Hepatorenal Syndrome

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Florence Wong, MD, FRACP, FRCP(C)

ESSENTIALS OF DIAGNOSIS

- Renal failure in patients with advanced liver failure (acute or chronic) in the absence of any identifiable causes of renal pathology.
- All other causes of renal failure, functional or organic, have been excluded.

General Considerations

Renal dysfunction is a common and serious problem in patients with advanced liver disease, estimated to occur in 10% of hospitalized patients with cirrhosis. It is a syndrome characterized by (1) oliguria, severe renal sodium retention, and rapidly progressive azotemia, (2) circulatory instability with marked systemic arterial vasodilation and activation of vasoactive systems, and (3) a very poor prognosis. Without treatment, the median survival for type 1 hepatorenal syndrome patients is on the order of 1–2 weeks, while that for type 2 hepatorenal syndrome is about 20% at 1 year. However, hepatorenal syndrome has always been considered to be a form of functional renal failure, as kidneys from patients with hepatorenal syndrome, when transplanted into someone with renal failure, regain their normal function. Similarly, renal function also improves in patients with end-stage cirrhosis following liver transplantation, although the renal function can remain abnormal for quite sometime in the postoperative period.

Hepatorenal syndrome is defined as the development of renal failure in patients with advanced liver failure (acute or chronic) in the absence of any identifiable causes of renal pathology. It is a diagnosis of exclusion, when all other causes of renal failure, functional or organic, have been excluded. The International Ascites Club further defines the criteria for the diagnosis of hepatorenal syndrome, as detailed in Table 10–1. It must be emphasized that urinary parameters are supportive, but not essential for the diagnosis of hepatorenal syndrome. For example, urinary volume is usually <500 mL/day, but there are nonoliguric forms of hepatorenal syndrome. Urinary sodium excretion is usually <10 mEq/day in hepatorenal syndrome. However, cases of well-documented hepatorenal syndrome with urinary sodium of >10 mEq/day have been reported. Finally, although the urinary osmolality is higher than the plasma osmolality in most patients with hepatorenal syndrome, a decrease in urinary osmolality may occur as renal failure progresses.

The Internal Ascites Club divided hepatorenal syndrome into type 1 and type 2. Type 1 hepatorenal syndrome is characterized by a rapid decline in renal function defined as a doubling of serum creatinine to a level greater than 220 μmol/L or a halving of the creatinine clearance to less than 20 mL/minute within 2 weeks. The clinical presentation is that of acute renal failure. The patient is usually very sick, with marked jaundice and severe coagulopathy. In type 2 hepatorenal syndrome, renal function deteriorates more slowly with the serum creatinine increasing to greater than 133 μmol/L or a creatinine clearance decreasing to less than 40 mL/minute over the course of weeks to months. The clinical presentation is that of gradual renal failure in a patient with cirrhosis and refractory ascites.

Pathogenesis

The pathophysiology of hepatorenal syndrome is complex. The hallmark of hepatorenal syndrome is renal hypoperfusion, which is due to a reduction in the renal perfusion pressure as well as to active renal vasoconstriction. This leads to a decrease in the renal blood flow and a reduction in the glomerular filtration rate. Many pathophysiologic factors are involved in the development of hepatorenal syndrome in patients with end-stage cirrhosis.

A. Hemodynamic Changes in Cirrhosis

Liver cirrhosis and portal hypertension are characterized by an increased cardiac output and decreased systemic vascular

Table 10–1. Diagnostic criteria for hepatorenal syndrome.

Cirrhosis with ascites
Serum creatinine >133 μmol/L (1.5 mg/dL)
No improvement of serum creatinine (decrease to a level of ≤133 μmol/L) after at least 2 days of diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg body weight/day up to a maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), and/or abnormal renal ultrasonography

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resistance, the so-called hyperdynamic circulation. The basis for the hyperdynamic circulation is systemic arterial vasodilation. This occurs mainly in the splanchnic circulation, a result of both increased resistance to portal flow due to the cirrhosis and to the presence of excess vasodilators and/or decreased responsiveness of the vasculature to endogenous vasoconstrictors. Clinically, this is manifested as systemic hypotension, tachycardia, wide pulse pressure, and warm peripheries. The homeostatic response is the activation of various vasoconstrictor systems, including the renin–angiotensin system, the sympathetic nervous system, and arginine vasopressin. These will counteract the vasodilatory effects of the vasodilators and direct the kidneys to retain sodium and water in order to maintain hemodynamic stability. As cirrhosis progresses, systemic hypotension worsens as the systemic arterial vasodilation increases, and at some point in time the renal perfusion pressure will fall. When combined with increasing levels of the systemic vasoconstrictors, total renal blood flow gradually falls. When the production of endogenous vasodilators cannot keep pace with the fall in renal blood flow, renal failure ensues (Figure 10–1).

