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REVIEW

Hepatorenal syndrome in patients with cirrhosis

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Abstract Type 1 hepatorenal syndrome (HRS) is a severe complication of end-stage cirrhosis. Type 1 HRS is an acute functional renal failure (i.e. glomerular hypofiltration) with no other explanation than the presence of the circulatory and neurohumoral alterations associated with severe chronic liver disease. Plasma volume expansion does not improve renal function. In contrast, administration of the vasopressin analog terlipressin, a splanchnic and systemic vasoconstrictor, may improve renal function and be used while awaiting liver transplantation.

Key words: cirrhosis, renal failure, vasoconstrictors.

DEFINITIONS AND DIAGNOSIS

Hepatorenal syndrome (HRS) is a renal failure which complicates end-stage cirrhosis with ascites.[1–5] There are two clinical types of HRS: type 1 and 2.[2] Type 1 HRS is characterized by the development of acute renal failure; that is, a doubling of initial serum creatinine to levels above 130 μmol/L or a 50% decrease in the initial 24-h creatinine clearance to below 20 mL/min in less than 2 weeks.[2] Patients with type 1 HRS are in poor condition. Type 2 HRS is characterized by moderate and stable renal failure in patients who have a better condition than those with type 1 HRS.[2] This review will focus on the mechanisms, diagnosis, prognosis and treatment of type 1 HRS, and the term HRS will be used instead of type 1 HRS.

Information on the frequency of HRS is controversial. In a large North American study of 3860 patients with ascites, HRS was diagnosed in less than 1% of patients.[6] Another study of 234 non-azotemic patients with ascites showed that the probability of developing HRS was 20% and 40% at 1 and 5 years, respectively.[7] The reasons for these apparent discrepant results are unclear.

In patients with cirrhosis, prerenal failure may be caused by events other than HRS (Table 1). Moreover, prerenal azotemia is not the only mechanism of acute renal failure. It may occur as a result of ischemic or toxic tubular necrosis or other intrinsic renal causes (Table 1). Furthermore, untreated or uncontrolled HRS may lead to ischemic tubular necrosis.

It has been suggested that the diagnosis of acute renal failure may be made by examining the urinary sediment.[7,8] For example, brown granular casts and tubular epithelial cells, alone or in casts, are present in acute tubular necrosis.[7,8] However, these alterations are absent in 20% of cases of acute tubular necrosis. The use of urinary indexes can help distinguish prerenal failure from intrinsic renal failure (Table 2). As prerenal failure is always associated with an increased stimulus of sodium and water tubular reabsorption, the ratio of urinary to plasma creatinine is usually higher, and the urinary concentration is lower than in intrinsic acute renal failure. However, urinary indexes should be interpreted with caution. Blood and urinary samples should be taken before any fluid replacement or the administration of dopamine, mannitol or other diuretic agents. The urine must not contain glucose or radiographic contrast material. In some cases of acute tubular necrosis, patients may have fractional excretion of sodium of less than 1%.[9,10] Conversely, in certain cases of prerenal failure (including HRS), patients may have fractional excretion of sodium of more than 1%.[2,9]

Thus, the diagnosis of HRS is not always easy, and the International Ascites Club has suggested that five criteria must be present to confirm the diagnosis of HRS[2]: (i) severe cirrhosis; (ii) glomerular hypofiltration based on a 24-h creatinine clearance below 40 mL/min or a serum creatinine above 130 μmol/L; (iii) absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs; absence of gastrointestinal fluid loss (weight loss > 500 g/day for

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Table 1 Causes of acute renal failure in patients with cirrhosis

Prerenal causes
Gastrointestinal, renal fluid losses
Hemorrhage
Shock
Sepsis
Congestive heart failure
Medications: NSAIDs*, radiocontrast agents
Hepatorenal syndrome
Intrinsic causes
Tubular necrosis
Ischemia: all causes of prerenal azotemia
Toxins: aminoglycosides, radiocontrast agents
Interstitial nephritis
Immuno-allergic (drugs)
Infection
Glomerulonephritis
Infection
Postrenal causes
Obstruction of urinary flow tract(s).

