Seminar

Hepatorenal syndrome

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Hepatorenal syndrome (HRS) is a common complication of advanced cirrhosis, characterised by renal failure and major disturbances in circulatory function. Renal failure is caused by intense vasoconstriction of the renal circulation. The syndrome is probably the final consequence of extreme underfilling of the arterial circulation secondary to arterial vasodilatation in the splanchnic vascular bed. As well as the renal circulation, most extrasplanchnic vascular beds are vasoconstricted. The diagnosis of HRS is currently based on the exclusion of other causes of renal failure. The prognosis is very poor, particularly when there is rapidly progressive renal failure (type 1). Liver transplantation is the best option in patients without contraindications to the procedure, but it is not always possible owing to the short survival expectancy. Therapies introduced during the past few years, such as vasoconstrictor drugs (vasopressin analogues, α-adrenergic agonists) or the transjugular intrahepatic portosystemic shunt, are effective in improving renal function. Nevertheless, liver transplantation should still be done in suitable patients even after improvement of renal function because the outcome of HRS is poor. Finally, recent findings suggest that the risk of developing HRS in the setting of spontaneous bacterial peritonitis may be reduced by the administration of albumin together with antibiotic therapy, and that of HRS occurring in severe alcoholic hepatitis can be lowered by administration of pentoxifylline. Although these findings need to be confirmed, these two strategies represent innovative approaches to lower the frequency of HRS in clinical practice.

Renal failure is a common complication of patients with advanced cirrhosis.[1,2] It generally indicates a poor prognosis because of the combined detrimental effect of renal and liver failure. In some cases, renal failure in cirrhosis is due to aetiological factors that also lead to renal failure in patients without liver disease, such as severe dehydration, shock (haemorrhagic or septic), or nephrotoxic drugs, or is the consequence of an intrinsic renal parenchymal disease, such as glomerulonephritis. However, in other cases renal failure in cirrhosis occurs in the absence of these factors and with normal renal histology. This disorder is known as hepatorenal syndrome (HRS). It is caused by intense vasoconstriction of the renal circulation, which leads to a pronounced reduction in glomerular filtration rate (GFR).[1–5] Although HRS was described more than 50 years ago, many features of its pathogenesis and natural history remained unknown for many years. No effective treatment existed until very recently. The aim of this seminar is to provide an up to date revision of HRS, with special emphasis on its diagnosis and management.

Definition

HRS generally occurs in patients with advanced liver disease and portal hypertension. It is characterised by a combination of disturbances in circulatory and kidney function.[6] The principal abnormality in the systemic circulation is low arterial pressure due to greatly reduced total systemic vascular resistance. Kidney function is much impaired because of severe reduction of renal blood flow. The reduction in renal blood flow is pathogenetically related to the impairment in the systemic circulatory function. HRS occurs predominantly in the setting of cirrhosis, but it can also develop in other types of severe chronic liver disease, such as alcoholic hepatitis, or in acute liver failure.[7–9]

Pathogenesis

The pathophysiological hallmark of HRS is vasoconstriction of the renal circulation.[1–4,6,10–13] The mechanism of the vasoconstriction is incompletely understood; it may be multifactorial, involving disturbances in the circulatory function and activity of systemic and renal vasoactive mechanisms. There is severe arterial underfilling in the systemic circulation due to pronounced arterial vasodilatation in the splanchnic circulation, which is related to the presence of portal hypertension. In the kidney, by contrast, there is striking vasoconstriction. A detailed analysis of these mechanisms and their possible role in the pathogenesis of HRS is beyond the scope of this paper and can be found elsewhere.[14,15]

The theory that best fits with the observed changes in renal and circulatory function in HRS is the arterial vasodilatation theory, which proposes that HRS is the result of the action of vasoconstrictor systems (ie, the renin-angiotensin system, the sympathetic nervous system, and arginine vasopressin) on the renal circulation activated as a homoeostatic response to improve the extreme underfilling of the arterial circulation

Search strategy and selection criteria

A systematic review of all articles published in English was done with the help of PubMed Services with the keywords "cirrhosis", "liver failure", "renal failure", and "hepatorenal syndrome" for the period 1960–2002. Priority was given to prospective clinical studies published in journals with high impact factors. For topics on which there was not enough published information to provide evidence-based criteria, we used our own clinical judgment and experience to fill the gaps.

