# Hepatorenal syndrome

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## INTRODUCTION

The hepatorenal syndrome is one of many potential causes of acute kidney injury in patients with acute or chronic liver disease. Affected patients usually have portal hypertension due to cirrhosis, severe alcoholic hepatitis, or (less often) metastatic tumors, but can also have fulminant hepatic failure from any cause [1-4]. The hepatorenal syndrome represents the end-stage of a sequence of reductions in kidney perfusion induced by increasingly severe hepatic injury. The hepatorenal syndrome is a diagnosis of exclusion ( algorithm 1), and is associated with a poor prognosis.

This topic will review the hepatorenal syndrome in detail. Overviews of the complications of fulminant hepatic failure and cirrhosis are provided elsewhere:

- (See "Acute liver failure in adults: Management and prognosis".)
- (See "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

## PATHOGENESIS

Arterial vasodilatation in the splanchnic circulation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in kidney function in

cirrhosis [1-3]. The presumed mechanism is increased production or activity of vasodilators, mainly in the splanchnic circulation, with nitric oxide thought to be most important [1,5,6].

As the hepatic disease becomes more severe, there is a progressive rise in cardiac output and fall in systemic vascular resistance; the latter change occurs despite local increases in renal and femoral vascular resistance that result in part from hypotension-induced activation of the renin-angiotensin and sympathetic nervous systems ( figure 1) [1-3,7]. Thus, the reduction in total vascular resistance results from decreased vascular resistance in the splanchnic circulation [7], perhaps in part under the influence of nitric oxide derived from the endothelium. Bacterial translocation from the intestine into the mesenteric lymph nodes may play an important role in this process [1,8,9]. A review of the hemodynamic changes seen with progressive cirrhosis can be found in a separate topic review. (See "Pathogenesis of ascites in patients with cirrhosis".)

The decline in kidney perfusion in this setting is associated with reductions in glomerular filtration rate (GFR) and sodium excretion (often to less than 10 mEq/day in advanced cirrhosis) [10,11] and a fall in mean arterial pressure, despite the intense renal vasoconstriction [11]. The importance of splanchnic vasodilatation in these changes can be indirectly illustrated by the response to ornipressin, an analog of antidiuretic hormone (arginine vasopressin) that is a preferential splanchnic vasoconstrictor [12].

In patients with advanced cirrhosis, the administration of ornipressin **or** other vasopressin analogs partially corrects many of the systemic and renal hemodynamic abnormalities that are present ( figure 2); these include an elevation in mean arterial pressure, reductions in plasma renin activity and norepinephrine concentration, and increases in renal blood flow, GFR (from 18 to 29 mL/min), and urinary sodium excretion and volume.

In addition, acutely lowering renal sympathetic tone and renal vascular resistance in the early stages of hepatorenal syndrome by the intravenous administration of the sympatholytic agent, clonidine, can raise the GFR by as much as 25 percent [13]. However, this benefit does not appear to be sustained with chronic oral therapy, despite a persistent reduction in sympathetic activity [14].

The response to creation of a portasystemic shunt also supports the importance of splanchnic hemodynamics in the genesis of the hepatorenal syndrome. Portasystemic shunting has improved kidney function in a limited number of patients with the hepatorenal syndrome [15], but it is infrequently used as treatment for this disorder [16]. One report, however, suggested that the reduction in intrahepatic pressure induced by this modality may **prevent** the development of the hepatorenal syndrome. This retrospective study evaluated 204 patients with variceal bleeding who were treated with either a portasystemic shunt or sclerotherapy (or other

nonshunt modalities) [17]. Portasystemic shunting was associated with a lower incidence of ascites (15 versus 73 percent) and hepatorenal syndrome (4 versus 21 percent), a higher incidence of encephalopathy, and no difference in overall patient survival.

## EPIDEMIOLOGY

Patients who develop the hepatorenal syndrome usually have portal hypertension due to cirrhosis, severe alcoholic hepatitis, or, less often, metastatic tumors [1-3]. However, patients with fulminant hepatic failure from any cause may develop hepatorenal syndrome.

The incidence of hepatorenal syndrome was evaluated in a prospective study of 229 nonazotemic patients with cirrhosis and ascites: the hepatorenal syndrome developed in 18 and 39 percent at one and five years, respectively [11]. Patients with hyponatremia and a high plasma renin activity were at highest risk. These signs of neurohumoral activation presumably reflected a more severe decline in effective perfusion [1,7].

Hepatorenal syndrome also occurs frequently in patients with acute liver disease. In a study of patients with alcoholic hepatitis, for example, hepatorenal syndrome occurred in 28 of 101 patients [18].

Although hepatorenal syndrome can be seen in most forms of severe hepatic disease, patients with primary biliary cholangitis appear relatively protected [19]. Sodium retention, ascites formation, and the hepatorenal syndrome all tend to occur less often in primary biliary cholangitis, possibly due in part to the natriuretic and renal vasodilator actions of retained bile salts.

## CLINICAL PRESENTATION

The hepatorenal syndrome is characterized by the following features in a patient who has established or clinically evident acute or chronic liver disease [1-3,11,20]:

- A progressive rise in serum creatinine
- An often normal urine sediment
- No or minimal proteinuria (less than 500 mg per day)
- A very low rate of sodium excretion (ie, urine sodium concentration frequently less than 10 mEq/L)
- Nonoliguria or oliguria, depending upon the severity and duration

Many patients with hepatorenal syndrome are nonoliguric (especially early in the course). Some studies, for example, have found that the urine volume may exceed 400 mL per day, with markedly lower output being observed only within a few days from death [21,22]. In addition, the serum creatinine may increase by as little as 0.1 mg/dL (9 micromol/L) per day, with intermittent periods of stabilization or even slight improvement. Lastly, the urine sediment may show a variety of abnormalities, such as hematuria due to bladder instrumentation and underlying coagulopathy, and granular casts due to hyperbilirubinemia.

Based upon the rapidity of the decline in kidney function, two forms of hepatorenal syndrome have been described [1,20,23,24]:

- **HRS-AKI (type 1 hepatorenal syndrome)** – This more serious type of hepatorenal syndrome is referred to as hepatorenal syndrome-acute kidney injury (HRS-AKI) or, traditionally, type 1 hepatorenal syndrome. It is defined as at least a twofold increase in serum creatinine (reflecting a 50 percent reduction in creatinine clearance) to a level greater than 2.5 mg/dL (221 micromol/L) during a period of less than two weeks. At the time of diagnosis, some patients with type 1 hepatorenal syndrome have a urine output less than 400 to 500 mL per day [20,22].

- **Diuretic-resistant ascites (type 2 hepatorenal syndrome)** – Diuretic-resistant ascites, or type 2 hepatorenal syndrome, is defined as kidney function impairment that is less severe than that observed with HRS-AKI/type 1 disease. The major clinical feature in patients with type 2 hepatorenal syndrome is ascites that is resistant to diuretics.

**Precipitants** — The onset of kidney failure is typically insidious but can be precipitated by an acute insult, such as bacterial infection or gastrointestinal bleeding [11,20,25]. Spontaneous bacterial peritonitis, for example, can trigger progressive hepatorenal syndrome, although it is more likely to occur in patients who already have some degree of kidney function impairment [26,27]. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Albumin administration for patients with renal dysfunction'.)

When type 1 hepatorenal syndrome results from bacterial infection, antibiotic therapy alone does **not** usually lead to improvement in kidney function. In one study, for example, hepatorenal syndrome failed to improve in 47 of 70 patients (67 percent) treated with antibiotics alone [28]. Thus, patients with type 1 hepatorenal syndrome precipitated by infection should receive other therapies described below, particularly if kidney function fails to improve after several days of antibiotic therapy. (See 'Treatment' below.)

Although overly rapid diuresis has often been mentioned as a precipitant of hepatorenal syndrome, perhaps because most patients are taking diuretics when the syndrome is

diagnosed, diuretics do **not** cause hepatorenal syndrome. Diuretics can, however, cause azotemia, particularly if fluid is removed too rapidly in patients without peripheral edema. Diuretic-induced azotemia improves with the cessation of therapy and fluid repletion. In comparison, the hepatorenal syndrome typically worsens inexorably, even after diuretics are stopped and albumin is infused. (See "Ascites in adults with cirrhosis: Initial therapy", section on 'Diuretic therapy'.)

