Review

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News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document☆

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Summary

Renal dysfunction is a common, life-threatening complication occurring in patients with liver disease. Hepatorenal syndrome (HRS) has been defined as a purely "functional" type of renal failure that often occurs in patients with cirrhosis in the setting of marked abnormalities in arterial circulation, as well as overactivity of the endogenous vasoactive systems.[4,5] In 2007, the International Club of Ascites (ICA) classified HRS into types 1 and 2 (HRS-1 and HRS-2).[5] HRS-1 is characterised by a rapid deterioration of renal function that often occurs because of a precipitating event, while HRS-2 is a moderate and stable or slowly progressive renal dysfunction that often occurs without an obvious precipitant. Clinically, HRS-1 is characterised by acute renal failure while HRS-2 is mainly characterised by refractory ascites. Nevertheless, after these two entities were first described, new concepts, definitions, and diagnostic criteria have been developed by nephrologists for renal dysfunction in the general population and hospitalised patients. In particular, the definitions and characterisation of acute kidney injury (AKI), acute kidney disease and chronic kidney disease have been introduced/refined.[6] Accordingly, a debate among hepatologists of the ICA led to a complete revision of the nomenclature and diagnosistic criteria for HRS-1, which was renamed HRS-AKI.[7] Additionally, over recent years, greater granularity has been gained regarding the pathogenesis of HRS; it is now increasingly recognised that it is not a purely "functional" entity with haemodynamic derangements, but that systemic inflammation, oxidative stress and bile salt-related tubular damage may contribute significantly to its development. That is, HRS has an additional structural component that would not only make traditional diagnostic criteria less reliable, but would explain the lack of response to pharmacological treatment with vasoconstrictors plus albumin that correlates with a progressive increase in inflammation.

Because classification, nomenclature, diagnostic criteria and pathogenic theories have evolved over the years since the traditional classification of HRS-1 and HRS-2 was first described, it was considered that all these novel aspects be reviewed and summarised in a position paper. The aim of this position paper authored by two hepatologists (members of ICA) and two nephrologists involved in the study of renal dysfunction in cirrhosis, is to complete the re-classification of HRS initiated by the ICA in 2012 and to provide an update on the definition, classification, diagnosis, pathophysiology and treatment of HRS.

Keywords: Liver Disease; Cirrhosis; Acute Liver Failure; Acute on chronic liver failure; Portal Hypertension; Systemic Inflammation; Acute kidney Injury; Acute Kidney Disease; Chronic Kidney Disease; Serum creatinine; Biomarkers; NGAL; Terlipressin; Albumin; Noradrenaline; Midodrine; Liver transplantation; Simultaneous liver Kidney Transplantation; MELD.

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Introduction

Renal dysfunction is a severe complication of advanced cirrhosis.[1–3] Traditionally, renal dysfunction in patients with liver disease has been defined by a serum creatinine (sCr) concentration of ≥1.5 mg/dl.[4,5] In this context, acute kidney injury (AKI) has been defined by the abrupt doubling of the baseline value of sCr to a final value >1.5 mg/dl. Beyond the well-known types of AKI that can occur in the general population, namely, prerenal, intrarenal or intrinsic, and post-renal, patients with cirrhosis may develop a specific type of renal dysfunction that has been called hepatorenal syndrome (HRS).[8] HRS has been defined as renal dysfunction that occurs because of reduced renal perfusion, due to haemodynamic alterations in arterial circulation, as well as overactivity of the endogenous vasoactive systems.[4,5] HRS has been classified into two different clinical types; type I HRS (HRS-1) involves a rapid reduction in renal function, defined by a doubling of the initial sCr to a level greater than 2.5 mg/dl or a 50% reduction of the initial 24 h creatinine clearance to a level lower than 20 ml/min in less than 2 weeks. HRS-1 is most often precipitated by a bacterial infection,[9–12] and to a lesser extent by gastrointestinal haemorrhage, large-volume paracentesis without albumin administration,[13] excessive response to diuretics[14] and acute liver injury due to alcohol,[15] drugs, or a flare of viral hepatitis.[16] Conversely, type 2 HRS (HRS-2) is characterised by renal dysfunction that does not progress rapidly and is associated with refractory ascites, which represents the main clinical problem. Regarding the pathophysiology of HRS, the main hypothesis in the last 20 years had been the "splanchnic arterial vasodilation theory".[17] This theory posits that HRS occurs only as a consequence of a marked reduction of effective circulating volume, which is caused by splanchnic and systemic arterial vasodilation and inadequate cardiac output.[18–21] The favourable response of half of patients with HRS to the administration of systemic vasoconstrictors

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plus intravenous albumin has been considered proof of this pathophysiological mechanism.[21,22]

In recent years, many concepts have been changed in the setting of HRS. First, the Hepatology community has abandoned the traditional definition of AKI in favour of the new one, defining it as an absolute increase in sCr of ≥0.3 mg/dl from baseline or a percentage increase of ≥50% from baseline.[7] The prognostic relevance of this new definition has been confirmed in patients with cirrhosis by several prospective studies.[23–26] Second, one relevant achievement – related to the recent description of acute-on-chronic liver failure (ACLF)[3,27–30] – was proving that systemic inflammation induced either by pathogen-associated molecular patterns (PAMPs) or by damage-associated molecular patterns (DAMPS) plays a key role in the development not only of organ failure (OF) but also of acute decompensation (AD) in patients with cirrhosis.[30] Finally, while in the past, patients with cirrhosis were unlikely to have underlying structural chronic kidney disease (CKD), this has become a more frequent finding as the number of patients with cirrhosis secondary to non-alcoholic steatohepatitis, with underlying metabolic syndrome (diabetes, hypertension), is increasing rapidly.[31,32] As a consequence of all these changes, there is an urgent unmet need for the Hepatology and Nephrology communities to update the definition, classification, pathophysiology, and management of HRS. The development of a conceptual framework that could lead to the further characterisation of renal dysfunction in cirrhosis is the objective of this review.

