


Patients with Hepatorenal Syndrome Should Be Dialyzed? COMMENTARY

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Introduction

The rate of RRT for AKI in patients with decompensated cirrhosis (DC) is on the rise. In a study of 3,655,700 DC hospitalizations, the proportion of DC hospitalizations with AKI requiring RRT doubled between 2009 and 2012 (1). Of the many causes of AKI in patients with DC, hepatorenal syndrome type 1 (HRS-1) is perhaps the most vexing. Reasons for this include its complex pathophysiology involving splanchnic vasodilation and intrarenal vasoconstriction; its everchanging diagnostic criteria and nomenclature; and high short-term mortality leading to a widespread perception of clinical futility (2). Liver transplantation (LT) is the definitive therapy for HRS-1 and liver failure, but HRS-1 often progresses to advanced kidney failure before LT (2,3). In this context, nephrologists are faced with the dilemma of initiating RRT in patients with exceptionally poor short-term survival. In this issue of *Kidney360*, Dr. Wadei and Dr. Velez were tasked with debating the use of RRT in patients with HRS-1. This commentary aims to provide background on HRS-1 and highlight this debate's key issues.

Approach to AKI in DC

Prerenal azotemia, acute tubular necrosis (ATN), and HRS-1 are the primary causes of AKI in patients with DC (4). The initial approach to AKI in these patients is diagnostic and therapeutic. To correct prerenal azotemia, diuretics are withdrawn, and intravascular volume is expanded with intravenous albumin for 48 hours. If AKI persists and other causes of AKI are excluded, clinicians must then differentiate between ATN and HRS-1 (2,3). HRS-1 is a diagnosis of exclusion and relies on the International Club of Ascites criteria for diagnosing AKI in cirrhosis (3,5). Treatment of ATN is supportive, whereas administration of albumin and vasoconstrictors (midodrine and octreotide, NE, or terlipressin, where available) may reverse HRS-1 (2,3). LT is the definitive treatment for liver failure and HRS-1 may subsequently resolve in some patients (2,3).

The standard indications for RRT in patients with DC and AKI include hyperkalemia, volume overload, uremia, or severe acidemia. Additional indications in patients with DC include severe hyponatremia or volume overload, leading to increased intracranial pressure and risk of brainstem herniation (6,7). Continuous

RRT (CRRT) is used in hemodynamically unstable patients and does not raise intracranial pressure, unlike intermittent hemodialysis (6,7). In selected patients, CRRT may be used to mitigate cerebral edema and encephalopathy due to severe hyperammonemia, but the threshold ammonia level requiring initiation of CRRT remains controversial (8). In patients with indications for RRT, clinicians must then assess the risk/benefit ratio of RRT and consider the patient's goals of care in the context of liver failure. Here, Dr. Velez and Dr. Wadei agree that RRT is appropriate in patients with HRS-1 as a bridge to LT. But how do we approach RRT in patients with HRS-1 who are not LT candidates?

Withholding RRT in DC

There are several situations in which withholding RRT might be appropriate in AKI, including: (1) patient refusal after informed consent or *via* advance directive; (2) severe, permanent neurologic impairment; (3) conditions where RRT is not technically feasible; (4) when the risk of RRT exceeds the benefit; or (5) in the presence of an extrarenal terminal illness (9). It is the latter three situations that are pertinent to this debate.

Several complications of RRT may limit feasibility and increase the risk of RRT in patients with DC. Hemodynamic instability can be precipitated by third spacing, bleeding, or cardiac dysfunction (6,7). Placement of dialysis catheters can be complicated by bleeding from coagulopathy and thrombocytopenia. Filter clotting may be increased in these patients, yet systemic anticoagulation can exacerbate bleeding and regional citrate anticoagulation can cause ionized hypocalcemia and metabolic acidosis, due to impaired hepatic citrate metabolism (7). Notably, these limitations result from liver failure rather than the specific cause of AKI. Withholding RRT in patients with HRS-1 must therefore hinge on the assumption that HRS-1 is a terminal illness with a prognosis significantly worse than ATN.

Classically, the survival for patients with HRS-1 was thought to be only a few weeks (2,10). As pointed out by Dr. Velez and Dr. Wadei, early studies in patients with DC demonstrated that RRT was associated with high short-term mortality, particularly in patients with HRS-1. However, Dr. Velez and Dr. Wadei both

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highlight a recent study by Allegretti *et al.* (10), which assessed the outcomes of 472 cirrhotic patients that required RRT for ATN or HRS-1. This study has two important implications for this debate. First, the 6-month mortality in patients not listed for LT was 85% and did not differ between HRS-1 and ATN (10). Second, higher model for end-stage liver disease score, older age, and critical illness were better predictors of mortality than the cause of AKI (10). These findings suggest that factors beyond the etiology of AKI should be considered in RRT decision making in patients with DC.

The accuracy of HRS-1 diagnosis is another critical issue raised in this debate. Even if the prognosis of HRS-1 is meaningfully different than ATN, can we be confident enough in the diagnosis to withhold RRT? As discussed by Velez *et al.* (2), the accuracy of a clinical diagnosis of HRS-1 is poor when compared with the consensus definition. A recent study of 504 patients with cirrhosis and AKI demonstrated that approximately 20% of AKI patients could not be categorized, despite the use of robust computational algorithms (11). These observations should caution clinicians against using the diagnosis of HRS-1 as the primary justification for withholding RRT.

Conclusions

Dr. Wadei and Dr. Velez agree that RRT is appropriate in patients with HRS-1 who are LT candidates. In non-LT candidates, the arguments presented in this debate imply that a decision about RRT initiation should not depend on the underlying cause of AKI for two reasons. First, clinical outcomes in patients with DC and ATN or HRS-1 are similarly poor. Improved pharmacologic treatments for HRS-1 could alter the course of this condition and have implications for RRT decision making in HRS-1 patients, irrespective of LT candidacy. Second, ATN and HRS-1 cannot be reliably differentiated with currently available clinical tools. Future research dedicated to improving the accuracy of HRS-1 diagnosis is needed. In the meantime, nephrologists must take an active role in counseling patients and other clinicians about the prognosis of AKI and set clear expectations for time-limited trials of RRT in selected patients with DC.

Disclosures

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Author Contributions

K.R. Regner conceptualized the study, was responsible for project administration and supervision, wrote the original draft, and reviewed and edited the manuscript.

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See related debates, “Patients with Hepatorenal Syndrome Should Be Dialyzed? PRO,” and “Patients with Hepatorenal Syndrome Should Be Dialyzed? CON,” on pages 406–409 and 410–412, respectively.