**Problems with estimating kidney function** — Patients with hepatorenal syndrome may have kidney dysfunction that is substantially more severe than is suggested by the serum creatinine.

Both urea and creatinine production may be substantially reduced in this setting, due to the liver disease and to decreased muscle mass and decreased protein and meat intake. The net effect is that a serum creatinine that appears to be within the normal range (eg, 1 to 1.3 mg/dL [88.4 to 115 micromol/L]) may be associated with a glomerular filtration rate (GFR) that ranges from as low as 20 to 60 mL/min to a clearly normal value above 100 mL/min, depending primarily upon muscle mass. (See "Assessment of kidney function".)

The blood urea nitrogen (BUN) is variable in these patients. For a given GFR, it may be lower or higher than expected. If protein intake is very low, reduced urea production may result in a low BUN and a low BUN to creatinine ratio. By contrast, if protein intake is adequate, increased passive reabsorption of urea in the proximal tubule, driven by enhanced proximal tubular reabsorption of sodium and water, can result in a high BUN and a high BUN to creatinine ratio. (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury in adults".)

## DIAGNOSIS

Hepatorenal syndrome is diagnosed based upon clinical criteria ( algorithm 1). There is no one specific test that can establish the diagnosis. Investigational urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) tend to be lower in prerenal azotemia and hepatorenal syndrome than in acute tubular necrosis (ATN), but there is considerable overlap between these conditions [29-31]. In addition, hepatorenal syndrome is a diagnosis of exclusion, meaning that other potential etiologies of acute or subacute kidney injury in patients with liver disease should be considered unlikely before a diagnosis of hepatorenal syndrome is made.

The following definition and diagnostic criteria for hepatorenal syndrome are broadly consistent with criteria proposed by expert panels, such as the American Association for the

Study of Liver Diseases (AASLD), the International Club of Ascites (ICA), and Kidney Disease: Improving Global Outcomes (KDIGO) ( algorithm 1) [1,20,23,24,32,33]:

- Chronic or acute hepatic disease with advanced hepatic failure and portal hypertension.
- Acute kidney injury, defined as an increase in serum creatinine of 0.3 mg/dL (26.5 micromol/L) or more within 48 hours, or an increase from baseline of 50 percent or more within seven days [32]; this definition of acute kidney injury is consistent with KDIGO criteria (see "Definition and staging criteria of acute kidney injury in adults"). However, some clinicians may prefer to use the older definition of acute or subacute kidney injury, specifically a rise in serum creatinine to above 1.5 mg/dL (133 micromol/L) that has progressed over days to weeks. As noted above, the rise in serum creatinine with reductions in glomerular filtration rate (GFR) may be minimal due to the marked reduction in creatinine production among such patients. (See 'Problems with estimating kidney function' above.)
- The absence of any other apparent cause for the acute kidney injury, including shock, current or recent treatment with nephrotoxic drugs, and the absence of ultrasonographic evidence of obstruction or parenchymal kidney disease. Spontaneous bacterial peritonitis is complicated by acute kidney injury that may be reversible in 30 to 40 percent of patients. It can be associated with ATN, but it is also a major precipitant of the hepatorenal syndrome. Thus, ongoing infection with spontaneous bacterial peritonitis should not exclude the possibility of hepatorenal syndrome. This means that therapy for hepatorenal syndrome can commence while the bacterial infection is still being treated. In addition, hepatorenal syndrome can occur in patients with preexisting chronic kidney disease [34]. Thus, the presence of another kidney diagnosis (eg, diabetic nephropathy) does not necessarily exclude hepatorenal syndrome. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Albumin administration for patients with renal dysfunction'.)

  In conjunction with excluding other apparent causes of kidney disease, the following criteria also apply:

  - Urine red cell excretion of less than 50 cells per high power field (when no urinary catheter is in place) and protein excretion less than 500 mg/day.
  - Lack of improvement in kidney function after volume expansion with intravenous albumin (1 g/kg of body weight per day up to 100 g/day) for at least two days and withdrawal of diuretics.

As noted above, patients diagnosed with hepatorenal syndrome are classified as hepatorenal syndrome-acute kidney injury (HRS-AKI)/type 1 hepatorenal syndrome (more severe) or diuretic-resistant ascites/type 2 hepatorenal syndrome (less severe) based upon the rapidity of the acute kidney injury and the degree of kidney function impairment. HRS-AKI/Type 1 hepatorenal syndrome is present if the serum creatinine increases by at least twofold to a value greater than 2.5 mg/dL (221 micromol/L) during a period of less than two weeks. Less rapidly progressive disease is classified as type 2.

## DIFFERENTIAL DIAGNOSIS

The diagnosis of the hepatorenal syndrome is one of **exclusion**, entertained only after other potential causes of acute or subacute kidney injury have been ruled out [24,35]. As an example, both glomerulonephritis and vasculitis can occur in patients with liver disease and should be suspected in patients with an active urine sediment containing red cells and red cell and other casts. (See "IgA nephropathy: Clinical features and diagnosis" and "Overview of kidney disease associated with hepatitis C virus infection" and "Kidney disease associated with hepatitis B virus infection".)

Obesity with fatty liver is a relatively common cause of cirrhosis. Many of these patients have diabetes and can develop diabetic nephropathy (see "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults"). A prospective study from 2011 that analyzed 562 patients with cirrhosis and kidney function impairment at a single center found that hepatorenal syndrome was less common than prerenal or infection-associated kidney injury [35]. Of the 463 patients in this study in whom a diagnosis could be made, the following frequencies were noted:

- Kidney injury associated with infection (such as sepsis or spontaneous bacterial peritonitis) – 46 percent
- Prerenal acute kidney injury – 32 percent
- Hepatorenal syndrome – 13 percent
- Parenchymal kidney disease (such as glomerulonephritis) – 9 percent

The frequency of acute tubular necrosis (ATN) in this study was not defined, although older case series report that 10 to 20 percent of patients with acute kidney injury in the setting of cirrhosis have ATN [35]. It is possible that ATN is less common now, due to avoidance of nephrotoxins such as nonsteroidal antiinflammatory drugs and aminoglycosides in these patients. In addition, some experts believe that some patients with ongoing infection (principally spontaneous bacterial peritonitis in the absence of septic shock) can have hepatorenal

syndrome since a substantial proportion of such patients (18 percent in one report) have persistent or progressive kidney injury despite successful antibiotic therapy for peritonitis [23]. Thus, as mentioned above, the presence of spontaneous bacterial peritonitis should not exclude the diagnosis of hepatorenal syndrome.

Kidney biopsy is not commonly performed in patients with cirrhosis and acute kidney injury, particularly when there is minimal hematuria and proteinuria. As an example, in a series of 65 patients with cirrhosis and kidney disease who underwent transjugular kidney biopsy, only 18 patients had no proteinuria and no hematuria [36]. Of these 18 patients, glomerular lesions were identified in 10 (such as IgA nephropathy, membranoproliferative glomerulonephritis, or diabetic nephropathy), and ATN was identified in 7. Transjugular kidney biopsy, performed by an interventional radiologist, can be considered if the result may have an impact on treatment and if such treatment could outweigh the potential harms associated with the interventional procedure. Although there is a common misconception that the kidneys are histologically normal, a relatively specific but subtle and reversible kidney lesion has been described—glomerular tubular reflux [37].

Distinguishing the hepatorenal syndrome from these other disorders is clinically important because of the marked difference in prognosis. ATN and most causes of prerenal disease are generally reversible. By contrast, the prognosis is poor in the hepatorenal syndrome (especially hepatorenal syndrome-acute kidney injury [HRS-AKI]/type 1 hepatorenal syndrome), with most patients dying within weeks of the onset of kidney injury unless liver transplantation is performed or effective treatment is given [11,38].

