, renin-angiotension-aldosterone, and vasopressin systems, fueling the development of a hyperdynamic circulation. As the disease progresses, cirrhotic cardiomyopathy and systemic inflammation develop; cardiac output no longer maintains adequate perfusion to vital organs. This renders the kidneys more dependent on autoregulation, or...
intrinsic intrarenal mechanisms to maintain renal blood flow and GFR despite mean arterial pressure drops. Some evidence is emerging\(^2\) that this process is impaired in ESLD, ie, there is a greater change in renal blood flow and GFR over the range of blood pressures commonly seen in ESLD patients (Fig. 2). These pathophysiologic processes underlie both AKI and CKD: the former, by rendering patients susceptible to insults from hemodynamic perturbation or infectious insult; the latter, by precipitating repeated episodes of AKI and by other possible immune-mediated phenomena as discussed in previous sections.

On the basis of this model, there are 2 phenotypic “flavors” of renal derangements in ESLD. In a study of 56 patients with cirrhosis,\(^2\) urinary sodium excretion, creatinine clearance, and renal blood flow decreased in parallel with worsening circulatory dysfunction. Clinically, these represent the continuum of diuretic-responsive ascites, refractory ascites, and type 2 HRS. In contrast, an extreme malfunction of renal autoregulation may be reflected in type 1 HRS, a rapidly progressive AKI characterized by intense renal vasoconstriction.\(^2\) The responsible factor is not known, although the best evidence points to renal prostaglandins.\(^19,23\) As will be discussed later, the treatment of choice for this condition is vasoconstrictor therapy. It remains poorly understood how a patient can remain in “remission” from type 1 HRS beyond the initial treatment period.

Recently, our understanding of renal failure in ESLD has been enhanced by the systemic “inflammation” hypothesis. Bacteria and/or pathogen-associated molecular patterns (PAMPs) translocate into the intestinal mucosa, where the PAMPs are released into the portal and eventually systemic circulation, triggering systemic inflammation.\(^2\) Inflammation translates to tissue injury in the kidneys in a manner that remains poorly understood.\(^2\) This explains the clinical observation that infection frequently triggers kidney failure, even in the absence of hypotension. The previous model of HRS, based solely on circulatory dysfunction, is thus a gross simplification, albeit still a useful one in approaching the risk factors and therapeutic principles of renal failure in ESLD.

**Pharmacologic Therapy**

**MANAGEMENT ALGORITHM**

The International Ascites Club has recently put forth a management algorithm for AKI in ESLD.\(^1\) It stratifies patients into 3 risk categories based on SCr rise and posits a tiered approach of risk factor modification, diuretic withdrawal, volume expansion, and vasoconstrictors. The risk categories have prognostic value but do not reflect underlying etiology. The resultant algorithm is therefore a practical approach to renal failure that still leaves room for different AKI phenotypes.

**MANAGEMENT OF RISK FACTORS**

The first step in management of renal failure is risk factor modification (Table 2). Hypotension is a key risk factor. As seen in Fig. 2, a simplified representation of the work done by Stadlbauer et al.,\(^2\) the relationship between renal blood flow and mean arterial pressure is increasingly altered as the cirrhosis stage worsens, a phenomenon known as loss of autoregulation. In a patient with advanced cirrhosis, who is frequently hypotensive at baseline, his or her kidneys “live” on the steep part of the curve, therefore any slight alteration in volume status or systemic vascular resistance with even a minor hypotensive effect can lead to a drastic reduction in renal blood flow and, subsequently, GFR. There are many exacerbating factors, but nonselective beta-blocker use deserves special
Nonselective beta-blockers prevent variceal hemorrhage through portal pressure reduction. A few recent observational studies\(^{(26,27)}\) suggested a potentially deleterious role of beta-blockers in more advanced ESLD, especially patients with refractory ascites requiring repeat paracentesis or experiencing spontaneous bacterial peritonitis (SBP). The cardiac reserve decreases as ESLD progresses to the point of developing refractory ascites and SBP, at which point beta-blockade may tip cardiac output to below the threshold of maintaining renal perfusion. This emerging concept, referred to as the “window” theory,\(^{(28)}\) suggests that beta blockade may be helpful only for a window of time between development of varices and complicated ascites. The prevention and early reversal of renal failure is thus critically dependent on careful pharmacologic management in advanced ESLD.

