Therapeutics and Clinical Risk Management

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REVIEW

Hepatorenal Syndrome Type 1: Current Challenges And Future Prospects

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Abstract: Renal dysfunction represents a dreadful complication of advanced liver cirrhosis. In addition to the traditional types of acute kidney injury (AKI) that can occur in the general population, cirrhotics might experience a different kind of renal dysfunction, called hepatorenal syndrome (HRS). The exact definition of HRS is a functional renal dysfunction caused by overactivity of the endogenous vasoactive systems (in particular intrarenal circulation) which lead to reduced renal perfusion. Type I HRS (HRS-1) is characterized by an abrupt deterioration in renal function (in less than 2 weeks), defined by a doubling of baseline sCr to >2.5 mg/dL or a 50% reduction in the initial 24 hrs creatinine clearance to <20 mL/min. Frequent precipitating events leading to HRS-1 are bacterial infections, gastrointestinal hemorrhage, or large-volume paracentesis without adequate albumin administration as well as massive diuretic use. In 2015, the international club of ascites (ICA) revised the definitions and recommendations concerning HRS. The revised definition allows to adopt effective pharmacological therapy based on albumin and vasoconstrictors in an earlier stage thus not influenced anymore by a rigid sCr cut-off value as by the previous definition of HRS-1. The aim of this article was to provide an updated overview of the latest advancements in the field of hepatorenal syndrome and of the recent amendments of the previous definitions of kidney injury in cirrhotic patients.

Keywords: kidney, liver cirrhosis, terlipressin, mortality

Introduction

Renal dysfunction represents a dreadful complication of advanced liver cirrhosis.[1,2]

The traditional definition of renal dysfunction in patients with liver disease is based on a serum creatinine (sCr) concentration of ≥1.5 mg/dl, and in this context, acute kidney injury (AKI) is diagnosed in the presence of the abrupt doubling of the baseline value of sCr beyond the threshold of 1.5 mg/dL.[3,4]

Classification Of Acute Kidney Injury In Cirrhotic Patients

In addition to the traditional types of AKI that can occur in the general population, namely, prerenal, intrarenal, and post-renal, cirrhotics might experience a different kind of renal dysfunction, called hepatorenal syndrome (HRS).[5] Specifically, acute tubular necrosis occurs in 41.7% of cirrhotics, prerenal AKI in 38% of patients, while postrenal AKI is rare in patients with liver cirrhosis (0.3%).[6] Therefore, while the recently published International Club of Ascites (ICA) guidelines have suggested that all cases of acute renal dysfunction in patients with cirrhosis should be classified under the broad heading of acute kidney injury (AKI), HRS is registered only in 20% of subjects with liver cirrhosis.[7]

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DovePress
http://doi.org/10.2147/TCRM.S205328

Definition Of Hepatorenal Syndrome And Sub-Classification

The exact definition of HRS is a functional renal dysfunction caused by overactivity of the endogenous vasoactive systems (in particular intrarenal circulation) which leads to reduced renal perfusion.[3,4]

HRS has been classified traditionally into two different clinical types; type I HRS (HRS-1) is characterized by an abrupt deterioration in renal function (in less than 2 weeks), defined by a doubling of baseline sCr to >2.5 mg/dL or a 50% reduction in the initial 24 hrs creatinine clearance to <20 mL/min.[3,4]

Based on the aforementioned assumptions, in the presence of a cirrhotic patient with rapid renal function deterioration, several differential diagnoses should be ruled out before considering HRS, such as prerenal AKI due to hypovolemia (for example, after massive variceal bleeding), acute tubular necrosis due to sepsis, iatrogenic injury, diabetic nephropathy.[8]

Frequent precipitating events leading to HRS-1 are bacterial infections, gastrointestinal hemorrhage, or large-volume paracentesis without adequate albumin administration as well as massive diuretic use.[7] On the other hand, type 2 HRS (HRS-2) is characterized by the slow occurrence of renal dysfunction and it is usually considered within the spectrum of refractory ascites.

Updated Definition And New Remarks

In 2015, the ICA revised the definitions and recommendations concerning HRS. In fact, creatinine levels are likely to remain low in cirrhotics even in the presence of advanced AKI mainly due to sarcopenia and this misleading diagnosis may negatively impact the earlier institution of therapy.[5] Therefore, the use of a fixed threshold of sCr should be abandoned, while the dynamic changes of sCR proved to provide an accurate definition of AKI and HRS in these patients.

