Hepatorenal syndrome: pathophysiology, diagnosis, and management

Douglas A Simonetto,1 Pere Gines,2 Patrick S Kamath1

1Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA
2Liver Unit, Hospital Clinic, University of Barcelona CIBERehd, Barcelona, Spain

Correspondence to:
P S Kamath
Kamath.patrick@mayo.edu

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ABSTRACT

Hepatorenal syndrome (HRS), the extreme manifestation of renal impairment in patients with cirrhosis, is characterized by reduction in renal blood flow and glomerular filtration rate. Hepatorenal syndrome is diagnosed when kidney function is reduced but evidence of intrinsic kidney disease, such as hematuria, proteinuria, or abnormal kidney ultrasonography, is absent. Unlike other causes of acute kidney injury (AKI), hepatorenal syndrome results from functional changes in the renal circulation and is potentially reversible with liver transplantation or vasoconstrictor drugs. Two forms of hepatorenal syndrome are recognized depending on the acuity and progression of kidney injury. The first represents an acute impairment of kidney function, HRS-AKI, whereas the second represents a more chronic kidney dysfunction, HRS-CKD (chronic kidney disease). In this review, we provide critical insight into the definition, pathophysiology, diagnosis, and management of hepatorenal syndrome.

Introduction

Hepatorenal syndrome is a serious complication of cirrhosis that is associated with high morbidity and mortality. It is characterized by functional circulatory changes in the kidneys that overpower physiologic compensatory mechanisms and lead to reduced glomerular filtration rate. Re-establishment of adequate renal blood flow leads to improvement in renal function and is achieved with liver transplantation or vasoconstrictor drugs. The terminology, definition, and classification of hepatorenal syndrome have evolved considerably in the past 10 years owing to changes proposed for the diagnosis and staging of acute kidney injury (AKI). In this state of the art review, we focus on recent advances that have shaped the contemporary definition, diagnosis, and management of hepatorenal syndrome.

Sources and selection criteria

We searched PubMed from January 2000 to October 2019 using the keyword "hepatorenal syndrome". We prioritized randomized clinical trials (RCTs), systematic reviews, and meta-analysis, when available, excluding case reports and case series. We also reviewed published management guidelines from websites of professional societies (American Association for the Study of Liver Diseases; European Association for the Study of the Liver; Kidney Disease: Improving Global Outcomes; and others). We included only full length, peer reviewed studies published in English, with the exception of recent high profile RCTs available only in abstract form.

Epidemiology and definitions

Acute impairment of renal function, as determined by an increase in serum creatinine, is reported in 19-26% of patients admitted to hospital with cirrhosis and 32% of patients with severe alcohol associated hepatitis.1-4 Serum creatinine, however, underestimates decline in renal function in patients with cirrhosis owing to impaired hepatic production of creatine (the precursor of creatinine), reduced muscle mass, tubular secretion of creatinine, and inaccurate measurement of creatinine by calorimetric methods in the presence of elevated serum bilirubin.5 6 Therefore, alternative biomarkers with greater accuracy in patients with cirrhosis are urgently needed. Incorporating cystatin C, a cysteine proteinase inhibitor, into conventional creatinine based glomerular filtration rate (GFR) equations results in better diagnostic performance compared with conventional equations alone.7

Despite the limitations, serum creatinine remains the most widely available and inexpensive assay for estimation of GFR. In a non-steady state such as acute renal failure, serial changes in creatinine and urine output better reflect renal function. Consequently, the definition of acute renal failure has evolved over the past two decades. The RIFLE (risk, injury, failure, loss, and end stage kidney disease) classification, generated at the Consensus Conference of the Acute Dialysis Quality Initiative Group in 2002, consisted of percentage changes in serum creatinine or GFR, a decrease in urine output, or both.8 This classification was later refined by a second multidisciplinary collaborative forum held in 2005, the Acute Kidney...
Injury Network (AKIN). The AKIN first proposed the term acute kidney injury (AKI) to include the entire spectrum of acute renal failure and also added an absolute increase in serum creatinine of 0.3 mg/dL within 48 hours of baseline as part of the definition of AKI. This change was based on accumulating evidence that even small acute increments in serum creatinine were associated with significant short term morbidity and mortality. In 2012 the Kidney Disease Improving Global Outcome (KDIGO) organization published clinical practice guidelines further refining the diagnosis of AKI on the basis of the RIFLE and AKIN criteria. The KDIGO defined AKI as an increase in serum creatinine by at least 0.3 mg/dL (26.5 µmol/L) within 48 hours, an increase in serum creatinine to at least 1.5 times baseline within the previous seven days, or urine volume below 0.5 mL/kg/h for six hours.

The definition of hepatorenal failure has likewise evolved in the past two decades to align with the changes proposed by the RIFLE, AKIN, and KDIGO guidelines. In 1990 the International Club of Ascites (ICA) defined acute renal failure in cirrhosis as an increase in serum creatinine of at least 50% from baseline to a final concentration of at least 1.5 mg/dL. Hepatorenal syndrome was further subclassified into two clinical types: type 1, defined as rapid reduction of renal function by doubling of initial serum creatinine to a concentration of at least 2.5 mg/dL or a 50% reduction in less than two weeks in the initial 24 hour creatinine clearance to below 20 mL/min; and type 2, in which renal failure progression did not meet the criteria for type 1.

Several recent studies showed that the diagnosis of AKI in patients with cirrhosis, based on an absolute increase in serum creatinine by at least 0.3 mg/dL or 50% from baseline, leads to earlier identification of patients at increased risk of longer hospital stay, multi-organ failure, admission to intensive care, and in-hospital mortality as well as 90 day mortality. This led the ICA to issue a revised set of consensus recommendations in 2015, incorporating a new definition and classification of AKI with modifications (box 1). A serum creatinine concentration obtained in the previous three months can be used as baseline when a concentration in the previous seven days is not available. The ICA also eliminated urine output in the revised definition of AKI, owing to expected lower urine output at baseline in patients with cirrhosis due to avid sodium and water retention. However, a recent study showed that patients in the intensive care unit with reduction in urine output to below 0.5 mL/kg for at least six hours had a higher mortality than did those who met only the creatinine criteria for AKI. Therefore, accurate urine output (for example, when obtained through a urinary catheter) may be used for diagnosis and staging of AKI.