B. The Role of Mesangial Contraction

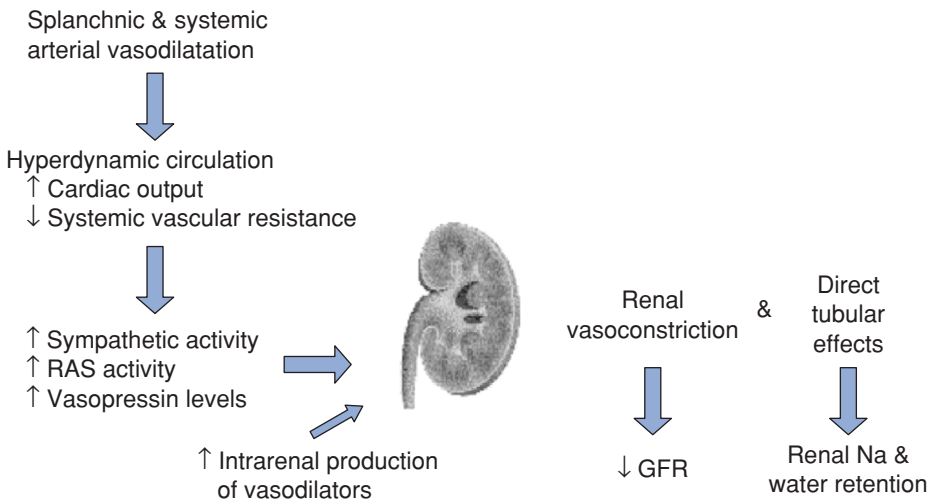
Not all cirrhotic patients with similarly reduced renal blood flow will develop hepatorenal syndrome. Therefore, other factors must also play a pathogenetic role. In addition to reduced renal blood flow, various vasoconstrictors, in particular, endothelin-1 and leukotrienes, may also cause mesangial contraction, thereby reducing the glomerular ultrafiltration coefficient and further decreasing the glomerular filtration rate.

C. The Role of Portal Hypertension

Portal hypertension is associated with a reduction of renal blood flow and may play a role in the pathogenesis of hepatorenal syndrome. The connection between portal hypertension and renal hemodynamics may be the sympathetic nervous system.

D. The Role of Hepatic Dysfunction

Renal hypoperfusion, due to a reduction of renal vasodilators, in cirrhosis could also be related to liver dysfunction. However, the mechanism whereby liver dysfunction could directly induce a reduction in renal vasodilators is unclear. It



▲ **Figure 10–1.** Pathophysiology of hepatorenal syndrome GFR, glomerular filtration rate; RAS, renin–angiotensin system.

is possible that the liver is involved in the synthesis or release of renal vasodilators such as nitric oxide. The severe jaundice associated with liver failure can sensitize the renal vasculature to the vasoconstrictive effects of norepinephrine, resulting in greater renal vasoconstriction with any given level of circulating norepinephrine. High levels of bile acids observed in cholestasis can cause arterial vasodilation, thereby exaggerating the hemodynamic instability. That is, hepatic dysfunction "makes a bad situation worse." In patients with severe jaundice (bilirubin >510 μmol/L), there is direct bilirubin nephrotoxicity.

E. Precipitating Factors

At least 50% of patients with hepatorenal syndrome arrive in the hospital with near normal renal function. Therefore, it is what clinicians do to these patients that frequently precipitates hepatorenal syndrome. These precipitating events cause a further reduction in the filling of the effective arterial circulation, exaggerating the hemodynamic instability, resulting in further renal hypoperfusion and a decrease in the glomerular filtration rate.

1. Diuretic therapy—Cirrhotic patients with refractory ascites (Table 10–2) experience a reduction in their effective arterial blood volume and do not respond well to diuretic therapy. Diuretic therapy, by decreasing the intravascular volume, further exaggerates the reduction in effective arterial blood volume, and predisposes the patient to the development of hepatorenal syndrome. Clinicians have a tendency to increase the diuretic doses when there is an inadequate diuretic and natriuretic response, despite rising serum creatinine levels. Cirrhotic patients with refractory ascites typically excrete only approximately 500 mL of urine per day even in the presence of a "normal" serum creatinine level. Therefore, when increasing doses of diuretics do not result in an increased urine volume or urinary sodium excretion, further increases in the diuretic doses will increase the likelihood of developing hepatorenal syndrome in these patients. Conversely, decreasing the diuretic doses in a patient with refractory ascites and rising serum creatinine may reverse the renal dysfunction.

Table 10–2. Definition of refractory ascites.[1]

Weight loss ≤1.5 kg/week while on	
400 mg of spironolactone or 30 mg of amiloride plus 160 mg of furosemide daily	≥1 week, while on
Dietary sodium restriction ≤50 mmol/day	

[1]Patients who are intolerant of diuretic therapy because of the development of complications are also regarded as having refractory ascites.

2. Large volume paracentesis—Large volume paracentesis leads to an exaggeration of the hyperdynamic circulation. The systemic circulation becomes more vasodilated about 24 hours after a large volume paracentesis. The subsequent further activation of the vasoconstrictor systems predisposes the patient to the development of hepatorenal syndrome. Reducing the rate of paracentesis could potentially prevent deleterious hemodynamic consequences and reduce the risk of developing hepatorenal syndrome.