According to the new definition, AKI is defined by the increase in sCr ≥0.3 mg/dl within 48 hrs, or a percentage increase sCr ≥50% from baseline.[5,9]

In this context, the definition of HRS-1 is based on the following criteria: (a) diagnosis of cirrhosis and ascites, (b) diagnosis of AKI according to ICA-AKI criteria (see above), (c) no response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight, (d) absence of shock and no current or recent use of nephrotoxic drugs, and (e) no macroscopic signs of structural kidney injury (defined as absence of proteinuria or microhaematuria, or normal findings on renal ultrasonography).[5]

The revised definition allows to adopt effective pharmacological therapy based on albumin and vasoconstrictors in an earlier stage thus not influenced anymore by the rigid sCr cut-off value of >2.5 mg/dl as in the previous definition of HRS-1. Although this aspect should lead theoretically to better therapeutic outcomes,[10,11] however, trials testing vasoconstrictors in patients with HRS and lower values of sCr are lacking, thus calling for a particular note of caution in this setting.[12]

Pathophysiology

Activation of renin-angiotensin-aldosterone system (RAAS) plays a key role in the pathogenesis of hydroelectrolytic imbalances in cirrhotics. Activation of RAAS, as well as activation of sympathetic nervous system (SNS) and hyperincretion of anti-diuretic hormone (ADH), is triggered as a response to maintain arterial pressure within normal ranges in cirrhotic patients with ascites.[13]

Role Of Portal Hypertension

The pathophysiological mechanisms underlying the development of hepatorenal syndrome are described in Figure 1.

Disruption of liver architecture occurring in cirrhotic patients increases the intrahepatic vascular resistance leading to worsening of portal pressure. This process releases several mediators including nitric oxide and endogenous cannabinoids causing the vasodilation of the splanchnic vascular bed.[14] In advanced cirrhotic patients, the cardiac output can no longer compensate for the reduced systemic vascular resistance triggered by the splanchnic vasodilation, determining a decreased effective circulating

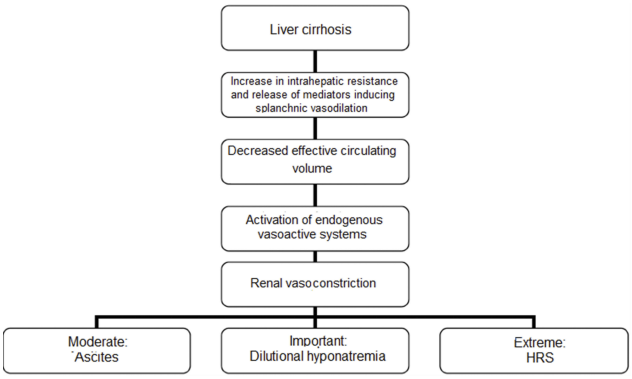

Figure 1 Pathogenesis of hepatorenal syndrome.
Abbreviation: HRS, hepatorenal syndrome.

volume.[8,14,15] This, in turn, leads to activation of the SNS and RAAS as well as vasopressin to help maintain circulating volume, leading to renal vasoconstriction and hypoperfusion of these organs.[16]

As aforementioned, the consequence of solute-free water excretion impairment (due to ADH incretion and renal dysfunction) is the occurrence of hyponatremia, so-called dilutional hyponatremia as it develops due to the increased total body water and dilution of extracellular fluid volume.[16,17]

The development of renal vasoconstriction in cirrhotic patients with ascites is clinically relevant as it predisposes to the development of HRS.[18]

In fact, HRS occurrence is determined by a complex interplay due to the increased activity of vasoconstrictor factors (mainly plasma renin activity and norepinephrine) and reduced activity of renal vasodilator factors.[19]

Urinary And Blood Biomarkers

In recent years, several urinary AKI markers that played a role in trying to determine the etiology of AKI in patients with cirrhosis were reported. For example, urinary neutrophil gelatinase-associated lipocalin (NGAL) levels were found to be increased in patients with cirrhosis and acute tubular necrosis compared with patients who had prerenal AKI and HRS.[20] Other urinary biomarkers tested are interleukin (IL)-18, kidney injury molecule-1, and liver-type fatty acid-binding protein.[21]

In addition to urinary biomarkers, also renal blood biomarkers have been evaluated to correctly estimate glomerular filtration rate (GFR), for example, cystatin C, b-trace protein, b-2 microglobulin, and dimethylarginines.[22–26]

However, in spite of the high number of studies testing new urinary and blood biomarkers, none of them are used routinely in the clinical practice due to the high costs and the scanty evidence supporting the superiority of a specific marker over the others in the early diagnosis and management of AKI and HRS.[27]

Management Of HRS

General Concepts

According to the aforementioned ICA consensus,[5] a novel definition of response to treatment was provided. In particular, partial response is defined as regression of AKI stage with a reduction in sCr to ≥0.3 mg/dl above the baseline value, whereas complete response is defined as the return of sCr to a value within 0.3 mg/dl of the baseline value.

