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Review

Pathogenesis and management of hepatorenal syndrome in patients with cirrhosis☆

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Hepatorenal syndrome is a severe complication of advanced liver cirrhosis, in patients with ascites and marked circulatory dysfunction. It is clearly established that it has a functional nature, and that it is related to intense renal vasoconstriction. Despite its functional origin, the prognosis is very poor. In the present review, the most recent advances in diagnosis, pathophysiology, and treatment are discussed. Recent developments in pathophysiology are the basis of the new therapeutic strategies, which are currently under evaluation in randomised clinical trials.

Keywords: **Renal failure; Vasoconstrictors; Human albumin; Terlipressin**

1. Introduction

The occurrence of liver failure in patients with cirrhosis was first described during the 19th century, but the term hepatorenal syndrome (HRS) was first introduced in 1932 by Helvig and Schutz [1] to describe a condition of acute renal failure occurring after biliary tract surgery in patients who showed a pathological pattern of acute tubular necrosis or tubular interstitial nephritis. Later on, this term reached a very wide diffusion, and was generally used to describe any kind of simultaneous severe impairment of liver and renal function. When, in the middle of the century it became progressively understood that pathophysiology of acute renal failure is grossly divided into an organic and a functional form of disease, it was clearly shown that renal involvement in advanced liver disease was generally a functional form of renal failure [2].

Further studies showed that functional renal failure in advanced cirrhosis may be further divided into two forms, a more frequent, easily reversible and less severe condition of pre-renal failure due to vascular underfilling (bleeding, diarrhoea, excessive use of diuretics, heart failure), and a more severe condition, which is characterized by intense renal vasoconstriction and is similar in pathophysiological characteristics to conventional pre-renal failure, but does not improve after correction of vascular underfilling. The term HRS was thus restricted to this form of unexplained pre-renal failure in the course of advanced liver disease [3]. Around the same time, it was observed that kidneys of patients dying of HRS could be successfully transplanted to patients with organic renal failure [4], and it was shown that the intense renal vasoconstriction, which is usually observed at renal arteriography in patients with HRS (Fig. 1), disappeared at post-mortem vascular injection [5], emphasizing the functional nature of such renal insufficiency.

In the last few years, there has been an extensive debate on the optimal criteria to define HRS and the first consensus definition was agreed upon at the 1994 meeting of the International Ascites Club [6] (Table 1).

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Abbreviations: HRS, hepatorenal syndrome; ATN, acute tubular necrosis; NO, nitric oxide; TIPS, transjugular intravenous porto-systemic shunt; OLT, orthotopic liver transplantation; MARS, molecular adsorbent recirculating system; SBP, spontaneous bacterial peritonitis.

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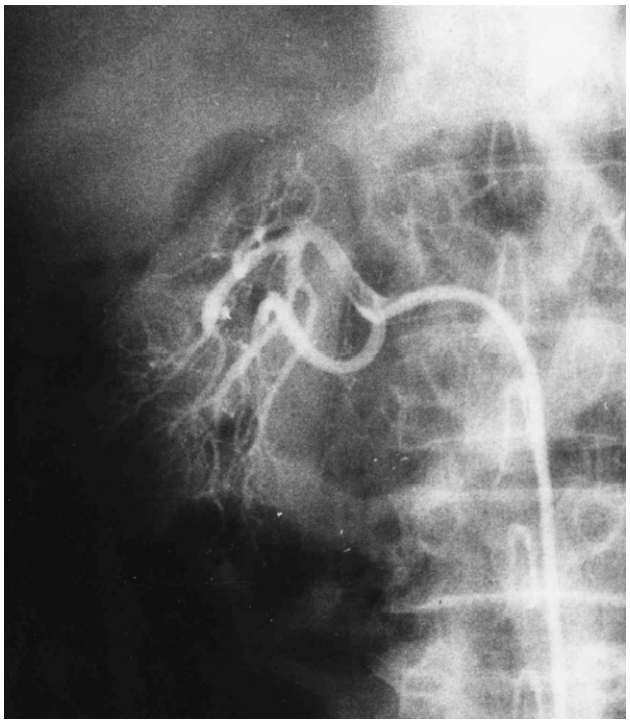

Fig. 1. Intense renal vasoconstriction with poor filling of arterial cortical vasculature at selective right renal arteriography in a patient with hepatorenal syndrome (Personal observation, 1975).

