

REVIEW ARTICLE

## An Update on Hepatorenal Syndrome

Samuel Chan<sup>1,2</sup>, Kenneth Au<sup>2,3</sup>, Ross Francis<sup>1</sup>, David W. Mudge<sup>1</sup>, David W. Johnson<sup>1</sup>, Tony Rahman<sup>3</sup>

<sup>1</sup>Department of Nephrology, Princess Alexandra Hospital, Brisbane, Queensland, Australia; <sup>2</sup>Centre for Health Services Research, University of Queensland, Brisbane, Queensland, Australia; <sup>3</sup>Department of Gastroenterology and Hepatology, The Prince Charles Hospital, Chermside, Queensland, Australia

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### Abstract

Hepatorenal syndrome (HRS) is one of the 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 whilst 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 to medical therapy whilst 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.

**Keywords:** acute kidney injury; hepatorenal syndrome; molecular absorbent recirculating system; renal replacement therapy; transjugular intrahepatic portosystemic shunt

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*Author for correspondence:* Samuel Chan, Department of Nephrology, Princess Alexandra Hospital, 199 Ipswich Road, Woolloongabba, Brisbane, Queensland, Australia. Email: [samuel.chan@uqconnect.edu.au](mailto:samuel.chan@uqconnect.edu.au)

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### Introduction

Renal failure is common amongst patients with decompensated cirrhosis and is associated with a poor prognosis, with life expectancy ranging from 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 article 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 it 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 (NSAIDs) 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

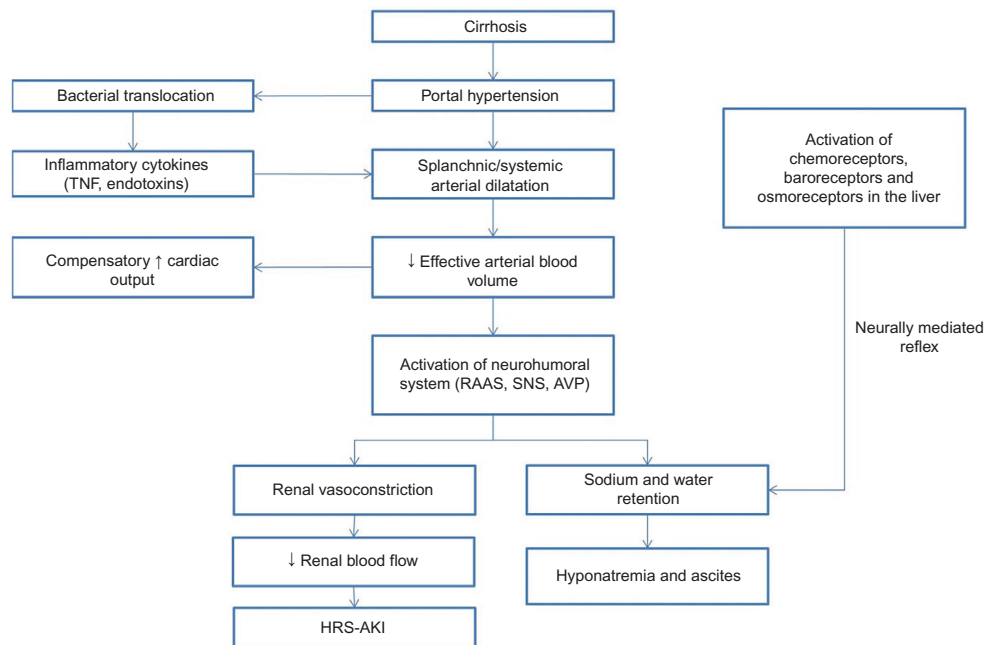
Arterial vasodilation appears to be the most plausible explanation for circulatory dysfunction that occurs in patients with cirrhosis and ascites (3). This involves two major mechanisms as follows: firstly, systemic circulatory disturbances and, secondly, activation of neurohumoral systems. Splanchnic 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 by 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 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 underfilling and worsening of renal function (4).

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 (5).

#### Renal factors

Prostaglandins (PGs), specifically PGI<sub>2</sub> and PGE<sub>2</sub>, induce renal vasodilation, thereby providing renal protective effects by compensating for the vasoconstrictor systems of RAAS,



**Figure 1.** Proposed mechanisms for pathophysiology of hepatorenal syndrome. AVP, arginine vasopressin; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TNF, tumour necrosis factor.

SNS and AVP. The levels of renal PGs are increased in patients with cirrhosis and ascites (6). 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 HRS (4). In the clinical setting, increased levels of pro-inflammatory cytokines, such as tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin-6 (IL-6) and NO, in the splanchnic area lead to reduced systemic vascular resistance and increased cardiac output (7).

*Hepatorenal reflex*

The existence of sensor(s) in the hepatic circulation, which play a role in regulating extracellular fluid volume, is 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 criteria**

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 (ICA) 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 ICA 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 2 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.

Currently, there are no clinical criteria 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 patients (4). However, these biomarkers are yet to be validated in large randomised control trials and therefore cannot be routinely recommended in clinical practice yet.