Patients with ascites and suspected HRS-1 should be immediately treated as follows: (a) reduction or withdrawal of diuretic therapy and withdrawal of all potentially nephrotoxic drugs, (b) effective plasma volume expansion in the case of hypovolaemia, and (c) prompt recognition and early treatment of bacterial infections when suspected.[5,28]

In the case of response (return of sCr to a value within 0.3 mg/dl of the baseline), patients should be followed closely for early identification of eventual recurrences.[29] Alternatively, in the case of non-response, it should be considered the expansion of plasma volume with intravenous albumin at the dose of 1 g per kg body weight per day for two consecutive days, in order to treat pre-renal AKI and to allow differential diagnosis of AKI.[5] Diagnosis of HRS should be formulated when all these therapeutic approaches result unsuccessful and after ruling out other causes of secondary nephropathy (Figure 2).

Role Of Albumin And Non-Selective Beta-Blockers

Albumin, whose concentration is the higher among serum proteins, is of fundamental importance in both maintaining fluid distribution in the body and influencing immune response through modulation of pro-inflammatory molecules. In end-stage liver disease, both albumin concentration and functionality are significantly impaired.[30] Therefore, patients with advanced cirrhosis and ascites might benefit from albumin infusions either in terms of the improved immune system with a consequent lower risk of experiencing severe complications such as spontaneous bacterial peritonitis (SBP) and renal perfusion.[31,32]

Non-selective beta-blockers (NSBBs) are the first-line pharmacological therapy for preventing variceal bleeding in both primary and secondary prophylaxis. Other proposed benefits of NSBB therapy which may lead to a decreased risk of infections might be the increased

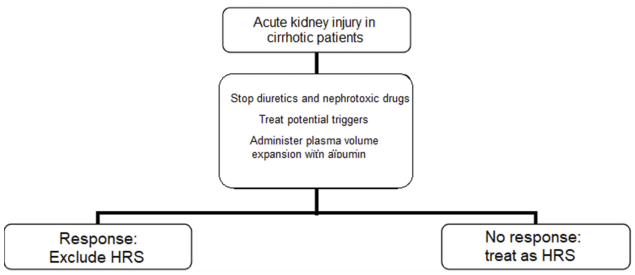

Figure 2 Therapeutic approach to the renal disease in cirrhotic patients.
Abbreviation: HRS, hepatorenal syndrome.

gut motility and reduced bacterial translocation.[33,34] Furthermore, a subgroup analysis of the CANONIC study found that NSBBs therapy leads to decreased severity of systemic inflammation and prolonged survival in subjects with ACLF.[35]

Interestingly, the role of NSBBs in advanced cirrhotic patients has been recently questioned by some retrospective studies, in particular, in the presence of refractory ascites[36] and SBP.[37] However, these findings of reduced survival in cirrhotic patients treated with NSBBs were not confirmed by subsequent studies.[38–41]

Therefore, the "window hypothesis" was formulated where NSBBs are beneficial only within a narrow window in cirrhotic patients and might decrease survival in end-stage patients[42] mainly due to reduced perfusion to vital organs (among them the kidney, hence the increased risk of HRS) caused by the excessive beta-adrenergic activity suppression. This interesting theory still needs to be supported by robust evidence and the exact time during the natural course of cirrhosis when that "window" should be considered closed is still unknown.[43,44]

In conclusion, due to the above-cited findings, NSBBs should not be withheld in cirrhotics even in an advanced stage as there is no definitive evidence on the increasing risk of developing HRS due to NSBB treatment.