3. Spontaneous bacterial peritonitis—It is estimated that at least 30% of patients with spontaneous bacterial peritonitis will develop hepatorenal syndrome despite adequate treatment of their infection. It has been postulated that sepsis in cirrhosis induces an increased production of various cytokines and endotoxins, which in turn stimulates the production of nitric oxide and other vasodilators, causing further arterial vasodilation. Therefore, spontaneous bacterial peritonitis exaggerates the reduction in the effective arterial blood volume and increases the risk of further deterioration of the systemic hemodynamics, leading to decreased renal function.

4. Gastrointestinal bleeding—Acute blood loss with acute blood volume contraction usually leads to acute tubular necrosis and not hepatorenal syndrome. However, patients with decompensated cirrhosis and gastrointestinal bleeding can develop a systemic inflammatory response syndrome, manifesting as an increase in temperature, tachycardia, tachypnoea, and leukocytosis with or without an infection, associated with the activation of many cytokines. Once again, these cytokines can stimulate the production of nitric oxide and other vasodilators. Thus, the patient with gastrointestinal bleeding is also predisposed to further exaggeration of the systemic arterial vasodilation, due to the fact that the accompanying inflammatory response will yield more vasodilators, aggravating the effective arterial underfilling. Gastrointestinal bleeding also predisposes the cirrhotic patient to the development of infection, which in turn predicts rebleeding after control of the initial bleeding episode. The presence of infection in a cirrhotic patient with gastrointestinal bleeding adds to the inflammatory response and to cytokine production, further exaggerating the hemodynamic instability and increasing the likelihood of developing hepatorenal syndrome. To support this hypothesis, the routine use of prophylactic antibiotics in cirrhosis with gastrointestinal bleeding has led to a significant reduction in the incidence of hepatorenal syndrome associated with the bleeding episode.

5. Cholestasis—Acute biliary obstruction is associated with the development of renal impairment, leading to the suggestion that increased production of F_2-isoprostanes in cholestasis was responsible for the development of renal failure, since F_2-isoprostanes are potent renal vasoconstrictors, and the administration of antioxidants that reduced

F_2-isoprostane levels was associated with improvement of renal function. Cholestasis per se appears to be detrimental to the systemic circulation. It is not surprising that when cholestasis is superimposed on cirrhosis and portal hypertension, the circulatory changes are likely to worsen, predisposing the patient to the development of hepatorenal syndrome.

6. Nephrotoxic agents—The use of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) in cirrhosis is associated with a reduction in renal perfusion and glomerular filtration rate, secondary to an inhibition of the renal production of vasodilatory prostaglandins. In addition, NSAIDs impair renal sodium and water excretion, and these effects are independent of the deterioration in renal hemodynamics. These effects are particularly pronounced in cirrhosis with ascites, as these patients are dependent on the intrarenal production of prostaglandins to counteract the effects of various vasoconstrictors. Therefore, ascitic cirrhotic patients should not receive NASIDs in order to avoid the precipitation of hepatorenal syndrome. Cirrhotic patients are dependent on the activated renin–angiotensin system to maintain systemic blood pressure. Therefore, the use of angiotensin-converting enzyme inhibitors and angiotensin II antagonists can result in arterial hypotension and precipitate renal failure in these patients.

The pathogenesis of hepatorenal syndrome can be best summed up by the 2-hit theory (Figure 10–2). The cirrhotic patient with advanced liver disease and massive ascites has a compromised circulatory state (the first hit). The activation of various compensatory mechanisms maintains the circulation. Further progression of liver disease with deterioration of the circulation will lead to the development of hepatorenal syndrome (nonprecipitated cases). Alternatively, the presence of a precipitating factor will lead to rapid deterioration of the systemic circulation and to the development of the hepatorenal syndrome (second hit).

Clinical Findings

A. Type 1

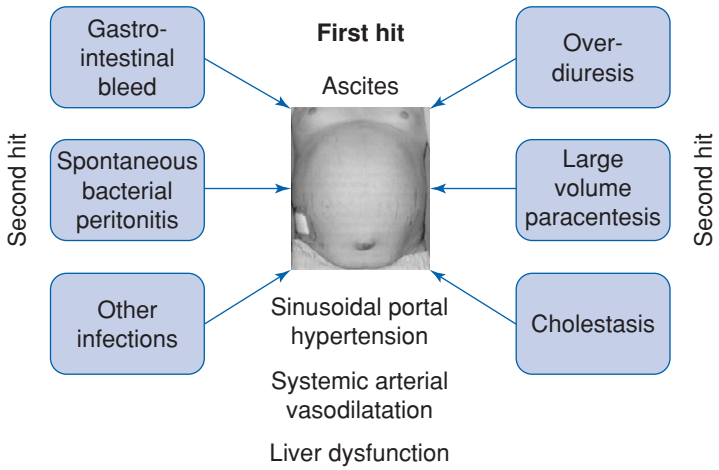
Type 1 hepatorenal syndrome is characterized by a rapid and progressive deterioration of renal function. The patient is usually ill with severely decompensated liver cirrhosis, jaundice, and hyponatremia. Oliguria and rising creatinine develop over the course of a few days. In about half the patients, there is no obvious precipitating cause. In the other half, the onset of hepatorenal syndrome follows some clear precipitating event such as infection, major gastrointestinal hemorrhage, or overaggressive diuresis or large volume paracentesis (>5 L) without replacement of the intravascular volume. On examination, these patients usually have florid signs or stigmata of liver failure. There may be evidence of encephalopathy with asterixis and hyperreflexia, but patients usually do not lapse into coma until the final stages.

