Renal failure in cirrhosis: Emerging concepts

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Acute renal failure, now termed acute kidney injury (AKI), is frequently found in patients with cirrhosis. The occurrence of AKI, irrespective of the underlying cause, is associated with reduced in-hospital, 3-mo and 1-year survival. Hepatorenal syndrome is associated with the worst outcome among AKI patients with cirrhosis. Several definitions for AKI that have been proposed are outlined and evaluated in this paper. Among these, the International Club for Ascites-AKI criteria substantially strengthen the quality of early diagnosis and intervention according to underlying cause of AKI.

Key words: Renal failure; End-stage liver disease; Acute kidney injury; Hepatorenal syndrome; Liver cirrhosis

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INTRODUCTION

Renal failure is a common complication of decompensated cirrhosis[1-8]. Acute renal failure, now termed acute kidney injury (AKI), has traditionally been defined by serum creatinine (Scr) levels higher than 1.5 mg/mL. It occurs in 11% of patients with upper gastrointestinal bleeding, in 34% of patients with...
spontaneous bacterial peritonitis (SBP), in 27% with bacterial infections other than SBP and in 40% to 49% of critically-ill patients with cirrhosis requiring intensive care support\textsuperscript{[1,7]}. Furthermore, 24% of outpatients with cirrhosis develop some type of renal failure within one year of the first episode of ascites\textsuperscript{[8]}. In most reports, renal failure significantly reduces survival rates\textsuperscript{[5-8]}. In this review, we outline and evaluate the definitions for kidney injury in patients with cirrhosis, particularly the emerging International Club for Ascites-AKI (ICA-AKI) criteria and advances in the management of AKI in cirrhosis.

**DIAGNOSIS AND ETIOLOGY OF RENAL FAILURE**

The most common causes of renal injury in patients with cirrhosis are: (1) circulatory dysfunction due to bacterial infection; (2) hypovolemia secondary to gastrointestinal bleeding, paracentesis or diuretic use; (3) contrast or drug-induced; (4) chronic kidney diseases (CKD); and (5) hepatorenal syndrome (HRS)\textsuperscript{[5-9]}. CKD, such as IgA nephropathy, glomerulonephritis or nephrosclerosis are commonly seen in patients with cirrhosis. In most cases, the underlying causes of both conditions are alcoholic liver disease, hepatitis B and C and non-alcoholic steatohepatitis with associated diabetes and/or hypertension\textsuperscript{[9]}. HRS is a functional type of renal failure\textsuperscript{[10,11]} found only in patients with advanced cirrhosis and ascites\textsuperscript{[12-14]}. It is reversible either with orthotopic liver transplantation (OLT)\textsuperscript{[11]} or with pharmacological treatment with splanchnic vasoconstrictors and albumin\textsuperscript{[15-18]}. HRS is the ultimate result of arterial underfilling due to splanchic and systemic vasodilation generally with high cardiac output. When the circulatory dysfunction is inadequate to restore hemodynamics, vasoconstrictor mediators are released, resulting in severe renal vasoconstriction\textsuperscript{[13-14]}.

HRS diagnosis was initially defined by the ICA based on major and minor criteria to characterize the occurrence of renal failure in a patient with cirrhosis (Table 1)\textsuperscript{[12]}. There are two types of HRS. Type-1 HRS is a rapidly progressive renal failure defined by a doubling of the baseline SCr to a level greater than 2.5 mg/dL in less than 2 wk from baseline. Type-2 HRS is characterized by a steady or slow increase in SCr levels to over 1.5 mg/dL. Type-2 HRS is frequently associated with refractory ascites, while type-1 HRS is usually triggered by infection, particularly SBP. Survival rates of patients with untreated type-1 HRS are extremely low when compared to type-2 HRS, whereas patients with type-2 HRS usually have shorter survival compared to patients with ascites but not HRS\textsuperscript{[12,13]}.