**INTRAVASCULAR VOLUME EXPANSION**

Given the circulatory dysfunction underlying advanced ESLD, measures to increase preload and thus cardiac output should improve renal function. Epstein et al.\(^{(29)}\) first demonstrated this by immersing patients with cirrhosis in water, a maneuver that resulted in natriuresis and diuresis. However, this maneuver did not improve renal function.

The infusion of concentrated albumin to promote diuresis in ESLD has been in use since the 1940s.\(^{(20)}\) Through a series of randomized controlled trials, albumin was shown to be effective in reducing postparacentesis circulatory dysfunction\(^{(30)}\) and preventing AKI and death from SBP.\(^{(31)}\) Its efficacy is not solely due to intravascular volume expansion, as other plasma expanders are not as effective.\(^{(32)}\) Antioxidant, detoxifying, fatty-acid transport, and vasoconstrictive properties of albumin have been suggested.\(^{(20)}\)

On the basis of these data, most trials evaluating pharmacologic agents in HRS have used albumin infusion concomitantly. It is indicated as first-line treatment of type 1 HRS.

### VASOCONSTRICTORS

Commonly used vasoconstrictors and their administrations are summarized in Table 3. The first use of vasoconstrictors in conjunction with intravascular expansion in ESLD was in 6 patients with mean GFR \(\sim 70 \text{ mL/minute} \) water immersion or norepinephrine alone did not improve urinary sodium excretion, but their combination did.\(^{(37)}\) Although it addressed management of refractory ascites and possibly type 2 HRS, the study did not answer how type 1 HRS should be treated.

A number of trials in the 1990s tested vasopressors, such as vasopressin agonists and catecholamines, for the treatment of HRS, which failed to show efficacy when used alone. Later trials showed, however, that a combination of vasopressor and albumin resulted in reversal of type 1 HRS.\(^{(38)}\) Terlipressin is now established as the standard of care in many parts of the world. In a meta analysis\(^{(33)}\) of 4 European

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Dose of Administration</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Terlipressin*</td>
<td>Bolus intravenous</td>
<td>1 mg every 12 hours – 1-2 mg every 4 hours; Sagi et al.(^{(33)}) (2010)</td>
<td>Until HRS reversal or 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 mg every 6 hours in recent negative trial; Boyer et al.(^{(34)}) (2016)</td>
<td></td>
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<tr>
<td>Norepinephrine</td>
<td>Continuous intravenous</td>
<td>Titrated to (\geq 10 \text{ mm Hg increase in mean arterial pressure or })</td>
<td>Until HRS reversal or 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\geq 200 \text{ mL increase in 4-hour urine output}; Duvoux et al.(^{(35)}) (2002)</td>
<td></td>
</tr>
<tr>
<td>Midodrine and octreotide</td>
<td>Oral and bolus subcutaneous</td>
<td>Midodrine 7.5-12.5 mg and octreotide 100-200 (\mu g) 3 times a day,</td>
<td>No protocol definition, up to 2 months; Angeli et al.(^{(36)}) (1999)</td>
</tr>
</tbody>
</table>

*Terlipressin is not available in the United States.
randomized controlled trials in 223 patients, bolus terlipressin for 14 days reversed type 1 HRS in 46% of patients versus 12% in control. Ischemic complications, including intestinal ischemia and myocardial infarction, were reported in 10% of study patients. Less encouraging were results from a large North American trial published this year,(34) wherein 196 patients were randomized to receive bolus terlipressin versus placebo. Although SCr decrease, which is a secondary outcome, was more pronounced in the terlipressin group, the study failed to achieve its primary endpoint: reversal of HRS. As HRS is characterized by a loss of renal autoregulation (Fig. 2), vasoconstrictor therapy resulting in an increase in blood pressure is expected to improve GFR and reduce SCr. The key is whether the underlying vicious cycle of renal vasoconstriction and azotemia is ameliorated, ie, whether HRS reversal has been achieved. One possible reason that the study was negative was that HRS reversal rate in the terlipressin arm was lower (24%) compared with previous studies (46%). This discrepancy may be a result of misclassification of patients with ATN as HRS, the short duration of terlipressin in the treatment arm, or frequent usage of competing treatment, including renal replacement therapy (RRT), as was pointed out in an accompanying editorial.(39)

