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Review paper

Hepatorenal syndrome type 2: a frequently missed diagnosis

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Abstract

The change in the view of hepatorenal syndrome (HRS) pathogenesis and implementation of the acute kidney injury (AKI) classification when evaluating renal damage in patients with liver cirrhosis led to a change in HRS classification. In the recently revised International Club of Ascites (ICA) classification, type 2 HRS includes "renal impairment which fulfills the criteria of HRS but not of AKI, namely non-AKI-HRS (NAKI) and only HRS-CKD as previously proposed". The theory of peripheral vasodilatation, which was historically accepted as the key factor in the HRS pathogenesis, was replaced by the theory of a systemic inflammatory response. The inflammation is the result of the bacterial translocation. The following production of the inflammatory cytokines leads to splanchnic vasodilatation and circulatory dysfunction. The cirrhotic cardiomyopathy plays an important role in the pathogenesis too. HRS-NAKI typically develops in patients with refractory ascites. The treatment of the refractory ascites and HRS-NAKI is identical. It involves large-volume paracentesis with administration of albumin, transjugular intrahepatic portosystemic shunt insertion and liver transplantation. There are only currently limited data for the use of automated low-flow ascites pumps. The renal condition in patients with HRS-NAKI improves after administration of splanchnic vasoconstrictors, but with a 50% relapse rate after treatment completion; therefore this treatment is not recommended. The prognosis of patients with HRS-NAKI is much better than that of patients with HRS-AKI.

Key words: hepatorenal syndrome, non-acute kidney injury, splanchnic vasodilation, refractory ascites, large-volume paracentesis, transjugular intrahepatic portosystemic shunts.

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Introduction

Renal complications are common in patients with decompensated cirrhosis and they can have a negative impact on survival. Hepatorenal syndrome is just one form of the spectrum of renal complications that occur in patients with advanced liver disease. It is characterized by over-activity of the endogenous vasoactive systems that leads to renal vasoconstriction resulting in impaired renal function [1]. The change in the view of the hepatorenal syndrome (HRS) pathogenesis and the implementation of acute kidney injury (AKI) classification when evaluating renal damage in patients with liver cirrhosis led to a change in HRS classification. Whereas type 1 HRS, currently designated as HRS-AKI, has a clear definition and a lot of literature is concerned with it, type 2 HRS (named HRS-NAKI or HRS-CKD) is a diagnosis of exclusion, and this topic is rarely mentioned in the literature.

Classification

The diagnostic criteria of renal failure in these patients developed since 1996 and were refined in subsequent years. Traditionally, they were based on the absolute serum creatinine level and HRS in them was defined as a solely functional renal complication in patients with cirrhosis and ascites. The main change in

HRS classification was introduced by the application of AKI diagnostic criteria to patients with liver cirrhosis. AKI as a dynamic staging system based on the change of serum creatinine level from the baseline to the final value proved to be a strong predictor of hospital mortality in patients with liver cirrhosis.

The main aim of the new classification is:

- to identify patients with cirrhosis who are at risk of renal damage and to start with the treatment at lower serum creatinine values earlier than when the classical definition was used,
- to broaden the scope of the classification of renal dysfunction in cirrhosis to include cases of acute and chronic renal failure not meeting the diagnostic criteria of hepatorenal syndrome types 1 and 2.

AKI diagnostic criteria in patients with cirrhosis accepted by the International Club of Ascites (ICA) are given in Table 1. They meant that it was necessary to update the HRS diagnostic criteria and the criteria for its individual subtypes, which are given in Tables 2 and 3. In the recently revised ICA classification, type 1 HRS includes renal impairment which fulfills the criteria of HRS and of AKI. Type 2 HRS includes renal impairment which cannot be classified as an AKI (nonAKI) but fulfills the criteria of HR, namely non-AKI-HRS (NAKI) and only HRS-CKD as previously proposed [2, 3].

