Renal Failure in Patients with Cirrhosis

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ASSESSMENT OF RENAL FUNCTION IN PATIENTS WITH CIRRHOSIS

Clinical measures tend to overestimate renal function in patients with cirrhosis, including laboratory values (serum creatinine and blood urea nitrogen levels), creatinine clearance calculated from timed urine collection, estimated creatinine clearance (using the Cockcroft-Gault formula), and estimated glomerular filtration rate (GFR). As a result, renal failure is often underdiagnosed in cirrhosis. Predictive equations (Modification of Diet in Renal Disease [MDRD], Cockcroft-Gault) can only be used when renal function is stable (steady state) and should not be used in acute renal failure, when creatinine is rising.\textsuperscript{1}

Creatinine is produced in patients with cirrhosis at half the normal rate.\textsuperscript{2} Possible reasons are malnutrition, low muscle mass, and impaired synthesis of creatine in cirrhotic liver.\textsuperscript{3} Lower serum creatinine values lead to overestimation of renal function by predictive equations. As renal function declines in cirrhosis, tubular secretion of creatinine increases, which can result in higher creatinine clearance calculated from timed urine collection compared with true GFR.\textsuperscript{4}

In 13 patients with cirrhosis and mean creatinine values of 1.1 ± 0.1 mg/dL, mean GFR by inulin clearance was 32 ± 4 mL/min, indicating that “normal” creatinine is a poor predictor of normal renal function.\textsuperscript{5} In the same group of patients, creatinine
clearance calculated from timed urine collection overestimated GFR by 96%, and use of the Cockcroft-Gault formula overestimated GFR by 208%.

A study of 1447 patients with cirrhosis about to undergo liver transplantation compared Cockcroft-Gault formula and 4-, 5-, and 6-variable MDRD equations with GFR measured by $^{125}$I-iothalamate clearance. In the subgroup with renal dysfunction (GFR < 40 mL/min), mean GFR was 22.6 ± 11.1 mL/min. Mean estimated creatinine clearance (Cockcroft-Gault) was 46.1 ± 27.1 mL/min, and mean estimated GFR (by 6-variable MDRD equation) was 39.0 ± 26.2 mL/min, grossly overestimating $^{125}$I-iothalamate GFR.

In some reports cystatin C–based estimates predict GFR somewhat better than creatinine-based equations in patients with cirrhosis. Evidence is insufficient to recommend cystatin C over other methods; however, this measurement is not available for routine use in clinical practice.

Creatinine measurement can be affected by hyperbilirubinemia. A study measured serum creatinine in 158 patients using 4 different creatinine assays. Interassay agreement was poor and Model for End-Stage Liver Disease (MELD) score variability was high, especially with high bilirubin concentrations (> 400 μmol/L). The kinetic Jaffe method, most commonly used in the United States, is susceptible to bilirubin interference, which can lead to falsely low serum creatinine values when bilirubin concentration is 10 mg/dL or higher. To avoid this problem, the enzymatic method should be used to measure serum creatinine when the bilirubin level is very high.

RENAL FAILURE AS A PROGNOSTIC INDICATOR IN CIRRHOSIS

Renal failure in cirrhosis confers increased risk of death. A study of 231 patients was conducted to devise a prediction model for 3-month mortality after placement of a transjugular intrahepatic portosystemic shunt. Multivariate analysis showed increased creatinine to be one of the factors (along with bilirubin and international normalized ratio) independently associated with higher mortality. A 100% rise in serum creatinine increased the risk of death 1.94-fold. Findings of this study led to the development of the MELD score, which was subsequently validated in a cohort of liver transplantation candidates and was adopted by the United Network for Organ Sharing (UNOS) to allocate donor livers based on severity of disease of the potential recipient. Thus, patients with higher creatinine or those requiring renal replacement therapy (RRT) have higher priority to receive liver allograft.