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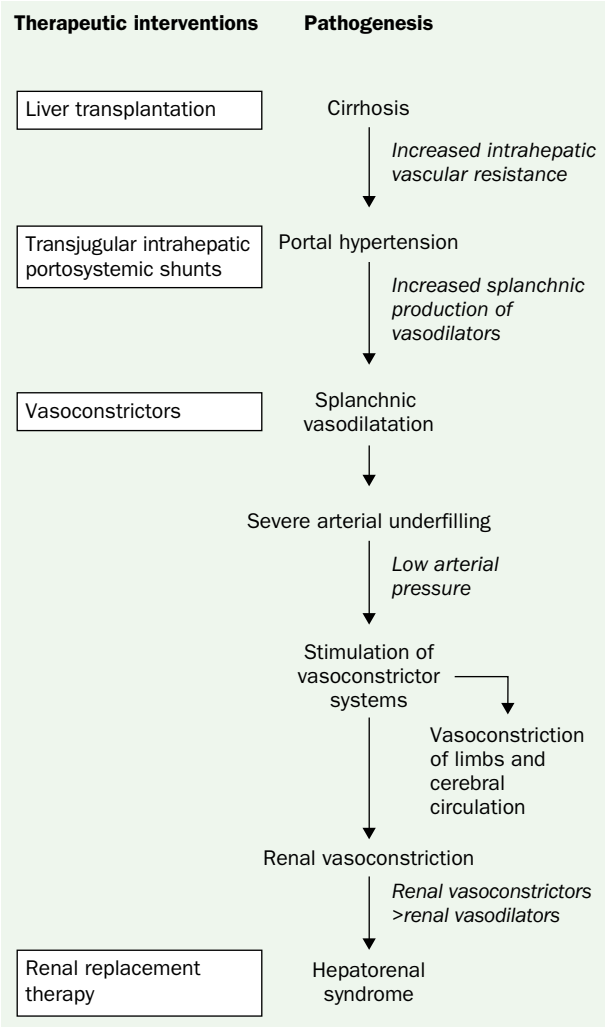

Figure 1: **Proposed pathogenesis of HRS in cirrhosis, according to the arterial vasodilatation theory, and effective therapeutic interventions**

(figure 1).[6,15–17] As a result of this increased activity of the vasoconstrictor systems, renal perfusion and GFR are greatly reduced but tubular function is preserved. These features differ from those of acute tubular necrosis, in which renal failure is associated with seriously impaired tubular function. The vasoconstrictor systems also lead to the retention of sodium (renin-angiotensin and sympathetic nervous system) and free water (arginine vasopressin) that occurs in advanced cirrhosis.[2,16,17] Most available data suggest that the arterial underfilling is due to vasodilatation of the splanchnic circulation related to increased splanchnic production of vasodilator substances, particularly nitric oxide.[18,19] In the early phases of decompensated cirrhosis, renal perfusion is maintained within the normal range because of increased synthesis of renal vasodilator factors (mainly prostaglandins). In later phases of the disorder, renal perfusion cannot be maintained because the extreme arterial underfilling causes maximum activation of vasoconstrictor systems, decreased production of renal vasodilator factors, or both, and HRS develops. The activation of vasoconstrictor systems also results in vasoconstriction of some vascular beds other than the kidneys, including the arms, legs, and brain.[20–23] The splanchnic area escapes the effect of vasconstrictors probably because of the greatly increased local production of vasodilators.

Incidence

HRS is thought to be a common complication of patients with advanced cirrhosis. However, most of the classic studies on the incidence of HRS in patients with cirrhosis were done many years ago and used non-standard diagnostic criteria.[1,24–27] Therefore, neither the current incidence of HRS nor its frequency relative to other causes of renal failure in cirrhosis is known. In the largest study published so far, the probability of HRS in patients with cirrhosis and ascites was 40% over 5 years.[27]

Clinical and laboratory findings

In the setting of cirrhosis, HRS generally occurs in late stages of the disease when patients have already had several episodes of some of the major complications of cirrhosis, especially ascites. Patients with ascites showing renal sodium retention together with dilutional hyponatraemia are at high risk of developing HRS.[27]

The dominant finding of HRS is renal failure, although many patients have other manifestations such as electrolyte disorders, cardiovascular and infectious complications, and complications related to liver disease. In the past, HRS was generally diagnosed when oligoanuria developed.[1,24–26] Currently, however, with the widespread use of frequent biochemical monitoring, HRS is most frequently first diagnosed by a finding of increasing concentrations of serum creatinine or blood urea nitrogen. In some patients, there is a rapid rise in serum concentrations of both creatinine and blood urea nitrogen to very high values.[3,26] Most of these patients show progressive oligoanuria. In other patients, the increases in serum creatinine and blood urea nitrogen are moderate, with no (or very little) tendency to progress over time, at least in the short term.[28,29] These two different patterns of progression of renal failure define two different clinical types of HRS.[6] The rate of progression used to define HRS type 1 has been arbitrarily set as a 100% increase in serum creatinine reaching a value greater than 221 μmol/L (2·5 mg/dL) in less than 2 weeks.[6] Patients who do not meet these criteria of progression are deemed to have type 2 HRS. Some patients with type 2 eventually develop a sudden progression of renal failure after weeks or months of stable serum creatinine concentrations and may then meet the criteria for type 1. In patients with type 1 HRS, GFR is very low, commonly below 20 mL/min, and serum creatinine concentrations are very high (average around 356 μmol/L). By contrast, most patients with type 2 HRS have less severely abnormal GFR and creatinine concentrations (average 178 μmol/L). The predominant clinical feature of patients with type 1 HRS is severe renal failure, and that of patients with type 2 HRS is recurrent ascites because there is little or no response to diuretics owing to the combination of low GFR and pronounced activation of antinatriuretic systems.[6] An important clinical difference between the two types of HRS is that patients with type 1 have a very poor short-term outcome compared with that of patients with type 2.

