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EDITORIAL

Hepatorenal syndrome: Update on diagnosis and therapy

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Abstract

Hepatorenal syndrome (HRS) is a manifestation of extreme circulatory dysfunction and entails high morbidity and mortality. A new definition has been recently recommended by the International Club of Ascites, according to which HRS diagnosis relies in serum creatinine changes instead that on a fixed high value. Moreover, new data on urinary biomarkers has been recently published. In this sense, the use of urinary neutrophil gelatinase-associated lipocalin seems useful to identify patients with acute tubular necrosis and should be employed in the diagnostic algorithm. Treatment with terlipressin and albumin is the current standard of care. Recent data show that terlipressin in intravenous continuous infusion is better tolerated than intravenous boluses and has the same efficacy. Terlipressin is effective in reversing HRS in only 40%-50% of patients. Serum bilirubin and creatinine levels along with the increase in blood pressure and the presence of systemic inflammatory response syndrome have been identified as predictors of response. Clearly, there is a need for further research in novel treatments. Other treatments have been assessed such as noradrenaline, dopamine, transjugular intrahepatic portosystemic shunt, renal and liver replacement therapy, *etc*. Among all of them, liver transplant is the only curative option and should be considered in all patients. HRS can be prevented with volume expansion with albumin during spontaneous bacterial peritonitis and after post large volume paracentesis, and with antibiotic prophylaxis in patients with advanced cirrhosis and low proteins in the ascitic fluid. This manuscript reviews the recent advances in the diagnosis and management of this life-threatening condition.

Key words: Hepatorenal syndrome; Acute-on-chronic liver failure; Liver cirrhosis; Terlipressin; Acute kidney injury

Core tip: Hepatorenal syndrome (HRS) is a life-threatening complication present in very advanced liver cirrhosis. This manuscript addresses many recent advances in this field, including the recent change in the definition of HRS according to acute kidney injury

criteria, the potential consequences of the adoption of this new definition, and the use of biomarkers to help in the diagnostic algorithm. Moreover, it reviews the recent advances in treatment of HRS such as the use of continuous infusion of terlipressin instead of bolus and the low efficacy of midodrine plus octreotide. Potential areas of research are identified as well.

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INTRODUCTION

Hepatorenal syndrome (HRS) is a manifestation of extreme circulatory dysfunction. It develops in the setting of advance stage in cirrhosis and carries an ominous prognosis.

HRS is diagnosed clinically. Its definition has been updated recently in accordance with the acute kidney injury (AKI) criteria.

Current standard of care involves the use of vasoconstrictor therapy (*i.e.*, terlipressin) and volume expansion with albumin. Treatment is effective in only 40%-50% of cases and it recurs in up to 50% of those cases responding to treatment. Liver transplant (LT) should be considered in all patients without contraindications for it.

Areas of research would be aimed at improving the accuracy of diagnosis of HRS, identifying predictors of non-response, and testing novel treatments.

PATHOPHYSIOLOGY

HRS is caused by extreme circulatory dysfunction. Hepatocytes and stellate cells in a cirrhotic liver produce numerous local acting vasodilators such as nitric oxide, cannabinoids, *etc*. These vasodilators act locally on the splanchnic circulation producing splanchnic arterial vasodilation. Splanchnic circulation represents an important part of the circulation of the body. Thus, splanchnic vasodilation produces a decrease in mean arterial pressure (MAP), which in turn triggers the activation of the sympathetic nervous system, leading to high levels of circulating noradrenaline, which along with an increase in cardiac output are the early mechanisms compensating circulatory dysfunction during this early stage and keep MAP stable[1].

As the disease progresses and splanchnic vasodilation gets worse other vasoconstrictor systems get activated such as the renin-angiotensin-aldosterone system and vasopressin release[1].