As terlipressin is unavailable in the United States, norepinephrine is probably the best alternative. In the study by Duvoux et al.(35) on 12 patients with type 1 HRS, norepinephrine infusion was titrated to a \( \geq 10 \text{ mm Hg} \) increase in mean arterial pressure or \( \geq 200 \text{ mL} \) increase in 4-hour urine output, until HRS reversal or for 15 days. Albumin and furosemide were administered to maintain central venous pressures of 4–10 mm Hg. HRS reversal was observed in 10 of 12 patients after a median of 7 days and, more importantly, these patients remained HRS-free after study completion. Four subsequent small studies, 3 from the same center, compared bolus terlipressin with norepinephrine infusion. A meta-analysis of these trials showed no difference in HRS reversal or 30-day mortality.\(^{(40)}\) Adverse events, generally cardiac, were less common in the norepinephrine group. Though limited by small sample size and poor study quality, collectively these studies support the use of norepinephrine, in conjunction with albumin infusion, as the current best available therapy for HRS in the United States.

Because norepinephrine use requires continuous cardiac monitoring, the combination of midodrine and octreotide has been tried. Midodrine is an alpha-adrenergic agonist and vasoconstrictor. Octreotide is a somatostatin analogue which reduces splanchnic hyperemia. The evidence for this combination is sparse: a 15-patient study, nonrandomized, compared midodrine and octreotide with dopamine and demonstrated improved renal and systemic hemodynamics.\(^{(36)}\) A more recent small, open-label, randomized study demonstrated that this combination was ineffective compared with continuous terlipressin infusion.\(^{(41)}\)

In conclusion, high-quality evidence is lacking, and existent data do not support the use of midodrine and octreotide.

A second indication for vasopressor use in AKI is hypotension. This is distinct and separate from use of vasopressors for type 1 HRS. The management of non-HRS AKI and CKD is largely supportive. A cornerstone to supportive renal therapy is reversing hypotension, with the usual mean arterial pressure goal being \( \geq 65 \text{ mm Hg} \), as has been incorporated in all critical care resuscitation protocols. Using vasopressors, especially catecholamines, to achieve this blood pressure goal in non-HRS AKIs is therefore a reasonable extrapolation from the critical care literature, although this has not been studied specifically in patients with ESLD.

Procedural Therapy and Renal Replacement Therapy

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Transjugular intrahepatic portosystemic shunt (TIPS) insertion immediately improves the elevated hepatic venous pressure gradient. Although initially it worsens the already low systemic vascular resistance and augments the hyperdynamic circulation, these effects normalize over weeks as blood volume shifts from the splanchnic bed into systemic circulation. The net effect is improved renal blood flow, translating into improved natriuresis and GFR. These physiologic and clinical changes are demonstrated in multiple studies.\(^{(21,42,43)}\)

Despite the physiologic evidence, most studies reporting clinical outcomes were uncontrolled and underpowered. In type 2 HRS, TIPS improved GFR by \( \sim 20 \text{ mL/minute} \) in 2 studies.\(^{(21,43)}\) In the only study\(^{(43)}\) that included 14 type 1 HRS patients, the results were very favorable: 3-month survival was 64%; 4/7 patients recovered off hemodialysis. These results have not been replicated, and there are clear concerns over the safety of the procedure in patients with ESLD.
significantly decompensated liver function. Overall, in the absence of contraindications, TIPS should be considered for patients with type 2 HRS with refractory ascites.

RENAL REPLACEMENT THERAPY

RRT, ie, dialysis, differs from aforementioned therapies in that it does not reverse the underlying process causing renal failure. RRT only “replaces” some renal functions, including clearance of uremic toxins, solutes, and extracellular volume, while the kidneys are not functioning at a level sufficient to support life. The goal of RRT, then, is to support the patient until underlying kidney function recovers, in the case of AKI, or until the patient can receive a kidney transplantation, in the case of ESRD.

