Review Article

An Update on Hepatorenal Syndrome

Samuel Chan*

Queensland Renal Transplant Service, Princess Alexandra Hospital, Australia

Abstract

The Hepatorenal Syndrome (HRS) is one of many potential causes of Acute Kidney Injury (AKI) in patients with decompensated liver disease.

HRS is associated with poor prognosis and represents the end-stage of a sequence of reductions in renal perfusion induced by progressively severe hepatic injury.

The pathophysiology of HRS is complex with multiple mechanisms interacting simultaneously, although HRS is primarily characterised by renal vasoconstriction.

A recently revised diagnostic criteria and management algorithm for AKI has been developed for patients with cirrhosis, allowing physicians to commence treatment promptly.

Vasopressor therapy and other general management, such as antibiotic prophylaxis, need to be initiated while patients are assessed for eligibility for transplantation. Liver transplantation remains the treatment of choice for HRS but is limited by organ shortage.

Other management options, such as transjugular intrahepatic portosystemic shunt, renal replacement therapy and molecular absorbent recirculating system, may provide short term benefit for patients not responding medical therapy while awaiting transplantation.

Clinicians need to be aware of the pathophysiology and management principles of HRS to provide quality care for patients with multi-organ failure.

Introduction

Renal failure is common amongst patients with decompensated cirrhosis and is associated with a poor prognosis, with life expectancy ranging between weeks to months. Hepatorenal Syndrome (HRS) is a functional form of acute kidney injury (AKI) characterised by renal vasoconstriction. Studies attempting to develop renal biomarkers to differentiate aetiologies of AKI have shown promise, but such endeavour remains in its infancy. There are different approaches to the management of HRS, although liver transplantation still shows the highest survival rates amongst patients with both hepatic and renal failure [1]. This review paper will provide an update on the pathophysiology, diagnostic criteria and treatment options, including prophylaxis, in patients with HRS.

Epidemiology

The incidence and the prevalence of HRS in patients with advanced liver disease are approximately 7.6% and 13%, respectively [2]. HRS occurs predominantly in portal hypertension associated with cirrhosis, but has been described in severe alcoholic hepatitis and fulminant hepatic failure [3]. HRS may occur either spontaneously, or may be precipitated by an acute insult, including Spontaneous Bacterial Peritonitis (SBP), non-steroidal anti-inflammatory drugs or upper gastrointestinal bleeding.

Pathophysiology

There are a plethora of simultaneous mechanisms underlying the pathophysiology of HRS including arterial vasodilatory effects, systemic inflammation, bacterial translocation and hepatorenal reflex [4] (Figure 1). These mechanisms appear to be mostly functional, as normalisation of kidney function may be achieved either by pharmacotherapy or by liver transplantation.

The arterial vasodilation theory

Arterial vasodilation appears to be the most plausible explanation for circulatory dysfunction which occurs in patients with cirrhosis and ascites [3]. This involves two major mechanisms; first, systemic circulatory disturbances and second, activation of neurohumoral systems. Splanchnic vasodilatation, resulting from portal hypertension secondary to cirrhosis, leads to decreased systemic vascular resistance and subsequent reduction in effective blood volume, which is clinically mediated via an increased production of Nitric Oxide (NO), carbon monoxide and/or endogenous cannabinoids [3]. In the early stages, the effective arterial blood volume and arterial pressure are maintained by increased cardiac output resulting in a hyperdynamic circulation. In later stages, the
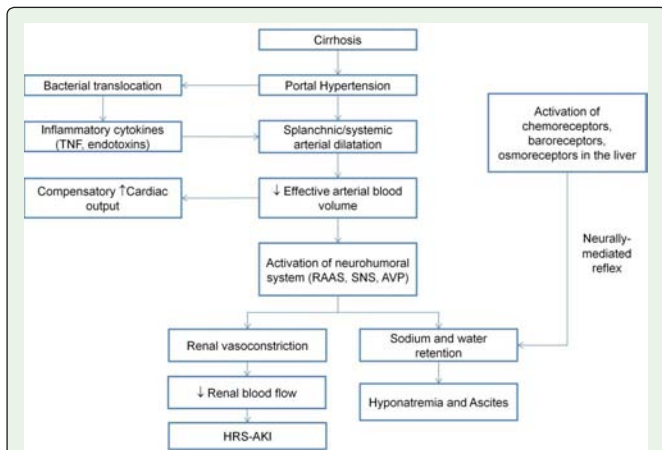
Figure 1: Proposed mechanisms for pathophysiology of hepatorenal syndrome.
Abbreviations: AVP: Arginine Vasopressin; RAAS: Renin-Angiotensin-Aldosterone System; SNS: Sympathetic Nervous System; TNF: Tumor Necrosis Factor.

