Review

Advances in the pathogenesis and treatment of type-1 and type-2 hepatorenal syndrome

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1. Introduction

Hepatorenal syndrome (HRS) is a frequent complication in patients with advanced cirrhosis and ascites. It is characterized by an intense renal vasoconstriction, which leads to very low renal perfusion and glomerular filtration rate (GRF). The renal ability to excrete sodium and free water is also severely reduced [1,2]. Renal histology shows no significant lesions sufficient to justify the impairment in renal function. HRS is the extreme expression of the circulatory dysfunction of cirrhosis. Patients present arterial hypotension and intense stimulation of the renin–angiotensin system, sympathetic nervous system and antidiuretic hormone. Circulatory dysfunction in cirrhosis has been classically considered to be the consequence of an arterial vasodilation in the splanchnic circulation (peripheral arterial vasodilation hypothesis). However, recent data indicate that a reduction in cardiac output also plays a significant role. Non-azotemic cirrhotic patients with ascites, and increased activity of both the renin–angiotensin and sympathetic nervous systems as well as intense sodium retention are specially predisposed to develop HRS [3]. The syndrome may develop spontaneously during the natural course of the disease or be precipitated by factors that induce renal hypoperfusion such as bacterial infections. The annual incidence of HRS in patients with cirrhosis and ascites has been estimated as 8% [3]. Due to the functional nature of renal failure, there is no specific diagnostic marker for HRS [2,4,5]. Thus, diagnosis relies on the exclusion of other causes of renal insufficiency [6]. HRS is the complication of cirrhosis associated with the worst prognosis and, for many years, it has been considered as a terminal event of the disease. However, effective treatments of HRS which improve survival have recently been introduced, and a significant number of patients may now benefit from liver transplantation.

2. Diagnosis

The first step in the diagnosis of HRS is the demonstration of a reduced GFR, and this is not easy in advanced cirrhosis. The muscle mass, and therefore, the release of creatinine, is considerably reduced in these patients and they may present normal serum creatinine concentration in the setting of a very low GFR (Fig. 1). Similarly, urea is synthesized by the liver and may be reduced as a consequence of hepatic insufficiency. Therefore, false negative diagnosis of HRS is relatively common [7–9]. There is consensus to establish the diagnosis of HRS when serum creatinine has risen above 1.5 mg/dl or creatinine clearance has decreased to less than 40 ml/min [10]. The second step is the differentiation of HRS from other types of renal failure. For many years this was based on the traditional parameters used to diagnose functional renal failure (oliguria, low urine sodium concentration, urine-to-plasma osmolality ratio greater than unity, normal fresh urine sediment and no

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proteinuria). However, acute tubular necrosis in patients with cirrhosis and ascites usually courses with oliguria, low urine sodium concentration and urine osmolality greater than plasma osmolality [11]. On the contrary, relatively high urinary sodium concentration has been exceptionally observed in patients with HRS [12].

Because of the lack of specific tests, diagnosis of HRS is based on the exclusion of other disorders that can cause renal failure in cirrhosis (Table 1) [10]. Acute renal failure of pre-renal origin due to renal (diuretics) or extrarenal fluid losses should be investigated. If renal failure is secondary to volume depletion, renal function improves rapidly after volume expansion, whereas no improvement occurs in HRS. Even if there is no history of fluid losses, renal function should be assessed after diuretic withdrawal and volume replacement to rule out any subtle reduction in plasma volume as the cause of renal failure. The diagnostic criteria of HRS proposed by the International Ascites Club in San Francisco in 2005 (Salerno et al., unpublished data) consider that volume replacement should be performed with i.v. albumin (1 g/kg body weight up to a maximum of 100 g), rather than with saline. This is based on a randomized study showing that albumin is more effective as a plasma expander than a saline solution of hydroxyethyl starch in patients with spontaneous bacterial peritonitis (SBP) [13]. The presence of shock before the onset of renal failure points towards a diagnosis of acute tubular necrosis. On the other hand, cirrhotic patients with infections may develop transient renal failure, which reverses with the resolution of the infection. This occurs in approximately one-third of patients with SBP. Therefore, HRS in cirrhotic patients with bacterial infections should be diagnosed in patients without septic shock in whom renal failure does not improve following antibiotic administration. Complete resolution of the infection, which was required for the diagnosis of HRS in the initial proposal by the International Ascites Club in 1996 [10], is not currently accepted because it may delay the initiation of treatment with vasoconstrictors and albumin (see below). Treatment of HRS could, therefore, be initiated prior to completion of antibiotic therapy in patients without improvement in serum creatinine concentration despite a clear amelioration in the signs of infection. Cirrhotic patients are predisposed to developing renal failure in the setting of treatments with aminoglycosides [14], nonsteroidal anti-inflammatory drugs [15] and vasodilators (renin–angiotensin system inhibitors, prazosin, nitrates) [16]. Therefore, treatment with these drugs in the days preceding the diagnosis of renal failure should be ruled out. Finally, patients with cirrhosis can develop renal failure due to intrinsic renal diseases, particularly glomerulonephritis. These cases can

