Review article: hepatorenal syndrome – definitions and diagnosis

R. MOREAU & D. LEBREC
Laboratoire d'Hémodynamique Splanchnique et de Biologie Vasculaire, INSERM U-481 and service d'Hépatologie, Hôpital Beaujon, Clichy, France

SUMMARY
Hepatorenal syndrome (HRS) is a severe complication of cirrhosis that develops in the final phase of the disease. Two types of HRS exist. Type 1 is defined by a rapid reduction of renal function and in type 2 HRS the reduction of renal function is slowly progressive. Type 1 HRS is diagnosed when the serum creatinine level increases by more than 50% of the baseline value to above 133 μmol/L. According to the International Ascites Club, HRS is defined by the presence of five criteria: (1) severe cirrhosis; (2) glomerular hypofiltration; (3) no other functional or organic causes; (4) failure of plasma volume expansion; (5) no proteinuria. Additional diagnostic criteria may be present. The diagnosis of HRS may be difficult in patients with severe cirrhosis. Other types of acute renal failure may occur. For example, ischaemic or toxic tubular necrosis or sepsis may cause renal failure in these patients. Furthermore, uncontrolled HRS may lead to ischaemic tubular necrosis; thus, these patients must be managed as soon as possible in an intensive care unit.

INTRODUCTION
Renal failure is characterized by the association of a decrease in glomerular filtration, perturbation of extracellular fluid volume, electrolyte and acid-base homoeostasis, and retention of nitrogenous waste from protein catabolism. Acute renal failure is thought to be common in patients with cirrhosis, but its exact incidence is unknown. Patients with cirrhosis are predisposed to acute renal failure following complications or the administration of drugs. Moreover, patients with cirrhosis may develop a specific acute renal failure called type 1 hepatorenal syndrome (HRS). HRS is a prerenal failure. There are two forms of HRS: type 1 is the severe and acute form, whereas type 2 is a moderate and chronic form. Prerenal failure is a preischaemic state; it may lead to ischaemic tubular necrosis when the reduction in blood flow is sufficient to result in the death of tubular cells.

Definitions
In patients with cirrhosis without renal impairment at admission, acute renal failure is diagnosed when the serum creatinine level increases by more than 50% of the baseline value or to above 133 μmol/L (1.5 mg/dL). In patients with pre-existing renal impairment, acute renal failure is diagnosed when serum creatinine increases by more than 50% above baseline. Acute renal failure resulting from renal hypoperfusion without renal cellular injury is called prerenal failure. Renal dysfunction due to obstruction of the urinary outflow tract is termed postrenal failure. Acute renal failure due to a primary intrarenal cause is called intrinsic renal failure. Intrinsic renal failure may be caused by either tubular necrosis, glomerulonephritis or interstitial nephritis.

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A recent multicentre retrospective study investigated 355 patients with cirrhosis and acute renal failure. A total of 206 patients (58.0%) had prerenal failure, including 71 who had type 1 HRS; 148 (41.7%) had acute tubular necrosis; ischaemic tubular injury occurred in 139 cases. Only one patient (0.3%) had
postrenal failure. In this study, there was no case of acute renal failure due to acute glomerulonephritis, confirming that this is an uncommon cause of acute renal failure in cirrhosis. Together, these findings indicate that renal hypoperfusion can explain more than 90% of cases of cirrhosis-associated acute renal failure.

**Causes of prerenal failure**

Prerenal failure may be rapidly reversible if the underlying cause is corrected. Hypovolaemia (induced by haemorrhage or gastrointestinal or renal fluid losses) associated with shock or arterial hypotension is one cause of prerenal failure. There is a short delay between haemorrhage and the resulting renal dysfunction.

Acute upper gastrointestinal bleeding is a common complication of cirrhosis. Studies investigating acute upper gastrointestinal bleeding in patients with cirrhosis show that 10–20% of patients have hypovolaemic shock at inclusion. Prerenal failure is expected to occur in patients with cirrhosis and gastrointestinal bleeding. However, the incidence of haemorrhage-induced renal failure is unknown because the immediate impact of shock or arterial hypotension on renal function was not an end-point in most studies. A retrospective study has shown that 5% of patients with cirrhosis hospitalized for acute upper gastrointestinal bleeding have early renal failure that lasts less than 7 days after index bleeding.

Finally, it should be emphasized that patients admitted for haemorrhage may develop prerenal failure due to other causes. Indeed, acute gastrointestinal bleeding predisposes patients with cirrhosis to bacterial infections which may induce prerenal failure or acute tubular necrosis. On the other hand, a significant proportion of patients with cirrhosis admitted for acute upper gastrointestinal bleeding have received nonsteroidal anti-inflammatory drugs (NSAIDs) in the week preceding bleeding which may cause prerenal failure.