With the extensive application of these diagnostic criteria, it soon became apparent that there were some ambiguities and pitfalls in the definition of HRS, and that new and more precise diagnostic criteria were required. These new criteria were developed by the International Ascites Club at a focused study group held in San Francisco in 2006, and reported in 2007 [7] (Table 2). It is evident that this new definition is more precise (clear definition of the procedures requested to exclude a pre-renal failure), but is less strict than the previous one, since patients with recent or present infections, in particularly spontaneous bacterial peritonitis (SBP), are not excluded from a diagnosis of HRS.

Such changes should be taken into consideration when comparing treatment results of new studies with those obtained in the previous years, because changes in definitions may lead to a sort of stage migration, a phenomenon that is well known to bio-statisticians [8], and is characterized by an improvement in outcome in both stages involved (Fig. 2). Indeed, if patients with infections unresponsive to a 2-day infusion of albumin have a mortality rate intermediate between classical HRS and pre-renal azotemia (with the values suggested in the figure), the migration of these patients towards the group of patients with HRS would decrease mortality in HRS from 80% to 65%, and that of pre-renal azotemia from 27.5% to 20%.

2. Natural history

HRS is a potentially reversible form of renal failure that occurs in patients with cirrhosis and ascites as well as in patients with acute liver failure. In cirrhotic patients with ascites, pre-renal failure (42%) and acute tubular necrosis (ATN) (38%) represent the most common forms of acute renal failure while HRS [9] is somewhat less frequent (20%) (Table 3). The incidence of HRS in patients with cirrhosis and ascites is equal to 18% after 1 year, and reaches 39% after 5 years [10]. In almost half the cases of HRS, one or more precipitating factors may be identified, including bacterial infections (57%), gastrointestinal hemorrhage (36%), and large volume paracentesis (7%) [10].

HRS is characterized by (a) marked renal vasoconstriction with a consequent reduction in renal plasma flow and glomerular filtration rate, (b) the absence of pathological changes in the renal tissue, and (c) preserved renal tubular function. HRS usually arises when the chronic liver disease is associated with a marked circulatory dysfunction with low values of arterial pressure despite an overactivity of the sympathetic nervous and renin–angiotensin systems, which, according to the

Table 1
International Ascites Club's diagnostic criteria of hepatorenal syndrome (1996; Ref. [6])

Major criteria:
- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate (s-creatinine >1.5 mg/dL or creatinine clearance <40 mL/min)
- 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 >500 g/day in patients with ascites without peripheral edema or 1000 g/day in patients with peripheral edema)
- No sustained improvement in renal function (decrease in s-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
- Proteinuria <500 mg/day nad no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Additional criteria (not necessary for the diagnosis):
- Urine volume <500 mL/day
- Urine sodium <10 mEq/L
- Urine osmolality greater than plasma osmolality
- Urine red blood cells <50/HPF
- Serum sodium concentration <130 mEq/L

Table 2
New International Ascites Club's diagnostic criteria of hepatorenal syndrome (2007; Ref. [7])

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL
- No improvement in serum creatinine (decrease to a level of <1.5 mg/dL) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (<50 RBC/high power field) and/or abnormal renal ultrasonography

"*arterial vasodilation hypothesis*" occurs as a consequence of a marked arterial vasodilation, mainly located in the splanchnic circulation [11]. Until a few years ago, the prognosis of cirrhotic patients developing HRS was very poor with mortality reaching 100% in some series, and a median survival time of two weeks from diagnosis [10]. Thereafter, some new promising treatments of HRS have been proposed, and improvement in survival has been observed in some studies.

