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AKI-HRS, more than a name change for type-1 hepatorenal syndrome

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HOW IMPORTANT IS RENAL FAILURE IN A PATIENT WITH LIVER CIRRHOSIS?

Acute renal failure (ARF) development is likely the most relevant event in the natural history of severely decompensated cirrhosis. It is a common complication affecting 20-49 % of inpatients with decompensated cirrhosis (1). Also, its presence is associated with a notable increase in morbidity and mortality, and hampers management of classical cirrhosis decompensations such as ascites or hepatic encephalopathy. In the CANONIC study, which defined the severity of acute-on-chronic liver failure (ACLF), the isolated presence of renal failure (defined as serum creatinine [Cr] higher than 2 mg/dl) was associated with a high short-term mortality rate that was strikingly higher

than that associated with failure of other significant organs in this context, including the liver and brain (2). While ARF has in most instances a prerenal origin (gastrointestinal bleeding, excessive use of diuretics or laxatives, etc.), it is important to highlight the presence of other causes of ARF. In this respect, ARF increasingly develops in patients with established chronic kidney disease (e. g., diabetic nephropathy in a patient with metabolic liver disease, etc.), which hinders diagnosis and worsens prognosis (3). There is no doubt, therefore, that renal function must be routinely monitored in patients with cirrhosis much in the same way as liver function or the presence of clinical decompensation.

WHAT IS MEANT BY HEPATORENAL SYNDROME, AND WHY WAS A REVISION OF THIS CONCEPT NECESSARY?

Type-1 hepatorenal syndrome (HRS-1) is a type of functional ARF that is characteristic of patients with cirrhosis and ascites. Its pathophysiology is related to the development of portal hypertension and the presence of bacterial translocation and cell damage associated with sterile inflammation, which favor the development of extreme splanchnic arterial vasodilation leading to effective hypovolemia. In this setting, compensatory mechanisms become activated, including renal arterial vasoconstriction, which results in a sudden drop in renal arterial flow and glomerular filtration rate (4). HRS-1 was defined in 1996 as a fast increase in Cr to double its baseline level within two weeks, up to above 2.5 mg/dl without evidence of structural kidney damage (5). Combined use of albumin and splanchnic vasoconstrictors such as terlipressin (preferably administered in continuous infusion [6]) remains the key pillar of therapy. While their use is associated with complete recovery of renal function in approximately one third of patients, no improvement in transplant-free survival at 90 days was observed but in the subgroup of patients responsive to telipressin (7,8). Presently, liver transplantation remains the sole curative treatment for HRS-1, hence patients should be referred early for assessment to a center with a liver transplantation program.

For decades, HRS-1 was synonym to rapidly progressing ARF with a poor prognosis even with treatment. Reducing short-term mortality for patients who do not respond

to drug therapy (approximately, two of every three patients with HRS-1), especially for those who are not eligible for liver transplantation, remains the primary challenge. Hence it was important to identify any factors related to higher odds of worse response to treatment. In this regard, lower Cr levels at the start of HRS-1 treatment have been independently associated with improved response to therapy and survival (9,10). Furthermore, a number of studies have shown that an increase in Cr ≥ 0.3 mg/dl over baseline implied a notable increase in short-term mortality (11). Because of this, it was soon agreed that the then-extant definition, based on a static Cr cut-off, had to be revised, as it delayed treatment onset and therefore increased mortality rates. Thus, in 2015, the International Ascites Club lined up with international consensus recommendations in the field of Nephrology (RIFLE [Risk, Injury, Failure, Loss y End Stage Kidney Disease], KDIGO [Kidney Disease: Improving Global Outcomes], and AKIN [Acute Kidney Injury Network] guidelines), and incorporated the *acute kidney injury* (AKI) concept into the setting of ARF in cirrhotic patients (12). The new definition is based on the dynamic change of Cr values (change ≥ 0.3 mg/dl) in the short run, establishing a serum Cr level cut-off (1.5 mg/dl) to identify the group at the highest risk of developing HRS. The new definition changed the ARF management paradigm in liver cirrhosis by transforming a dichotomous definition based on a fixed cut-off value into a dynamic entity with intermediate stages and specific therapeutic measures to render treatment homogeneous; more importantly, it allows anticipating the AKI-HRS diagnosis (current term replacing HRS-1). The table 1 included shows the new AKI classification according to Cr levels and the new definition of AKI-HRS.