Clinically, the patient may appear hypovolemic with a low jugular venous pressure. There is an obvious hyperdynamic circulation with bounding tachycardia, low normal blood pressure, or frank hypotension, and a precordial systolic flow murmur. The ascites is often massive with or without associated leg edema.

Over the years, several factors have been found to be associated with a greater risk for the development of type 1 hepatorenal syndrome (Table 10–3). These parameters are all related to severe hemodynamic instability and marked renal sodium and water retention.

B. Type 2

Patients with type 2 hepatorenal syndrome have a relatively stable serum creatinine that gradually climbs over a period of months. They are usually stable Child–Pugh Class B patients with relatively preserved liver function, but with a history of diuretic-resistant ascites. Jaundice is mild, and the patient



▲ **Figure 10–2.** The pathogenesis of hepatorenal syndrome.

Table 10–3. Factors associated with a greater risk for the development of type 1 hepatorenal syndrome.

Low arterial pressure
Glomerular filtration rate of <50 mL/minute
Serum creatinine >133 μmol/L
Blood urea nitrogen >21 mmol/L
Hyponatremia
Hyperkalemia
Low urinary sodium excretion
Low plasma osmolality
High urinary osmolality
Reduced free water excretion after water load
High plasma renin activity
High plasma norepinephrine

usually has some degree of coagulopathy. Hepatic encephalopathy is usually absent. Urine output is maintained over the course of weeks to months and only slowly diminishes as the serum creatinine climbs.

Differential Diagnosis

The clinician needs to recognize that renal dysfunction may be present despite a normal serum creatinine. This may be due to two factors: (1) cirrhotic patients are often wasted with a reduced muscle mass and hence lower normal serum creatinine levels and (2) a high bilirubin level may interfere with the creatinine assay. A creatinine >88 μmol/L in a patient with cirrhosis should alert the clinician to the presence of renal dysfunction.

Hepatorenal syndrome represents only a small portion of all causes of renal failure in decompensated cirrhotic patients with ascites. It is a diagnosis of exclusion. To arrive at a diagnosis of hepatorenal syndrome, the circulation of the patient has to be full and there has to be no evidence of intrinsic (organic) kidney disease.

A. Prerenal Renal Failure

Patients with decompensated cirrhosis and ascites and hemodynamic instability are poised to develop renal impairment if their circulation is further compromised. Therefore, events that tend to reduce the intravascular volume further such as gastrointestinal bleed, large volume paracentesis, or overzealous diuresis are likely to lead to renal failure. It follows that patients who have evidence of significant arterial vasodilation clinically, such as low arterial blood pressure and tachycardia, should be assessed to receive intravascular volume replacement for their large volume paracentesis. Likewise, resuscitation following gastrointestinal bleeding should be as complete as possible. It is very tempting to increase the diuretic doses in patients who have large ascites and an inadequate urine output. The end result may be further reduction in renal function as the intravascular volume is further compromised. Often, by reducing or eliminating the diuretic doses, the serum creatinine may decrease, accompanied by an improved urine output. A low urinary sodium excretion cannot be used as a guide to the presence of prerenal failure, as patients with hepatorenal syndrome have a reduced effective arterial blood volume and therefore will also have a low urinary sodium excretion. Rather, patients with decompensated cirrhosis, ascites, and renal failure should be challenged with a fluid load, with their central venous blood pressure filled up to 10 cm of water. Colloid solutions are preferred, as crystalloids tend to be distributed directly to the peritoneal cavity as ascites and not be retained in the circulation. If the patient has prerenal renal failure, the serum creatinine should slowly decrease as the circulation is gradually refilled.

B. Organic Renal Disease

Patients with decompensated cirrhosis can also develop organic renal disease. In fact, many organic renal diseases occur as a result of the liver disease (Table 10–4). Alternatively, there are many systemic diseases that can affect the liver and the kidney simultaneously (Table 10–5). Intrinsic or structural renal disease can be excluded by inactive urinary sediment, a urinary protein excretion of <500 mg/day, and a normal ultrasound examination of both kidneys. Differentiating hepatorenal syndrome from acute tubular necrosis is often difficult. Distinguishing the two is important when considering therapy and for prognostication. Typically, urine sodium of <10 mmol/L occurs in hepatorenal syndrome, while a urine sodium of >20 mmol/L is typical for acute tubular necrosis due to impaired reabsorption of sodium from damaged renal tubules. However, this distinction is not always reliable, especially in the late stages of hepatorenal syndrome.

Table 10–4. Primary liver diseases complicated by renal diseases.