**Acute tubular necrosis** — Patients with cirrhosis may develop ATN after a course of aminoglycoside therapy, the administration of a radiocontrast agent, or an episode of sepsis or bleeding with a decrease in blood pressure [1]. The presence of ATN is usually suspected from the history and from the often rapid rise in the serum creatinine, which contrasts to the usually gradual rise in hepatorenal syndrome. An unresolved issue is whether the prolonged kidney ischemia in the hepatorenal syndrome can, in some cases, lead to ATN [1,20].

Some of the traditional laboratory methods used to distinguish prerenal disease from ATN may not be helpful in patients with hepatic disease. As an example, ATN is usually associated with a fractional excretion of sodium above 2 percent and granular and epithelial cell casts in the urine sediment. Calculators are available to compute the fractional excretion of sodium (calculator 1) and (calculator 2).

However, the fractional excretion of sodium may remain below 1 percent in patients with cirrhosis who develop ATN due to the persistent kidney ischemia induced by the hepatic disease

[39]. The urinalysis also may be misleading. Granular and epithelial cell casts may be seen with marked hyperbilirubinemia alone and are therefore not diagnostic of ATN; how this occurs is not understood. (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury in adults" and "Fractional excretion of sodium, urea, and other molecules in acute kidney injury".)

**Prerenal disease** — The hepatorenal syndrome has been difficult to distinguish from prerenal azotemia. Prerenal disease in patients with cirrhosis can be induced by gastrointestinal fluid losses, bleeding, or therapy with a diuretic or a nonsteroidal antiinflammatory drug (since renal vasodilator prostaglandins in part maintain kidney perfusion in this setting) [1,40]. (See "NSAIDs: Acute kidney injury".)

In addition, patients with worsening cirrhosis and ascites develop progressive declines in systemic vascular resistance and mean arterial pressure. (See 'Pathogenesis' above.)

Many patients, especially those with obesity and cirrhosis due to nonalcohol steatohepatitis, are hypertensive before this occurs. Although "cirrhosis cures hypertension," antihypertensive therapy is continued in many patients and, in conjunction with systemic vasodilation due to cirrhosis, contributes to low mean arterial pressures. Too often, clinicians who start antihypertensive agents fail to follow these patients over time and may not realize that these medications produce worsening hypotension and azotemia as liver disease progresses and patients develop ascites.

**Beta blockers** — Beta blockers are commonly used in patients with cirrhosis to prevent variceal hemorrhage. (See "Primary prevention of bleeding from esophageal varices in patients with cirrhosis", section on 'Preventive strategies'.)

However, these agents may be hazardous in patients with ascites and hypotension [41], and their discontinuation may lead to resolution of apparent hepatorenal syndrome. Although some organizations suggest continuing beta blocker therapy unless the mean arterial pressure falls below 65 mmHg [42], mean arterial pressures below 82 mmHg are associated with substantially higher mortality in such patients. Beta blocker use below this level is likely associated with a higher risk of acute kidney injury and apparent hepatorenal syndrome.

Thus, the diagnosis of the hepatorenal syndrome requires that there be no improvement in kidney function following discontinuation of potential nephrotoxins, cessation of antihypertensive medications (if prescribed), and a trial of fluid repletion. In addition, emerging kidney biomarkers may prove helpful in distinguishing prerenal disease, hepatorenal syndrome, and ATN in patients with cirrhosis [29].

## TREATMENT

**Approach to therapy** — The ideal therapy for hepatorenal syndrome is improvement of liver function from recovery of alcoholic hepatitis, treatment of decompensated hepatitis B with effective antiviral therapy, recovery from acute hepatic failure, or liver transplantation [43-45]. The ability of liver function to improve with abstinence from alcohol and effective antiviral therapy of hepatitis B is remarkable. (See 'Improving hepatic function' below.)

However, when improvement of liver function is not possible in the short term, we recommend that medical therapy be instituted in an attempt to reverse the acute kidney injury associated with hepatorenal syndrome. Our suggestions regarding the choice of medical therapy depend upon several factors, including: whether the patient is admitted to the intensive care unit; the availability of certain drugs, for which there is national and regional variability; and whether the patient is a candidate for liver transplantation. In general, patients who are not liver transplant candidates are not transferred to the intensive care unit.

- Antihypertensive agents, including beta blockers, should be discontinued in **all patients** with hepatorenal syndrome.

- In patients with hepatorenal syndrome who are **in the intensive care unit**, we suggest initial treatment with norepinephrine in combination with albumin. Norepinephrine is given intravenously as a continuous infusion (0.5 to 3 mg/hr) with the goal of raising the mean arterial pressure by 10 mmHg, and albumin is given for at least two days as an intravenous bolus (1 g/kg per day [100 g maximum]). Intravenous vasopressin may also be effective, starting at 0.01 units/min and titrating upward as needed to raise the mean arterial pressure as noted below. (See 'Norepinephrine for patients in the intensive care unit' below.)

- In patients with hepatorenal syndrome who are **not in the intensive care unit**, our suggestions depend upon the availability of certain drugs:

  - Where terlipressin therapy is available, we suggest initial treatment with terlipressin in combination with albumin. Terlipressin is given as an intravenous bolus (1 to 2 mg every four to six hours), and albumin is given for two days as an intravenous bolus (1 g/kg per day [100 g maximum]), followed by 25 to 50 grams per day until terlipressin therapy is discontinued. (See 'Terlipressin plus albumin where available' below.)

  - Where terlipressin therapy is not available, we suggest initial treatment with a combination of midodrine, octreotide, and albumin. Midodrine is given orally (starting

at 7.5 mg and increasing the dose at eight-hour intervals up to a maximum of 15 mg by mouth three times daily), octreotide is either given as a continuous intravenous infusion (50 mcg/hr) or subcutaneously (100 to 200 mcg three times daily), and albumin is given for two days as an intravenous bolus (1 g/kg per day [100 g maximum]), followed by 25 to 50 grams per day until midodrine and octreotide therapy is discontinued. (See 'Midodrine, octreotide, and albumin where terlipressin is not available' below.)

- In highly selected **patients who fail to respond to medical therapy** with the above regimens and who are considered well enough to undergo the procedure, transjugular intrahepatic portosystemic shunt (TIPS) is sometimes successful. However, this procedure is associated with numerous complications and, because of the need for intravenous contrast, it may cause acute kidney injury. For this reason, some experts prefer dialysis as a first option (continuous kidney replacement therapy) in most cases, particularly for patients whose serum creatinine remains above 1.5 mg/dL despite medical therapy. (See 'Transjugular intrahepatic portosystemic shunt' below.)

- In patients who fail to respond to the above therapies, develop severely impaired kidney function, and either are candidates for liver transplantation or have a reversible form of liver injury and are expected to survive, we recommend dialysis as a bridge to liver transplantation or liver recovery. (See 'Kidney replacement therapy' below.)

The goal of medical therapy or TIPS in patients with hepatorenal syndrome is reversal of the acute kidney injury. In addition, when patients are treated with norepinephrine, terlipressin, or midodrine plus octreotide, an immediate goal of therapy is to raise the mean arterial pressure by approximately 10 to 15 mmHg to a level of >82 mmHg. In a systematic review of 501 patients with hepatorenal syndrome from 21 studies, the magnitude of the increase in mean arterial pressure induced by these vasoconstrictors was significantly associated with the magnitude of the decrease in serum creatinine [46]. As an example, a 9 mmHg increase in mean arterial pressure predicted a 1 mg/dL (88.4 micromol/L) decrease in serum creatinine. The authors also predicted that an increase in mean arterial pressure of 9 to 13 mmHg would be necessary to achieve resolution in most patients with hepatorenal syndrome-acute kidney injury (HRS-AKI)/type 1 hepatorenal syndrome.

In patients treated with norepinephrine, terlipressin, or octreotide, we usually treat for a total of **two weeks**. However, we and others occasionally treat for longer durations (up to one month or more) if there is some but not complete improvement in kidney function after two weeks of therapy. In patients who respond to therapy, we occasionally treat indefinitely with midodrine to maintain a higher mean arterial pressure (or until liver transplantation or resolution of liver

injury). Many patients who recover from HRS-AKI/type 1 hepatorenal syndrome continue to have hypotension and refractory ascites, and midodrine may be effective in such patients [47]. By contrast, if a patient has no improvement in kidney function after two weeks, therapy with these drugs can be considered futile.