*Non-steroidal anti-inflammatory drugs.

Table 2 Urinary indexes in patients with acute renal failure due to prerenal (functional) or renal (intrinsic) causes

Index	Prerenal causes	Renal causes
Urinary sodium concentration (mmol/L)	< 20	> 40
Fractional excretion of sodium (%)	< 1	> 1
Ratio of urinary to plasma creatinine	> 40	< 20
Ratio of urinary to plasma osmolality	> 1.5	< 1.1

several days in patients with ascites without peripheral edema or 1000 g/day in patients with peripheral edema); (iv) no sustained improvement in renal function (decrease in serum creatinine to ≤ 130 μmol/L or increase in 24-h creatinine clearance to ≥ 40 mL/min) despite the optimization of volemia (by stopping diuretics and infusing 1.5 L of isotonic saline); and (v) proteinuria below 0.5 mg/L and no ultrasonographic evidence of renal obstructive disease.

MECHANISMS OF HEPATORENAL SYNDROME

Patients with HRS have marked vasoconstriction of renal arterioles leading to decreases in renal blood flow and the glomerular filtration rate (GFR).[1–4,11] As renal hypoperfusion is not associated with cellular injury, patients have functional renal failure (also called prerenal failure or prerenal azotemia).[1–4,8,9]

Patients with HRS have marked splanchnic vasodilation, which causes a reduction in systemic vascular resistance (i.e. systemic vasodilation), and a decrease in effective arterial blood volume, inducing overactivation of endogenous vasoconstrictor neurohumoral systems; that is, the sympathetic nervous system and the renin–angiotensin system.[11] The respective mediators of these systems, norepinephrine and angiotensin II, are potent renal vasoconstrictors and contribute to renal hypoperfusion and the resulting glomerular hypofiltration (Fig. 1).[1–4,11] The finding that vasodilation in the splanchnic vascular bed leads to vasoconstriction in the renal circulation is the rationale for using a splanchnic vasoconstrictor in the treatment of renal failure in patients with HRS.

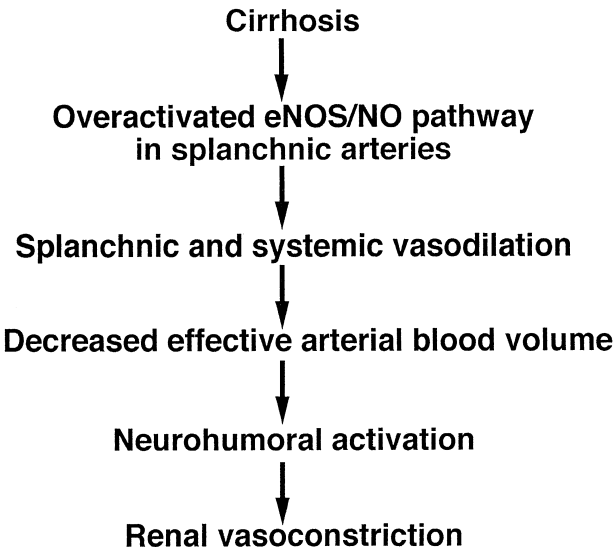

Figure 1 Proposed mechanism of renal vasoconstriction in patients with hepatorenal syndrome. eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

In patients with cirrhosis and ascites, serum concentrations of nitrite and nitrate (products that indicate nitric oxide (NO) oxidation) have been shown to be higher in those patients with HRS than in those without.[12] This suggests that patients with HRS have marked increases in endogenous NO production. As NO is a potent endothelium-derived relaxing factor,[13] marked vasodilation in patients with HRS may be due to an overproduction of NO by the endothelium in splanchnic arterial walls (Fig. 1). This hypothesis is indirectly supported by results showing increased NO production in isolated superior mesenteric arteries in cirrhotic rats with ascites.[14] Moreover, splanchnic arterial overproduction of NO in cirrhotic rats has been shown to be caused by an upregulation of the endothelial NO synthase (NOS).[15]