The renal failure HRS-NAKI does not have such a rapid progressive course as in HRS-AKI. There is chronic impairment of kidney function; these patients therefore fall into the category of chronic kidney disease (CKD) because of a chronic reduction of GFR [1, 6]. Therefore, it is often referred to by some authors as HRS-CKD. However, the new terminology brings about some confusion, because CKD is normally irreversible and HRS is potentially reversible. There is only limited information on HRS-NAKI incidence and prevalence. It is estimated that approximately 25% of all HRS cases are HRS-NAKI type [7]. HRS-NAKI has a better prognosis than HRS-AKI.

Unlike HRS-AKI, where infection, especially spontaneous bacterial peritonitis (SBP), is the main trigger factor, HRS-NAKI usually arises spontaneously as a result of refractory ascites. Refractory ascites occurs in 5-10% of patients with cirrhosis and ascites [8, 9]. It is defined as ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy [3]. It consists of two clinical subtypes: diuretic-resistant ascites (ascites with a poor response to dietary sodium restriction and diuretic treatment) and diuretic-intractable ascites (ascites in patients who do not tolerate the required dosage of diuretics to mobilize or prevent the recurrence of the ascites because of the development of diuretic-induced complications) [8, 9].

Pathogenesis

Renal vasoconstriction is the main factor in the development of HRS [10]. For a long period of time HRS pathogenesis was explained by the peripheral arterial vasodilation theory. Progressive splanchnic vasodilation mediated principally by nitric oxide, which occurs as a consequence of portal hypertension, played the

Table 1. International Club of Ascites – Acute Kidney Injury (ICA-AKI) criteria (altered according to [3, 4])

Subject	Definition
Baseline sCr	• sCr obtained within 3 months prior to admission • If > 1 value within the 3 previous months, the value closest to the admission • If no previous sCr, the sCr at admission should be used as baseline
Definition of AKI	• Increase in sCr ⩾ 0.3 mg/dl (⩾ 26.5 µmol/l) within 48 h; or, • a percentage increase sCr ⩾ 50% which is known, or presumed, to have occurred within the prior seven days
Staging of AKI	• Stage 1: increase in sCr ⩾ 0.3 mg/dl (⩾ 26.5 µmol/l) or an increase in sCr ⩾ 1.5-fold to 2-fold from baseline • Stage 2: increase in sCr > 2-fold to 3-fold from baseline • Stage 3: increase of sCr > 3-fold from baseline or sCr ⩾ 4.0 mg/dl (353.6 µmol/l) with an acute increase ⩾ 0.3 mg/dl (⩾ 26.5 µmol/l) or initiation of renal replacement therapy
Progression of AKI	**Progression** Progression of AKI to a higher stage and/or need for RRT **Regression** Regression of AKI to a lower stage
Response to treatment	**No response** No regression of AKI **Partial response** Regression of AKI stage with a reduction of sCr to ⩾ 0.3 mg/dl (⩾ 26.5 µmol/l) above the baseline value **Full response** Return of sCr to a value within 0.3 mg/dl (⩾ 26.5 µmol/l) of the baseline value

Table 2. New diagnostic criteria of hepatorenal syndrome (altered according to [1, 3-5])

Classical criteria of HRS	New diagnostic criteria of HRS-AKI
Cirrhosis with ascites	Cirrhosis with ascites
Serum creatinine > 1.5 mg/dl (> 133 mmol/l)	Diagnosis of acute kidney injury according to International Club of Ascites – Acute Kidney Injury (ICA-AKI) criteria
No improvement of serum creatinine (decrease to a level of ⩽ 1.5 mg/dl) after at least 2 days with diuretic withdrawal and volume expansion with albumin	No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin
Absence of shock	Absence of shock
No current or recent treatment with nephrotoxic drugs	No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides or iodinated contrast media)
Absence of parenchymal kidney disease. Parenchymal kidney disease is indicated by: proteinuria (> 500 mg/day), microhematuria (> 50 red blood cells per high-power field) and/or abnormal renal ultrasonography	No signs of structural kidney injury. Structural kidney injury is indicated by: proteinuria (> 500 mg/day), microhematuria (> 50 red blood cells per high-power field) and/or abnormal renal ultrasonography

Table 3. Clinical types of hepatorenal syndrome (altered according to [1, 3])