Our approach outlined above is broadly consistent with 2021 practice guidance from the American Association for the Study of Liver Diseases (AASLD) [24].

The following sections will review the different therapies that have been evaluated in the treatment of hepatorenal syndrome. Issues related to the treatment of ascites in patients with cirrhosis (eg, fluid and sodium intake, diuretic therapy) are discussed separately. (See "Ascites in adults with cirrhosis: Initial therapy" and "Ascites in adults with cirrhosis: Diuretic-resistant ascites" and 'Precipitants' above.)

**Improving hepatic function** — The best hope for reversal of the kidney failure is an improvement in hepatic function due to partial resolution of the primary disease or to successful liver transplantation [48-51]. Improvement in the underlying liver disease is most impressive in patients with alcoholic liver disease (particularly severe alcoholic hepatitis) with abstinence or with decompensated cirrhosis due to hepatitis B virus infection treated with antiviral therapy [52,53].

Resolution of HRS-AKI/type 1 hepatorenal syndrome was examined in 62 patients undergoing liver transplantation (mean pretransplant serum creatinine, 3.4 mg/dL [300 micromol/L]) at a single center over a 10-year period [51]. Of these, resolution of hepatorenal syndrome (defined as a serum creatinine <1.5 mg/dL [133 micromol/L] and no dialysis requirement) occurred in 47 patients (76 percent). The remaining patients either died or required long-term dialysis. The mean duration of dialysis prior to liver transplantation was the only significant predictor of resolution (10 days among those who resolved versus 25 days among those who did not).

**Norepinephrine for patients in the intensive care unit** — Although not usually available on the general medical ward, norepinephrine can be administered in the intensive care unit and has been used successfully in patients with hepatorenal syndrome [54]. Vasopressin, also available in the intensive care unit, may be effective in patients with hepatorenal syndrome [55].

A meta-analysis of seven open-label trials including 306 patients with HRS-AKI/type 1 hepatorenal syndrome compared therapy with terlipressin plus albumin versus norepinephrine plus albumin [56]. The following results were obtained, neither of which were statistically significant:

- Resolution of hepatorenal syndrome (defined as a fall in the serum creatinine to below 1.5 mg/dL [133 micromol/L]) occurred in 55 percent of patients receiving terlipressin and 53 percent of patients receiving norepinephrine.

- The 30-day survival rate was 42 percent in both groups.

Although the efficacy of terlipressin and norepinephrine were similar, adverse events were more common with terlipressin. In addition, the cost of terlipressin therapy is more than three times the cost of norepinephrine therapy [57].

Thus, we suggest norepinephrine rather than terlipressin or other therapies for treatment of hepatorenal syndrome in patients who are admitted to the intensive care unit.

Other data suggest superiority of terlipressin compared with norepinephrine. As an example, one trial of 120 patients with acute on chronic liver failure reported reduced need for kidney replacement therapy and improved survival with terlipressin [58]. However, several features of this trial, including lack of blinding, different dosing adjustments in the two groups, and the very large and unexpected effects (eg, a 23 percent absolute reduction in need for kidney replacement therapy and a 28 percent absolute reduction in mortality) limit the conclusions that can be drawn.

**Patients not in the intensive care unit** — Optimal medical therapy for patients with hepatorenal syndrome who are not admitted to the intensive care unit varies according to whether terlipressin is available.

**Terlipressin plus albumin where available** — Vasopressin and its analogs (ornipressin and terlipressin) should theoretically reduce splanchnic vasodilation. As an example, when ornipressin was administered in combination with either infusion of albumin or a peritoneovenous shunt (to expand the effective arterial blood volume and reduce the release of vasoconstrictors such as angiotensin II and norepinephrine), there was an increase in glomerular filtration rate (GFR) ( figure 2) [12,59,60].

Another vasopressin analog, terlipressin, has also been examined as a treatment for hepatorenal syndrome in several randomized trials and, when available, is preferred therapy in patients with hepatorenal syndrome who cannot receive norepinephrine (typically those not in an intensive care setting) [56,61-67]. The best data come from a trial that randomly assigned 49 patients to terlipressin (starting at 3 mg infused over 24 hours, titrated as needed to 12 mg over 24 hours) or midodrine plus octreotide (midodrine starting orally at 7.5 mg thrice daily and octreotide at 100 mcg subcutaneously thrice daily, increased as needed to 12.5 mg thrice daily and 200 mcg thrice daily, respectively); all patients also received intravenous albumin (1 g/kg on

day 1, and then 20 to 40 g/day thereafter) [61]. Terlipressin significantly increased the rate of complete response (a decrease in serum creatinine to less than 1.5 mg/dL [133 micromol/L] at 14 days) compared with midodrine and octreotide (56 versus 5 percent), and the trial was terminated early because of this result. A partial response (a 50 percent or greater improvement in serum creatinine without falling below the complete response threshold) occurred in 15 percent of patients receiving terlipressin and in 24 percent of patients receiving midodrine and octreotide. Survival did not differ between the groups, although six patients who failed to respond with midodrine and octreotide were treated with terlipressin and had improvement in their kidney function. Treatment-related adverse events did not differ between the two therapies.

This study has several limitations. As an example, blood pressure was significantly higher in patients receiving terlipressin than in patients receiving midodrine, and midodrine doses were not increased to 15 mg thrice daily as they often are in clinical practice. Thus, the difference in outcomes could represent a difference in the degree of splanchnic vasoconstriction and blood pressure rather than a difference attributable to drug class [68]. Also, the study did not treat to a target increase in blood pressure (see 'Approach to therapy' above). As a result, studies are needed in which the midodrine dose is chosen to attain an increase in blood pressure comparable to terlipressin.

Although this head-to-head trial was small and unblinded, other trials of terlipressin in patients with hepatorenal syndrome compared the drug with albumin alone, placebo, or no therapy, rather than an active comparator. In a meta-analysis trials that lacked an active comparator, terlipressin therapy significantly reduced mortality compared with albumin alone or no therapy (54 versus 73 percent) and increased the proportion of patients who achieved reversal of hepatorenal syndrome (54 versus 11 percent), but it also increased the rate of cardiovascular adverse events (11 versus 0 percent) [69]. However, in a larger, subsequent trial, mortality at 90 days was higher with terlipressin compared with placebo (51 versus 45 percent); although this increase in all-cause mortality was not statistically different, death from respiratory failure was significantly higher with terlipressin (11 versus 2 percent) [70]. Kidney outcomes were superior with terlipressin, including a higher rate of reversal of hepatorenal syndrome (32 versus 17 percent) and a reduced need for kidney replacement therapy by day 30 (26 versus 36 percent).

These data suggest that terlipressin therapy may improve kidney function compared with other therapies, but the effect on mortality is unclear. Thus, for patients with hepatorenal syndrome for whom intensive care is not appropriate (eg, hemodynamically stable patients, patients who are not liver transplantation candidates), we suggest combination therapy with terlipressin plus

albumin rather than other therapies. Respiratory function should be carefully monitored during treatment with terlipressin [70].

Where terlipressin is not available, combination therapy with midodrine, octreotide, and albumin is used for patients not in the intensive care unit. (See 'Midodrine, octreotide, and albumin where terlipressin is not available' below.)

**Midodrine, octreotide, and albumin where terlipressin is not available** — Therapy with midodrine (a selective alpha-1 adrenergic agonist), octreotide (a somatostatin analog), and albumin may be highly effective and safe in patients with hepatorenal syndrome. Midodrine is a systemic vasoconstrictor, and octreotide is an inhibitor of endogenous vasodilator release (which produces splanchnic vasoconstriction); combined therapy theoretically improves renal and systemic hemodynamics [71].

