

## REVIEW ARTICLE

## MEDICAL PROGRESS

## Renal Failure in Cirrhosis

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RENAL FAILURE IS A CHALLENGING COMPLICATION OF CIRRHOSIS<sup>1,2</sup> AND is one of the most important risk factors when liver transplantation is being considered. Patients with cirrhosis and renal failure are at high risk for death while awaiting transplantation and have an increased frequency of complications and reduced survival after transplantation, as compared with those without renal failure.<sup>3,4</sup> In 2002, the Model for End-Stage Liver Disease (MELD) score — derived from measurements of serum bilirubin, the international normalized ratio of prothrombin time, and serum creatinine to evaluate pretransplantation renal function — was introduced as an aid to organ allocation among candidates for liver transplantation. Use of this scoring system has increased the number of patients with renal failure who receive a liver transplant<sup>5-7</sup> and has reduced mortality among patients awaiting liver transplantation.

In recent years, substantial progress has been made toward understanding the pathogenesis and natural history of renal failure in cirrhosis. Moreover, newly identified clinical interventions may assist in the prevention and management of this complication.

## PATHOPHYSIOLOGY OF RENAL FAILURE

There is considerable evidence that renal failure in patients with cirrhosis is primarily related to disturbances in circulatory function — mainly, a reduction in systemic vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension.<sup>1,8-10</sup> The cause of this arterial vasodilatation is increased production or activity of vasodilator factors — particularly nitric oxide, carbon monoxide, and endogenous cannabinoids — mainly in the splanchnic circulation.<sup>8-12</sup>

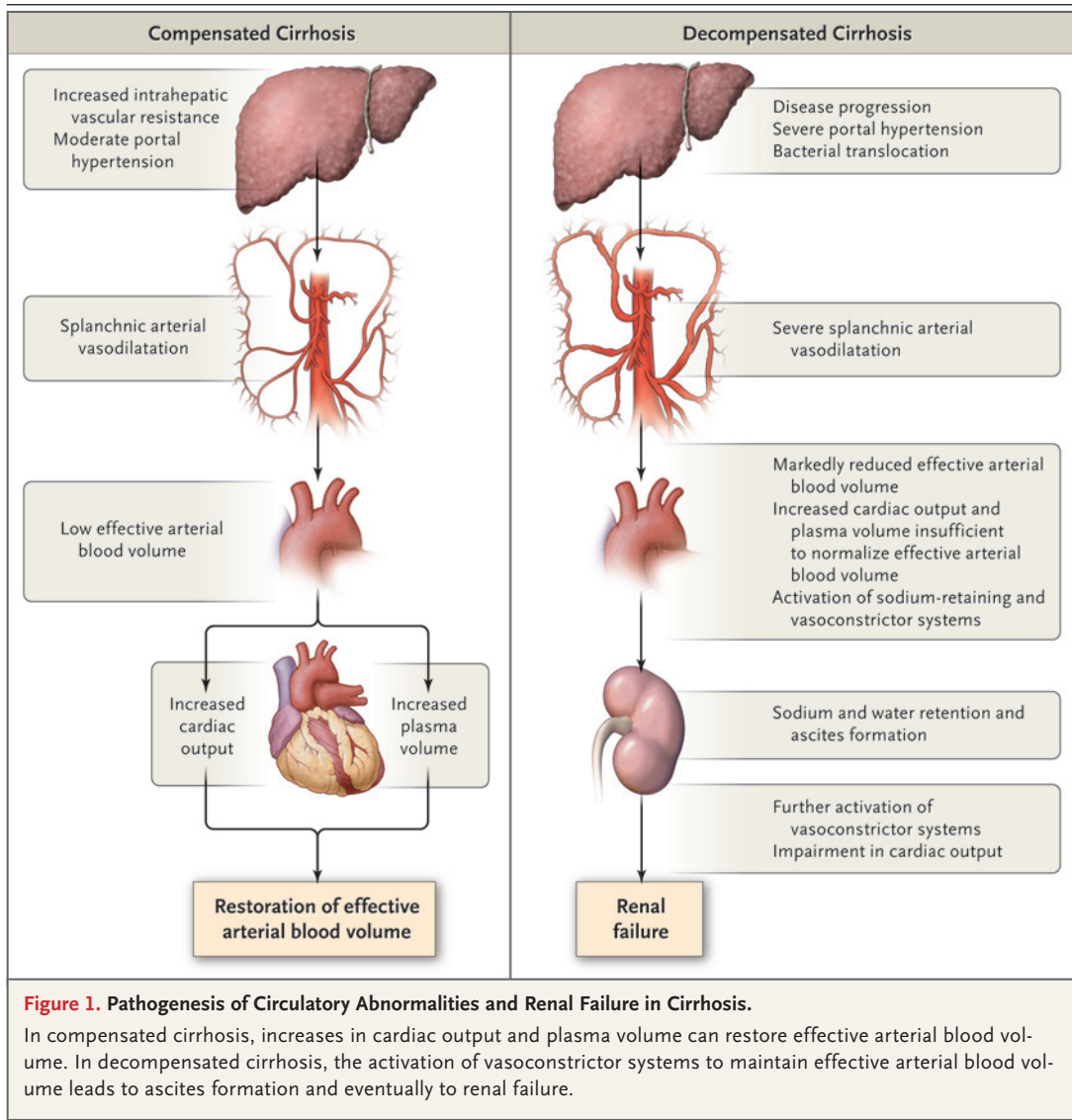
In the early stages of cirrhosis, when portal hypertension is moderate, increased cardiac output compensates for a modest reduction in systemic vascular resistance, permitting the arterial pressure and effective arterial blood volume to remain within normal limits<sup>8,9</sup> (Fig. 1). In advanced stages of cirrhosis, systemic vascular resistance is markedly reduced, and additional increases in cardiac output cannot compensate, leading to underfilling of the arterial circulation.<sup>8</sup> Moreover, there is evidence that cardiac output decreases as cirrhosis progresses.<sup>13</sup> In advanced cirrhosis, arterial pressure must be maintained through the activation of vasoconstrictor systems, including the renin–angiotensin system, the sympathetic nervous system, and, in late stages, nonosmotic hypersecretion of arginine vasopressin (antidiuretic hormone). These compensatory mechanisms help maintain effective arterial blood volume and relatively normal arterial pressure but have important effects on kidney function, particularly sodium and solute-free water retention, that may eventually lead to ascites and edema and to renal failure by causing intrarenal vasoconstriction and hypoperfusion.<sup>8,9</sup> Indeed, renal failure rarely occurs in cirrhosis without ascites and is very frequent in advanced cirrhosis with ascites and edema.