In 2007, the ICA revised HRS diagnosis definition (Table 1) to improve accuracy and applicability\textsuperscript{[13]}. Creatinine clearance and all minor criteria were excluded because they are difficult to comply with on a regular basis. Ongoing bacterial infection without septic shock was no longer regarded as among the exclusion criteria, reflecting the fact that bacterial infections are a major cause of HRS. A relevant recommendation of the ICA revised criteria is that albumin infusion should be preferred over the traditional volume expansion with saline. Although simplified, this criteria diagnosed HRS in a lower than expected number of patients with cirrhosis and AKI in different cohorts\textsuperscript{[5,7,8]}.

This is important because prognosis is related to the cause of renal failure, as shown by a recent report in which 3-mo survival rates of patients with cirrhosis were 73% for CKD, 46% for hypovolemia, 31% for bacterial infection and 15% for HRS\textsuperscript{[11]}.

Renal failure in patients with cirrhosis, defined by abnormally high SCr levels, is clearly associated with increased mortality either in the intensive care unit (ICU) or during hospital stay and reduced 3- and 12-mo survival\textsuperscript{[5,7,8]}. Patients with HRS and bacterial infections requiring renal replacement therapy have the worst prognoses\textsuperscript{[7]}.

However, there are several drawbacks to the use of absolute SCr value and creatinine clearance for the assessment of kidney function in patients with cirrhosis\textsuperscript{[19]}. The endogenous production of SCr varies according to muscle mass, which is often markedly decreased in patients with cirrhosis, age, gender and diet. Estimation of kidney function by glomerular filtration rate (GFR) is unreliable because tubular secretion is also involved in SCr elimination, and therefore is a confounding factor\textsuperscript{[19]}.

In 2004 the Acute Dialysis Quality Initiative group for the study of AKI proposed the Risk, Injury, Failure, Loss of Kidney Function and End Stage (RIFLE) classification for AKI in patients without cirrhosis. It is based on the dynamic but sustained increase in SCr, GFR assessment by creatinine clearance and urinary output over a 7-d period\textsuperscript{[20]}. RIFLE has three stages of AKI (Risk, Injury and Failure) and two outcomes; loss of kidney function and end-stage kidney disease (Table 2). RIFLE accurately identifies AKI and predicts prognosis, including progression to CKD and higher risk of mortality in the ICU\textsuperscript{[20,21]}. Using the RIFLE criteria, several authors have described a strong correlation between mortality and the presence and severity of AKI in patients with and without cirrhosis\textsuperscript{[21-24]}.

However, the RIFLE criteria were difficult to apply in a significant proportion of ICU patients, since it ideally requires the measurement of baseline SCr levels. In the absence of information regarding baseline SCr it can be calculated, using the modification of diet in renal disease equation. This assumes a baseline GFR of 75 mL/min per 1.73 m\textsuperscript{2} in the absence of CKD.

Subsequently, the acute kidney injury network (AKIN) revised the RIFLE criteria and proposed their consensus definition, the AKIN criteria\textsuperscript{[25,26]}. The three stages of AKIN are shown in Table 3. Adequate volume expansion and exclusion of urinary tract obstruction are required for establishing the diagnosis of AKI. The diagnostic criteria have been modified to take into
account changes in urinary output and SCr levels within a pre-established time period, allowing early detection of AKI even with modest increases in SCr (Table 3). In AKIN, estimation of creatinine clearance and baseline SCr values are not required for the diagnosis of AKI. AKIN classification allows better identification of severity of AKI during hospital stay or peak SCr had increased mortality rates.

The Kidney Disease Improving Global Outcomes (KDIGO) criteria were published in 2012. They differ slightly from AKIN and RIFLE in the following parameters: (1) Increase in SCr by 0.3 mg/dL or more within 48 h; or (2) Increase in SCr to 1.5 times baseline or more within the last 7 d; or (3) Urine output less than 0.5 mL/kg per hour for 12 h.

