CHAPTER 128

Pathophysiology and Management of the Hepatorenal Syndrome

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OBJECTIVES

This chapter will:
1. Discuss the characteristics and the clinical impact of hepatorenal syndrome.
2. Discuss the pathophysiology of hepatorenal syndrome.
3. Discuss the management and the available treatments of hepatorenal syndrome.

Patients with advanced cirrhosis frequently show a certain degree of renal dysfunction, and a strong relationship between severity cirrhosis and renal dysfunction has been shown.

It has been estimated that more than 20% of patients hospitalized for an acute decompensation of cirrhosis develop acute kidney injury (AKI).[1] Cirrhotic patients can develop any kind of renal failure, namely prerenal, intrarenal, and postrenal types. In this setting hepatorenal syndrome (HRS)

represents a peculiar kind of prerenal AKI described in patients with advanced liver failure. HRS occurs in cirrhotic patients with ascites, and it is characterized by an intense renal vasoconstriction that does not improve with the correction of vascular underfilling. Two strong observations suggested a functional form for HRS: (1) kidneys from patients with cirrhosis and HRS could be successfully transplanted to patients with chronic kidney disease[2]; (2) the severe arterial vasoconstriction observed at renal arteriography in patients with HRS disappeared postmortem.[3] These concepts recently have been questioned and will be clarified later in this chapter.

HRS accounts for 20% of AKI episodes in patients with cirrhosis, whereas prerenal failure and acute tubular necrosis (ATN) are more frequent (41.7% and 38%, respectively). Postrenal failure accounts for 0.3% of AKI in patients with cirrhosis.[4] The incidence of HRS in the natural history of cirrhosis is estimated to be 18% after 1 year and 39% after 5 years.[5]

Classically two different clinical types of HRS can be identified[6]:

1. Type 1 HRS, which is characterized by a rapidly progressive reduction of renal function, classically defined by a doubling of the initial serum creatinine (SCr) concentration to more than 226 mmol/L (2.5 mg/dL) in less than 2 weeks
2. Type 2 HRS, which is a moderate renal failure (SCr from 133 to 226 mmol/L or from 1.5 to 2.5 mg/dL), with a steady or slowly progressive course, which usually is associated with refractory ascites

Type 1 HRS prognosis is usually more severe than type 2 prognosis with a median survival of 1 month versus 6 months.[7] Moreover, type 1 HRS often develops after a precipitating event, such as spontaneous bacterial peritonitis (SBP) or other bacterial infections, gastrointestinal bleeding, alcoholic hepatitis, or paracentesis without plasma expansion.[8] The development of SBP, in particular, is the most important risk factor for HRS.

DIAGNOSTIC CRITERIA OF HEPATORENAL SYNDROME

During the past 20 years, three consensus meetings aimed to define diagnostic criteria of HRS were held. In 1996 Arroyo V et al. produced the first consensus definition of HRS.[6] According to these criteria HRS was defined as a functional form of AKI that does not improve after plasma expansion with saline. The presence of an ongoing bacterial infection was an exclusion criteria for HRS. In the following years, several studies showed a very high incidence of AKI with the features of HRS after bacterial infections[9–10] and in 2007 Salerno et al. modified the former criteria removing an ongoing bacterial infections among exclusion criteria.[8] Furthermore, Salerno et al. suggested use of albumin (at the dosage of 1 g per kg per day) for plasma volume expansion in patients with suspected HRS, because albumin appeared to be the best plasma expander in patients with cirrhosis.[9] More recently, with the development of AKI concept,[11] it has become more evident that variations of SCr values are more important than a cutoff of SCr in predicting mortality. Indeed, several studies showed a high mortality rate for a small increase in SCr,[1,12,13] questioning the cutoff of SCr of 2.5 mg/dL required for the diagnosis of type 1 HRS. As a result in 2016 Angeli P et al. introduced new criteria for the definition of AKI in patients with cirrhosis and removed any cutoff of SCr required for the diagnosis of HRS, while confirming the other criteria (Box 128.1).[14] According to these new observations, type 1 HRS also has been defined as HRS-AKI, whereas the classical type 2 HRS is considered to be a type of CKD in patients with cirrhosis (HRS-CKD).

