Patients with Hepatorenal Syndrome Should Be Dialyzed? CON

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Introduction
AKI is a common and notorious complication that affects up to 20% of hospitalized patients with cirrhosis (1). The incidence of AKI, however, increases in parallel with the progression of the liver disease. The incidence of AKI in patients with cirrhosis also varies according to how AKI was defined. For example, if the updated International Ascites Club definition of AKI in patients with cirrhosis is utilized to define AKI, the risk of AKI in patients with cirrhosis has been reported to occur in up to 30% of hospitalized patients with cirrhosis (2,3). Fortunately, almost two-thirds of AKI cases in patients with cirrhosis respond to volume expansion, especially with albumin infusion, whereas the remaining one-third is attributed to either hepatorenal syndrome (HRS) or acute tubular necrosis (ATN) (1).

HRS is a specialized functional type of prerenal AKI that occurs exclusively in patients with advanced cirrhosis and those with fulminant hepatic failure. Although the overall pathophysiology of HRS is complex, the main underlying mechanism of AKI is intense renal vasoconstriction, and therefore, HRS AKI is resistant to volume expansion (4). Despite the continuous efforts to update the HRS diagnostic criteria, differentiating HRS from other causes of AKI, especially ATN, is often difficult in clinical practice (5).

Irrespective of the etiology of AKI, it is well established that AKI in patients with cirrhosis is associated with worse prognosis, with the highest mortality being observed in the 20%–25% of patients with progressive AKI that necessitates RRT initiation (6,7). Recent studies have also demonstrated that there are no major differences in outcomes in patients with cirrhosis and AKI due to HRS compared with those with ATN after RRT has been initiated (8). Moreover, most studies that addressed the outcome of patients with cirrhosis who started RRT did not specify the etiology of AKI, except for the studies by Allegretti et al. (8) and Zhang et al. (9). It is important to mention that despite that the merit of RRT initiation has been questionable in patients with cirrhosis, especially in those with no chance of getting on the liver transplant (LT) waiting list, recent evidence demonstrates that the rate of RRT initiation in patients with cirrhosis and AKI in the United States has increased from 1.5% in 2006 to 2.2% in 2012 (7). In this report, we will systematically address the evidence against RRT initiation in patients with cirrhosis and AKI irrespective of the AKI etiology and will propose a real life plan of action when managing these patients.

Historical Perspective
The idea of RRT in patients with cirrhosis and AKI is not new. In 1977, Wilkinson et al. (10) initiated 25 patients with cirrhosis and AKI on RRT. The authors observed a high rate of complications, including intradialytic hypotension, bleeding, peritonitis, and prolonged hospital stay (10). In addition to these complications, RRT did not save patients’ lives, with an observed mortality rate of 100% that left the authors wondering the utility of RRT without definitive treatment for the underlying disease. In 2005, Wong et al. (11) revisited the utility of RRT in 102 patients with cirrhosis and AKI. Fortunately, by that time LT was widely accepted, and almost half of the patients included in that study were on the LT waiting list. More than two-thirds (69%) of those listed for an LT, however, died waiting for a suitable organ, and 30% of the remaining one-third who received an LT died within 1 year from receiving an LT (11). Notably, mortality was nearly universal (94%) in those who were not listed for an LT.

RRT in Patients with Cirrhosis and AKI in the Contemporary Era
Over the course of the last decade, few reports emerged describing the outcome of patients with cirrhosis who developed AKI requiring RRT in the contemporary era. Zhang et al. (9) published their experience with 80 patients with HRS AKI who failed vasoconstrictor therapy. Thirty-seven (46%) patients received RRT, whereas in the remaining 43 patients, AKI was managed conservatively without needing RRT (9). The overall 30-day mortality and LT-free mortality rates were 50% and 70%, respectively, and were comparable between the RRT and no RRT groups, indicating no clear survival advantage of RRT in these patients. Patients on RRT, however, had more prolonged hospitalization (17 versus 12 days in the no RRT group) (9).

Allegretti et al. (8) identified 472 patients with cirrhosis who were acutely initiated on RRT at five
hospitals in the Boston area. Of these, 131 (28%) were listed for an LT (47 of these were listed after RRT initiation), whereas the remaining 341 were not considered to be LT candidates. The 6-month mortality for the whole cohort was 76% and was higher (85%) in those not listed, whereas the 6-month survival for those listed for an LT was slightly better at 40%–50%, with no difference in mortality between those with HRS and ATN as the cause of AKI. This study identified factors associated with the risk of death within 6 months from RRT initiation that included not being listed for an LT (adjusted hazard ratio [aHR], 2.67; 95% confidence interval [95% CI], 2.02 to 3.51), need for intensive care unit (ICU) care (aHR, 1.99; 95% CI, 1.37 to 1.68), concomitant mechanical ventilation (aHR, 1.32; 95% CI, 1.04 to 1.67), and continuous RRT as the initial RRT modality (aHR, 1.25; 95% CI, 1 to 1.57). Only 59 (12%) patients were alive at 6 months, and without receiving an LT, of these only 34 (7%) recovered kidney function. RRT slightly prolonged survival in the nonlisted group on RRT with a median (interquartile range [IQR]) survival of 14 (IQR, 4–50) days compared with 2 (IQR, 1–7) days in a reference group of 159 patients with cirrhosis in whom RRT was not offered due to patient or provider preference. For those who were listed for an LT and on RRT, 63 (48%) patients were transplanted. The median (IQR) transplant-free survival was 14 (IQR, 4–34) days, 6-month mortality was 50%, and 30-day transplant-free survival was only 25% (8).