Besides renal failure, patients with HRS have sodium retention with features of salt and water overload. In most, sodium retention is already present and pronounced before the development of HRS, but renal sodium excretion can be impaired further when renal failure develops owing to the reduction in GFR and greater activation of antinatriuretic systems. The consequently increased positive sodium balance results in weight gain due to an increase in ascites volume and peripheral oedema. Hyponatraemia is almost universal in HRS, so if the serum sodium concentration in a patient with cirrhosis

and renal failure is normal, the diagnosis of HRS is very unlikely and the patient should be investigated for a different cause of renal failure. Hyponatraemia is due to impaired renal capacity to excrete solute-free water, which results in disproportionate retention of water relative to the amount of sodium retained (dilutional hyponatraemia).[30] This disorder is pathogenetically related to increased arginine vasopressin release in response to severe arterial underfilling and exists in most cases before the development of HRS, but it worsens as renal failure progresses.[16,17,30] Hyperkalaemia is also common but moderate in most cases. High rates of increase in plasma potassium concentrations are infrequent. Nevertheless, potassium concentrations should be monitored frequently and hyperkalaemia treated aggresively, if present, to avoid cardiac complications. Severe metabolic acidosis is also uncommon in HRS except for patients who develop a severe infection.

Cardiovascular function is severely affected in patients with HRS. The total systemic vascular resistance is much reduced, and arterial pressure low in most cases despite pronounced activation of major vasoconstrictor mechanisms, such as the renin-angiotensin and sympathetic nervous systems.[2,6,17,20,21,31,32] Cardiac output is increased in most patients but may be reduced in some,[15,20,21,33] whereas arterial pressure is low but stable (average mean arterial pressure around 70 mm Hg). When there is haemodynamic instability, an infectious complication should be suspected. Except for arterial pressure, the other cardiovascular abnormalities mentioned are not recognised in the clinical setting unless invasive vascular monitoring is done and vasoconstrictor factors are measured. However, these procedures are generally not required in the clinical management of patients with HRS. Pulmonary oedema, which is a common and severe complication of acute renal failure in the absence of liver disease, is very rare in patients with HRS unless they are treated aggressively with plasma expanders.

Severe bacterial infections, especially septicaemia (either spontaneous or related to indwelling catheters), spontaneous bacterial peritonitis, and pneumonia, are common complications in patients with HRS and are major causes of death.[27,34,35] Both the renal failure and advanced liver disease probably account for increased susceptibility to the infections.

Finally, most patients with HRS show signs and symptoms of advanced liver failure and portal hypertension, particularly jaundice, coagulopathy, malnutrition, and hepatic encephalopathy, although HRS develops in a few patients with only moderate liver insufficiency.[32,34,35] The presence of ascites is universal in patients with HRS, so the lack of ascites in a patient with cirrhosis and renal failure argues against HRS as the cause of renal failure and points towards other causes, particularly prerenal failure due to volume depletion because of excessive diuresis.

Precipitating factors

In some patients, HRS develops spontaneously without any apparent triggering event, whereas in others it occurs in close chronological relation to some precipitating factors that can cause circulatory dysfunction and subsequent renal hypoperfusion.[1,3,15,24,36] Well-known precipitating factors include bacterial infections, large-volume paracentesis without plasma expansion, and gastrointestinal bleeding. Among the different types of bacterial infections that occur in cirrhosis, a clear chronological and pathogenetic relation between the infection and HRS has been established only for spontaneous bacterial peritonitis.[37,38] This disorder is characterised by the spontaneous infection of ascites, in most cases by gram-negative bacteria of enteric origin, in the absence of infection of intra-abdominal organs or gut perforation.[39] About 20% of patients with spontaneous bacterial peritonitis develop HRS during or immediately after the infection—type 1 in most cases.[37,38] Whether HRS can also occur as a consequence of other severe bacterial infections has not been studied. Another well-known precipitating factor of HRS is large-volume paracentesis without plasma expansion.[40] Up to 15% of patients with ascites develop HRS when large volumes of ascitic fluid (more than 5 L) are removed without the administration of a plasma expander. This association is one of the reasons why intravenous albumin should be administered when large-volume paracentesis is done.[41] Finally, renal failure occurs in about 10% of patients with cirrhosis and gastrointestinal bleeding.[42,43] However, a substantial proportion of episodes of renal failure after gastrointestinal bleeding are due to acute tubular necrosis related to hypovolaemic shock and not to HRS.[43] Intravascular volume depletion (ie, diuretic-induced, extrarenal fluid losses) has classically been considered as a triggering factor for HRS.[1] However, no convincing evidence has yet been reported to support this pathogenetic relation.

