Patients with Hepatorenal Syndrome Should Be Dialyzed? PRO

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Decompensated cirrhosis is an ominous medical condition that often places health care providers at a quandary of managing very complex clinical scenarios. The complexity of those scenarios further escalates when AKI superimposes over decompensated cirrhosis, signifying the collision of two life-threatening disorders. Arguably, the difficulty of managing the coexistence of decompensated cirrhosis and AKI reaches its peak when the medical decision-making conundrum around the provision of dialysis is faced, particularly when the etiology of AKI is presumed to be hepatorenal syndrome type 1 (HRS-1).

HRS-1 is a unique form of AKI in patients with cirrhosis and portal hypertension mainly characterized by a profound reduction in kidney perfusion (1,2). The cornerstone of treatment of HRS-1 is vasoconstrictor therapy. However, vasoconstrictor therapy may only lead to improvement in kidney function in up to about 30–40% of patients (3). Thus, patients with HRS-1 often rapidly deteriorate and reach a point when dialysis becomes medically necessary. Then, the traditional view has been that HRS-1 is associated with a uniquely high mortality rate (4–7). In the absence of liver transplantation, its in-hospital mortality rate was reported to be around 90%, not affected by dialysis, and has a median survival of 2 weeks (5,6). As a result, because of its presumed inability to extend survival, dialysis in such settings has been historically deemed futile.

Is the Evidence that the Mortality of HRS-1 that Progressed to Need for Dialysis is Worse than that of Any Other Cause of AKI Unequivocal?

The assertion that the mortality rate associated with HRS-1 is greater than that of other causes of AKI in cirrhosis originated from a report on 463 patients with cirrhosis and kidney failure (4). The reported 90-day survival rate of 201 patients diagnosed with HRS-1 was 23%, compared with 71% for those with a parenchymal cause of AKI. HRS-1 was linked to an odds ratio of 6.9 (95% confidence interval, 2.2 to 21.6) for 3-month mortality. The authors also reported a survival rate of 42% for hypovolemic AKI, surprisingly worse than that of parenchymal AKI, a counterintuitive finding that raises concerns about proper adjudication of diagnoses. Importantly, the study did not report whether the survival rate differences among types of AKI were applicable to those requiring dialysis. Earlier studies limited to patients with cirrhosis who required dialysis reported dismal outcomes (8,9). Among 25 patients with cirrhosis and AKI requiring dialysis, the in-hospital mortality rate was 100% (9). However, the cohort included ten patients with HRS-1 and 11 with acute tubular necrosis (ATN), and fatalities occurred in both subgroups. Furthermore, most patients in that study were treated with peritoneal dialysis rather than hemodialysis. Therefore, the observations may not be fully applicable to current practice that heavily leans toward hemodialysis and continuous RRT (CRRT). Nevertheless, a more recent European study demonstrated that among cirrhotics, AKI requiring dialysis (intermittent hemodialysis or CRRT) was associated with 91% 90-day mortality compared with 43% for AKI not requiring dialysis (10). However, no distinction was made on the basis of cause of AKI.

A more recent study has further challenged the notion of worse outcomes of HRS-1 compared with ATN when the AKI state reaches the point of dialysis requirement. In a large cohort of 472 patients with cirrhosis and AKI who underwent dialysis, the mortality rates of those with HRS-1 as a cause of AKI were compared with those with ATN (11). Among those not listed for liver transplantation, 47 of 56 (84%) patients with HRS-1 and 242 of 285 (85%) of those with ATN died within 6 months. In addition, for those listed for liver transplantation, 24 of 62 (39%) patients with HRS-1 and 35 of 69 (52%) patients with ATN died within 6 months. Therefore, the authors concluded there was no clear evidence that HRS-1 is linked to greater mortality compared with that of ATN. A preliminary examination to this question in our single center has revealed similar findings (12). Consequently, the existing evidence puts in question earlier observations and traditional assertions. Notably, the observational nature of the aforementioned studies further hampers the ability to draw unequivocal conclusions.

Can the Diagnosis of HRS-1 be Made with Certainty? If so, can that Certainty be Carried over to Make Decisions Around Provision of Dialysis?