BOX 128.1

Diagnostic Criteria of Hepatorenal Syndrome According to International Club of Ascites Criteria

Hepatorenal Syndrome
Diagnosis of cirrhosis and ascites
Renal impairment
- Diagnosis of acute kidney injury according to ICA criteria for type 1 HRS (HRS-AKI)
- Serum creatinine > 1.5 mg/dL for more than 3 months for type 2 HRS (HRS-CKD)

No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
Absence of shock
No current or recent use of nephrotoxic drugs (e.g., NSAIDs, aminoglycosides, iodinated contrast media)
No macroscopic signs of structural kidney injury, defined as:
- Absence of proteinuria (>500 mg/day)
- Absence of microhematuria (>50 RBCs per high-power field)
- Normal findings on renal ultrasonography

ICA, International Club of Ascites; *NSAIDs,* nonsteroidal antiinflammatory drugs; *RBC,* red blood cells.
Modified from Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut.* 2007;56:1310–1318[8] and Angeli P, Ginès P, Wong F, Bernardi M, Boyer T, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. *J Hepatol.* 2015;62:968–974.

In summary, new proposed criteria for the diagnosis of HRS-AKI are the following:

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to International Club of Ascites (ICA)–AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of body weight)
- Absence of shock
- No current or recent use of nephrotoxic drugs (e.g., NSAIDs, aminoglycosides, iodinated contrast media)

No macroscopic signs of structural kidney injury, defined as follows:

- Absence of proteinuria (>500 mg/day)
- Absence of microhematuria (>50 RBCs per high-power field)
- Normal findings on renal ultrasonography

One may argue that these criteria cannot rule out the presence of a subclinical renal damage and more sensitive biomarkers could be useful in this setting. Several urinary biomarkers have been developed in recent years; urinary neutrophil-gelatinase lipocalin is the most promising biomarker in the differential diagnosis of AKI in patients with cirrhosis.[15,16] Nevertheless, further studies are needed before any of these biomarkers could be included in the diagnostic criteria of HRS.

PATHOPHYSIOLOGY OF HEPATORENAL SYNDROME

Peripheral Arterial Vasodilation Hypothesis

For several years the "peripheral arterial vasodilation hypothesis" (PAVH) represented the best pathophysiologic

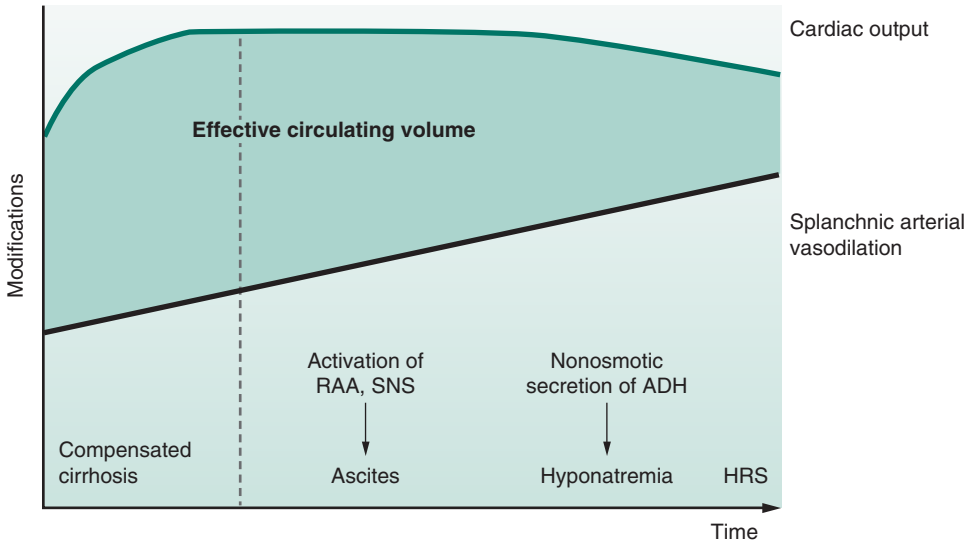

FIGURE 128.1 Pathogenesis of hepatorenal syndrome according to the "peripheral arterial vasodilation hypothesis vasodilation hypothesis." *ADH,* antidiuretic hormone; *HRS,* hepatorenal syndrome; *RAA,* renin-angiotensin-aldosterone system; *SNS,* sympathetic nervous system.