Liver Disease	Kidney Disease
Alcoholic hepatitis	IgA nephropathy
Hepatitis B	Glomerulonephritis Polyarteritis nodosa Cryoglobulinemia
Hepatitis C	Glomerulonephritis Cryoglobulinemia
Obstructive jaundice	Acute renal failure
Primary biliary cirrhosis	Renal tubular acidosis Interstitial nephritis
Wilson's disease	Renal tubular acidosis

Table 10–5. Systemic diseases affecting both liver and kidney.

Drugs		
Acetaminophen	Liver failure	Acute/chronic renal failure
Aspirin	Acute hepatitis Reye's syndrome	Papillary necrosis
Pregnancy	HELLP Hepatic rupture	Preeclampsia
Cysts	Polycystic liver disease	Polycystic kidney disease
Sarcoidosis	Liver granulomas Portal hypertension	Renal stones
Diabetes	Steatohepatitis	Diabetic nephropathy
Amyloidosis	Hepatomegaly	Nephrotic syndrome
Sickle cell anemia	Hyperbilirubinemia Gallstonews Cholecystitis Secondary hemochromatosis	Hematuria Renal infarct
Paroxysmal nocturnal hemoglobinuria	Budd-Chiari syndrome Portal vein thrombosis	Hemoglobinuria
Shock	Ischemic hepatitis	Acute tubular necrosis

Acute tubular necrosis can also occur. This should be considered when renal failure develops abruptly following hypovolemia, septic shock, or exposure to nephrotoxins.

Treatment

In patients with cirrhosis and acute or chronic liver failure who present with a serum creatinine of >133 μ mol/L (1.5 mg/dL), a thorough workup should be done to exclude other causes of renal disease. In addition, patients should be initially challenged with fluid to assess response and to treat subclinical hypovolemia. All precipitants of hepatorenal syndrome should be sought and corrected. A careful assessment of the patient's history should identify preceding events such as gastrointestinal bleeding, overdiuresis, or aggressive paracentesis. Sepsis should be suspected in any cirrhotic patient with renal deterioration even in the absence of symptoms. Fever and leukocytosis may not be present. A full septic workup should be done and cultures should be obtained, including examination of the ascitic fluid to rule out spontaneous bacterial peritonitis. Recent exposure to nephrotoxins such as NSAIDs or aminoglycosides prior to the increase in serum creatinine should be ruled out. In contrast to the general belief, the use of radiocontrast dye has not been shown to be detrimental to renal function in cirrhosis. If proteinuria and/or hematuria are present, additional investigations should be undertaken to rule out renal parenchymal diseases. Renal biopsy should be considered if there is a strong suspicion for glomerulonephritis. Finally, an abdominal ultrasound should be performed to determine if the patient has postobstructive renal failure.

Once the diagnosis of hepatorenal syndrome is firmly established, the treatment options are aimed at correcting different aspects of the pathophysiology of hepatorenal syndrome. Patients should be supported until liver recovery or transplantation.

A. Pharmacology

The aim of pharmacotherapy is to improve systemic hemodynamics. This can be achieved by increasing either systemic or splanchnic vasoconstriction. The former improves renal perfusion pressure, while the latter redistributes part of the splanchnic volume to the systemic circulation, thereby improving the systemic arterial blood volume, with consequent improved renal perfusion and glomerular filtration.

1. Dopamine—Low-dose dopamine is a renal vasodilator. Despite this, it has not been shown to be effective in improving the glomerular filtration rate in either cirrhotic patients with refractory ascites but no hepatorenal syndrome or in cirrhotic patients with established hepatorenal syndrome. Furthermore, in cirrhotic patients with refractory ascites but without hepatorenal syndrome, dopamine has been shown to decrease arterial pressure and accentuate portal hypertension. Therefore, it should not be used in cirrhotic patients with refractory ascites or hepatorenal syndrome.

2. Norepinephrine—Although the use of intravenous norepinephrine (0.5–3 mg/hour) in combination with intravenous albumin and furosemide resulted in the reversal of hepatorenal syndrome in a small study, until the results of randomized controlled trials are available the routine use of norepinephrine for hepatorenal syndrome cannot be recommended.

3. Vasopressin analogues

A. Ornipressin—Ornipressin is a nonselective agonist of the V1 vasopressin receptors. It preferentially causes vasoconstriction of the splanchnic vasculature, thus increasing systemic pressure and renal perfusion pressure. While treatment with ornipressin and albumin has improved renal function in cirrhotic patients with hepatorenal syndrome, there is an increased risk of serious, life-threatening, ischemic complications associated with the use of ornipressin. Therefore, the use of this agent for hepatorenal syndrome is rather limited, and it is no longer commercially available.