Prognosis

Of all the complications of cirrhosis, HRS has the worst prognosis. The survival expectancy is very low[1,2,6,27] and spontaneous recovery very rare. The main determinant of survival is the type of HRS. In type 1, hospital survival is less than 10% and the expected median survival time only 2 weeks.[26,27] By contrast, patients with type 2 have a much longer median survival time (about 6 months; figure 2). The second determinant of survival is the severity of liver disease.[34,35] Patients with severe liver failure (Child-Pugh class C) have a much worse outcome than those with moderate liver failure (class B). For many years, the development of renal failure was judged not to contribute to the dismal outcome of the HRS, and death was thought to be due mainly to the liver disease. However, recent studies suggest that renal failure is an important determinant of the outcome, since patients in whom renal

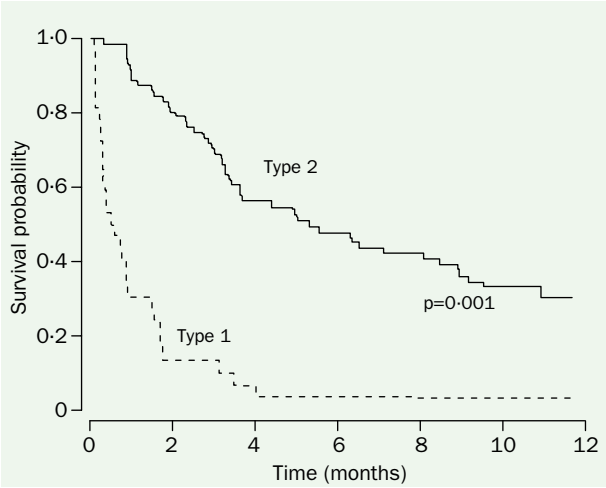

Figure 2: **Survival of patients with cirrhosis after the diagnosis of type 1 or type 2 HRS**
PG, unpublished observations.

function improves after therapy survive longer than those without such improvement.[34,35]

Diagnostic approach

The initial step in the diagnosis of HRS is to demonstrate the existence of renal failure (ie, low GFR). The serum creatinine concentration is generally deemed a better marker of GFR than the blood urea nitrogen concentration, because the latter can vary in the absence of changes of GFR (eg, gastrointestinal bleeding, diets high or low in protein). However, serum creatinine concentration is not an ideal marker of GFR in cirrhosis because it is generally lower than expected for any given GFR owing to low endogenous production of creatinine related to the reduced muscle mass that occurs in most patients with advanced cirrhosis.[44,45] Nevertheless, since the use of more sensitive clearance techniques to measure GFR is expensive and not available in all settings, serum creatinine concentration is currently the method of choice to estimate GFR in cirrhosis.[6] In patients with cirrhosis, steady-state GFR of 100 mL/min, 50 mL/min, 25 mL/min, 12 mL/min, and 6 mL/min are associated with serum creatinine concentrations of about 71 μmol/L, 88 μmol/L, 160 μmol/L, 195 μmol/L, and 354 μmol/L, respectively (MG, unpublished observations). There is consensus to establish the diagnosis of HRS when serum creatinine has risen above 133 μmol/L.[6] In patients with high serum creatinine concentrations who are receiving diuretics, serum creatinine should be remeasured after diuretic withdrawal, since the use of diuretics can be associated with a slight and reversible increase in serum creatinine concentrations.

Because of the lack of specific diagnostic tests, the diagnosis of HRS must always be made after exclusion of other disorders that can cause renal failure in cirrhosis.[6] An algorithm for the diagnosis of HRS is shown in figure 3. Acute renal failure of prerenal origin due to gastrointestinal fluid losses (vomiting, diarrhoea, nasogastric tube) or renal fluid losses (overdiuresis due to excessive diuretic treatment) should be investigated by history and physical examination in all patients with renal failure. If renal failure is secondary to volume depletion, renal function improves rapidly after volume expansion, whereas no improvement occurs in patients with 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. Although there is no absolute agreement as to the type and amount of plasma expander to be used for this purpose, there is international consensus on the use of 1500 mL isotonic saline.[6] The presence of shock before the onset of renal failure precludes the diagnosis of HRS and points towards a diagnosis of acute tubular necrosis.[43] Hypovolaemic shock due to gastrointestinal bleeding is common in cirrhosis and is easily recognised. However, septic shock may be more difficult to diagnose because of the lack of symptoms of bacterial infection in some patients with cirrhosis and the fact that arterial hypotension due to sepsis can be erroneously attributed, at least in the early stages, to the advanced liver disease.[46] Therefore, a bacterial infection should always be ruled out (leucocyte count, examination of ascitic fluid, cultures, C-reactive protein) before the diagnosis of HRS is made. Conversely, some patients with cirrhosis and bacterial infections develop transient renal failure, which resolves in most after resolution of the infection.[37] Therefore, HRS should be diagnosed only if renal failure persists after complete resolution of the infection. Patients with cirrhosis are at high risk of developing renal failure during treatment with non-steroidal anti-inflammatory drugs or aminoglycosides.[47–49] Therefore, treatment with these drugs in the days or weeks preceding the development of renal failure should always be ruled out. Renal failure can also occur after the administration of radiocontrast agents.[50] However, whether patients with cirrhosis are at high risk for the development of this complication has never been assessed. Finally, patients with cirrhosis can also develop renal failure due to parenchymal renal diseases, particularly glomerulonephritis.[51,52] This may