3. Diagnosis of HRS

The diagnostic criteria for a diagnosis of HRS have been reported above in the introduction (Tables 1 and 2). Within the diagnostic category of HRS, two different types of HRS can be distinguished (Table 4). Type-1 HRS is characterized by a rapid progression of renal failure; therefore the main clinical presentation is overt acute renal failure. By contrast, in patients with Type 2 HRS the degree of the impairment of renal failure is less severe and more stable over time. As a consequence, the main clinical problem in these patients is refractory ascites (Table 4). The two types of HRS substantially differ in prognosis, since median survival of type-1 HRS averages 2 weeks, whilst that of type 2 is generally around 4–6 months [12]. Besides the obvious differences in the severity of renal function impairment, further pathophysiological differences between type-1 and type-2 HRS are not fully elucidated, and it is not clearly defined if the two types share all the same pathophysiological mechanisms; nevertheless, it may be observed that Type-1 HRS is often induced by a precipitating event (Table 5), in particular spontaneous bacterial peritonitis [13,14]. Almost one third of patients with spontaneous bacterial peritonitis develop a progressive form of renal failure [13,14] which in most cases fulfils the most recent diagnostic criteria of type 1 HRS [14]. More

Table 3
Acute renal failure in patients with cirrhosis and ascites (Ref. [9])

1. Acute tubular necrosis (41.7%)
2. Pre-renal failure (38%)
3. Hepatorenal syndrome (20%)
4. Post-renal failure (0.3%)

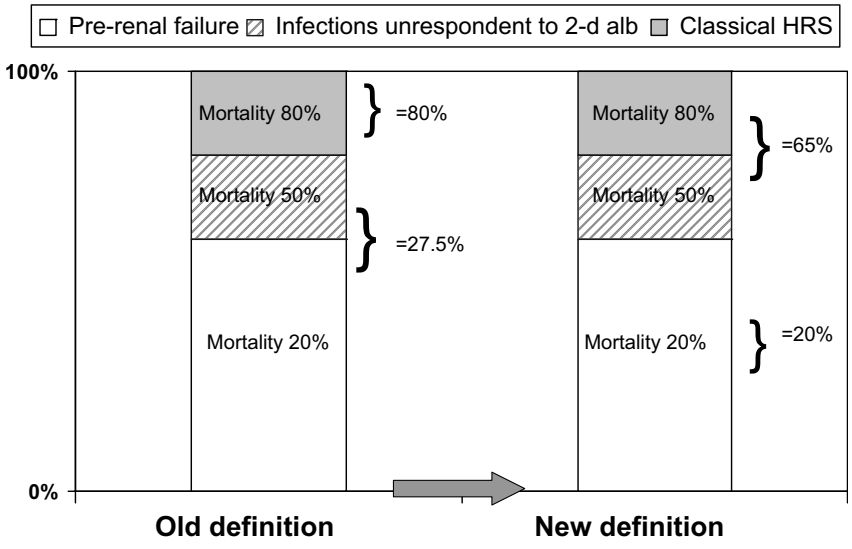

Fig. 2. Expected changes in mortality rate of HRS and of pre-renal failure according to the old (1996 – Ref. [6]) and new (2007- Ref. [7]) definitions of HRS because of the stage-migration effect of patients with infections not responding to a 2-day course of albumin. Frequencies and mortality rates are approximate and only used for exemplifying purpose.

Table 4
Clinical types of hepatorenal syndrome (Ref. [7])

- Type-1 hepatorenal syndrome: rapidly progressive reduction of renal function as defined by doubling of the initial s-creatinine to a level >2.5 mg/dL (226 μM/L) in less than two weeks Clinical pattern: acute renal failure
- Type-2 hepatorenal syndrome: moderate renal failure (s-creatinine ranging from 1.25 to 2.5 mg/dL or 113–226 μM/L) with a steady or slowly progressive course Clinical pattern: refractory ascites