	Classical definition	New definition
Acute	**Type 1 HRS** Increase 100% SCr value SCr > 2.5 mg/dl	**AKI-HRS** Meet ICA-AKI criteria Meet HRS criteria
Chronic	**Type 2 HRS** Increase SCr 1.5-2.5 mg/dl	**CKD-HRS/NAKI-HRS** No ICA-AKI criteria Meet HRS criteria

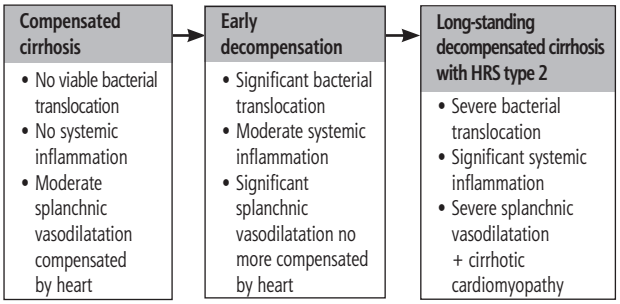

Fig. 1. Hepatorenal syndrome not acute kidney injury (HRS-NAKI) pathogenesis (altered according to [12])

key role in it. According to the theory the pathogenetic mechanism is as follows (Fig. 1):

1. Splanchnic vasodilation reduces effective arterial blood volume, which leads to compensatory increased cardiac output. This compensatory mechanism temporarily maintains the effective arterial blood volume and induces circulatory stability in a patient with compensated cirrhosis.
2. However, the myocardium cannot compensate continuing splanchnic vasodilation, which leads to activation of neurohormonal vasoconstrictor systems such as the renin-angiotensin-aldosterone system (RAAS), arginine vasopressin and the sympathetic nervous system (SNS), with consequent sodium and water retention and development of ascites.
3. Finally, when splanchnic arterial vasodilation is extreme, intense intrarenal vasoconstriction develops. Local renal vasodilators such as prostaglandins are able to compensate the effects of the vasoconstrictors for the time being. Nevertheless, the final result of this process is a large decrease in renal blood flow leading to a reduced glomerular filtration rate (GFR) and the development of HRS-NAKI [11].

The peripheral arterial vasodilation theory claims that splanchnic arterial vasodilation and activation of vasoconstrictors progressively increase and are the only cause of circulatory dysfunction. The examination of the concentration of circulatory dysfunction markers such as plasma renin activity (PRA) and plasma aldosterone and norepinephrine at different stages of decompensated cirrhosis has questioned the peripheral arterial vasodilation theory and showed that circulatory dysfunction is not progressive. The levels of circulatory dysfunction markers change as follows:

1. Early ascites with moderate sodium retention is associated with normal circulatory dysfunction marker levels.
2. The circulatory dysfunction markers significantly increased from early ascites to long-standing ascites.
3. However, these markers did not increase with the HRS-NAKI development any more [12].

It means that the circulatory dysfunction develops rapidly from the early to the refractory ascites, but HRS-NAKI occurs without further worsening of circulatory dysfunction. On the basis of this we can predict that splanchnic arterial vasodilation is not the only factor, but several agents play a role in the development of HRS-NAKI in patients with cirrhosis. One of them is cirrhotic cardiomyopathy characterized by impaired chronotropic and inotropic heart function.

The peripheral arterial vasodilation theory was replaced by the theory of a systemic inflammatory response. The inflammation is able to trigger pathophysiologi-

cal pathways in a complex manner. It is the result of the bacterial translocation. The intestinal immune system is a killer for viable bacteria, from which bacterial byproducts known as pathogen-associated molecular patterns (PAMPs) are released [12, 13]. One of the most important of them is lipopolysaccharide. PAMPs interact with the receptors in gut-associated lymphoid tissue and mesenteric lymph nodes. These receptors (e.g. Toll-like receptor 4, TLR4, Toll-like receptor 9, TLR9) named as pattern recognition receptors (PRRs) are located on the cell surface and in the endolysosome and cytosol [14]. The subsequent production of proinflammatory cytokines (e.g. IL6, TNFα) leads to sterile inflammation. The splanchnic arterioles and the heart are the main objects for the proinflammatory cytokines and PAMPs [12]. The result is splanchnic vasodilation and cirrhotic cardiomyopathy. Both of them are the cause of HRS-NAKI.