hypothesis of HRS[17] (Fig. 128.1). This hypothesis comes from the observation of an abnormal vasodilation in the splanchnic vascular bed in patients with cirrhosis. This abnormal vasodilation is the consequence of portal hypertension and is mediated by several vasodilators such as nitric oxide (NO), carbon monoxide (CO), glucagon, adrenomedullin, prostacyclin, and others in splanchnic circulation, leading to an abnormal vasodilation. This event causes a reduction in effective circulating volume and the activation of baroreceptors leading to activation of vasoconstrictors systems (sympathetic system, renin-angiotensin-aldosterone system, and nonosmotic production of vasopressin). Sympathetic nervous system activation causes an increase in heart rate and cardiac contractility, resulting in a global increase of cardiac output. Renin-angiotensin-aldosterone system activation causes an increase in distal absorption of sodium. Furthermore, the increase in sympathetic tone and angiotensin II stimulates sodium reabsorption in the proximal tubule. Finally, vasopressin is responsible of free water reabsorption in the distal tubule. Thus the effects of the activation of vasoconstrictors systems result in (1) an increase in cardiac output and (2) an expansion of body fluid resulting from sodium and water retention. In the early phases of the disease, these mechanisms restore the effective circulating volume. In this phase the so-called "hyperdynamic circulation" is the main feature. However, as liver disease worsens, the further increase in splanchnic vasodilation cannot be compensated for by a further increase in cardiac output. Thus the massive activation of the vasoconstrictor systems leads to abnormal renal sodium and water retention and arterial vasoconstriction in the kidney, which are responsible for the development of ascites, and, in the most advanced stages, dilutional hyponatremia, refractory ascites, and HRS.[17] HRS usually develops in the most advanced stages of the disease, when there is an extreme reduction of the effective circulating volume and an extreme activation of the systemic vasoconstrictor systems.

Cirrhotic Cardiomyopathy and the Systemic Inflammation Hypothesis

In recent years new concepts partially challenged the PAVH. The first one is the evidence of a reduction in cardiac output in patients who develop HRS, and the second is the key role of bacterial translocation-induced inflammation in patients with cirrhosis. Three hemodynamics studies showed the important role of a reduced cardiac output in patients who develop HRS. The first study compared baseline characteristics of patients who did or did not develop HRS after an episode of SBP.[18] Patients developing HRS showed significantly higher values of plasma renin activity, noradrenaline, peripheral vascular resistance, and lower cardiac output than patients not developing HRS. Interestingly, values of tumor necrosis factor-alpha (TNF-α) were significantly higher in patients who developed HRS, highlighting the role of inflammation. The second study was performed in patients with cirrhosis, ascites, and normal renal function. Patients who developed HRS during the follow-up showed a significantly lower cardiac output and mean arterial pressure and a significantly higher plasma renin activity and noradrenaline concentration than patients who did not.[19] Interestingly, no difference was found in systemic vascular resistance between the two groups. Furthermore, when HRS occurred, a further reduction of cardiac output was observed, suggesting that HRS is the result of a decrease in cardiac output in the setting of a severe arterial vasodilation. In the third study, again, a reduction in cardiac index was found to be a strong predictor of HRS development.[20] The reasons for the cardiac impairment in patients with cirrhosis still is elucidated poorly but in specific cardiac abnormalities have been recognized in these patients, including systolic and diastolic dysfunction, electrophysiologic repolarization changes, and enlargement of cardiac chambers. Overall, these abnormalities commonly are termed as "cirrhotic cardiomiopathy."[21]

The key role of inflammation in the development of HRS recently was highlighted in a new hypothesis named the "systemic inflammation hypothesis"[22] (Fig. 128.2). The input to the development of these new hypothesis came from the observation that acute-on-chronic liver failure (ACLF), a syndrome characterized by organ failures (renal, hepatic, circulatory, respiratory, cerebral, and coagulation failures) and a high mortality rate, may occur also in patients without a previous decompensation of cirrhosis and surrogate markers of inflammation such as leukocytes count and C-reactive protein strongly related with ACLF and