B. Terlipressin—Terlipressin is a synthetic analogue of vasopressin with intrinsic vasoconstrictor activity. It is also a nonselective V1 vasopressin agonist but has a lower incidence of ischemic complications than vasopressin or ornipressin. It

also has the advantage over vasopressin of a longer half-life, allowing administration as a 4 hourly bolus. The infusion of terlipressin at a dose of 0.5–2 mg/4–6 hours intravenously up to 15 days is associated with improved renal function, although usually not to normal, with suppressed plasma renin activity and aldosterone levels, increased atrial natriuretic factor levels, and some improvement of urinary sodium excretion, without serious side effects in the majority of patients. It is not clear whether treatment beyond 15 days would result in further improvement of renal function. Terlipressin is not available in North America, but is the first-line therapy for hepatorenal syndrome in Europe.

4. Midodrine and octreotide—Midodrine is an oral α-adrenergic agonist that improves systemic blood pressure and hence improves renal perfusion pressure. Octreotide is a long-acting analogue of somatostatin that antagonizes the action of various splanchnic vasodilators and reduces the mismatch between the extent of arterial vasodilation and the intravascular volume. The use of midodrine or octreotide alone has not proved useful for patients with hepatorenal syndrome. However, when midodrine is combined with plasma volume expansion and octreotide, there is often a significant improvement in both the systemic and renal hemodynamics and urinary sodium excretion, along with a partial improvement in renal function. The use of this combination is popular in North America because of the nonavailability of terlipressin. However, its place in the treatment of hepatorenal syndrome still awaits the results of larger randomized controlled trials.

5. Endothelin receptor antagonists—Endothelin has been postulated to be a mediator of intrarenal vasoconstriction in hepatorenal syndrome, and treatment with endothelin receptor antagonists has been associated with dose-related increases in both the glomerular filtration rate and renal plasma flow. However, based on personal experience, the use of a nonselective endothelin receptor antagonist in cirrhotic patients with hepatorenal syndrome resulted in both decreased renal function and urinary volume (unpublished data). Therefore, such agents should be used only in a clinical trial setting.

6. Pentoxifylline—Pentoxifylline is a phosphodiesterase inhibitor with antitumor necrosis factor activity. While use of pentoxifylline in patients with acute alcoholic cirrhosis has resulted in a significant reduction in the incidence of hepatorenal syndrome, there are no studies assessing the use of pentoxifylline as a treatment for established hepatorenal syndrome.

B. Extracorporeal Albumin Dialysis

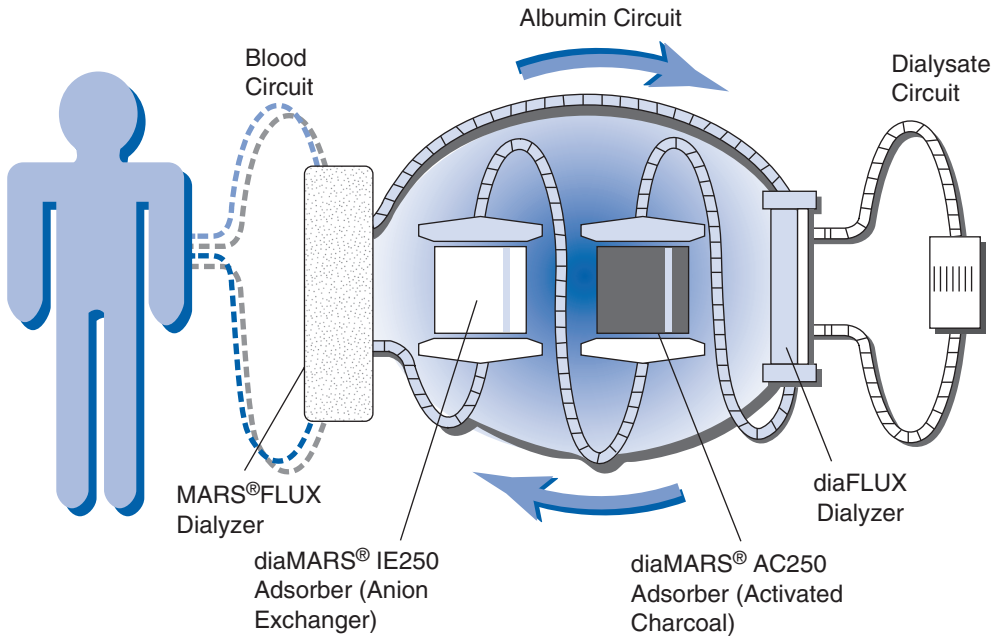
Extracorporeal albumin dialysis is a system that uses a cell-free, albumin-containing dialysate that is recirculated and perfused through charcoal and anion exchange columns. One such extracorporeal albumin dialysis device is the molecular absorbent recirculating system (MARS). During dialysis, a closed loop dialysate circuit allows the transfer of albumin-bound toxins from plasma onto a permeable polysulfone-saturated membrane. The membrane-bound albumin plus toxin is recycled by continuous deligandization. Water-soluble toxins can then be removed with the use of charcoal columns and ion-exchange resins as the adsorbents (Figure 10–3). The system is very efficient in removing molecules with a molecular weight of less than 50 kDa. The rationale for using MARS as a treatment for hepatorenal syndrome is that it can remove many cytokines such as tumor necrosis factors and interleukin 6, which have been implicated in the production of various vasodilators. Therefore, by reducing the levels of vasodilators, the expected result is improved systemic hemodynamics and hence better renal perfusion and renal function.