The second cause of sterile inflammation is damage-associated molecular patterns (DAMPs). They are released from damaged hepatocytes and recognized by pattern recognition receptors too. Different PAMPs and DAMPs interact with specific pattern recognition receptors and promote the specific signaling and transcription process.

Bacterial translocation in patients with liver cirrhosis is a result of the increased gut permeability and of the changes in the gut microbiome. The gut microbiome is altered in cirrhosis in two ways: quantitative (overgrowth) or qualitative (dysbiosis). Progressive changes in the gut microbiome accompany cirrhosis and become more severe in the setting of decompensation [15].

Cirrhotic cardiomyopathy is a term that describes chronic cardiac dysfunction in cirrhotic patients without previously known heart disease, irrespective of the etiology of cirrhosis. It is characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities [16, 17]. The spectrum of cardiovascular abnormalities in cirrhotic cardiomyopathy includes a hyperdynamic circulatory state, altered diastolic relaxation, impaired contractility and electrophysiological abnormalities, particularity QT interval prolongation [18]. Impaired function of beta-receptors, altered sodium and calcium transport in myocardium and overproduction of cardiodepressant factors, such as nitric oxide, cytokines and endogenous cannabinoids, play the main role in the pathogenesis.

Based on these data we can predict the following:

1. In compensated cirrhosis, there would be no viable bacterial translocation, splanchnic inflammation or sustained splanchnic arterial vasodilation.
2. Early decompensation is characterized by significant bacterial translocation, moderate systemic inflammation and significant arterial vasodilation. The result is significant effective hypovolemia and organ dysfunction.
3. In long-standing decompensated cirrhosis, with refractory ascites and HRS-NAKI, bacterial translocation is severe, splanchnic vasodilation and systemic inflammation is significant, and organ failure fully develops [12].

Treatment

Splanchnic vasoconstrictors

Splanchnic vasoconstrictors administered with albumin at the dose of 20-40 g/day are the gold standard for patients with HRS-AKI because of their good impact on the survival of these patients [19-22]. The aim of the treatment is reverse splanchnic vasodilation and increase of the renal blood flow. Splanchnic vasoconstrictors are divided into the following groups:

- vasopressin analogs (terlipressin and ornipressin),
- somatostatin analogs (octreotide),
- alpha-1 adrenergic receptor agonists (midodrine and norepinephrine).

The most commonly used is terlipressin.

There are only limited data for the treatment of HRS-NAKI with splanchnic vasoconstrictors.

Alessandria *et al.* [23] treated 16 patients with terlipressin 1 mg/4 h intravenously for 7 days; 11 of them had HRS type 2, and the remaining 5 suffered from organic renal disease. The treatment was effective in patients with HRS type 2, but not in patients with organic renal impairment (8/11 patients [73%] vs. 1/5 [20%]; $p < 0.05$).

Ghosh *et al.* [24] used terlipressin and noradrenalin with albumin for the treatment of 46 patients with HRS type 2 and they found that noradrenalin and terlipressin were effective and safe. A therapeutic response was achieved in 17/23 (73.9%) patients in the group treated with terlipressin as well as in the group treated with noradrenalin ($p = 1.0$).

Even further studies [25-27] evaluated the effect of vasoconstrictors with or without albumin in patients with HRS type 2; however, the number of HRS type 2 patients in them was very low. All given studies assessed only the short-term effect of the treatment. No information exists on the long-term efficacy and safety of terlipressin therapy in type 2 HRS [28].