Table 1
International Ascites Club’s diagnostic criteria of HRS [10]

<table>
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<th>Major criteria</th>
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<tr>
<td>Chronic or acute liver disease with advanced hepatic failure and portal hypertension</td>
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<tr>
<td>Low glomerular filtration rate, as indicated by serum creatinine of &gt;1.5 mg/dL or 24-h creatinine clearance &lt;40 ml/min</td>
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<tr>
<td>Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhoea) or renal fluid losses (weight loss &gt;500 g/day for several days in patients with ascites without peripheral edema or 1,000 g/day in patients with peripheral edema)</td>
</tr>
<tr>
<td>No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline</td>
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<tr>
<td>Proteinuria &lt;500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease</td>
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<th>Additional criteria</th>
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<tr>
<td>Urine volume &lt;500 mL/day</td>
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<td>Urine sodium &lt;10 mEq/L</td>
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<td>Urine osmolality greater than plasma osmolality</td>
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<tr>
<td>Urine red blood cells &lt;50 per high power field</td>
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<tr>
<td>Serum sodium concentration &lt;130 mEq/L</td>
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* The additional criteria are not necessary for the diagnosis.
be recognised by the presence of proteinuria, hematuria or both.

3. Clinical types of HRS

There are two types of HRS [10]. Type-1 HRS is characterized by a severe and rapidly progressive renal failure, which has been defined as doubling of serum creatinine reaching a level greater than 2.5 mg/dl in less than 2 weeks. Although type-1 HRS may arise spontaneously it frequently occurs in close relationship with a precipitating factor, such as severe bacterial infection, mainly SBP, gastrointestinal hemorrhage, major surgical procedure or acute hepatitis superimposed to cirrhosis. The association of HRS and SBP has been carefully investigated [17–19]. Type-1 HRS develops in approximately 25% of patients with SBP, and occurs in most patients despite a rapid resolution of the infection with non-nephrotoxic antibiotics. Patients with severe circulatory dysfunction prior to infection or intense inflammatory response (high concentration of polymorphonuclear leukocytes in ascitic fluid and high cytokine levels in plasma and ascitic fluid) are prone to develop type-1 HRS after the infection. Besides renal failure, patients with type-1 HRS associated to SBP show signs and symptoms of rapid and severe deterioration of liver function (jaundice, coagulopathy and hepatic encephalopathy) and circulatory function (arterial hypotension, very high plasma levels of renin and norepinephrine) [17–19]. The relationship between the type and characteristics of the bacterial infection and the development of type-1 HRS has been recently explored in two studies. The first showed that at variance to SBP, sepsis related with other types of infection in patients with cirrhosis induces type-1 HRS mainly in the setting of lack of response to antibiotics [20]. In most patients with sepsis unrelated to SBP responding to antibiotics, renal impairment, which is also a frequent event, is reversible.

In the second study, however, a significant proportion of patients with symptomatic urinary tract infection developed type-1 HRS despite a rapid resolution of the infection [21]. Without treatment, type-1 HRS is the complication of cirrhosis with the poorest prognosis with a median survival time after the onset of renal failure of only 2 weeks (Fig. 2) [3].

Type-2 HRS is characterized by a moderate and steady or slowly progressive renal failure (serum creatinine lower than 2.5 mg/dl). Patients with type-2 HRS show signs of liver failure and arterial hypotension but to a lesser degree than patients with type-1 HRS. The dominant clinical feature is severe ascites with poor or no response to diuretics (a condition known as refractory ascites). Patients with type-2 HRS are predisposed to develop type-1 HRS following infections or other precipitating events [17–19]. Median survival of patients with type-2 HRS (4–6 months) is worse than that of patients with non-azotemic cirrhosis with ascites [6,22] (Fig. 2).