In a nonrandomized study of 13 consecutive patients with HRS-AKI/type 1 hepatorenal syndrome, the first eight were treated with intravenous dopamine (2 to 4 mcg/kg per min) and the last five patients were treated with oral midodrine (7.5 to 12.5 mg three times daily) plus octreotide (100 to 200 mcg subcutaneously three times daily) [72]. Both groups also received intravenous albumin daily during treatment. The goal of therapy was to raise the mean arterial pressure by 15 mmHg. The following results were reported:

- Among the five patients who received midodrine and octreotide, mean arterial pressure, renal plasma flow, GFR, and urine volume all increased. Among those who received dopamine, there was no change in these parameters.

- Three of the five patients treated with midodrine and octreotide survived to hospital discharge. Of these, one successfully underwent liver transplantation, another was alive at 472 days, and the third ultimately died after discontinuing therapy. Among the two who were not discharged, one discontinued therapy after two months and was successfully transplanted, while the other died at 29 days of pneumonia despite total recovery of kidney function. Minimal side effects, including tingling, goose bumps, and diarrhea, were observed. By contrast, seven of the eight patients who received dopamine died during the first twelve days. One patient recovered kidney function and survived to be transplanted.

Additional data substantiate the potential efficacy and safety of octreotide and midodrine. In a retrospective study, 60 patients with hepatorenal syndrome were treated with midodrine (up to 15 mg three times daily), octreotide (200 mcg subcutaneously three times daily), and albumin, and 21 concurrent patients only received albumin [22]. Therapy with midodrine and octreotide was associated with significantly lower mortality (43 versus 71 percent) and a significantly

higher proportion of patients who had resolution of hepatorenal syndrome (40 versus 10 percent).

In our experience, the speed with which effective treatment is achieved appears to be important. Thus, we prefer continuous infusion of octreotide at 50 mcg/hr rather than subcutaneous injection. This can be delivered on a general medical ward. The midodrine dose should be increased with each consecutive dose in order to achieve an increase in blood pressure rapidly. It is our experience that 15 mg three times per day may be more effective than 12.5 mg three times per day. Changing the dose after 24 hours on the prior dose raises the blood pressure too slowly and may lead to failure of therapy.

In contrast to combination therapy with midodrine and octreotide, octreotide monotherapy does not appear to be beneficial. In a randomized crossover study, 14 patients with hepatorenal syndrome were treated with four days of octreotide plus albumin and four days of albumin alone in random order [73]. Response to therapy was identical with both treatments. Midodrine alone or in combination with albumin (but without octreotide) has not been evaluated in patients with HRS-AKI/type 1 hepatorenal syndrome.

Thus, for patients with hepatorenal syndrome who are not admitted to the intensive care unit and for whom terlipressin is unavailable, we suggest combination therapy with octreotide, midodrine, and albumin rather than other therapies.

**Patients who do not respond to initial medical therapy** — Treatment options for patients who do not respond to one of the medical therapies listed above include TIPS and dialysis.

**Transjugular intrahepatic portosystemic shunt** — The transjugular intrahepatic portosystemic shunt (TIPS) has been used in the treatment of refractory ascites. (See "Overview of transjugular intrahepatic portosystemic shunts (TIPS)".)

When used in this setting, there may also be a delayed improvement in kidney function [74-78]. In one study, for example, the average plasma creatinine concentration was 1.5 mg/dL (132 micromol/L) at baseline, was unchanged at one week, and fell to 0.9 mg/dL (80 micromol/L) by six months [74]. In another series, there was a nonsignificant trend toward an increase in GFR (65 mL/min at baseline to 76 mL/min at four weeks) [76].

There is much less information on the use of TIPS in patients who fulfill criteria for the hepatorenal syndrome [16]. One report described 16 such patients, six of whom had severe hepatorenal syndrome (defined as a serum creatinine of 2.5 mg/dL [220 micromol/L] or higher, or a creatinine clearance below 20 mL/min) [77]. Within two weeks, there was an approximate doubling of the creatinine clearance with a proportionate reduction in the serum creatinine and

an increase in urinary sodium excretion. Additional improvements in kidney function occurred over the ensuing six to eight weeks. Only three patients failed to respond, all of whom died within six weeks after TIPS.

Another series evaluated seven patients with cirrhosis and hepatorenal syndrome, defined as a doubling of the serum creatinine to more than 2.5 mg/dL (221 micromol/L) or a 50 percent reduction in creatinine clearance to below 20 mL/min in less than two weeks, despite volume expansion [78]. Insertion of a TIPS was associated with a gradual improvement in GFR (9 to 27 mL/min), reductions in the blood urea nitrogen (BUN) and serum creatinine, and, in most patients, a reduction in the activity of the renin-angiotensin and sympathetic nervous systems suggesting an improvement in systemic hemodynamics. The average survival following TIPS placement was approximately five months, which is longer than the expected survival of such patients.

Unfortunately, many patients with hepatorenal syndrome are too ill to undergo TIPS. In a study that devised a prediction model to determine survival following elective TIPS, those patients with HRS-AKI/type 1 hepatorenal syndrome have a predicted 90-day mortality following TIPS of at least 25 percent if cirrhosis is due to alcoholic or cholestatic liver disease and at least 80 percent if cirrhosis is due to other causes [79]. A prediction model scoring system based upon the survival of 231 patients who underwent elective TIPS was devised to predict survival after the procedure.

In addition, TIPS is associated with various complications [16]:

- An increase in the rate of hepatic encephalopathy
- A worsening of liver function (marked by a rise in serum bilirubin)
- A bleeding complication due to the procedure
- A risk of kidney injury associated with intravenous contrast, which is often necessary, even if carbon dioxide is used as the main contrast agent

Overall, these results suggest that, in selected patients with hepatorenal syndrome, TIPS may provide short-term benefit. Given the risks associated with this procedure (particularly the high incidence of encephalopathy), it should be considered only as a last resort in selected patients.

**Kidney replacement therapy** — Patients with hepatorenal syndrome who progress to kidney failure can be treated with kidney replacement therapy (hemodialysis or continuous venovenous hemofiltration [CVVH]), which is most commonly done when patients are awaiting a liver transplant or when there is the possibility of improvement in liver function. In addition, kidney replacement therapy improves the priority score for the transplant in the United States.

In two retrospective studies, 30 to 50 percent of transplant candidates who developed acute kidney injury requiring dialysis survived to liver transplantation [80,81].

Survival on dialysis is generally limited by the severity of the hepatic failure [82], as well as concurrent respiratory failure [83]. Patients with an acute and potentially reversible hepatic insult may particularly benefit from dialysis since kidney function will recover in parallel with improving hepatic function [49]. By contrast, patients with cirrhosis who develop hepatorenal syndrome and require kidney replacement therapy have a dismal prognosis unless they are listed for liver transplant. In one study, for example, mortality at six months was 84 percent (median survival, 21 days) among such patients not listed for transplant but was 39 percent in patients listed for liver transplant [81].

Hemodialysis is frequently difficult to perform in patients with hepatorenal syndrome since decompensated hepatic function is associated with hemodynamic instability and hypotension that can be difficult to support. Hemodialysis in such cases can precipitate cardiac arrest and death, thereby shortening rather than prolonging survival. Some success has been realized with continuous kidney replacement modalities [84]. (See "Continuous kidney replacement therapy in acute kidney injury".)

**Other therapies** — A number of other drugs have been tried for the treatment of hepatorenal syndrome, such as misoprostol, N-acetylcysteine, and angiotensin-converting enzyme inhibitors. None of these approaches are consistently associated with benefit, and therefore none are recommended. In rare patients, a peritoneovenous shunt is used.

**Peritoneovenous shunt** — A peritoneovenous shunt, which drains peritoneal fluid from the peritoneum into the internal jugular vein, reinfuses ascites into the vascular space. This modality has been used in patients with refractory ascites and kidney failure due to the hepatorenal syndrome [38,85-89]. In these settings, the increase in fluid return to the cardiopulmonary circulation can lead sequentially to decreased activity of sodium-retaining and vasoconstrictive mechanisms (such as the renin-angiotensin-aldosterone system), a marked rise in urinary sodium excretion, and a modest elevation in GFR [38,85,88].

However, it is now rarely used because of an appreciable rate of complications and the lack of evidence that peritoneovenous shunting prolongs patient survival, which may be several years in patients with normal or near-normal hepatic and kidney function tests but less than six weeks in patients with the hepatorenal syndrome [38,86,87,90,91].