What is new in the definition and classification of renal dysfunction in cirrhosis?

After the consensus definition of AKI in patients with cirrhosis by the International Club of Ascites (ICA) in 2015,[7] there has been confusion in the field regarding the definitions of HRS-1 and HRS-2. This section aims to provide a clearer definition of both of these clinical entities, moving to a new pragmatic definition of HRS and palcing it in the context of those of AKI, acute kidney disease (AKD) and CKD.

We propose that HRS be defined as one possible phenotype of renal dysfunction that occurs in patients with liver disease, particularly in those with cirrhosis and ascites. In these patients, HRS is often precipitated by hepatic (alcohol abuse, drugs, flare of hepatitis) and/or extrahepatic (bacterial infections and/or bacterial translocation) factors. The specific subtypes of HRS and their definitions will be based on whether renal dysfunction is acute (AKI), sub-acute (AKD) or chronic (CKD).

Acute kidney injury

AKI is a broad clinical syndrome encompassing various aetiologies that cause either direct injury to the kidney (structural injury) or an acute impairment of function (functional injury).

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define AKI as any of the following: 1) increase in sCr by ≥0.3 mg/dl (≥26.5 μmol/L) within 48 h; or 2) increase in sCr to ≥1.5x baseline, which is known or presumed to have occurred within the prior 7 days; or 3) urine volume <0.5 ml/kg/h for 6 h.[5]

In patients with cirrhosis, previous consensus statements from the ICA had defined renal dysfunction as an sCr concentration of ≥1.5 mg/dl (≥133 μmol/).[4,5] However, in the most recent ICA consensus the definition of AKI in cirrhosis was modified to align with KDIGO sCr criteria[7] (Box 1).

Once AKI is diagnosed, it is classified based on severity; with stage 1 defined as an increase in sCr ≥0.3 mg/dl (26.5 μmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline; stage 2 defined as an increase in sCr >2-fold to 3-fold from baseline; and stage 3 defined as an increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 μmol/L), with an acute increase ≥0.3 mg/dl (26.5 μmol/L) or initiation of renal replacement therapy.[7] More recently it was observed that adding the urine output (UO) diagnostic criteria of AKI to the assessment of critically ill patients with chronic liver disease, in the intensive care unit, improved the identification of patients with AKI, as well as of those with stage 2–3 AKI.[33] Additionally, patients identified based on UO criteria without sCr elevation had a significantly higher mortality.[33] In patients with cirrhosis, as in patients without cirrhosis, AKI can be due to prerenal, intrarenal or intrinsic (acute tubular necrosis, acute interstitial nephritis, acute glomerular and vasculitic renal diseases) and/or post-renal (acute obstructive nephropathy) causes. Additionally, HRS-1 should be included in the differential diagnosis.[3]

In previous ICA consensus conferences,[4,5] different criteria defined HRS *vs.* HRS-1. Major criteria for HRS were 1) cirrhosis with ascites, 2) sCr >1.5 mg/dl, (133 mmol/L), 3) no improvement of sCr (decrease to a level of 133 mmol/L or 1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin, 4) absence of shock, 5) no current or recent treatment with nephrotoxic drugs, 6) absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, micro haematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.[5] On the other hand, HRS-1 was defined as a "rapidly progressive reduction of renal function as defined by a doubling of the initial sCr to a level greater than 2.5 mg/dl or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 ml/min in less than 2 weeks".[4]

As a result of the 2015 ICA consensus definition of AKI in patients with cirrhosis,[7] it was proposed that the traditional nomenclature and definition of HRS and HRS-1 be revised.

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Because HRS-1 is a form of AKI, we propose that it be renamed HRS-AKI and be defined based on *changes* in sCr and/or changes in UO, defined by KDIGO criteria, in addition to other criteria aimed at excluding other causes of AKI as specified in Table 1.

The original definition of HRS-1 required that the diagnosis be established at an advanced stage of AKI (at least stage 2) that limits the efficacy of vasoconstrictor therapy.[34,35] Our new definition of HRS-AKI, without the final cut-off value of sCr ≥1.5 mg/dl from the most recent ICA consensus,[7] aims to encourage clinicians to initiate treatment of patients rapidly, even when increases in sCr are small, specifically, an absolute increase in sCr ≥0.3 mg/dl within 48 h or an increase in sCr ≥50% from an sCr obtained within the prior 3 months (Fig. 1). We have also added UO to the criteria defining HRS-AKI (Box 1 and Table 1). Because obtaining accurate UO measurements is challenging, this criterion would only apply when obtained through a urinary catheter.

