Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome

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Abstract
Renal dysfunction is a common complication of liver cirrhosis and of utmost clinical and prognostic relevance. Patients with cirrhosis are more prone to developing acute kidney injury (AKI) than the non-cirrhotic population. Pre-renal AKI, the hepatorenal syndrome type of AKI (HRS-AKI, formerly known as ‘type 1’) and acute tubular necrosis represent the most common causes of AKI in cirrhosis. Correct differentiation is imperative, as treatment differs substantially. While pre-renal AKI usually responds well to plasma volume expansion, HRS-AKI and ATN require different specific approaches and are associated with substantial mortality. Several paradigms, such as the threshold of 2.5 mg/dL for diagnosis of HRS-AKI, have recently been abolished and novel urinary biomarkers are being investigated in order to facilitate early and correct diagnosis and treatment of HRS-AKI and other forms of AKI in patients with cirrhosis. This review summarizes the current diagnostic criteria, as well as pathophysiologic and therapeutic concepts for AKI and HRS-AKI in cirrhosis.

Key words: liver cirrhosis, acute kidney injury, hepatorenal syndrome

Introduction

Acute kidney injury (AKI), defined by a significant reduction in glomerular filtration rate (GFR) over a short time period, is a common and severe complication in patients with cirrhosis and is often triggered by a precipitating event (i.e. overdose of diuretics, large-volume paracentesis without albumin replacement, gastrointestinal bleeding, bacterial infections, etc.) [5]. AKI has an estimated prevalence of approximately 20–50% among hospitalized patients with cirrhosis [6–9] and patients with cirrhosis are more likely to develop renal failure compared to individuals without liver disease [10]. AKI is associated with poor prognosis and represents an important predictor for short-term mortality in patients with cirrhosis [6,7,11–13].
The spectrum of causes for AKI in cirrhosis includes (i) prerenal AKI (i.e., hypovolemia due to gastrointestinal bleeding, aggressive diuretic treatment, lactulose-induced diarrhea or infections), (ii) the hepatorenal syndrome-type AKI (HRS-AKI), which is defined as a potentially reversible deterioration of renal function unresponsive to volume resuscitation, caused by renal vasoconstriction in the absence of alternative identifiable causes [14,15], (iii) intrinsic causes such as acute tubular necrosis and, although very rare, (iv) postrenal causes [9].

With a yearly incidence of 8–12%, HRS-AKI is quite common in decompensated cirrhosis with ascites [16–18]. The correct classification of AKI is essential since HRS-AKI, representing one of the most lethal complications of portal hypertension, requires a specific treatment approach. However, despite adequate treatment mortality is still about 60% and higher [13,19,20]. HRS-AKI is a diagnosis by exclusion and thus, often difficult to establish [21,22].

**Association between the liver and the kidney from a historical point of view**

The association of fulminant renal failure with diseases of the liver and the biliary tract is known for more than a century and has already been reported, in 1863 by Austin Flint, in a case series of patients with cirrhosis and ascites [23]. From the 1920s up to the 1950s, the abdominal surgeon James Gordon Heyd described this clinical phenomenon thoroughly, which has thus also been referred to as Flint’s syndrome or Heyd’s syndrome, respectively [24,25]. During the past century, the term ‘hepatorenal syndrome’ has undergone several and often drastic redefinitions and reclassifications while the understanding of the underlying pathophysiology was improving.

Heyd’s syndrome was initially described as a fulminant clinical deterioration following bilio-hepatic surgery (i.e. cholecystectomy) or appendectomy that was associated with progressive reduction in vigilance and often resulted in death [26]. Heyd defined a syndrome that was characterized by anuria and a rise in blood urea nitrogen despite after 24-36 hours apparently normal renal function prior to surgery which was later referred to as ‘hepatorenal failure’ [26,27]. In 1927, Furtwangler was the first to report a case series on fulminant cortical necrosis in both kidneys following hepatic trauma [28]. He suspected endotoxin-induced vasospasm and ischemia as the pathophysiologic mechanism [29]. During the following decades, the ‘hepatorenal syndrome’ became increasingly recognized as its own entity as an own entity of renal failure in patients with cirrhosis characterized by fulminant progression and high mortality [24,25,30–33].

The first consensus conference on a uniform definition for the hepatorenal syndrome (HRS) took place in 1978 in Sassary, Italy [34,35]. HRS was then considered an acute renal dysfunction associated with extensive renal sodium retention associated with acute or chronic liver disease [35]. However, the evolving understanding of the pathophysiology of HRS has led to several reclassifications and redefinitions (Table 1) [14,21,35–39].

In the past two decades, two different types of HRS have been distinguished. While type 1 HRS describes a fulminant decline in renal function in patients with advanced liver disease that is associated with a detrimental prognosis, type 2 HRS is defined as slowly progressive functional renal failure that typically occurs in patients with refractory ascites. The traditional diagnostic criteria for acute renal failure in cirrhosis—a relative increase in serum creatinine (sCr) by ≥50% from baseline to a final value ≥1.5 mg/dL [21]—were replaced by the Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcome (KDIGO) diagnostic criteria for AKI [39,40] and specifically adapted for patients with cirrhosis in order to improve applicability into clinical practice (ICA criteria) [37].

The most recent definition criteria were published in 2015 by both a community of hepatologists (ICA) together with the Acute Dialysis Quality Initiative (ADQI), a community of nephrologists, and reclassified the former type 1 HRS as a special entity of acute kidney injury: the ‘HRS type of AKI’ (HRS-AKI) [37].