In one study in patients with HRS, plasma endothelin-1 concentrations were significantly higher in the renal vein than in the renal artery,[16] suggesting overproduction of endothelin-1 (or a decrease in the plasma clearance of endothelin-1) in the kidneys of these patients. Thus, in patients with HRS, renal arterioles

may be exposed to elevated endothelin levels. As endothelin-1 is a potent renal vasoconstrictor,[17] elevated endothelin levels may contribute to renal vasoconstriction in these cases. This hypothesis is supported by preliminary results showing that the administration of an endothelin receptor antagonist induced an increase in GFR in patients with HRS.[18]

In patients with ascites, the urinary excretion of vasodilator prostaglandins (PG) such as PGE_2 and 6-keto-$PGF_{1\alpha}$ (a stable metabolite of the vasodilator PGI_2) has been shown to be lower in patients with HRS than in patients without.[3] Interestingly, the urinary excretion of vasoconstrictor PG, such as thromboxane B_2, was lower in patients with HRS than in non-azotemic cirrhotic patients with ascites.[3] Finally, inhibition of PG synthesis following the administration of a non-steroidal anti-inflammatory drug is known to induce a marked decrease in GFR in non-azotemic cirrhotic patients with ascites.[3] These findings suggest that a decrease in vasodilator PG production (without any associated increase in vasoconstrictor PG) may contribute to renal vasoconstriction in patients with HRS.[3,4]

CLINICAL PRESENTATION

At diagnosis, patients with HRS have severe cirrhosis with ascites, low arterial pressure and hyponatremia.[5] In 50–70% of patients, HRS is preceded by an event that may be a precipitating factor.[5,7] Several precipitating factors have been identified: severe bacterial infections (without shock) such as spontaneous bacterial peritonitis (SBP) or septicemia;[5,7] portal hypertensive bleeding (without shock);[5,7,19] therapeutic paracentesis (even if ascites removal is followed by the administration of a plasma expander);[7] and acute alcoholic hepatitis.[20] Certain patients may have more than one precipitating factor.[5]

PROGNOSIS OF HEPATORENAL SYNDROME

Spontaneous regression of HRS is very rare.[7] Hepatorenal syndrome is a life-threatening complication of cirrhosis.[5,7] The median survival time is less than 2 weeks.[7] A retrospective multicenter study investigating the predictive factors of survival in 99 patients with HRS treated with terlipressin, showed that the only independent predictive factors of survival were a Child–Pugh score ≤ 11 and the improvement of renal function during terlipressin therapy.[5] In other words, this study shows for the first time that renal failure has an impact on survival independent of that related to the severity of the underlying liver disease. Interestingly, another study performed in cirrhotic patients admitted for upper gastrointestinal bleeding showed that the only variables with predictive value for in-hospital mortality were the presence of hemorrhagic shock and the development of renal failure.[19]

Most patients die from multiorgan failure: liver failure, renal failure (terminal ischemic tubular necrosis), circulatory failure and acute respiratory distress syndrome.[5] Multiorgan failure is precipitated by severe bacterial infections that are known to occur during the course of HRS.[5,6]

TREATMENT OF HEPATORENAL SYNDROME

Liver transplantation is the only treatment that can cure end-stage cirrhosis and thus HRS.[3] However, patients who are transplanted with HRS have a lower probability of postoperative survival (e.g. 71% compared to 83% at 1 year) and a higher probability of developing postoperative complications than patients without HRS.[21] Therefore, bridges to liver transplantation are needed. In addition, treatment for HRS is needed in patients who are not candidates for liver transplantation.