Hypovolaemia and subsequent renal failure may be a result of vomiting or diarrhoea. Diuretic treatment to mobilize tense or large ascites may induce prerenal failure. Glycosuria is a cause of renal fluid loss, which may lead to renal dysfunction.

Severe sepsis is defined as the association of sepsis and acute organ dysfunction. In the general population, patients with severe sepsis frequently develop prerenal failure as a result of septic shock. Renal vasoconstriction plays a role in sepsis-induced prerenal failure. Since decreased intravascular volume is a mechanism of sepsis-induced renal vasoconstriction, prerenal failure may be sensitive to fluid replacement. Patients with cirrhosis are susceptible to bacterial infections, in particular spontaneous bacterial peritonitis (SBP). Septic shock and subsequent renal impairment occurs in 10% of patients with SBP. At the onset of SBP, 20–40% of patients have renal failure without shock. However, studies on SBP provide little information on the cause of this renal dysfunction.

A total of 5% of patients hospitalized for acute upper gastrointestinal haemorrhage and 30% of those admitted for SBP develop type 1 HRS during hospitalization. Type 1 HRS also occurs in 10% of patients with ascites treated by total paracentesis and in 25% of patients with severe acute alcoholic hepatitis.

Renal failure in patients with HRS is explained by marked renal vasoconstriction. However, the mechanisms of renal vasoconstriction have not yet been fully elucidated. In type 1 HRS, there is a rapid increase in serum creatinine. At diagnosis of HRS, there is no recent history of circulatory shock, increased intestinal or renal fluid loss or nephrotoxic drug administration. In addition, there is no evidence for ongoing bleeding or sepsis. Finally, renal failure does not improve following administration of plasma expanders and discontinuation of diuretics.

The intravenous administration of iodinated radiocontrast agents may cause prerenal failure by inducing renal vasoconstriction. There are three important risk factors for radiocontrast-induced acute renal failure: chronic renal failure, diabetes and decreased effective arterial blood volume. Nonazotemic patients with cirrhosis and ascites have decreased effective arterial blood volume. They may also have ‘chronic renal impairment’ or diabetes. Since patients with cirrhosis often receive radiocontrast agents, they may develop prerenal failure due to these agents. However, preliminary results show that radiocontrast agents did not impair renal plasma flow and glomerular filtration rate (GFR) in patients with cirrhosis. It should be noted that these results were obtained in a small series of patients, however, one-third of whom did not have ascites. More information is needed on the effects of radiocontrast agents on renal function in patients with cirrhosis.

Drugs such as nitrovasodilators or substances inhibiting the action of angiotensin II that are used in the treatment of portal hypertension may induce renal dysfunction in patients with cirrhosis and ascites. It has been shown that acute administration of the nitrovasodilator 5-mononi-
trate induced decreases in effective arterial blood volume, arterial pressure, renal plasma flow and GFR. However, other studies did not show any increase in the incidence of prerenal failure in patients receiving long-term administration of 5-mononitrate isosorbide. Inhibition of angiotensin II action by inhibiting the angiotensin-converting enzyme with captopril or blocking type 1 angiotensin receptors with losartan or irbesartan may induce marked arterial hypotension and vasodilation of postglomerular arterioles, causing prerenal failure in patients with cirrhosis and ascites.

**INTRINSIC RENAL FAILURE**

*Acute tubular necrosis*

Injury to the renal tubules may be ischaemic or toxic in origin. The mechanisms of renal failure are very similar in ischaemic and toxic tubular necrosis. The course of acute tubular necrosis can be divided into the initiation, maintenance and recovery phases. All causes of prerenal failure may lead to ischaemic tubular injury. Administration of aminoglycoside antibiotics is thought to be the most common cause of toxic tubular necrosis in patients with cirrhosis. The incidence of radiocontrast agent-induced tubular necrosis is unknown in patients with cirrhosis. Ischaemia and toxins may combine to cause renal failure in severely ill patients.

*Acute glomerulonephritis*

Some cases of infectious acute glomerulonephritis have been reported in patients with cirrhosis. The site of infection was the oropharynx, the skin or the endocardium. In patients with cirrhosis due to hepatitis C virus, cryoglobulinaemic membranoproliferative glomerulonephritis is a rare cause of acute renal failure. Macroscopic haematuria associated with acute renal failure may occur in certain patients with alcohol-induced cirrhosis and IgA nephropathy. In these patients, acute renal failure is due to tubular necrosis and not caused by glomerular lesions. Tubular necrosis may be caused by a direct toxic insult to the tubules by red blood cells that are present in the tubular lumen.

**DIAGNOSIS**

Since acute renal failure mainly occurs in patients with decompensated cirrhosis, diagnosis of chronic liver disease is generally easy. In contrast, the diagnosis of the cause of renal failure may be difficult.