4. Factors associated to hepatorenal syndrome

4.1. Splanchnic arterial vasodilation

The development of portal hypertension in cirrhosis is associated to arterial vasodilation in the splanchnic circulation due to the local release of nitric oxide and other vasodilatory substances [23–26]. Early in the course of the disease, the decrease in systemic vascular resistance is compensated by the development of a hyperdynamic circulation (increased heart rate and cardiac output) [27–29]. However, as the disease progresses and arterial vasodilation increases, the hyperdynamic circulation is insufficient to correct the effective arterial hypovolemia (Fig. 3) [30]. Arterial hypotension develops, leading to activation of high pressure baroreceptors, reflex stimulation of the renin–angiotensin and sympathetic nervous systems, increase in arterial pressure to normal or near normal levels, sodium and water retention and the formation of ascites. The activation of antidiuretic hormone causes water retention and dilutional hyponatremia, which occurs at later phases of decompensated cirrhosis. At this stage of the disease, the renin–angiotensin and sympathetic nervous systems are markedly stimulated and arterial pressure is critically dependent on the vascular effect of the sympathetic nervous activity, angiotensin-II and antidiuretic hormone [31]. Since the splanchnic circulation is resistant to the effect of angiotensin-II, noradrenaline and vasopressin due to the local release of nitric oxide and other vasodilators [32,33], the maintenance of arterial pressure is due to vasoconstriction in extra-splanchnic vascular territories such as the kidneys and brain [34–36]. HRS develops at the latest phase of the disease when there
is extreme deterioration in effective arterial blood volume and severe arterial hypotension. The homeostatic stimulation of the renin–angiotensin system, the sympathetic nervous system and antidiuretic hormone is very intense leading to extreme renal vasoconstriction, a marked decrease in renal perfusion and GFR, azotemia and increased serum creatinine concentration.

4.2. Reduction in cardiac output

Most hemodynamic studies in cirrhosis have been performed in non-azotemic patients with and without ascites, but their findings have been extended to the entire population of decompensated cirrhosis. Based on their data, it has been assumed that HRS develops in the setting of a hyperdynamic circulation, being the extreme expression of the arterial vasodilation present in these patients. However, in the few studies assessing cardiovascular function in patients with HRS or refractory ascites (most of them with type-2 HRS), cardiac output was found to be significantly reduced compared to patients without HRS [37,38]. In some cases cardiac output was even lower than in normal subjects, suggesting that circulatory dysfunction associated with HRS is due not only to arterial vasodilation but also to a decrease in cardiac function.

Two recent studies by Ruiz-del-Arbol et al. support this feature [39,40]. In the first study [39], systemic hemodynamics and the endogenous vasoactive systems were measured in patients with SBP at infection diagnosis and following infection resolution. Development of type-1 HRS was associated to a significant decrease in arterial pressure and a marked stimulation of the renin–angiotensin and sympathetic nervous systems. Peripheral vascular resistance did not change, which is consistent with a progression of the arterial vasodilation obscured by the vasoconstrictor effect of angiotensin-II and noradrenaline. A marked decrease in cardiac output was detected in all cases. These changes were not observed in patients who did not develop HRS. The second study [40] consisted in a longitudinal investigation in a large series of non-azotemic cirrhotic patients with ascites. Forty percent of patients developed HRS. These patients were studied at inclusion and following the development of HRS. In the initial study, those patients who went on to develop HRS had significantly lower mean arterial pressure and cardiac output, and significantly higher plasma renin activity and norepinephrine concentration compared with those who did not develop HRS. Moreover, those who developed HRS had a further decrease in arterial pressure and cardiac output and increase in renin and norepinephrine without changes in peripheral vascular resistance (Table 2). These two studies strongly suggest that circulatory dys-

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**Table 2**

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<th>NA-1</th>
<th>NA-2</th>
<th>At diagnosis of HRS</th>
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<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>88 ± 9</td>
<td>83 ± 9</td>
<td>75 ± 7</td>
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<tr>
<td>Plasma renin activity (ng/mL h)</td>
<td>3 ± 2</td>
<td>9.9 ± 5.2</td>
<td>17.5 ± 11.4</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL h)</td>
<td>221 ± 68</td>
<td>571 ± 241</td>
<td>965 ± 502</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne/cm²)</td>
<td>962 ± 256</td>
<td>1058 ± 265</td>
<td>1096 ± 327</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>7.2 ± 1.8</td>
<td>6.0 ± 1.2</td>
<td>5.4 ± 1.5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>87 ± 15</td>
<td>85 ± 13</td>
<td>82 ± 14</td>
</tr>
<tr>
<td>Hepatic blood flow (mL/min)</td>
<td>1123 ± 328</td>
<td>948 ± 221</td>
<td>713 ± 188</td>
</tr>
<tr>
<td>Hepatic venous pressure gradient (mmHg)</td>
<td>16.5 ± 3</td>
<td>19.5 ± 3</td>
<td>21 ± 4</td>
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NA-1, baseline measurement in non-azotemic cirrhotic patients that had not developed hepatorenal syndrome in the follow-up.