Studies in both laboratory animals and patients with cirrhosis suggest that bacte-

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rial translocation — that is, the passage of bacteria from the intestinal lumen to the mesenteric lymph nodes — may play an important role in impairing circulatory function in advanced cirrhosis.<sup>14,15</sup> Bacterial translocation may elicit an inflammatory response, with increased production of proinflammatory cytokines (mainly tumor necrosis factor  $\alpha$  and interleukin-6) and vasodilator factors (e.g., nitric oxide) in the splanchnic area; this response in turn may lead to vasodilatation of the splanchnic arterial vessels (Fig. 2). Patients with cirrhosis and increased levels of lipopolysaccharide-binding protein or circulating levels of bacterial DNA (which may be considered surrogate markers of bacterial translocation) have increased serum levels of cytokines, reduced sys-

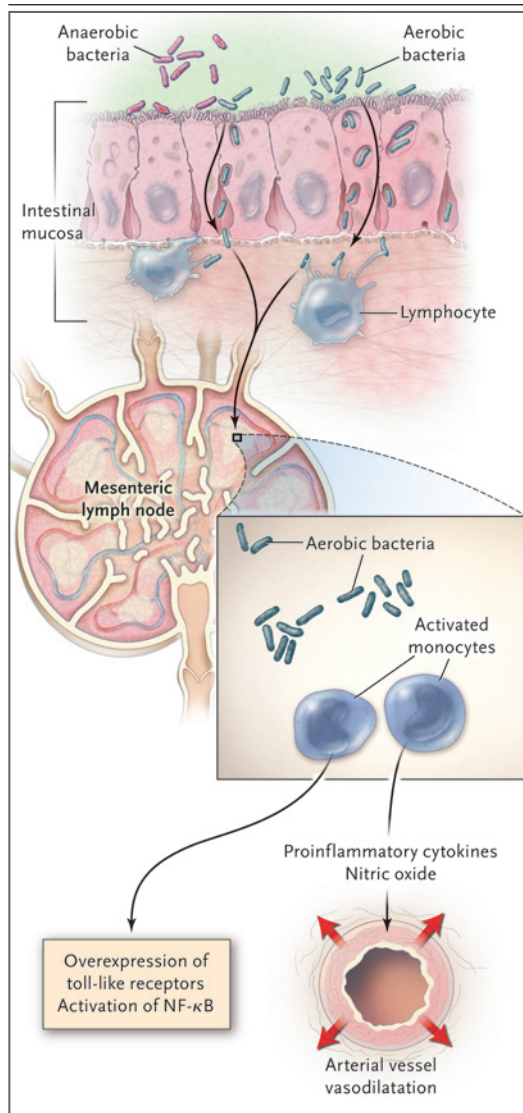
temic vascular resistance, and increased cardiac output, as compared with those who have cirrhosis but do not have these markers of bacterial translocation.<sup>16,17</sup> Moreover, the administration of norfloxacin, an antibiotic that results in selective intestinal decontamination and reduces bacterial translocation, ameliorates but does not normalize the hemodynamic abnormalities in patients with cirrhosis.<sup>18,19</sup>