recently it has been observed that renal failure can be precipitated in cirrhotic patients with ascites by all types of bacterial infections. In most cases renal failure is transient and recovers after the resolution of the infection. However, in some cases an acute renal failure with the hallmarks of type 1 HRS can also be precipitated by urinary, biliary, or intestinal infections [15]. The risk factors for the development of renal failure after bacterial infections are (a) the severity of infection, (b) the MELD score at the diagnosis of infection and (c) the persistence of infection despite antibiotic treatment [15,16]. In addition, the risk of developing type-1 HRS following a bacterial infection is higher in patients with cirrhosis who already present a type-2 HRS [13,14]. There are some observations suggesting that type-1 HRS in this clinical situation may occur as a consequence of an abrupt and severe additional deterioration in circulatory dysfunction characterized by a further enhancement in splanchnic arterial vasodilation and a decrease in cardiac output.

4. Pathophysiology of HRS

The causes of the intense renal vasoconstriction underlying the occurrence of HRS are not fully understood. Compared to control subjects or cirrhotic patients with ascites but without HRS, patients with HRS consistently show lower splanchnic vascular resistance. Renal vasoconstriction, which is the pathophysiological basis of HRS, therefore develops in a context of a marked reduction of effective circulating volume related to peripheral arterial vasodilation [6,13]. The involvement of endogenous vasoconstrictor systems induced by the reduction of effective circulating volume in the development of HRS is clearly shown in clinical [17–19] and experimental studies [20]. The most recent advances in our understanding of the pathogenesis of HRS have focused on mainly two new aspects. The first one is that the peripheral arterial vasodilation occurs mainly in the splanchnic arterial vascular bed and the second is that in patients with cirrhosis and HRS, the modulation of cardiac output is relatively unable to prevent the severe reduction of effective circulating volume due to the splanchnic arterial vasodilation.

Table 5
Precipitating events of hepatorenal syndrome

- Spontaneous bacterial peritonitis
- Paracentesis without plasma expansion
- Gastrointestinal hemorrhage
- Alcoholic hepatitis

The first of these concepts has been formulated on the basis of the results of some clinical studies in which Doppler ultrasonography was used to evaluate regional blood flow in cirrhotic patients. These studies consistently demonstrated that arterial vasodilation occurs in the splanchnic circulation in patients with cirrhosis, while arterial vasoconstriction occurs in other vascular beds, including renal, brachial, femoral, and cerebral beds [21–28]. At the same time, clinical studies directed to assess tissue-related blood flows, such as cutaneous and muscular blood flows, gave contrasting results, ranging from low to normal or even increased values [29]. These discrepancies were also dependent on the methods used to estimate blood flow, which included color Doppler ultrasonography [21,30], nuclear medicine techniques [31], and plethysmography [32]. The main clinical problem related to abnormalities of muscle blood flow is the occurrence of muscle cramps, which may be improved by a chronic expansion of effective plasma volume by means of albumin administration [33], a procedure which probably contributes to correct the abnormalities of muscle blood flow.

Splanchnic arterial vasodilatation is thought to be the consequence of an increased release of endogenous vasodilators due to portal hypertension and/or hepatic failure. Among the endogenous vasodilators, nitric oxide [34], carbon monoxide [35], glucagon [36], prostacyclin [37], adrenomedullin [38] and endogenous opiates [39] seem to be the most clearly involved. A detailed analysis of all possible vasodilators involved in the pathogenesis of splanchnic arterial vasodilations goes beyond the purposes of this paper; however it is apparent that several endogenous vasodilators can contribute to splanchnic arterial vasodilation in every stage of progression of cirrhosis, and that the relative role of each of them can vary in the different stages of the liver disease [40]. Indeed, early in the course of the disease, the decrease in the systemic vascular resistance due to the arterial splanchnic vasodilation is compensated by the increase in heart rate and in cardiac output (the so-called "hyperdynamic circulation"). However, as the liver disease progresses leading to a further impairment in portal hypertension and hepatic failure, the hyperdynamic cir-

culation is no longer adequate to compensate the severity of the reduction of the effective blood volume due to the splanchnic arterial vasodilation. This leads to a further activation of the systemic endogenous vasoconstrictor systems (the sympathetic nervous system, the renin–angiotensin system, and the non-osmotic release of vasopressin). The activation of these systems is thought to be the main efferent mechanism of the functional renal abnormalities which characterizes the course of the liver disease such as, renal sodium retention leading to ascites, renal water retention leading to hyponatremia, and severe arterial renal vasoconstriction leading to HRS. HRS develops during the most advanced stages of cirrhosis in the presence of an extreme reduction of the effective blood volume and, as a consequence, in presence of a extreme activation of the systemic vasoconstrictor systems [22].