The new ICA-AKI criteria give a new approach to the definition and staging of AKI, of the definition of AKI progression and response to treatment (Table 4). The major change was the exclusion of urine output as a parameter. Urine output in patients with cirrhosis and ascites is often an unreliable indicator because the GFR may be preserved in spite of the continuous sodium

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**Table 1** The diagnosis of hepatorenal syndrome according to the original (1996) and revised (2007) International Ascites Club criteria

| Criteria for HRS-1 (1996) | Revised criteria for HRS-1 (2007) |
|---------------------------|----------------------------------|
| Major criteria            | Presence of cirrhosis with ascites |
| Chronic or acute liver disease with advanced hepatic failure and portal hypertension | SCr > 1.5 mg/dL |
| Low GFR: SCr > 1.5 mg/mL or 24 h SCr clearance < 40 mL/min | No improvement of SCr levels after at least 2 d of diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/d) |
| Absence of shock, ongoing bacterial infection or treatment with nephrotoxic drugs or gastrointestinal or renal fluid losses | Absence of shock |
| No sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with at least 1500 mL of isotonic saline Proteinuria < 0.5 g/d and no evidence of obstructive nephropathy or parenchymal renal disease on ultrasound | No current or recent treatment with nephrotoxic drugs |

**Table 2** Risk, injury, failure, loss of kidney function and end-stage kidney disease classification for acute kidney injury

| Class | Baseline SCr levels and GFR within 7 d | Urinary output |
|-------|----------------------------------------|----------------|
| Risk  | ↑ SCr 1.5-1.9 times over baseline or ↓ GFR > 25% | < 0.5 mL/kg per hour for 6 h |
| Injury| ↑ SCr 2.0-2.9 times over baseline or ↓ GFR > 50% | < 0.5 mL/kg per hour for 12 h |
| Failure| ↑ SCr ≥ 3 times over baseline or ↓ GFR > 75% or if baseline SCr ≥ 4 mg/dL: ↑ SCr > 0.5 mg/dL. | < 0.5 mL/kg per hour for 24 h or anuria for 12 h |
| Loss of kidney function | Complete loss of kidney function > 4 wk |
| End-stage kidney disease | Complete loss of kidney function > 3 mo |

**Table 3** The Acute Kidney Injury Network classification of acute kidney injury

| Stage | Baseline SCr within 48 h | Urinary output |
|-------|--------------------------|----------------|
| 1     | ↑ SCr ≥ 0.3 mg/dL or ↑ SCr 1.5-1.9 times over baseline | < 0.5 mL/kg per hour for 6 h |
| 2     | ↑ SCr 2.0-2.9 times over baseline | < 0.5 mL/kg per hour for 12 h |
| 3     | ↑ SCr ≥ 3 times over baseline or if baseline SCr ≥ 4 mg/dL: ↑ SCr ≥ 0.5 mg/dL. | < 0.5 mL/kg per hour for 24 h or anuria for 12 h |

Adapted from Arroyo et al and Salerno et al. SCr: Serum creatinine; GFR: Glomerular filtration rate; HRS: Hepatorenal syndrome.
Management of AKI

Management of AKI in cirrhosis has moved towards prioritizing early recognition and intervention, according to the most probable cause of renal failure[14]. Patients with cirrhosis and ascites and AKI grade I should be carefully monitored with regards to all risk factors for renal injury. Nephrotoxic agents (including non-steroidal anti-inflammatory, aminoglycoside, contrast agents), vasodilators and beta-blockers should be immediately withdrawn. Diuretics should be decreased or ideally withdrawn. This is particularly true when the patient has refractory ascites because several drugs can induce AKI.

In all patients with clinical and laboratorial signs of hypovolemia, volume expansion with crystalloids, colloids or packed red blood cells should be administered according to clinical need. Patients should always be screened for bacterial infection, and treated as appropriate. If the AKI regresses, patients should be closely followed-up with SCR measurements. In the case of AKI stages II or III at admission or progression of AKI stage I to stages II or III, in addition to those initial measures, it is recommended to proceed with plasma expansion with albumin 1 g/kg per day to a maximum dose of 100 mg/d for two consecutive days. If not already done, diuretics must be withdrawn. In the absence of AKI regression, the course of treatment is dictated by the underlying cause of renal failure. In patients with type-1 HRS, a course of splanchnic vasoconstrictors and albumin is recommended, particularly if SCR levels are higher than 1.5 mg/mL.