The ICA also updated the definition of hepatorenal syndrome (HRS) type 1, now termed HRS-AKI. The two week interval required for doubling in serum creatinine in the previous definition could lead to a delay in starting treatment for hepatorenal syndrome; several studies have shown that the higher the creatinine at the start of treatment, the lower the probability of reversal of hepatorenal syndrome. Therefore, no minimum creatinine value is needed for the diagnosis of HRS-AKI according to the updated definition. That is, HRS-AKI can be diagnosed even when the serum creatinine is below 2.5 mg/dL.

Functional kidney injury in patients with cirrhosis that does not meet the criteria for HRS-AKI is termed NAKI (that is, non-AKI) and is defined by estimated glomerular filtration rate (eGFR) rather than serum creatinine. NAKI is divided into HRS-acute kidney disease (HRS-AKD) if the eGFR is less than 60 mL/min/1.73 m² for less than three months and HRS-chronic kidney disease (HRS-CKD) if it is less than this for more than three months (fig 1).

Pathophysiology
Our understanding of the pathophysiology of hepatorenal syndrome is mostly based on observational studies in humans because of the lack of a reproducible experimental model of hepatorenal syndrome. The challenge faced with animal models is the inability to induce severe liver injury without direct kidney toxicity as with carbon tetrachloride and thioacetamide. Nevertheless, clinical and histopathologic observations point to an uncompensated hyperdynamic circulation as the hallmark of AKI-HRS. Additional contributors to development of AKI-HRS include systemic inflammation, cirrhotic cardiomyopathy, and adrenal insufficiency.

Circulatory dysfunction
The hemodynamic changes in patients with cirrhosis are linked to sodium retention, development of ascites, and subsequent renal dysfunction. Cirrhosis results in elevated intrahepatic vascular resistance but splanchic vasodilatation due to
increased production of vasodilators, including nitric oxide, carbon monoxide, prostacyclins, and endocannabinoids, in the splanchnic circulation. Systemic vasodilation results in reduction of effective arterial blood volume (EABV) and systemic arterial pressure. With progression of liver disease, reduction in cardiac output often precedes the development of hepatorenal syndrome, while the peripheral vascular resistance remains unchanged. These findings suggest a role for cirrhotic cardiomyopathy in the pathogenesis of hepatorenal syndrome.

Systemic vasoconstrictor pathways, such as the renin-angiotensin-aldosterone system, sympathetic nervous system, and arginine vasopressin, are activated as a means of increasing the EABV. These mechanisms result in sodium retention, impaired solute-free water excretion and renal vasoconstriction, and, consequently, reduced renal blood flow (fig 2).

In earlier stages, the kidneys are able to maintain a normal glomerular filtration rate owing to the vasodilatory effect of renal prostaglandins (prostaglandin I2 and prostaglandin E2) on afferent renal arterioles. Thus, glomerular pressure can initially be maintained despite reduced renal blood flow. This balance is disrupted with progression of liver disease and by drugs such as non-steroidal anti-inflammatory agents that inhibit prostaglandin synthesis and reduce filtration fraction, leading to AKI.

Elevated ammonia in cirrhosis disrupts metabolism of arginine, an essential amino acid for the synthesis of nitric oxide. Decreased availability of nitric oxide in the renal microcirculation contributes to impaired renal blood flow and consequent functional and ischemic kidney injury.

**Systemic inflammation**

Systemic inflammatory response syndrome has been observed in almost half of patients with AKI-HRS, independent of the presence of infection. Moreover, plasma concentrations of pro-inflammatory...
cytokines (interleukin-6, tumor necrosis factor-α (TNF-α), vascular cell adhesion protein-1, and interleukin-8) and urinary concentrations of monocyte chemoattractant protein-1 are increased in patients with AKI-HRS compared with those with decompensated cirrhosis without AKI and patients with AKI secondary to pre-renal azotemia.29

Inflammation in cirrhosis is driven by two groups of molecules: pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs). PAMPs represent bacterial products, such as lipopolysaccharide, flagellin, and nigericin, which result from translocation of gut bacteria or bacterial infections, whereas DAMPs represent intracellular components released from injured hepatocytes, including high mobility group protein B1, heat shock protein, adenosine triphosphate, double stranded genomic DNA, and others. In the absence of overt bacterial infection, both PAMPs and DAMPs may drive inflammation and release of pro-inflammatory cytokines through activation of pattern recognition receptors such as toll-like receptors (TLRs). The systemic pro-inflammatory response, in turn, may lead to increased arterial production of vasodilators (such as nitric oxide) and, consequently, further reduction in systemic vascular resistance and EABV.

In addition to a systemic effect, DAMPs and PAMPs may have a direct role in the kidneys. Patients with cirrhosis and renal dysfunction show increased expression of TLR4 receptors and caspase-3 in tubular renal cells, both important components of the innate immune system.30 Gut decontamination has been shown to reduce renal expression of TLR4 and prevent renal dysfunction and tubular damage in animal models of cirrhosis, suggesting that increased TLR4 expression in the kidneys may result from exposure to PAMPs.31 Expression of TLR4 and other pattern recognition receptors may also increase as a result of renal ischemia secondary to reduced renal blood flow in hepatorenal syndrome.32 33 In experimental models of ischemic AKI, innate immunity has been shown to be responsible for the renal damage.34 Nevertheless, further studies are needed to elucidate the exact mechanisms by which systemic inflammation leads to hepatorenal syndrome.

### Hepato-adrenal syndrome

Relative adrenal insufficiency (RAI) is present in 24–47% of patients with decompensated cirrhosis and ascites and may play a role in the development of hepatorenal syndrome.35–37 Compared with patients with normal adrenal function, those with RAI have lower arterial pressure and higher serum concentrations of renin and noradrenaline and are at increased risk of AKI-HRS, sepsis, and short term mortality.37–40

The mechanisms leading to the development of hepatoadrenal syndrome remain elusive but may relate to exhaustion of substrates for synthesis of cortisol and impairment of the hypothalamo-pituitary axis by circulating PAMPs and pro-inflammatory cytokines.
inflammatory cytokines. Treatment with hydrocortisone may improve outcomes in patients with RAI and septic shock, including shock resolution and short term survival. However, the effect of glucocorticoid replacement therapy for hepatorenal syndrome in the absence of shock and its role in prevention and treatment of hepatorenal syndrome remain to be determined.