An overview over the most influential classifications for HRS in cirrhosis is listed in Table 1.

**Current diagnostic criteria of AKI and HRS-AKI in patients with cirrhosis**

AKI in cirrhosis is defined as an acute increase in serum creatinine of ≥0.3 mg/dL within 48 hours or by ≥50% from a stable baseline serum creatinine (sCr) within 3 months (presumed to have developed within the past 7 days when no prior readings are available) [37]. The main modifications over the former, rather stringent criteria that were based on absolute serum creatinine level, was abandoning the arbitrary threshold of sCr ≥1.5 mg/dL to diagnose AKI, since milder degrees of renal failure in patients with cirrhosis had often remained underdiagnosed [41,42]. In addition, the use of urine output as part of the diagnostic criteria was eliminated, since many patients with cirrhosis and ascites maintain a preserved renal function despite being oliguric due to sodium and water retention [37,43].

AKI can be classified into three stages according to severity. Stage 1 AKI is defined by rather small changes in sCr, while stages 2 and 3 AKI are defined by a two-fold and three-fold increase in sCr, respectively (Table 2) [37,44].

Several clinical studies have evaluated the prognostic value of the AKIN/KDIGO criteria that constitute the basis for the International Club of Ascites (ICA)-AKI criteria in patients with cirrhosis [6,45–47]. Similarly to the ICA-AKI criteria, most of these studies diagnosed AKI solely on sCr. In 2013, one study group developed a modified, AKIN-derived score for cirrhosis, by splitting AKI stage 1 into two groups depending on whether or not sCr surpassed the (former) threshold of 1.5 mg/dL. (stages “B” and “A”, respectively), and by merging AKI stages 2 and 3 into stage “C” [13]; however, this re-classification did not gain wide acceptance [46,48,49]. Since their publication in 2015, the newer and cirrhosis-specific ICA criteria have been assessed within one retrospective study in hospitalized patients with cirrhosis [49]. Within this study, approximately 40% of patients experienced AKI during their hospitalization with the majority of cases having been diagnosed at stage 1. Also, in patients with AKI stage 1 and a sCr of <1.5 mg/dL already a 3.5-fold increase in 30-day mortality as compared to patients without AKI was reported [49], again underlining the prognostic importance of even small increases in sCr levels.

**HRS type of AKI (HRS-AKI, formerly known as type 1 HRS)**

The hepatorenal syndrome type of AKI (HRS-AKI) is defined as ≥ stage 2 ICA-AKI that is diagnosed after other causes of renal failure have been ruled out [37]. The proper diagnosis of HRS-AKI further requires the fulfillment of several specific diagnostic criteria that are summarized in Table 3.