Spontaneous Bacterial Peritonitis

As SBP occurrence plays a fundamental role as a triggering event of HRS-1, primary and secondary prevention of SBP should be adopted when indicated. Traditional indications to antibiotic prevention are upper gastrointestinal hemorrhage, low protein concentration in the ascitic fluid (<1.5 g/dL) when combined with any of the following features: Child-Pugh score ≥B9, serum bilirubin level ≥3 mg/dL, impaired renal function or hyponatremia (≤130 mEq/L), and previous episodes of SBP.[45]

In the case of gastrointestinal bleeding, prophylaxis with intravenous ceftriaxone (1 g/day) should be started when bleeding occurs and continued for up to 7 days.[45] Conclusion of a recent network meta-analysis supports with moderate-quality evidence the use of quinolones (both norfloxacin and ciprofloxacin) in patients with low protein content in the ascitic fluid and only with low-quality evidence the use of rifaximin over placebo.[46]

As a consequence of earlier studies,[47] current guidelines recommend secondary lifelong prophylaxis with norfloxacin (400 mg/day) after the first occurrence of SBP.[45]

Of course, any eventual cause of the underlying liver disease should be treated. In particular, the great impact of novel antiviral therapies in viral cirrhosis[48,49] is expected to play a fundamental role in the prevention of cirrhosis complications such as HRS.

Vasoconstrictor Agents

The rationale for the use of vasoconstrictor agents in HRS is related to the splanchnic vasodilation underlying the renal dysfunction.

Vasoconstrictors actually in use for the management of HRS are: terlipressin, noradrenaline and the combination of midodrine + octreotide. Terlipressin represents the most used and tested drug in the therapeutic algorithm of HRS. A number of studies showed the combination of terlipressin plus albumin to be more effective than albumin alone in these patients.[50–53] The REVERSE trial compared 97 patients treated with terlipressin + albumin vs 99 patients treated with placebo (+ albumin) and did not find a significant benefit in terms of HRS reversal rate (19.6% with terlipressin and 13.1% with albumin alone, p=0.22), whereas the change in creatinine levels at end of treatment was significantly superior with terlipressin (−1.1 mg/dl vs −0.6 mg/dl, p<0.001).[53] Of note, this landmark trial did not show any difference between the two arms in terms of transplant-free survival.[53]

Terlipressin can be administered both as intravenous boluses (from 0.5–1 mg every 4–6 hrs to 2 mg every 4 hrs) and as a continuous intravenous infusion (from 2 mg/day to 12 mg/day). The two administration regimens were found to be equally effective with the latter being associated with a significantly lower incidence of severe side effects such as diarrhea, ischemia, or circulatory overload in a recent Italian trial.[54]

In absence of response, terlipressin dose should be increased in a stepwise manner, while albumin should be administered at the dose of 20–40 g/day. Anyway, the treatment should be discontinued within 14 days. The recurrence rate after discontinuation is less than 20% and retreatment is frequently effective.[5]

In spite of the increasing body of evidence supporting its use, terlipressin has not been approved for use in the United States yet.

Midodrine (an α1-agonist drug) is usually administered in combination with octreotide (a somatostatin analogue) and albumin, and it represents the current standard of care in the United States. A single Italian randomized controlled trial showed that terlipressin plus albumin clearly

outperformed midodrine plus octreotide and albumin in the management of HRS.[55]

The administration of norepinephrine (administered in continuous infusion at a dose of 0.5–3 mg/h) plus albumin has been investigated in the treatment of HRS-1, and it was showed to be as effective as terlipressin in the treatment of HRS in a number of trials (mainly small single-center series).[56–59] Of note, noradrenaline has no effect on portal pressure (unlike terlipressin) and this aspect may be of interest in the management of HRS in acute-on-chronic liver failure (ACLF) patients.[60]

Currently, the use of norepinephrine in treating HRS is limited by the need for a central venous line and continuous monitoring, thus rendering the treatment unfeasible outside intensive care units.

Table 1 reports the available trials testing pharmacological agents in cirrhotic patients with type-1 hepatorenal syndrome.

Comparative Efficacy Of Treatments For HRS-1

The efficacy of vasoconstrictor agents was confirmed in several meta-analyses.[63–70] A meta-analysis by Gluud et al showed that vasoconstrictor drugs alone or with albumin reduce mortality compared with no intervention or albumin alone (risk ratio 0.82).[63] In subgroup analyses, the effect on mortality was seen at 15 days but not at 30 days, 90 days, or 180 days.[63]

Conclusions of a recent network meta-analysis support with moderate-quality evidence a benefit of terlipressin in terms of improved survival in patients with HRS-1 and only with low-quality evidence the use of other pharmacological agents compared with placebo.[66] The same review suggests the use of terlipressin over placebo (low-quality evidence) and over midodrine plus octreotide (moderate-quality evidence) in terms of HRS reversal whereas terlipressin and norepinephrine showed similar results, albeit the former was supported by the higher quality of evidence.[66]