Patients with cirrhosis who have circulatory dysfunction and arterial underfilling, increased endogenous vasoconstrictor activity affecting the intrarenal circulation, and increased systemic inflammatory responses are particularly prone to renal failure, which may occur spontaneously or may be triggered by a number of events that occur

frequently in advanced cirrhosis. Such events include hypovolemia, induced by renal or gastrointestinal fluid losses, and bacterial infections.<sup>2,20,21</sup> Hypovolemia as a consequence of gastrointestinal bleeding, diarrhea, or excessive administration of diuretics is a common cause of impaired renal function in cirrhosis.<sup>21,22</sup>

Renal failure is common and particularly severe in patients with spontaneous bacterial peritonitis; in these cases, the peritonitis is most often caused by gram-negative bacteria due to bacterial translocation.<sup>23,24</sup> Such an infection elicits a severe inflammatory response in the peritoneal cavity, with increased levels of proinflammatory cytokines and long-lasting production of vasoactive mediators that can impair circulatory function and cause renal failure.<sup>25,26</sup> Other types of bacterial infection may also cause renal failure in patients with cirrhosis, yet the severity of the inflammatory response and renal impairment is not as marked as in spontaneous bacterial peritonitis.<sup>27,28</sup>

Nonsteroidal antiinflammatory drugs may also cause renal failure in patients with cirrhosis, since their kidney function is extremely dependent on renal prostaglandin synthesis.<sup>1,9,29</sup> Finally, in some patients with cirrhosis, intrinsic renal diseases may be present that are related not to alterations in systemic hemodynamics but rather to the etiologic factors underlying the liver disease. These forms of nephropathy include glomerulonephritis associated with hepatitis B or hepatitis C infection and alcoholic cirrhosis.<sup>30,31</sup>



**Figure 2. Potential Role of Bacterial Translocation and Cytokine Overproduction on Splanchnic Arterial Vasodilatation.**

A number of factors, such as intestinal bacterial overgrowth, impaired intestinal motility, alterations in gut permeability, and disturbances in local immune systems, can lead to passage of aerobic bacteria from the intestinal lumen to the mesenteric lymph nodes. This translocation results in activation of monocytes with overexpression of toll-like receptors, activation of nuclear factor kappa B (NF-κB), and increased local production of proinflammatory cytokines and vasodilator factors, such as nitric oxide. These cytokines and vasodilator factors cause further vasodilatation of splanchnic arterial vessels. In general, anaerobic bacteria do not translocate.

impractical for the repeated assessments of renal function that are required in these circumstances. Formulas such as the Cockcroft–Gault and

EVALUATION OF PATIENTS WITH CIRRHOSIS AND RENAL FAILURE

ASSESSMENT OF RENAL FUNCTION

Renal function should be routinely monitored in all patients with advanced cirrhosis, especially those with ascites (Table 1). Patients who have ascites, particularly those with hyponatremia, bacterial infections, gastrointestinal bleeding, or severe sodium retention, are at high risk for renal failure, as are all patients hospitalized for acute decompensation of cirrhosis.<sup>1,2,22,23,32</sup> In clinical practice, serum creatinine measurement is still the most useful and widely accepted method for estimating renal function in patients with cirrhosis.<sup>9,33</sup> Although measurement of the glomerular filtration rate (GFR) on the basis of the clearance of inulin or radioisotopic substances is more accurate and represents the standard, it is

**Table 1. Evaluation of Patients with Cirrhosis and Renal Failure.****Evaluation of renal function**

Serum creatinine should be measured daily in patients with acute impairment of renal function; increases of 0.3 to 0.5 mg/dl (27 to 44  $\mu$ mol/liter) may indicate marked reductions in glomerular filtration rate.

Serum sodium and potassium concentrations should be monitored daily in patients with acute renal failure and monthly or every other month in patients with chronic renal failure; hyponatremia is common; potassium-sparing diuretics should be discontinued to prevent hyperkalemia.

Electrolytes and protein should be measured (preferably in 24-hr urine samples) in all patients with renal failure; significant proteinuria (>500 mg of protein/day) and urine-sediment abnormalities usually indicate parenchymal renal disease.

Renal ultrasonography rules out urinary tract obstruction, but the ultrasonographic appearance of the kidney is normal in most cases of cirrhosis with renal failure; abnormal renal ultrasonograms indicate chronic parenchymal renal disease.

A renal biopsy is helpful when parenchymal renal disease is suspected because of proteinuria, hematuria, or both and is also helpful in deciding on simultaneous kidney transplantation in candidates for liver transplantation; renal biopsy is contraindicated if severe coagulation abnormalities are present; there is little information on the use of transvenous renal biopsy.

**Evaluation of liver function**

Liver disease should be evaluated by means of standard liver-function tests and abdominal ultrasonography.

Liver biopsy should be performed if the diagnosis of liver disease is not clear and if biopsy is not contraindicated by the results of clotting studies.

Upper gastrointestinal endoscopy is helpful for detecting gastroesophageal varices; if large varices are present, prophylactic measures should be taken (i.e., beta-blocker therapy, variceal ligation, or both).

**Assessment of bacterial infection**

Bacterial infection should be ruled out in all patients with acute renal failure or worsening of renal function.

Leukocytosis may be absent owing to hypersplenism in patients with cirrhosis and infection.