Recent guidelines, in particular the Guidelines of the American Association for the Study of the Liver (AASLD) and the European
| Year | Author                          | Title                                                                 | Major criteria                                                                                                                                                                                                 | Minor criteria                                                                                                                                                                                                 |
|------|--------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1979 | Earley [34]                    | Sassari’s Diagnostic Criteria                                        | Progression of blood creatinine > 1.5 mg/dL over several days in absence of nephrotoxins                                                                                                                       | Volume < 800 mL/day; ± urinary protein excretion                                                                                                                                             |
|      |                                |                                                                      | Urine/plasma osmolality > 1.0                                                                                                                                                                                     | Onset of disease spontaneously over course of liver disease or                                                                                                                                  |
|      |                                |                                                                      | Urine sodium < 10 mEq/L, often < 5 mEq/L                                                                                                                                                                           | Onset in association with infections, bleeding, paracentesis, diuretic therapy or other forms of volume loss                                                                                   |
|      |                                |                                                                      | No sustained improvement after plasma expansion to a central venous pressure of 10 cm H₂O                                                                                                                        | Characteristics may be followed by tubular dysfunction                                                                                                                                          |
|      |                                |                                                                      | No sustained improvement after plasma expansion to a central venous pressure of 10 cm H₂O                                                                                                                        | Post-mortem renal histology may be normal                                                                                                                                                     |
| 1996 | Arroyo et al. [35]             | Definition and Diagnostic Criteria of Refractory Ascites and Hepatorenal Syndrome in Cirrhosis | Chronic or a acute liver disease with hepatic failure and portal hypertension                                                                                                                                | Urine volume < 500 mL/d                                                                                                                                                                         |
|      |                                |                                                                      | Low GFR (sCr > 1.5 mg/dL or 24-hour creatinine clearance < 40 mL/min)                                                                                                                                            | Urine sodium < 10 mEq/L                                                                                                                                                                         |
|      |                                |                                                                      | Absence of shock, bacterial infection, recent treatment with nephrotoxic drugs, absence of gastrointestinal or renal fluid loss                                                                                | Urine osmolality greater than plasma osmolality                                                                                                                                               |
|      |                                |                                                                      | No sustained improvement in renal function following withdrawal of diuretics and plasma expansion with 1.5 L of isotonic saline                                                                                 | Serum sodium concentration < 130 mEq/L                                                                                                                                                         |
|      |                                |                                                                      | Proteinuria < 500 mg/dL and absence of obstructive uropathy or renal parenchymal disease in ultrasound                                                                                                         | Type I HRS: Rapid progressive reduction of renal function in < 2 weeks as marked by: (i) a doubling of serum creatinine to > 2.5 mg/dL or (ii) 24-hour creatinine clearance < 20 mL/min |
| 2007 | Salerno et al. [21]            | Diagnosis, Prevention and Management of Adult Patients with Ascites Due to Cirrhosis: An Update | Cirrhosis with ascites                                                                                                                                                                                       | Type II HRS: Slower course (< 2 weeks)                                                                                                                                                        |
|      |                                |                                                                      | Serum creatinine > 1.5 mg/dL.                                                                                                                                                                                      | Type II HRS is typically associated with refractory ascites                                                                                                                                                 |
|      |                                |                                                                      | No improvement of serum creatinine (decrease to < 1.5 mg/dL) after at least 2 days of diuretic withdrawal and volume expansion with albumin                                                                 | Other minor diagnostic criteria have been removed                                                                                                                                                    |
|      |                                |                                                                      | Absence of shock                                                                                                                                                                                               | Urinary neutrophil gelatinase-associated lipocalin may be used to distinguish HRS from other causes of renal failure. It is 20 ng/mL in healthy controls or pre-renal azotemia, 50 ng/mL in chronic kidney disease, 105 ng/mL in HRS and 325 ng/L in AKI. However, it is not presently available in many countries. |
| 2009 | Runyon [132]                   | AASLD Practice Guidelines: Treatment of Hepatorenal Syndrome in Cirrhosis | No current or recent treatment with nephrotoxic drugs.                                                                                                                                                        | Glocmerular tubular reflux is a histologic lesion associated with hepatorenal syndrome; however, renal biopsy must be weighed carefully against the benefits of strategy. |
|      |                                |                                                                      | Absence of parenchymal kidney damage (proteinuria > 500 mg/dL, > 50 RBCs/high-power field) or abnormal renal ultrasonography                                                                 | Type 1 HRS: Rapid progressive renal failure with: (i) doubling of serum creatinine to > 2.5 mg/dL in less than 2 weeks or (ii) 50% reduction of 24-hour creatinine clearance to < 20 mL/min in less than 2 weeks |
| 2012 | Runyon [36]                    | Introduction to the revised AASLD Practice Guideline management of adult patients with ascites due to cirrhosis 2012 | Type 1 HRS: Rapid progressive renal failure with: (i) doubling of serum creatinine to > 2.5 mg/dL in less than 2 weeks or (ii) 50% reduction of 24-hour creatinine clearance to < 20 mL/min in less than 2 weeks | Type 2 HRS: Moderate renal failure (serum creatinine 1.5–2.5 mg/dL) with steady and slowly progressive course                                                                                               |
| Year  | Author                                                                 | Title                                                                 | Major criteria                                                                                                                                                                                                 | Minor criteria                                                                                                                                                                                                 |
|-------|------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2010  | The European Association for the Study of the Liver [124]              | EASL Practice Guidelines on the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis | Cirrhosis with ascites  
Serum creatinine > 1.5 mg/dL  
Absence of shock  
Absence of hypovolemia as defined by no sustained improvement of renal function following at least 2 days of diuretic withdrawal and volume expansion with albumin at 1 g/kg/day, up to a maximum of 100 g/day  
No current or recent treatment with nephrotoxic drugs  
Absence of parenchymal renal disease as defined by proteinuria < 0.5 g/day, microhematuria of < 50 RBCs/high-power field and normal ultrasonography  
**Type 1 HRS:**  
Rapid progressive renal failure: increase of serum creatinine by > 100% from baseline to > 2.5 mg/dL in < 2 weeks, often in temporal relationship with a precipitating factor for deterioration of liver and other organ function  
**Type 2 HRS:**  
Steady and moderate progressive impairment of renal function  
| It is important to exclude other causes of renal failure as early as possible, such as: hypovolemia, shock, parenchymal renal diseases, concomitant use of nephrotoxic drugs  
Parenchymal renal diseases should be suspected in presence of significant proteinuria or microhematuria, or if renal ultrasound demonstrates abnormalities; a renal biopsy may aid in exclusion of other renal diseases  
HRS should be considered in case of a significant increase in serum creatinine to > 1.5 mg/dL  
Repeated measurement of serum creatinine over time is helpful in early diagnosis of HRS, particularly in hospitalized patients  
Patients with type 2 HRS may eventually develop type 1 HRS |
| 2012  | Nadim et al. [14]                                                      | Hepatorenal syndrome: the 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group [133] | Type 1 HRS is a specific form of AKI according to the ADQI/RIFLE criteria [140]  
Type 2 HRS is a specific form of chronic kidney disease as measured by eGFR < 60 mL/min/1.73 m² using the MDRD-6 formula  
| The term 'hepatorenal disorders' should be used for any renal dysfunction in advanced cirrhosis  
AKI: rise in sCr > 50% from baseline or by > 0.3 mg/dL  
HRS-AKI does not exclude structural or tubular damage  
Urinal biomarkers may become important in the differential diagnosis of HRS and ATN |
| 2015  | Angeli et al. [37]                                                     | Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites | HRS-AKI (former type 1 HRS):  
Diagnosis of cirrhosis and ascites  
Diagnosis of AKI according to International Club of Ascites-AKI criteria (AKI stage 2 or 3)  
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with 1 g albumin per kg body weight  
Absence of shock  
No current or recent use of nephrotoxic drugs (NSAIDs, contrast media, etc.)  
No evidence of structural kidney injury (proteinuria > 500 mg/day, > 50 RBCs/high-power field, parenchymal damage in renal ultrasonography)  
| HRS-AKI does not exclude structural or tubular damage  
Urinal biomarkers may become important in the differential diagnosis of HRS and ATN |