Therefore, although current American guidelines still recommend the use of midodrine plus octreotide with albumin in these patients, only low-quality evidence was found to support this recommendation, without any significant benefit for short-term survival or in reversing hepatorenal syndrome.[66] As clearly reported by Gines in the editorial to the above-cited network meta-analysis, it is time to consider terlipressin "ready for prime time" in the management of HRS-1 due to the great body of evidence and the unequivocal results supporting its use.[71]

Non-pharmacological treatments of HRS include renal replacement therapy, molecular adsorbent recirculating system (MARS), and transjugular intrahepatic portosystemic shunting (TIPS). In patients with irreversible HRS with no response to pharmacological agents, renal replacement therapy either in the form of hemodialysis or continuous veno-venous hemofiltration should be considered, particularly in presence of intractable fluid overload and acidosis, uremic symptoms, and electrolyte abnormalities.[72–74]

MARS resulted able to significantly decrease sCr level in patients with HRS on ACLF, although with no difference in 28-day mortality as compared to standard medical therapy.[75]

Another randomized controlled trial showed that MARS significantly reduces sCr in addition to standard medical treatment and hemodiafiltration.[76]

Although TIPS was traditionally contraindicated in patients with unresolved HRS-1, a recent meta-analysis including nine studies (128 patients) found pooled short-term and 1-year survival rates as high as 72% and 47% in HRS-1 with no lethal procedure-related complications observed.[77] The pooled rate of renal function improvement after transjugular intrahepatic portosystemic shunt was 93% in type 1 hepatorenal syndrome and 83% in any type of hepatorenal syndrome.[77]

Liver Transplantation

Orthotopic liver transplantation (OLT) represents the best therapeutic option in these subjects regardless of their response to pharmacological therapy.[78] However, there are still some unsolved issues concerning the use of OLT in HRS patients. First, mean sCr was found to be higher even after OLT in patients transplanted for HRS as compared to other cirrhotic patients.[78,79] Therefore, simultaneous liver-kidney transplant should be considered in these subjects not only based on the concern of increased mortality post-transplant, but also due to the concern of lack of renal recovery after OLT.[80,81]

Identification and validation of predictors of renal recovery and the estimation of the extent of that recovery following liver transplantation represent an unsolved issue in the field.

Finally, concerning the priority in the waiting list, the paradoxical effect of pharmacological treatment in responders should be considered. In fact, effective treatment by lowering sCr can reduce the baseline MELD score, thus delaying the timing of OLT. This paradoxical effect of treatment in responders should be obviated either by considering only the baseline MELD, or by including eventual

Table 1 Characteristics And Outcomes Of Published Randomized Controlled Trials Comparing Different Pharmacological Interventions For Management Of Type 1 Hepatorenal Syndrome