Clinical judgment is crucial to distinguish between those patients with AKI caused by HRS who would benefit from pharmacological therapy from those with acute tubular necrosis or obstructive nephropathy, where the medical therapy would have no effect. In this scenario, biomarkers such as urinary neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 and kidney injury molecule-1, may help differentially diagnose acute tubular necrosis rather than common causes of AKI in patients with cirrhosis. NGAL levels are markedly higher in patients with cirrhosis with ATN compared to patients with AKI caused by hypovolemia, HRS or CKD[32]. However, it has not yet been established whether or not NGAL levels could identify patients with suspected HRS who would benefit from pharmacological therapy with albumin and splanchnic vasoconstrictors.

The diagnosis of type-1 HRS was updated to include patients with ICA-AKI II and III at admission or subjects who progressed from AKI I to AKI II or III despite volume expansion with albumin[14]. No other previously established criteria were modified (Table 5), but the requirement of SCR threshold levels higher than 2.5 mg/dL for diagnosis of type-1 HRS was abandoned. This high threshold may delay therapy with splanchnic vasoconstrictors and albumin, with a detrimental effect on response to treatment[14].

OLT is considered the best treatment for hepatorenal syndrome[32]. It improves renal function and is the definitive treatment for cirrhosis, which is responsible for severe circulatory dysfunction in patients with type-1 HRS. Due to the poor short-term prognosis for patients with type-1 HRS, OLT was rarely performed in these patients. Nevertheless, after the introduction of MELD score, priority has been given to HRS patients, and many of them reach OLT. While on the waiting list, patients with type-1 HRS must receive bridging treatment of acute kidney injury in patients with cirrhosis

Table 4 International Club of Ascites-acute kidney injury criteria for diagnosis, grading, assessment of progression and response to treatment of acute kidney injury in patients with cirrhosis

| Class | Baseline SCR within 3 mo, most recent prior to hospital admission | Urinary output |
|-------|---------------------------------------------------------------|----------------|
| I     | ↑ SCR ≥ 0.3 mg/dL or ↑ SCR 1.5-2.9 times over baseline<sup>1</sup> | Not required   |
| II    | ↑ SCR 2.0-2.9 times over baseline                             | Not required   |
| III   | ↑ SCR ≥ 3 times over baseline or if baseline SCR ≥ 4 mg/dL: ↑ SCR ≥ 0.3 mg/dL<sup>1</sup> or initiation of renal replacement therapy | Not required   |

Progression of AKI: Progression of AKI to a higher stage and/or need for renal replacement therapy
Regression of AKI: Regression of AKI to a lower stage
No response: No regression of AKI
Partial response: Regression of AKI stage with a reduction of SCR to < 0.3 mg/dL above the baseline value
Full response: Return of SCR to a value within 0.3 mg/dL of the baseline value

<sup>1</sup>Which is known, or presumed, to have occurred within the prior 7 d. Adapted from Angeli et al[16]. SCR: Serum creatinine; AKI: Acute kidney injury.

Table 5 Updated diagnosis of hepatorenal syndrome type of acute kidney injury according to the International Club of Ascites

| Presence of cirrhosis with ascites | Diagnosis of AKI according to ICA-AKI criteria |
|-----------------------------------|-----------------------------------------------|
| No improvement of SCR after at least 2 d of diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/d) | Absence of shock |
| No current or recent treatment with nephrotoxic drugs | No macroscopic signs of structural kidney injury: normal findings on renal ultrasonography, absence of proteinuria > 500 mg/d and absence of microhematuria |

Adapted from Angeli et al[16]. SCR: Serum creatinine; AKI: Acute kidney injury; ICA-AKI: International Club for Ascites-AKI.

retention and oliguria and many patients are under diuretic therapy (Table 5). This requirement is a major disadvantage of RIFLE, AKIN and KDIGO criteria.
treatments to improve short-term survival.