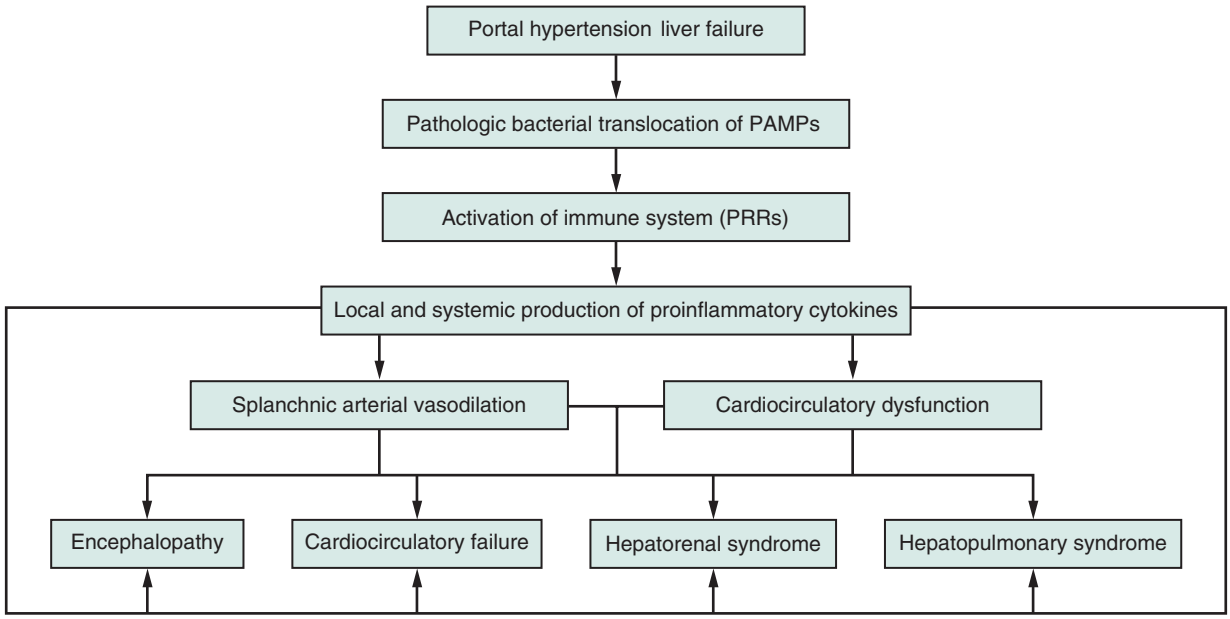

FIGURE 128.2 Pathogenesis of hepatorenal syndrome and acute-on-chronic liver failure according to the "systemic inflammation hypothesis." *PAMPs,* Pathogen-associated molecular patterns; *PRRs,* pattern recognition receptors.

survival.[23] In cirrhotic patients portal hypertension causes ultrastructural alterations of intestinal mucosa, increasing intestinal permeability. These alterations as well as the intestinal bacterial overgrowth and a change in microbiome facilitate a pathologic bacterial translocation from intestinal lumen to mesenteric lymph node and systemic circulation.[24] Bacteria and bacterial product (pathogen-associated molecular patterns [PAMPs]) are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) on immune cells, leading to the production of proinflammatory cytokines (TNF-α, interleukin-6, interleukin-1, and others). In experimental cirrhosis these cytokines stimulate endothelial nitric oxide synthase to produce NO in splanchnic circulation, worsening arterial vasodilation.[25] Importantly, the activation of cytokines and NO is reduced dramatically after 5 days of intestinal decontamination with norfloxacin.[25] These findings suggest that bacterial translocation induces a systemic and local proinflammatory responses that increase arterial NO production. Furthermore, there is evidence that bacterial translocation may impair cardiac function in cirrhosis. In experimental models Yang et al. showed an impairment in cardiac contractility in cirrhotic rats, strictly dependent by an overproduction of TNF-α acting via nuclear factor-κB and inducible NO synthase (iNOS) pathways.[26] The consequent production of NO blunts cardiac contractility increasing nitration of cardiac proteins and increasing cGMP production.[26]

Finally, bacterial translocation also may affect the kidney directly. Clinical and experimental data showed an upregulation of TLR4 in renal tubular cells in the setting of cirrhosis associated with the development of renal dysfunction, tubular damage, and apoptosis, suggesting a potential role of TLR4 as mediator of renal injury.[27,28] Although the mechanism of upregulation of tubular TLR4 is not entirely clear, it seems likely to be a consequence of the continuous exposure to gut bacterial translocation[28] and may be prevented by gut decontamination with norfloxacin.[28] These data suggest that increased bacterial translocation may exert a detrimental effect in the kidney through the upregulation of tubular TLR4. In summary, according to the "systemic inflammation hypothesis," bacterial translocation causes systemic inflammation, release of vasodilators, increase in splanchnic vasodilation, reduction in cardiac contractility, and direct damage in the kidney and in other organs representing the pathophysiologic basis of HRS and ACLF (Fig. 128.2).

Hepatorenal Syndrome: Still Completely Functional?