The major problem with the peritoneovenous shunt is the relatively high rate of complications, including disseminated intravascular coagulation (due to entry into the blood stream of endotoxin or other procoagulant material in the ascitic fluid), infection of the shunt, which can

lead to bacteremia, variceal bleeding resulting from volume expansion and a concurrent rise in portal venous pressure, and small bowel obstruction [85,92,93].

The net effect is that the perioperative mortality can reach 25 percent in patients with advanced disease [92,93]. In comparison, peritoneovenous shunting is relatively well-tolerated in patients with ascites but relatively normal kidney function [86,87]. Furthermore, the perioperative morbidity can be diminished if, prior to insertion of the shunt, there is intraoperative drainage of the ascites, which is then replaced by 5 liters of isotonic saline [86,93]. This regimen can minimize those complications related to massive ascites infusion: disseminated intravascular coagulation and increased portal pressure.

The only remaining indications for peritoneovenous shunt are:

- Unusual forms of ascites such as chylous ascites.
- Post-liver transplant patient with refractory ascites.
- Patients with cirrhosis and diuretic-resistant ascites who are not candidates for transplantation or TIPS and who are too obese or have too many abdominal surgical scars to permit safe, successful paracentesis. (See "Ascites in adults with cirrhosis: Diuretic-resistant ascites".)

## PREVENTION

Hepatorenal syndrome regularly develops in patients with systemic bacterial infection (eg, spontaneous bacterial peritonitis [SBP]) and/or severe alcoholic hepatitis. The following therapies may prevent the development of hepatorenal syndrome in these patients:

- Intravenous albumin – In patients with SBP, the administration of intravenous albumin (1.5 g/kg) at the time of diagnosis of infection and another dose of albumin (1 g/kg) on day 3 of antibiotic treatment reduces the incidence of both kidney function impairment and mortality. A meta-analysis of four controlled trials (with a total of 288 patients) evaluated the impact of albumin infusion (in addition to antibiotics) on kidney function impairment and mortality in patients with SBP [94]. Albumin infusion was associated with a significant decrease in the incidence of kidney function impairment (8 versus 31 percent) and a significant reduction in mortality (16 versus 35 percent). These data support the use of albumin infusion in patients with SBP. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Albumin administration for patients with renal dysfunction'.)

- Norfloxacin – A randomized trial reported significant benefits with the oral administration of norfloxacin at 400 mg/day to 68 patients with cirrhosis and ascitic fluid total protein <1.5 g/dL who fulfilled either of the following two criteria: a Child-Pugh score >9 points and serum bilirubin >3 mg/dL (51.3 micromol/L); or a serum creatinine >1.2 mg/dL [106 micromol/L] or blood urea nitrogen (BUN) >20 mg/dL or serum sodium <130 mEq/L [95]. Norfloxacin was associated with the following significant benefits: decreased one-year probability of SBP (7 versus 61 percent) and hepatorenal syndrome (28 versus 41 percent), and improved survival at three months (94 versus 62 percent) and one year (60 percent versus 48 percent). Based upon these and other findings, we use of norfloxacin in selected patients with cirrhosis and ascites. However, in countries where norfloxacin is not available, trimethoprim-sulfamethoxazole is an alternative. Specific recommendations are discussed elsewhere. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Prophylaxis'.)

- Pentoxifylline – An initial trial of 61 patients with cirrhosis, ascites, and a baseline creatinine clearance of 41 to 80 mL/min per 1.73 $m^2$ showed significant benefit with pentoxifylline (1200 mg/day) for six months as compared with placebo [96]. However, a subsequent meta-analysis demonstrated no benefit on hepatorenal syndrome or mortality [97]. (See "Management and prognosis of alcoholic hepatitis", section on 'Pentoxifylline'.)

## PROGNOSIS

Overall, the mortality of patients with liver failure is substantially worse if they develop hepatorenal syndrome [98]. Without therapy, most patients die within weeks of the onset of the kidney function impairment. In turn, the outcome of patients with hepatorenal syndrome, as well as recovery of kidney function, is strongly dependent upon reversal of the hepatic failure, whether spontaneous, following medical therapy, or following successful liver transplantation [99].

In a prospective study of 272 outpatients with cirrhosis, 80 patients (29 percent) developed acute kidney disease over five years [100]. Of these, 42 patients (52 percent) recovered and 16 of those patients (38 percent) had a recurrence of acute kidney disease. In total, 11 patients with acute kidney disease (14 percent) progressed to chronic kidney disease and 36 patients (45 percent) died.

The rate of recovery of kidney function following recovery of liver failure is uncertain; reported rates are affected by varying pretransplant kidney function and differences over time in indications for dialysis and in eligibility for liver transplantation. However, a substantial

proportion of patients who have progressed to dialysis and survive to receive a liver transplant do recover kidney function [101]. (See "Kidney function and non-kidney solid organ transplantation".)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders in adults".)

## SUMMARY AND RECOMMENDATIONS

- **Definition and etiology** – The hepatorenal syndrome is one of many potential causes of acute kidney injury in patients with acute or chronic liver disease. Patients who develop the hepatorenal syndrome usually have portal hypertension due to cirrhosis, severe alcoholic hepatitis, and, less often, metastatic tumors. However, patients with fulminant hepatic failure from any cause may develop hepatorenal syndrome. In patients with cirrhosis and ascites, the hepatorenal syndrome occurs in approximately 20 and 40 percent at one and five years, respectively. In patients with acute liver disease, the hepatorenal syndrome occurs in approximately 25 to 30 percent. (See 'Introduction' above and 'Epidemiology' above.)

- **Pathogenesis** – Arterial vasodilatation in the splanchnic circulation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in kidney function in the hepatorenal syndrome. The presumed mechanism is increased production or activity of vasodilators, mainly in the splanchnic circulation, with nitric oxide thought to be most important. As the hepatic disease becomes more severe, there is a progressive rise in cardiac output and fall in systemic vascular resistance; the latter change occurs despite local increases in renal and femoral vascular resistance that result in part from hypotension-induced activation of the renin-angiotensin and sympathetic nervous systems ( figure 1). (See 'Pathogenesis' above.)

- **Clinical manifestations** – The hepatorenal syndrome is usually characterized by the following features in a patient who has established or clinically evident acute or chronic liver disease (see 'Clinical presentation' above):

  - A progressive rise in serum creatinine
  - A benign urine sediment

- No or minimal proteinuria (less than 500 mg per day)
- A very low rate of sodium excretion (ie, urine sodium concentration less than 10 mEq/L)
- Nonoliguria or oliguria, depending upon the severity

Based upon the rapidity of the decline in kidney function, two forms of hepatorenal syndrome have been described (see 'Clinical presentation' above):

- HRS-AKI (type 1 hepatorenal syndrome) – This more serious type of hepatorenal syndrome is referred to as hepatorenal syndrome-acute kidney injury (HRS-AKI) or, traditionally, type 1 hepatorenal syndrome. It is defined as at least a twofold increase in serum creatinine (reflecting a 50 percent reduction in creatinine clearance) to a level greater than 2.5 mg/dL (221 micromol/L) during a period of less than two weeks.

- Diuretic-resistant ascites (type 2 hepatorenal syndrome) – Diuretic-resistant ascites, or type 2 hepatorenal syndrome, is defined as kidney function impairment that is less severe than that observed with HRS-AKI/type 1 disease. The major clinical feature in patients with type 2 hepatorenal syndrome is ascites that is resistant to diuretics.

The onset of kidney failure is typically insidious but can be precipitated by an acute insult, such as bacterial infection (often spontaneous bacterial peritonitis) or gastrointestinal bleeding. Diuretics do not cause hepatorenal syndrome. (See 'Precipitants' above.)

Patients with hepatorenal syndrome may have kidney dysfunction that is substantially more severe than is suggested by the serum creatinine. (See 'Problems with estimating kidney function' above.)

- **Diagnosis** – Hepatorenal syndrome is diagnosed based upon clinical criteria ( algorithm 1). There is no one specific test that can establish the diagnosis. The following definition and diagnostic criteria have been proposed for the hepatorenal syndrome (see 'Diagnosis' above):

  - Chronic or acute hepatic disease with advanced hepatic failure and portal hypertension.