progressive splanchnic vasodilatation results in a decrease in effective arterial blood volume that can no longer be compensated by cardiac output. Moreover, the subsequent decrease in cardiac output may be due to cirrhotic cardiomyopathy, thereby contributing to further arterial under filling and worsening of renal function [5].

In order to maintain arterial pressure, systemic vasoconstrictor systems, such as the Renin-Angiotensin-Aldosterone System (RAAS), the Sympathetic Nervous System (SNS) and the non-osmotic hypersecretion of Arginine Vasopressin (AVP), are activated leading to increased plasma renin activity and increased plasma norepinephrine levels. However, the activation of neurohumoral systems has harmful impacts on kidneys. Development of renal sodium and solute-free water retention leads to ascites and oedema, and hypervolemic hyponatremia, respectively. This results in significant renal vasoconstriction, which leads to a decrease in glomerular filtration rate and subsequently HRS.

Renal factors

Prostaglandins (PGs), specifically PGI2 and PGE2, induce renal vasodilation, thereby providing renal protective effects by compensating for the vasoconstrictor systems of RAAS, SNS and AVP. The levels of renal PGs are increased in patients with cirrhosis

and ascites [6]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are a common cause of kidney failure in patients with cirrhosis [6], illustrating the probable important role of PG production for maintaining renal function in patients with cirrhosis.

Cytokines and vasoactive mediators

Systemic inflammation plays a role in the pathophysiology of HRS. Bacterial translocation has been implicated in the haemodynamic derangement of cirrhotic patients, thereby leading to HRS4. In the clinical setting, increased levels of pro-inflammatory cytokines, such as Tumour Necrosis Factor α (TNFα), interleukin-6 (IL-6) and nitric oxide, in the splanchnic area lead to reduced systemic vascular resistance and increased cardiac output [7].

Hepatorenal reflex

The existences of sensor(s) in the hepatic circulation, which play a role in regulating extracellular fluid volume, are pathologically stimulated by hepatic haemodynamic irregularities. This may contribute to volume overload and ascites by activating renal sympathetic nerves to promote salt and water retention [8].

Diagnostic Critera

Acute Kidney Injury (AKI) is a frequent complication in patients with advanced liver disease, with several potential causes. Recent consensus guidelines have been published by the International Club of Ascites updating the recommended threshold for diagnosing AKI in patients with cirrhosis (Table 1), which now align with the Kidney Disease Improving Global Outcomes (KDIGO) AKI classification [2]. HRS is a diagnosis of exclusion, and should be suspected in patients presenting with new renal impairment in the setting of cirrhosis with ascites. Criteria for the diagnosis of HRS were first published by the International Club of Ascites in 1996 with subsequent revisions [2,9] and the current recommended criteria are listed in table 2. A vital step in evaluating patients with potential HRS is to exclude other possible causes of AKI.

HRS has traditionally been subdivided into type 1 or type 2 disease based on the rate of onset of AKI, and prognosis. Type 1 HRS is characterised by a rapid (less than two weeks) onset of AKI, often precipitated by other events, in particular SBP. Type 1 HRS is usually associated with a poor prognosis. Type 2 HRS typically presents with a more insidious onset of renal impairment over several weeks in patients with cirrhosis and refractory ascites.

Table 1: International Club of Ascites (ICA-AKI) new definitions for the diagnosis of AKI in patients with cirrhosis.

Subject	Definition
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used.
	In patients without a previous sCr value, the sCr on admission should be used as baseline.
Definition of AKI	Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours; or,
	A percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days
Staging of AKI	**Stage 1:** 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: increase in sCr >2-fold to 3-fold from baseline
	Stage 3: 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

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Abbreviations: AKI: Acute Kidney Injury; sCr: Serum Creatinine.

