Hepatorenal Syndrome: A Decade Later

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Abstract

Hepatorenal syndrome is a unique form of acute kidney injury seen in patients with acute liver failure or chronic liver disease in absence of any other identifiable cause of renal failure. It is primarily a diagnosis of exclusion. Despite of good pathophysiological understanding and better available therapeutic options for management of hepatorenal syndrome, it is still associated with significant morbidity and mortality. Liver transplantation forms the cornerstone for its management. In this review article, we have attempted to assimilate and summarise the advances made in the previous decade with regards to pathophysiology, classification and management of this entity.

Introduction

Hepatorenal syndrome (HRS) is a unique form of acute kidney injury seen in patients with acute liver failure or chronic liver disease in absence of any other identifiable cause of renal failure. It is primarily a diagnosis of exclusion. We have come a long way in understanding the pathophysiology and treatment of hepatorenal syndrome. In this review article, we have attempted to assimilate and summarise the advances made in the previous decade with regards to pathophysiology, classification and management of this entity, which was once considered ambiguous.

Diagnostic criteria: The International Ascites Club (IAC) revised the criteria for diagnosis of HRS in 2007.¹,² These consist of:

1. Cirrhosis with ascites
2. Serum creatinine >1.5 mg/dL
3. No improvement of serum creatinine (a decrease in serum < 1.5 mg/dL) after 2 days off diuretics and volume expansion with albumin (1g/kg body weight up to a maximum of 100 g/d)
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of signs of parenchymal renal disease, as suggested by proteinuria (> 500 mg/d) or haematuria (> 50 red blood cells per high-power field) and/or abnormal renal ultrasound

The main differences from the old diagnostic criteria (1996) are:

1. The use of creatinine clearance has been abandoned for the diagnosis of HRS
2. As long as septic shock is absent, the presence of ongoing bacterial infection does not preclude the diagnosis of HRS
3. Albumin is preferred over saline for plasma volume expansion to exclude pre-renal aetiology of acute kidney injury (AKI)
4. Minor diagnostic criteria including low fractional excretion of sodium and oliguria have now been omitted.

Even the new diagnostic criteria have been scrutinised and criticised in view of the following shortcomings and pitfalls.³,⁴
1. Patients with chronic kidney disease (CKD)/Anuric patients cannot be diagnosed with HRS.

2. The discrepancy between acute kidney injury network (AKIN) diagnostic definition and classification of AKI and IAC diagnostic criteria for HRS prevents early diagnosis of renal dysfunction in cirrhotic patients. A patient having increase in creatinine of 0.3 mg/dl in 48 hrs. will be classified as having AKI but if the serum creatinine is < 1.5mg/dl, the diagnosis of HRS is not possible. In cirrhotics, where the baseline creatinine is low, this excludes a group of patients with impending HRS who may benefit by instituting specific treatment at an earlier stage.

Acute dialysis quality initiative (ADQI) in their 8th international consensus conference on hepatorenal syndrome has tried to address the various shortcomings of previous definitions. Their recommendations are to be considered as the first step towards standardisation of the definition of AKI in patients with cirrhosis.

As the diagnosis of AKI as defined by RIFLE criteria has been shown to be a predictor of hospital survival. The consensus of the workgroup has been to apply the modified RIFLE criteria to define AKI in patients with cirrhosis irrespective on the cause-structural or functional.

The early identification of change in serum creatinine in patients with AKI not fulfilling the criteria for HRS but having low GFR will allow early institution of therapy for these patients and prevent rapid progression of the pathology.

The workgroup also goes on to suggest the term hepatorenal disorders be used to describe all patients with advanced cirrhosis and concurrent kidney dysfunction encompassing both functional and structural. The classification of the severity of dysfunction will be based on the RIFLE criteria.

This will allow cirrhotic patients with renal dysfunction to be properly classified –allowing studies to be conducted to define their prognosis and to devise treatment options.

### Classification of HRS

The classification of hepatorenal syndrome into two types has remained unchanged even in the updated diagnostic criteria. It is crucial to differentiate between the 2 types, not just for the clinical management, but also for appropriate prognostication and risk assessment.