Approximately 20–30% of AKI cases in patients with cirrhosis develop prior to hospital admission.[36] In order to make a prompt diagnosis of AKI on admission to the hospital, the consensus definition of AKI defines baseline sCr as the *lowest* sCr obtained within the prior 3 months,[7] choosing the most recent measurement during that period if available (Fig. 1). This will avoid a diagnostic delay of at least 2 days. While recognising that outpatient sCr values may show significant variation and that the choice of the most appropriate sCr value may be a clinician's judgment call, it would still be better than imputing the baseline sCr. The imputation method recommended by KDIGO consists of the inverse application of the Modification of Diet in Renal Disease (MDRD)-6 variable equation, which assumes a baseline glomerular filtration rate (GFR) of 75 ml/min per 1.73 m^2.[36] This approach cannot be used in patients with cirrhosis because any creatinine-based formula will overestimate the true GFR,[36–38] reducing the probability of detecting AKI upon admission.[36]

The second step in the diagnostic process of AKI in cirrhosis is the differential diagnosis among the different AKI phenotypes, namely, acute tubular necrosis AKI (ATN-AKI), prerenal AKI, HRS-AKI and post-renal AKI. Because most prerenal-AKI cases can be resolved by plasma volume expansion and because post-renal AKI is rare, the real clinical challenge is to differentiate between HRS-AKI and ATN-AKI. The diagnostic limitation is that sCr is a marker of kidney filtration, not injury, and, thus, cannot distinguish functional from structural aetiologies of AKI. Tubular injury biomarkers reflect frank structural injury and, thus, when appearing in consort with an acute drop in GFR, should indicate the drop is attributable to structural damage.[39] Among the most promising are urinary biomarkers, interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver type fatty acid-binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL).[40] Urinary values of NGAL, IL-18, KIM-1, L-FABP, and albumin, were found to be significantly higher in patients with ATN than in those without ATN.[41] Comparing the three distinct diagnoses, all biomarkers were significantly elevated in ATN-AKI relative to prerenal AKI, but only NGAL, IL-18, and albumin were statistically higher in ATN compared with HRS and no injury markers distinguished prerenal AKI from HRS. Nevertheless, the presence of increased levels of some tubular biomarkers in patients with HRS-AKI may suggest that there is a continuum from HRS to ATN.[44] Across the majority of studies[42–45] levels of NGAL, the most investigated biomarker, have been remarkably consistent in patients diagnosed with HRS, raising the possibility of NGAL as an objective test to distinguish primarily functional AKI from structural AKI in patients with cirrhosis[45] and guide decisions regarding vasoconstrictor therapy.[45] More specifically, the cut-off with the best predictive accuracy for ATN diagnosis was found

Box 1. New diagnostic criteria for HRS-AKI.

Diagnostic criteria

- Cirrhosis; acute liver failure; acute-on-chronic liver failure
- Increase in serum creatinine ≥0.3 mg/dl within 48 h or ≥50% from baseline value according to ICA consensus document
  and/or
  Urinary output ≤0.5 ml/kg B.W. ≥6 h*
- No full or partial response, according to the ICA consensus document[20], after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography**.
  Suggestion of renal vasoconstriction with FENa of <0.2% (with levels <0.1% being highly predictive)

*The evaluation of this parameter requires a urinary catheter. **This criterion would not be included in cases of known pre-existing structural chronic kidney disease (*e.g.* diabetic or hypertensive nephropathy). AKI, acute kidney injury; FENa, fractional excretion of sodium; HRS, hepatorenal syndrome; ICA, International Club of Ascites.

Key point

We propose that HRS-1 be renamed HRS-AKI and be defined based on changes in serum creatinine and/or changes in urinary output.

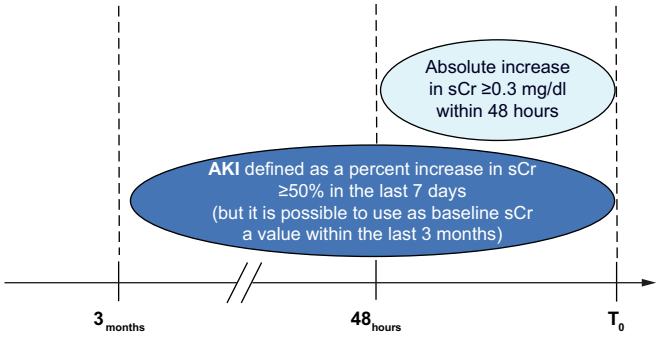

Fig. 1. Criteria for the diagnosis of AKI based on absolute or percent increase of serum creatinine based on the time of initial presentation (T_0). AKI, acute kidney injury; sCr, serum creatinine.

Table 1. New classification of HRS subtypes.

Old classification	New classification		Criteria
HRS-1[#]	HRS-AKI		a) Absolute increase in sCr ≥0.3 mg/dl within 48 h *and/or* b) Urinary output ≤ 0.5 ml/kg B.W. ≥6 h[*] *or* c) Percent increase in sCr ≥50% using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2[#]	HRS-NAKI	HRS-AKD	a) eGFR <60 ml/min per 1.73 m^2 for <3 months in the absence of other (structural) causes b) Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value
		HRS-CKD	a) eGFR <60 ml/min per 1.73 m^2 for ≥3 months in the absence of other (structural) causes

AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; sCr, serum creatinine.
[#] Fulfillment of all the new International Ascites Club criteria for the diagnosis of HRS (Box 1).
[*] the evaluation of this parameter requires a urinary catheter.

Key point

We propose that the diagnosis of HRS-NAKI be made in the context of CKD, or AKD that does not meet the criteria for AKI and lasts for <90 days.

to be 220 μg/g of creatinine.[45] Most patients with ATN-AKI (86%) had values of urinary NGAL above this threshold, whereas the majority of patients with HRS-AKI or prerenal AKI (88% and 93%, respectively) had values below it.[45] However, none of these studies included a gold standard (histology) for the diagnosis of ATN and thus, a diagnosis of ATN remains difficult to establish in patients with cirrhosis and AKI; indeed, HRS and ATN may be considered a continuum rather than two distinct entities.