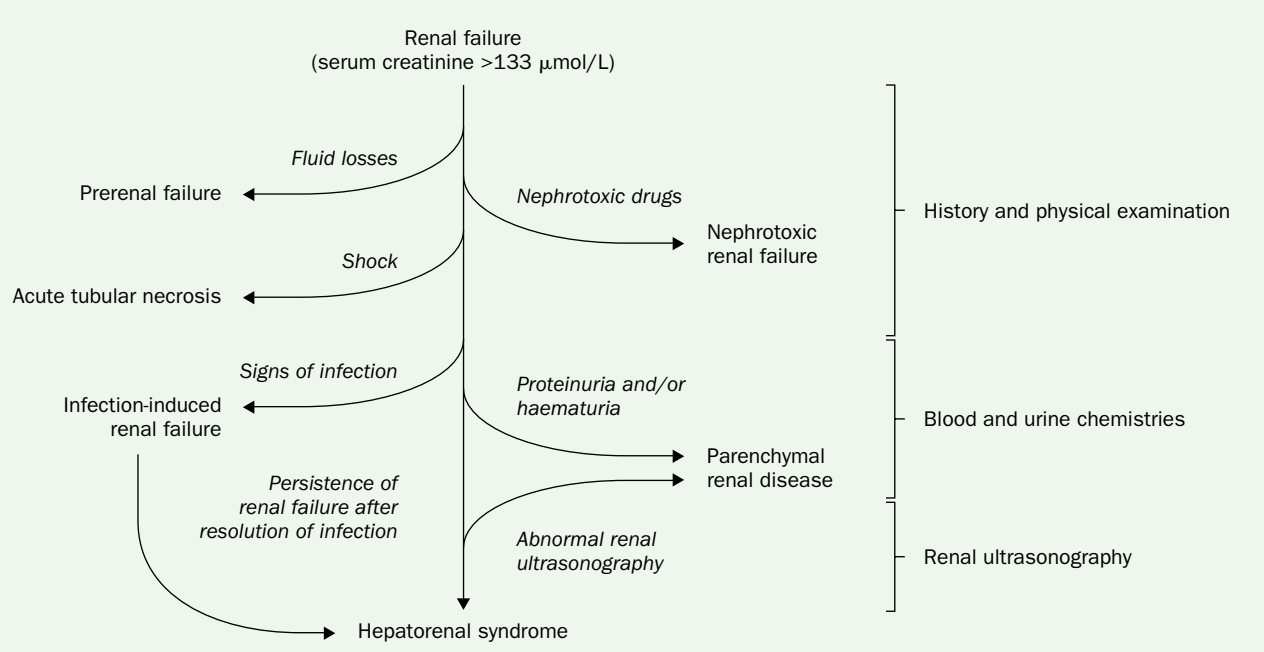

Figure 3: **Diagnostic flow chart of HRS in patients with cirrhosis**
In some cases, renal failure may not be due to a single cause but to a combination. In these cases, the identification of the causative factors may be difficult with the current diagnostic tools.

occur in all causes of cirrhosis but is particularly common in the setting of chronic hepatitis B or C infection or chronic alcoholism. These cases can be recognised by the presence of proteinuria, haematuria, or both. The diagnosis can be confirmed by renal biopsy in selected cases.

The differential diagnosis between HRS and acute tubular necrosis is especially difficult. Early studies emphasised the importance of urinary indices, especially urine sodium concentration, in the differential diagnosis.[1,24] Urine sodium concentration is very low (<10 mmol/L) in most patients with HRS as a result of the preserved tubular function and concomitant activation of sodium-retaining systems. In acute tubular necrosis, by contrast, urine sodium concentration is not low (>10 mmol/L); the altered tubular function impairs the reabsorption of sodium. However, urine sodium concentration can be very low in patients with cirrhosis and acute tubular necrosis and may not be very low in some patients with HRS.[6,53] Therefore, an international consensus was reached that this variable should not be used as a major criterion to differentiate between HRS and acute tubular necrosis in cirrhosis.[6] Because of the lack of objective measures, acute tubular necrosis in cirrhosis should be suspected when renal failure develops in the setting of hypovolaemic or septic shock or administration of nephrotoxic agents. Therefore, the presence of these conditions immediately before the development of renal failure is currently deemed sufficient to exclude HRS and make the diagnosis of acute tubular necrosis.[6] Nevertheless, there is a clear need for objective indices to differentiate between HRS and acute tubular necrosis in cirrhosis. In this regard, the possible use of other renal indices, such as the fractional excretion of urea, should be explored.[54]

There is no published information on the comparative frequency of the different causes of renal failure in patients with cirrhosis. In a current prospective study of renal failure in patients with cirrhosis being carried out at our unit, which so far includes 142 episodes of renal failure diagnosed over 1 year, the frequency of the different causes of renal failure is: 32% infection-induced renal failure; 24% parenchymal renal diseases; 22% prerenal failure; 11% acute tubular necrosis; 8% HRS; and 3% nephrotoxic renal failure (PG, unpublished).