Study	Intervention, Number Of Patients	Control, Number Of Patients	30 Days-Mortality	Reversal Of HRS
Terlipressin vs Placebo/Control				
Solanki et al,[50] 2003	Terlipressin 1 mg/12 h x 15d (+albumin); 12	Placebo x 15d (+albumin); 12	Terlipressin: 7/12 Placebo: 12/12	NR
Neri et al,[51] 2008	Terlipressin 1 mg/8h × 5d followed by 0.5 mg/8h × 14d (+albumin); 26	Albumin alone × 15d; 26	Terlipressin: 7/26 Placebo: 15/26	Terlipressin: 21/26 Placebo: 5/26
Sanyal et al,[52] 2008	Terlipressin 1 mg/6 h up to 2 mg/6 h × 14d (+albumin); 56	Placebo × 14d (+albumin); 56	Terlipressin: 32/56 Placebo: 35/56	Terlipressin: 19/56 Placebo: 7/56
Martin-Llahi et al,[82] 2008	Terlipressin 1 mg/4 h up to 2 mg/4 h × 15d (+albumin); 17	Albumin alone × 15d; 18	Terlipressin: 17/23 Placebo: 19/23	Terlipressin: 6/17 Placebo: 2/18
Zafar et al,[83] 2012[a]	Terlipressin 1mg/4 h × 7-10d (+albumin); 25	Albumin alone × 7-10d; 25	Terlipressin: 19/25 Placebo: 20/25	Terlipressin: 10/25 Placebo: 2/25
Boyer et al,[53] 2016	Terlipressin 1 mg/6h up to 2 mg/6 h × 14d (+albumin); 97	Placebo × 14d (+albumin); 99	Terlipressin: 32/97 Placebo: 35/99	Terlipressin: 19/97 Placebo: 13/99
Noradrenaline vs Terlipressin				
Alessandria et al,[59] 2007	Noradrenaline 0.1 µg/Kg/min up to 0.7 µg/Kg/min until HRS reversal or a ma×imum of 14d (+albumin); 5	Terlipressin 1 mg/4h up to 2 mg/4h × 28d; 25 until HRS reversal or a ma×imum of 14d (+albumin); 4	Noradrenaline: 1/5 Terlipressin: 1/4	Noradrenaline: 4/5 Terlipressin: 3/4
Indrabi et al,[56] 2013[a]	Noradrenaline (dose and duration not reported) (+albumin); 30	Terlipressin (dose and duration not reported) (+albumin); 30	Noradrenaline: 29/30 Terlipressin: 28/30	Noradrenaline: 16/30 Terlipressin: 17/30
Sharma et al,[57] 2008	Noradrenaline 0.5 mg/h up to 3 mg/h × 15d (+albumin); 20	Terlipressin 0.5 mg/6h up to 2 mg/6 h × 15d (+albumin); 20	Noradrenaline: 9/20 Terlipressin: 9/20	Noradrenaline: 10/20 Terlipressin: 8/20
Singh et al,[58] 2012	Noradrenaline 0.5 mg/h up to 3 mg/h until HRS reversal or a maximum of 14d (+albumin); 23	Terlipressin 0.5 mg/6 h up to 2 mg/6h until HRS reversal or a maximum of 14d (+albumin); 23	Noradrenaline: 15/23 Terlipressin: 16/23	Noradrenaline: 10/23 Terlipressin: 9/23
Octreotide + Midodrine vs Terlipressin				
Cavallin et al,[55] 2015	Midodrine p.o.7.5 mg/8 h up to 12.5mg/8 h + Octreotide s.c. 100 µg/8h up to 200 µg/8h until HRS reversal or a maximum of 14d (+albumin); 22	Terlipressin 3 mg/24 h up to 12 mg/24 h until HRS reversal or a maximum of 14d (+albumin); 27	Octreotide +Midodrine: 7/22 Terlipressin: 8/27	Octreotide+Midodrine: 1/22 Terlipressin: 15/27
Dopamine + Furosemide vs Terlipressin				
Srivastava et al,[61] 2015	Dopamine 2 µg/Kg/min + Furosemide 0.01 mg/Kg/h × 5 days (+albumin); 20	Terlipressin 0.5 mg/6h × 5 days (+albumin); 20	Dopamine +Furosemide: 17/20 Terlipressin: 17/20	NR
Octreotide + Midodrine vs Noradrenaline				
Tavakkoli et al,[62] 2012	Midodrine po 5 mg × 3/day up to 15 mg × 3/day + octreotide s.c. 100 µg/8h up to 200 µg/8h until HRS reversal or a maximum of 15d (+albumin); 9	Noradrenalin 0.1 µg/Kg/min up to 0.7 µg/Kg/min until HRS reversal or a maximum of 15d (+albumin); 6	Octreotide +Midodrine: 4/9 Noradrenaline: 4/6	Octreotide+Midodrine: 6/9 Noradrenaline: 5/6

Note: [a]Data reported as congress abstracts.
Abbreviations: HRS, hepatorenal syndrome; NR, not reported.

other treatments such as dialysis in the calculation of the MELD score according to the kind of response.[82]

Although renal recovery and patient survival after liver transplant were described to be significantly poorer for patients with AKI due to acute tubular necrosis than hepatorenal syndrome,[83] correct prediction of reversal of kidney injury and the extent of that recovery following OLT represent still a challenge. In fact, a number of confounders should be considered, such as pre-existing comorbidities, undiagnosed primary renal disease, perioperative events, and post-transplant immunosuppression; therefore, it is difficult to delineate the contribution of each of these factors to the clinical course after liver transplantation.

Conclusion

Renal dysfunction is a common complication in patients with end-stage cirrhosis, with or without ACLF. Several issues remain to be addressed such as the impact of the management of AKI according to the new algorithm on the outcome of these patients and the role of the new biomarkers of renal tubular damage in predicting the progression and prognosis of HRS, and in the differential diagnosis of the different types of AKI.

In summary, the results of the latest consensus conference of the ICA introduce a new dynamic definition of AKI and HRS in patients with cirrhosis, representing a substantial change from the traditional criteria used so far in the definition of AKI and HRS-1.

Disclosure

The author reports no conflicts of interest in this work.

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