AKI, acute kidney injury; ATN, acute tubular necrosis; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; RIFLE, Risk (of renal function)–Injury (to the kidney)–Failure (of liver function)–Loss (of kidney function)–End-stage (kidney disease); MDRD, modification of diet in renal disease; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.
Table 2. Acute kidney injury (AKI) stages according to the International Club of Ascites (ICA) criteria

| ICA-AKI Stage | Increase in serum creatinine ≥0.3 mg/dL or increase in serum creatinine by ≥50–100% from baseline |
|---------------|-------------------------------------------------------------------------------------------------|
| ICA-AKI Stage 2 | Increase in serum creatinine by ≥100–200% from baseline |
| ICA-AKI Stage 3 | Increase in serum creatinine by ≥200% from baseline or Increase in serum creatinine to ≥4 mg/dL with an acute increase by ≥0.3 mg/dL or Need for renal replacement therapy |

Modified from references [45] and [37].

Association for the Study of Liver Diseases (EASL) Clinical Practice Guidelines for ascites and hepatorenal syndrome, still proclaim the threshold of 2.5 mg/dL for diagnosing HRS-AKI [50,51]. However, using this threshold in clinical practice would mean that proper diagnosis and treatment of HRS would be withheld as long as sCr does not reach this threshold. In order to prevent misclassification or even treatment delay, the newer ICA criteria focus on the relative increase in creatinine rather than absolute values, since also smaller rises in SCR (e.g. in case of stage 1 AKI) have been shown to have a negative prognostic impact in patients with cirrhosis [41].

From a clinical perspective, HRS-AKI is characterized by a rapid increase in SCR and progressive oliguria in the absence of other identifiable causes of AKI such as hypovolemia, shock, parenchymal renal diseases, urinary tract obstruction and presence of nephrotoxins (compare Table 3) [21,37]. In contrast to other forms of prerenal AKI, renal function in HRS-AKI does not improve by withdrawal of diuretics and plasma expansion using i.v. albumin [52]. It can develop spontaneously or be triggered by a precipitating event that causes deterioration of the systemic circulation, most prominently bacterial infections such as spontaneous bacterial peritonitis or variceal bleeding [4,35,53]. Concordantly, it has been shown that non-selective beta-blockers might also trigger HRS-AKI due to their impact on the systemic circulation [54].

Hepatorenal syndrome type 2 (hepatorenal syndrome type of chronic kidney disease)

Type 2 HRS is characterized by a stable or slowly progressive impairment in renal function in patients with decompensated liver disease who suffer from refractory ascites [14]. Patients usually develop oliguria over a course of several weeks or months, marked by excessive salt and water retention and a slow but steady incline in renal retention parameters [21,55]. Apart from the time of development, the same specific diagnostic criteria for HRS-AKI also apply for HRS type 2 (see Table 3) [21].

Type 2 HRS has been classified as a form of chronic kidney disease (CKD) in patients with cirrhosis, and (hepatorenal syndrome-type of chronic kidney disease, HRS-CKD) [20]. However, type 2 HRS or HRS-CKD is challenging to diagnose in clinical practice, as it is a diagnosis by exclusion, yet patients with liver cirrhosis often present with one or several other potential causes for kidney disease. However, according to the ADQI group, CKD due to other causes may develop on top of HRS type 2 [14]. As a result, only a few studies have been published on type 2 HRS and data vary substantially. For instance, the reported prevalence among patients with HRS ranges from 16% to 61% [1,56–58]. In general, prognosis in HRS type 2 is poor, but more favorable when compared to AKI-HRS [56–59].

Table 3. Diagnostic criteria for hepatorenal syndrome

| Diagnostic criteria for hepatorenal syndrome |
|---------------------------------------------|
| Presence of cirrhosis and ascites |
| No improvement in serum creatinine after 2 consecutive days of withdrawal of diuretics and plasma volume expansion with albumin (1 g per kg of body weight, maximum 100 g/day) |
| Absence of shock |
| Exclusion of recurrent or recent use of nephrotoxic agents (e.g. NSAIDs, aminoglycosides, contrast media) |
| Exclusion of parenchymal kidney disease: |
| • absence of proteinuria (>500 mg/day) |
| • absence of microhematuria (>50 RBCs per high-power field) |
| • normal renal ultrasonography |

Based on reference [37]. NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.

Pathophysiology of the hepatorenal syndrome

The understanding of the various pathophysiological pathomechanisms of renal dysfunction in cirrhosis has drastically evolved over the past few years and decades (Figure 1). Impairment of renal function in cirrhosis may occur within a wide spectrum of diseases, some related to abnormalities in renal function, others related to renal damage. Although being widely accepted for many years in clinical practice, the term...
In situations of hemodynamic stress such as in case of volume loss (e.g. due to diuretics, dehydration or gastrointestinal bleeding) or bacterial infections, RAAS activation and circulatory dysfunction may reach a point at which renal function can no longer be maintained—and HRS-AKI ensues [4].