The ideal treatment must meet at least three aims. First, it should replace or restore certain homeostatic functions (e.g. elimination of water-soluble metabolic waste products other than carbon dioxide)[22] that have been lost during kidney failure. Second, a substantial increase in survival must be achieved, for example in type 1 HRS, from less than 2 weeks to 3–6 months, which is the mean delay to obtain a liver transplant. Finally, treatment should not have any severe adverse effects.

Renal replacement therapy

Although there are numerous renal replacement therapies, there is only one randomized study in a small series of patients, comparing the molecular adsorbent recirculating system (MARS) (eventually combined with intermittent venovenous hemofiltration) with intermittent venovenous hemofiltration alone.[23] The probability of survival was significantly higher in the 'MARS' group than in the 'hemofiltration-alone' group (median survival was 10 days and 4 days, respectively). It is very important to note that values for median survival were shorter than the median survival of 12 days found in another study in untreated patients with HRS.[7]

Alternatively, uncontrolled studies using mainly intermittent hemodialysis[3] suggest that this treatment is not effective because most patients die during treatment and because of a high incidence of severe side-effects: arterial hypotension, coagulopathy, and gastrointestinal bleeding. Thus, in patients with HRS, intermittent hemodialysis should only be used in selected cases, mainly in patients with life-threatening complications of uremia: pulmonary edema, hyperkalemia and acidemia.[8,9]

The effectiveness of other renal replacement therapies such as continuous venovenous hemofiltration, continuous venovenous hemodialysis and slow low-efficient daily dialysis,[24] are unknown in patients with HRS. Clearly, randomized studies are needed to evaluate the effects of MARS and other renal replacement therapies on the recovery of renal function and survival in patients with HRS.

Another possible therapeutic approach is targeting the mechanism of renal failure (i.e. renal vasoconstriction causing glomerular hypofiltration) to restore renal function. The end-point of treatment would be to increase the GFR to above 40 mL/min or to decrease serum creatinine to below 130 μmol/L.

Renal vasodilators

Prostaglandins

The effects of the oral administration of the prostaglandin misoprostol in patients with HRS are controversial. One study showed a marked improvement in renal function in four patients[25] whereas another found no improvement in renal function in nine patients.[26] Conversely, intravenous or intrarenal administration of different types of prostaglandins had no significant effect on patients with HRS.[26–28] The effects of prostaglandin administration on survival are unknown.

Dopamine

In patients with HRS, non-pressor doses of dopamine have been shown to induce a slight increase in renal blood flow without any change in GFR.[29] Moreover, in patients with cirrhosis (without HRS), dopamine has been shown to decrease arterial pressure and accentuate portal hypertension.[30] The effects of dopamine on survival in HRS are unknown. Therefore, the use of dopamine alone cannot be recommended for the management of HRS.

Peritoneovenous shunts

Peritoneovenous shunting cannot be recommended for the treatment of HRS. Indeed, two controlled studies have shown only a slight improvement in renal function following peritoneovenous shunting in these patients.[31,32] Moreover, shunt-induced peritoneal alterations (i.e. shunt-related fibrous adhesions and even 'cocoon' formation) can make subsequent liver transplantation difficult.[33] Finally, in three randomized studies comparing peritoneovenous shunting to standard medical treatment, survival did not significantly differ between the 'shunt' group and the 'medical treatment' group.[6,31,32,34]