A study from our laboratory seems to confirm that HRS is the clinical equivalent of the extreme reduction of the effective blood volume due to splanchnic arterial vasodilation with an extreme hyperdynamic circulation since we observed higher heart rate and higher cardiac output in patients with cirrhosis and type-2 HRS than in those without HRS [41]. However, these observations were not in agreement with some previous studies which reported that in HRS cardiac output was similar or even reduced as compared to normal subjects or to patients with cirrhosis without HRS or without refractory ascites [42,43]. A possible interpretation of these discrepancies could take into consideration the fact that effective circulating volume does not depend only on vascular peripheral resistance, but also on a series of other factors (Table 6) which are prone to be altered in patients with cirrhosis [44].

A recent study investigated cardiac output in patients who developed type-1 HRS following spontaneous bacterial peritonitis, and observed that the development of type-1 HRS was associated with a decrease in arterial pressure, a marked decrease in cardiac output, and a marked activation of the systemic vasoconstrictor systems, but was not associated with a further decrease of peripheral vascular resistance [45]. A further study investigated the clinical course of cirrhotic patients before and after the onset of HRS. Patients who developed HRS had lower baseline values of arterial pressure and cardiac output and higher baseline values of plasma renin activity and plasma norepinephrine concentration as compared with those who did not develop this complication. In addition, patients who developed HRS had a further reduction of arterial pressure and cardiac output and a further increase of plasma renin activity and of plasma norepinephrine at the time of the onset of HRS [46]. Taking together these findings, it may be hypothesized that an hyperdynamic circulation is essential for the maintenance of an effective blood volume in patients with cirrhosis and that a decrease of cardiac output, due to a precipitating event such as a bacterial infection or to other factors, can lead to a severe effective hypovolemia, a severe arterial vasoconstriction, thus precipitating HRS.

Table 6
Determinants of effective circulating volume (Ref. [44])

- Systemic vascular resistance
- Blood volume
- Redistribution of blood volume
- Total vascular compliance
- Cardiac output
- Arterial compliance

The reasons why cardiac output decreases in end-stage liver disease is still poorly elucidated, but in recent years several specific cardiac abnormalities have been recognized, including reduced systolic and diastolic responses to stress stimuli, electrophysiological repolarization changes, and enlargement of cardiac chambers. Overall, these abnormalities are commonly termed as "cirrhotic cardiomiopathy" [47]. In addition, other factors, such as the release of endotoxins, or a further release of biologically active substances (inflammatory cytokines, nitric oxide, carbon monoxide and other vasoactive substances evoked by the reaction to bacterial infection) may further impair cardiac function in patients with end-stage liver disease. Furthermore, a severe sepsis or a septic shock is often associated with adrenal insufficiency in patients with cirrhosis and ascites and it correlates with hemodynamic instability and the development of HRS in these patients [48,49]. However, several findings suggest that the decrease in cardiac output in cirrhotic patients who are going to develop HRS is mainly related to a reduction of the venous return of blood to the heart (pre-load). The reasons for this are that (i) the reduction of cardiac output in these patients is not associated with an increase in cardiopulmonary pressure [46,47]; (ii) the hemodynamic scenario which represents the basis of HRS may be frequently reverted by the insertion of a transjugular intravenous porto-systemic shunt (TIPS) which increases pre-load, and consequently cardiac output [50].