While NGAL and other biomarkers of structural injury hold great promise for distinguishing between HRS from ATN, the test is not clinically available in much of the world. Thus, clinically available tests that make this distinction are lacking. The diagnosis of HRS is a clinical one and often one of exclusion. It is possible that a frequently utilised test in AKI, the fractional excretion of sodium (FENa), may assist with this differential diagnosis. In many settings of AKI, fractional excretion of sodium FENa is useful for distinguishing functional from structural disease. In functional AKI, such as with prerenal azotemia, tubules are structurally intact and sodium avid due to renal hypoperfusion, thus FENa is low, below 1%. With structural aetiologies such as ATN, tubular injury limits sodium reabsorption and FENa increases, typically by >2–3%. Due to the physiology of cirrhotic circulation, virtually all patients with advanced cirrhosis have chronic renal hypoperfusion and have an FENa <1%, even in the absence of AKI. As sodium avidity is pronounced in advanced cirrhosis, even patients with ATN typically have an FENa <1%. Thus, the test has historically been considered unhelpful in distinguishing HRS from ATN.[5] However, in several studies the FENa in patients diagnosed with HRS was around 0.2% and, in each study, significantly lower than in patients with ATN. While the values for ATN varied across studies based on diagnostic definitions, it appears that FENa, with a new lower cut-off of 0.2% may in fact be clinically useful for distinguishing HRS from ATN.[46] Fractional excretion of urea[47] and albuminuria[41] have been also proposed as tools for the differential diagnosis of AKI in patients with cirrhosis.

Acute and chronic kidney disease

KDIGO guidelines define CKD as abnormalities in kidney structure or function (GFR <60 ml/min/1.72 m^2) that persist for >90 days,[6] and AKD, as AKI or as abnormalities in kidney structure or function (GFR <60 ml/min/1.72 m^2) that persist for <90 days.[6] Because HRS-2 was poorly defined and just assumed more chronic abnormalities in sCr[49] without a definite timeline, arriving at a new more granular definition of HRS-2 is more complicated. Recently, in the European Association for the Study of the Liver guidelines on the "management of decompensated cirrhosis" it was proposed that HRS-2 should be referred to as HRS-NAKI (*i.e.* non-AKI).[50]

We propose that the diagnosis of HRS-NAKI be made either in the context of CKD, that is, in a patient with cirrhosis and a GFR <60 ml/min per 1.73 m^2 for >3 months (HRS-CKD) in whom other causes have been excluded, or in the context of AKD, defined as a renal dysfunction that does not meet criteria for AKI and lasts for less than 90 days (Table 1, Fig. 2).

Although, recently the Acute Disease Quality Initiative (ADQI) proposed considering AKI and AKD as a continuum, where AKI is considered to have evolved to AKD when it persists for ≥7 days after the precipitating event,[48] we think that this paradigm cannot be applied to HRS because: a) the duration of treatment of HRS-AKI with vasoconstrictors plus albumin could be extended for more than 7 days and up to 2 weeks and b) the course of patients with HRS-AKI whose sCr decreases but not to baseline would appear to be different than that of patients who met the previous definition of HRS-2. These issues require more investigation. In the meantime, for research purposes, persistent HRS-AKI despite adequate treatment should be considered clinically and pathophysiologically distinct from HRS-NAKI.

Although there may be inaccuracies in the definition of HRS-NAKI since it includes the use of

eGFR, it would facilitate a diagnosis of HRS-AKI superimposed on HRS-CKD or HRS-AKD, unlike the previous HRS-1 or HRS-2 nomenclature. Importantly, the new nomenclature may enable clinicians' to define the presence of HRS-AKI superimposed on CKD in a patient with structural damage of the kidney, as evidenced by abnormal biopsy, renal ultrasonography or by significant proteinuria (*i.e.* diabetic nephropathy). This need is pressing given the increasing rate of cirrhosis due to non-alcoholic steatohepatitis that is characterised by the presence of comorbidities, such as diabetes mellitus and arterial hypertension, that may lead to structural CKD. Although further diagnostic and prognostic studies are necessary in this context, the criteria for HRS-AKI (Box 1), except for criterion 6, would still apply to patients with underlying structural kidney disease. In the context of the new definition of HRS-AKI on CKD we have provided different clinical settings: HRS-AKI on HRS-CKD, in which there would be no evidence of chronic structural damage, and, on an individual basis, HRS-AKI on CKD in which there would be evidence of chronic structural damage (*i.e.* chronic proteinuria and/or abnormal renal ultrasonography) but with a high suspicion of HRS-AKI.

It should be highlighted that the limited information on several pathophysiological and clinical aspects of HRS still limits the delineation of the new definitions and classification. Therefore, the new HRS definitions and classifications should be validated in future prospective studies. Nevertheless, these new definitions will be immediately useful in the design of clinical trials on diagnosis, pathophysiology and the clinical management of this severe complication.