Management of type 1 HRS

Patients with suspected type 1 HRS should be managed as inpatients for diagnostic investigation and treatment. Vital signs, urine output, and blood chemistry should be closely monitored. Because most patients have dilutional hyponatraemia (serum sodium below 130 mmol/L), total fluid intake (both oral and intravenous fluids) should be restricted to avoid a positive fluid balance, which would lead to a further reduction in serum sodium concentration. In most cases, total fluid intake should be kept around 1000 mL daily. In patients with severe oligoanuria, more severe fluid restriction (500–1000 mL daily) may be needed to prevent a positive fluid balance and a progressive decline in serum sodium concentration. However, such a low input can be difficult to achieve because the administration of fluids cannot be reduced to such an extent in some patients and restriction is poorly tolerated by conscious patients. The administration of saline solutions can increase ascites and oedema greatly because of the presence of severe renal sodium retention and therefore is not recommended. For this reason and the absence of severe metabolic acidosis in most patients, the routine administration of sodium bicarbonate is also not advisable. Potassium-sparing diuretics should be withheld because of the risk of inducing severe hyperkalaemia. Early identification of infections and treatment with broad-spectrum antibiotics is fundamental, since severe infections are common and contribute to death in these patients. The efficacy of antibiotic prophylaxis for the prevention of infections in patients with HRS has not been assessed.

Several therapeutic approaches can be used in the management of type 1 HRS (panel 1).

Liver transplantation

The treatment of choice for patients with cirrhosis and type 1 HRS who are suitable for the procedure is liver transplantation, because it allows both the liver disease and the associated renal failure to be cured.[55–58] The most common contraindications for transplantation in HRS are advanced age, active alcoholism, and infection. The main problem in the use of liver transplantation for type 1 HRS is that many patients die before transplantation is possible because of the short survival expectancy and long waiting times in most transplant centres. The issue can be solved by assigning these patients a high priority for transplantation from a cadaveric donor. This approach was used with the former method of organ allocation used by the United Network for Organ Sharing in the USA, which classified patients with HRS in the 2a status, with a median waiting time of about 7 days.[59] Now this system has been changed and livers are allocated on the basis of the MELD (model of end-stage liver disease) score, which is obtained by a formula including serum bilirubin, serum creatinine, and international normalised ratio.[60–62] Patients with HRS have high MELD scores even when liver function is preserved. This system was implemented in the USA in early 2002, and the initial results of its use have been reported recently.[63] The policies for allocation of livers from cadaveric donors are not uniform in other countries. Whatever the system used for organ allocation, HRS should probably be treated before transplantation is done in an attempt to improve renal function. This step may help reduce the (moderately) higher morbidity and mortality after transplantation reported in patients with HRS than in those without HRS.[64–66] In fact, the outcome of transplantation for patients with HRS treated with vasoconstrictors (vasopressin analogues) before the procedure does not differ from that of patients without HRS.[67] Combined liver and kidney transplantation for patients with HRS does not improve the overall results obtained with liver transplantation alone and should not be used.[68]

Another theoretical option for transplantation of patients with HRS is transplantation of the right hepatic

Panel 1: **Recommendations for the management of type 1 HRS**

Consider the patient for liver transplantation.
Set up high priority for transplantation in suitable patients.
Start vasoconstrictors plus intravenous albumin.
Consider TIPS in patients without severe liver failure in whom vasoconstrictors have failed.
Consider renal replacement therapy if there is pulmonary oedema, severe hypokalaemia, or metabolic acidosis not responding to medical therapy.
If high priority for cadaveric liver transplantation is not possible, consider liver transplantation from a living relative in patients with moderate liver failure in whom renal function has improved after therapy.

lobe from a living donor.[69] However, this is not the option of choice because few patients have suitable living donors and the assessment of the donor requires extensive investigation, which in some cases may take too long. Moreover, this procedure carries a significant risk for the healthy donor, and the results obtained in patients with severely decompensated liver disease are probably not as good as those obtained with cadaveric liver transplantation.[70] Therefore, type 1 HRS is probably not an indication for living-related liver transplantation at least at present. Nevertheless, this procedure may be considered for selected patients with preserved liver function in whom renal function has improved after therapy in settings or countries where livers are not prioritised according to disease severity.