In patients with ascites, cell count and culture should be performed to rule out infection of ascitic fluid.

Blood and urine cultures should be carried out even in the absence of obvious signs of infection.

Chest radiography should be performed to rule out lung infection.

Modification of Diet in Renal Disease, which are based on the serum creatinine concentration and other measurements, overestimate the GFR in patients with cirrhosis and are generally not used to evaluate renal function in such clinical patients.<sup>34,35</sup> Finally, creatinine clearance also overestimates the GFR and requires accurate urine collection, which is also not practical, particularly in the outpatient setting.<sup>36</sup>

To date, most studies and consensus conferences have defined renal failure in cirrhosis as a serum creatinine concentration above 1.5 mg per deciliter (133  $\mu$ mol per liter).<sup>2,9,33,37</sup> In patients with cirrhosis due to low creatinine production because of reduced muscle mass, the low serum creatinine level results in an underestimation of the GFR.<sup>38-40</sup> Thus, the current definition of renal failure in cirrhosis identifies only those patients with a severely reduced GFR (<30 ml per

minute) and undoubtedly underestimates the prevalence of this clinical problem. Accordingly, the definition of renal failure in patients with cirrhosis may require a reevaluation, with new criteria proposed for defining acutely impaired renal function and chronic kidney disease.<sup>41-43</sup>

The assessment of renal function should also include a thorough evaluation of urinary and serum electrolyte levels. Renal ultrasonography is important for ruling out structural abnormalities suggestive of chronic kidney disease or urinary tract obstruction. The usefulness of new urinary biomarkers in the assessment of renal failure in cirrhosis has not yet been evaluated.<sup>44</sup>

**GENERAL ASSESSMENT**

The evaluation of patients with cirrhosis and renal failure should include not only the assessment of renal function but also an assessment of



**Table 2. Main Types of Renal Failure in Patients with Cirrhosis.**

Disorder	Comments
Hepatorenal syndrome*	The hepatorenal syndrome is diagnosed on the basis of a serum creatinine concentration of more than 1.5 mg/dl (133 $\mu$ mol/liter), which is not reduced (to <1.5 mg/dl) with the administration of albumin (1 g/kg of body weight) and after a minimum of 2 days off diuretics, along with the absence of current or recent treatment with potentially nephrotoxic drugs, the absence of shock, and the absence of findings suggestive of parenchymal renal disease (urinary excretion of >500 mg of protein/day, >50 red cells/high-power field, or abnormal kidneys on ultrasonography). The syndrome is classified into two types: type 1 is characterized by a doubling of the serum creatinine level to more than 2.5 mg/dl (221 $\mu$ mol/liter) in less than 2 weeks; type 2 is characterized by a stable or less rapidly progressive course than in type 1.
Hypovolemia-induced renal failure	Hypovolemia is usually due to hemorrhage (in most cases gastrointestinal bleeding) or to fluid losses — either renal losses because of excessive diuretic therapy or gastrointestinal losses as a result of diarrhea from excessive lactulose administration or gastrointestinal infection. Renal failure occurs soon after the onset of hypovolemia.
Parenchymal renal disease	Parenchymal renal disease should be suspected as a cause of renal failure when proteinuria (>500 mg of protein/day), hematuria (>50 red cells/high-power field), or both are present and ideally should be confirmed by renal biopsy, if this procedure is not contraindicated. The differential diagnosis between acute tubular necrosis and the hepatorenal syndrome remains a difficult issue; the presence of renal tubular epithelial cells in the urine sediment favors the diagnosis of acute tubular necrosis.
Drug-induced renal failure	Current or recent treatment with nonsteroidal antiinflammatory drugs or aminoglycosides suggests drug-induced renal failure.

\* Data are from Arroyo et al.<sup>9</sup> and Salerno et al.<sup>33</sup>

liver function, as well as the exclusion of possible bacterial infections (Table 1). The possibility of gastrointestinal blood losses should be assessed by clinical examination and measurement of hemoglobin levels. The patient's medications should be reviewed, and diuretics should be discontinued, since these agents may either be the cause of the renal failure or contribute to the impairment of renal function.

#### DIFFERENTIAL DIAGNOSIS OF RENAL FAILURE IN CIRRHOSIS

Pinpointing the specific type of renal failure in cirrhosis is important for both prognostic and therapeutic purposes, as discussed below (Table 2).