Despite the belief that HRS is just a functional form of renal failure, two lines of evidence suggest that HRS may be not completely functional. Trawalè et al. analyzed renal biopsies performed in patients with cirrhosis who had an unexplained renal impairment (SCr > 1.5 mg/dL), identifying 18 patients with neither hematuria nor proteinuria exceeding 500 mg/day, thus matching the characteristics of patients with HRS.[29] They found glomerular lesions in 10 patients, chronic tubulointerstitial lesions in 13 patients, and acute tubulointerstitial lesions in 12 patients, questioning the ability of current criteria for HRS in excluding parenchymal renal damage. Another line of evidence comes from the use of urinary biomarkers of tubular damage. Fagundes et al. investigated the ability of urinary neutrophil gelatinase-associated lipocalin (uNGAL), a marker of renal tubular injury, in discriminating the cause of renal failure in patients with cirrhosis. uNGAL was found to be a good biomarker of acute tubular necrosis, but values of uNGAL were significantly higher in patients with type 1 HRS than in those with prerenal AKI, in particular in patients with type 1 HRS precipitated by a bacterial infection.[15]

As previously discussed, there is evidence that in patients with HRS, and in particular in those with HRS precipitated by a bacterial infection, renal impairment may be the result of not only a renal vasoconstriction but also a direct effect of PAMPs and DAMPs in the kidney.[30] In experimental sepsis it has been shown that renal microcirculation undergoes important change, with the appearance of areas of hypoperfusion and hypoxia. This is due to the metabolic downregulation of tubular cells and to the overexpression

of iNOS in response to systemic inflammation. According to new theories, it appears that tubular cells respond to oxidative stress resulting from inflammation with a down-regulation of the metabolism, and the arrest of the cell cycle. This mechanism seems to be regulated by mitochondria to prevent further cellular damage.[31] These new concepts are very important for future studies aimed to improve the treatment of HRS; in fact, current medical treatments mainly focus on counteracting splanchnic vasodilation and improving the reduction of effective circulating volume.

PROPHYLAXIS OF HEPATORENAL SYNDROME

As reported above the occurrence of HRS in patients with cirrhosis is associated with a poor prognosis, and any effort should be made to avoid the onset of HRS. Patients with bacterial infections and, in particular, SBP, have a high risk to develop HRS. Thus they represent optimal candidates for the development of strategies aimed to prevent the development of HRS. A randomized controlled clinical trial showed that the administration of antibiotics plus albumin (1.5 g per kg of body weight on day 1 and 1 g per kg of body weight on day 3) in patients with SBP is associated with a lower risk to develop HRS than antibiotic alone.[9] Furthermore, the mortality rate was significantly lower in patients treated with albumin than in those treated with standard of care.[9]

In patients with bacterial infections other than SBP, the results are controversial. Guevara et al. found a significant improvement in renal function and a trend towards an improvement in survival with the administration of albumin.[32] On the contrary, Thevenot et al. found albumin able to delay the onset of renal failure, although the 3-month renal failure rate and survival rate were not different between the two groups.[33] Importantly, they reported eight cases of pulmonary edema in patients treated with albumin. Currently, to address this issue, a large multicenter, randomized controlled trial is ongoing in Europe.

Another strategy to prevent HRS is the prophylaxis of SBP. In a randomized placebo-controlled trial Fernandez et al. compared norfloxacin (400 mg/day) versus placebo in patients with advanced cirrhosis (Child-Pugh score ≥ 9, serum bilirubin level ≥3 mg/dL) or impaired renal function (serum creatinine > 1.2 mg/dL or serum sodium < 130 mmol/L) and a low protein concentration in ascitic fluid (<15 g/L).[34] Patients treated with norfloxacin showed a significant reduction in the probability to develop HRS and a significantly higher survival than patients treated with placebo.

MANAGEMENT OF HEPATORENAL SYNDROME

The first measure to take when AKI occurs is a prompt differential diagnosis. According to the ICA algorithm for the management of AKI in cirrhosis, the first step is to reduce or, if possible, to stop any potential nephrotoxic drug (e.g., diuretics, antibiotics, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors).[14] Then it is important to verify the presence of hypovolemia and, if necessary, to correct it. In patients with an increase of SCr of at least 100% of baseline, or if there is a progression of AKI from stage 1 to stage 2 or 3 despite this measures albumin, at the dose of 1g/kg of body weight should be administered for 2 days. If there is no response to therapy (no regression of AKI stage) and AKI meets the ICA criteria for HRS-AKI, a prompt, appropriate treatment is needed.[35]

General Measures

When HRS is diagnosed, a specific treatment should start as soon as possible. Beyond that, supportive measures should be taken. It is essential to monitor the patient's parameters, such as fluid balance, arterial pressure, and vital signs. A concomitant bacterial infection should always be suspected, diagnosed, and treated.[36] In particular, a diagnostic paracentesis and a chest x-ray always should be performed. There are no data supporting the use of empiric antibiotic treatment for unproven infections. Large volume paracentesis with albumin is not controindicated in patients with HRS and tense ascites. However, it is safe to remove a maximum of 5 liters of ascites per paracentesis. There is currently no recommendation about the use or the discontinuation of beta blockers used for the prophylaxis of variceal bleeding. The use of diuretics should be avoided, but furosemide may be useful to treat central volume overload. In Fig. 128.3 a summary of available treatments for HRS and the targets of these treatments according to pathogenesis of HRS is reported.