Table 2: Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis.

HRS - AKI
Diagnosis of cirrhosis and ascites
Diagnosis of AKI according to ICA-AKI criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)
No macroscopic signs of structural kidney injury*, defined as:
Absence of proteinuria (>500 mg/day)
Absence of microhaematuria (>50 RBCs per high power field)
Normal findings on renal ultrasonography

Reproduced with permission from Angeli P et al [2]
Abbreviations: ICA: International Club of Ascites; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; RBCs: Red Blood Cells.
*Patients who fulfil these criteria may still have structural damage such as tubular damage.

Currently there are no clinical criteria able to reliably distinguish between HRS and other causes of AKI. This has prompted researchers to search for biomarkers, such as urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), with the potential to aid the differential diagnosis and management of AKI occurring in cirrhotic patients4. However, these biomarkers are yet to be validated in large randomised control trials and therefore cannot be routinely recommended in clinical practice yet.

Prognosis

Prognosis is poor when patients with cirrhosis develop renal impairment and HRS is associated with the worst mortality among the different causes of AKI in the setting of cirrhosis [10]. A study in 2005 showed the median survival times for Type 1 HRS and Type 2 HRS were 1 month and 6 months, respectively [11]. Further prognostic studies with the newly revised HRS diagnostic criteria will be required.

Management

The International Club of Ascites have proposed a new algorithm for managing AKI based on the ICA-AKI criteria (Figure 2), which potentially allows patients to receive earlier treatment for AKI-HRS2. Due to scarce supply of organs for transplantation, medical treatments are often initiated first.

Prevention of HRS

In patients with SBP, a meta-analysis of four randomised trials demonstrated that treatment with antibiotics and albumin was associated with a significant reduction in renal impairment (8% versus 31%) and mortality (16% versus 35%) compared with controls [12]. Furthermore, another randomised controlled trial reported that primary prophylaxis with norfloxacin reduced the incidence of SBP, delayed the development of HRS and improved survival in patients with cirrhosis, ascites and either advanced liver failure or impaired renal function [13]. The phosphodiesterase inhibitor, pentoxifylline, which has anti-inflammatory properties via inhibition of leukotriene and TNFα synthesis, was included in management for prevention of HRS. However, a recent randomised study demonstrated pentoxifylline is not statistically equivalent to the efficacy of prednisolone in patients with severe alcoholic hepatitis [14].

Vasoconstrictor therapy

Medical treatment for patients with suspected HRS usually consists of vasopressor and albumin infusion, with the aims of improving splanchnic arterial circulation and plasma volume expansion, respectively. Several vasopressor therapies have been trialled in HRS, including terlipressin, norepinephrine, and midodrine plus octreotide. Terlipressin is not licensed for use in the USA nor is it on the Pharmaceutical Beneficial Scheme (PBS) in Australia, while midodrine is only available through Special Assess Scheme (SAS). A pooled analysis of 501 patients in 21 studies showed that an increase in mean arterial pressure of at least 5 mmHg correlated with improvement in renal function regardless of which vasopressor was used [15].

A systematic review and meta-analysis of randomised controlled trials of norepinephrine versus terlipressin in patients with Type 1 HRS found no significant difference in reversal of HRS, mortality
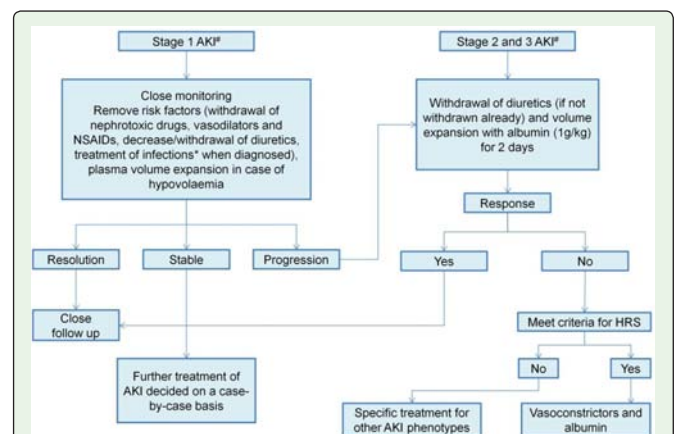