Vasoconstrictors

The only effective medical therapy currently available for the management of HRS is administration of vasoconstrictors. The rationale behind this approach is to improve circulatory function by causing vasoconstriction of the extremely dilated splanchnic arterial bed, which subsequently suppresses the activity of the endogenous vasoconstrictor systems and results in an increase in renal perfusion (figure 1).[71] Two types of drugs have been used so far: vasopressin analogues (ornipressin and terlipressin) and α-adrenergic agonists (norepinephrine and midodrine), which act on V1 vasopressin receptors and α1-adrenergic receptors, respectively, present in vascular smooth-muscle cells. In most studies, both types of drug[11] have been given in combination with intravenous albumin to improve further the arterial underfilling (table). The use of albumin appears to increase the efficacy of vasoconstrictor drugs.[35] Ornipressin is effective but its use is not recommended because of the development of severe ischaemic complications in up to a third of patients.[32,72] Terlipressin is the vasoconstrictor that has been used most frequently in HRS.[34,35,73–76] Administration of this drug (0·5–2·0 mg over 4–6 h intravenously) is associated with a complete renal response (reduction of serum creatinine below 133 μmol/L) in 50–75% of patients, according to various studies. Predictors of lack of response to terlipressin include old age, severe liver failure (Child-Pugh score greater than 13), and omission of concomitant albumin administration.[34,35] The improvement in GFR occurs slowly over several days and is associated in some, but not all, cases with an increase in excretion of sodium and free water and improvement in serum sodium concentration. Despite the improvement in GFR and the decrease in serum creatinine to normal or near-normal concentrations, GFR remains below normal values in most responding patients.[35,74] Recurrence of HRS after treatment withdrawal in responders is uncommon (about 15% of patients) and retreatment is effective in most cases. The frequency of ischaemic side-effects requiring the discontinuation of terlipressin treatment (5–10%) is lower than that with ornipressin (30–50%). Responders to terlipressin have better survival than non-responders, which suggests an effect of the drug on survival.[34,35] There are two major shortcomings of treatment with terlipressin: the drug is not available in some countries and its cost is high, which limits its use in some parts of the world. α-adrenergic agonists (norepinephrine, midodrine) are an attractive alternative to terlipressin because they are cheaper, widely available, and apparently as effective as terlipressin.[77,78] However, information on the efficacy and side-effects of α-adrenergic agonists in patients with type 1 HRS is still very limited. Octreotide, which causes splanchnic vasoconstriction probably mediated by inhibition of some vasodilator peptides of splanchnic origin and not through a direct effect on vascular smooth-muscle cells, is not effective in the management of HRS.[79]

Drug and references	Dose range	Maximum duration of therapy (days)	Potential side-effects
Terlipressin[34,35,73–76]	0·5–2·0 mg every 4 h as intravenous bolus	15	Peripheral, splanchnic, or cardiac ischaemia
Norepinephrine[78]	0·5–3·0 mg/h intravenous infusion	15	Peripheral, splanchnic, or cardiac ischaemia
Midodrine[77]	7·5–12·5 mg every 8 h by mouth	Indefinite?	Not reported

Drugs used in the therapy of hepatorenal syndrome

Transjugular intrahepatic portosystemic shunts

Only a few studies have reported on the effects of transjugular intrahepatic portosystemic shunts (TIPS) in patients with type 1 HRS.[80,81] This procedure consists of insertion of an intrahepatic stent between the portal and hepatic veins by a transjugular approach. The main effect is to lower portal pressure.[82] In type 1 HRS, TIPS improve circulatory function and reduce the activity of vasoconstrictor systems.[80,81] These effects are associated with a slow, moderate to strong increase in renal perfusion and GFR and a fall in serum creatinine concentrations in about 60% of patients. Median survival after TIPS in type 1 HRS is between 2 months and 4 months.[80,81] As with vasoconstrictor drugs, the improved renal function probably, but not definitely, results in longer survival.[81] Information currently available on the use of TIPS in type 1 HRS has been obtained in a very selected population of patients and may not be applicable to the whole population of such patients. In fact, TIPS are thought to be contraindicated in patients with severe liver failure (high serum bilirubin concentrations and/or Child-Pugh score greater than 12) or severe hepatic encephalopathy because of the risk of inducing irreversible liver failure or chronic disabling hepatic encephalopathy.[82,83] No studies have been reported that compared TIPS and vasoconstrictors in type 1 HRS. Until comparative studies are undertaken, vasoconstrictors appear to be the treatment of choice in type 1 HRS because of apparently similar efficacy, wider availability, and lower costs than TIPS.

Other therapeutic methods

Renal replacement therapy (haemodialysis) is frequently used in the management of patients with type 1 HRS, especially those who are candidates for liver transplantation, in an attempt to keep them alive until the transplantation can be done or a spontaneous improvement in renal function occurs.[57,84] However, the potential benefit of this approach has not been unequivocally established. Clinical experience is that most patients do not tolerate haemodialysis and develop important side-effects, including severe arterial hypotension, bleeding, and infections that can lead to death during treatment. Moreover, findings that indicate the need for renal replacement therapy (severe fluid overload, acidosis, or hyperkalaemia) are uncommon, at least in early stages of type 1 HRS. Therefore, the initial therapy for these patients should probably include measures aimed at improving circulatory function (vasoconstrictors, TIPS) and not haemodialysis. Other techniques such as continuous arteriovenous or

venovenous haemofiltration or haemodiafiltration have been used in isolated cases.[84] These techniques may be helpful in selected patients with severe anasarca because they may help achieve negative fluid balance without causing hypotension. However, the available evidence is insufficient and the role of these techniques in the management of patients with HRS remains undefined.