**Cholemic (or bile cast) nephropathy**

Cholemic nephropathy has long been reported in patients with cirrhosis and high serum bilirubin concentrations and is thought to be caused by formation of obstructing intratubular bile acid casts and direct bile acid toxicity to tubular cells. Histopathologic studies have shown the presence of intratubular bile acid casts in 18-75% of patients with AKI-HRS. Urinary bilirubin and urobilinogen are elevated in most patients and may be clues to the diagnosis. Cholemic nephropathy may be present in most patients with jaundice and AKI-HRS and possibly affects outcomes and treatment response, but the prevalence is likely underestimated. Serum bilirubin concentrations above 10 mg/dL have been associated with a lower rate of response to vasoconstrictors in patients with AKI-HRS compared with patients with serum bilirubin below 10 mg/dL (13% vs 67%; P=0.001). Treatments targeting bile acids in patients with jaundice and AKI-HRS may therefore be beneficial. A recent study in an experimental model of biliary cirrhosis showed that administration of norursodeoxycholic acid ameliorates renal function and histologic findings and may represent a therapeutic option for cholemic nephropathy. Nevertheless, the pathophysiologic contribution of cholemic nephropathy to AKI-HRS has not been convincingly demonstrated and needs further investigation.

**Intra-abdominal hypertension**

Elevated intra-abdominal pressure (>12 mm Hg) is an underappreciated cause of AKI and may play a role in the development of hepatorenal syndrome in patients with refractory ascites. A small study assessing the short term effects of paracentesis in patients with hepatorenal syndrome showed a significant improvement in creatinine clearance after reduction of intra-abdominal pressure. Careful monitoring of systemic hemodynamic parameters with guided plasma expansion to prevent development of post-paracentesis circulatory dysfunction is paramount. The use of bedside echocardiography for estimation of inferior vena cava diameter and collapsibility may help to determine whether intra-abdominal hypertension might be contributing to renal dysfunction and, thus, help to identify which patients may benefit from large volume paracenteses.

**Hepatorenal reflex hypothesis**

A link between the kidneys and the liver has long been proposed, suggesting the presence of osmoreceptors, chemoreceptors, and baroreceptors in the liver that directly affect kidney function through complex neural circuits. This hypothesis has been supported by several experimental studies through manipulation of portal blood osmolality and/or chemical composition, as well as changes in portal pressure. One animal study showed that activation of intrahepatic adenosine receptors in response to reduced portal venous blood flow results in renal sodium and water retention, similar to that observed in hepatorenal syndrome. Although these findings may have important clinical implications, further studies translating these results to humans are needed.

**Differential diagnosis and biomarkers**

One important diagnostic criterion for AKI-HRS is exclusion of structural kidney injury, which relies on urine microscopy and urine sodium excretion. Pre-renal azotemia represents the leading cause of AKI in patients with cirrhosis (46-66% of all cases), owing to frequent use of diuretics, large volume paracenteses without albumin, gastrointestinal bleeding, and gastrointestinal fluid losses secondary to lactulose induced diarrhea. The reported prevalence of AKI-HRS and acute tubular necrosis (ATN) varies widely, likely reflecting the challenge in differentiating the two conditions. The diagnosis of AKI-HRS requires the absence of shock, proteinuria (>500 mg/day), and microhematuria (>50 red blood cells per high power field), along with normal renal ultrasonography. However, patients who fulfill these criteria may still have tubular damage, so ATN cannot be confidently excluded. Some experts have used urinary sodium (>40 mEq/L), fractional excretion of sodium (FeNa >2%), and low urine osmolality (<400 mOsm/L) as suggestive of ATN; however, urinary sodium and FeNa are no longer part of the diagnostic criteria of AKI-HRS. Studies in patients without liver disease have found that fractional excretion of urea is superior to FeNa in differentiating AKI-HRS from ATN in patients taking diuretics. Reabsorption of urea, as opposed to sodium, occurs primarily in the proximal renal tubules and, therefore, is not affected by diuretics such as furosemide and spironolactone, which act in the loop of Henle and distal tubules, respectively. In a recent study assessing the role of fractional excretion of urea in derivation and validation cohorts of patients with cirrhosis and AKI taking diuretics, the area under the receiver operating characteristic curve to differentiate ATN from other causes (cut-off 33.4, sensitivity 85, and specificity 100) was 0.96. Novel urine biomarkers of tubular injury have long been sought to differentiate AKI-HRS and ATN in patients with cirrhosis. Candidate biomarkers include tubular proteins released during cell damage...
(N-acetyl-β-D-glucosaminidase, α-glutathione S-transferase), tubular proteins up regulated by injury (kidney injury molecule-1, neutrophil gelatinase associated lipocalin (NGAL), liver-type fatty acid binding protein), plasma proteins with diminished tubular reabsorption (α-1-microglobulin, β-2-microglobulin, retinol binding protein), and markers of inflammation (interleukin-18). Among these, NGAL has been the most widely studied biomarker in patients with cirrhosis and has shown the greatest diagnostic accuracy in differentiating ATN from AKI-HRS.

Urinary NGAL seems to be superior to plasma concentrations and performs better when measured after the two day volume challenge recommended in the management of AKI. The urinary NGAL cut-off value of 220 µg/g of creatinine obtained after the fluid challenge has the highest diagnostic accuracy for ATN (odds ratio 42.9, 95% confidence interval 13.9 to 132.3). Moreover, urinary NGAL is an independent predictor of short term mortality. One of the limitations of biomarker studies in this population is the lack of a gold standard short of kidney biopsy. Because of the inherent risks, kidney biopsies are not routinely obtained in clinical practice, and human studies rely on expert adjudication for differentiating ATN from AKI-HRS. Nevertheless, the results are encouraging and justify further study.

### Risk factors and prevention

Hyponatremia, high plasma renin activity, and liver size, as well as severity of ascites, are predictors of AKI-HRS. Acute hemodynamic changes associated with infections and large volume paracentesis without albumin administration represent the most common precipitants of AKI-HRS. The prevalence of unprecipitated AKI is low (1.8%). AKI-HRS develops in as many as 30% of patients with spontaneous bacterial peritonitis (SBP), as well as other infections, and is associated with worse outcomes. Infection associated AKI-HRS may be prevented by administration of intravenous albumin in addition to antibiotic treatment in the setting of SBP (8.3% v 30.6% with antibiotics alone; P=0.01) and may reduce overall mortality (16% v 35.4%; odds ratio 0.34, 0.19 to 0.60). Albumin administration in patients with infections other than SBP may also improve circulatory function and delay the development of renal dysfunction, but it has not been shown to prevent AKI-HRS or improve survival.