Figure 2: Proposed algorithm for the management of Acute Kidney Injury (AKI) in patients with cirrhosis and ascites.
*Treatment of spontaneous bacterial peritonitis should include albumin infusion according to current guidelines.
#Initial AKI stage is defined as AKI stage at the time of first fulfillment of the AKI criteria.
Abbreviations: HRS: Hepatorenal Syndrome; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs. Reproduced with permission from Angeli P et al [2].

at 30 days or recurrence of HRS [16]. Furthermore, a recent study indicated that the efficacy of a midodrine plus octreotide regimen might not be as significant as previous studies suggested [17]. In 2015, a randomised controlled trial of 49 patients comparing terlipressin to octreotide/midodrine illustrated a significantly higher rate of improvement in renal function with terlipressin (≥50% serum creatinine decrease 70.4% versus 28.6%, p=0.01) although there was no significant difference in survival between the two groups [18]. Terlipressin is a bridging option, despite its high cost, to liver transplantation in patients who are transplant candidates as it may improve both renal function and short term survival for patients awaiting for a liver transplant. Further clinical trials will be required to assess the indication, efficacy and duration of different vasopressors under the new ICA-AKI criteria and management algorithm.

Transjugular Intrahepatic Portosystemic shunt (TIPS)

Whilst limited studies have suggested TIPS may lead to improvement of renal function in a well-selected group of patients [19], poor prognosis has been associated with patients with advanced liver disease undergoing TIPS procedure [20]. TIPS aims to reduce portal pressure by inserting an intrahepatic stent which shunts portal blood into the systemic circulation, and in theory may benefit some patients with HRS. However, many patients with HRS are ineligible for TIPS due to contraindications including severe hyperbilirubinaemia or Child-Pugh Class C (e.g. Bilirubin >5mg/dL, Child-Pugh score >11). Moreover, the risks associated with TIPS, namely hepatic encephalopathy, liver failure, cardiac failure and renal injury due to contrast, also need to considered [21].

Extracorporeal Support Systems

Renal Replacement Therapy (RRT) has been shown to improve short-term survival in patients with AKI and may provide a bridge to liver transplantation for patients with HRS who are unresponsive to vasopressors and ineligible for TIPS [22]. However, in the absence of an acute reversible component to the AKI or a plan for liver transplantation, initiation and/or continuation of RRT should be evaluated carefully, since these patients have a poor prognosis and are unlikely to recover with RRT alone [22].

Molecular absorbent recirculating system (MARS) removes albumin-bound and water-soluble substances including NO and TNF, which are involved in pathogenesis of HRS. MARS has been shown to improve neurological function and coagulation parameters although a randomised trial (RELIEF) of 189 patients reported no beneficial effect on survival of MARS therapy in patients with acute or chronic liver failure [23].

Liver transplantation

The definitive treatment for Type I HRS is liver transplantation, as this will reverse both portal hypertension and liver failure, the two main factors leading to systemic circulatory disturbances in HRS. A case control study suggested that patients with HRS treated with vasopressin before transplantation had similar outcomes compared with patients transplanted with normal renal function [24]. However, other studies have demonstrated that vasopressors, regardless of the agent used, had no significant impact on survival1, [25]. Simultaneous liver-kidney transplantation is not necessary for patients with isolated HRS, and should only be considered in selected patients at high risk for non-recovery of renal function, such as patients with heavy proteinuria and other evidence of advanced primary renal disease.

Conclusion

HRS remains an important and life-threatening complication of patients with advanced liver disease. Recent advances in the understanding of the pathophysiology of HRS have identified potential targets for novel diagnostic and therapeutic approaches. HRS is now recognised as HRS-AKI and the diagnostic criteria have recently been revised. Whilst liver transplantation in appropriate patients is the only definitive treatment for HRS, vasopressors and albumin remain the key supportive medical therapy for HRS-AKI. Novel biomarkers may play a future significant role in helping clinicians to identify the aetiology of AKI in patients with cirrhosis.

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