Hepatorenal syndrome is a frequent cause of renal failure in cirrhosis and is characterized by functional renal vasoconstriction that leads to a severe reduction in GFR with minimal renal histologic abnormalities.<sup>1,2,9,32,33,38</sup> Since specific diagnostic tests are lacking, several diagnostic criteria are used (Table 2).<sup>9,33</sup> As discussed earlier,

bacterial infections (particularly spontaneous bacterial peritonitis) often precipitate renal failure. In some patients the hepatorenal syndrome may be reversible after the infection has resolved, but in others, it may persist or even progress rapidly despite resolution of the infection.<sup>23,24,45</sup> The hepatorenal syndrome can be classified into two types, each having different clinical and prognostic characteristics.<sup>9,33</sup> Type 1 is characterized by a doubling of the serum creatinine concentration (above 2.5 mg per deciliter [221  $\mu$ mol per liter]) in less than 2 weeks; type 2 follows a stable, less progressive course than does type 1. Patients with type 1 hepatorenal syndrome have severe multiorgan dysfunction, which affects not only the kidneys but also the heart, systemic circulation, brain, adrenal glands, and liver, whereas the clinical course of patients with type 2 hepatorenal syndrome is mainly characterized by refractory ascites.<sup>46</sup>

Differentiating the hepatorenal syndrome from acute tubular necrosis remains difficult.<sup>1,2,33</sup> Granular casts can be observed in the urinary sediment

in both conditions, but the presence of renal tubular epithelial cells favors a diagnosis of acute tubular necrosis. Urinary indexes are not interpretable in the presence of diuretics; however, in the absence of diuretics, a fractional excretion of sodium of less than 1.0% indicates tubular reabsorptive integrity and favors a diagnosis of the hepatorenal syndrome. The occurrence of hypovolemic or septic shock immediately before renal failure favors a diagnosis of acute tubular necrosis. The possibility that prolonged hepatorenal syndrome may eventually progress to acute tubular necrosis has been suggested, but no convincing evidence has been provided to support this assumption.

Other causes of renal failure associated with cirrhosis (i.e., hypovolemia, parenchymal disease, and use of certain drugs) are described in Table 2.

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MANAGEMENT OF RENAL FAILURE  
IN CIRRHOSIS

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**GENERAL MEASURES**

The general care of patients with cirrhosis and renal failure is dictated by the severity of the renal failure and its associated complications. Severe acute renal failure, particularly in patients awaiting liver transplantation, should be managed in an intensive care setting. Associated complications, particularly bacterial infections and gastrointestinal bleeding, should be identified and treated early.<sup>47</sup> Third-generation cephalosporins are the initial treatment of choice for bacterial infections.<sup>45</sup> Patients with renal failure and severe sepsis may have associated relative adrenal insufficiency and may benefit from hydrocortisone administration.<sup>48,49</sup>

Particular attention should be paid to avoiding excessive intravenous fluid administration, because renal failure in the presence of sodium and solute-free water retention due to cirrhosis may cause fluid overload, resulting in hyponatremia, increases in ascites and edema, or both. In the presence of renal failure, potassium-sparing diuretics (such as spironolactone) are contraindicated because of the risk of hyperkalemia, and loop diuretics (such as furosemide) may be ineffective.<sup>9,33,37</sup> Therefore, large-volume ascites should be treated with repeated large-volume paracenteses and the intravenous administration

of albumin (8 g of albumin per liter of ascites removed).<sup>37,50</sup> Patients with cirrhosis who have chronic kidney disease and no associated complications can be treated on an outpatient basis.

**SPECIFIC MEASURES**

*Treatment of Renal Failure*

Early identification and treatment of the cause of the renal failure are fundamental to the success of therapy in patients with cirrhosis. For example, in renal failure due to the use of nonsteroidal antiinflammatory drugs, withdrawal of treatment is usually sufficient to improve renal function.<sup>2,29</sup> Antiviral therapy may be effective in some patients with renal failure due to hepatitis C virus–related glomerulonephritis, but the relatively low efficacy of such treatment should be weighed against the frequent adverse effects in patients with advanced cirrhosis.<sup>30,51</sup>

Patients with renal failure due to hypovolemia that is caused by bleeding should be treated promptly with fluids and blood-derived products plus measures to stop the bleeding (e.g., variceal ligation) and thus prevent the progression of renal failure and the development of frank acute tubular necrosis.<sup>11,47</sup> In patients with renal failure due to an excessive response to diuretics, these agents should be discontinued, and intravenous saline should be administered if concomitant hypovolemic hyponatremia is present without ascites and edema.

Although cirrhosis has not been reported as an important risk factor for contrast-induced nephropathy, patients who undergo radiologic studies that require contrast medium should be treated with standard prophylactic measures such as saline hydration, and renal function should be monitored after the procedure.<sup>2,52</sup>

*Management of the Hepatorenal Syndrome*

The best approach to the management of the hepatorenal syndrome, based on knowledge of its pathogenesis, is the administration of vasoconstrictor drugs.<sup>53-69</sup> Treatment with renal vasodilators such as dopamine or prostaglandins is ineffective.<sup>1,2</sup> Several studies have shown that vasopressin analogues (e.g., terlipressin) are effective in approximately 40 to 50% of patients with the hepatorenal syndrome<sup>57-64</sup> and should be considered as initial therapy (Table 3). Other vasoconstrictors, including alpha-adrenergic ago-

nists such as norepinephrine and midodrine, appear to be effective, but information on their use is still limited.<sup>65-68</sup>