**Clinical evaluation**

A history of exposure to nephrotoxic medications, a recent history of angiography, and physical findings of gastrointestinal haemorrhage or suggesting sepsis all provide important diagnostic information. Anuria suggests prerenal failure. The existence of arterial hypertension, which is an unexpected finding in cirrhosis, suggests glomerulonephritis. Macroscopic haematuria should suggest IgA nephropathy as a cause. Purpura, arthralgia, weakness, Raynaud’s syndrome, or leg ulcers suggest cryoglobulinaemia.

**Urine evaluation**

Diagnostic information may be obtained from the urinalysis. For example, pigmented granular casts are typical of ischaemic and toxic acute renal failure and red cell casts typical of glomerulonephritis. Patients with renal failure due to acute or subacute glomerulonephritis have significant proteinuria (around 3 g/day). In contrast, proteinuria is absent or moderate in other causes of acute renal failure.

Urine indices (urine osmolality, urinary sodium concentration and fractional excretion of sodium) may help distinguish prerenal failure (including type 1 HRS) from tubular necrosis. The tubular ability to reabsorb sodium and to concentrate urine is preserved in prerenal failure and impaired in tubular necrosis. Thus, patients with prerenal failure have low urinary sodium concentrations (below 20 mmol/L) and elevated urine osmolality (higher than 500 mOsm/kg). In contrast, patients with tubular necrosis have high urinary sodium concentrations (above 40 mmol/L) and urine osmolality below 350 mOsm/kg. However, the urinary sodium concentration may be low early in the course of certain processes that lead to tubular necrosis such as sepsis, exposure to radiocontrast agents or obstruction. In addition, some cases of HRS with elevated urinary sodium concentrations have been reported.

These findings indicate that in clinical practice, it is difficult to differentiate type 1 HRS from other causes of acute renal failure. The International Ascites Club has suggested that five major criteria be present to confirm the diagnosis of HRS: (1) severe cirrhosis; (2) glomerular hypofiltration; (3) no other functional or organic...
causes; (4) failure of plasma volume expansion; (5) no proteinuria. Of these, one of the most important is the lack of improved renal response following optimization of intravascular volume in patients with type 1 HRS. Indeed, although there is an increase in GFR following fluid replacement in most causes of prerenal failure, GFR continues to rise despite fluid challenge in patients with type 1 HRS. On the other hand, because patients with acute tubular necrosis do not respond to fluid replacement, a lack of renal response to fluid challenge does not differentiate HRS from tubular necrosis. This is a limitation of the International Ascites Club criteria. It should be emphasized that patients with type 1 HRS have improved renal function following administration of vasoconstrictors such as terlipressin (Glypressin\(^{7}\)), whereas vasoconstrictor therapy does not improve renal function in patients with acute tubular necrosis. Thus, the renal response to vasoconstrictor agents might be used to differentiate HRS from tubular necrosis.

**Blood tests**

The presence of antibodies to hepatitis C virus and hepatitis C virus RNA, high concentrations of cryoglobulins, positive rheumatoid factor assays, and low concentrations of complement suggest hepatitis C virus-associated cryoglobulinaemic glomerulonephritis.

**Evaluation of obstruction**

Early diagnosis of obstruction is important because most cases can be treated and a delayed therapy can result in irreversible renal injury.\(^1\) Bladder catheterization should be performed initially if bladder neck obstruction is suspected. Renal ultrasonography is the test of choice to exclude the diagnosis of obstruction at the ureters or above (specificity: 93%). A nondilated collecting system does not necessarily exclude obstruction, e.g. in patients with hypovolaemia.

**Renal biopsy**

Renal biopsy is generally not necessary in the diagnosis of acute renal failure.\(^1\) However, when in-depth clinical assessment and laboratory and radiological investigations have ruled out prerenal and postrenal failure and suggest a diagnosis of an intrinsic renal disorder other than acute tubular necrosis, a kidney biopsy may determine the diagnosis and treatment.\(^1\) Percutaneous renal biopsy may be contraindicated in patients with cirrhosis and coagulation disorders and transjugular renal biopsy has been shown to be a safe procedure in these patients.\(^20\) In addition to kidney biopsy, a transjugular liver biopsy can confirm the diagnosis of cirrhosis.

**CONCLUSION**

In patients with cirrhosis, acute renal failure is mainly due to prerenal failure and tubular necrosis. However, except for type 1 HRS, little is known about the incidence, natural course and treatment of the different causes of cirrhosis-associated acute renal failure. Studies are needed, in particular for severe sepsis, radiocontrast-induced nephrotoxicity, and renal-replacement therapies, given that renal transplantation is not an option except when combined with liver transplantation.

**REFERENCES**