Rodriguez *et al.* [29] dealt with the effect of the treatment with terlipressin plus albumin in patients with HRS type 2 on the waiting list for liver transplantation. 56 patients were included; 31 of them were treated with terlipressin and albumin. Pretransplanta-

tion and posttransplantation outcomes were assessed. 61% of patients responded to the therapy, but 58% of responders relapsed after the treatment withdrawal at a mean of 19-28 days. No differences in mortality on the waiting list were observed between responders and nonresponders. 46 patients underwent liver transplantation. Also, no significant differences in the risk of acute kidney injury, need for renal replacement therapy, frequency of chronic kidney disease 1 year after transplant, length of hospitalization, or survival were observed. The study of Rodriguez *et al*. has two main contributions: it points to a high probability of HRS type 2 relapse after treatment withdrawal and also to an uncertain benefit of the treatment in patients waiting for liver transplantation. HRS type 2 relapse has also been mentioned in a several other studies [24, 30], and it seems that it occurs more frequently than in patients with HRS-AKI.

Because of limited and controversial data about the impact of vasoconstrictors and albumin on outcomes, especially in candidates for liver transplantation, this therapy is not recommended in HRS-NAKI [3].

Large-volume paracentesis

Refractory ascites dominates the clinical picture of HRS-NAKI; therefore the treatment of HRS-NAKI is mainly aimed at the treatment of refractory ascites. The first line treatment for refractory ascites is repeated large-volume paracentesis (LVP) plus albumin (8 g/l of ascites removed) [3]. LVP brings about the risk of postparacentesis circulatory dysfunction. Albumin infusion reduces the incidence of postparacentesis circulatory dysfunction among patients with refractory ascites not only compared with no treatment, but also compared with other treatment options such as vasoconstrictors and colloids. A meta-analysis [31] that included randomized trials evaluating albumin infusion in patients with refractory ascites confirmed it. Compared with colloids and vasoconstrictors, albumin reduced the incidence of postparacentesis circulatory dysfunction (odds ratio [OR] = 0.39; 95% confidence interval [CI]: 0.27-0.55). Mortality was lower in patients receiving albumin compared to alternative treatments (OR = 0.64; 95% CI: 0.41-0.98).

It is obvious that albumin is a substance with pleiotropic effects. It has an anti-inflammatory impact, because of its high capacity to bind and inactivate pro-inflammatory substances and restart molecular abnormalities in cirrhotic cardiomyopathy [32].

LVP with albumin improves renal function, probably by improving renal blood flow [33]. The main disadvantage is that LVP does not correct the mechanisms causing ascites and has to be repeated.

Transjugular intrahepatic portosystemic shunt

Insufficient possibilities of HRS-NAKI treatment make transjugular intrahepatic portosystemic shunt (TIPS) an interesting alternative. The idea of using TIPS in patients with refractory ascites with or without HRS-NAKI has been known for decades. The rationale for TIPS in patients with HRS-NAKI is as follows:

- TIPS decreases portal hypertension,
- TIPS leads to the refilling of the central venous system,
- improved refilling of the central venous system reduces vasoconstrictors and improves renal blood flow.

In the past the effect of TIPS in patients with HRS was evaluated in several studies [34-36]. Their main drawback was a small number of patients, short-term follow-up and uncertain definition of HRS and its subtypes.

Testino *et al*. [37] assessed the effect of TIPS in 18 patients with HRS type 2. Renal parameters improved after TIPS in all patients with HRS type 2 within 12 weeks after TIPS insertion; total disappearance of ascites was obtained in 8 patients.

Brensing *et al*. [38] focused on non-transplantable cirrhotics with HRS. 21 patients had HRS type 1, 20 patients had HRS type 2, TIPS was received in 14 patients with HRS type 1 and 17 patients with HRS type 2. Renal function improved within two weeks after TIPS in 77% of patients. Following TIPS, 3, 6, 12, and 18 month survival rates were 81%, 71%, 48%, and 35%. Type 2 HRS patients had a better chance of survival compared to type 1 patients (log rank 5.04; $p = 0.025$). In multivariate analysis HRS type was an independent survival predictor ($p < 0.05$). The study has four key benefits:

- it delivers long-term data;
- it calls our attention to the need of selection of patients suitable for TIPS regarding the degree of liver dysfunction and of appropriate timing of TIPS insertion. Patients with Child-Pugh scores > 12, bilirubin levels > 15 mg/dl, or those with severe spontaneous encephalopathy were excluded;
- it points to a better effect of TIPS in HRS type 2 patients compared to HRS type 1 patients;
- it focuses on the group of non-transplantable patients, which often occurs v daily practice. These patients are contraindicated for transplantation for various reasons, e.g. malnutrition, or alcohol abuse, but they require intensive management.

