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Review

REVIEW

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

The pivotal prognostic role of renal function in cirrhosis is reflected by the inclusion of serum creatinine (sCr) in the Model for End Stage Liver Disease (MELD) Score, which is currently used for assessment of severity of liver disease and prioritization of patients with advanced liver disease for liver transplantation [1–3]. As a consequence of systemic and splanchnic arterial vasodilatation and consecutive reduction in effective circulating blood volume, renal perfusion may be critically impaired in patients with advanced cirrhosis and portal hypertension [4]. As a result, patients with cirrhosis are prone to developing renal dysfunction.

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].

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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, Furtwängler 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 $\geq$ 50% from baseline to a final value $\geq$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 $\geq$ 0.3 mg/dL within 48 hours or by $\geq$ 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 $\geq$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 $\geq$ 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

Table 1. Past and current diagnostic criteria for hepatorenal syndrome (HRS)

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 Urine/plasma osmolality >1.0 Urine/plasma creatinine >30 Urine sodium <10 mEq/L, often <5 mEq/L No sustained improvement after plasma expansion to a central venous pressure of 10 cm H_2O	Volume <800 mL/day; ± urinary protein excretion Onset of disease spontaneously over course of liver disease or Onset in association with infections, bleeding, paracentesis, diuretic therapy or other forms of volume loss Characteristics may be followed by tubular dysfunction 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 acute liver disease with hepatic failure and portal hypertension Low GFR (sCr >1.5 mg/dL or 24-hour creatinine clearance <40 mL/min) Absence of shock, bacterial infection, recent treatment with nephrotoxic drugs, absence of gastrointestinal or renal fluid loss No sustained improvement in renal function following withdrawal of diuretics and plasma expansion with 1.5 L of isotonic saline 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 **Type II HRS:** Slower course (>2 weeks)	Urine volume <500 mL/d Urine sodium <10 mEq/L Urine osmolality greater than plasma osmolality Serum sodium concentration <130 mEq/L
2007	Salerno *et al.* [21]	Diagnosis, Prevention and Treatment of Hepatorenal Syndrome in Cirrhosis	Cirrhosis with ascites Serum creatinine >1.5 mg/dL No improvement of serum creatinine (decrease to < 1.5 mg/dL) after at least 2 days of diuretic withdrawal and volume expansion with albumin Absence of shock No current or recent treatment with nephrotoxic drugs Absence of parenchymal kidney damage (proteinuria >500 mg/d, >50 RBCs/high-power field) or abnormal renal ultrasonography	Ongoing bacterial infections are not an exclusion criterion for the diagnosis of HRS Type I HRS typically occurs in acute deterioration of circulatory function, characterized by arterial hypotension and activation of endogenous vasoconstrictor systems Type II HRS is typically associated with refractory ascites Other minor diagnostic criteria have been removed
2009	Runyon [132]	AASLD Practice Guidelines Management of Adult Patients with Ascites Due to Cirrhosis: An Update		
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 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	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. Glomerular tubular reflux is a histologic lesion associated with hepatorenal syndrome; however, renal biopsy must be weighed carefully against the benefits

(continued)

Table 1. Continued

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 a eGFR <60 mL/min/1.73 m^2 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
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 1	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 of 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.

Pitfalls in the diagnosis of AKI and HRS

Although sCr is an easily measurable and widely available marker of excretory renal function, it has limitations in assessing glomerular filtration rate (GFR) in patients with cirrhosis. Creatinine is non-enzymatically converted from creatinine, which is produced by the liver and stored in muscle cells, and eliminated via glomerular filtration [60]. Due to impairment in liver function, muscle wasting, decreased creatinine synthesis and increased tubular secretion of creatinine at advanced stages of cirrhosis, baseline creatinine production is lower in patients with cirrhosis compared to the non-cirrhotic population, thus sCr-based equations (i.e. Modification of Diet in Renal Disease, MDRD; Chronic Kidney Disease Epidemiology Collaboration formula, CKD-EPI) tend to overestimate GFR in cirrhosis [18,60–62].

Nonetheless, due to its wide applicability, the MDRD-6 formula has been recommended to estimate GFR in patients with cirrhosis until better alternatives become available in clinical routines [14].