Development of HRS significantly shortens survival in patients with cirrhosis. A study of 105 patients with HRS assessed prognostic factors and outcome in patients with cirrhosis and HRS. In a multivariate analysis, type of HRS (type 1 vs type 2) and MELD score were the only independent prognostic factors. All patients with type 1 HRS had MELD scores of 20 or greater, and their median survival was 1 month. Survival with type 2 HRS was dependent on MELD score: patients with MELD scores of 20 or greater survived for a median of 3 months; for those with MELD scores lower than 20, median survival was 11 months.

Development of renal failure before liver transplantation has a negative impact on posttransplant outcomes. In a large retrospective review of UNOS database for adults undergoing orthotopic liver transplantation (OLT), moderate to severe renal failure at the time of OLT was associated with significantly lower short-term and long-term graft and patient survival rates.

CLASSIFICATION

Based on etiology, renal failure is divided into prerenal, renal, and postrenal categories. Renal failure is caused by a variety of factors, some specific to cirrhosis (eg,
hepatorenal syndrome), and others affecting the general patient population. Common causes of renal failure in patients with cirrhosis are listed below.

**PRERENAL**

- Vomiting, diarrhea, nasogastric suction
- Excessive diuresis
- Hemorrhage
- Circulatory dysfunction following large-volume paracentesis (LVP)
- HRS
- Abdominal compartment syndrome
- Medications causing hemodynamic changes, for example, nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors

**INTRINSIC RENAL**

- Glomerulonephritis
- Membranoproliferative glomerulonephritis (MPGN), cryoglobulinemia (hepatitis C virus [HCV]-related)
- Membranous nephropathy (hepatitis B virus [HBV]-related)
- IgA nephropathy
- Interstitial nephritis
- Acute tubular necrosis (ATN):
  - Toxic ATN, for example, due to aminoglycoside or radiocontrast exposure
  - Ischemic ATN, for example, in the setting of septic or hemorrhagic shock

**POSTRENAL**

- Benign prostatic hyperplasia
- Neurogenic bladder
- Nephrolithiasis
- Papillary necrosis in alcoholic liver disease

An episode of acute renal failure may be reversible, but renal function may remain diminished over the long term, and patients develop chronic kidney disease.

A suggested diagnostic approach to renal failure in cirrhosis is provided in [Fig. 1](#).

**Prerenal Causes**

Excessive diuresis, vomiting, diarrhea, poor oral intake, and gastrointestinal hemorrhage may lead to extracellular fluid volume depletion and renal failure. In cirrhosis and portal hypertension, effective arterial blood volume (EABV) may be decreased, leading to renal hypoperfusion and failure even in the presence of gross extracellular fluid overload.

**Diuretic Use**

Extracellular fluid overload develops in patients with cirrhosis and portal hypertension. Increased local production of vasodilatory substances, mostly nitric oxide, stimulates splanchnic vasodilation. Decreased systemic vascular resistance, arterial hypotension, and low EABV activate the renin-angiotensin-aldosterone system, the
sympathetic nervous system,19 and vasopressin,20 leading to salt and water retention. Diuretics, usually a combination of furosemide and spironolactone, are the mainstay of therapy in volume-overloaded patients who are diuretic sensitive. Excessive or too rapid diuresis can lead to volume depletion, causing renal failure.

Patients with peripheral edema can tolerate more rapid diuresis than can patients with ascites alone. A study of 14 patients with cirrhosis treated with a combination of oral diuretics showed that edema fluid was preferentially mobilized. Patients with edema did not develop renal impairment or a decrease in plasma volume despite a mean negative fluid balance of 1.79 kg/d.21 Patients with ascites, but no edema at enrollment, were prone to a decrease in plasma volume and to the development of reversible decline in renal function; mean negative balance was 1.27 kg/d. Extrapolating from the findings of this study, it is safe to achieve rapid diuresis (≤ 2 L/d) when edema is present. In patients with ascites but no edema, negative balance should be kept at 750 mL/d or less.