Vasoconstrictors Plus Albumin

Many studies have shown that the use of arterial vasoconstrictors in combination with albumin improves renal function in patients with HRS. The rationale behind the use of vasoconstrictors is to counteract the splanchnic arterial vasodilation. On the other hand, albumin expands effective blood volume. Furthermore, clinical and experimental studies suggest that albumin acts far beyond its role as plasma expander in cirrhosis. When compared with hydroxyethyl starch in patients with cirrhosis and SBP, albumin was capable of increasing cardiac stroke volume and systemic vascular resistance.[37] Conversely, no difference was found before and after the administration of hydroxyethyl starch, suggesting that albumin may improve cardiac output and vascular resistance with mechanisms other than plasma expansion. Albumin has several nononcotic properties, such as the capacity to bind and inactivate PAMPs, NO, and reactive oxygen species, which play a major role in the pathogenesis of systemic inflammation and systemic circulatory dysfunction. Indeed in experimental cirrhosis albumin was found to be able to restore cardiac contractility throughout a reduction of TNF-α–induced activation of NF-κB-iNOS pathway and oxidative stress in the cardiac tissue.[38] The importance of the combination of albumin and vasoconstrictors is supported by the extremely low rate of response when each of these drugs are used alone.[39]

Three types of vasoconstrictors are currently available in the treatment of HRS: terlipressin, noradrenaline, and the combination of midodrine and octreotide. Terlipressin is the most investigated vasoconstrictor in this field. Several pilot studies[40,41] as well as three randomized controlled trials[42–44] showed that the combination of terlipressin plus albumin is more effective than albumin alone in the treatment of HRS. The combination of terlipressin plus albumin was found to be effective in solving HRS in 34% to 54% of treated patients. These percentages are even higher in

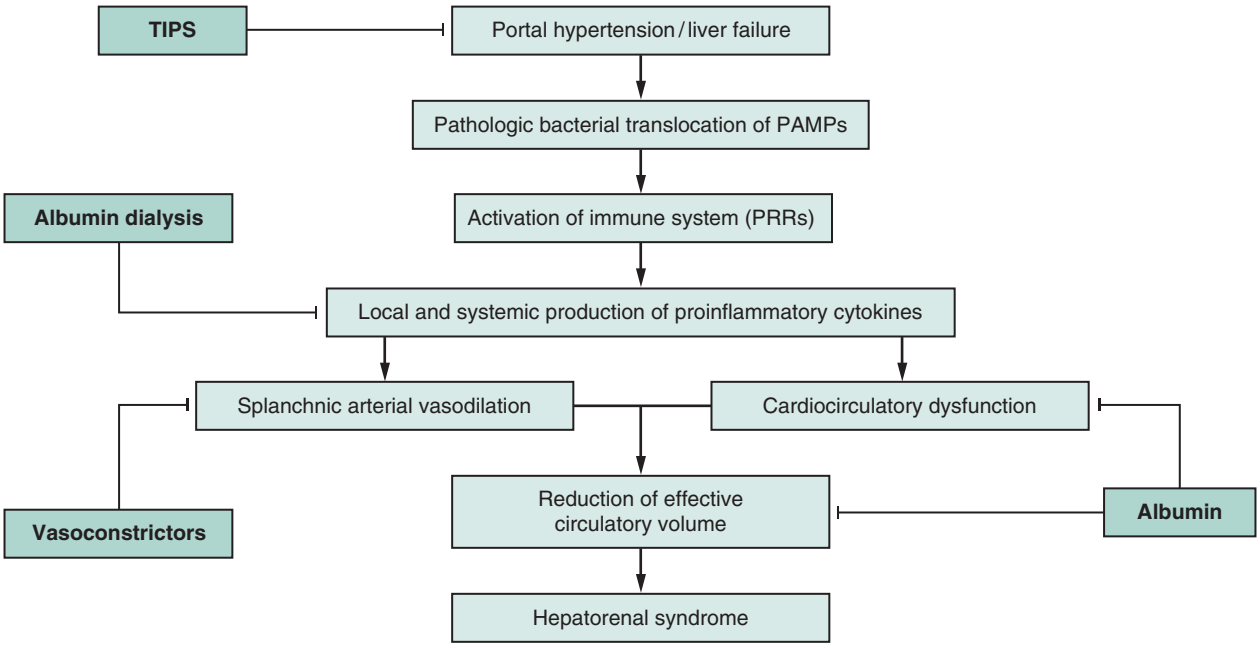

FIGURE 128.3 Pathophysiologic basis and targets of available treatments for hepatorenal syndrome. *PAMPs,* Pathogen-associated molecular patterns; *PRRs,* pattern recognition receptors; *TIPS,* transjugular intrahepatic portosystemic shunt.