WHAT BENEFITS DOES THE NEW AKI-HRS DEFINITION OFFER IN CLINICAL PRACTICE?

The new definition emphasizes that, rather than only a fixed Cr concentration, other factors are available that better predict the prognosis of patients with AKI: a) the dynamic changes of serum Cr levels; and b) the patient's response to initial measures (discontinuing diuretics, adjusting beta-blocker doses, adequate treatment of infection, etc.) (13). Similarly, the new definition focuses on patients at high risk of progression to AKI-HRS, allowing an early identification of those benefiting from close management to anticipate vasoconstrictor therapy should there be no response to

fluid overload and should the patient meet AKI-HRS criteria (Fig. 1). In this respect, a post-hoc analysis of the patients included in the REVERSE trial (terlipressin *vs* placebo in patients with HRS -1 according to the classical definition) (14) revealed that by using the new AKI-HRS definition treatment onset would have occurred earlier by a mean of four days, with a significantly lower degree of kidney function impairment. Although the impact on survival was not specifically analyzed, the authors conclude that the aforementioned anticipation may be expected to have a beneficial influence on therapy response and patient survival. In 2021, the findings of the CONFIRM study, a multicenter, randomized, double-blind trial to assess the effectiveness of terlipressin and albumin *vs* albumin monotherapy for reverting HRS-1, were reported (7). With 300 patients included, this is the largest clinical trial of terlipressin thus far in this indication. The study showed that the likelihood of HRS-1 resolution was higher in the group receiving terlipressin (32 *vs* 17 %, $p < 0.05$). However, the study showed no benefit on transplant-free survival at 90 days, and there was a higher percentage of severe adverse events (respiratory failure, particularly) (15). The main limitation of this study was that it used the older definition of HRS rather than the newer definition of AKI-HRS, hence it remains once more unknown whether an earlier diagnosis with AKI-HRS and early onset of vasoconstrictor therapy might have resulted in higher odds of renal failure resolution, a lower adverse events rate, and improved survival.

WHICH FACTORS MAKE IT DIFFICULT TO APPLY THE NEW AKI-HRS DEFINITION IN CLINICAL PRACTICE?

Over the past few years we have incorporated a number of diagnostic and therapeutic approaches into clinical practice, which have contributed to improve prognosis for patients with cirrhosis. The use of non-cardioselective beta-blockers in patients with clinically significant portal hypertension in order to prevent first decompensation or chronic intravenous albumin infusions for outpatients are both examples of how early modulation of key aspects in the pathophysiology of portal hypertension may allow increase survival (16,17). The new AKI classification and the updated AKI-HRS concept are most likely part of these advances. However, the use of the new AKI-HRS concept remains only partially incorporated into routine clinical practice for several reasons. On

the one hand, it takes time for a deeply updated concept to become widespread and eventually replace the older version; it is the case now with ARF as was with ACLF or, more recently, with the non-invasive diagnosis and management of patients with portal hypertension (18). On the other hand, terlipressin therapy onset tends to be delayed because of the need for patient monitoring during treatment or of reluctant concern for its safety profile. However, terlipressin may be administered as continuous infusion through a peripheral venous catheter with a lower risk for adverse events. Also, while the fact that terlipressin may improve renal function has not been extensively demonstrated, no clinical trials are available that unequivocally show a benefit on survival, particularly in patients not eligible for a rescue liver transplant. Finally, while the current definition of AKI-HRS represents an undeniable advance in the management of these patients, it remains an exclusion diagnosis that is often mixed up with other AKI causes such as acute tubular necrosis. It is therefore desirable that biomarkers (for instance, neutrophil gelatinase-associated lipocalin [NGAL]) become incorporated into routine clinical practice (19).