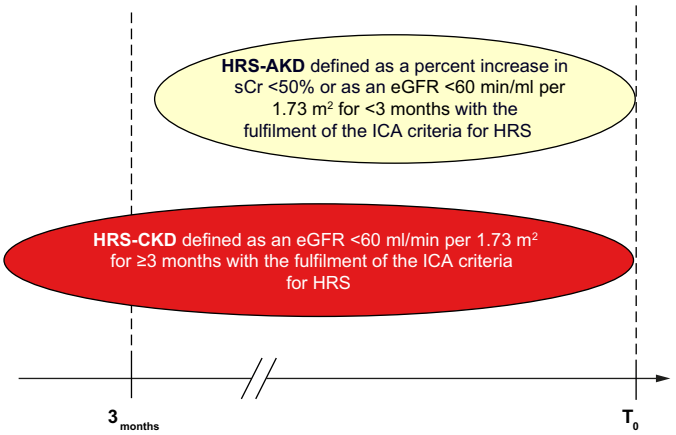

Fig. 2. Criteria for the diagnosis of HRS-NAKI based on the time of initial presentation (T_0). #Fulfillment of all the new ICA criteria for the diagnosis of HRS. AKD, acute kidney disease; CKD, chronic kidney disease; ICA, International Club of Ascites; HRS, hepatorenal syndrome; sCr, serum creatinine; NAKI, non-acute kidney injury.

What is new in the pathophysiology of hepatorenal syndrome?

According to the new theory on the development of decompensation and OFs in patients with cirrhosis, it is now recognised that HRS not only involves circulatory dysfunction but also systemic inflammation (Fig. 3). Looking at the heat-map highlighting the levels of the different biomarkers of systemic inflammation in patients with cirrhosis and AD, three different patterns were recently observed, according to three clinical phenotypes: cirrhosis with AD-1 defined as patients without any single OF, with sCr <1.5 mg/dl (133 μmol/L) and without hepatic encephalopathy (HE); cirrhosis with AD-2 defined as patients with sCr >1.5 mg/dl (133 μmol/L), but <2 mg/dl (177 μmol/L) and/or mild to moderate HE without any associated single non-renal or non-cerebral OF; and cirrhosis with AD-3 defined as patients with a single non-renal OF, with an sCr <1.5 mg/dl (133 μmol/L). Although patterns were different, all patients exhibitedat least partial activation of systemic inflammation. In addition, those with the most extensive baseline systemic inflammation had the highest risk of ACLF development and death.[30] Translating these alterations to the pathogenesis of renal dysfunction in patients with cirrhosis, it should be recognised that the systemic inflammation associated with AKI, and in particular HRS-AKI, is frequently due to pathological bacterial translocation or an overt bacterial infection.[30] Bacterial translocation is the main mechanism by which portal hypertension induces the circulatory dysfunction characteristic of HRS and is the main mechanism involved in the pathogenesis of spontaneous bacterial peritonitis and other infections in patients with cirrhosis.[51] Bacterial translocation leads to monocyte activation by PAMPs such as endotoxins and bacterial DNA. Monocyte activation results in the release of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β).[52] These cytokines have been associated with impairment of renal function in patients with cirrhosis, as well as in patients with ACLF and acute liver failure (ALF).[3,53] In both clinical[54] and experimental studies,[55] it has been shown that renal tubular toll-like receptor 4 (TLR4) may be upregulated, which is associated with the development of florid renal dysfunction, tubular damage and apoptosis. Although the mechanism of tubular TLR4 upregulation is not entirely clear, it likely results from bacterial translocation. Experimentally, significant tubular damage has been detected in rats with cirrhosis following administration of a sub-lethal dose of lipopolysaccharide.[55] Specifically, the presence of vacuolar degeneration with accompanying tubular cell sloughing was present, indicating tubular apoptosis. In order to better understand the mechanism by which bacterial products and proinflammatory cytokines, which filter at the glomerular level, interact with tubular function, one suggestion is to consider the possible overlap in the pathogenetic mechanisms of HRS-AKI and sepsis-induced AKI.[56] Thus, interplay of inflammation

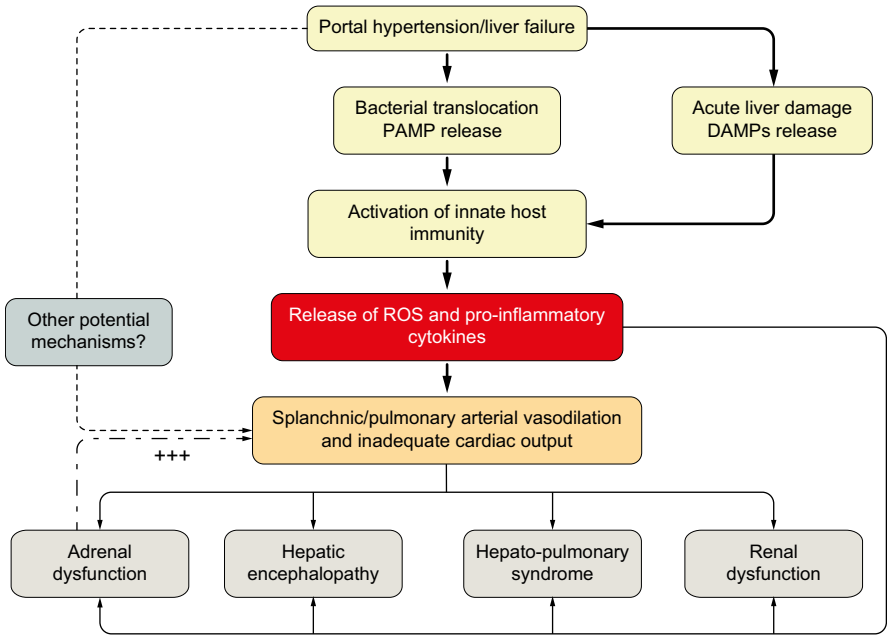

Fig. 3. New pathopshysiological hypothesis of acute decompensation and development of organ dysfunction in patients with cirrhosis. ROS, reactive oxygen species.