Extracorporeal albumin dialysis, a system that uses an albumin-containing dialysate that is recirculated and perfused through charcoal and anion-exchanger columns, has been reported to improve renal function and survival in a small series of patients with HRS, but these results require confirmation in larger series of patients.[85] The efficacy of drugs with renal vasodilator activity, such as dopamine or prostaglandins, has not been proven and they are therefore not recommended.[57] N-acetylcysteine has shown some efficacy in a small series of patients but these results need confirmation.[86]

Management of type 2 HRS

Unlike patients with type 1 HRS, those with type 2 HRS can be managed as outpatients unless they develop complications of cirrhosis that necessitate hospital admission. The commonest clinical finding in these patients is refractory ascites. Diuretics should be given only if they cause a significant natriuresis (ie, urine sodium excretion of more than 30 mmoles daily). Care should be taken with the use of spironolactone in these patients because of the risk of hyperkalaemia. Dietary sodium restriction (40–80 mmoles per day) is important to decrease the ascites formation rate, since sodium excretion is severely impaired and most patients respond poorly or not at all to diuretics. Repeated paracentesis with intravenous albumin is probably the method of choice for the treatment of episodes of large ascites in these patients.[87] If dilutional hyponatraemia is present, total fluid intake should be restricted to about 1000 mL/day. Bacterial infections should be diagnosed and treated early to avoid the risk of precipitating type 1 HRS. The usefulness of prophylactic antibiotics has not been assessed and would be worthy of study. Recommendations for the management of patients with type 2 HRS are outlined in panel 2.

Liver transplantation

Liver transplantation is the treatment of choice for suitable patients. The short survival of patients with type 2 HRS (median 6 months) should be taken into account when these patients are assessed for liver transplantation. Treatment of HRS before transplantation with some of the procedures discussed below may be beneficial to improve the short-term and long-term outcome after transplantation.[67]

Vasoconstrictors

There is limited information on the use of vasoconstrictors in the treatment of patients with type 2 HRS, but some reports suggest that, as in type 1, the administration of vasoconstrictors improves renal function in these patients.[35,88] However, more information is required before a definitive conclusion about this therapeutic approach can be taken.

Transjugular intrahepatic portosystemic shunts

The use of TIPS in patients with type 2 HRS is associated with an improvement of renal function, better control of ascites, and reduced risk of progression to type 1 HRS.[81,87,89–92] However, a subanalysis of patients with type 2 HRS included in a randomised study comparing TIPS and repeated paracentesis plus intravenous albumin in patients with cirrhosis and refractory ascites showed that the use of TIPS was not associated with improved survival compared with the other two treatments.[87] Therefore, the beneficial effects of TIPS in reducing the rates of ascites recurrence and progression to type 1 HRS should weighed against the lack of improvement in survival, increased risk of encephalopathy, and high costs.

Panel 2: Recommendations for management of type 2 HRS

- Consider the patient for liver transplantation.
- Use diuretics for management of ascites only if they cause significant natriuresis (>30 mmoles per day). Restrict dietary sodium intake to 40–80 mmoles per day.
- Use repeated paracentesis plus intravenous albumin to treat recurrent large/tense ascites.
- Restrict fluid intake if hyponatraemia is present.
- Consider vasoconstrictors or TIPS before liver transplantation.

Prevention

Until very recently, no effective methods for prevention of HRS existed. However, two recent studies have shown that the syndrome can be prevented effectively in two specific clinical settings: spontaneous bacterial peritonitis and alcoholic hepatitis. In spontaneous bacterial peritonitis, the intravenous administration of albumin (1·5 g/kg at the diagnosis of the infection and 1 g/kg 48 h later) together with antibiotics greatly decreases the risk of HRS compared with the standard treatment of antibiotics alone (10% in the albumin group *vs* 33% in the non-albumin group).[38] Moreover, hospital mortality is also lower in patients receiving albumin (10% *vs* 29%). The beneficial effect of albumin is probably related to its capacity to prevent arterial underfilling and subsequent activation of vasoconstrictor systems during the infection. In patients with alcoholic hepatitis, the administration of pentoxifylline (400 mg three times daily) decreases the rate of occurrence of HRS and mortality (8% and 24%, respectively) compared with a control group (35% and 46%, respectively).[9] The beneficial effect of pentoxifylline is probably related to its capacity to inhibit production of tumour necrosis factor, but other mechanisms such as inhibition of vascular endothelial growth factor and tissue factor may also have a role.[93] Although the beneficial effects obtained in these two clinical trials need to be confirmed in other studies, the treatments represent the first big step towards effective prevention of HRS in patients with end-stage liver disease. Furthermore, the relation between prevention of HRS and improved survival in the two settings strongly supports the concept that the presence of renal failure adversely affects the survival of patients with end-stage liver disease.

Conflict of interest statement

Pere Ginès has participated in scientific symposia sponsored by Grífols International (Barcelona, Spain) and Laboratoire Français du Fractionnement et des Biotechnologies (LBF, Paris, France); both companies manufacture human albumin. Vicente Arroyo has participated in scientific symposia sponsored by Grífols International and is a member of a steering committee of Teraklin AG (Rostock, Germany), the manufacturer of the molecular adsorbents recirculating system (MARS) device. Juan Rodés and Mónica Guevara have no conflicts of interest. No financial support has been received from the companies producing drugs or medical devices described in this seminar.

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