Long term use of weekly albumin in patients with decompensated cirrhosis and ascites has been assessed in a large RCT (n=431). Compared with standard of care, the addition of weekly albumin for 18 months improved overall survival (77% v 66%; P=0.028) and also reduced the incidence of hepatorenal syndrome (odds ratio 0.39, 0.19 to 0.76). In contrast, a similar trial evaluating the long term use of albumin and midodrine in 196 patients with decompensated cirrhosis on the waitlist for liver transplantation failed to show a survival benefit at one year, and complications of cirrhosis were not prevented. However, in this latter study only a small number of patients completed a full year on the study and the median length of treatment was only 80 days. The forthcoming PRECIOSA12 (Effects of Long term Administration of Human Albumin in Subjects With Decompensated Cirrhosis and Ascites) trial will hopefully elucidate the role of long term albumin use in this population.

Antibiotic prophylaxis in patients at risk of SBP, as determined by low ascitic fluid protein (<1.5 mg/dL) associated with liver and/or kidney dysfunction (bilirubin >3 mg/dL, serum sodium <130 mEq/L, Child-Turcotte-Pugh score >10, and/or serum creatinine >1.2 mg/dL), not only prevents development of SBP but also significantly reduces the risk of AKI-HRS and overall mortality.

Post-paracentesis circulatory dysfunction occurs after large volume paracenteses (~4-5 L) and is associated with hypotension, hyponatremia, and increased risk of AKI-HRS. Albumin administration following a large volume paracentesis significantly reduces this risk and improves overall survival in these patients. This protective effect seems to be unique to albumin, compared with other volume expanders, which suggests an additional benefit of albumin beyond simply volume expansion. Albumin has important antioxidant and anti-inflammatory properties and helps to stabilize endothelial function. Moreover, human albumin is able to bind and potentially inactivate endotoxins (lipopolysaccharides) and so may reduce their negative effect on circulatory and kidney functions. Given its potential immunomodulatory effects, albumin is being investigated in an RCT for prevention of infection in cirrhosis.

### Management

The updated diagnostic criteria, with removal of a minimum serum creatinine concentration, allow for earlier diagnosis and treatment of AKI-HRS. Rather than waiting for a doubling of creatinine to reach 2.5 g/dL, drug treatment may now be started immediately after an unsuccessful fluid challenge. This is likely to result in higher reversal rates and better outcomes, as response to vasoconstrictors is indicated for hepatorenal syndrome type 1, based on the old definition, and is expected to resolve in more than 90% of patients at this stage, compared with a half of patients with stage 1B disease (serum creatinine ≥1.5 g/dL). Therefore, European Association for the Study of the Liver (EASL) guidelines recommend reserving the use of vasoconstrictors for patients with AKI-HRS stage 1B or greater (fig 3). However, in most countries, the use of vasoconstrictors is indicated for hepatorenal syndrome type 1, based on the old definition, and the use of vasoconstrictors in patients with creatinine below 2.5 mg/dL is considered off-label.

Once a diagnosis of AKI is made, management of hepatorenal syndrome starts with a fluid challenge.
of 20-25% intravenous albumin at 1 g/kg/day for two days and withdrawal of diuretics. This is not only needed to rule out pre-renal azotemia but also promotes early plasma volume expansion in the setting of reduced EABV. This initial phase also includes temporary discontinuation of non-selective β blockers given their negative inotropic effect, which reduces cardiac output.93 94 These should be carefully reinstituted once renal function and mean arterial pressure (MAP) improve.

The specific treatment of AKI-HRS comprises vasoconstrictors in combination with albumin infusion and reversal of precipitant factors. Bacterial infections, particularly SBP, should be ruled out by blood, urine, and ascitic fluid cultures and a chest radiograph. Although antibiotics may help to prevent development of AKI-HRS,81 95 96 their benefit in patients with established AKI-HRS in the absence of infection has not been demonstrated.

Vasoconstrictors
Splanchnic vasoconstriction in patients with cirrhosis results in a reduction in portal pressure and an increase in EABV and renal blood flow, especially when combined with intravenous administration of albumin. Renal perfusion directly correlates with changes in MAP and is negatively affected by intra-abdominal pressure driven by ascites. A significant increase in MAP promoted by the use of vasoconstrictors is associated with a higher likelihood of reversal of hepatorenal syndrome.97

Several RCTs have confirmed the efficacy of vasoconstrictors, which represent the mainstay treatment of AKI-HRS.98 The available options include terlipressin, noradrenaline, and the combination of midodrine plus octreotide.

Terlipressin is not yet available in North America but can be prescribed to treat AKI-HRS in many European and Asian countries. Terlipressin, a synthetic vasopressin analog with predominant vasopressin 1A receptor effect, acts primarily as a splanchnic vasoconstrictor.99 In addition, terlipressin activates vasopressin 1B receptors, which stimulate release of adrenocorticotropic hormone and cortisol and might counteract the relative adrenal insufficiency commonly observed in patients with decompensated cirrhosis.100 Furthermore, terlipressin shows greater efficacy in reversal of AKI-HRS in patients with a systemic inflammatory response,101 which may relate to indirect vasopressin mediated anti-inflammatory effects.102 An agent with selective vasopressin 1 activity is preferable in patients with cirrhosis to

Fig 3 | Algorithm for management of acute kidney injury (AKI) in patients with cirrhosis. ATN=acute tubular necrosis; HRS=hepatorenal syndrome. *Risk factor management: hold nephrotoxic drugs/β blockers, withdraw diuretics, treat infections, plasma volume expansion as needed
prevent unwanted solute-free water absorption and consequent worsening hyponatremia and volume overload induced by renal vasopressin 2 receptor activation.103 Because terlipressin is also a modest vasopressin 2 receptor agonist,109 an acute reduction in serum sodium concentration may occur, although this effect is mainly observed in patients with cirrhosis without ascites treated with terlipressin for variceal bleeding.108 A novel selective vasopressin 1A receptor agonist, selepressin, has recently been investigated as an alternative to vasopressin in management of septic shock and has shown a lower risk of hyponatremia, volume overload, and pulmonary edema in animal models of sepsis.105 106 The role of selepressin in hepatorenal syndrome warrants further study.