Aldosterone enhances retention of sodium and water by the kidneys leading to development of ascites. Vasopressin enhances retention of free water conducting to hyponatremia. The splanchnic vascular bed is refractory to the action of all these vasoconstrictor systems which on the contrary act effectively on other vascular beds such as the femoral and brachial vessels (producing cramps), in vessels in the brain (potentially playing a role in encephalopathy) and in the renal arteries (leading to HRS)[1,2]. In this sense, mean renal artery resistive index increases gradually from patients with cirrhosis but no ascites, in those with ascites, refractory ascites and HRS[3,4].

Therefore, HRS is a functional disease characterised by marked vasoconstriction of the renal arteries secondary to the effect of hyper-activation of different vasoconstrictor systems aimed at compensating the systemic vasodilation caused by the initial splanchnic vasodilation. HRS always develops in the setting of advance circulatory dysfunction and it is always accompanied by ascites and usually by hyponatremia[1].

HRS can develop in the setting of infection, mainly after spontaneous bacterial peritonitis (SBP), as a consequence of a worsening degree of circulatory dysfunction caused by sepsis. Volume expansion with albumin prevents effectively development of HRS in patients with SBP[5].

HRS can also develop in the setting of circulatory dysfunction after large volume paracentesis (LVP). This complication is prevented by replacing albumin after LVP[6].

DIAGNOSIS OF HRS ACCORDING TO THE NEW DEFINITION OF AKI

Classically, acute renal failure in cirrhosis was defined as an increase in serum creatinine (sCr) levels of $\geqslant$ 50% from baseline to a final level above 1.5 mg/dL (133 μmol/L), and classical definition of HRS type-1 was doubling sCr levels over 2.5 mg/dL or 220 μmol/L within 2 wk. Serum creatinine overestimates renal function in cirrhotic patients due to a number of factors: Creatinine production in patients with cirrhosis is reduced due to muscle wasting, there is an increased secretion of creatinine in the renal tubules, sCr may be diluted due to an increased volume of distribution, and finally, high bilirubin levels may interfere with the assays to measure accurately its level. Recently, the International Club of Ascites (ICA) has adopted the concept of AKI which was developed originally to be used in general critically-ill patients. AKI is defined as the increase of at least 0.3 mg/dL (26 μmol/L) and/or $\geqslant$ 50% from baseline, within 48 h[7].

Diagnostic criteria of HRS according to ICA-AKI criteria are the following[7]: (1) diagnosis of cirrhosis and ascites; (2) diagnosis of AKI according to ICA-AKI criteria; (3) no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight); (4) absence of shock; (5) no current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, *etc.*); and (6) no macroscopic signs of structural kidney injury, defined as absence of proteinuria (> 500 mg/d), absence of microhematuria (> 50 red blood

cells per high power field) and normal findings on renal ultrasound.

The main change produced by adopting the new definition of HRS is the removal of a rigid very high cut-off value of sCr (2.5 mg/dL or 220 μmol/L) to start pharmacologic treatment. In this way, treatment can be administered early and potentially better efficacy could be achieved.

However, these clinical criteria do not allow differentiation between HRS and parenchymal renal disease, which is extremely important because vasoconstrictors will not be effective and could even worsen the renal dysfunction. Thus, there is a wide interest in developing urinary biomarkers to help in the differential diagnosis of HRS.

URINARY BIOMARKERS IN AKI

Currently, numerous biomarkers have been assessed in the setting of AKI and liver cirrhosis including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, liver-type fatty acid binding protein (L-FABP), kidney injury molecule-1, toll-like receptor 4, π-glutathione S-transferase and α-glutathione S-transferase[8]. Among all of them, current data show that NGAL is the most useful marker. NGAL detects patients with acute tubular necrosis (ATN). On the contrary, NGAL is not helpful to differentiate between pre-renal azotemia and HRS. NGAL urinary levels are much higher in patients with ATN compared to patients with other causes of AKI. Urinary levels of NGAL in ATN were 417 μg/L, compared with levels at 30 μg/L in pre-renal azotemia, 82 μg/L in chronic kidney disease and 76 μg/L in HRS, $P < 0.001$[9,10]. Thus, incorporating NGAL into the clinical decision algorithm would be of benefit to rule out structural kidney injury and detecting a group of patients in whom treatment with vasoconstrictors wouldn't be effective and only would produce potentially serious side effects[11].