Further, pathophysiological issues are still under debate, including (i) the pathophysiological difference between type-1 and type-2 HRS, and (ii) the role of intrarenal vasoconstrictors and vasodilators in the pathogenesis of HRS. It is generally held that type-1 HRS in cirrhosis is often precipitated by bacterial infections or gastrointestinal bleeding, and often develops in a context of multi-organ failure characterized by heart failure, encephalopathy, and further impairment in liver function. This complex clinical situation is frequently defined as "acute on chronic liver failure". On the contrary, type-2 HRS develops spontaneously in many patients with cirrhosis and ascites representing the real functional renal failure associated with cirrhosis. However,

it is not completely defined if a reduction of cardiac output is essential for the occurrence of type-2 HRS, as it appears to be for the development of type-1 HRS.

The administration of an antagonist of the endothelin's receptors has been shown to improve renal perfusion in patients with HRS without affecting arterial pressure systems, demonstrating that endothelin may mainly act as an intrarenal vasoconstrictor [51]. This interpretation has been recently challenged by a study showing that the administration of a non-selective endothelin receptor antagonist cause a deterioration of renal function in patients with type 2 HRS [52]. Thus, the role of endothelin in the pathogenesis of HRS needs further investigation. Other studies in patients with cirrhosis and ascites have reported an increase in intrarenal release of other very potent vasoconstrictors, such as 20-HETE and leukotrienes [53–56].

Finally, in cirrhotic animals with ascites a progressive renal failure may be provoked by the administration of inhibitors of the renal release of local vasodilators, which include prostaglandins E2 e I2 [57], endogenous natriuretic peptides [58] and nitric oxide [56]. Conversely, in cirrhotic patients with ascites the administration of non-steroidal anti-inflammatory drugs may cause an acute form of renal failure which is quite similar to HRS for clinical and biochemical aspects [59].

5. Therapy of HRS

Orthotopic liver transplantation (OLT) represents the ideal treatment option in cirrhotic patients with HRS, because of its ability to remove the main causes of this complication (portal hypertension and liver failure). However, the presence of HRS at the time of transplant has a negative influence on the transplant outcome as assessed by survival, costs and quality of life [60]. This influence is not very marked, however, since survival rate averages 60% at three years, compared with an expected 70–80% in patients without HRS. Patients with HRS undergoing OLT have an increased risk of complications after OLT, spend a longer time in the intensive care unit, and in hospital, and overall have a higher in-hospital mortality. As far as renal function is concerned, soon after OLT glomerular filtration rate further decreases in patients with HRS because of surgery stress, infections, use of immunosuppressants, and other factors, so that many patients require hemodialysis (35% as compared with 5% of patients without HRS at the time of OLT) [60]. Despite the prompt correction of the hemodynamic and neurohumoral abnormalities which is clearly apparent within one month after OLT [61], glomerular filtration rate only partially recovers, reaching 30–40 ml/min by 1–2 months. This moderate renal insufficiency persists during follow-up, and may progress to an end-stage renal failure, if the immunosuppressive strategy is not adequate [62].

Up to the end of the 90's very few patients with cirrhosis and HRS underwent OLT, since, due to the rapid evolution of Type-1 HRS, most patients died before OLT could be performed. The introduction of MELD and the strategy of stratifying OLT priority according to MELD, have partially solved this problem, since patients with high serum creatinine values have now a higher priority for OLT. In addition, from the end of the 90's new treatment options for HRS have been proposed. Among them, the use of albumin and vasoconstrictors has proved to be an effective "treatment bridge" towards OLT, thus increasing the number of patients with type-1 HRS who reach OLT [63]. These new therapeutical options will be discussed separately for type-1 and type-2 HRS.

5.1. Therapeutic options for type 1 HRS

The efficacy of TIPS in the treatment of type-1 HRS has been evaluated only in a few pilot studies [50,64]. A significant suppression of the endogenous vasoconstrictor systems and a decrease in s-creatinine levels were observed after TIPS in most patients, but the rate of the s-creatinine decrease was slower than that generally reported after albumin infusion and vasoconstrictors. The reversal of type-1 HRS was observed in 57–71% of patients. The recurrence of HRS was rare, provided that no TIPS dysfunction occurred. Survival rates at 1 and 3 months ranged between 71% and 100% and 28.5% and 64%, respectively. Both studies excluded patients with a history of severe encephalopathy, or serum bilirubin levels over 85 μmol/l (5 mg/dl) or Child–Turcotte–Pugh score >12 (all conditions frequently observed in unselected patients with type-1 HRS); therefore the applicability of TIPS in this clinical setting is rather limited.