NA-2, baseline measurement in non-azotemic cirrhotic patients that had developed hepatorenal syndrome in the follow-up.

* p < 0.01.
function and HRS in cirrhosis are due both to an increase in arterial vasodilation and a decrease in cardiac function (Fig. 4).

4.3. Regional hemodynamics associated with HRS

For many years patients with HRS were considered to have two major problems, a terminal and irreversible liver failure due to advanced cirrhosis and a functional renal failure secondary to renal vasoconstriction. Although most investigators considered that the link between the diseased liver and the failing kidney was a deterioration of systemic hemodynamics secondary to an arterial vasodilation in the splanchnic circulation, other authors have speculated that it could be related to a direct influence of the diseased liver upon the kidney (i.e. a hepatorenal reflex). During the last decade, however, increasing evidence suggests that HRS is a much more complex syndrome affecting organs other than the liver and the kidney. Moreover, indirect data have been presented suggesting that the impairment in the systemic circulatory function associated with HRS affects not only the renal circulation but also other regional circulations including the intrahepatic circulation [40] and that this may contribute to the severity of hepatic failure in HRS. Liver failure in HRS could, therefore, be potentially reversible if circulatory dysfunction is improved.

4.3.1. Renal impairment

HRS develops at the latest phase of cirrhosis, when patients already present severe circulatory dysfunction, arterial hypotension, marked activation of the renin–angiotensin–aldosterone system, sympathetic nervous system and antidiuretic hormone, renal sodium and water retention, ascites and dilutional hyponatremia. The mechanism of the renal vasoconstriction that causes HRS is complex. Since renal perfusion in decompensated cirrhosis correlates inversely with the activity of the renin–angiotensin and sympathetic nervous systems [34,36,41,42], HRS is thought to be related to the extreme stimulation of these systems. The urinary excretion of prostaglandin E2, 6-keto prostaglandin F1α (a prostacyclin metabolite) and kallikrein is decreased in patients with HRS, which is compatible with a reduced renal production of these vasodilatory substances [43,44]. Renal failure in HRS could, therefore, be the consequence of an imbalance between the activity of the systemic vasoconstrictor systems and the renal production of vasodilators. Finally, renal hypoperfusion in HRS could be amplified by the stimulation of intrarenal vasoconstrictors. For example, renal ischemia increases the generation of angiotensin-II by the juxtaglomerular apparatus, the intrarenal production of adenosine which, in addition to being a renal vasoconstrictor, potentiates the vascular effect of angiotensin-II, and the synthesis of endothelin [45]. Other intrarenal vasoconstrictors that have been implicated in HRS are leukotrienes and F2-isoprostanes [46]. Renal vasoconstriction in HRS is, therefore, the consequence of the simultaneous effect of numerous vasoactive mechanisms on the intrarenal circulation.

4.3.2. Vasoconstriction in the cutaneous, muscular and cerebral circulations in HRS

Brachial and femoral blood flows have been found markedly reduced by echo-Doppler in patients with HRS in comparison to patients without HRS [34]. These results suggest that HRS is associated to vasoconstriction in the cutaneous and muscular arterial vascular beds, although this must be confirmed in studies using other techniques [34]. The resistive index in the mean cerebral artery is also increased in these patients indicating cerebral vasoconstriction [47] (Fig. 5). The degree of vasoconstriction in cutaneous, muscular and cerebral territories found in these studies correlated directly with the degree of renal vasoconstriction and with the plasma levels of renin.
The clinical consequence of the decreased muscular blood flow in advanced cirrhosis has not been explored. Patients with type-2 HRS and refractory ascites frequently present muscle cramps. Although the pathogenesis of this abnormality is unknown, muscle cramps disappear or improve following plasma volume expansion with albumin [48] suggesting that they could be related to this reduction of muscular blood flow. Hepatic encephalopathy is common in patients with type-1 HRS. There are many possible mechanisms of this complication, including the precipitating event of HRS, which can also cause hepatic encephalopathy, and the deterioration of hepatic function seen in these patients. Cerebral vasocostriction, however, could be an additional factor.

4.3.3. Cardiac function is severely impaired in type-1 and type-2 HRS

The physiological response to arterial hypotension consists in the activation of the renin–angiotensin and sympathetic nervous systems, which produces arterial vasocostriction, increase in heart rate, ventricular contractility and cardiac output, as well as an increase in arterial pressure to normal or near normal levels. In patients with type-2 HRS, the arterial hypotension induced by the splanchnic arterial vasodilation is followed by an appropriate response of the vasoactive neurohormonal systems with vasoconstriction in the extra-splanchnic organs that maintains arterial pressure [34,47]. However, the cardiac response is clearly abnormal in these patients. Type-2 HRS is associated with a decrease in cardiac output. Moreover, despite the activation of the sympathetic nervous activity, no change in heart rate is observed (Table 2) [40]. These data indicate a clear impairment in cardiac inotropic and chronotropic functions. In patients with type-1 HRS a similar but more intense deterioration of cardiac function is observed [40].