CURRENT TREATMENT (STANDARD OF CARE)

Once patients with AKI have received volume expansion with albumin (1 g per kilogram) with no response achieved in the following 48 h, and criteria of HRS are fulfilled, then treatment with terlipressin is recommended. Expansion with albumin should be continued at the dose of 20-40 g daily.

Response to treatment should be assessed regularly and terlipressin should be titrated gradually up to a maximum dose of 12 mg per day. Terlipressin should be used for a maximum of 14 d and stopped in case of lack of response[7].

Response is defined as a reduction of at least 25% from baseline sCr level, that is from sCr level before treatment with terlipressin was started[7].

Response is achieved in around 40%-50% of patients. The rate of recurrence of HRS is 30%. A definitive treatment of the circulatory dysfunction and the underlying liver cirrhosis with liver transplantation should be considered in all cases with no contraindications. Otherwise, the persistent advanced circulatory dysfunction makes HRS recur frequently and predispose the patient to other major decompensations[12]. This is the rationale supporting prioritization of patients with HRS on the waiting list for LT in some centres. Terlipressin and albumin is not a definitive treatment but should be considered as a bridge to a definitive treatment, *i.e.*, LT.

Two randomized studies showed that HRS reversal rate when terlipressin plus albumin was employed was higher compared to the reversal achieved employing albumin alone. Martín-Llahí *et al*[13] reported a much higher rate of improvement in renal function in patients treated with terlipressin and albumin compared to those patients treated only with albumin (43.5% *vs* 8.7%, $P = 0.017$). This result may be influenced by the fact that patients who did not tolerate terlipressin were excluded from the analysis. Sanyal *et al*[14] also showed that HRS reversal was achieved more frequently in those patients treated with terlipressin and albumin compared with those treated only with albumin (33.9% *vs* 12.5%, $P = 0.008$). Any of these studies showed difference in survival at 3-mo and 6-mo. A large randomized trial has been published recently and it showed a higher rate of HRS reversal in those patients receiving terlipressin (23.7% *vs* 15.2%, $P = 0.13$). This difference did not reach statistical significance, probably due to the fact that one third of patients received fewer than three days of treatment, which could affect the effectiveness of the treatment. When the analyses were done stratifying patients by the degree of reduction in serum creatinine level, data showed that a decrease in sCr level, even if not reaching a complete reversal, has a positive impact on survival[15].

Traditionally, terlipressin has been used in bolus 0.5-1.0 mg every 4-6 h. Recent data show that continuous infusion of terlipressin has the same efficacy compared with bolus administration and it is better tolerated presenting fewer side effects (35.29% *vs* 62.16%, $P < 0.025$). Probably, side effects were lower because the total effective daily dose required was lower in the infusion groups compared to the bolus group (2.23 ± 0.65 mg/d *vs* 3.51 ± 1.77 mg/d, $P < 0.05$)[16].

Therefore, we recommend employing terlipressin at 2 mg per day in continuous infusion (diluted in 250 mL of Dextrose 5%) along with albumin (20-40 g per day). Response should be assessed every 48 h. If response is not achieved in 48 h, then terlipressin dose should be increased in a stepwise manner (increase in 2 mg per day).

These patients need careful observation, including review of ischaemic side effects on acral parts, ischaemic heart events, bowel ischaemia (diarrhoea). They can also develop hyponatremia and arrhythmias.