patients with type 2 HRS.[36] Terlipressin can be administered as intravenous boluses (starting from 0.5 to 1 mg every 4 to 6 hours to a maximum dosage of 2 mg every 4 hours) and as continuous intravenous infusion (starting from 2 mg per day to maximum dosage of 12 mg per day).[35] The latter way of administration showed to be associated with a significant lower incidence of side effects than the former one.[45] Furthermore, the continuous infusion was effective at a lower dose than intravenous boluses.[45] These findings are probably consistent with the short half-life of terlipressin, with an effect that lasts after 3 to 4 hours. Terlipressin dose should be increased in a stepwise manner if serum creatinine does not decrease at least 25% after 3 days of treatment.[35] Albumin should be administered at the dosage of 20 to 40 g per day.[35-36] Usually, full response to treatment occurs within 14 days. After discontinuation of terlipressin and albumin, a recurrence of HRS can be observed in less than 20% of patients with type 1 HRS and retreatment is usually effective. Conversely, recurrence of HRS is common in patients with type 2 HRS and treatment should be reserved for the most severe patients (SCr > 2 mg/dL).

It has been claimed that treatment with terlipressin and albumin before liver transplantation (LT) could be associated with better post-LT outcomes in patients with type 2 HRS. However, a recent case control study did not show any difference in terms of post-LT outcomes in patients treated or not with terlipressin.[46] Patients who respond to treatment with terlipressin plus albumin show a better survival than nonresponder to treatment[45,47]; moreover, in a meta-analysis of a randomized trial, the use of terlipressin was associated with a significant improvement in survival at 15 days.[48] This moderate increase in survival may be important in patients developing HRS while on the waiting list for LT.

Adverse effects of the treatment with terlipressin are usually diarrhea, abdominal cramps, nausea, and headache. Severe side effects have been described, such as angina, cardiac arrhythmias, intestinal ischemia, and severe hypertension, and patients with ischemic heart disease and peripheral vascular disease should not be treated with terlipressin.

Midodrine (an α_1-agonist drug) combined with octreotide (a somatostatin analogue), together with albumin infusion showed to be effective in treating HRS.[49] Midodrine is administered orally at a dosage of 2.5 mg three times daily, which can be increased to 12.5 mg three times daily if there is no reduction in serum creatinine of at least 25% compared with baseline at day 3 of treatment. The starting dosage of octreotide is 100 mcg three times daily and can be increased to a maximum of 200 mcg three times daily with the same indications of midodrine. The dose of albumin is the same as provided for terlipressin. The combination of midodrine octreotide and albumin was able to restore renal function in about 40% of patients with type 1 HRS.[35] However, in a randomized controlled trial, the combination of terlipressin and albumin showed to be significantly more effective than the combination of midodrine and octreotide and albumin in the treatment of HRS (improvement of renal function in 70% vs. 29%, respectively; $p = .01$).[47]

The administration of norepinephrine (administered at a dose of 0.5–3 mg/hr) plus albumin has been investigated as a treatment in type 1 HRS. In a small, randomized controlled trial noradrenalin showed to be as effective as terlipressin in the treatment of HRS.[50] The use of norepinephrine in treating HRS is tempting because it is a cheaper than terlipressin; however, it should be administered in a central venous line and under continuous monitoring, thus it cannot be used in outside intensive care units. Therefore further studies are needed to determine the reliability of this treatment.

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is a technique used to create a shunt between the portal vein and the hepatic vein in the liver. In selected patients, TIPS

usually is well tolerated; however, some complications can occur, such as thrombosis or occlusion of the shunt, fistulae, hemolysis, infections, and, more commonly, hepatic encephalopathy (HE).[51]

From a pathophysiologic point of view, the use of TIPS is interesting, because it reduces portal hypertension and increases cardiac output. TIPS improves renal perfusion and sodium and water excretion and has been reported to reduce serum creatinine in selected patients with HRS.[52,53] However, the applicability of TIPS in patients with HRS is very limited, because many patients have contraindications to the use of TIPS. Furthermore, data available on the use of TIPS in patients with type 1 HRS are based primarily on case series, and randomized controlled trials are needed to evaluate the use of TIPS in patients with type 1 HRS.