The mechanism of the impaired cardiac response to arterial vasodilation in patients with HRS is unknown. A specific cardiomyopathy characterized by attenuated systolic and diastolic responses to stress stimuli, electrophysiological repolarization changes and enlargement and hypertrophy of cardiac chambers is common in patients with advanced cirrhosis [49]. This cirrhotic cardiomyopathy has been suggested to play a role in the pathogenesis of heart failure seen after the insertion of a transjugular intrahepatic portosystemic stent-shunt (TIPS) [50,51], major surgery or liver transplantation [52,53] and in HRS [39,40]. However, several features suggest that cardiac dysfunction in HRS is of a functional nature probably related to a decrease in venous return. First, the reduced cardiac output in patients with HRS occurs in the setting of a decrease in cardiopulmonary pressures, which is compatible with a fall in cardiac preload [40]. Second, circulatory dysfunction in HRS can be reverted by the i.v. administration of albumin associated with vasoconstrictors or after the insertion of a TIPS [54–58]. Both treatments increase venous return and cardiac output. Finally, expansion of plasma volume with albumin is highly effective in the prevention of type-1 HRS in patients with SBP [59].

4.3.4. Circulatory dysfunction affects the intrahepatic circulation in type-1 and type-2 HRS

Angiotensin-II, noradrenaline and vasopressin have powerful effects on the intrahepatic circulation. They produce arterial vasoconstriction and increase the intrahepatic resistance to the portal venous flow at different levels (small portal venules, sinusoids and small hepatic venules). In patients with cirrhosis the vasoconstrictor effect of these substances in the hepatic circulation is increased due to a reduced intrahepatic synthesis of nitric oxide [60]. It is, therefore, not surprising that the stimulation of the endogenous vasoactive systems in HRS could induce an aggravation of portal hypertension and a marked reduction in hepatic blood flow. This has recently been assessed by Ruiz-del-Arbol et al. They studied hepatic hemodynamics in a large series of nonazotemic cirrhotics with tense ascites and repeated the study after a follow-up period of several months when patients had developed type-1 or type-2 HRS [40]. The wedged hepatic venous pressure gradient was significantly higher in the follow-up study than in the baseline study in patients developing type-1 HRS. Type-1 HRS

![Graph showing resistive index in the middle cerebral artery in patients with compensated cirrhosis, patients with ascites and healthy subjects.](image-url)
was also associated with a dramatic reduction in hepatic blood flow. In patients developing type-2 HRS significant differences were only observed in the hepatic blood flow. In a second investigation from the same group, hepatic hemodynamics was assessed in patients with SBP at infection diagnosis and following infection resolution [39]. There was only a period of 7 days of interval between both studies. Hepatic venous pressure gradient increased markedly in patients who developed type-1 HRS but not in patients who did not develop renal failure. Changes in intrahepatic hemodynamics in the two studies correlated significantly with the increase in plasma renin activity, suggesting that circulatory dysfunction associated with hepatorenal syndrome and the secondary activation of the endogenous vasoconstrictor systems adversely influence intrahepatic hemodynamics.

Acute deterioration of hepatic function is a common event in patients with type-1 HRS. Variceal bleeding is also frequent in patients with severe bacterial infections and HRS. The intense reduction in hepatic blood flow and the increase in portal pressure associated with type-1 HRS could play a role in the development of these complications. A clear disassociation between the improvement in circulatory and renal function and changes in hepatic function, however, can be observed in cirrhotic patients with HRS treated by vasoconstrictors and albumin.

4.3.5. Adrenal dysfunction in cirrhotic patients with sepsis and severe circulatory dysfunction

Two recent studies indicate that adrenal dysfunction is a common problem in patients with acute liver failure and in those with cirrhosis and acute-on-chronic liver failure secondary to severe sepsis [61,62].

In patients with cirrhosis [62], adrenal insufficiency was detected in 80% of patients with HRS but only in 34% with serum creatinine below 1.5 mg/dl. A close relationship, therefore, exists between adrenal insufficiency and HRS in patients with severe infection. Other features associated with adrenal insufficiency were severe liver failure, arterial hypotension, vasopressor dependency and hospital mortality. Since normal adrenal function is essential for an adequate response of the arterial circulation to endogenous vasoconstrictors, adrenal insufficiency could be an important contributory mechanism of circulatory dysfunction associated with HRS in patients with severe bacterial infections. A third study [63] has presented data that treatment with hydrocortisone in cirrhotic patients with severe sepsis and adrenal insufficiency is associated with rapid improvement in systemic hemodynamics, reduction in vasoconstrictor requirements and high hospital survival.