MARS dialysis reduces serum bilirubin and creatinine levels and has been ssociated with a small prolongation of survival. It is not clear at present whether the reduction in serum creatinine with MARS treatment is maintained after withdrawal of MARS. It is also not clear how long MARS treatment should be given before sustained improvement in renal function can be achieved. Therefore, MARS should not be used in the treatment of patients with hepatorenal syndrome, except in the context of a clinical trial.

C. Transjugular Intrahepatic Portosystemic Stent Shunt (TIPS)

TIPS is prosthesis that bridges a branch of the portal vein with a branch of the hepatic vein (Figure 10–4), effectively functioning as a side-to-side portal caval shunt. It is very effective in reducing portal pressure. Since sinusoidal portal hypertension plays a pivotal role in the control of renal hemodynamics, it is not surprising that the insertion of TIPS, especially in cirrhotic patients with refractory ascites and some degree of renal dysfunction, is associated with improvement in both the glomerular filtration rate and renal blood flow. In addition, TIPS returns a significant portion of the splanchnic volume into the systemic circulation, leading to suppression of various vasoactive neurohormones, resulting in better renal perfusion. The successful treatment of type 2 hepatorenal syndrome in cirrhotic patients with refractory ascites can also result in elimination of ascites. It must be emphasized that TIPS often leads to improvement in but cannot normalize renal function.

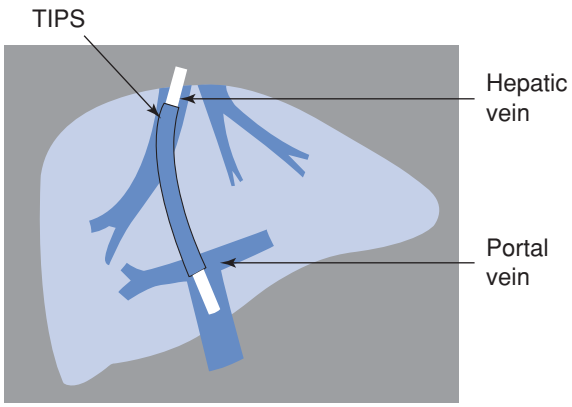
Attempts have been made to combine various treatment options to correct several aspects of the pathophysiology of hepatorenal syndrome. One such combination is the use of pharmacotherapy followed by TIPS for patients with type 1 hepatorenal syndrome. For instance, midodrine, octreotide, and albumin followed by TIPS insertion in those who responded to treatment and were deemed to be suitable to receive a TIPS has been associated with maintenance of normal renal function and eventual elimination of ascites with improvement in survival. The challenge is how to select the most appropriate combination therapy for each individual patients.



▲ **Figure 10–3.** Molecular adsorbent recirculating system.

D. Liver Transplantation

Liver transplantation remains the only effective permanent treatment for hepatorenal syndrome, as it corrects liver dysfunction and eliminates portal hypertension. Renal function improves in patients with hepatorenal syndrome after transplantation, associated with a reduction in plasma levels of vasoactive factors, although the glomerular filtration rate generally remains subnormal. Hepatorenal syndrome patients who are transplanted have a lower probability of both graft and patient survival after liver transplantation, compared to patients without hepatorenal syndrome. Furthermore, patients with hepatorenal syndrome require a longer stay in intensive care units, longer hospitalization, and more dialysis treatments after liver transplantation. In patients whose hepatorenal syndrome is treated prior to liver transplantation, the posttransplantation clinical outcome is significantly improved, being similar to transplanted patients without hepatorenal syndrome. Therefore, in patients with end-stage cirrhosis awaiting liver transplantation, every attempt should be made to improve renal function in order to maximize the posttransplantation outcome.



▲ **Figure 10–4.** Schematic picture of a transjugular intrahepatic portosystemic stent shunt (TIPS) *in situ*.

Prevention

The most important aspect of management of hepatorenal syndrome is to prevent its occurrence. This is achieved by avoiding or minimizing further deterioration in liver and circulatory functions and renal hypoperfusion.

A. Judicious Use of Diuretics

Diuretic-induced renal impairment occurs in 20% of patients with ascites. This happens when the rate of diuresis exceeds the rate of ascites reabsorption resulting in a reduction in effective arterial blood volume. The renal failure is usually reversible with cessation of the diuretics. Patients with ascites and no edema are able to mobilize maximally only 700 mL of ascitic fluid per day. Any diuresis of more than 700 mL/day will occur at the expense of plasma volume contraction

and the risk of renal insufficiency. Patients with peripheral edema appear to be protected from these effects because of the preferential mobilization of edema and may safely undergo diuresis at a more rapid rate (greater than 2 kg/day) until the edema disappears.

B. Avoidance of Nephrotoxic Agents

NSAIDs should not be given to cirrhotic patients with ascites because the incidence of renal failure with their use is much higher than in the general population. They inhibit the formation of intrarenal prostaglandins, which are vasodilatory compounds that counteract the effects of various vasoconstrictors on the renal circulation. Patients with cirrhosis and ascites are predisposed to acute tubular necrosis with the use of aminoglycosides and thus these should be avoided. Angiotensin-converting enzyme inhibitors and angiotensin II blockers result in arterial hypotension and predispose cirrhotic patients to the development of renal failure. They therefore should also be avoided.