**HRS-AKI as part of a multiorgan failure syndrome/systemic inflammatory response syndrome (SIRS) - a new hypothesis**

There is increasing evidence that systemic inflammation also plays an important role in the development of complications of portal hypertension in cirrhosis [78]. Until 2007, sepsis was an exclusion criterion for HRS [35]. However, in cirrhosis, renal dysfunction often develops secondarily to bacterial infections. SIRS and sepsis supposedly lead to renal blood flow redistribution, resulting in ischemia and subsequent tubular injury [79,80].

Toll-like receptor 4 (TLR4) is the main pattern-recognition receptor in the detection of inflammatory signals that has been identified to play an important role in the development of HRS-AKI in experimental models of cirrhosis. TLR4 is overexpressed in kidney tissue and urine in patients with cirrhosis and AKI (including HRS-AKI patients) following an inflammatory insult [81,82]. Endotoxins or lipopolysaccharides (LPS) are particles of the cell wall of Gram-negative bacteria and represent natural ligands to TLR4. LPS are strong pro-inflammatory factors by inducing TNF-α [83]. In cirrhosis, high levels of LPS (e.g. in case of spontaneous bacterial peritonitis [SBP] or sepsis) increase portal pressure and may induce hepatocyte death—thereby promoting hepatic decompensation [84–86]. This may eventually lead to deterioration of the systemic circulation, shock and multiorgan failure, including (HRS-) AKI. Indeed, SBP and sepsis represent the most common precipitating events for HRS-AKI. Recent studies on terlipressin for treatment of HRS-AKI showed similar outcomes of patients with sepsis- and SIRS-induced HRS-AKI treated with terlipressin, which indicates similarities in pathophysiology between patients with and without infections as triggers [87–89].

Besides cirrhosis, HRS-like AKI may also develop in acute settings, (i.e. acute or acute-on-chronic liver failure or steatohepatitis) due to excess liberation of pro-inflammatory cytokines or chemokines. These acute situations may also induce renal tubular damage due to upregulation of inflammatory mediators, chemokines and cytokines that may directly cause renal damage and further induce circulatory dysfunction and worsening of systemic vasodilatation (Acute tubular necrosis, ATN). As a result, in contrast to HRS-AKI as functional renal failure, ATN may not respond to vasoconstrictor therapy [87].

**Structural changes in HRS-AKI**

There is increasing evidence for structural renal changes at least in a subgroup of patients with end-stage liver diseases. Patients with cirrhosis and impaired renal function were reported to show glomerular, vascular and tubulo-interstitial pathologies even in the absence of proteinuria and hematuria [90,91]. Patients with cirrhosis might suffer from specific renal pathologies associated with liver diseases such as IgA nephropathy in alcoholic cirrhosis or cryoglobulinemia in hepatitis C or other, non-cirrhosis-specific nephropathies (e.g. diabetic nephropathy). These renal pathologies should be screened for and treated adequately.

An important differential diagnosis for HRS-AKI is ATN. Next to pre-renal azotemia including HRS-AKI, ATN is the most common cause of AKI in cirrhosis [9]. ATN is mainly caused by...
ischemic damage to the tubules following a hypotensive event, such as variceal bleeding or sepsis. Clinical presentation of ATN is often very similar to HRS and routine biomarkers are often unable to properly discriminate between these entities, especially in cirrhosis [9,92]. Its prognosis is comparable to that of HRS-AKI [92].

Management of AKI and specific treatment for HRS-AKI

Management of AKI in cirrhosis

The initial management of AKI should focus on early recognition and correction of potential trigger events and on preventing further hemodynamic deterioration [37,44,93]. This includes careful review of all medications including over-the-counter drugs and nephrotropic agents (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) need to be withdrawn. The use of drugs that may induce or aggravate arterial hypotension (e.g. vaso-dilators or non-selective beta-blockers [NSBBs]) should be carefully evaluated [54,96]. In volume-depleted patients, diuretic therapy and/or lactulose should be withdrawn and plasma volume should be expanded with albumin, or blood transfusions in anemic patients due to gastrointestinal blood loss.

Since bacterial infections are the most common precipitant of AKI in cirrhosis, patients should be thoroughly screened for (e.g. by performing diagnostic paracentesis to rule in/out SBP). Early empiric antibiotic treatment should be initiated already on clinical suspicion and be based on local epidemiology and resistance patterns [20,95,96].

In case of therapeutic response, which is defined as a decrease of sCr to a value within 0.3 mg/dL of baseline, patients should be followed closely for early detection of recurrent episodes of AKI. Follow-up assessment of sCr every 2–4 days during hospitalization and every 2–4 weeks during the first 6 months after discharge is advised [11,37].

In case of stage 2 or 3 or progression to a higher AKI stage, patients need to be assessed for the presence of HRS-AKI and diuretics should be withdrawn immediately [37]. In addition, patients should receive plasma volume expansion with albumin for 2 consecutive days (1 g per kg of body weight, maximum 100 g/day) [37]. Albumin is particularly beneficial in patients with SIRS or sepsis, since it has scavenging, anti-oxidant and endothelial-stabilizing functions in addition to its volume-expanding effect [97].