The mechanism of adrenal dysfunction in cirrhosis with severe sepsis has not been explored. It may be related to a reduction in adrenal blood flow secondary to regional vasoconstriction. Moreover, very high levels of inflammatory cytokines, as observed in cirrhotic patients with sepsis, directly inhibit adrenal cortisol synthesis.

5. Pathogenesis of type-1 and type-2 HRS

Clinical data suggest that type-1 and type-2 HRS are different syndromes and not different expressions of a common underlying disorder. Renal failure in type-1 HRS is severe and progressive whereas in type-2 it is moderate and steady. As expected, circulatory function is also stable in type-2 HRS whereas a rapidly progressive impairment in circulatory function occurs in type-1 HRS. Type-1 HRS is frequently associated to a precipitant event, mainly SBP. In contrast, type-2 HRS develops spontaneously in most cases. Finally, the main clinical consequence of type-1 HRS is severe hepatorenal failure and death whereas it is refractory ascites in type-2 HRS. Type-2 HRS probably represents the genuine functional renal failure of cirrhosis. It would be the extreme expression of the impairment in circulatory function that spontaneously develops during the course of the disease (Fig. 3). In contrast, type-1 HRS mimics the acute renal failure associated with other conditions such as sepsis or severe pancreatitis, with features of multiorgan failure including acute impairment in cardiovascular, renal, hepatic and cerebral function and relative adrenal insufficiency (Fig. 6).

![Fig. 6. HRS as a part of a multiorgan failure. Abbreviations: A-II, angiotensin II; NE, norepinephrine; ADH, antidiuretic hormone; HRS, hepatorenal syndrome.](image-url)
6. Available treatments for type-1 HRS

6.1. Liver transplantation

Liver transplantation is the treatment of choice of HRS [64–67]. Immediately after transplantation a further impairment in GFR may be observed and many patients require hemodialysis (35% of patients with HRS as compared with 5% of patients without HRS) [64]. Because cyclosporine or tacrolimus may contribute to this impairment in renal function, it has been suggested to delay the administration of these drugs until a recovery of renal function is noted, usually 48–72 h after transplantation. After this initial impairment in renal function, GFR starts to improve and reaches an average of 30–40 ml/min by 1–2 months postoperatively. This moderate renal failure persists during follow-up, is more marked than that observed in transplantation patients without HRS, and is probably due to a greater nephrotoxicity of cyclosporine or tacrolimus in patients with renal impairment prior to transplantation. The hemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after the operation and the patients regain a normal ability to excrete sodium and free water [68].

Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplantation patients without HRS. The long term survival of patients with HRS who undergo liver transplantation however is good, with a 3-year probability of survival of 60%. This survival rate is only slightly reduced compared to that of transplantation in patients without HRS (which ranges between 70% and 80%) [65].

The main problem of liver transplantation in type-1 HRS is the applicability. Due to their extremely short survival, most patients die before transplantation. The introduction of the MELD score, which includes serum creatinine, bilirubin and the international normalized ratio, for listing has partially solved the problem since patients with HRS are generally allocated in the first places of the waiting list. Treatment of type-1 HRS with vasoconstrictors and albumin (see below) increases survival and the number of patients reaching living transplantation and decreases early morbidity and mortality after surgery [65,69].

6.2. Vasoconstrictors and albumin

The i.v. administration of vasoconstrictor agents (vasopressin, ornipressin, terlipressin, noradrenaline) or the combination of oral midodrine (an α-agonistic agent) and intravenous or subcutaneous octreotide during 1–3 weeks is an effective treatment of type-1 HRS. Eleven pilot studies including 154 patients with HRS (132 with type-1 HRS) have so far been published on this topic [54, 55, 70–78]. In most patients i.v. albumin was also given. The overall rate of positive response was 61.6% (95 patients). In eight of these studies (including 128 patients) a positive response was considered when there was reversal of HRS as defined by a decrease of serum creatinine below 1.5 mg/dl. This feature was observed in 79 patients (61.7%). A second important observation was that type-1 HRS does not recur after discontinuation of the treatment in most patients. Five studies including 65 patients have reported data on this feature. Forty-four patients responded to therapy and HRS recurred in only nine. These findings contrast sharply with those of 7 studies in patients with type-1 HRS not receiving specific treatment or treated with plasma volume expansion alone or associated with vasodilators (dopamine) or octreotide or with peritoneo-venous shunting [18,19,59,72,77,79,80]. Reversal of HRS was observed in only 4 out of the 137 patients (2.9%) included in these studies. Survival data were recorded in 13 studies (8 using vasoconstrictors and 5 using other treatments). Forty (41.6%) and 29 (30%) of the 96 patients with type-1 HRS treated with vasoconstrictors were alive 1 and 3 months after treatment. The corresponding data in 65 patients receiving other treatments were 2 (3%) and 0 (0%), respectively. Nineteen patients treated with vasoconstrictors reached a liver transplant.