Staufer et al. (12) studied the outcomes of 193 critically ill patients from Europe with cirrhosis and AKI without specifying the etiology of AKI. Of these, 78 received RRT, and 115 did not. Compared with the no RRT group, patients who initiated RRT had lower 28-day survival (17% versus 30%, P=0.01). Only 23 of the 78 (30%) patients survived their ICU stay; of these, only ten recovered kidney function, and three patients eventually received an LT. Almost all (12 of 13, 92%) patients who did not recover kidney function died. Although this study confirms the high mortality rate of patients requiring RRT initiation, the authors identified higher chronic liver failure-sequential organ failure assessment score and chronic liver failure-consortium acute on chronic liver failure score scores assessed 48 hours after RRT initiation but not at ICU admission to predict ICU mortality (AUCs of 0.86 and 0.87, respectively) (12). It is important to mention that the 28-day survival in another recent series from the United States for patients with cirrhosis who started RRT was 44%, indicating that center practice and improvement in patient care affect the outcome of critically ill patients with cirrhosis and RRT-requiring AKI (13).

Taken together, both old and recent literature confirm that RRT initiation in patients with cirrhosis and AKI carries a very poor prognosis and is associated with a high mortality rate that ranges between 60% and 80% within 28 days from RRT initiation. Even in those listed for an LT, the 30-day transplant-free survival from RRT initiation was 23%, indicating that the high mortality rate is not related to other comorbidities that might preclude LT (e.g., cancer) but rather, is due to the severity of the underlying disease. Factors that correlated with disease severity predicted higher mortality after RRT initiation and were remarkably consistent among studies (both old and new). These factors included concomitant mechanical ventilation, vasopressor support, and higher ICU scores 48 hours after RRT initiation. It is important to mention that although RRT initiation was associated with slightly prolonged short-term survival compared with no RRT irrespective of the LT listing status (8,12), the long-term survival remained poor, which makes the higher rate of complications and the prolonged hospitalization unjustifiable, especially for those who have no hope of receiving an LT.

How to Deal with Patients with Cirrhosis and AKI Requiring RRT Who Are LT Candidates
On the basis of the available evidence, RRT should not be denied to patients with cirrhosis listed for an LT and those who are in the evaluation process with the understanding that the decision of RRT initiation/continuation will be revisited if changes in transplant eligibility occur. As mentioned earlier, these patients are at high risk of dying without getting a timely LT. Hepatology, nephrology, and intensive care teams should concentrate their efforts to optimize the patient for an LT.

How to Deal with Patients with Cirrhosis and AKI Requiring RRT Who Are Not LT Candidates
In patients with cirrhosis who are not considered to be LT candidates, the decision of RRT initiation has been considered futile in many cases, especially with the high mortality rate, low rate of renal recovery, high risk of complications such as bleeding, and more prolonged hospitalization, which consumes health care resources. In many situations, it is absolutely clear that RRT should not be offered to some patients. This includes patients in the ICU with multiorgan failure who are receiving concomitant mechanical and vasopressor supports, especially when the denial for an LT is irrefutable (e.g., metastatic cancer). In these patients, we believe RRT initiation will be unjustifiable and potentially harmful. However, in other situations, it is difficult to determine who will recover kidney function. RRT initiation might also buy the patient and the family valuable time for a last-minute family reunion. For that reason, a time-limited trial of RRT to assess the potential of renal recovery and to allow time and comfort to the patient and family is a reasonable option, especially in those with a reasonable chance of renal recovery (young age, no history of ascites, and those with AKI related to sepsis) and lower chance of death (no concomitant mechanical ventilation, vasopressor support, ICU care, or multiorgan failure). Early involvement of the palliative care team will be beneficial in setting goals and preparing the patient and family to discuss a goal-directed plan of care. After the duration of the time-limited RRT trial has expired and if there are still no signs of renal recovery or change in transplant candidacy, further continuation of RRT is not justifiable, and transfer to hospice care should be considered.

Disclosures
H.M. Wadei has provided consultation and participated in advisory board meetings for Mallinckrodt Pharmaceuticals (maker of terlipressin).

Funding
None.
Acknowledgments
The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions
H.M. Wadei wrote the original draft.

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Received: November 16, 2020 Accepted: December 8, 2020

See related debate, “Patients with Hepatorenal Syndrome Should Be Dialyzed? PRO,” and commentary, “Patients with Hepatorenal Syndrome Should Be Dialyzed? COMMENTARY,” on pages 406–409 and 413–414, respectively.