Norepinephrine (intravenous) and midodrine (oral) are systemic vasoconstrictors through activation of α-1 adrenergic receptors on vascular smooth muscle cells. Octreotide, a somatostatin analog, acts by inhibiting secretion of glucagon, a splanchnic vasodilator, and is a direct mesenteric vasoconstrictor.105 However, the effect of octreotide in patients with cirrhosis is dampened by antagonistic effects of local nitric oxide release.108 and octreotide alone has limited benefit in hepatorenal syndrome.109 Midodrine monotherapy also does not improve renal function in patients with hepatorenal syndrome despite its hemodynamic effects.110 In contrast, a combination of octreotide and midodrine has potential benefit in hepatorenal syndrome and has become the standard of care in countries where terlipressin is not yet approved.111 112

Efficacy

Comparative studies (some of them open label) evaluating terlipressin, norepinephrine, and/or octreotide/midodrine have found terlipressin, in combination with intravenous albumin, to be the most effective drug treatment for AKI-HRS (table 1).113 114 122 The efficacy of terlipressin plus albumin in achieving complete reversal of hepatorenal syndrome, defined as at least 50% reduction in serum creatinine to a final value below 1.5 mg/dL, ranges from 19% to 56% compared with 3-14% with albumin alone.123 101 115 118 121 Conversely, administration of terlipressin alone is markedly inferior to a combination of terlipressin and albumin (complete hepatorenal syndrome reversal rates of 25% and 77%, respectively).123 Two large European trials and one North American trial have shown efficacy for terlipressin.124 115 124 However, in the REVERSE study, a large multicenter phase III trial, terlipressin led to complete reversal of hepatorenal syndrome in only 19.6% of patients compared with 13.1% in the placebo group (P=0.22).116 One of the potential reasons for the discrepant results was the requirement for a confirmatory creatinine concentration below 1.5 mg/dL 48 hours after initial hepatorenal syndrome reversal, which was not available in many patients owing to discharge from hospital or transplantation. Another reason could be the short duration of treatment with terlipressin in a large number of patients. This has led to the execution of yet another RCT in North America designed to overcome the methodological obstacles encountered in the REVERSE trial. The CONFIRM study has been published only in abstract form. The verified hepatorenal syndrome reversal rate with terlipressin plus albumin was 29.1% compared with 15.8% with albumin plus placebo (P<0.012).117

Norepinephrine is also effective and safe in AKI-HRS,125 with similar rates of hepatorenal syndrome reversal to terlipressin in small randomized studies, ranging between 39% and 70%.118 120 Norepinephrine is less expensive than terlipressin; however, central line placement and admission to an intensive care unit are needed for administration, which may offset the cost benefit. Terlipressin may be given through a peripheral line on the medical floor.119

Only one study has directly compared combination midodrine/octreotide with terlipressin.121 The complete response rate for midodrine/octreotide was only 4.8% compared with 55.5% with terlipressin, and the overall response (complete or partial) rates were 28.6% and 70.4%, respectively. Although no placebo controlled studies have been done with either norepinephrine or midodrine/octreotide, a recent network meta-analysis has allowed for indirect comparisons across trials. Compared with placebo, combination midodrine/octreotide was not significantly superior in achieving reversal of hepatorenal syndrome (odds ratio 0.44, 0.06 to 3.23), whereas norepinephrine and terlipressin were both superior to midodrine/octreotide and placebo and were equally effective.98

Side effects

The most common side effects of terlipressin are diarrhea and abdominal pain, reported in 10-20% of patients overall. Discontinuation of terlipressin due to serious adverse events is needed in 4-22% (median 8%) of patients, with a rate of peripheral ischemic events between 4% and 13%. The rate of myocardial infarction or intestinal ischemia ranges from 2% to 13%.98 Pulmonary edema may occur in patients with hepatorenal syndrome treated with terlipressin and albumin, and volume status should be carefully monitored in these patients.116 Continuous terlipressin infusion is associated with a lower rate of adverse events compared with bolus administration, likely owing to lower dosing needed.124 Nevertheless, patients should be monitored at least twice daily for signs of ischemia in skin, tongue, and fingers while on therapy, and terlipressin should be avoided in patients with a history of coronary artery disease or peripheral vascular disease.92 Discontinuation of treatment due to adverse events is less common with norepinephrine and midodrine/octreotide; however, tachyarrhythmias or bradycardia can be seen (table 2).121

Predictors of treatment response

Several factors have been shown to negatively affect response of hepatorenal syndrome to drug
Table 1 | Study design and outcomes of randomized controlled trials of vasoactive drugs for treatment of hepatorenal syndrome-acute kidney injury (HRS-AKI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Drug comparisons (No of patients)</th>
<th>No (%) HRS reversal</th>
<th>No (%) mortality</th>
</tr>
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<tbody>
<tr>
<td>Solanki et al, 2003</td>
<td>113 Single center, single blind, placebo controlled</td>
<td>Terlipressin 1 mg every 12 h for 15 days (n=12) v placebo (n=12)</td>
<td>NA</td>
<td>Terlipressin 7/12 (58.3) v placebo 12/12 (100)</td>
</tr>
<tr>
<td>Neri et al, 2008</td>
<td>118 Single center, open label</td>
<td>Terlipressin 1 mg every 8 h for 5 days followed by 0.5 mg every 8 h for 14 days (n=26) v albumin only for 15 days (n=26)</td>
<td>Terlipressin 21/26 (80) v control 5/26 (19)</td>
<td>Terlipressin 7/26 (26.9) v control 15/26 (57.7)</td>
</tr>
<tr>
<td>Sanyal et al, 2008</td>
<td>114 Single center, open label</td>
<td>Terlipressin 1 mg every 8 h for 14 days (n=56) v placebo for 14 days (n=56)</td>
<td>Terlipressin 19/56 (33.9) v placebo 7/56 (12.5)</td>
<td>Terlipressin 32/56 (57.1) v placebo 35/56 (62.5)</td>
</tr>
<tr>
<td>Martin-Llahi et al, 2008</td>
<td>23 Multicenter, open label</td>
<td>Terlipressin 1 mg every 4 h up to 2 mg every 4 h for 14 days (n=17) v albumin only daily for 15 days (n=18)</td>
<td>Terlipressin 6/17 (35.3) v control 2/18 (11.1)</td>
<td>Terlipressin 17/23 (73.9) v control 19/23 (82.6)</td>
</tr>
<tr>
<td>Boyer et al, 2016</td>
<td>116 Multicenter, double blind, placebo controlled</td>
<td>Terlipressin 1 mg every 6 h up to 2 mg every 6 h for 14 days (n=97) v placebo for 14 days (n=99)</td>
<td>Terlipressin 19/97 (19.6) v placebo 13/99 (13.1)</td>
<td>Terlipressin 32/97 (33) v placebo 35/99 (35.3)</td>
</tr>
<tr>
<td>Wong et al, 2019*</td>
<td>117 Multicenter, double blind, placebo controlled</td>
<td>Terlipressin 1 mg every 6 h until verified HRS reversal or for maximum 14 days (n=199) v placebo until verified HRS reversal or for maximum 14 days (n=101)</td>
<td>Terlipressin 58/199 (29.1) v placebo 16/101 (15.8)</td>
<td>Terlipressin 145/199 (72.9) v placebo 72/101 (71.3)</td>
</tr>
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Terlipressin versus norepinephrine