A retrospective survey in 99 patients with type-1 HRS admitted to 22 hospitals in France and treated with terlipressin (all cases) and albumin (70% of cases) showed a rate of improvement in renal function of 58% [56]. The probability of survival was 40% at 1 month and 22% at 3 months. Improvement of survival was related to reversal of HRS. Thirteen patients received a liver transplant. This study, which can be taken as an indication of what occurs in regular clinical practice, therefore, confirms the results obtained in the pilot studies in short series of patients previously described.

Two randomized controlled studies have recently been finished comparing albumin versus albumin plus terlipressin in patients with type-1 HRS (Sanyal et al. and Guevara et al., unpublished results) and they confirm the results obtained in the pilot studies. Reversal of HRS was significantly more frequent in patients treated with terlipressin and albumin. On the other hand, survival of patients responding to treatment was longer than that of patients not responding to treatment.

These studies clearly indicate that vasoconstrictor associated with i.v. albumin should be recommended for the management of patients with type-1 HRS since they normalize serum creatinine in a high proportion of patients and may improve survival. Terlipressin has been the most widely used vasoconstrictor agent in type-1 HRS. It is very effective and is associated to low incidence of side effects. The efficacy of the association of oral midodrine and intravenous or subcutaneous octreotide
is probably due exclusively to the vasoconstrictor effect of midodrine [72,81]. Noradrenaline has also been shown to be effective and safe [76] and it is less expensive than terlipressin. However, whereas there is large experience with terlipressin, noradrenaline and midodrine have been used in only few studies [72,76,78,81]. Based on these considerations terlipressin should be the drug of choice for the treatment of type-1 HRS.

Reversal of type-1 HRS in two pilot studies in which terlipressin was given alone (7 out of 28 patients, 25%) [55,74] was lower than that in the studies in which vasoconstrictors were associated with i.v. albumin, suggesting that albumin is an important component in the pharmacological treatment of type-1 HRS. Two recent studies [82,83] suggest that the beneficial effect of albumin on circulatory and renal function in patients with type-1 HRS is related not only to the expansion of the plasma volume but also to a direct vasoconstrictor effect on the peripheral arterial circulation.

Terlipressin dosage should be progressive, starting with 0.5 mg/4 h. If serum creatinine does not decrease by more than 30% in 3 days, the dose should be doubled. The maximal dose of terlipressin has not been defined, although there is consensus that patients not responding to 12 mg/day will not respond to higher doses. Albumin should be given starting with a priming dose of 1 g/kg of body weight followed by 20–40 g/day. It is advisable to monitor central venous pressure. In patients responding to therapy, treatment should be kept until normalization of serum creatinine (<1.5 mg/dl).

6.3. Transjugular intrahepatic portacaval shunt (TIPS)

Three pilot studies have evaluated TIPS in type-1 HRS [57,58,78]. In the first study [57], 14 patients with type-1 HRS (12 with alcoholic cirrhosis, 9 with active alcoholism) and 17 with refractory ascites (some of them with type-2 HRS) not suitable for liver transplantation were treated. Patients with bilirubin >15 mg/dl, Child–Pugh score >12 or hepatic encephalopathy were excluded. Eleven out of the 31 patients developed de novo hepatic encephalopathy or deterioration of previous hepatic encephalopathy. The 3, 6 and 12 month survival rates in patients with type-1 HRS were 64%, 50% and 20%, respectively. The second study [58] was performed in 7 patients (4 alcoholics) with type-1 HRS and a Child–Pugh score <12. Marked decrease in serum creatinine was observed in six patients and reversal of HRS in 4. Five patients developed episodes of hepatic encephalopathy after TIPS but they responded satisfactorily to medical treatment. Five patients were alive after 1 month of TIPS but only two after 3 months. The third study [78] was performed in 14 patients (13 with alcoholic cirrhosis) with type-1 HRS treated initially with vasoconstrictors (midodrine and octreotide) plus albumin. Reversal of HRS was obtained in 10 patients. TIPS was subsequently inserted in 5 of these 10 patients who had bilirubin <5 mg/dl, INR <2, Child–Pugh score <12. Normalization of GFR was obtained in all cases and they were alive between 6 and 30 months after TIPS. TIPS, therefore, is effective in normalizing serum creatinine in a significant proportion of patients with cirrhosis and severe azotemia and is an alternative treatment of type-1 HRS.