Key point

New insights into the pathophysiology of HRS must be considered in relation to their potential impact on pharmacological treatment.

and microvascular dysfunction characterizes and amplifies the signal that PAMPs and DAMPs exert on epithelial cells of the proximal tubule. The recognition of this signal and its subsequent extension to all other proximal tubule epithelial cells causes mitochondria-mediated metabolic down-regulation and reprioritisation of cell functions favouring survival processes above all others. Functions that are thereby sacrificed include the absorption on the luminal side of sodium and chloride. The increased delivery of sodium chloride to the macula densa triggers further intrarenal activation of the renin–angiotensin system and thus lowers the GFR. Finally, cholestasis that can be present in several patients with HRS-AKI may further impair renal function by worsening inflammation and/or macrovascular dysfunction, or by promoting bile salt-related direct tubular damage.[57,58]

All these features (Fig. 4), which can develop even in the absence of circulatory dysfunction and thus of renal hypoperfusion, suggest that the pathophysiology of HRS-AKI can deviate from what has been traditionally accepted for more than 20 years. This may explain the progressive lack of response to vasoconstrictors observed in patients with ACLF as the number of OFs increases.[34]

What is new in the pathology of hepatorenal syndrome?

The functional nature of renal dysfunction in HRS, based on the assumed absence of renal parenchymal damage, has been substantiated mainly based on the following: a) renal dysfunction in cirrhosis usually occurs in the absence of significant renal histological changes as seen in post-mortem examinations, b) classical images of HRS showing extreme but reversible renal vasoconstriction, c) reversibility of renal dysfunction by liver transplant alone and d) the ability to use kidneys from patients with HRS as grafts for renal transplantation.[4] Accordingly, risk factors for renal parenchymal damage (septic shock, treatment with nephrotoxic drugs) or evidence of such damage (significant proteinuria, haematuria, abnormal renal ultrasonography) should be excluded before the diagnosis of HRS can be established.[4,5] However, the absence of renal parenchymal damage in HRS has never been definitively proven. In fact, the need to exclude parenchymal damage in HRS appears to be questionable in light of two recent lines of evidence:

The first line of evidence derives from studies analyzing renal biopsies of patients with cirrhosis and renal dysfunction, which demonstrates a discrepancy between renal histological findings and clinical presentation in patients with cirrhosis. The absence of significant proteinuria and haematuria did not rule out the presence of renal lesions.[59,60] Specifically, in one of these studies, among 18 of the patients with a previous diagnosis of CKD based on an sCr >1.5 mg/d (133 μmol), but with proteinuria <500 mg/day and no haematuria, thus with a possible diagnosis of HRS-CKD, renal histology revealed chronic tubular interstitial injury in 13, acute tubular interstitial injury in 12, glomerular injury in 10, and vascular injury in 12.[59]

The second line of evidence emerged from studies investigating novel biomarkers of tubular damage that could be used to make the differential diagnosis between the different phenotypes of AKI, particularly between HRS and ATN. These

studies show, as previously discussed, that high levels of multiple biomarkers in the urine, particularly NGAL, are indicative of the presence of ATN.[40–45] However, they also demonstrate that in HRS, as defined in Box 1, these biomarkers are also increased, albeit not as in patients with ATN but more than in patients with prerenal AKI.[41,44]

Based on this evidence, the idea that HRS is purely a "functional" renal failure appears unsustainable. Instead, HRS appears to include a spectrum of kidney injury, which can be predominantly functional or associated with some degree of parenchymal damage, a concept that may have therapeutic and prognostic implications.

We propose defining HRS based on one of the possible phenotypes of renal dysfunction in patients with liver disease (cirrhosis, ACLF or ALF). In these patients, HRS is often precipitated by hepatic (*i.e.* alcohol abuse, drugs) and/or extrahepatic (*i.e.* bacterial infections and/or bacterial translocation) events. The pathogenesis of HRS is complex, including: macrovascular dysfunction (systemic vasodilatation, inadequate cardiac output), microvascular dysfunction, danger/inflammation signals from either pathogen- (PAMPs) or tissue-associated (DAMPs) molecular patterns, and direct tubular damage. The nature of HRS can be predominantly functional or associated with some degree of parenchymal damage in a continuous spectrum of kidney injury.

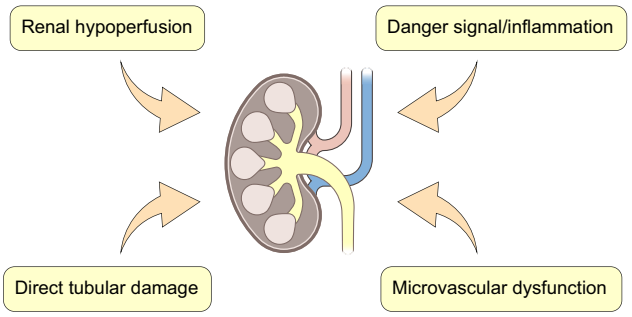

Fig. 4. Mechanisms of renal injury potentially involved in HRS-AKI in patients with cirrhosis. AKI, acute kidney injury; HRS, hepatorenal syndrome.

What is new in the treatment of hepatorenal syndrome?