Most studies of vasoconstrictor therapy for the hepatorenal syndrome have been performed in patients with type 1, and limited information is available for those with type 2. Moreover, data on the efficacy of such treatment in patients who have type 1 hepatorenal syndrome and concomitant bacterial infections are lacking. During vasoconstrictor therapy, patients should be evaluated for the possible development of cardiovascular or ischemic complications, which have been reported in an average of 12% of patients so treated.<sup>57-64</sup> In most studies, vasoconstrictors have been given in conjunction with albumin. Although albumin appears to enhance the beneficial effects of vasoconstrictor therapy, use of these drugs in combination has not been evaluated in randomized studies.<sup>69</sup> Recurrence of the hepatorenal syndrome after vasoconstrictors are discontinued has been reported, particularly in patients with type 2 hepatorenal syndrome, but in general, retreatment appears to be effective.<sup>61,62</sup>

Renal-replacement therapy in the form of hemodialysis or continuous venovenous hemofiltration has been used in the management of the hepatorenal syndrome, particularly in patients awaiting transplantation or in those with acute, potentially reversible conditions (e.g., alcoholic hepatitis).<sup>70,71</sup> Complications during hemodialysis, particularly hypotension, bleeding, and infections, are common. Unfortunately, the optimal renal-replacement method for patients with the hepatorenal syndrome is not clear, nor is it clear whether renal-replacement therapy will improve the prognosis for patients who are not candidates for a liver transplant. Moreover, there are no data from studies comparing renal-replacement therapy with vasoconstrictor administration. Until such data are available, it seems reasonable to start therapy with vasoconstrictors and albumin alone unless there is an urgent need for hemodialysis (i.e., because of severe hyperkalemia, metabolic acidosis, or volume overload), and to reserve hemodialysis for patients who do not have a response to vasoconstrictor therapy.

Several nonpharmacologic treatments have been used, including placement of transjugular intrahepatic portosystemic shunts and dialysis with molecular adsorbent recirculating systems, but

**Table 3. Specific Therapies for the Hepatorenal Syndrome in Patients with Cirrhosis.**

Therapy	Regimen and Comments
Vasoconstrictor drugs	
Terlipressin*	0.5–1 mg every 4–6 hr intravenously, with an increase up to 2 mg every 4–6 hr until serum creatinine decreases to 1–1.2 mg/dl (88–106 $\mu$ mol/liter); usual duration of therapy, 5 to 15 days.
Norepinephrine†	0.5–3 mg/hr given as continuous intravenous infusion with the aim of increasing mean arterial pressure by 10 mm Hg; treatment is maintained until serum creatinine decreases to 1–1.2 mg/dl (88–106 $\mu$ mol/liter).
Midodrine‡	7.5 mg given orally 3 times daily, with an increase to 12.5 mg 3 times daily if needed, in association with octreotide (100 $\mu$ g given subcutaneously 3 times daily, with an increase to 200 $\mu$ g 3 times daily if needed).
Albumin§	Intravenous administration of albumin together with vasoconstrictor drugs (1 g of albumin/kg of body weight on day 1, followed by 20–40 g/day).
Other therapies	Transjugular intrahepatic portosystemic shunts may be effective in selected patients, but available data are very limited. Renal-replacement therapy should be considered in patients who do not have a response to vasoconstrictor drugs.

\* Data are from Moreau et al.,<sup>60</sup> Fabrizi et al.,<sup>61</sup> Gluud et al.,<sup>62</sup> Sanyal et al.,<sup>63</sup> and Martín-Llahí et al.<sup>64</sup>

† Data are from Duvoux et al.<sup>66</sup>

‡ Data are from Angeli et al.<sup>65</sup> and Wong et al.<sup>67</sup>

§ Data are from Sanyal et al.,<sup>63</sup> Martín-Llahí et al.,<sup>64</sup> Angeli et al.,<sup>65</sup> Duvoux et al.,<sup>66</sup> Wong et al.,<sup>67</sup> Esrailian et al.,<sup>68</sup> and Ortega et al.<sup>69</sup>

these approaches should be considered investigational until more data are available.<sup>72,73</sup>

## PROGNOSIS

The prognosis for patients with cirrhosis and renal failure is poor.<sup>1,2,27,28,32,60,74,75</sup> The overall survival rate is approximately 50% at 1 month and 20% at 6 months. This extremely poor outcome is probably related to the combination of liver and renal failure, as well as to associated complications. However, survival rates can differ according to the type of renal failure. The hepatorenal syndrome is associated with the worst prognosis. The great majority of patients with the hepatorenal syndrome have a poor short-term outcome unless they undergo liver transplantation. Mortality is higher with type 1 hepatore-

nal syndrome than with type 2 (median survival, 1 month vs. 6 months).<sup>75</sup> Vasoconstrictor therapy has not been shown to improve survival in patients with type 1 hepatorenal syndrome, but patients in whom the hepatorenal syndrome is reversed with vasoconstrictor therapy live longer than patients who do not have a response to such therapy.<sup>60,63,64</sup> The relevant studies were performed in relatively small series of patients, however, so larger studies are required to assess more definitively whether vasoconstrictors improve survival in patients with the hepatorenal syndrome.