**Large-Volume Paracentesis**

With progressive liver disease and increasing activity of endogenous neurohormonal systems, sodium avidity rises. Patients develop diuretic resistance, which is defined

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Fig. 1. Suggested diagnostic approach to renal failure in a patient with cirrhosis. ACE-I, angiotensin-converting enzyme inhibitor; ATN, acute tubular necrosis; Cr, creatinine; CT, computed tomography; ECF, extracellular fluid; GN, glomerulonephritis; LVP, large-volume paracentesis; NSAID, nonsteroidal antiinflammatory drug; RBC, red blood cell.
as the inability to achieve weight loss despite adherence to dietary salt restriction and maximum-dose diuretics.\textsuperscript{22} In this setting, LVP is performed serially to alleviate discomfort and other problems associated with rapidly accumulating ascites. Sometimes LVP is performed in patients who are sensitive to diuretics to quickly relieve tense ascites. Following LVP, some patients develop a further decrease in intravascular volume, termed postparacentesis circulatory dysfunction, which may cause renal failure.

One study assessed the effect of volume expansion with albumin on postparacentesis circulatory dysfunction. One hundred five patients presenting with tense ascites were randomly assigned to undergo paracentesis (4–6 L/d until resolution of ascites) with or without albumin infusion (40 g) after each procedure.\textsuperscript{23} Diuretic resistance was not a prerequisite to enter the study. Patients not receiving albumin developed a marked elevation in plasma renin activity and aldosterone level, indicating impairment in systemic hemodynamics. There was also a rise in blood urea nitrogen and a reduction in serum sodium with no albumin replacement. These changes were not seen in the group that received albumin infusions. No difference was found in survival between study groups. Until further evidence is available, intravenous albumin (10 g/L of fluid removed) may be considered for LVP but is not necessary for single paracentesis of less than 5 L.\textsuperscript{24}

Hepatorenal Syndrome

Typically, HRS develops in advanced liver disease, when other complications of cirrhosis are already present, including ascites and hyponatremia.\textsuperscript{25} Among patients with ascites, HRS develops in about 20\% and 40\% of the patients, at 1 and 5 years, respectively.\textsuperscript{25}

Progressive liver disease causes a further decrease in systemic vascular resistance and activation of compensatory neurohormonal systems. Rising renal vasoconstriction and decreasing GFR culminates in HRS.\textsuperscript{26} Relatively low and insufficient cardiac output may contribute to renal hypoperfusion in patients with cirrhosis who have HRS.\textsuperscript{27} HRS is a functional disorder, without underlying structural kidney damage.

The most common trigger for the development of type-1 HRS is bacterial infection, mainly spontaneous bacterial peritonitis (SBP). According to a study of 252 SBP episodes in patients with cirrhosis, renal failure developed in 33\% of the episodes, and had a progressive course in 14\%.\textsuperscript{28}

Diagnosis

Diagnosis of HRS is based on exclusion of other types of renal failure. Diagnostic criteria for HRS in cirrhosis were updated in a recent meeting of the International Ascites Club.\textsuperscript{29}

- Cirrhosis with ascites
- Serum creatinine greater than 1.5 mg/dL
- No improvement in serum creatinine (to $\leq 1.5$ mg/dL) after 2 days or more of diuretic withdrawal and volume expansion with albumin (1 g/kg/d, up to 100 g/d)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria greater than 500 mg/d, microhematuria greater than 50 red blood cells per high-power field or abnormal renal ultrasonographic findings

The previous definition\textsuperscript{22} was modified to allow the diagnosis of HRS when renal failure occurs in the setting of bacterial infection (eg, SBP) without shock, and hence
facilitating earlier initiation of specific therapies for HRS without waiting for complete recovery from the infection. Creatinine clearance is no longer recommended for the diagnosis of HRS. The revised guidelines also recommend albumin over 0.9% saline as an intravascular volume expander. Minor diagnostic criteria, including oliguria and urine Na\(^+\) values less than 10 mEq/L, were considered nonessential and therefore were eliminated.

Based on severity of renal impairment, HRS is arbitrarily divided into type 1 and type 2. Type 1 HRS is defined as rapidly progressive renal failure (doubling of the initial serum creatinine to a level > 2.5 mg/dL in less than 2 weeks). Type 2 HRS is characterized by moderate renal failure (creatinine 1.5–2.5 mg/dL) with a steady or slowly progressive course. It is often associated with refractory ascites.