Gines *et al.* [39] compared TIPS and repeated paracentesis plus albumin in 70 patients with refractory ascites. The probability of survival without liver transplantation was 41% at 1 year and 26% at 2 years in the TIPS group, as compared with 35% and 30% in the paracentesis group ($p = 0.51$), TIPS does not improve survival in patients with refractory ascites. However, recurrence of ascites and development of hepatorenal syndrome were lower in the TIPS group compared to the paracentesis group. TIPS reduced the risk of progression to HRS type 1. On the other hand, the frequency of severe encephalopathy was higher in the TIPS group.

Skladaný *et al.* [40] published a retrospective analysis of patients indicated with TIPS between 2001-2013. In total, 128 patients were indicated; TIPS was installed in 118 of them. In 22% of patients refractory ascites and HRS was the reason for the insertion. Refractory ascites was kept under control in 13 patients (62%). The main complication was encephalopathy.

Based on these data TIPS could be recommended in selected patients with HRS-NAKI [3]. TIPS in these patients improves renal parameters and improves keeping ascites under control. Further studies are necessary to evaluate the impact of TIPS on the survival of HRS-NAKI patients. It seems that the patients in whom LVP plus albumin fails and who, on the other hand, have sufficient hepatic capacity and have no other contraindications for TIPS insertion can benefit from the treatment. It is suitable to use small-diameter polytetrafluoroethylene-covered stents in order to prevent encephalopathy development.

The automated low-flow ascites pump

The automated low-flow ascites pump system makes transfer of ascites from the peritoneal cavity to the bladder possible. They are a subcutaneously implanted. Ascites is eliminated from the bladder with urine. The pumping cycle is controlled by pressure in the bladder and in the peritoneal cavity. It is started if the bladder pressure is below a certain threshold and finished if the pressure in the peritoneal cavity drops. Bellot *et al.* [41] evaluated the safety and efficacy of an automated pump system for treatment of refractory ascites in a multicenter, non-randomized trial. 40 patients were included, and the follow-up was 6 months. The pump system removed 90% of the ascites and significantly reduced the median number of large volume paracenteses per month [3.4 (range 1-6) vs. 0.2 (range 0-4); $p < 0.01$].

Stirnimann *et al.* [42] focused on patients with refractory ascites and who are contraindicated for TIPS. 46 patients were included, and the follow-up was 24 months. Median frequency of paracentesis dropped from 2.17 to 0.17 per month, but 17 patients needed pump system explantation due to severe adverse events. A recent randomized controlled trial [43] compared the automated low-flow ascites pump with VLP to standard care in patients with refractory ascites and brought similar results as in previous cases with regard to the reduction of the need for paracentesis.

However, the increase in creatinine, until the level of AKI in some of the patients, was observed in all three studies, mainly in the first week after pump installation. This evidence was confirmed by a prospective study [44], whose aim was to investigate the effects of the treatment with the automated low-flow ascites pump on renal function in patients with refractory ascites. The changes in glomerular filtration rate (GFR), the changes in activity of vasoconstrictor systems and the changes in circulatory function stemming from them were the primary outcomes. GFR decreased significantly from 67 ml/minute/1.73 m^2 (4190 ml/minute/1.73 m^2) at baseline to 45 ml/minute/1.73 m^2 (3674 ml/minute/1.73 m^2) at month 6 ($p = 0.04$). There was a marked increase in plasma vasoconstrictor concentration (median percent increase with respect to baseline +191% and 59%, respectively). The most frequent complication in patients was AKI.

Treatment with the automated low-flow ascites pump is associated with impairment of renal function. Therefore, the automated low-flow ascites pump system is not the optimum treatment for patients with HRS-NAKI. It is possible that the administration of albumin will prevent circulatory dysfunction after pump installation. However, further studies are necessary.