**Table 1.** 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	<ul style="list-style-type: none"> <li>• Increase in sCr <math>\geq 0.3</math> mg/dl (<math>\geq 26.5</math> <math>\mu</math>mol/L) within 48 h; or</li> <li>• A percentage increase in sCr <math>\geq 50\%</math> from baseline that is known, or presumed, to have occurred within the previous 7 days.</li> </ul>
Staging of AKI	<ul style="list-style-type: none"> <li>• Stage 1: increase in sCr <math>\geq 0.3</math> mg/dl (26.5 <math>\mu</math>mol/L) or an increase in sCr <math>\geq 1.5</math>-fold to 2-fold from baseline.</li> <li>• Stage 2: increase in sCr <math>&gt;2</math>-fold to 3-fold from baseline.</li> <li>• Stage 3: increase of sCr <math>&gt;3</math>-fold from baseline or sCr <math>\geq 4.0</math> mg/dl (353.6 <math>\mu</math>mol/L) with an acute increase <math>\geq 0.3</math> mg/dl (26.5 <math>\mu</math>mol/L) or initiation of renal replacement therapy.</li> </ul>

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AKI, acute kidney injury; ICA, International Club of Ascites; sCr, serum creatinine.

**Table 2.** Diagnostic criteria of HRS type of AKI in patients with cirrhosis

HRS – AKI
<ul style="list-style-type: none"> <li>• Diagnosis of cirrhosis and ascites</li> <li>• Diagnosis of AKI according to ICA-AKI criteria</li> <li>• No response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight</li> <li>• Absence of shock</li> <li>• No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)</li> <li>• No macroscopic signs of structural kidney injury*, defined as: <ul style="list-style-type: none"> <li>◦ Absence of proteinuria (&gt;500 mg/day)</li> <li>◦ Absence of microhaematuria (&gt;50 RBCs per high power field)</li> <li>◦ Normal findings on renal ultrasonography</li> </ul> </li> </ul>

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AKI, acute kidney injury; HRS, hepatorenal syndrome; 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.

## Prognosis

Prognosis is poor when patients with cirrhosis develop renal impairment, and HRS is associated with the worst mortality rate amongst 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 to be 1 month and 6 months, respectively (11). Further prognostic studies with the newly revised HRS diagnostic criteria will be required.

## Management

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

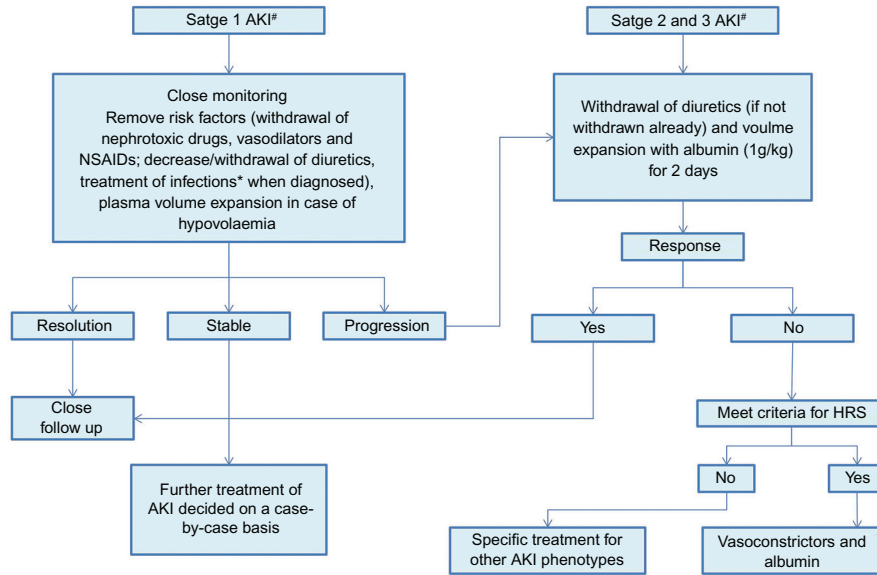
### Prevention of HRS

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% vs. 31%) and mortality (16% vs. 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 through inhibition of leukotriene and TNF $\alpha$  synthesis, was included in management for prevention of HRS. However, a recent randomised study demonstrated that 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 United States nor is it on the Pharmaceutical Beneficial Scheme (PBS) in Australia, whilst 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 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 with octreotide/midodrine illustrated a significantly higher rate of improvement in renal function with terlipressin ( $\geq 50\%$  serum creatinine decrease, 70.4% vs. 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 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.



**Figure 2.** Proposed algorithm for the management of acute kidney injury 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 fulfilment of the AKI criteria. AKI, acute kidney injury; HRS, hepatorenal syndrome; NSAIDs, non-steroidal anti-inflammatory drugs. Reproduced with permission from Angeli et al. (2).

### Transjugular intrahepatic portosystemic shunt

Although limited studies have suggested that transjugular intrahepatic portosystemic shunt (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 >5 mg/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 be 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, as 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 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 1 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 survival (1, 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 for 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.

### Conflict of interest

David Johnson has previously received consultancy fees, research grants, speaker's honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care. He has also received consultancy fees from Astra Zeneca and travel sponsorship from Amgen. All other authors declare no conflicts of interest with respect to research, authorship or publication of this article.

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