Management of HRS-AKI and HRS type 2

Patients with AKI stages 2 and 3 who meet diagnostic criteria of HRS-AKI should be treated with vasoconstrictors (i.e. terlipressin, norepinephrine or midodrine plus octreotide) in combination with i.v. albumin [37]. Albumin should be administered initially with 1 g/kg body weight up to 100 g on the first day, then ongoing with 20–40 g/day, as it has been shown that the effects of i.v. albumin in the prevention and treatment of HRS are dose-dependent, with better results when higher cumulative doses were administered [98,99]. For prevention of HRS-AKI and HRS type 2, albumin should be administered in all large-volume paracenteses (>5 L, with 8 g/L of ascites removed), since it prevents post-paracentesis circulatory dysfunction, reduces the risk of renal dysfunction and might even improve survival [100,101].

The vasopressin analogue terlipressin is the most intensively studied vasoconstrictor for the treatment of HRS-AKI and therefore commonly used in Europe. A bolus of terlipressin induces a statistically significant reduction in portal pressure over a 3- to 4-hour period and also increases mean arterial pressure [102]. Terlipressin should be used with caution in patients with cardiovascular disease, since it may induce ischemia. Patients should be monitored for hyponatremia, which more commonly occurs in less advanced liver disease and (near-) normal baseline serum sodium levels [103]. A recent study demonstrated fewer adverse events and lower total doses with equal efficacy by administering terlipressin via continuous intravenous infusion [104]. Considering the costs and the pharmacodynamic profile of terlipressin, continuous infusion might be preferred over bolus administration. Although terlipressin has been consistently shown to improve renal function, its impact on survival is less clear [105]. Terlipressin is particularly beneficial in patients with SIRS or sepsis and might also prevent variceal bleeding during the period of discontinuation of NSBBs [106].

Complete response is defined by a decrease in sCr to a value within 0.3 mg/dL of baseline, while a regression of at least one AKI stage is considered as partial response [37]. If there is no response after 3 days of treatment, the vasoconstrictor dose should be increased. In non-responders, treatment should be discontinued after 14 days. In responders, longer treatment durations can be used as a bridging therapy to liver transplantation.

Due to poor prognosis, patients with HRS-AKI or HRS type 2 should be evaluated for liver transplantation as soon as possible. The insertion of a transjugular intrahepatic portosystemic shunt (TIPS) may represent a good bridging strategy to liver transplantation—especially in patients with HRS type 2 [112–115]. The TIPS improves both renal function and survival in patients with severe/refractory ascites most commonly associated with HRS type 2 [112–114]. Absolute contraindications for TIPS comprise cardiac insufficiency, pulmonary hypertension, uncontrolled systemic infections (this underlines the need to screen for SBP prior to TIPS) or sepsis and biliary obstruction, as well as anatomical abnormalities preventing TIPS implantation. Since liver dysfunction may deteriorate after TIPS, serum bilirubin >5 mg/dL and recurring spontaneous hepatic encephalopathy (HE) episodes represent (relative) contraindications against TIPS for treatment of refractory ascites [115,117–120]. Caution should generally be applied in patients with high MELD scores who may not benefit from TIPS implantation [121].

Randomized-controlled trials have failed to demonstrate a survival benefit of renal replacement therapy (RRT) or extracorporeal liver support (ELS) for HRS-AKI and HRS type 2 [122,123]. Continuous RRT use may, however, be advantageous in patients who are hemodynamically unstable or at risk of elevated intracranial pressure [14]. RRT and ELS should thus be restricted to patients who are eligible for liver transplantation. Combined liver and kidney transplantation should be considered in patients on RRT for more than 12 weeks [124].

Outlook and future perspectives

Novel urinary biomarkers are currently being explored for improved AKI diagnosis and will likely help in daily clinical
practice to differentiate between the various forms of renal dysfunction in cirrhosis [44]. The most frequently studied biomarker of renal dysfunction in cirrhosis is urinary neutrophil gelatinase-associated lipocalin (NGAL). uNGAL is a urinary biomarker for tubular damage that facilitates the differentiation between functional and structural causes of renal failure in cirrhosis. Throughout the various studies, NGAL levels correlated with renal damage. As such, NGAL levels were high in patients with ATN and low in patients with pre renal azotemia, with levels in HRS-AKI in the intermediate range, helping to distinguish between the different entities of AKI in patients with cirrhosis [125–129]. Besides uNGAL, other biomarkers such as interleukin 18 (IL-18), kidney injury molecule-1 (Kim-1) and liver-type fatty-acid binding protein were studied in patients with cirrhosis. In summary, all biomarkers for tubular damage were significantly increased in ATN as compared non-ATN AKI to varying degrees [130]. Similarly to uNGAL, IL18 as a mediator of inflammation is expressed in renal tubular cells and macrophages, and released into the urine in case of tubular injury. As a consequence, urinary levels are significantly higher in ATN than in HRS-AKI, where, due to the inherent inflammatory state, levels are still above those measured in pre-renal AKI or in patients without renal failure [131].

At the moment, urinary biomarkers are still mainly tools for research purposes, as their costs are high, biochemical assays have not yet been introduced into standard laboratory testing and applicability in clinical practice is still unclear. Although study results appear promising, it is debatable whether or not the new biomarkers will find their way into routine examinations. Until then, physicians will have to rely on careful assessment of renal failure in order to correctly classify AKI.