The management of AKI should be started immediately once a diagnosis has been made and the cause of AKI identified. In patients taking diuretics and/or β-blockers these should be discontinued. In addition, drugs that could be associated with AKI such as vasodilators, non-steroidal anti-inflammatory drugs and other nephrotoxic drugs should be immediately stopped. Volume replacement should be used in accordance with the cause and severity of fluid losses. When HRS-AKI is diagnosed, a specific pharmacological treatment should start as soon as possible. There is no doubt about this approach since several randomised studies have shown that vasoconstrictors[21,61,63–72] particularly terlipressin plus albumin,[21,61–68,70,71] have significantly improved renal function in patients with HRS-1. Moreover, patients who responded to treatment with terlipressin plus albumin showed better survival than non-responders to treatment;[65,66] moreover, in three meta-analyses of randomised trials, the use of terlipressin was associated with a significant improvement in short-term survival in all patients.[22,73,74] However, it should be noted that all these studies were performed in patients with HRS-1, defined according to the old classification of ICA, that is, a baseline sCr >2.5 mg/dl. Finding that a higher baseline value of sCr is definitively an independent predictor of no response to the vasoconstrictor treatment[34,35] was one of the main reasons that led the ICA to introduce the new definition of "HRS-AKI" (Box 1). According to the new definition, a final cut-off value of sCr is no longer needed to make the diagnosis of HRS-AKI and to start its pharmacological treatment.[7] Although a positive impact of the new definition on the rate of response to the pharmacological treatment is expected, it should be confirmed by further studies.

Another factor that may have a deep impact on the response to the pharmacological treatment of HRS-AKI is the complexity of the pathophysiology, as previously described, with the potential development of some degree of renal parenchymal damage. The possibility of structural damage should be strongly factored in when evaluating the lack of response or, even, a partial response to pharmacological treatment in patients with HRS-AKI. Factors that can affect the response to treatment have recently been split into two categories, those related to the therapeutic agents used and those which are independent from them.[75]

Factors independent of the agents used

The rationale behind the introduction of vasoconstrictors in the treatment of HRS-1 was based on the previous theory of splanchnic arterial vasodilatation. Accordingly, terlipressin was introduced to counteract splanchnic arterial vasodilation[17] while albumin was introduced to further improve effective circulating volume and to improve cardiac contractility.[17,76–78] However, according to recent developments in the pathophysiology of HRS, two main questions arise. Firstly, to what extent does the presence of systemic inflammation and oxidative stress affect the rate of response to vasoconstrictors plus albumin? Secondly, to what extent does the presence of some degree of parenchymal damage limit the efficacy of treatment in patients with HRS. With regard to the first question, it has been observed that in patients with ACLF the number of OFs, which correlate with the degree of systemic inflammation, affects the response of HRS-AKI to medical treatment.[34]

Key point

We propose defining HRS based on renal dysfunction in patients with liver disease (cirrhosis with ascites, ALF, or ACLF).

Regarding the second question, although a high urinary level of NGAL is an independent predictor of AKI progression, no difference in NGAL levels was found in patients with HRS-1 between responders and non-responders to terlipressin and albumin.[45] Finally, among the factors that are not related to therapeutic agents, the pretreatment level of sCr should also be considered, as previously discussed.[33,34]

Factors related to the agents used

Type of vasoconstrictor

Three types of vasoconstrictors are currently available for the treatment of HRS: terlipressin, noradrenaline and the combination of midodrine + octreotide. Terlipressin is the most investigated vasoconstrictor in this field. Two pilot studies,[61,62] as well as three randomised controlled trials,[21,64,67] have demonstrated that the combination of terlipressin plus albumin is more effective than albumin alone in the treatment of HRS. Terlipressin can be administered both as intravenous boluses (starting from 0.5–1 mg every 4–6 h to a maximum dose of 2 mg every 4 h)[21,64,67] and as continuous intravenous infusions (starting from 2 mg/day to maximum dose of 12 mg/day).[66,68] The latter administration has been associated with a significantly lower incidence of severe side effects which include persistent diarrhea, abdominal ischemia, peripheral ischemia, angina pectoris, and circulatory overload.[68] These findings are probably consistent with the short-term effect (3–4 h) of terlipressin on portal pressure.[79] Thus, careful clinical screening is recommended before starting treatment, with close monitoring of patients continued for the duration of treatment. The dose of terlipressin should be increased in a stepwise manner if sCr does not decrease by at least 25% after 3 days of treatment. Albumin should be administered at the dose of 20–40 g/day. The treatment with vasoconstrictors plus albumin should be continued until sCr reaches a final value within 0.3 mg of the patient's baseline sCr. In patients with no response or partial response, the treatment should be discontinued within 14 days. In the last two randomised controlled clinical trials the percentage of patients with HRS-1 who showed a complete response to terlipressin plus albumin, defined as a reduction of sCr >50% to a final value <1.5 mg/dl (133 μmol/L) was 55.5%.[66,68] After discontinuation, a recurrence of HRS may be observed in less than 20% of patients with HRS-1 and retreatment is usually effective.

Conversely, despite higher rates of response to terlipressin and albumin, in patients with type 2 HRS, recurrence of HRS is quite common.[80] In addition, a recent case-control study did not show any difference in terms of post liver transplantation (LT) outcomes in patients treated or not with terlipressin.[81] For these reasons, HRS-2, now termed HRS-NAKI, cannot be considered an indication for the use of terlipressin plus albumin even in patients who are on the waiting list for LT. Terlipressin has not been approved for use in the United States.