C. Prophylaxis Against the Development of Bacterial Infections

Cirrhotic patents with gastrointestinal bleeding have a high incidence of infection, especially spontaneous bacterial peritonitis. Since infections, whether occult or proven, are the trigger for renal failure in cirrhosis, patients with gastrointestinal bleeding should be given antibiotic prophylaxis. Short-term antibiotic prophylaxis has been shown to increase the survival rate in cirrhotic patients with gastrointestinal bleeding. However, it is unclear as to how long prophylactic antibiotics should be given during any episode of gastrointestinal bleeding.

D. Prophylaxis in Cases of Established Bacterial Infections

Once an infection is established, the release of various cytokines and endotoxins associated with the inflammatory response will trigger the production of many vasodilators. The resultant systemic arterial vasodilation will exaggerate the imbalance between the vascular capacitance and the intravascular volume in the cirrhotic patient, thereby predisposing the patient to the development of renal failure. Albumin infusions have been shown to reduce the incidence of renal failure and improve mortality compared to antibiotics alone in patients with spontaneous bacterial peritonitis. There is still much resistance to the use of albumin in certain parts of the world because of the concern of transmitting unknown diseases. Furthermore, albumin is expensive. It is also not clear whether fluid support with crystalloids or other colloids in patients who did not receive albumin would have produced the same results. Until the results of further trials are available, it seems prudent to give albumin to prevent renal failure in episodes of infection.

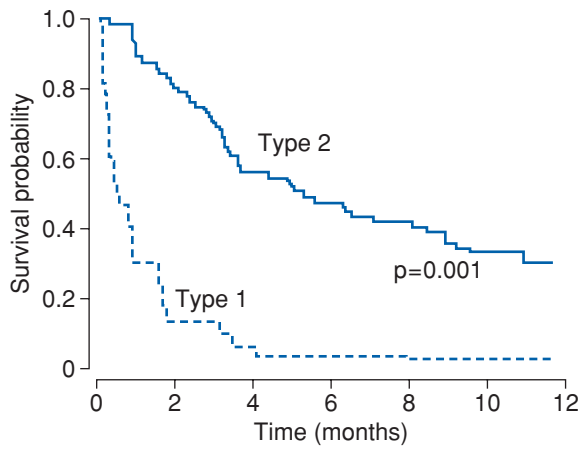
E. Prophylaxis against Circulatory Dysfunction

Large volume paracentesis of >5 L is associated with the deterioration of systemic hemodynamics, with a reduction in systemic vascular resistance and hence vasodilation, the so-called postparacentesis circulatory dysfunction. Therefore, it may be prudent to use vasoconstrictor agents such as terlipressin to limit the arterial vasodilation and prevent the circulatory changes that occur in patients undergoing large volume paracentesis.

It has been suggested that pentoxifylline be administered as a prophylaxis against the development of hepatorenal syndrome in patients with alcoholic hepatitis as it has been shown to reduce the incidence of hepatorenal syndrome. Since it is a relatively harmless drug, and the cost is not prohibitive, it may be administered to patients with alcoholic hepatitis until the results of randomized control trials are available.

Prognosis

Hepatorenal syndrome is a dreaded complication of cirrhosis with a dismal outcome. Untreated patients with type 2 hepatorenal syndrome have a slightly better prognosis than patients with type 1 hepatorenal syndrome, with a median survival of months rather than weeks (Figure 10–5). However, their survival is still shorter than that of cirrhotic patients with ascites but no renal dysfunction. Patients without precipitating factors of hepatorenal syndrome tend to survive slightly longer, while those who develop hepatorenal syndrome as a result of sepsis tend to do worse. With a better understanding of the pathophysiology and more effective treatment of hepatorenal syndrome, there has been significant improvement in the outcome of these patients. Since there is a worldwide shortage of donor organs available



▲ **Figure 10–5.** Survival of patients with hepatorenal syndrome. (Adapted with permission from Gines P et al: Hepatorenal syndrome. Lancet 2003;362:1819.)

for liver transplantation, the strategy may be to use either pharmacotherapy, or TIPS, or a combination of both as a bridge to liver transplantation.

Significant strides have been made in the treatment of hepatorenal syndrome, which used to carry a mortality rate of almost 100%. Based on sound pathophysiologic principles with the reversal of factors causing extreme but potentially reversible renal vasoconstriction, we now have a therapeutic armamentarium to deal with hepatorenal syndrome. The diagnosis of hepatorenal syndrome is no longer synonymous with a death sentence, but rather a therapeutic challenge involving a team approach of intensivists, hepatologists, nephrologists, interventional radiologists, and transplant surgeons to continue to improve the prognosis of these patients. The onus is on us as the treating physicians to recognize the onset of hepatorenal syndrome and to initiate prompt treatment before these patients spiral down the inevitable path of liver failure.

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