Summary

Patients with cirrhosis are prone to developing AKI. The new ICA-AKI criteria provide a simple, but prognostically relevant staging system for AKI in cirrhosis based on relative increases in sCr. Potential triggers of AKI should be recognized and removed; this includes discontinuation of diuretics and nephrotoxic drugs, treatment of infections and gastrointestinal bleeding, and plasma expansion in case of hypovolemia. Vasopressors such as terlipressin and norepinephrine in combination with intravenous albumin represent the first-line therapy for HRS-AKI. While RRT does not improve outcome of patients with HRS-AKI, liver transplantation is considered an effective cure for HRS. Differential diagnosis of HRS-AKI from other forms of AKI, such as ATN, is often difficult. Specific biomarkers such as NGAL, Kim-1 or IL-18 may aid in the correct diagnosis of AKI in cirrhosis but have not yet been introduced into clinical routine.

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References

1. Alessandria C, Ozdogan O, Guevara M et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology 2005;41:1282–9.
2. Nair S, Verma S, Thuluvath P. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35:1179–85.
3. Wiesner R, Edwards E, Freeman R et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–6.
4. Wong F. Recent advances in our understanding of hepatorenal syndrome. Nat Rev Gastroenterol Hepatol 2012;9:382–91.
5. Gerbes AL. Liver cirrhosis and kidney. Dig Dis 2016;34:387–90.
6. Piana S, Rosi S, Maressio G et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013;59:482–9.
7. Follo A, Llovet J, Navasa M et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20:1495–501.
8. Hampel H, Bynum GD, Zamora E, El-Serag HB. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. Am J Gastroenterol 2001;96:2206–10.
9. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48:2064–77.
10. Cárdenas A, Ginés P, Uriz J et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology 2001;34:671–6.
11. Tsien CD, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. Gut 2013;62:131–7.
12. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2011;9:260–5.
13. Fagundes C, Barreto R, Guevara M et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2013;59:474–81.
14. Nadim MK, Kellum JA, Davenport A et al. Hepatorenal syndrome: the 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2012;16:R23.
15. Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. Curr Opin Crit Care 2002;8:509–14.
16. Bern MM. Hepatorenal syndrome: study of clinical characteristics in a large series. South Med J 1973;66:775–8.
17. Ginés A, Escorsell A, Ginés P et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229–36.
18. Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol 2010;52:605–13.
19. Fernández J, Navasa M, Planas R et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24.
20. Schwabl P, Bucsis T, Soucek K et al. Risk factors for development of spontaneous bacterial peritonitis and subsequent mortality in cirrhotic patients with ascites. Liver Int 2015;35:2121–8.
21. Salerno F, Geres B, Giné J, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310–18.
22. Wong F. The evolving concept of acute kidney injury in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2015;12:711–19.
23. Flint A. Clinical report on hydro-peritoneum, based on an analysis of forty-six cases. Am J Med Sci 1863;45:306–39.
64. Randers E, Erlandsen SJ. Serum cystatin C as an endogenous marker of the renal function—a review. Clin Chem Lab Med 1999;37:389–95.
65. Cholongitas E, Shusang V, Marelli L et al. Review article: renal function assessment in cirrhosis—difficulties and alternative measurements. Aliment Pharmacol Ther 2007;26:969–78.
66. Stevens LA, Schmid CH, Greene T et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009;75:652–60.
67. Krones E, Fickert P, Zitta S et al. The chronic kidney disease epidemiology collaboration equation combining creatinine and cystatin C accurately assesses renal function in patients with cirrhosis. BMC Nephrol 2015;16:1–10.
68. Mindikoglu AL, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. J Hepatol 2014;59:1532–42.
69. Arroyo V. Acute kidney injury (AKI) in cirrhosis: should we change current definition and diagnostic criteria of renal failure in cirrhosis? J Hepatol 2015;59:415–17.
70. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilatation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8:1151–7.
71. Schrier RW, Niederberger M, Weigert A, Gines P. Peripheral arterial vasodilatation: determinant of functional spectrum of cirrhosis. Semin Liver Dis 1994;14:14–22.
72. Hu LS, George J, Wang JH. Current concepts on the role of nitric oxide in portal hypertension. World J Gastroenterol 2013;19:1707–17.
73. Gracia-sanchez J, Bosch J. Functional aspects on the pathophysiology of portal hypertension in cirrhosis. J Hepatol 2012;57:458–61.
74. Kajita M, Murata T, Horiguchi K, Iizuka M, Hori M, Ozaki H. iNOS expression in vascular resident macrophages contributes to circulatory dysfunction of splanchnic vascular smooth muscle contractions in portal hypertensive rats. Am J Physiol Heart Circ Physiol 2011;300:1021–31.
75. Meller S, Bendtsen F, Henriksen JH. Splanchnic and systemic hemodynamic derangement in decompensated cirrhosis. Can J Gastroenterol 2001;15:94–106.
76. Meller S, Hobolth L, Winkler C, Bendtsen F, Christensen E. Determinants of the hyperdynamic circulation and central hypovolaemia in cirrhosis. Gut 2011;60:1254–9.
77. Epstein M, Berk DP, Hollenberg NK et al. Renal failure in the patient with cirrhosis: the role of active vasconstriction. Am J Med 1970;49:175–85.
78. Thabut D, Massard J, Gangloff A et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. Hepatology 2007;46:1872–82.
79. Bernardi M, Moreau R, Angeli P, Schnabl B. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilatation to systemic inflammation hypothesis. J Hepatol 2015;63:1272–84.
80. Prowle JR, Bellomo R. Sepsis-associated acute kidney injury: macrohemodynamic and microhemodynamic alterations in the renal circulation. Semin Nephrol 2015;35:64–74.
81. Shah N, Mohamed FE, Jover-cobos M, Macnaughtan J, Davies N. Increased renal expression and urinary excretion of TLR4 in acute kidney injury associated with cirrhosis. Liver Int 2013;33:398–409.
82. Shah N, Dhar D, El F et al. Prevention of acute kidney injury in a rodent model of cirrhosis following selective gut decontamination is associated with reduced renal TLR4 expression. J Hepatol 2012;56:1047–53.
83. Wang JB, Wang HT, Li LP et al. Development of a rat model of D-galactosamine/lipopolysaccharide induced hepatorenal syndrome. World J Gastroenterol 2015;21:9927–35.
84. Steib CJ, Hartmann AC, v Hesler C et al. Intraportal LPS amplifies portal hypertension in rat liver fibrosis. Lab Invest 2010;90:1024–32.
85. Reiberger T, Feletitsch A, Payer BA et al. Non-selective beta-blocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. J Hepatol 2013;58:911–21.
86. Gustot T, Durand F, Lebrec D, Vincent J-L, Moreau R. Severe sepsis in cirrhosis. Hepatology 2009;50:2022–33.
87. Francoz C, Durand F. Editorial Type-1 hepatorenal syndrome in patients with cirrhosis and infection vs. sepsis-induced acute kidney injury: what matters? J Hepatol 2014;60:907–9.
88. Rodriguez E, Elia C, Solà E et al. Terlipressin and albumin for type-1 hepatorenal syndrome associated with sepsis. J Hepatol 2014;60:955–61.
89. Wang F, Pappas SC, Boyer TD et al. Terlipressin improves renal function and reverses hepatorenal syndrome in patients with systemic inflammatory response syndrome. Clin Gastroenterol Hepatol 2017;15:266–272.e1.
90. Eyriër ALM, Al DRM, Allard PAC, Uettler CAG, Tordeur DI. Transjugular renal biopsy in the treatment of patients with cirrhosis and renal abnormalities. Hepatology 1996;24:1–5.
91. Trawalé J, Paradis V, Rautou PE et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Int 2010;30:725–32.
92. Allegretti AS, Ortiz G, Wenger J et al. Prognosis of acute kidney injury and hepatorenal syndrome in patients with cirrhosis: a prospective cohort study. Int J Nephrol 2015;2015:1–9.
93. Wong F. Diagnosing and treating renal disease in cirrhotic patients. Minerva Gastroenterol Dietol 2016;62:253–66.
94. Mandorfer M, Reiberger T. Beta blockers and cirrhosis, 2016. Dig Liver Dis 2017;49:3–10.
95. Arabi YM, Dara SI, Memish Z et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology 2012;56:2305–15.
96. Jalan R, Fernandez J, Wiest R et al. The chronic kidney disease epidemiology collaboration creatinine-cystatin C equation combining creatinine and cystatin C for estimating kidney function in cirrhosis. J Hepatol 2014;60:1250–9.
97. Bernardi M, Ricci CS, Zacerchini G. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol 2014;4:302–11.
98. Afnogenova Y, Tapper EB. The efficacy and safety profile of albumin administration for patients with cirrhosis at high risk of hepatorenal syndrome is dose dependent. Gastroenterol Rep (Oxf) 2015;3:216–21.
99. Salerno F. Albumin treatment regimens for type 1 hepatorenal syndrome: a dose–response meta-analysis. BMC Gastroenterol 2015;15:1–11.
100. Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusions in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012;55:1172–81.
101. Ginés P, Tilò L, Arroyo V et al. Randomized comparative study of therapeutic paracentesis with and without
intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493–502.