  - Acute kidney injury, defined as an increase in serum creatinine of 0.3 mg/dL (26.5 micromol/L) or more within 48 hours, or an increase from baseline of 50 percent or more within seven days.

  - The absence of any other apparent cause for the acute kidney injury, including shock, current, or recent treatment with nephrotoxic drugs, and the absence of ultrasonographic evidence of obstruction or parenchymal kidney disease. Spontaneous

bacterial peritonitis is complicated by acute kidney injury that may be reversible in 30 to 40 percent of patients. It can be associated with acute tubular necrosis (ATN), but it is also a major precipitant of the hepatorenal syndrome. Thus, ongoing infection with spontaneous bacterial peritonitis should not exclude the possibility of hepatorenal syndrome. This means that therapy for hepatorenal syndrome can commence while the bacterial infection is still being treated. In addition, hepatorenal syndrome can occur in patients with preexisting chronic kidney disease. Thus, the presence of another kidney diagnosis (eg, diabetic nephropathy) does not necessarily exclude hepatorenal syndrome.

- In conjunction with excluding other apparent causes of kidney disease, the following criteria also apply:

  Urine red cell excretion of less than 50 cells per high power field (when no urinary catheter is in place) and protein excretion less than 500 mg/day.

  Lack of improvement in kidney function after volume expansion with intravenous albumin (1 g/kg of body weight per day up to 100 g/day) for at least two days and withdrawal of diuretics.

The diagnosis of the hepatorenal syndrome is one of **exclusion**, entertained only after other potential causes of acute or subacute kidney injury have been ruled out. Alternate etiologies include, but are not limited to, glomerulonephritis, prerenal disease, and ATN. (See 'Differential diagnosis' above.)

- **Management** – The ideal therapy for hepatorenal syndrome is improvement of liver function from either recovery of alcoholic hepatitis, treatment of decompensated hepatitis B with effective antiviral therapy, recovery from acute hepatic failure, or liver transplantation. (See 'Approach to therapy' above and 'Improving hepatic function' above.)

  - **Initial medical therapy** – However, when improvement of liver function is not possible in the short term, medical therapy should be instituted in an attempt to reverse the acute kidney injury associated with hepatorenal syndrome. Our suggestions regarding the choice of medical therapy depend upon several factors, including: whether the patient is admitted to the intensive care unit; the availability of certain drugs, for which there is national and regional variability; and whether the patient is a candidate for liver transplantation. (See 'Approach to therapy' above.)

    Antihypertensive agents, including beta blockers, should be discontinued in **all patients** with hepatorenal syndrome.

In patients with hepatorenal syndrome who are **admitted to the intensive care unit**, we suggest initial treatment with norepinephrine in combination with albumin rather than other medical therapies (**Grade 2B**). Norepinephrine is given intravenously as a continuous infusion (0.5 to 3 mg/hr) with the goal of raising the mean arterial pressure by 10 mmHg, and albumin is given for at least two days as an intravenous bolus (1 g/kg per day [100 g maximum]). Intravenous vasopressin may also be effective, starting at 0.01 units/min. (See 'Norepinephrine for patients in the intensive care unit' above.)

In patients with hepatorenal syndrome who are **not admitted to the intensive care unit**, our suggestions depend upon the availability of certain drugs:

- Where terlipressin therapy is available, we suggest initial treatment with terlipressin in combination with albumin rather than midodrine, octreotide, and albumin (**Grade 2C**). Terlipressin is given as an intravenous bolus (1 to 2 mg every four to six hours), and albumin is given for two days as an intravenous bolus (1 g/kg per day [100 g maximum]), followed by 25 to 50 grams per day until terlipressin therapy is discontinued. (See 'Terlipressin plus albumin where available' above.)

- Where terlipressin therapy is not available, we suggest initial treatment with a combination of midodrine, octreotide, and albumin (**Grade 2C**). Midodrine is given orally (7.5 to 15 mg by mouth three times daily), octreotide is either given as a continuous intravenous infusion (50 mcg/hr) or subcutaneously (100 to 200 mcg three times daily), and albumin is given for two days as an intravenous bolus (1 g/kg per day [100 g maximum]), followed by 25 to 50 grams per day until midodrine and octreotide therapy is discontinued. (See 'Midodrine, octreotide, and albumin where terlipressin is not available' above.)

In patients treated with norepinephrine, terlipressin, or octreotide, we usually treat for a total of two weeks. However, we and others occasionally treat for longer durations (up to one month or more) if there is some but not complete improvement in kidney function after two weeks of therapy. In patients who respond to therapy, we occasionally treat indefinitely with midodrine to maintain a higher mean arterial pressure (or until liver transplantation or resolution of liver injury). By contrast, if a patient has no improvement in kidney function after two weeks, therapy with these drugs can be considered futile. (See 'Approach to therapy' above.)

- **If initial medical therapy fails** – In highly selected patients who fail to respond to medical therapy with the above regimens, who are awaiting liver transplantation, and

who are considered well enough to undergo the procedure, transjugular intrahepatic portosystemic shunt (TIPS) is sometimes successful; however the procedure is associated with numerous complications. (See 'Transjugular intrahepatic portosystemic shunt' above.)

In patients who fail to respond to the above therapies, develop severely impaired kidney function, are not considered candidates for TIPS, and either are candidates for liver transplantation or have a reversible form of liver injury and are expected to survive, we recommend kidney replacement therapy as a bridge to liver transplantation or liver recovery (**Grade 1B**). Hemodialysis is frequently difficult to perform in patients with hepatorenal syndrome, and survival is generally limited by the severity of the hepatic failure, as well as concurrent respiratory failure. (See 'Kidney replacement therapy' above.)

- **Goals of therapy** – The goal of medical therapy or TIPS in patients with hepatorenal syndrome is reversal of the acute kidney injury. In addition, when patients are treated with norepinephrine, terlipressin, or midodrine plus octreotide, an immediate goal of therapy is to raise the mean arterial pressure by approximately 10 to 15 mmHg. (See 'Approach to therapy' above.)

- **Prevention** – The following therapies may prevent the development of hepatorenal syndrome in these patients (see 'Prevention' above):

  - In patients with spontaneous bacterial peritonitis, we recommend the administration of intravenous albumin (1.5 g/kg) at the time of diagnosis of infection and another dose of albumin (1 g/kg) on day 3 of antibiotic treatment (**Grade 1B**). (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis".)

  - In selected patients with cirrhosis and ascites, we recommend chronic norfloxacin therapy (400 mg/day) (**Grade 1B**). However, in countries where this drug is not available, trimethoprim-sulfamethoxazole can be substituted. A discussion of which patients should receive chronic norfloxacin (or trimethoprim-sulfamethoxazole) therapy, as well as the evidence for this graded recommendation, are presented elsewhere. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis".)

- **Prognosis** – Without therapy, most patients with hepatorenal syndrome die within weeks of the onset of the kidney function impairment. The outcome of patients with hepatorenal syndrome, as well as recovery of kidney function, is strongly dependent upon reversal of

the hepatic failure, whether spontaneous, following medical therapy, or following successful liver transplantation. (See 'Prognosis' above.)