CONCLUSION

The HRS concept has notably evolved over the past few decades in close association with the conduction of large registry trials for vasconstrictor therapies. Besides demonstrating benefits for HRS resolution, these trials served to generate a valuable dataset allowing a revision of the ARF concept in cirrhosis. The latest revision, also the most ambitious since the syndrome was first described, focused on the importance of diagnostic anticipation for, until alternative therapies are developed for this severe complication, the sole measure potentially capable of improving patient prognosis involves earlier diagnosis and therapy onset. Multiple issues remain to be resolved for this condition, including clarification of the usefulness of renal replacement therapy and of the impact of TIPS in the prevention of this syndrome, among many others. A number of clinical studies are ongoing, precisely with the objective of assessing how do biomarker use and the new syndrome definition affect survival in these patients. Most likely, their results will prompt a new concept revision to allow an individualized approach to this complex syndrome.

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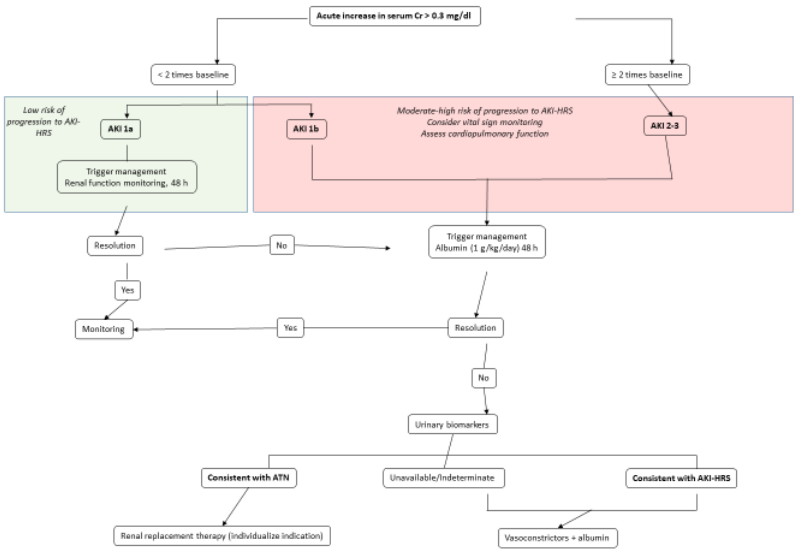

Fig. 1.

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Table 1. Definition of AKI stages according to the International Ascites Club classification

Stage 1: increase in serum creatinine ≥ 0.3 mg/dl *or* increase in serum creatinine by 1.5- to 2-fold from baseline (based on measurements in the past 3 months, using the value closest to AKI onset): • Stage 1a: creatinine < 1.5 mg/dl • Stage 1b: creatinine ≥ 1.5 mg/dl
Stage 2: increase in serum creatinine by 2- to 3-fold from baseline
Stage 3: increase in serum creatinine above 3-fold from baseline *or* serum creatinine ≥ 4 mg/dl with acute increase ≥ 0.3 mg/dl *or* initiation of renal replacement therapy
New diagnostic criteria for AKI-HRS
Increase in serum creatinine ≥ 0.3 mg/dl over 48 hours or increase in serum creatinine by ≥ 1.5-fold from baseline
Presence of liver cirrhosis with ascites
No response to: • Discontinuation of diuretics • Expansion with 20 % albumin (1 g/kg/day) for 48 hours
No shock
No recent or concomitant use of nephrotoxic drugs (radiographic contrast dye, NSAIDs, etc.)
No evidence of renal parenchymal damage: • No proteinuria (> 500 mg/day) • No hematuria (> 50 red blood cells per field) • Normal findings in bladder-kidney ultrasound

NSAIDs: non-steroidal anti-inflammatory drugs.

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