Portosystemic shunts

Surgical portacaval shunts cannot be recommended for the treatment of HRS because they induce high morbidity and mortality in patients in poor condition.[3] A non-surgical method of portal decompression, the transjugular intrahepatic portosystemic shunt (TIPS), has recently been introduced.[35] Two uncontrolled studies performed with 21 patients suggest that TIPS may be useful in the treatment of HRS (Table 3).[36,37] Indeed, TIPS insertion was associated with improved renal function and remarkably high survival (Table 3).[36,37] However, it should be kept in mind that a controlled study comparing TIPS to paracentesis in patients with refractory ascites has shown that, in grade C (Child–Pugh's classification)[38] patients, mortality was significantly higher with TIPS than with paracentesis.[39] In contrast, TIPS did not increase mortality in grade B patients.[39] Similar findings have been shown by others.[40,41] Thus, the use of TIPS is not recommended in patients with ascites in poor condition.[42] It seems reasonable to apply this recommendation to patients with HRS and poor liver function. Interestingly, in the above-mentioned studies of TIPS in patients with HRS, patients with Child–Pughs scores ≥ 12 were not enrolled and the mean values of Child–Pugh scores at inclusion indicate that patients belonged mainly to grade B (Table 3).[36,37]

Endothelin receptor antagonists

As endothelin-1 may be involved in the mechanism of renal vasoconstriction causing HRS, endothelin receptor antagonists could be useful in the treatment of HRS. A pilot study in three patients with HRS showed that the acute administration of BQ123, a selective antagonist of type A endothelin receptors, induced a dose-dependent increase in GFR.[18]

N-Acetylcysteine

Twelve patients were included in a non-randomized study and received intravenous *N*-acetylcysteine (1250 μg/kg per min for 2 h followed by 6.9 μg/kg per min for 5 days).[43] Treatment induced a significant increase in GFR above 40 mL/min and was well tolerated.

Table 3 Transjugular intrahepatic portosystemic shunt in patients with type 1 hepatorenal syndrome

First author	Number of patients	Child–Pugh score at inclusion	GFR (mL/min) Baseline	GFR (mL/min) TIPS	3-month survival (%)
Guevara[36]	7	9.8 ± 1.6	9 ± 4	27 ± 7*	43
Brensing[37]	14	9.8 ± 1.5	18 ± 15	48 ± 42**	65

* $P < 0.05$ at 1 month.

** $P < 0.05$ at 2 weeks.

GFR, glomerular filtration rate; TIPS, transjugular intrahepatic portosystemic shunt.

Midodrine combined with octreotide

In a non-randomized study of five patients with HRS who received a combination of midodrine (an oral agonist of α-adrenoceptors, 22.5–37.5 mg/day) and octreotide (a somatostatin analog, 300–600 μg/day), for at least 20 days, the GFR increased to above 40 mL/min.[44] In addition, tolerance to the combination of midodrine and octreotide was good.

Norepinephrine

Norepinephrine induces splanchnic vasoconstriction by stimulating α_1-adrenoceptors. A non-randomized study of 12 patients with HRS who received norepinephrine (0.8 ± 0.3 mg/h intravenous (i.v.) for 10 days), showed a significant increase in creatinine clearance from 16 ± 14 mL/min to 40 ± 15 mL/min.[45] One patient had an episode of myocardial ischemia.

Vasopressin analogs

Ornipressin

The vasopressin analog ornipressin is a very potent splanchnic vasoconstrictor used to treat variceal bleeding in patients with cirrhosis. It has been hypothesized that ornipressin-induced splanchnic vasoconstriction may be useful in the treatment of renal failure in patients with HRS (Fig. 2).[46]

Eight patients were enrolled in a non-randomized study and received ornipressin (2 IU/h) and intravenous albumin (1 g/kg at day 1 and then 20–40 g per day).[47] Ornipressin administration was scheduled for 15 days. However, during the first week of the study, treatment had to be discontinued in four patients. Discontinuation was a result of complications elicited by ornipressin-induced arteriolar vasoconstriction in at least three patients: one had ischemic colitis, one had tongue ischemia and the third had myocardial ischemia. All these complications improved after ornipressin was stopped. The remaining four patients received ornipressin for 15 days. In these patients, the glomerular filtation rate significantly increased above the critical value of 40 mL/min.

In a non-randomized study, seven patients received a combination of ornipressin (6 IU/h, i.v.) and dopamine (2–3 μg/kg per min, i.v.) until GFR had increased to above 40 mL/min or until adverse events prevented further treatment.[48] Renal function improved in four patients after 5–27 days. In two patients, treatment was discontinued because renal function did not improve. In the remaining patient, treatment was withdrawn because of the occurrence of ornipressin-induced intestinal ischemia.