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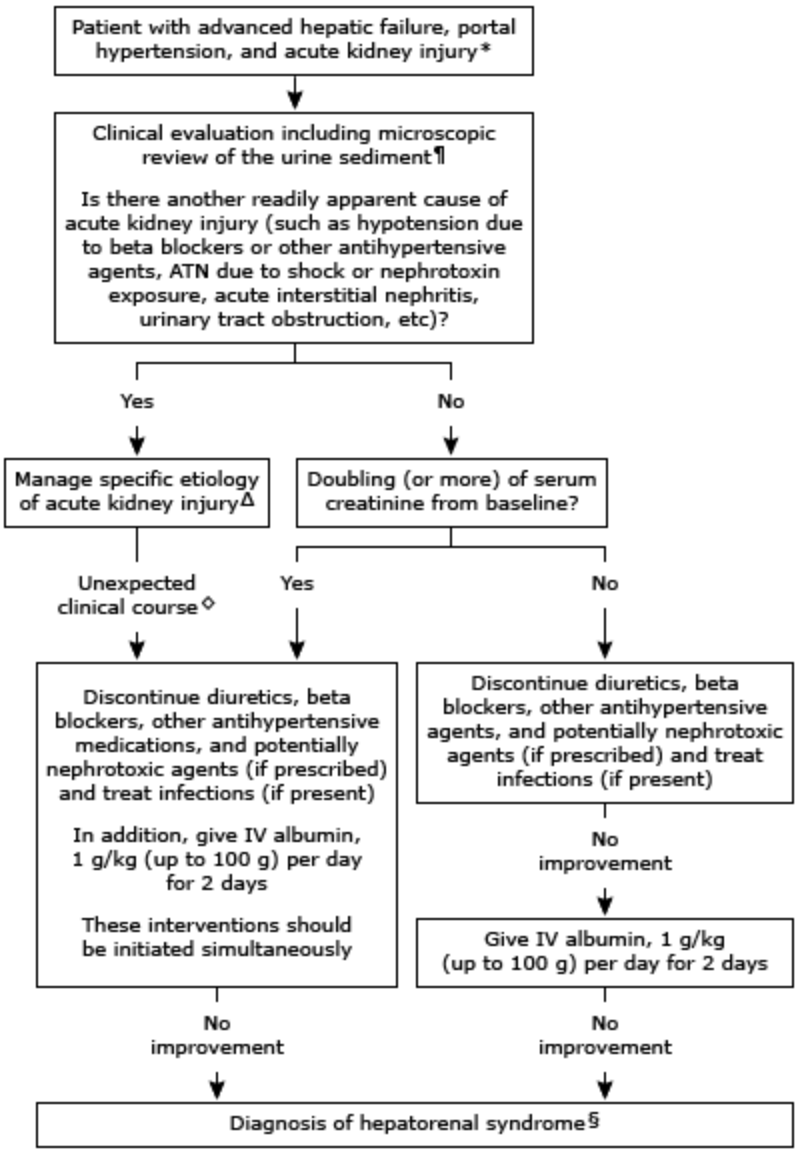
Topic 2308 Version 38.0

## GRAPHICS

### Diagnosis of hepatorenal syndrome




ATN: acute tubular necrosis; KDIGO: Kidney Disease: Improving Global Outcomes.

* Acute kidney injury is defined in this context as an increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% within 7 days; this is consistent with KDIGO criteria.

¶ Refer to UpToDate content on the evaluation of patients with acute kidney injury.

Δ Evidence for a alternative etiology of acute kidney injury makes hepatorenal syndrome less likely (hepatorenal syndrome is generally a diagnosis of exclusion). However, such patients may also have superimposed hepatorenal syndrome as a second disorder.

◇ Unexpected clinical course indicates that management of presumed etiology did not result in the expected outcome (eg, worsening kidney function despite relief of diagnosed urinary tract obstruction, failure of contrast-associated injury to resolve in the anticipated timeline, etc).

§ This disorder is referred to as hepatorenal syndrome with acute kidney injury (HRS-AKI) by some experts; other experts refer to this entity as type 1 hepatorenal syndrome.

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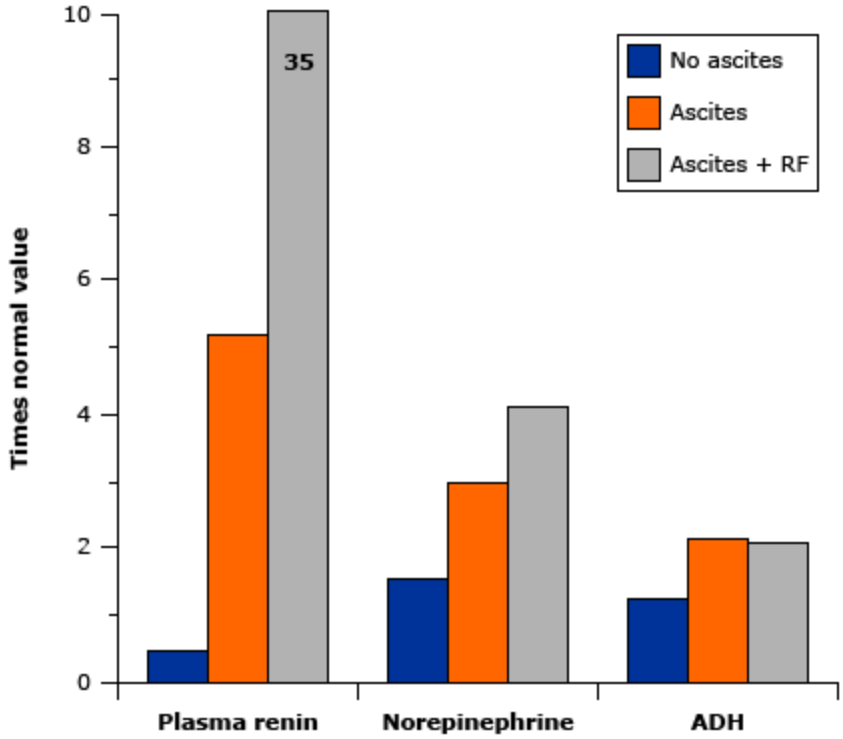
Graphic 132775 Version 2.0

## Hormonal response to cirrhosis



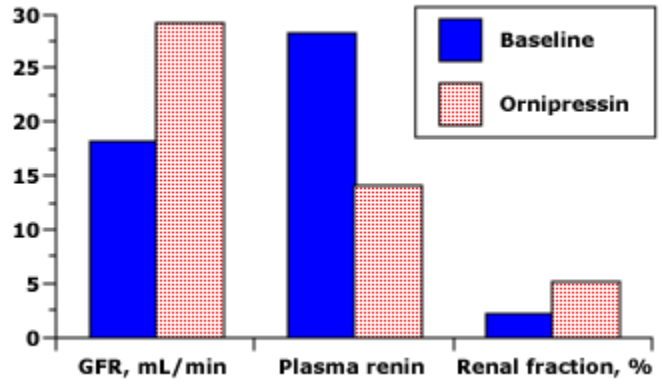

Cirrhosis of increasing severity—no ascites, ascites, and ascites plus RF due to hepatorenal syndrome—is associated with a progressive increase in plasma renin activity (ng/mL per hour) and in the plasma levels of norepinephrine (pg/mL), and antidiuretic hormone (pg/mL). This progressive rise in the secretion of hypovolemic hormones is associated with a vasodilatation-induced fall in mean arterial pressure (from 89 to 75 mmHg) and a reduction in the plasma sodium concentration (from 138 to 128 mEq/L).

RF: renal failure; ADH: antidiuretic hormone.

*Data from: Asbert M, Gines A, Gines P, et al. Gastroenterology 1993; 104:1485.*

Graphic 74244 Version 3.0

## Ornipressin improves renal function in advanced hepatic cirrhosis




Effect of infusion of ornipressin, an analog of antidiuretic hormone that causes preferential splanchnic vasoconstriction, in patients with advanced hepatic cirrhosis and functional renal failure (the hepatorenal syndrome). Ornipressin raised the glomerular filtration rate (GFR) from 18 to 29 mL/min, lowered the plasma renin activity from 28 to 14 (normal equals less than 3 ng/mL per hour on a regular salt intake), and raised the fraction of the cardiac output delivered to the kidneys from 2 to 5 percent (normal equals 20 percent). Each of these abnormalities was only partially corrected, although it is not known if a greater response would be seen with less severe disease or with a higher dose.

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*Adapted from: Lenz K, Hortnagl H, Druml W, et al. Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis. Effects on renal hemodynamics and atrial natriuretic factor. Gastroenterology 1991; 101:1060.*

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Graphic 68506 Version 2.0

## Contributor Disclosures

**Bruce A Runyon, MD, FAASLD** No relevant financial relationship(s) with ineligible companies to disclose. **Richard H Sterns, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Eric N Taylor, MD, MSc, FASN** No relevant financial relationship(s) with ineligible companies to disclose.

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