PREDICTORS OF RESPONSE TO TERLIPRESSIN AND ALBUMIN

There are only few published studies assessing pre-

dictors of response to treatment in HRS. These studies show there is a close relationship between effectiveness of treatment and capacity to improve systemic hemodynamics. Patients in whom terlipressin did not increase the MAP in at least 5 mmHg at day 3 of treatment had a lower rate of response. Effectiveness of treatment is also related with degree of liver dysfunction. Those patients who did not increase MAP at day 3 and who also had high baseline bilirubin levels ⩾ 171 μmol/L (10 mg/dL) had a poor response rate, of only 9%[17]. Another study showed that baseline creatinine levels predicted HRS reversal, suggesting that early intervention would be more effective[18]. A recent retrospective study showed that those patients with systemic inflammatory response syndrome (SIRS) had a much higher response rate to terlipressin (42.9% *vs* 6.7%, $P = 0.018$), while terlipressin did not show more efficacy than placebo when employed in patients without SIRS (15.9% *vs* 18.8%, P = NS)[19].

A recent abstract showed that no response to treatment was associated with higher urinary NGAL levels (728.8 μg/L *vs* 182.9 μg/L, $P = 0.02$), probably related to the presence of acute tubular necrosis in those patients[20].

In summary, the following markers to predict response to treatment (terlipressin) have been identified: Low baseline creatinine and bilirubin levels, increase in blood pressure, presence of SIRS and low urinary NGAL.

OTHER TREATMENTS

LT

Patients with HRS type-1 with no contraindications for a LT should be invariably worked up and place in the LT waiting list because LT is the only definitive treatment for HRS. LT reverses liver dysfunction and portal hypertension. Patients with HRS have worse survival expectancy than other patients with cirrhosis for any given value of MELD score, which suggests HRS is a factor of poor prognosis independently from MELD score[21,22]. Furthermore, there is evidence that structural injury to the renal tubules occur early in the course of HRS-1 and the longer the patient is awaiting the transplant and suffering from HRS the higher the risk of not recovering their renal function or even requiring a renal transplant after LT[23]. In this sense, experts recommend to prioritize these patients by using pre-treatment levels of creatinine or considering the pharmacological treatment of HRS as haemodialysis when calculating MELD score[24]. Currently, there is no general consensus about prioritization of patients with HRS awaiting a LT. Some centres prioritize these patients and some others don't. The major challenge LT programmes face is the shortage of donors and consequently optimization in the allocation of the few organs available becomes extremely necessary. Thus, we suggest that those patients with recurrent episodes of HRS-1, hence at high risk of developing refractory HRS, are at high risk of dropping out of the LT waiting list or at risk of not recovering their renal function after LT, and therefore will get most benefit from early transplantation.

Midodrine and octreotide

Combination of midodrine and octreotide (MID/OCT) plus albumin is widely used in countries where terlipressin is not available. A recent randomized trial showed a much lower response rate in patients treated with MID/OCT compared to patients treated with terlipressin (4.8% *vs* 55.6%, $P < 0.01$). Three-month survival rate, after exclusion of patients who received rescue treatment, was also lower in the MID/OCT group (29% *vs* 56%, $P = 0.06$)[25]. These data show midodrine in combination with octreotide is not an effective treatment for HRS.

Noradrenaline

A recent randomized study comparing noradrenaline with terlipressin showed HRS reversal is achieved in 43.4%, similar to the reversal rate achieved with terlipressin (39.1%). Survival at 15 d of therapy was similar in the noradrenaline and terlipressin group (39.1% *vs* 47.8%, $P = 0.461$)[26]. A recent meta-analysis analysed 4 studies including 152 patients and suggested that treatment with noradrenaline is as effective as terlipressin in reversing HRS when used along with albumin[27]. Therefore, noradrenaline is an effective therapy for HRS. Noradrenaline main drawback is that its use generally requires an intensive care unit setting.

Dopamine

Low-dose dopamine increases renal blood flow but shows no effect on glomerular filtration rate or on the outcome in HRS. In a recent study, dopamine didn't show reduction of creatinine levels after 5 d of treatment[28,29]. It is not considered an appropriate treatment for HRS.

Transjugular intrahepatic portosystemic shunt

HRS type-1 usually occurs in the setting of advanced liver dysfunction and transjugular intrahepatic portosystemic shunt (TIPS) is usually contraindicated on this basis. There are few small trials showing improvement on renal function and deactivation of vasoconstrictor system, *i.e.*, reduction in levels of renin, aldosterone and noradrenaline after TIPS insertion[30,31]. However, data is very limited to recommend its use in clinical practice.