102. Escorsell A, Bandi JC, Moitinho E et al. Time profile of the haemodynamic effects of terlipressin in portal hypertension. J Hepatol 1997;26:621–7.

103. Solà E, Lens S, Guevara M et al. Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. Hepatology 2010;52:1783–90.

104. Cavallin M, Piano S, Romano A et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology 2016;63:983–92.

105. Boyer TD, Sanyal AJ, Wong F et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. Gastroenterology 2016;150:1579–89.

106. Choudhury A, Kedarisetty CK, Vashishtha C et al. (16 September 2016) A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock 2016;1–10.

107. Mattos AZ De, Mattos AA De, Ribeiro RA. Terlipressin versus albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology 2008;134:1352–9.

108. Alessandria C, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. Eur J Gastroenterol Hepatol 2002;14:1363–8.

109. Piano S, Tonon M, Cavallin M et al. Reply to: ‘A cut-off serum creatinine value of 1.5 mg/dl for AKI—to be or not to be’. J Hepatol 2015;62:744–6.

110. Rodriguez E, Pereira GH, Solà E et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: effects on kidney function and transplantation outcomes. Liver Transplant 2015;21:1347–54.

111. Guevara M, Ginès P, Bandi JC et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 1998;28:416–22.

112. Breuhaus KA, Textor J, Perez J et al. Long term outcome after transjugular intrahepatic portosystemic shunt-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000;47:288–95.

113. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004;40:55–64.

114. Salerno F, Cammá C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology 2007;133:825–34.

115. Bureau C, Thabut D, Oberti F et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. Gastroenterology 2016;152:157–63.

116. Rössle M, Gerbes AL. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. Gut 2010;59:988–1000.