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<tr>
<th>Study</th>
<th>Trial design</th>
<th>Drug comparisons (No of patients)</th>
<th>No (%) HRS reversal</th>
<th>No (%) mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandria et al, 2007</td>
<td>118 Single center, open label</td>
<td>Terlipressin 1 mg every 4 h up to 2 mg every 4 h until HRS reversal or for maximum 14 days (n=22) v norepinephrine 0.1 µg/kg/min up to 0.7 µg/kg/min until HRS reversal or maximum 14 days (n=5)</td>
<td>Terlipressin 3/4 (75) v norepinephrine 4/5 (80)</td>
<td>Terlipressin 1/4 (25) v norepinephrine 1/5 (20)</td>
</tr>
<tr>
<td>Sharma et al, 2008</td>
<td>119 Single center, open label</td>
<td>Terlipressin 0.5 mg every 6 h up to 2 mg every 6 h for 15 days (n=20) v norepinephrine 0.5 mg/h up to 3 mg/h for 15 days (n=20)</td>
<td>Terlipressin 8/20 (40) v norepinephrine 10/20 (50)</td>
<td>Terlipressin 9/20 (45) v norepinephrine 9/20 (45)</td>
</tr>
<tr>
<td>Singh et al, 2012</td>
<td>120 Single center, open label</td>
<td>Terlipressin 0.5 mg every 6 h up to 2 mg every 6 h until HRS reversal or for maximum 14 days (n=23) v norepinephrine 0.5 mg/h up to 3 mg/h until HRS reversal or for maximum 14 days (n=23)</td>
<td>Terlipressin 9/23 (39.1) v norepinephrine 10/23 (43.5)</td>
<td>Terlipressin 16/23 (69.5) v norepinephrine 15/23 (65.2)</td>
</tr>
</tbody>
</table>

Terlipressin versus midodrine plus octreotide

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Drug comparisons (No of patients)</th>
<th>No (%) HRS reversal</th>
<th>No (%) mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavalini et al, 2015</td>
<td>117 Multicenter, open label</td>
<td>Terlipressin 3-12 mg per 24 h until HRS reversal or for maximum 14 days (n=27) v midodrine 7.5-12.5 mg every 8 h orally plus octreotide 100-200 µg every 8 h subcutaneously until HRS reversal or for maximum 14 days (n=22)</td>
<td>Terlipressin 15/27 (55.5) v midodrine plus octreotide 1/22 (4.5)</td>
<td>Terlipressin 8/27 (29.6) v midodrine plus octreotide 7/22 (31.8)</td>
</tr>
</tbody>
</table>

NA=not available.
*Data published in abstract format.

Albumin infusion is essential for effective management of AKI-HRS. Several studies provide supportive evidence for a multifaceted mode of action by albumin, which may also include volume expansion and positive cardiac inotropic effect, as well as antioxidant and immunomodulatory properties. In a single non-randomized study comparing terlipressin plus albumin versus terlipressin alone, the combination with albumin resulted in a significantly higher response (77% vs 25%; P<0.003). In addition to plasma volume expansion and consequent increase in EABV, albumin has shown several other benefits in hepatorenal syndrome. One important property of albumin is its ability to bind a wide range of substances including bile acids, hormones, cytokines, long chain fatty acids, nitric oxide, endotoxin, and other bacterial products. This is the basis for the advent of molecular absorbent recirculatory systems, a modified dialysis method that clears substances bound to albumin. This results in a significant reduction in serum creatinine concentrations in patients with hepatorenal syndrome. However, improvement in renal function and systemic hemodynamics is not observed in patients with hepatorenal syndrome refractory to vasoconstrictors, despite reduction in nitric oxide concentrations.
Vasoconstrictors and albumin are recommended in all patients meeting the current definition of AKI-HRS stage >1A. Such patients should be expeditiously treated with vasoconstrictors and albumin.

Table 3 | Recommendations adapted from American Association for the Study of Liver Disease and European Association for the Study of the Liver92 149