Renal and liver replacement therapy

Haemodialysis is employed in those patients awaiting LT whose renal function failed to respond to medical treatment and at the same time bring the extra points required for prioritization.

Liver support with molecular adsorbent recirculating system (MARS) has been tested in small cohorts of patients who did not respond to vasoconstrictors and had advanced liver dysfunction, which usually precludes TIPS insertion. One trial showed the reduction in creatinine and bilirubin levels was higher in the MARS group compared with the continuous haemodialysis group[32]. Another study showed no significant changes in systemic

haemodynamics and glomerular filtration rates following MARS treatment[33]. Treatments employed at this stage should be restricted to patients awaiting a definitive treatment (*i.e.*, LT). It would be controversial to employ such invasive treatments in patients with contraindication for LT, and thus with no option for a definitive treatment.

Serelaxin

Serelaxin is a recombinant form of the human peptide hormone relaxin-2, increases renal perfusion in healthy human volunteers. Its properties have been explored in a pilot study on compensated cirrhotic patients and it showed increase renal blood flow by 65.4% from baseline with no effect on systemic blood pressure[34]. Data on this hormone is still scarce.

PREVENTION

HRS can be prevented in different clinical scenarios. The first one is in the setting of SBP. The deleterious effect on circulatory dysfunction produced by SBP can be prevented by volume expansion with albumin. The pioneer study of the Barcelona group showed that those patients receiving albumin prevented development of renal failure (10% *vs* 33%, $P = 0.002$) and reduced short-term mortality (mortality at 3-mo, 22% *vs* 41%, $P = 0.03$)[9]. There are still no convincing data to recommend plasmatic expansion with albumin in patients with other types of infections different from SBP. One trial showed a tendency to develop renal failure less frequently in those patients without renal failure at baseline and receiving expansion with albumin (3% *vs* 10%, P = NS)[35].

HRS can be prevented after LVP, albumin at a dose of 6-8 g per litre of ascites removed is the dose most commonly used to prevent worsening of circulatory dysfunction, and thus minimize the impact on electrolytes, creatinine and renin levels. Volume expansion with albumin also improves survival after LVP and it is recommended by international societies[36,37].

HRS can also be prevented with primary antibiotic prophylaxis of SBP. Fernández *et al*[38] showed in a cohort of patients with advanced cirrhosis that SBP primary prophylaxis reduced development of HRS (28% *vs* 41%, $P = 0.02$) and mortality at 3 mo (94% *vs* 62%, $P = 0.003$), this effect is probably related to the effect of Norfloxacin in reducing the levels of bacterial products within the gut and hence reducing bacterial translocation.

AREAS FOR FUTURE RESEARCH

Definition of HRS is continuously changing and it is based on clinical grounds, relying on serum creatinine levels, which has many limitations as marker of renal function. Research focused on new biomarkers, such as urinary NGAL, to make the diagnostic algorithm of HRS more accurate is clearly needed and fortunately, interest in this field is increasing.

Moreover, identifying patients with low probability of responding to treatment is of major importance in order to start early alternative treatments and potentially prioritize these patients on the LT waiting list.

Finally, research looking for novel treatments besides intravenous terlipressin and expansion with albumin is also needed.

CONCLUSION

HRS is a major decompensation in advanced liver cirrhosis. It entails a high short-term mortality rate. Current definition is based on clinical grounds and has been recently modified adopting AKI definition. Recent data on urinary NGAL show it is useful to differentiate acute tubular necrosis and should be incorporated in the diagnostic algorithm of HRS. Terlipressin and noradrenaline are the only effective treatment currently available and reversal rate is only 40%-50% of cases. Data on predictors of response to treatment suggest that treatment should be started as early as possible. In this sense, ICA new definition of HRS allows an early diagnosis. New treatments should be tested for this life-threatening condition. Finally, LT is the only curative treatment and should be always considered.

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