#### PREVENTION

The risk of the hepatorenal syndrome is substantial in patients with cirrhosis and spontaneous bacterial peritonitis but may be markedly reduced with the intravenous administration of albumin (1.5 g per kilogram of body weight at diagnosis and 1.0 g per kilogram 48 hours later).<sup>76</sup> The mechanism by which albumin prevents the hepatorenal syndrome is incompletely understood but may be related to albumin's positive effects on circulatory function and other effects, such as its antioxidant properties.<sup>77,78</sup> A recent investigation showed that in patients with ascitic fluid that contains less than 15 g of protein per liter and who have associated impairment of liver function, renal function, or both (a bilirubin level above 3 mg per deciliter [51  $\mu$ mol per liter], a Child-Pugh score greater than 10, a serum sodium level below 130 mmol per liter, or a serum creatinine concentration above 1.2 mg per deciliter [106  $\mu$ mol per liter]), the long-term administration of oral norfloxacin (400 mg per day) reduces the risk of the hepatorenal syndrome and improves survival.<sup>79</sup> The observed beneficial effects of norfloxacin are probably related to its ability to prevent bacterial translocation, suppress proinflammatory cytokines, and improve circulatory function.<sup>15-19,45</sup>

Judicious use of diuretics prevents renal failure. Renal failure due to gastrointestinal bleeding may be prevented by the prompt reversal of hypovolemia, early treatment of causes of bleeding, and the use of antibiotic prophylaxis (either norfloxacin or third-generation cephalosporins) to prevent bacterial infections.<sup>11,47,80,81</sup> Administration of nonsteroidal antiinflammatory drugs or aminoglycosides should be avoided in all patients with cirrhosis because these agents may

impair renal function. Finally, there is no effective method for preventing glomerulonephritis associated with liver diseases.

#### RENAL FAILURE AND LIVER TRANSPLANTATION

As discussed above, mortality among patients with cirrhosis and renal failure is very high, particularly among those with type 1 hepatorenal syndrome.<sup>32,74,75</sup> Therefore, liver transplantation should be considered in all patients who have no contraindications to this procedure, and it should be performed as early as possible, because severe renal failure is predictive of a poor outcome after transplantation.<sup>3,4,6,82</sup> Treatment of the hepatorenal syndrome with albumin and the vasopressin analogue terlipressin before transplantation may improve the post-transplantation outcome.<sup>83</sup>

#### EFFECTS OF MELD SCORING ON TRANSPLANTATION OUTCOMES

Indeed, the MELD scoring system was developed to give higher priority to liver-transplant candidates who have cirrhosis and renal dysfunction.<sup>5,7</sup> Although high MELD scores facilitate earlier liver transplantation, several concerns have been raised (as discussed below). It will be important to compare the results of liver transplantation before and after the introduction of MELD scoring, since it is not yet clear whether post-transplantation survival will be better or worse, whether the incidence of acute or chronic renal dysfunction will be increased or decreased, and whether the number of combined liver and kidney transplants will increase or decrease as a result of MELD scoring.

#### *Patient Survival*

Since the introduction of the MELD scoring system in the United States in February 2002, the number of patients with renal failure who undergo liver transplantation has increased. The percentage of transplant recipients with a serum creatinine concentration greater than 2.0 mg per deciliter (177  $\mu$ mol per liter) rose from 7.9% in the pre-MELD period to 10% in the MELD period, and the percentage of patients who received transplants while undergoing renal-replacement therapy increased from 3.7% in the pre-MELD period to 5.3% in the MELD period.<sup>6,84</sup> Nevertheless, the 3-year rate of patient survival was reported not to be decreased in the MELD period, as compared



with the pre-MELD period (74.7% vs. 73.1%).<sup>6</sup> Thus, overall patient survival after MELD scoring had been introduced was not worse than survival based on pre-MELD criteria.

#### Renal Function

Any analysis of renal function after liver transplantation must consider the incidence of both early and late renal dysfunction. Among patients in whom the mean GFR before transplantation was at least 80 ml per minute per 1.73 m<sup>2</sup> of body-surface area, dialysis was required after transplantation in less than 10% of recipients.<sup>85</sup> Moreover, only 7% of patients whose pretransplantation renal function was good have reported severe kidney dysfunction (GFR, <30 ml per minute) for at least 6 months after transplantation.

For patients who have cirrhosis before the hepatorenal syndrome develops but who are resistant to diuretic therapy (i.e., no response to 200 to 400 mg of spironolactone and 80 to 160 mg of furosemide), liver transplantation is generally associated with relatively good kidney function (GFR, >60 ml per minute) 6 months after transplantation.<sup>85</sup> Moreover, as many as 60% of patients with a GFR below 40 ml per minute before liver transplantation have a higher GFR 1 year after transplantation. Thus renal dysfunction may be ameliorated to some extent after liver transplantation even in the presence of chronic calcineurin inhibition. In general, however, the better the renal function before transplantation, the better the expected GFR at 1 year. Nevertheless, it should be noted that chronic allograft nephropathy occurring in recipients of liver, heart, lung, and kidney transplants is now the third most common reason for patients to be put on the waiting list for a kidney transplant.<sup>86</sup>