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association for the Study of Liver Diseases guidelines 2012</td>
<td></td>
</tr>
<tr>
<td>Urinary biomarkers such as neutrophil gelatinase associated lipocalin may assist in the differential diagnosis of azotemia in patients with cirrhosis</td>
<td>Weak</td>
</tr>
<tr>
<td>Albumin infusion plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I hepatorenal syndrome</td>
<td>Weak</td>
</tr>
<tr>
<td>Albumin infusion plus administration of norepinephrine should also be considered in the treatment of type I hepatorenal syndrome, when the patient is in the intensive care unit</td>
<td>Weak</td>
</tr>
<tr>
<td>Patients with cirrhosis, ascites, and type I or type II hepatorenal syndrome should have an expedited referral for liver transplantation</td>
<td>Strong</td>
</tr>
<tr>
<td>European Association for the Study of the Liver guidelines 2018</td>
<td></td>
</tr>
<tr>
<td>Vasoconstrictors and albumin are recommended in all patients meeting the current definition of AKI-HRS stage &gt;1A. Such patients should be expeditiously treated with vasoconstrictors and albumin.</td>
<td>Strong</td>
</tr>
<tr>
<td>Terlipressin plus albumin should be considered as the first line therapeutic option for the treatment of HRS-AKI. Terlipressin can be used by IV boluses at the initial dose of 1 mg every 4-6 h. However, giving terlipressin by continuous IV infusion at initial dose of 2 mg/day makes the sudden increase in mean arterial pressure impossible. In case of non-response (decrease in SCr ≥0.3 mg/dL (26.5 μmol/L) from the baseline value), the dose of terlipressin should be increased in a stepwise manner to a maximum of 12 mg/day</td>
<td>Strong</td>
</tr>
<tr>
<td>Albumin solution (20%) should be used at a dose of 20-40 g/day. Ideally, apart from routinely monitoring patients with HRS-AKI, the serial measurement of CVP or other measures of assessing central blood volume can help to prevent circulatory overload by optimizing the fluid balance and helping to titrate the dose of albumin</td>
<td>Strong</td>
</tr>
<tr>
<td>Noradrenaline can also be an alternative to terlipressin. However, limited information is available</td>
<td>Weak</td>
</tr>
<tr>
<td>In contrast to terlipressin, the use of noradrenaline always requires a central venous line and, in several countries, the transfer of the patient to an ICU. Midodrine plus octreotide can be an option only when terlipressin and noradrenaline are not available, but its efficacy is much lower than that of terlipressin</td>
<td></td>
</tr>
<tr>
<td>According to the new definition of HRS-AKI, complete response to treatment should be defined by a final SCr which is ≤0.3 mg/dL (26.5 μmol/L) from the baseline value, while partial response should be defined by the regression of AKI stage to a final SCr &lt;0.3 mg/dL (26.5 μmol/L) from the baseline value</td>
<td>Strong</td>
</tr>
<tr>
<td>Adverse events related to terlipressin or noradrenaline include ischemic and cardiovascular events. Thus, a careful clinical screening including electrocardiography is recommended before starting the treatment. Patients can be treated on a regular ward, but the decision to transfer to higher dependency care should be case based. For the duration of treatment, close monitoring of patients is important. According to the type and severity of side effects, treatment should be modified or discontinued</td>
<td>Strong</td>
</tr>
<tr>
<td>In cases of recurrence of HRS-AKI on cessation of treatment, a repeat course of therapy should be given</td>
<td>Strong</td>
</tr>
<tr>
<td>Terlipressin plus albumin is also effective in the treatment of HRS outside the criteria of AKI (HRS-NAXI), formerly known as HRS type II. Unfortunately, recurrence after the withdrawal of treatment is the norm, and data on the effect of the treatment on long term clinical outcome are controversial, particularly from the perspective of LT. As such, vasoconstrictors and albumin are not recommended in this clinical scenario</td>
<td>Strong</td>
</tr>
<tr>
<td>Insufficient data exist to allow TIPS to be advocated in HRS-AKI, but it could be suggested in selected patients with HRS-NAXI</td>
<td>Weak</td>
</tr>
<tr>
<td>LT is the best therapeutic option for patients with HRS regardless of the response to drug therapy</td>
<td>Strong</td>
</tr>
<tr>
<td>The decision to initiate RRT should be based on the individual severity of illness</td>
<td>Weak</td>
</tr>
<tr>
<td>The indication for liver-kidney transplantation remains controversial. This procedure should be considered in patients with significant CKD or with sustained AKI including HRS-AKI with no response to drug therapy</td>
<td>Strong</td>
</tr>
<tr>
<td>Albumin (1.5 g/kg at diagnosis and 1 g/kg on day 3) should be given in patients with SBP to prevent AKI</td>
<td>Strong</td>
</tr>
<tr>
<td>Norfloxacin (400 mg/day) should be given as prophyaxis of SBP to prevent HRS-AKI</td>
<td>Strong</td>
</tr>
</tbody>
</table>

**Transjugular intrahepatic portosystemic shunt**

The creation of an intrahepatic shunt aimed at reducing portal pressure has shown significant benefit in patients with cirrhosis who cannot tolerate diuretics or have refractory ascites and who have uncontrolled variceal bleeding.134 However, only a few studies have explored the role of transjugular intrahepatic portosystemic shunt (TIPS) insertion in AKI-HRS, so its use remains investigational in this group. One small non-randomized study showed significant improvement in renal function after TIPS insertion for AKI-HRS, with reduction in plasma renin activity and aldosterone and norepinephrine concentrations.136 A meta-analysis including nine studies in which 128 patients with hepatorenal syndrome underwent TIPS insertion (77 patients with hepatorenal syndrome type 1 and 51 patients with type 2), showed significant improvement in serum creatinine, serum sodium, and urine output.137 Patients with markedly elevated bilirubin, active infection, or overt hepatic encephalopathy were excluded, so the role of TIPS in hepatorenal syndrome may be limited to a highly selected group of patients. On the other hand, TIPS may have a greater...
protective effect as shown by reduced incidence of hepatorenal syndrome in patients with cirrhosis and diuretic refractory ascites post-TIPS.\textsuperscript{136}

Renal replacement therapy
Renal replacement therapy (RRT) may be indicated for patients with AKI-HRS unresponsive to drug treatment and with volume overload, uremia, or electrolyte derangements; however, RRT does not improve survival in hepatorenal syndrome,\textsuperscript{138} and it should be reserved for use as a bridge to transplantation, when transplantation is an option.\textsuperscript{139} Short term mortality in patients with cirrhosis and AKI who are ineligible for transplantation approaches 90%,\textsuperscript{140,141} independently of the cause of AKI.\textsuperscript{142} Therefore, RRT is often futile in this setting.