**Type 1 HRS:** Defined as doubling of the serum creatinine to more than 2.5 mg/dl in duration of less than 2 weeks. It is more acute, associated with precipitating factors and has a grave prognosis.

**Type 2HRS:** Defined as a slowly progressive rise in serum creatinine to more than 1.5 mg/dl. It is usually associated with diuretic resistant refractory ascites.

### Epidemiology

HRS occurs almost exclusively in patients with ascites and the estimated probability of developing HRS at 1 and 5 years in patients with ascites being 18 and 39% respectively.6

In a retrospective multicentric study conducted a decade back by Moreau et al. found that in 423 patients with cirrhosis and AKI; Type 1 and 2 HRS were implicated in 20% and 6.6% cases respectively.7

In a recent study Montoliu et al. assessed the incidence and prognosis of different types of functional renal failure in 263 consecutive cirrhotic patients with ascites. All patients were followed up for 41±3 months after their first incidence of ascites. During the follow-up period, out of the 129 (49%) patients who developed some type of functional renal failure, hepatorenal syndrome was causative in only 7.6%. The cumulative probability of developing HRS was 11.4%. The independent predictors for development of functional renal failure were age, Child-Pugh score, and serum creatinine.8 However, another prospective study conducted in a tertiary transplant centre documented that 40% patient with cirrhosis and kidney failure had HRS.9

### Pathogenic Mechanisms

Many interrelated pathophysiological processes have been implicated in the development of HRS which include the diseased liver, portal hypertension and development of ascites, splanchnic vasodilation, myocardial depression, abnormal systemic and renal neurohumoral regulation, lower renal prostaglandin production and adrenal insufficiency.10 The severity of deterioration of liver function affects the development of renal dysfunction.

Arterial hypotension along with relatively insufficient CO (in spite being high) is the key factor in development of compensatory mechanisms contributing to development of HRS. The traditional model of the hepatorenal axis and HRS includes splanchnic hyperaemia and vasodilation with compensatory activation of the renin–angiotensin aldosterone (RAAS) and sympathetic systems (SNS) to maintain blood pressure. Contributory to this is the non-osmotic release of endogenous vasopressin. The resultant increase in serum catecholamine and angiotensin levels causes intra-renal vasoconstriction and hypoperfusion resulting in a decrease in glomerular filtration rate (GFR). With increasing serum creatinine levels, HRS ensues especially when additional precipitating factors like spontaneous
bacterial peritonitis, upper GI bleeding, large volume paracentesis, further increase renal vasoconstriction. Translocation of bacteria from the intestinal lumen to mesenteric lymph nodes (MLNs) and then into the systemic circulation lead to an inflammatory state and vasodilation. Recent studies have shown the role of the Renin–angiotensin–aldosterone system (RAAS) not only in propagating renal injury through intra-renal vasoconstriction but also as a cause for hepatic fibrosis. For pathophysiological phases responsible for the development of ascites and HRS is summarised in Table 1.

### Precipitating Factors for HRS

In 50% cases, the development of HRS is spontaneous, whereas in other half 1 or more identifiable triggers may be found which include:

1. Bacterial infections—Ascitic fluid, respiratory system, urinary tract, GI tract infections and infections of the biliary tract.
2. Diarrhoea and vomiting
3. Diuretics
4. Gastrointestinal bleeding—variceal bleeding
5. Large volume paracentesis (LVP)—more than 5 litres without adequate blood volume expansion.

### Prevention of HRS

The development of HRS is associated with significantly increased morbidity and mortality. With better understanding of the pathophysiology of HRS, certain specific strategies have been identified to prevent HRS in specific clinical situations. A systematic literature review was conducted by acute dialysis quality initiative (ADQI) in 2010, where the experts developed a consensus recommendation for standardised care of cirrhotics with HRS. The preventive strategies outlined by ADQI are mentioned below along with the review of other literature for prevention of HRS:

1. Careful assessment, close monitoring and prevention of precipitating factors in cirrhotics with ascites.
2. Consider covert hypoadrenalism in patients with cirrhosis to improve response to vasopressors and survival.
3. Drugs which reduce renal perfusion and those causing nephrotoxicity have been reported to precipitate HRS, should be avoided.
4. Antibiotic prophylaxis has shown to reduce spontaneous bacterial peritonitis (SBP). Studies using norfloxacin have reported not only a reduction in SBP (7 versus 61%) but also a reduction in the incidence of HRS (28 versus 41%).
5. Albumin infusions have been reported to decrease the incidence of HRS in patients with SBP. Consecutive trials have shown that in context of SBP, albumin infusion is more effective than other plasma expanders. In severely ill cirrhotic patients, volume expansion with albumin has been shown to reduce plasma renin, suggesting an improvement in the effective circulating volume. In randomised controlled clinical trials, albumin infusions reduced both the incidence of HRS and mortality.
6. Prophylactic pentoxifylline, a tumour necrosis factor-α antagonist, reduces complications in patients with advanced cirrhosis including renal dysfunction.
7. Large volume paracentesis (LVP) may induce paracentesis induced circulatory dysfunction (PICD) leading to development or exacerbation of AKI and HRS. Administration of albumin 8 g/litre of fluid aspirated (specially if the aspiration is more than or equal to 5 litres) leads to prevention of PICD.

### General Management

Once the diagnosis of HRS is confirmed, it is important to classify the disease into either of the two types. Patients with Type 1 HRS need to be managed in an intensive care unit, in view of the associated inherent risk of multi-organ failure. Patients with Type 2 HRS may be managed on an outpatient basis with thorough workup and supportive care.

### Monitoring

Patients with type 1 HRS should be monitored carefully. Parameters to be monitored include urine output, fluid balance, and arterial pressure, and standard vital signs. Ideally central venous pressure...
should be monitored to help with the management of fluid balance and prevent volume overload.

**Screening for Sepsis**

Bacterial infection should be identified early, by blood, urine and ascitic fluid cultures, and treated with antibiotics. Patients who do not have signs of infection should continue taking prophylactic antibiotics, if previously prescribed.

**Use of Paracentesis**

There are few data on the use of paracentesis in patients with type 1 HRS. Nevertheless, if patients have tense ascites, large-volume paracentesis with albumin may be useful.

**Volume Resuscitation**

Excessive administration of fluids should be avoided to prevent volume overload due to the presence of kidney injury and development or progression of dilutional hyponatraemia. Use of Functional haemodynamic monitoring to assess the dynamic response to a fluid volume bolus is desirable. All diuretics should be stopped in patients at the initial evaluation and diagnosis of HRS. There are no data to support the use of furosemide in patients with ongoing type 1 HRS. Nevertheless furosemide may be useful to maintain urine output and treat central volume overload if present. Spironolactone is contraindicated because of high risk of life-threatening hyperkalaemia. Patients with HRS should be optimally resuscitated, with intravenous administration of albumin (initially 1 g of albumin/kg of body weight up to a maximum of 100 g, followed by 20-40 g/day) in combination with vasoressor therapy, for up to 14 days.

**Pharmacological Treatment of HRS**

Most of these therapies have targeted the haemodynamic perturbations that are thought to underlie the pathophysiology of HRS, including systemic and splanchnic vasodilation.

**Vasopressin Analogues**

Vasopressin analogues form the first line management of type 1 HRS as a bridge to transplant. Among all vasopressin analogues, the drug most widely used for treatment of type 1 HRS is terlipressin (three glycyI residues and lysine-VP). Following intravenous administration, the glycyI residues are cleaved by endothelial peptidases allowing slow, prolonged release of lysine-VP. This mechanism prolongs the half-life of terlipressin, enabling administration in divided doses without the need for an infusion, and minimises systemic toxicity.

Terlipressin has a preferential effect on V1 receptors, which are densely located in the splanchnic bed. The improvement in renal perfusion is attributed to splanchnic vasoconstriction, rise in the effective circulating volume, mean arterial pressure, and decrease in the plasma renin and aldosterone and overall improvement in renal perfusion pressure. Terlipressin is not yet approved by the Food and Drug Administration (FDA) in the USA for use in HRS, though it is commonly used in Europe and Asia. In a recent meta-analysis of randomised controlled trials, it was observed that the therapy with terlipressin and albumin improves the renal function in patients with cirrhosis and HRS type 1. This improvement was sustained in most of the patients for the duration of follow-up (90 to 180 days) leading to an improvement in overall and transplant-free survival. The pooled percentage of HRS reversal was 46% and recurrence in 8%.