6.4. Extracorporeal albumin dialysis (MARS)

Three pilot studies including 29 patients (26 with type-1 HRS and 21 with alcoholic cirrhosis and/or severe acute alcoholic hepatitis) aimed at assessing MARS in patients with type-1 HRS have been reported [84–86]. Since MARS incorporates standard hemodialysis or continuous veno-venous hemofiltration and GFR was not measured, it is not possible to know the effect of this treatment on renal function. The decrease in serum creatinine observed in most patients could be related to the dialysis or filtration process. However, clear beneficial effects on systemic hemodynamics and on hepatic encephalopathy were observed. The survival rate 1 and 3 months after treatment was 41% (12 patients) and 34% (10 patients), respectively. A recent randomized controlled trial in a large series of cirrhotic patients with hepatic encephalopathy [87], many of them with HRS, has demonstrated a clear beneficial effect of MARS on the rate and time of recovery of encephalopathy. Since the end point of this trial was encephalopathy, no conclusion could be obtained in relation to survival.

7. Available treatments for type-2 HRS

In patients with type-2 HRS the main clinical problem is refractory ascites. Therefore, treatment of type-2 HRS should consider not only survival but also the control of ascites.

7.1. Transjugular intrahepatic portacaval shunt

There are only two pilot studies specifically assessing TIPS in type-2 HRS [57,88]. In one study [88] a significant reduction of serum creatinine (from 2.1 ± 0.6 to 1.4 ± 0.3 one month after TIPS) was observed in 8 out of 9 patients. This was associated to a significant improvement in the control of ascites. Four of these patients died, two within the first month and two 12 and 14 months after the procedure. The remaining 5 patients had longer survival. No data were given on the type and rate of complications associated to TIPS. A second study included 14 patients with type-1 HRS and 17 with type-2 HRS treated by TIPS [57]. Mean baseline serum creatinine concentration in patients with type-2 HRS was only 1.44 ± 0.3 mg/dl but mean creatinine clearance was 28 ± 14 ml/min. A significant improvement in serum creatinine and creatinine
clearance was observed in the whole group of 31 patients as well as an improvement in the control of ascites in 24 cases. Six patients developed TIPS dysfunction and 11 developed hepatic encephalopathy during follow-up. The 1-year probability of survival in the 17 patients with type-2 HRS treated by TIPS was 70%. TIPS is therefore effective in reversing type-2 HRS, although more data on complication rate and survival are needed before advocating widespread use of this procedure. The introduction of covered stents should be a stimulus to re-evaluate the role of TIPS in the management of refractory ascites and type-2 HRS.

7.2. Vasoconstrictors and albumin

Three pilot studies provided data on the effect of terlipressin plus albumin in 26 patients with type-2 HRS [54,55,88]. Reversal of HRS was obtained in most cases (21 cases, 80%). In one of these studies [88] in 11 patients the course of renal function after stopping treatment was assessed, and HRS recurred in all cases. There were no data on survival. The current state of knowledge on vasoconstrictor therapy in type-2 HRS is therefore very poor. It appears to be not as effective as in type-1 HRS due to the high rate of HRS recurrence.

8. Prevention of HRS

Three randomized controlled studies in large series of patients have shown that HRS can be prevented in specific clinical settings. In the first study [59], the administration of albumin (1.5 g/kg IV at infection diagnosis and 1 g/kg IV 48 h later) to patients with cirrhosis and spontaneous bacterial peritonitis markedly reduced the incidence of circulatory dysfunction and type-1 HRS (10% incidence of type-1 HRS in patients receiving albumin vs. 33% in the control group). Hospital mortality rate (10% vs. 29%) and the 3 month mortality rate (22% vs. 41%) were lower in patients receiving albumin. The second study was performed in cirrhotic patients with a high risk of developing SBP and type-1 HRS. Primary prophylaxis of SBP using long-term oral norfloxacin in this study was associated to a significant decrease in 1-year probability of development of SBP and type-1 HRS and a significant increase in the 3-month and 1-year probability of survival [89]. In the third study [90], the administration of the tumor necrosis factor inhibitor pentoxifylline (400 mg 3 times a day) to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (8% in the pentoxifylline group vs. 35% in the placebo group) and the hospital mortality (24% vs. 46%, respectively). Because bacterial infections and acute alcoholic hepatitis are important precipitating factors of type-1 HRS, these prophylactic measures may decrease the incidence of this complication.

References