Although results obtained by these studies are encouraging, ornipressin cannot be used in patients with HRS because of its severe side-effects. Moreover, the effects of ornipressin on survival are unknown.

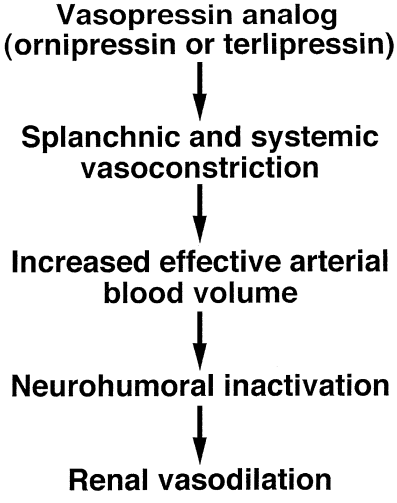

Figure 2 Mechanism of action of vasopressin analogs in patients with hepatorenal syndrome.

Terlipressin

Terlipressin is another vasopressin analog, which is used to treat variceal bleeding because it elicits potent splanchnic vasoconstriction. Terlipressin is known to have fewer side-effects than other vasopressin analogs.[49]

Case reports have suggested that terlipressin may be useful in the treatment of HRS.[50–52] One study has included nine patients with type 1 HRS in a double-blind, cross-over randomized study.[53] Patients received either terlipressin (2 mg/day i.v. for 2 days) or placebo. Terlipressin significantly increased GFR from 15 ± 2mL/min to 27 ± 4 mL/min. Moreover, terlipressin significantly decreased plasma concentrations of renin and aldosterone.

A retrospective multicenter study was performed in 99 patients with HRS treated with terlipressin.[5] The primary end-points of the study were to investigate improvement of renal function during terlipressin administration and survival. Improvement of renal function was assessed between the first and last day of terlipressin administration and was defined as a decrease in serum creatinine, either to below 130 μmol/L or of at least 20% compared to the pretreatment value on the first day of treatment. The dose of terlipressin used was 3.2 ± 1.3 mg/day and the treatment was administered for 11.4 ± 12.3 days. Fifty-eight patients (58%) had improved renal function during terlipressin therapy. In these patients, serum creatinine significantly decreased by 46 ± 17% (from 272 ± 114 μmol/L to 138 ± 59 μmol/L). In the remaining patients (42%) serum creatinine significantly increased by 30 ± 38% (from 289 ± 129 μmol/L to 382 ± 210 μmol/L). The independent predictors of improved renal function were younger age and a Child–Pugh score no greater than 13 at inclusion. The dose of terlipressin did not significantly differ between patients with improved renal function and those without. There

were no significant differences between the two groups for concomitant treatments. Seventy-five patients died during the study. Thirteen patients underwent liver transplantation. Among the transplanted patients, renal function had improved during terlipressin therapy in 10 patients. The median survival time was 3 weeks in this study, and the chance of survival was 60%, 40% and 28%, at day 15, 1 month and 2 months, respectively. After the first 3 months, the probability of survival remained stable at 19%, for several months.[5] It should be emphasized that these results are different from those reported in a previous study investigating the natural history of HRS.[7] In this previous study, the median survival time was 1.7 weeks and the probability of survival was 40%, 25% and 18%, at day 15, 1 month and 2 months, respectively.[7] Taken together, these findings suggest that terlipressin may improve survival in patients with HRS.