Although there are no systematically collected data, implementation of the MELD scoring system does not seem to have increased the incidence of acute or chronic kidney dysfunction after liver transplantation. A comparison of liver transplantations performed after the introduction of MELD scoring with those performed before the use of MELD scoring has shown no increase in the serum creatinine concentration during follow-up periods of up to 3 years and no increased need for hemodialysis after transplantation. Moreover, after the introduction of MELD scoring, patients who did not require dialysis before transplantation actually had somewhat lower serum

creatinine concentrations at 3 years of follow-up (1.4 mg per deciliter [124 μmol per liter] vs. 1.7 mg per deciliter [150 μmol per liter],  $P < 0.001$ ).<sup>87,88</sup>

#### Combined Liver and Kidney Transplantation

One potential consequence of using the MELD scoring system was a rise in the use of combined liver–kidney transplantation, and this has in fact come to pass. Before MELD scoring was applied, 2.6% of liver transplantations were performed in conjunction with a kidney transplantation; in the MELD period, this percentage has increased to 4.4%.<sup>6,89</sup>

Theoretically, combined liver–kidney transplantation should be used only for patients who have irreversible renal failure.<sup>82,90</sup> However, reliable predictive factors for the reversibility of renal failure after liver transplantation alone have not yet been identified. The presence of sustained renal failure before transplantation was shown to be a potentially useful indication for combined liver–kidney transplantation in some studies but not in others.<sup>91,92</sup> The presence of the hepatorenal syndrome does not seem to be an absolute indication for combined transplantation, because the survival of patients with the hepatorenal syndrome who are treated with liver transplantation alone is similar to that of patients treated with combined liver–kidney transplantation, and most patients recover renal function after liver transplantation alone.<sup>93</sup> Another factor that has been investigated is the duration of renal-replacement therapy before liver transplantation. Among patients who have been receiving renal-replacement therapy for more than 8 to 12 weeks, survival is better with combined liver–kidney transplantation than with liver transplantation alone.<sup>89,90,94</sup> Therefore, it has been proposed that patients receiving long-term renal-replacement therapy be treated with combined transplantation.

A recent analysis using results reported by the United Network for Organ Sharing (UNOS) was initiated to assess the benefit of combined liver–kidney transplantation.<sup>95</sup> In the MELD era — after matching for the donor's age, race, and cause of death and for the recipient's MELD score and dialysis status before transplantation — there was no significant difference in the 1-year rate of patient survival between the group of patients who underwent combined liver–kidney transplantation and the group that underwent liver transplantation alone (82.0% and 81.8%, respectively).<sup>89</sup>

Analysis of all patients who had been on dialysis before transplantation also showed no significant difference in patient survival between these two groups. However, in a matched, case-control analysis, among patients who had been on dialysis for longer than 3 months, an increase in the 1-year rate of patient survival was observed in the combined-transplantation group, as compared with the group that underwent liver transplantation alone (87.2% vs. 74.5%,  $P=0.02$ ). Among patients who had been on dialysis for longer than 3 months, the risk of liver-graft failure was also significantly reduced in the combined liver-kidney transplantation group, as compared with the group that underwent liver transplantation alone (84.5% vs. 70.8%,  $P=0.008$ ). The 1-year rate of kidney-graft survival after combined liver-kidney transplantation compared unfavorably with the rate after kidney transplantation alone (77.2% vs. 89.3%,  $P<0.001$ ). This decline in kidney-graft survival in the combined liver-kidney transplantation group persisted even among patients who had been on dialysis for longer than 3 months.

Since there are approximately 94,000 patients on the waiting list for kidney transplants in the United States, an argument could be made for waiting until after the liver transplantation to decide whether a kidney transplantation is needed, particularly in patients with the hepatorenal syndrome.<sup>95,96</sup> Of note, however, is the observation that combined liver-kidney allografts may offer protection against rejection in the kidney graft in highly sensitized, cross-match-positive recipients.<sup>97</sup>

Guidelines to determine when combined liver-

kidney transplantation is indicated have been proposed on the basis of current data. They include end-stage renal disease associated with cirrhosis and symptomatic portal hypertension or a hepatic venous pressure gradient of 10 mm Hg or higher, acute renal failure or the hepatorenal syndrome with a serum creatinine level of 2.0 mg per deciliter (177  $\mu\text{mol}$  per liter) or higher and treatment with dialysis for longer than 8 weeks, and liver failure and chronic kidney disease with a GFR below 30 ml per minute or more than 30% glomerulosclerosis or fibrosis in a renal-biopsy specimen.<sup>98</sup>

## SUMMARY

Renal failure is a very common, severe complication in patients with decompensated cirrhosis and is a risk factor for a poor outcome of liver transplantation. Recently introduced therapies have demonstrated efficacy in the prevention and management of the hepatorenal syndrome, a particularly severe form of renal failure characteristic of cirrhosis. Use of these therapies in patients awaiting liver transplantation may help improve the outcome after transplantation.

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