GFR estimates using CysC, a non-glycosylated low-molecular-weight protein of the cystatin superfamiliy of cysteine protease inhibitors, have been proposed to be superior predictors of renal function than sCr-based equations. Unlike sCr, CysC is not influenced by age, muscle mass, the presence of high bilirubin or malignancy [63–65]. Measurement of CysC has, however, been reported to be influenced by factors such as low serum albumin levels, elevated white blood cell count and elevated C-reactive protein levels. These abnormalities are frequently present and are thus likely to impair the reliability of cystatin C-based equations in cirrhosis [66]. Several studies have shown that equations combining sCr and CysC predict glomerular filtration more accurately than those using sCr or CysC alone (i.e. the CKD-EPI equation combining sCr and CysC) [67,68].

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

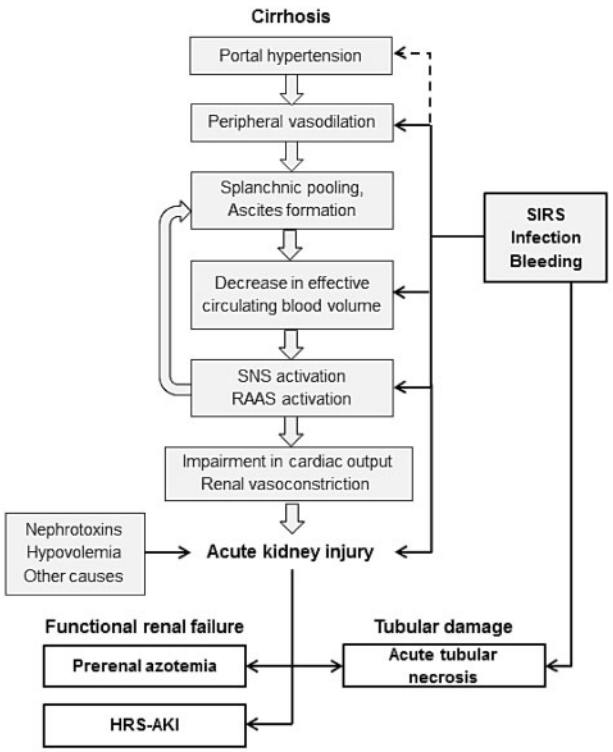

Figure 1. Pathophysiology of acute kidney injury (AKI) and hepatorenal syndrome (HRS) in decompensated cirrhosis. Broad arrows: vasodilation theory of ascites formation. Black arrows: 'inflammation theory' and further aspects of AKI development. Dashed line: impact of infections (i.e. spontaneous bacterial peritonitis) on portal hypertension. SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; SIRS, systemic inflammatory response syndrome; HRS-AKI, hepatorenal syndrome type of acute kidney injury

HRS certainly does not reflect the whole spectrum of renal dysfunction in cirrhosis, but rather refers to a specific form with a unique pathophysiology [22,52,69].

HRS-AKI—the 'classical vasodilation theory'

The development of HRS-AKI is supposedly caused by intrarenal vasoconstriction due to circulatory dysfunction in decompensated cirrhosis. Indeed, the pathophysiology of HRS is closely linked to the development of ascites, which is considered a prerequisite for the development of HRS [35,50,51]. In 1988, Schrier and colleagues proposed the *peripheral arterial vasodilation hypothesis* for ascites [70,71]. According to this hypothesis, due to structural changes in the fibrotic tissue, intrahepatic vascular resistance is increased, causing portal hypertension and an overexpression of compensatory vasodilating factors [72]. The vasodilating factors accumulate in the splanchnic area and, in later stages, in the systemic circulation [73,74]. This causes a pooling effect in the splanchnic vessels, leading to increased shear-wall stress and transudation of plasma into the abdominal cavity: ascites [75]. As a consequence, effective circulating blood volume and mean arterial pressure are decreased. This activates the sympathetic nervous system, initiating a hyperdynamic circulation, but also stimulating the renin-angiotensin-aldosterone system (RAAS) [76]. Excessive RAAS activation promotes water and sodium retention, thereby aggravating ascites formation via aldosterone and high levels of angiotensin II induce renal vasoconstriction. [77]. 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 nephrotoxic 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. vasodilators or non-selective beta-blockers [NSBBs]) should be carefully evaluated [54,94]. 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].

Norepinephrine (initial dose: 0.5 mg/hour; max. dose studied in randomized controlled trials: 3 mg/hour) is an equally effective and inexpensive alternative to terlipressin. A recent meta-analysis of four randomized–controlled trials (although at substantial risk of bias) demonstrated similar efficacy in terms of HRS reversal, when compared to terlipressin [107]. The suggested therapy for type 2 HRS is similar [108–110]; however, HRS type 2 commonly recurs after cessation of vasoconstrictor treatment [111].

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 prerenal 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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