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 cirrhotic patients. The incidence of AKI however increases in parallel with the progression of the liver disease. The incidence of AKI in cirrhotic patients also varies according to how AKI was defined. For example, if the updated International Ascites Club (IAC) definition of AKI in cirrhotic patients is utilized to define AKI, the risk of AKI in cirrhotic patients has been reported to occur in up to 30% of hospitalized cirrhotic patients. Fortunately, almost two-thirds of AKI cases in cirrhotics respond to volume expansion especially with albumin infusion while the remaining one-third is attributed to either hepatorenal syndrome (HRS) or acute tubular necrosis (ATN).

HRS is a specialized functional type of pre-renal AKI that occurs exclusively in patients with advanced cirrhosis and those with fulminant hepatic failure. While 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. 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.

Irrespective of the etiology of AKI, it is well established that AKI in cirrhotic patients is associated with worse prognosis with the highest mortality being observed in the 20-25% of patients with progressive AKI that necessitate RRT initiation. Recent studies have also demonstrated that there are no major differences in outcome in cirrhotic patients with AKI due to HRS compared to those with ATN once RRT has been initiated. Moreover, most studies that addressed the outcome of cirrhotic patients who started RRT did not specify the etiology of AKI except for the studies by Allegretti and Zhang. It is important to mention that despite that the merit of RRT initiation has been questionable in cirrhotic patients especially in those with no chance of getting on the liver transplant waiting list (LT), recent evidence demonstrates that the rate of RRT initiation in cirrhotic patients with AKI in the US has increased from 1.5% in 2006 to
2.2% in 2012. In this report, we will systematically address the evidence against RRT initiation in cirrhotic patients with 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 cirrhotic patients with AKI is not new. In 1977, Wilkinson initiated 25 cirrhotic patients with AKI on RRT. The authors observed a high rate of complications including intradialytic hypotension, bleeding, peritonitis and prolonged hospital stay. In addition to these complications, RRT did not save patients’ lives with an observed mortality rate of 100% which left the authors wondering the utility of RRT without definitive treatment for the underlying disease. In 1995, Wong and colleagues revisited the utility of RRT in 102 cirrhotic patients with 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 LT however died waiting for a suitable organ and 30% of the remaining third who received a LT died within 1 year from receiving a LT. Notably, mortality was nearly universal (94%) in those who were not listed for LT.

**RRT in AKI cirrhotic patients in the contemporary era**

Over the course of the last decade, few reports emerged describing the outcome of cirrhotic patients that developed RRT requiring AKI in the contemporary era. Zhang and colleagues published their experience with 80 hepatorenal syndrome (HRS) with AKI who failed vasoconstrictor therapy. Thirty-seven (46%) patients received RRT while in the remaining 43 patients AKI was managed conservatively without needing RRT. The overall 30 days mortality and LT-free mortality 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. RRT
patients however had more prolonged hospitalization (17 days versus 12 days in the no RRT group)\textsuperscript{9}.

Allegretti and colleagues identified 472 cirrhotic patients who were acutely initiated on RRT at five hospitals in the Boston area\textsuperscript{8}. Of these, 131 (28\%) were listed for LT (47 of these were listed after RRT initiation) while the remaining 341 were not considered to be LT candidates. The 6-month mortality for the whole cohort was 76\% and it was higher (85\%) in those not listed while the 6-month survival for those listed for 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 LT (aHR: 2.67), need for ICU care (aHR:1.99), concomitant mechanical ventilation (HR: 1.32), and continuous RRT (CRRT) as the initial RRT modality (aHR 1.25). Only 59 (12\%) patients were alive at 6 month and without receiving a LT, of these only 34 (7\%) recovered kidney function. RRT slightly prolonged survival in the non-listed group on RRT with a median (IQR) survival of 14 (4, 50) days compared to 2 (1, 7) days in a reference group of 159 cirrhotic patients in whom RRT was not offered due to patient or provider preference. For those who were listed for LT and on RRT, 63 (48\%) patients were transplanted. The median (IQR) transplant-free survival was 14 (4,34) days, 6-month mortality was 50\% and 30 days transplant-free survival was only 25\%\textsuperscript{8}.

Stauffer and colleagues studied the outcomes of 193 critically ill cirrhotic patients from Europe with AKI without specifying the etiology of AKI. Of these 78 received RRT and 115 did not. Compared to 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 10 recovered kidney function and 3 patients eventually received a LT. Almost all (12/13, 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 a higher CLIF-SOFA and
CILF-C ACLF scores assessed 48 hours after RRT initiation but not at ICU admission to predict ICU mortality (AUC of 0.86 and 0.87, respectively)\textsuperscript{12}. It is important to mention that the 28 days survival in another recent series from the US for cirrhotic patients who started RRT was 44% indicating that center practice and improvement in patient care affect the outcome of critically ill cirrhotic patients with RRT-requiring AKI\textsuperscript{13}.

Taken together, both old and recent literature confirm that RRT initiation in cirrhotic patients with 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 LT, the 30-day transplant-free survival from RRT initiation was 25% indicating that the high mortality rate is not related to other comorbidities that might preclude LT (e.g. cancer) but rather 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 to no RRT irrespective of the LT listing status\textsuperscript{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 in receiving a LT.

**How to deal with cirrhotic patients with AKI requiring RRT who are LT candidates?**

Based on the available evidence, RRT should not be denied to cirrhotic patients listed for 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 LT.

**How to deal with cirrhotic patients with AKI requiring RRT who are not LT candidates?**

In cirrhotic patients 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 rates 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 ICU patients with multi-organ failure who are receiving concomitant mechanical and vasopressor supports especially when the denial for 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 multi-organ 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.
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Author contributions

H.M. Wadei: Writing - original draft
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