The most promising new therapeutical option for Type-1 HRS is based on the recent pathophysiological acquisitions about the relationships between splanchnic vasodilation and renal vasoconstriction that were reported above. Indeed, a series of recent studies have suggested that the prolonged use of vasopressin derivatives, such as ornipressin [65,66] or terlipressin [67–75], or of α-adrenergic agonists (noradrenaline, midodrine) [76–79] in association with the prolonged infusion of human albumin are useful in the treatment of patients with type-1 HRS. Overall, although most of the information comes from non-randomised studies, the effect of this treatment can be summarized as follows: (1) recovery of renal function is obtained in 40–60% [66–78], (2) the recovery of renal function is maintained in over 70–80% of patients after the treatment is withdrawn [67–79], (3) if recurrent HRS occurs after treatment withdrawal, re-treatment is often effective, (4) 40–50% one-month transplant-free survival can be

expected [67–77,80], which is much better that of untreated patients [80,81], (5) in most cases dilutional hyponatremia associated with HRS improves.

The choice of drug and the schedule of treatment varied across these studies. To date, terlipressin is the most widely used vasoconstrictor in the treatment of type-1 HRS [67–79]. In several pilot studies, terlipressin has been used in more than 200 patients either as i.v. bolus injections starting from an initial dose of 0.5 mg every 4–6 h or as a continuous intravenous infusion starting from an initial dose of 2 mg/day. In patients without a response (reduction of serum creatinine less than 30% in 3 days), the initial dose of terlipressin was generally doubled. The maximum doses of terlipressin used in the treatment of type 1 HRS were 2 mg as i.v. bolus injections every 4–6 h or 12 mg/day in continuous infusion. Partial or complete reversal of type-1 HRS was observed in almost 59% of patients. In two studies in which terlipressin was given alone, recovery of renal failure was less frequent that in the studies in which terlipressin was associated with albumin [73,77]. Up to now, a shorter experience is available on midodrine or octreotide. These drugs were used in three pilot studies in a total of 79 patients [76,79,80]. A complete recovery of renal failure was observed in 49% of patients. In most patients midodrine administration started at 5-10 mg *t.i.d.* orally, with the goal of increasing the dose to 12.5 or 15 mg *t.i.d.* if a reduction of serum creatinine was not observed. Octreotide administration started at 100 μg subcutaneously *t.i.d.* with the goal of increasing the dose to 200 μg subcutaneously *t.i.d.* if a reduction of serum creatinine was not observed. Experience of the use of i.v. norepinephrine in the treatment of patients with type-1 HRS is much more limited [78].

Nevertheless, the preliminary results of the two first controlled clinical trials comparing terlipressin and albumin with albumin alone did not confirm a beneficial effect of terlipressin and albumin on 2 or 3 month survival in patients with type-1 HRS (Table 7) [82,83]. Unfortunately, detailed information on these trials is still unavailable, and it is difficult to draw firm conclusions from these preliminary data. In particular, it is unclear if the differences between the two outcome measurements, i.e. recovery of renal function and survival, are related to a transient benefit in renal function, or to the occurrence of different complications eventually leading to death. Nevertheless, the overall survival, which was much higher than usually expected, is surprising, particularly in the American study; this was particularly evident for patients who received the conventional treatment, which suggests the possible use of different inclusion criteria or a possible benefit from the use of albumin by itself.

The recent introduction of innovative techniques for extracorporeal liver function support like the molecular adsorbent recirculating system (MARS) has made it possible to recover hepatic function to some extent, even transiently. When MARS was applied to the treatment of type-1 HRS, a possible benefit from this treatment was suggested as a consequence of removal of albumin-driven vasoactive substances such as nitric oxide, tumor necrosis factor, and other proinflammatory cytokines. Such effects resulted in clinical improvement in renal function, and this also produced a positive effect on 30 day survival in these patients (37.5% versus 0%) [84]. So, it is easy to hypothesize that in the near future MARS should be tested as an additional treatment together with vasoconstrictor and albumin in the treatment of type-1 HRS in patients with marked impairment of liver function.