A non-randomized study investigated nine patients with HRS (six patients with type 1 HRS and three with type 2 HRS) who received terlipressin (0.5–2 mg/4h i.v. for 9 days) and intravenous albumin (1 g/kg on the first day and 20–40 g/day thereafter).[54] Treatment was given until serum creatinine decreased to below 130 μmol/L or for a maximum of 15 days in case of no response to therapy. Serum creatinine decreased from 345 ± 62 μmol/L to 115 ± 9 μmol/L during the terlipressin administration. A non-randomized study performed in patients with HRS compared the effects of terlipressin alone in eight patients to the effects of terlipressin and albumin in 13 patients.[55] Preliminary results of this study show that serum creatinine did not significantly change in the 'terlipressin-alone' group (318 ± 53 μmol/L compared to 301 ± 62 μmol/L, under baseline conditions and at the end of treatment, respectively) while it significantly decreased in the 'terlipressin-plus-albumin' group (from 310 ± 44 μmol/L to 133 ± 9 μmol/L).[55] Together, these findings suggest that albumin administration may be essential for the beneficial effects of terlipressin on renal function. However, the non-randomized study performed in 99 patients treated with terlipressin showed no significant difference between patients with improved renal function and those without in terms of the number of patients receiving albumin and the dose of albumin.[5] Thus, the role of albumin in the renal response to terlipressin needs to be clarified.

Terlipressin administration was well tolerated in all studies.[5,53–55]

Summary

Several treatments may be effective in patients with HRS. Randomized studies should be performed to investigate the effects of these treatments on renal function and survival in patients with HRS, particularly terlipressin because, unlike the others, it may fulfill the criteria for ideal therapy. Indeed, terlipressin may decrease renal failure and increase the chance of survival and it is well tolerated.

GENERAL CARE DURING THE COURSE OF HEPATORENAL SYNDROME

Several complications may occur in patients with HRS. Bacterial infections and portal hypertensive bleeding are frequent and occur in 53% and 20% of patients, respectively.[6] Respiratory or circulatory failure should be treated by appropriate means. However, there are no studies that have specifically investigated the general care of patients with HRS. In particular, there are no answers to the following questions: (i) should bacterial infections and portal hypertensive bleeding be prevented by administering specific treatments as soon as the diagnosis of HRS is made?; (ii) how important is the day-by-day prevention of any decrease in effective arterial blood volume? (by using human albumin as in a previous study?);[6] (iii) should large or tense ascites be treated and, if so, how? (by removing only 2–5 L of ascites, as in a previous study?);[6] and (iv) should loop diuretics be used and, if so, how? (Should we use diuretics as in a previous study,[6] i.e. to maintain a urine output of 500–800 mL per day without inducing a negative balance in body fluid?)

PREVENTION OF HEPATORENAL SYNDROME

Liver transplantation before HRS is probably the best treatment for preventing HRS.[3] In fact, there is consensus that liver transplantation should be considered in eligible patients with cirrhosis and refractory ascites[33] and in patients who recover from an episode of SBP.[56]

Bacterial infections or portal hypertensive bleeding are precipitating factors of HRS.[5,7,19] Thus, prevention of precipitating factors may be useful in preventing HRS. In a recent consensus conference, the use of norfloxacin in patients admitted for gastrointestinal bleeding and in patients who recovered from an episode of SBP was recommended to prevent bacterial infections.[56] In another consensus conference, the use of non-selective beta-blockers was suggested to prevent a first gastrointestinal bleeding in patients with large varices.[57] Beta-blockers or band ligation may be used to prevent recurrent gastrointestinal rebleeding.[57] The impact of the prevention of precipitating factors of HRS on the occurrence of HRS is unknown.