Vaptans

Vaptans are arginine vasopressin receptor antagonists. They work as antagonists of the V2 receptors of vasopressin which regulate the reabsorption of free water. Vaptans inhibit V2 receptors and in this way increase free water excretion.

Two studies assessed the effect of tolvaptan on refractory ascites in patients with liver cirrhosis. In a multicenter, randomized, double-blind, placebo-controlled trial [45], add-on therapy with tolvaptan 7.5 mg/day led to a significant change in bodyweight compared to placebo. Japanese authors [46] showed retrospectively that tolvaptan in addition to sodium restriction (> 7 g/d), albumin infusion (10-20 g/wk), and standard diuretic therapy leads to keeping ascites under control in 63.38% of patients, but it does not improve the survival compared to standard care including LVP.

Wong *et al*. [47] evaluated the effect of satavaptan (three doses: 5, 12.5, and 25 mg/day) in cirrhotic patients with ascites treated with LVP and diuretics. The main outcome was to evaluate the interval between two paracenteses; however, this outcome was not achieved.

Vaptans have only a minor effect in keeping ascites under control. They are more effective in the correction of hyponatremia. The limitation of their use is adverse events such as orthostatic hypotension.

Renal replacement therapy

Renal replacement therapy is not indicated in the management of patients with HRS-NAKI [48].

Liver transplantation

Liver transplantation is the best therapeutic option for patients with HRS independent of the treatment response and type of HRS [3]. There are only limited indications for simultaneous liver-kidney transplantation.

Conclusions

HRS is a serious complication in patients with liver cirrhosis. The introduction of a new AKI classification whose aim is to identify patients earlier does not simplify making the HRS-NAKI diagnosis and these patients are not discovered in daily praxis in time. HRS-NAKI treatment is identical to the treatment of refractory ascites. Despite the fact that the prognosis of HRS-NAKI patients is better than that of HRS-AKI patients, liver transplantation is the final solution for these patients.

Disclosure

Authors report no conflict of interest.

References

1. Gines P, Sola E, Angeli P, et al. Hepatorenal syndrome. Nat Rev Dis Primers 2018; 4: 23.
2. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut 2011; 60: 702-709.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018; 69: 406-460.
4. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015; 62: 968-974.
5. Salerno F, Gerbes A, Ginès P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007; 56: 1310-1318.
6. Cavallin M, Fasolato S, Marenco S, et al. The treatment of hepatorenal syndrome. Dig Dis 2015; 33: 548-554.
7. Russ KB, Stevens TM, Singal AK. Acute kidney injury in patients with cirrhosis. J Clin Transl Hepatol 2015; 3: 195-204.
8. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003; 38: 258-266.
9. Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology1996; 23: 164-176.
10. Dundar HZ, Yilmazlar T. Management of hepatorenal syndrome. World J Nephrol 2015; 4: 277-286.
11. Low G, Alexander GJ, Lomas DJ. Hepatorenal syndrome: aetiology, diagnosis, and treatment. Gastroenterol Res Pract 2015; 2015: 207012.
12. Bernardi M, Moreau R, Angeli P. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015; 63: 1272-1284.
13. Piano S, Tonon M, Angeli P. Management of ascites and hepatorenal syndrome. Hepatol Int 2018; 12 (Suppl 1): 122-134.
14. Gandoura S, Weiss E, Ratou PE, et al. Gene and exon-expression profiling reveals an extensive LPS-induced response in immune cells in patients with cirrhosis. J Hepatol 2013; 58: 936-948.
15. Bajaj JS, Heuman DM, Hylemon PB, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014; 60: 940-947.
16. Moller S, Dumcke CW, Krag A. The heart and the liver. Expert Rev Gastroenterol Hepatol 2009; 3: 51-64.
17. Wiese S, Hove JD, Bendtsen F, Moller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol 2014; 11: 177-186.
18. Carvalho MV, Kroll PC, Kroll RT, et al. Cirrhotic cardiomyopathy: the liver affects the heart. Braz J Med Biol Res 2019; 52: e7809.
19. Sanyal AJ, Boyer T, Garcia-Tsao G, et al. for Terlipressin Study Group. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008; 134: 1360-1368.
20. Gluud LL, Christensen K, Christensen E, Krag A. Terlipressin for hepatorenal syndrome. Cochrane Database Syst Rev 2012; 9: CD005162.
21. Singh V, Ghosh S, Singh B, et al. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. J Hepatol 2012; 56: 1293-1298.
22. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatology 2015; 62: 567-574.
23. Alessandria C, Venon WD, Marzano A et al. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. Eur J Gastroenterol Hepatol 2002; 14: 1363-1368.
24. Ghosh S, Choudhary NS, Sharma AK, et al. Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study. Liver Int 2013; 33: 1187-1193.
25. Uriz J, Gine`s P, Cárdenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 2000; 33: 43-48.
26. Ortega R, Gine's P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002; 36 (Pt 1): 941-948.