The timing of dialysis initiation in patients with ESLD has not been studied. In general AKI and CKD, early versus late dialysis initiation in patients have been compared in multiple prospective, interventional trials (eg, 2 recent examples for AKI and CKD). In neither case has an advantage to early initiation been established. Dialysis initiation, in both AKI and CKD, has therefore been dictated by the appearance of uremic complications, electrolyte disturbances, or volume overload that is refractory to maximal medical therapy. The same pattern of practice applies to patients with ESLD.

RRT exists in intermittent and continuous modalities. Continuous RRT includes continuous venovenous hemofiltration, continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration, which do not differ significantly from each other in practice. Continuous RRT removes toxins, solutes, and volume at a much slower rate than does intermittent hemodialysis but achieves comparable overall clearance due to its continuous nature. Its theoretical benefits over intermittent dialysis are as follows:

2. Less likely to worsen intracranial pressure arising from slower solute removal.

It thus makes physiologic sense to preferentially use continuous RRT in patients with severely decompensated ESLD as a bridge to LT. Outcome data for this practice are scarce. When extrapolations are made from the general AKI literature, definitive evidence in favor of continuous RRT over intermittent hemodialysis remains to be established.

INTRAOPERATIVE RENAL REPLACEMENT THERAPY

Some North American centers practice peri-LT RRT. Sedra and Strum summarize the rationale for intraoperative renal replacement therapy (ioRRT) as achieving better control of the following:

1. Metabolic acidosis in the anhepatic phase.
2. Hyperkalemia during reperfusion.
3. Hyponatremia before transplant and abrupt correction during reperfusion.

A glimpse of the performance of ioRRT is afforded by 3 single-center studies. In a total of 378 adult LT recipients who received ioRRT, 83% were on RRT before transplant. One-year posttransplant patient and graft survival were comparable to patients not requiring ioRRT at 2 of the 3 centers. The last center reported worse outcomes, but restricted ioRRT to only patients on preoperative RRT. On the basis of these data, the benefit of ioRRT over standard intraoperative support is entirely uncertain. According to clinicaltrials.gov, a single-center, phase 2 randomized controlled trial, INCEPTION, is ongoing to answer this question.

TRANSPLANT-RELATED THERAPY

“Renal-Sparing” Immunosuppression After Liver Transplantation

Incidence of advanced CKD and ESRD approaches 20% over 5 years in LT recipients. This is a combination of pretransplant renal dysfunction, immunosuppressant medications, and chronic metabolic changes, especially posttransplant diabetes. The first step to optimizing posttransplant renal outcomes is thus to manage these CKD risk factors. In addition, “renal-sparing” immunosuppression has been suggested. Calcineurin inhibitors (CNIs) have immediate, vasoconstriction-mediated, and longterm nephrotoxicity in addition to severe metabolic side effects. Multiple large multicenter studies have investigated successful strategies to reduce CNI exposure after LT, including everolimus use and delaying CNI introduction. However, these findings may be difficult to extrapolate to LT recipients with pretransplant renal failure by virtue of their study design: the ReSpECT trial, for instance, studied the feasibility of delayed CNI introduction but excluded patients with SCR
above 2.3 mg/dL on the day of transplant or who needed RRT.\(^{(55)}\)

For patients with pretransplant renal dysfunction, data on immediate postoperative immunosuppressant management are scarce. A representative study reports the experience with a CNI-free regimen of mycophenolate mofetil, steroids, and basiliximab induction with delayed introduction of sirolimus in 27 patients with a median preoperative GFR of 24 mL/minute.\(^{(56)}\) Over the 1-year follow-up, these patients experienced no rejection and marked GFR improvements, though there was no comparator group. Despite the scarcity of evidence, there is a trend in 2000-2009 toward increased use of CNI-free regimens, paralleling an increase in the prevalence of pretransplant renal dysfunction.\(^{(57)}\) High-quality studies are needed to optimize the immunosuppressive regimen in this setting.