Although the most important aim of treating patients with type-1 HRS with vasoconstrictors and albumin is that of bridging these patients towards OLT, it is evident that such treatment should also be tested in non-transplant candidates, with the aim of prolonging survival, since in some patients possible survival benefits are far from trivial [85].

5.2. Therapeutic options for type-2 HRS

The main clinical problem in patients with type-2 HRS is not acute renal failure, but refractory ascites. TIPS is frequently used as an alternative to therapeutic paracentesis in the treatment of refractory ascites associated or not with type-2 HRS. Up to now, five controlled studies comparing therapeutic paracentesis to TIPS in refractory or tense ascites have been published [86–90]. Although no separate analysis for patients with type-2 HRS were performed in these trials, it is reasonable to conclude that (1) TIPS is more effective than paracente-

Table 7
Terlipressin and albumin vs. albumin alone in cirrhotic patients with type-1 hepatorenal syndrome

	[83]		[82]	
	Terlipressin + Albumin	Albumin	Terlipressin + Albumin	Albumin
Response rate (%)	39*	9	34**	13
Survival rate (%)	At 3 months	At 3 months	At 2 months	At 2 months
	26	18	48	48

Preliminary results of two randomised controlled studies (Ref. [82,83]).
* $p < 0.05$.
** $p < 0.01$.

sis in the control of ascites, (2) the risk of encephalopathy is greater in patients who are treated with TIPS, and (3) survival is similar. Nevertheless, recent meta-analyses show that TIPS significantly improve transplant-free survival in cirrhotic patients with refractory ascites [91–93]. There are only two pilot studies specifically addressing the effect of TIPS in patients with type-2 HRS [50,94], but there are reports of series of consecutive patients treated with TIPS, and no comparison with different treatments is possible. In both reports s-creatinine decreased, and ascites was more easily controlled. The 1-year survival was encouraging (70%) [50].

The effects of vasoconstrictors and albumin in type-2 HRS treatment have been the subject of few studies, none of which is an RCT. The percentage of response to the treatment in terms of recovery of renal function was similar to that reported in patients with type-1 HRS [72,73,94], while survival was clearly longer (100% at 3 months), as expected from the data on the natural history of this condition.

5.3. Prevention of HRS

Being the consequence of many complex alterations in systemic and local hemodynamics, HRS could be unspecifically prevented by all treatments contrasting these alterations. In this context, prevention of bacterial infections, and in particular of SBP, also plays a role in the prevention of HRS following infections. This has been demonstrated in a clinical trial of long-term norfloxacin prophylaxis of SBP, in which a decrease in the risk of developing type-1 HRS was also shown [95]. A more specific approach to the prevention of SBP-induced HRS has been suggested by Sort et al. in a RCT of intensive albumin treatment of SBP (1.5 g/kg b.w. the first day, plus 1 g/Kg b.w. the third day) [96]. In this trial, patients receiving this intense albumin treatment showed a marked decrease in risk of developing HRS, and in hospital and 3-month mortality (relative risk decrease ranging from half to two thirds). The mechanisms underlying this important preventive effect of albumin on the occurrence of HRS after SBP are not fully elucidated, but these may include the prevention of further reduction of the effective circulating volume mediated by an increase in cardiac preload and/or an improvement of cardiac contractility [97]. This latter effect of albumin is probably related to its ability to bind NO and proinflammatory cytokines, which may cause a negative inotropic effect on the heart [98].

6. Conclusions

The most recent advancements in our understanding of the pathophysiology of HRS are the basis of the new therapeutic interventions. Besides OLT, which is the best treatment but is seldom applicable, the combined use of vasoconstrictors and albumin is the most promising option. However, further studies are needed to prove its clinical usefulness.

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