If it is assumed HRS-1 that progresses to necessitating dialysis has distinctly greater mortality compared with ATN or other forms of AKI, it then becomes critical to correctly diagnose the cause of AKI in patients with...
To accomplish this, the standard approach is to utilize the diagnostic criteria established by the International Club of Ascites. However, those criteria are not without pitfalls. Multiple confounding factors exist in real clinical scenarios when one tries to apply those criteria (3). Illustrating those pitfalls, an examination of documented discharge diagnosis codes revealed that a correct diagnosis of HRS-1 was only assigned to 27 of 46 (59%) of hospitalized patients with cirrhosis (13). Similarly, in a single-center study, manual review of medical records determined that correct adjudication of HRS-1 as a cause of AKI occurred in only 27 of 73 (37%) individuals with AKI and decompensated cirrhosis (14). Even in an attempt to employ computational diagnostic algorithms, 104 of 504 (21%) of patients were categorized as “maybe HRS-1” or “indeterminate” (15). Thus, given the uncertainty and the lack of a gold-standard test for diagnosis, it seems unwise to place much weight on the distinction between HRS-1 and ATN when it comes to serious end-of-life recommendations. At best, practitioners can only suspect the cause of AKI may be HRS-1. This uncertainty should translate into an open-minded approach when it comes to provision of dialysis.

**Is Dialyzing a Patient with Cirrhosis Not Eligible for Liver Transplantation Completely Futile?**

Patients with cirrhosis who require acute dialysis, particularly those in intensive care units, are very complex, with a high risk of death. Because dialysis is not offered in many instances under the premise of futility, there is paucity of data assessing their outcomes. In a descriptive study of 107 patients with decompensated chronic liver disease and AKI, which included 27 patients with HRS-1 as a cause of AKI, the role of hemodialysis was examined (16). The 1-year survival rate for those who received acute hemodialysis was 28% compared with only 2% for those with AKI who were not dialyzed, although it was indicated. Patients who were not dialyzed were significantly older and with greater incidence of coma, whereas those who received hemodialysis had higher rates of sepsis. The effect of hemodialysis on survival was further examined in the subgroup of patients with HRS-1 revealing a similar survival advantage, with seven of 16 (43%) who received hemodialysis remaining alive at 1 year compared with one of nine (11%) of those who did not receive dialysis. The same study looked at risk factors for mortality. Among those who received hemodialysis, thrombocytopenia, malignancy, and encephalopathy were identified as being associated with higher mortality rate, but not HRS-1 diagnosis (16). In another study assessing factors affecting mortality rate in patients with cirrhosis and HRS-1 undergoing hemodialysis, it was found that requirement of CRRT, mechanical ventilation, and catecholamine support were strongly associated with greater death rates (17). A more recent study in patients with alcoholic liver disease also reported the use of vasopressors and CRRT as the strongest indicators of
What Conclusions can be Made?

What Are the Collateral Implications of Life-Sustaining Measures in Patients with Decompensated Cirrhosis Ineligible for Liver Transplantation?

Whereas cumulative data may point toward a paradigm shift toward reconsideration for offering dialysis to patients with cirrhosis and AKI due to HRS-1, close attention has to be paid to examining the overall implications of keeping those patients alive without a path for liver transplantation. A short report of four patients with HRS-1 who received hemodialysis despite being ineligible for liver transplantation illustrated a wide range of length of survival of 5–65 weeks (19). However, the extended survival was closely associated with frequent hospitalizations and an average 33% of the time spent in this hospital. This phenomenon aligns with a growing number of hospitalizations among cirrhotic patients, despite a trend for decreased mortality in the United States between 2002 and 2010 (20). Therefore, it is recommended to carefully weigh out the potential for reversibility of the AKI and the morbidity associated with a short-lived extension of life span with dialysis in a patient with cirrhosis and AKI not eligible for liver transplantation.

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Author Contributions

J.C.Q. Velez was responsible for the conceptualization, data curation, investigation, methodology, and validation, wrote the original draft, and reviewed and edited the manuscript.

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See related debate, “Patients with Hepatorenal Syndrome Should Be Dialyzed? CON,” and commentary, “Patients with Hepatorenal Syndrome Should Be Dialyzed? COMMENTARY,” on pages 410–412 and 413–414, respectively.