In recent randomised, prospective, placebo-controlled clinical trials, terlipressin was found significantly more effective than placebo in reversing type 1 HRS with a similar safety profile. Caraceni et al. reported their experience with terlipressin and albumin treatment as a bridge to liver transplantation in three patients with cirrhosis and recurrent HRS. They concluded that terlipressin prevents irreversible renal failure and the need for dialysis until an organ becomes available. Though most studies on terlipressin have been conducted in patients with Type 1 HRS, but recently its use has also been evaluated in patients with type 2 HRS. This study demonstrated a combined reversal rate for type 2 HRS with terlipressin and albumin of about 80% which, recurred after discontinuation of therapy.

The ADQI recommends that patients with Type 1 HRS should be optimally resuscitated with albumin (initially 1 g of albumin/kg of body weight for 2 days, up to a maximum of 100 g/day, followed by 20-40 g/day) in combination with a vasoconstrictor, preferentially terlipressin. The terlipressin treatment protocol comprises an initial dose of 0.5-1 mg terlipressin applied by intravenous injection every 4-6 h or continuous intravenous infusion starting at an initial dose of 2 mg/d. The therapy is aimed to improve renal function and to decrease serum creatinine to less than 1.5 mg/dl (complete response). If serum creatinine does not decrease at least 25% of its base value or < 133 μmol/L after 3 days, the dose of terlipressin should be increased in a stepwise manner up to a maximum of 2 mg/4 hour. For patients with partial response (serum creatinine does not decrease < 133 μmol/L) or in those patients without reduction of serum creatinine, treatment should
be discontinued within 14 days. If terlipressin is not available, alternative vasoconstrictors, such as norepinephrine or combination octreotide/midodrine, together with albumin should be considered. Therapy should be discontinued after 14 days in non-responders and only continued thereafter in partial responders while awaiting the outcome of salvage techniques. Contraindications to terlipressin therapy include ischaemic cardiovascular diseases. Patients on terlipressin should be carefully monitored for development of cardiac arrhythmias or signs of splanchnic or digital ischaemia, and treatment modified or stopped accordingly. Recurrence of type 1 HRS after discontinuation of terlipressin therapy is relatively uncommon. Treatment with terlipressin should be repeated and is frequently successful.

Norepinephrine

Norepinephrine, an α-1 adrenergic agonist drug, has been found to be effective in the treatment of HRS. Noradrenaline (0.5-3 mg/h) is administered as a continuous infusion and the dose is increased to achieve a raise in arterial pressure and also improves renal function in patients with type 1 HRS. In a prospective, randomised study of 46 patients, the safety and efficacy of norepinephrine was compared with terlipressin in treatment of type 1 HRS. Albumin was administered in both the groups. Noradrenaline was found to be as safe and effective as terlipressin, but less expensive in the treatment of HRS. On multivariate analysis, only baseline CTP score was found to be predictive of response. It is also recommended by ADQI as an alternative to terlipressin along with albumin for the treatment of HRS. A recent meta analysis also confirmed that norepinephrine and terlipressin are equivalent in efficacy and side effect profile in reversing HRS.

Midodrine and Octreotide

Midodrine, an α-1 agonist has been used in both type 1 and 2 HRS. It causes vascular smooth muscle constriction and the availability of an oral preparation makes administration of this drug on an outpatient basis feasible. Studies have shown that it is the combination of thrice daily midodrine (7.5-12.5 mg) with octreotide (100-200 μg subcutaneously) and albumin, which actually improves renal plasma flow, GFR, urinary sodium excretion along with a reduction in renin, vasopressin and glucagon after 3 weeks of treatment. In a recent study of 162 patients with HRS type 1 and type 2, the effect of octreotide, midodrine, and albumin on survival and renal function was compared with a cohort that did not receive this therapy. Transplantation could be performed in 45% of patients in the treatment group as compared with 26% of patients in the control group. It was concluded that the therapeutic regimen of octreotide, midodrine, and albumin significantly improved short-term survival and renal function in both HRS type 1 and type 2 and provided a significant benefit as a bridge to liver transplantation in HRS type 1 and prevent progression of HRS type 2 to HRS type 1.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

