

## Hepatorenal syndrome: current diagnostic and therapeutic concepts

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Of the various complications in liver cirrhosis including intestinal bleeding, ascites and hepatocellular carcinoma, the rapidly progressive form of kidney dysfunction in cirrhosis, i.e. hepatorenal syndrome type 1, still carries the worst prognosis. In the early 1990s, median survival of these patients was reported to be as short as two weeks [1] and some more recent papers indicate that, in terms of prognosis, there has not been much progress since [2]. However, during the past two decades, new treatment concepts based on an improved pathophysiological understanding of the mechanisms ultimately leading to hepatorenal syndrome (HRS) have been introduced, and—very recently—a first randomized, controlled trial evaluating one of these concepts (i.e. vasoconstrictor treatment with the vasopressin analogue terlipressin) has been published in abstract form [3]. Despite successful drug treatment approaches, to date, the only definitive treatment of HRS type 1 is liver transplantation or even combined liver/kidney transplantation in some patients. This article aims at reviewing the currently available data on diagnosis, prognosis and treatment of hepatorenal syndrome.

### Pathophysiological background

A common pathophysiological feature of patients with advanced cirrhosis is systemic, particularly splanchnic, vasodilatation associated with decreased systemic vascular resistance [4]. These changes lead to a peripheral and splanchnic blood pooling resulting in a reduction of the effective arterial blood volume. In order to replenish the intravascular blood volume, vasoconstrictive neurohumoral systems including catecholamines, the renin-angiotensin-aldosterone system and others are activated. On the one hand, this leads to sodium and water retention, while on the other hand, it induces intrarenal vasoconstriction. A number of specific clinical situations can aggravate these pathophysiological changes and further reduce

kidney perfusion. These include septic conditions (e.g. spontaneous bacterial peritonitis), large-volume paracentesis, intestinal blood loss, alcoholic steatohepatitis, cardiac failure or excessive use of diuretics, and may lead to further peripheral vasodilatation, ‘arterial underfilling’, and intrarenal vasoconstriction and, thus, induce renal failure.

### *Diagnosis, incidence and prognosis*

According to the diagnostic criteria of the International Ascites Club published in 1996 [5], hepatorenal syndrome is an exclusion diagnosis in patients with kidney failure, advanced liver disease and absence of other causes of renal impairment, e.g. excess use of diuretics, nephrotoxic drugs, dehydration, infections, tubular necrosis or structural kidney diseases, such as glomerulonephritis or tubular necrosis. An update of these diagnostic criteria is under way and will include minor changes regarding the role of infections and of plasma expansion prior to the diagnosis of HRS (Gerbes A, personal communication). The distinction between a rapidly progressive form of HRS (i.e. HRS type 1, defined as increase of serum creatinine up to at least 2.5 mg/dl within two weeks) and a less progressive form with a serum creatinine of at least 1.5 mg/dl (HRS type 2) will remain unchanged in the updated diagnostic criteria.

Only a minority of patients with cirrhosis and elevated serum creatinine fulfills the criteria of hepatorenal syndrome [6]. One prospective study found that in a tertiary care transplant center, 40% of patients with cirrhosis and kidney failure had HRS, followed by renal parenchymal disease in 23% and drug-induced kidney failure in 19% of patients [7]. However, depending on the selection of patients in referring hospitals, these data will probably differ widely between different centers [6].

Not only for clinical management, but also for proper prognostic appraisal of patients with cirrhosis and kidney failure, it is crucial to distinguish between patients with hepatorenal syndrome and those with other causes of renal impairment. The presence of type 1 HRS has been shown to be an independent predictor of survival in these patients, even if the

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MELD score (which also reflects kidney function) is included in the analysis [2,7]. Thus, patients with type 1 HRS have a worse prognosis than their respective MELD score would predict, which is of major importance in the context of priority listing for transplantation. Similarly, it has been shown that (dilutional) hyponatraemia, which is a consequence of water retention caused by the complex pathophysiological changes that may ultimately lead to HRS as outlined above, is associated with a poor outcome and probably adds relevant prognostic information to the MELD score [8,9]. On the other hand, in terms of prognosis, the diagnosis of type 2 HRS is probably less relevant since these patients have a similar prognosis as cirrhotic patients with other causes of kidney impairment [7]. Furthermore, according to prospective data on the course of these patients, the progression of HRS 2 to HRS 1 occurs probably relatively seldom [7].

Our own clinical experience as well as data from the largest retrospective multicenter analysis on HRS type 1 [10] suggest that in patients with this dramatic complication of cirrhosis, two major determinants of survival exist, namely the degree of liver failure (commonly assessed as Child-Pugh score) and the response to pharmacologic treatment. In HRS 1 patients with chronically decompensated cirrhosis (i.e. Child-Pugh score of 12 or more) and HRS 1 patients unresponsive to a ten to fourteen day treatment of HRS 1 with terlipressin ( $\pm$ albumin), prognosis is dismal and these patients will probably die before a transplant organ becomes available.

### *Prevention and treatment*

Splanchnic vasodilatation, diminished effective arterial blood volume and consecutive sodium and water retention are commonly found in patients with advanced cirrhosis. However, only a minority of these patients develops hepatorenal syndrome. Typically, a clinical situation aggravating these changes and/or reducing cardiac output—a so-called ‘second hit’—is required to induce hepatorenal syndrome. Thus, in conditions associated with a high risk to develop a hepatorenal syndrome, strategies aiming at preventing this dramatic complication are warranted.