27. Triantos CK, Samonakis D, Thalheimer U, et al. Terlipressin therapy for renal failure in cirrhosis. Eur J Gastroenterol Hepatol 2010; 22: 481-486.
28. 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 Transpl 2015; 21: 1347-1354.
29. Sarin SK, Sharma P. Terlipressin: an asset for hepatologists! Hepatology 2011; 54: 724-728.
30. Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol 2007; 47: 499-505.
31. Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012; 55: 1172-1181.
32. Bernardi M, Ricci CS, Zaccherini J. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol 2014; 4: 302-311.
33. Umgelter A, Reindl W, Franzen M, et al. Renal resistive index and renal function before and after paracentesis in patients with hepatorenal syndrome and tense ascites. Intensive Care Med 2009; 35: 152-156.
34. Lake JR, Ring E, LaBerge JM, et al. Transjugular intrahepatic portacaval stent shunts in patients with renal insuficiency. Transplant Proc 1993; 25: 1766-1767.
35. Ochs A, Rössle M, Haag K, et al. TIPS for hepatorenal syndrome. Hepatology 1994; 20 (Pt 2): 114A.
36. Brensing KA, Textor J, Strunk H, et al. Transjugular intrahepatic portosystemic stentshunt for hepatorenal syndrome. Lancet 1997; 349: 697-698.
37. Testino G, Ferro C, Sumberaz A, et al. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. Hepatogastroenterology 2003; 50: 1753-1755.
38. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000; 47: 288-295.
39. Ginès P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002; 123: 1839-1847.
40. Skladaný Ľ, Okapec S, Mesárošová Z, et al. Transjugulárny intrahepatálny portosystémový skrat – tips: skúsenosti jedného centra. Trendy v hepatológii 2015; 1: 27.
41. Bellot P, Welker MW, Soriano G, et al. Automated low flow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study. J Hepatol 2013; 58: 922-927.
42. Stirnimann G, Berg T, Spahr L, et al. Treatment of refractory ascites with an automated low-flow ascites pump in patients with cirrhosis. Aliment Pharmacol Ther 2017; 46: 981-991.
43. Bureau C, Adebayo D, Chalret de Rieu M, et al. Alfapump® system vs. large volume paracentesis for refractory ascites: a multicenter randomized controlled study. J Hepatol 2017; 67: 940-949.
44. Solà E, Sanchez-Cabús S, Rodriguez E, et al. Effects of alfapump™ system on kidney and circulatory function in patients with cirrhosis and refractory ascites. Liver Transpl 2017; 23: 583-593.
45. Sakaida I, Kawazoe S, Kajimura K, et al. Tolvaptan for improvement of hepatic edema: a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. Hepatol Res 2014; 44: 73-82.
46. Takamasa O, Koki S, Tomoharu Y, et al. Efficacy of tolvaptan in patients with refractory ascites in a clinical setting. World J Hepatol 2015; 7: 1685-1693.
47. Wong F, Gines P, Watson H, et al. Effects of a selective vasopressin V2 receptor antagonist, Satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. J Hepatol 2010; 53: 283-290.
48. Fagundes C, Gines P. Hepatorenal syndrome: a severe, but treatable cause of kidney failure in cirrhosis. Am J Kidney Dis 2012; 59: 874-885.