The hemodynamic and neurohormonal abnormalities associated with type-1 HRS disappear within the first month after OLT and patients regain a normal ability to excrete sodium and free water. The long-term survival of patients with HRS who undergo OLT is good (60% at 3 years). However, a study by Nair et al. showed that renal failure is an independent predictor of 30-d and 2-year mortality after OLT. A case-control study showed that patients with type-1 HRS treated with vasoconstrictors before OLT have post-transplantation outcomes similar to OLT patients with normal renal function. These results suggest that in type-1 HRS, treatment with vasoconstrictors before OLT could be an important factor for post-transplantation outcome.

Pharmacological treatment of type-1 HRS consists of the infusion of vasoconstrictors and intravenous human albumin. Vasoconstrictors are administered to reverse the splanchnic arterial vasodilation, and albumin for volume expansion. This combination improves venous return and cardiac output.

Several studies have shown that medical treatment is effective in reversing type-1 HRS in 40%-60% of patients. Complete therapeutic response to therapy, as defined by a reduction of SCr to below 1.5 mg/dL, is associated with a marked suppression of plasma renin activity and a significant increase in mean arterial pressure.

Terlipressin, a vasopressin analogue, has been the most frequently used drug to improve splanchnic circulation. In most studies intravenous terlipressin bolus ranged from 0.5 to 2 mg/4-6 h. There are data indicating that the therapeutic response to terlipressin is very poor if not administered with albumin. A recommended dose for albumin administration is 1 g/kg on the first day followed by 20-40 g/d thereafter.

A retrospective survey of 99 patients with type-1 HRS treated with terlipressin and albumin showed a rate of improvement in renal function of 58% and increased survival rates.

Two randomized, placebo-controlled trials have been performed in order to evaluate the efficacy and safety of terlipressin for treatment of type-1 HRS. Patients were randomly assigned to receive either terlipressin plus albumin or albumin alone (control group). Compared to controls, the group treated with terlipressin plus albumin had significant improvement in renal function (43.5% compared to 8.7%; P = 0.017 in one study and 34% compared to 13%; P = 0.008 in the other). In both studies type-1 HRS reversal significantly improved survival. The main conclusions are that: (1) treatment with terlipressin and albumin is effective in improving renal function in patients with cirrhosis; and (2) type-1 HRS reversal significantly improves survival.

Although not often used outside the ICU, norepinephrine has also been successfully used in patients with HRS. Pilot studies suggest that norepinephrine is as effective as terlipressin in the treatment of type-1 HRS.

A recent systematic review and meta-analysis evaluated the efficacy and safety of norepinephrine compared to terlipressin in the management of type-1 HRS. There was no difference between norepinephrine and terlipressin in the reversal of HRS (RR = 0.97; 95%CI: 0.76 to 1.23), mortality at 30 d (RR = 0.89; 95%CI: 0.68 to 1.17) and recurrence of HRS (RR = 0.72; 95%CI: 0.36 to 1.45). Based on these studies, the authors conclude that norepinephrine seems to be an attractive alternative to terlipressin in the treatment of type-1 HRS, particularly in the ICU. Some studies without controls have reported improved renal function in patients with HRS treated with a combination of midodrine and octreotide plus albumin. However, one recent randomized controlled trial demonstrated that terlipressin and albumin were clearly superior treatment options to midodrine, octreotide and albumin in reversal of HRS.

Recurrence of type-1 HRS after discontinuation of treatment is observed in approximately 15% of patients. Treatment of recurrent HRS is usually effective. The incidence of ischemic side effects requiring discontinuation of terlipressin is around 5%-10%, although most studies excluded high-risk patients with ischemic heart or artery diseases.

Data concerning the use of transjugular intrahepatic portosystemic shunts (TIPS) in type-1 HRS are scarce; only three studies have been published as full papers, comprising a total of 30 treated patients. These studies showed that GFR improved markedly within 1-4 wk after TIPS. In one study specifically investigating neurohormonal systems, improvement in GFR and SCr was related to a significant suppression of both plasma renin activity and antidiuretic hormone. Survival data were provided in two of the studies. In the study by Guevara et al., 7 patients were included and the mean survival was 4.7 ± 2 mo. In the paper by Bensing et al., the mean survival was 75 wk, with 3- and 6-mo survival rates of 64% and 50%, respectively. These data sharply contrast with those usually reported in patients with untreated type-1 HRS (median survival of 2 wk).

