Acute Kidney Injury Treatment in Decompensated Cirrhosis: A Focus on Kidney Replacement Therapy

Andrew S. Allegretti

Acute kidney injury (AKI) is a common complication of decompensated cirrhosis and is associated with high morbidity and mortality.[1] This population experiences 3 main types of AKI: volume mediated (prerenal), ischemic/nephrotoxic injury (acute tubular necrosis [ATN]), and hepatorenal syndrome (HRS). HRS is a functional injury unique to cirrhosis, characterized by decreased effective arterial circulation, renal vasoconstriction, and ultimately AKI.[2] Importantly, HRS can overlap or co-present with other types of AKI, further complicating the clinical picture. Early identification and management of AKI in cirrhosis is crucial because the severity of injury and delay in intervention is strongly associated with mortality.[3,4]

Supportive therapies include addressing complications of liver disease, reversing hemodynamic insults (bleeding, infection, volume depletion, etc), and in the case of HRS, plasma expansion with intravenous albumin and initiation of splanchnic vasoconstrictors (terlipressin is approved outside the United States and is first line in international guidelines).[2] Even with optimal medical therapy, many patients develop progressive AKI and an indication for kidney replacement therapy (KRT). In some cases, this puts a burden on treating clinicians to decide whether KRT fits within a patient's overall goals of care, and whether the benefits of KRT outweigh its risks. This article reviews the existing evidence and factors that should influence decisions around the use of KRT for AKI in cirrhosis.

As in the general population, KRT is used in cirrhosis when a patient develops an indication for dialysis that is refractory to medical management. The choice of KRT modality includes hemodialysis (HD), continuous KRT (CKRT), and peritoneal dialysis (PD). PD is largely understudied in cirrhosis and has interesting potential applications because it also provides a direct outflow port to drain concomitant ascites. Published data for PD use in cirrhosis are favorable, though these are limited to small case series and are at high risk for positive publication bias.[5] Concerns around PD use in this population include exacerbation of malnutrition through albumin loss in dialysate, increased risk for peritonitis, and inadequate infrastructure to transition from acute-start to maintenance PD treatment in this high-risk population. Still, given the push to increase home KRT modalities and the anticipated increase in PD use in the United States, further study here is warranted. Transitional dialysis units, which are growing in popularity and provide additional support during the peridialysis initiation period, may be an optimal venue for such investigation.[6]

Historically, HD and CKRT are the most commonly used KRT modalities in cirrhosis. Mechanically, intermittent HD may be less burdensome to patients and requires fewer hospital resources compared with CKRT in the intensive care unit.[7] However, cirrhotic patients often have low baseline blood pressure, and concern that this will limit ultrafiltration may push providers toward CKRT. Relative to HD, CKRT better preserves cerebral perfusion pressure, which is important in patients with fulminant hepatic failure and hyperammonemia who are at increased risk for cerebral edema.[8] Despite these theoretical advantages, CKRT has been associated with increased mortality in cirrhosis,[9,10] though this simply may reflect its necessity in the most critically ill patients in this cohort. Overall, the choice of HD versus CKRT in cirrhosis should be individualized for each patient based on hemodynamic factors, degree of volume removal required, and vulnerability to complications of dialysis.

By far the most important factor in deciding whether a patient with AKI and cirrhosis should receive KRT is the potential candidacy for liver transplantation. In the simplest terms, cirrhotic patients who require KRT fall into 1 of 3 categories: (1) already listed for a liver transplant, (2) not listed but are potentially eligible, or (3) have a clear contraindication to liver transplantation. Those already listed for a liver transplant are the most straightforward group. These patients should be transferred to their listing institution and initiate KRT as a bridge to transplantation. Once on KRT, published rates of survival to liver transplantation range from 23% to 48%,[9,11,12] depending on transplantation region, era of study, and age range (pediatric vs adult). Decisions about KRT prescription, modality, and goals of KRT should be made in concert with the multidisciplinary transplant team. The second group, patients who are not listed but may be eligible, has a similarly straightforward KRT plan. In this case, they should be urgently transferred to a liver transplantation center for an expedited transplantation evaluation, as well as initiated on KRT while the evaluation is ongoing. Few studies have examined whether timing of KRT initiation (either before or after liver transplant listing) is associated with survival; 1 study that analyzed this did not find a statistical difference in mortality based on the timing of listing.[9]

Perhaps the most challenging subgroup of the 3 includes cirrhotic patients with contraindications to liver transplantation. There has long been a bias against providing KRT for AKI in cirrhosis without the opportunity for transplantation, particularly in HRS. This belief seems to stem from a small cases series from the 1970s, as well as expert opinion at the time, in which dialysis was often deemed "futile" in cases of HRS.[13,14] However, there