Data on the prevention of HRS are available for some of the well-known triggers of hepatorenal syndrome. In one randomized trial in patients with proven spontaneous bacterial peritonitis (SBP), a combination treatment of Cefotaxime plus albumin (1.5 g/kg on day 1, 1 g/kg on day 3) has been compared with Cefotaxime alone. In that study, the addition of albumin was associated with a significant survival benefit which was notably almost exclusively due to a reduction of HRS incidence in that cohort [11]. Consecutive trials showed that in the context of SBP, albumin infusion is more effective than infusion of other plasma expanders [12]. Thus, the

administration of albumin in patients with SBP is a proven and recommended strategy to prevent hepatorenal syndrome [13].

Large volume paracentesis (i.e. more than five to six liters of ascites) may also induce hepatorenal syndrome by aggravating the ‘circulatory dysfunction’, usually assessed as plasma renin increase approximately one week after paracentesis. The administration of albumin (8 g/l ascites) has been shown to be more effective than use of other plasma expanders [14] or saline [15] in preventing this circulatory dysfunction and it is therefore recommended after large-volume paracentesis.

One further preventive strategy which is based on a randomized, placebo-controlled, double-blind trial is the administration of pentoxifyllin in patients with acute alcoholic hepatitis [16]. In that study, 400 mg pentoxifyllin t.i.d. effectively prevented HRS and improved the overall survival in patients with alcoholic hepatitis.

Once a type 1 hepatorenal syndrome has been established, treatment options that have proven effective in that condition are liver transplantation, vasoconstrictor drugs (commonly combined with albumin) and—for highly selected patients—possibly also the transjugular intrahepatic portosystemic shunt (TIPS). Larger studies supporting the use of the ‘molecular adsorbent recirculating system’ (MARS) in these patients are lacking to date.

A number of retrospective series indicate that hepatorenal syndrome commonly recovers after liver transplantation. However, in most patients with pre-transplant HRS type 1, a minor renal impairment can be found after liver transplantation and in some patients, even a severe kidney dysfunction persists. Two recent studies addressed the issue as to which patients with cirrhosis and hepatorenal syndrome may be candidates for combined liver/kidney transplantation. In a retrospective series in 148 patients, Ruiz and coworkers showed that patients who required hemodialysis for more than eight weeks prior to transplant had a better outcome after combined transplantation than after liver transplantation [17]. However, a retrospective study from Pittsburgh that included 28 transplanted patients with HRS type 1 could not confirm these findings: the authors identified the presence of an alcoholic liver disease and a post-transplant dialysis-requirement as predictors of a poor post-transplant outcome [18]. Interestingly, in that study, neither the pre-transplant duration of HRS nor a pre-transplant dialysis-requirement was associated with a worse post-transplant outcome. Thus, there is still no consensus as to which patients which HRS should preferably receive a liver and kidney graft or only a liver transplant. A transvenous kidney biopsy is probably a helpful tool in the decision-making in this context.

Although liver transplantation is definitively effective in these patients and should be evaluated in every patient with HRS, only a minority of patients is eventually transplanted. In a prospective series, none of

15 type 1 HRS patients referred to a tertiary care transplant center was transplanted: 12 patients had contraindications against transplantation and the remaining three patients died while awaiting transplant [7].

The currently preferred first-line treatment of hepatorenal syndrome type 1 is the combination of vasoconstrictors (e.g. terlipressin, octreotide, midodrine, noradrenalin) and albumin [3,6]. A number of small, mostly retrospective studies showed that this approach improves kidney function (which is probably associated with an increased survival) in more than half of the patients with HRS type 1 (review in [19]). Very recently, a first large-scale, randomized, placebo-controlled trial that evaluated the vasopressin analogue terlipressin (plus albumin) for this indication has been published in abstract form [3]. In that study, terlipressin was significantly superior to placebo with respect to reversal of HRS (34% versus 13% in the placebo group). However, that study failed to demonstrate a survival benefit, probably due to a high proportion of patients with far advanced liver failure.

The transjugular, intrahepatic, portosystemic stent shunt (TIPS) corrects portal hypertension, is effective in the treatment of refractory ascites and may therefore be also beneficial in patients with hepatorenal syndrome. In fact, early reports have shown that TIPS insertion may improve the glomerular filtration rate in patients with hepatorenal syndrome [20]. Notably, it has been shown that HRS patients with maintained liver function who respond to an initial vasoactive treatment with midodrine and octreotide may be good candidates for TIPS insertion [21]. However, in most patients with HRS, the degree of liver failure is a contraindication against the placement of a portosystemic shunt as it further reduces the portal perfusion of the liver parenchyma possibly resulting in further deterioration of liver function. Thus, TIPS is only indicated in highly selected patients with HRS and therefore has only played a marginal role in the treatment of HRS to date.

In summary, the diagnosis of hepatorenal syndrome is still associated with a poor prognosis and should therefore prompt transplant evaluation. Effective strategies for the prevention of hepatorenal syndrome in patients with spontaneous bacterial peritonitis, alcoholic hepatitis and after large-volume paracentesis have been established. The current first-line treatment of hepatorenal syndrome type 1 is the combination of vasoconstrictors and albumin. Very recent placebo-controlled phase 3 data demonstrate the beneficial effect of terlipressin on kidney function in patients with hepatorenal syndrome type 1.

*Conflict of interest statement.* None declared.

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