Extracorporeal Liver Support Systems

Extracorporeal liver support systems aim to remove toxins (e.g., bilirubin, bile acids, aromatic amino acids, cytokines) accumulated in the circulation because of liver failure, mainly using an albumin dialysis–based technique. Two devices have been explored in patients with cirrhosis and acute-on-chronic liver failure: the molecular adsorbent recirculating system (MARS) and the fractionated plasma separation and adsorption system (Prometheus). The use of MARS showed no benefit on survival versus standard of care; however, there was a significant higher reduction in SCr in patients treated with MARS than controls.[54] Furthermore, in a subanalysis including only patients with HRS, reversal of HRS tended to be higher in patients treated with MARS than control at day 4 (47% vs. 26%, $p = .07$). In a randomized, controlled trial the Prometheus device did not show benefit in terms of survival nor in terms of improvement in renal function in patients with ACLF.[55] However, in a subanalysis including only patients with type 1 HRS, treatment with Prometheus system was associated with improved survival compared with standard treatment.[55] Interestingly, in both the trials patients with HRS were treated with vasoconstrictors plus albumin.

Renal Replacement Therapy

Poor data are available on the impact of renal replacement therapy (RRT) in patients with HRS. No survival advantage has been demonstrated in patients with HRS treated with RRT. However, in patients not responding to vasoconstrictors plus albumin, with volume overload, metabolic acidosis, severe hyperkalemia, and/or hyponatremia, RRT should be considered,[56] in particular in patients on liver transplant waiting list. No data are available on the optimal technique of RRT (intermittent hemodialysis vs. continuous RRT) in these patients. However, it has been suggested that continuous RRT may be the best option, considering the lower risk of hypotension than intermittent hemodialysis. In patients who are not eligible for liver transplantation, the decision to perform RRT should be made case by case to avoid futility of treatment.

Liver Transplantation

Liver transplantation (LT) is the optimal treatment in patients with cirrhosis with HRS. It is considered the best treatment for type 1 and type 2 HRS.[35,36,57] Unfortunately, the timing to get a graft is unpredictable vasoconstrictors plus albumin. Patients with HRS responding to terlipressin and albumin while on the waiting list had a better posttransplantation course, fewer complications, a shorter period of hospitalization, and less need for RRT after liver transplantation.[58] The criteria for prioritization in the LT waiting list are based on the model of end-stage liver disease (MELD) score. This prognostic score is based on an equation that considers the value of serum creatinine (with an extra point if on RRT), bilirubin, and INR and is a good predictor of 3 months' risk of death for patients with cirrhosis. However, patients with HRS responding to treatment with vasoconstrictors plus albumin may be penalized by this method. In fact, it is known that the development of type 1 HRS is associated with a higher mortality than other cirrhotic patients with the same MELD score.[7] Furthermore, patients showing continuous recurrence of HRS at any attempt to withdraw vasoconstrictors and albumin, therefore requiring a long-term treatment with vasoconstrictors and albumin may be disadvantaged further.[59] In these two groups of patients it has been suggested to use the peak of SCr for the estimation of MELD score (for responders to vasoconstrictors) and to compute MELD score as provided for patients in dialysis (for patients on long-term treatment with terlipressin).[58]

Key Points

1. Hepatorenal syndrome (HRS) is a functional renal failure occurring in patients with advanced liver disease. Two types of HRS can be identified: type 1 HRS, which is characterized by an acute onset and a poor short term prognosis, and type 2 HRS, characterized by a slowly progressive course, associated with refractory ascites and a better survival rate than type 1 HRS. Type 1 HRS currently is considered a type of acute kidney injury and type 2 a type of chronic kidney disease.
2. The reduction of effective circulating volume is the main pathogenetic mechanism of HRS. Effective hypovolemia is caused by a splanchnic arterial vasodilation and a reduction in cardiac output. The compensatory activation of endogenous vasoconstrictors systems such as sympathetic nervous system, the renin-angiotensin-aldosterone system, and nonosmotic secretion of vasopressin leads to severe prerenal arterial vasoconstriction.
3. Translocation of bacteria and/or bacterial product from intestinal lumen to systemic circulation causes a systemic inflammatory response, further increasing the splanchnic arterial vasodilation and impairing the cardiac output. Bacterial infections are the main triggers of type 1 HRS.
4. Recently, some evidence suggests that HRS may be not completely functional, and some signs of parenchymal renal damage can be found in these patients.
5. Liver transplantation is the best treatment of HRS. The use of vasoconstrictors plus albumin represents the best medical treatment of HRS. The potential benefit of transjugular intrahepatic portosystemic shunt and extracorporeal systems as a bridge to liver transplantation is still to be determined.

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