In a recent study, 61 TIPS patients who had a subsequent liver transplantation were evaluated and compared with 591 patients transplanted with cirrhosis without TIPS. It was shown that TIPS improves post-transplant graft and patient survival significantly, possibly due to an improved pre-transplant renal function and portal blood supply of the graft. EASL guidelines recommend that though the insertion of TIPS may improve renal function in some patients, there are insufficient data to support the use of TIPS as a treatment of patients with type 1 HRS. Recent ADQI editorial reviews recommend use of TIPS as a treatment option for patients with type-2 HRS with refractory ascites who require large-volume paracentesis.

Renal replacement therapy (RRT)

Although there is a preference for continuous renal replacement therapy (CRRT) over intermittent haemodialysis in haemodynamically unstable patients, analysis of the currently published studies does not provide enough evidence for the selection of RRT as a modality for the treatment of AKI in the setting of HRS. CRRT use may be advantageous in the management of HRS patients with AKI who are haemodynamically unstable or those patients at risk of elevated intracranial pressure such as patients with acute fulminant liver failure or acute on chronic liver failure. In type-1 HRS, RRT should be avoided unless there is either an acute reversible component or a plan for liver transplantation. EASL recommends that renal replacement therapy may be useful in patients who do not respond to vasoconstrictor therapy, and who fulfill criteria for renal support.

Artificial Liver Support Systems

There are very limited data on artificial liver support systems, and further studies are needed before its use in clinical practice can be recommended.

Transplantation

HRS is a marker of poor hepatic function, which will recover only when there is some degree of improvement in liver function. In most patients, this
will occur only after liver transplantation, which is the best treatment for both type 1 and type 2 HRS. HRS should be treated before liver transplantation, since this may improve post-liver transplant outcome. Patients with HRS who do not respond to vasopressor therapy, and who require renal support should generally be treated by liver transplantation alone, since the majority will achieve a recovery of renal function post-liver transplantation. There is a subgroup of patients who require prolonged renal support (> 12 weeks), and it is this group that should be considered for combined liver and kidney transplantation. Nadim et al. have suggested liver transplantation alone for candidates with type 1 HRS for less than 4 weeks and simultaneous liver-kidney (SLK) for those at risk of non recovery of renal function. The united network of organ sharing (UNOS) recommendations for SLK transplant in patients with AKI include those with hepatorenal syndrome with creatinine ≥ 2 mg/dl and duration of dialysis more than 8 weeks.

For any given value of MELD or MELD-Na score, patients with HRS have a shorter survival expectancy than patients with chronic liver disease who are candidates for LT. However, patients with HRS are not given priority to liver transplantation as per the policy of “exceptions to the MELD score” that are currently used in several Western countries. In a recent article, Angelli et al. suggested that to optimise the results of the pharmacological treatment of HRS, responders should receive the right priority in the waiting list, taking into account not only the value of HRS per se on three-month mortality beyond the MELD score, but also considering that the pharmacological treatment of HRS can reduce the baseline MELD score in these patients.

Prognosis

The median survival of patients with type 1 HRS is only 10% at 90 days, whereas for type 2 HRS it is 6 months without treatment. Prognosis is however improved with treatment with the 3 month survival of 20 and 40% respectively for type 1 and 2 HRS.

The survival in these groups of patients is dictated by the deterioration in liver function, and the response to pharmacological treatment. If there is no improvement with treatment of vasoconstrictors for 10-14 days, it indicates a poor prognosis.

Conclusion

Despite of good pathophysiological understanding and better available therapeutic options for management of hepatorenal syndrome, it is still associated with significant morbidity and mortality. Liver transplantation forms the cornerstone for its management. Timely identification, prioritisation for transplant, and early initiation of vasoconstrictor therapy may contribute to better management plan.

References