**Simultaneous Liver-Kidney Transplantation**

The Model for End-Stage Liver Disease era has seen an increase in the number of simultaneous liver-kidney transplantations (SLKTs), where both organs from the deceased donor are transplanted into 1 recipient. The incremental benefit conferred by the kidney is still debated. In a representative study based on Organ Procurement and Transplantation Network (OPTN) data,\(^{(58)}\) patients undergoing LT with SCr \(\geq 2.0\) mg/dL have significantly worse outcomes than patients with SCr \(< 1.0\) mg/dL (63% versus 79% 5-year survival). SLKT ameliorates this, albeit incompletely: 5-year survival improves to 70%. Another study based on propensity score–based analysis of OPTN data,\(^{(59)}\) suggested that survival benefit may be as little as 1 month at 5 years after transplant.

Determining eligibility for this procedure is highly controversial: AKI can reverse with LT and time alone.\(^{(60,61)}\) However, due the multietiologic nature of renal failure in ESLD and unpredictability of the pretransplant and posttransplant course, it is difficult to predict prospectively whether pretransplant AKI will reverse. Current OPTN guidelines for SLKT listing criteria are limited by inaccurate assessment of GFR at the time of transplant\(^{(62)}\) and by discordance between guidelines and actual native kidney recovery after LT. In reports from 2 UNOS regions,\(^{(63,64)}\) 101 SLKT recipients underwent radionuclide renal scans after transplant: an astounding 46% had functioning native kidneys with GFR > 20 mL/minute, which would not usually qualify them for kidney transplant listing. Kidney biomarkers have been proposed to address this gap. However, research has not yet established whether biomarkers can predict longterm kidney function recovery in the general AKI, much less the LT, setting.

Ultimately, much of the controversy surrounding SLKT is driven by scarcity of organs. Underutilizing SLKT exposes LT recipients to excess mortality risk, whereas overutilizing SLKT reduces access of renal transplant candidates to life-prolonging transplants. The OPTN is in the process of standardizing listing criteria for SLKT as the following: metabolic diseases requiring SLKT (eg, primary hyperoxaluria), CKD (defined as estimated glomerular filtration rate [eGFR] \(< 60\) mL/minute for >90 days prior to listing and \(< 30\) mL/minute at the time of listing), sustained AKI (eGFR \(< 25\) mL/minute for 6 consecutive weeks).\(^{(65)}\) The field is therefore expected to undergo significant changes in the near future.

**Conclusion**

Renal failure, a marker of the severity of ESLD, represents a major driver of morbidity and mortality. The pathophysiology is complex and incompletely understood. Circulatory dysfunction, inappropriate systemic inflammation, and impaired renal autoregulation are felt to be key features. Major precipitating factors include predisposing factors of hypotension and medications interfering with renal autoregulation. Treatment is centered around restoring systemic circulation through intravascular volume expansion and vasoconstrictor therapy. There is a dearth of data on how to best deliver RRT when needed. Using a TIPS may ameliorate refractory ascites and type 2 HRS. LT, possibly with simultaneous kidney transplantation, remains the only cure.

**REFERENCES**


1. A patient with cirrhosis and ascites is admitted with AKI, serum creatinine is 2.1 mg/dL 24 hours later, after 2 liters of saline and cessation of antibiotics, serum creatinine is 2.0, urine sodium is <10 meq. This establishes the diagnosis of
   a. Hepatorenal syndrome
   b. acute tubular necrosis
   c. pre-renal azotemia
   d. none of the above

**True or False**

2. Infection can trigger kidney injury in cirrhosis even in the absence of hypotension

3. Acute kidney injury in cirrhosis is defined as an increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% from baseline within 7 days

4. Albumin prevents post paracentesis circulatory dysfunction mainly by acting as an intravascular volume expander

5. During episodes of hepatorenal syndrome, intrinsic kidney damage likely occurs

6. The combination of midodrine + octreotide is equivalent to norepinephrine + albumin in the treatment of hepatorenal syndrome

7. In advanced liver disease, renal function declines when cirrhotic cardiomyopathy can no longer supply the necessary cardiac output to perfuse the kidneys.

8. For patients with serum creatinine ≥ 2.0 do much better with combined liver/kidney transplant compared to liver transplant only.