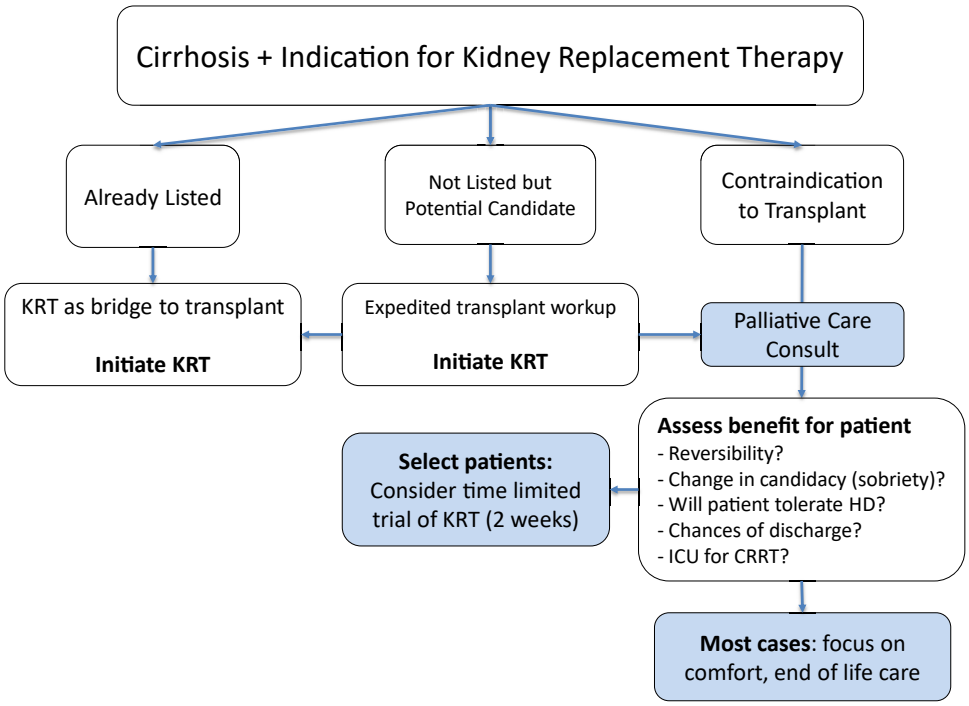

Figure 1. Suggested treatment approach for patients who require kidney replacement therapy (KRT) for acute kidney injury in cirrhosis. Abbreviations: CRRT, continuous renal replacement therapy; HD, hemodialysis; ICU, intensive care unit.

is no clear evidence that patients with HRS do any worse with KRT than those with other causes of AKI. As early as 1995, Keller et al[15] analyzed 82 patients with AKI and cirrhosis who met criteria for KRT and found that thrombocytopenia. encephalopathy, and malignancy, but not HRS, were risk factors for mortality.

In the modern era, several studies have examined predictors of short-term survival around KRT for AKI in cirrhosis, with similar results. Witzke et al[10] examined 30 patients with HRS receiving CKRT or HD and found that no patients who required mechanical ventilation survived. Staufer et al[16] analyzed 78 cirrhotic patients in the intensive care unit undergoing KRT, noting 83% mortality at 28 days and 100% mortality in patients with more than 5 organ failures. Similarly, a recent series of 66 cirrhotic patients requiring CKRT reported 89% in-hospital mortality.[17]

The largest observational study to address predictors of survival on KRT was from our transplantation center, which looked at 472 consecutive patients who received KRT either for HRS or ATN. Among 341 patients not listed for liver transplantation, 6-month mortality was identical between the HRS and ATN (84% vs 85%) groups. For all patients, median transplantation-free survival was 15 and 14 days for HRS and ATN, respectively ($P = 0.60$), and only 9% of patients recovered off dialysis in the absence of transplantation. Traditional measures of illness in this population, including Model for End-Stage Liver Disease (MELD) score, admission to the intensive care unit, and use of CKRT, were significant predictors of mortality, while HRS (compared with ATN) was not.[9]

Current evidence supports that most patients, regardless of cause of AKI, are likely to die in the hospital after starting KRT, especially those with critical illness. However, the decision to dialyze is not always made purely on medical criteria. Often providers feel a burden that they are "withholding" a life-sustaining therapy by not offering KRT, even if evidence suggests that it does not provide a meaningful chance of recovery for most patients. In the last year of life, 80% of patients with decompensated cirrhosis die in the hospital (70% in the intensive care unit), and 70% receive life-sustaining procedures (mechanical ventilation, KRT, or cardiopulmonary resuscitation).[18] More work is needed to optimize end-of-life care in this group.

Still, there are a select group of patients for whom a time-limited trial of KRT may be warranted in the absence of transplantation options, particularly for those for whom eligibility may change in the future or when underlying liver dysfunction may improve. A young patient with acute alcoholic hepatitis on advanced liver disease seemingly fits these criteria. One study of 47 patients requiring KRT with alcoholic liver disease demonstrated similarly high 6-month mortality (79%) and low kidney recovery rates (13%) as the larger cirrhotic population.[19] The ability to tolerate long-term dialysis also should be considered because the capacity to treat such complex patients at an outpatient dialysis center may be limited. Although clinicians often consider future changes in transplantation eligibility in this decision-making process, the data suggest that it is statistically unlikely for a cirrhotic patient initiating KRT to survive long enough for their eligibility to change.

Overall, more studies and innovations for patients with cirrhosis and severe AKI are sorely needed. The positive findings of the CONFIRM trial, the largest terlipressin versus placebo trial for HRS, were recently presented and corroborate prior pivotal trials from Europe.[20] However, at the time of this publication, terlipressin is not approved by the US Food and Drug Administration in the United States.

Despite the challenges described, I have 3 clear recommendations. First, all therapeutic options should be exhausted before considering KRT for AKI in cirrhosis (including terlipressin, if it is available). Second, the cause of AKI (HRS vs ATN) should not factor into the decision to initiate KRT. Third, the following algorithm should be used for approaching this population (Fig 1). Most patients who are ineligible for liver transplantation would most likely benefit from a conservative and comfort-based management of AKI, including palliative care consultation, whereas a select group of patients warrant a time-limited trial of KRT. A clear discussion of expectations of outcomes before initiation of KRT is integral to synergizing patient and provider expectations and minimizing potentially harmful and unnecessary invasive measures.

ARTICLE INFORMATION

Author's Full Name and Academic Degrees: Andrew S. Allegretti, MD, MSc

Author's Affiliation: Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, MA.

Address for Correspondence: Andrew S. Allegretti, MD, MSc, Division of Nephrology, Department of Medicine, Massachusetts General Hospital, 55 Fruit St, GRB 1008, Boston, MA 02114. E-mail: aallegretti@mgh.harvard.edu

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