Midodrine (an α1-agonist drug) combined with octreotide (a somatostatin analogue), together with albumin infusion has been shown to be effective in treating HRS-1.[69,72] However, in a small, single center, randomised controlled trial, the combination of terlipressin plus albumin was shown to be significantly more effective than the combination of midodrine plus octreotide and albumin in the treatment of HRS (improvement of renal function in 70 *vs.* 29%, respectively; $p = 0.01$).[66] The administration of norepinephrine (administered at a dose of 0.5–3 mg/hour) plus albumin has been investigated in the treatment of HRS. In patients with HRS-1, noradrenaline was shown to be as effective as terlipressin in the treatment of HRS in two small controlled clinical trials[70,71] and in a recent prospective study.[82] However, in a recent randomised trial, terlipressin was shown to be more effective than noradrenaline in the treatment of HRS in patients with ACLF;[83] this is probably related to the fact that noradrenaline, unlike terlipressin, has no effect on portal pressure[84] or on the expression of inducible NOS.[85] Despite these limitations, the use of norepinephrine for the treatment of HRS is tempting because it is a cheaper than terlipressin, although it should be administered through a central venous line and under continuous monitoring, so it cannot be used outside intensive care units. Therefore, further studies are needed to determine the feasibility of norepinephrine.

Dose of albumin

Albumin is crucial for the effectiveness of the treatment of HRS. In the only study in which terlipressin was used alone in the treatment of HRS, it was much less effective than when it was used together with albumin.[62] One possible explanation is that a fall in cardiac output (CO), which is a crucial event in the pathophysiology of HRS,[18,19] could be exacerbated by the effect of terlipressin.[86] In contrast, albumin is capable of maintaining or increasing the CO even in the most advanced phases of liver disease.[87] To date, albumin has been given at a dose of 20–40 g/day and managed only according to the level of central venous pressure in order to avoid circulatory overload. Now, there is increasing experimental[77] and clinical[76,78] evidence that the increase in systemic vascular resistance and CO due to albumin are mainly related to the non-oncotic properties of the molecule and particularly to its capacity to exert anti-oxidant and anti-inflammatory actions. The role and details of these actions go beyond the scope of this manuscript, nevertheless, it is important to highlight two concepts. The first is that when albumin is used alone, the dose needed to obtain and to maintain an effective improve-

ment of the cardio circulatory function as well as an anti-inflammatory effect is quite high (1.5 g/kg of bodyweight/week).[78] Up to now, this dose has never been usedin patients with HRS-AKI, thus its efficacy and safety should be proved in RCTs. The second is that while exerting its non-oncotic actions, the molecule of albumin goes through post-transitional changes that consume its biological potential.[88] Thus, either the pretreatment concentration of endogenous effective albumin or the dose of exogenous effective albumin administered could be future targets for the optimisation of treatment responses in HRS.

What is new in the perspective of liver transplantation in patients with hepatorenal syndrome?

LT represents the optimal treatment for patients with HRS-AKI regardless of their response to pharmacological treatment.[89] However three main points deserve further investigation: a) to what extent renal failure is reversible after LT, b) when should a simultaneous liver kidney transplantation (SLK) be considered in non-responders to pharmacological treatment and c) how to ascribe the correct priority on the waiting list to responders to pharmacological treatment. Regarding the first and the second points, which are strongly related, several studies have shown that mean sCr after LT is higher in patients transplanted for HRS than for patients without HRS, thus reproposing the question about the real nature of HRS.[89,90] The introduction of model for end-stage liver disease (MELD) score-based allocation in 2002 coincided with a dramatic increase in the number of SLK transplants, representing 10% of all liver transplants in 2017 in the United States.[91] The decision to perform SLK *vs.* LT alone, with a possible kidney transplant after the LT,[92] is driven not only by concerns relating to increased mortality post-transplant, but also to the lack of renal recovery which is felt to contribute to increased mortality. Currently in the United States, a listing policy for SLK now exists based on prior consensus recommendations[93–95] and includes elements such as duration of AKI, need for dialysis, and evidence of CKD. Factors that may impact the recovery of renal function after LT such as age, comorbidities or aetiology of AKI are currently not included in the criteria. However, renal recovery and patient survival 1 and 5 years after liver transplant are significantly worse for patients with renal dysfunction secondary to ATN in comparison to patients with HRS.[96] Prediction of renal recovery and the extent of that recovery following LT is a challenge which has plagued the transplant community, as the relative contributions of pre-existing comorbidities, unrecognised intrinsic renal disease, perioperative events, and post-transplant immunosuppression, to renal dysfunction after LT are difficult to delineate.

Regarding the third point, in order to optimize the results of pharmacological treatment in patients with HRS-AKI, responders should receive the right priority in the waiting list, taking into account not only the specific value of HRS *per se* on 3-month mortality beyond the MELD score,[97] but also considering that lowering sCr can reduce the baseline MELD score and thus, delay the timing of LT. This paradoxical effect of treatment in the responders can be avoided either by continuing to consider the baseline MELD, or by considering the pharmacological treatment of HRS as dialysis in the calculation of the MELD score, according to the type of response.[98]

Conclusions

Renal dysfunction is a common complication in patients with cirrhosis, ACLF, and ALF. This review proposes a new definition and overall a new classification for HRS that expands on the recent ICA consensus document. It should be highlighted that the new proposal is based on new data, which are quite interesting but still limited. Therefore, the new proposed definition and classification of HRS should be validated in future prospective studies. Nevertheless, they will be immediately useful in the design of clinical trials on the pathophysiology and the management of HRS in patients with liver disease.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

All the Authors designed, drafted and finalized the manuscript

Supplementary data

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