De novo encephalopathy or deterioration in pre-existing encephalopathy developed in 35%-50% of the patients after TIPS, but most patients were successfully managed with standard treatment. During the first year of follow-up the shunt stenosis rate was 22%.

After pharmacological treatment of type-1 HRS, despite marked suppression of renin-angiotensin axis and sympathetic nervous system and normalization of SCr, renal function does not reach normal levels in most cases (GFR ranges between 30 to 50 mL/min).

However, treatment for type-1 HRS with TIPS in patients responding to pharmacological treatment (midodrine or octreotide and albumin) normalizes GFR in most cases. Together these studies strongly suggest that TIPS is useful in the management of type-1 HRS and probably improves survival. Unfortunately the number of treated patients was very low and controlled.
studies in larger series must be performed to draw stronger conclusions. Whether the use of covered stents improves outcomes when compared to bare stents is worthy of attention in future studies of TIPS for patients with type-1 HRS.

There are a variety of other treatment options that have been considered for HRS. The beneficial effects of haemodialysis have not been convincingly demonstrated in type-1 HRS. Complications during haemodialysis are common and include arterial hypotension, bleeding, and infections. Extracorporeal albumin dialysis has been reported to improve renal function and survival in a small series of patients with HRS. Further studies are required on this topic.

Survival for patients with type-2 HRS is usually longer compared to type-1, and many survive to OLT. Treatment with vasoconstrictors plus albumin can be used, but recurrence is common after stopping therapy. There are few data on the treatment of type-2 HRS with TIPS. In studies evaluating this issue significant improvement in renal function was observed. However, a low number of patients have been assessed.

Hepatorenal syndrome can be prevented at least in two clinical scenarios; SBP therapy and SBP prophylaxis. Sort et al randomized 126 patients with cirrhosis and SBP to receive treatment with cefotaxime or cefotaxime plus intravenous albumin (1.5 g/kg at the time of diagnosis, followed by 1 g/kg on day 3). Type-1 HRS was reported in 10% of patients in the group of combination therapy and in 33% of cefotaxime monotherapy. In-hospital mortality (10% compared to 29%) and 3-mo mortality (22% compared to 41%) were also lower in patients who received combination therapy.

Fernández et al performed a randomized controlled trial to assess the effectiveness of norfloxacin as primary prophylaxis in patients with cirrhosis and high risk of developing SBP and HRS. These patients had one or more of the following: Protein ascites levels below 15 g/L, Child-Pugh score ≥ 9 points, serum bilirubin ≥ 3 mg/dL, SCR ≥ 1.2 mg/dL, blood urea nitrogen ≥ 25 mg/dL, or serum sodium ≤ 130 mEq/L. Norfloxacin reduced the incidence of SBP (7% compared to 61%, P < 0.001) and HRS (28% compared to 41%, P = 0.02), and improved survival (60% compared to 48%, P = 0.05).

CONCLUSION

AKI is a frequent complication of cirrhosis, and has adverse impact on outcomes, particularly in those with decompensated disease requiring hospital or ICU admission. New definitions for AKI, such as RIFLE, AKIN and KDIGO have been introduced to standardize diagnostic criteria as well as to recognize patients at risk or in the early stages of AKI, whose survival rates would improve significantly with early detection and intervention. The ICA revised their definition of AKI and type-1 HRS (ICA-AKI criteria) to propose a new consensus recommendation. Although the impact on outcome of these new criteria needs further exploration, the ICA-AKI criteria substantially strengthen the quality of early diagnosis and intervention of HRS. Use of splanchnic vasoconstrictors, either terlipressin or noradrenaline and high-dose albumin remains the standard treatment for type-1 HRS.

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