Liver transplantation
The functional nature of hepatorenal syndrome means that improvement in renal function is expected with liver transplantation, which remains the optimal treatment of AKI-HRS whenever feasible.\textsuperscript{143-145} However, kidney recovery is not universal and is dependent on multiple factors, particularly duration of kidney injury.\textsuperscript{146} In such cases, simultaneous liver-kidney transplantation is recommended rather than liver transplantation alone. However, accurately predicting native kidney recovery after liver transplantation remains a challenge. In the US, the Organ Procurement and Transplantation Network policy for simultaneous liver-kidney organ allocation requires sustained AKI defined as need for dialysis or measured or calculated creatinine clearance or GFR of 25 mL/min or below for a minimum of six consecutive weeks.\textsuperscript{147} Despite best efforts, almost 10% of patients with either AKI or CKD who receive a liver alone may have persistent or progressive renal failure after transplant.\textsuperscript{148} Patients with ATN are at particularly increased risk of chronic kidney disease (stage 4 or 5) post-transplant, and the lack of ideal biomarkers often results in misdiagnosis.\textsuperscript{149} This has led to a consensus “safety net” for prioritization of liver recipients on the kidney waiting list if they are registered within a year after their liver transplant.\textsuperscript{150}

Guidelines
Prevention, diagnosis, and management of hepatorenal syndrome are included in both the American Association for the Study of Liver Diseases (AASLD) and the EASL guidelines on the management of patients with ascites or decompensated cirrhosis (table 3).\textsuperscript{92,151} The AASLD guidelines were last updated in 2012 and do not contain the most up-to-date diagnostic criteria and classification of hepatorenal syndrome adopted in 2015. In contrast, the European guidelines published in 2018 incorporate the recent changes, including the exclusion of a creatinine cut-off for diagnosis of HRS-AKI. This important change now allows for earlier treatment of HRS-AKI with vasoactive agents as discussed earlier. Another important difference between the two guidelines is the options for medical management of hepatorenal syndrome. Terlipressin plus albumin is considered first line treatment of HRS-AKI according to the EASL guidelines; however, terlipressin is not yet available in the US, and management of HRS-AKI is limited to albumin, octreotide plus midodrine, or norepinephrine as per the American guidelines.

Emerging treatments
New treatment options are urgently needed, as efficacy of vasoconstrictors and albumin is limited to less than half of patients with AKI-HRS. Serelaxin (recombinant human relaxin-2) is novel agent that acts on renal vasculature and results in increased renal blood flow, reduced renal vascular resistance, and reversal of endothelial dysfunction.\textsuperscript{152} Furthermore, serelaxin has been shown to reduce intrahepatic vascular resistance in animal models of cirrhosis, thereby ameliorating portal hypertension.\textsuperscript{153} An exploratory randomized phase II study showed an increase in total renal arterial blood flow by 65% in patients with compensated cirrhosis treated with serelaxin.\textsuperscript{154} No studies have been reported in patients with hepatorenal syndrome.

In addition to vasoactive drugs, treatments targeting systemic inflammation, including DAMPs, PAMPs, and downstream signaling, could be explored in hepatorenal syndrome. One small randomized study showed that pentoxifylline, a phosphodiesterase inhibitor with anti-TNF-α activity and anti-inflammatory effect, is safe in patients with AKI-HRS. However, the study failed to show an added benefit compared with standard of care alone (midodrine, octreotide, and albumin).\textsuperscript{155} The role of serelaxin and novel therapies targeting inflammation in the clinical management of AKI-HRS needs to be explored in future studies.

Conclusions
Despite advances in biomarker discovery and evolving definitions of hepatorenal syndrome, much of its pathophysiology beyond circulatory dysfunction still remains to be uncovered. Systemic inflammation, in the presence or absence of infection, remains an untapped territory in the understanding of hepatorenal syndrome. Novel translational experimental models of hepatorenal syndrome are needed to fill this gap and, hopefully, will help to identify novel targets for potential drug development. In the meantime, emphasis should be on preventive measures for patients at risk of hepatorenal syndrome, including appropriate antibiotic prophylaxis and albumin use when indicated. For patients with established hepatorenal syndrome, terlipressin with albumin is considered first line medical treatment; however, liver transplantation remains the optimal treatment, and timely referral for transplant evaluation is crucial to avoid permanent kidney damage and the need for simultaneous liver and kidney transplant.
STATE OF THE ART REVIEW

GLOSSARY OF ABBREVIATIONS

- AASLD—American Association for the Study of Liver Diseases
- AKI—acute kidney injury
- AKIN—Acute Kidney Injury Network
- ATN—acute tubular necrosis
- CKD—chronic kidney disease
- DAMP—damage associated molecular pattern
- EABV—effective arterial blood volume
- EASL—European Association for the Study of the Liver
- eGFR—estimated glomerular filtration rate
- FeNa—fractional excretion of sodium
- GFR—glomerular filtration rate
- HRS—hepatorenal syndrome
- ICA—International Club of Ascites
- KDIGO—Kidney Disease Improving Global Outcome
- MAP—mean arterial pressure
- MELD—model for end-stage liver disease
- NAKI—non-acute kidney injury
- NGAL—neutrophil gelatinase associated lipocalin
- PAMP—pathogen associated molecular pattern
- RAI—relative adrenal insufficiency
- RCT—randomized clinical trial
- RIFLE—risk, injury, failure, loss, and end stage kidney disease
- RRT—renal replacement therapy
- SBP—spontaneous bacterial peritonitis
- TIPS—transjugular intrahepatic portosystemic shunt
- TLR—toll-like receptor
- TNF—tumor necrosis factor

QUESTIONS FOR FUTURE RESEARCH

- Can we identify serum and urine biomarkers that allow for earlier diagnosis of hepatorenal syndrome–acute kidney injury (HRS-AKI) and exclusion of acute tubular necrosis?
- What is the optimal stage of HRS-AKI that results in reversal of renal dysfunction and improved survival?
- What is the role of therapies targeting systemic inflammation, including damage associated molecular patterns, pathogen associated molecular patterns, and/or downstream signaling, in the management of hepatorenal syndrome?

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Provenance and peer review: Commissioned; externally peer reviewed.

Patient involvement: No patients were asked for input in the creation of this article.


nephropathy is a common pathologic finding for kidney injury.

Causes Acute Kidney Injury and Is Accompanied by Loss of Aquaporin

in patients with cirrhosis and septic shock: Effect of treatment

insufficiency in Patients with Cirrhosis: A Systematic Review and

syndrome).

Meta-Analysis.


Reduction of renal cortical blood flow assessed by Doppler in cirrhotic patients with refractory ascites.


and type 1 hepatorenal syndrome.

and hepatorenal syndrome: a prospective uncontrolled trial. Crit


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134 Wong F, Raina N, Richardson R. Molecular adenosine receptor recycling system is ineffective in the management of type 1 hepatorenal syndrome in patients with cirrhosis with ascites who have failed vasocorconstrictor treatment. *Gut* 2010;59:381-6.