In patients with SBP, non-nephrotoxic antibiotics (such as cefotaxime) have been shown to control infection in more than 90% of cases and to reduce infection-related mortality to less than 5%.[58,59] However, about 30% of patients do not survive the admission to hospital during which the infection is detected and HRS (which occurs in 30% of patients) is the most common cause of death.[60]

Spontaneous bacterial peritonitis stimulates the production of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α),[61] which is known to induce inducible NO synthase (iNOS) synthesis in arterial walls.[62] As iNOS produces large amounts of the vasorelaxant factor NO,[62] the SBP-induced, TNF-α-mediated

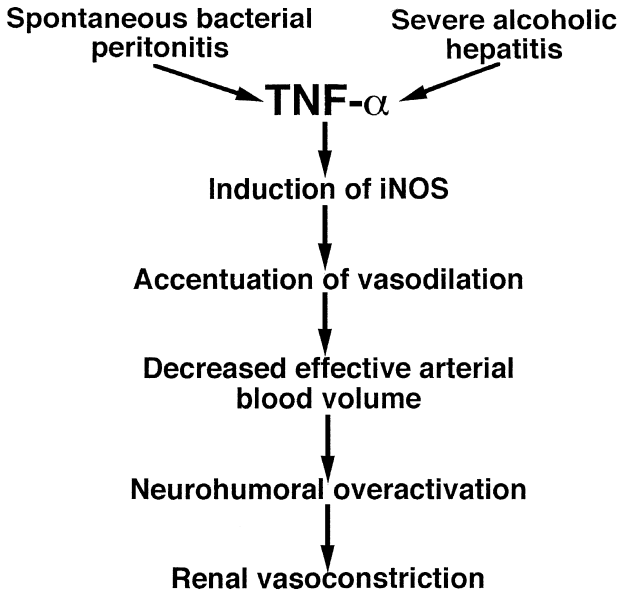

Figure 3 Proposed mechanisms by which complications (spontaneous bacterial peritonitis or severe acute alcoholic hepatitis) may precipitate hepatorenal syndrome. iNOS, inducible nitric oxide synthase; TNF-α, tumor necrosis factor-α.

activation of the iNOS/NO pathway in arterial walls may enhance pre-existent systemic vasodilation (and arterial hypovolemia) and precipitate HRS (Fig. 3).

It has been hypothesized that in patients with SBP, simultaneous intravenous administration of albumin and antibiotics could prevent the sepsis-induced decrease in effective arterial blood volume and resulting HRS.[63] One hundred and twenty-six patients with SBP were randomly assigned to receive either cefotaxime alone or cefotaxime plus intravenous albumin. Albumin was given at a dose of 1.5 g/kg at diagnosis of SBP followed by 1 g/kg on day 3. The two treatment groups were similar for the resolution of infection (more than 90% of cases) and the duration of antibiotic therapy (1 week). The proportion of patients who developed HRS was significantly lower in the cefotaxime-plus-albumin group than in the cefotaxime group (10% compared to 30%, respectively). In addition, the in-hospital mortality rate was significantly lower in the cefotaxime-plus-albumin group than in the cefotaxime group (10% compared to 30%, respectively). Finally, at 3 months, the mortality rate was still significantly lower in the cefotaxime-plus-albumin group than in the cefotaxime group (22% compared to 40%, respectively).

Hepatorenal syndrome is the main cause of in-hospital death in patients with cirrhosis and severe acute alcoholic hepatitis.[20] Severe acute alcoholic hepatitis may precipitate HRS by activating the above-mentioned TNF-α-mediated stimulation of the iNOS/NO pathway in arterial walls (Fig. 3). A randomized, placebo-controlled study investigated the effects of pentoxifylline, a TNF-α synthesis inhibitor, in patients with severe alcoholic hepatitis.[20] In-hospital mortality was significantly lower in the 'pentoxifylline' group than in the 'placebo' group (25% compared to 46%, respectively). The proportion of deaths as a result of HRS was significantly lower in the 'pentoxifylline' group than in the 'placebo' group (50% compared to 92%, respectively).[20]

CONCLUSIONS

Type 1 HRS is a severe complication of end-stage cirrhosis. Renal failure is a result of renal vasoconstriction that develops in response to marked splanchnic and systemic vasodilation. The administration of terlipressin, a splanchnic and systemic vasoconstrictor, may improve renal function and be used while awaiting liver transplantation.

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