**Prevention**

A study of 126 patients assessed the role of intravenous albumin in preventing HRS in the setting of SBP.\(^{30}\) Patients were assigned to receive treatment either with cefotaxime alone or a combination of cefotaxime plus intravenous albumin infusion at a dose of 1.5 g/kg within 6 hours after randomization and repeat infusion at a dose of 1 g/kg on day 3. Progressive renal failure developed in 33% of patients in the cefotaxime group compared with 6% in the group receiving a combination of cefotaxime and albumin, despite rapid resolution of infection in both groups. In-hospital mortality was 29% in the cefotaxime group, as compared with 10% in the cefotaxime and albumin group. Addition of albumin significantly decreased plasma renin activity, compared with cefotaxime alone. In a subgroup of patients with bilirubin less than 4 mg/dL and creatinine less than 1 mg/dL, the risk of renal failure was very low, regardless of treatment strategy.

A randomized trial of 68 cirrhotic patients at high risk for HRS-1 and SBP compared daily norfloxacin to placebo for primary prophylaxis of SBP.\(^{31}\) In addition to improved mortality and lower incidence of SBP, norfloxacin group was also found to have lower incidence of HRS at 1 year (28% vs 41%).

**Treatment**

General measures include withdrawal of diuretics and intravascular volume expansion with albumin to rule out prerenal component and discontinuation of nephrotoxic medications, including NSAIDs and aminoglycosides.

Numerous reports have been published on treating type-1 HRS patients with vasoconstrictors such as combined midodrine and octreotide,\(^{32}\) terlipressin (a synthetic vasopressin analog),\(^ {33,34}\) and norepinephrine\(^ {35}\) to counteract splanchnic vasodilation, usually in combination with intravenous albumin. Although some of these reports demonstrate improvement in renal function with vasopressors, no clear survival benefit has been shown. Terlipressin is not currently available in the United States. It is a potential concern that vasopressor-induced improvement in creatinine may decrease MELD scores and delay liver transplantation in prospective recipients. Several sources\(^ {36,37}\) provide detailed summaries of previous studies of vasopressors in hepatorenal syndrome.

RRT is initiated for standard indications in patients with HRS (volume overload, electrolyte and acid-base disturbances).

The greatest chance to recover renal function and improve overall survival in patients with HRS is successful liver transplantation. In one retrospective review of HRS patients undergoing OLT, GFR increased from 19.9 ± 3.6 mL/min preoperatively to 32.5 ± 3.1 mL/min at 6 weeks and 45.9 ± 5.5 mL/min at 1 year following OLT.\(^ {38}\) Despite overall improvement in renal function in patients with HRS, 10% of HRS
patients developed end-stage renal disease (ESRD) compared with 0.8% non-HRS patients posttransplant. Although the actuarial 1- and 2-year survival rates were 76.6% in HRS patients following OLT, they were still less when compared with patients without HRS (1- and 2-year survival rates of 87.2% and 82.1%, respectively).

**Abdominal Compartment Syndrome**

Abdominal compartment syndrome should be suspected in a patient with cirrhosis who has massive ascites and decreased urine output. It is defined as sustained intra-abdominal pressure (IAP) of greater than 20 mm Hg, associated with new organ dysfunction. Normal IAP in critically ill patients is 5 to 7 mm Hg. Renal impairment in patients with increased IAP occurs due to renal vein compression and arterial vasoconstriction, caused by activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system.

Severity of abdominal distention observed on physical examination does not aid in the diagnosis of abdominal compartment syndrome. In one study, IAP was assessed by physical examination in 128 postoperative patients in the intensive care unit. Using transvesicular pressure measurement as a reference, the positive predictive value of physical examination to detect IAP greater than 18 mm Hg was 45.2%, and the negative predictive value was 88.6%. Thus, transvesicular pressure measurements are required to make the diagnosis. If abdominal compartment syndrome is suspected, LVP should be performed.

**Intrinsic Renal Causes**

Several glomerular diseases are associated with cirrhosis: IgA nephropathy, membranous nephropathy, and MPGN. HBV and HCV infections are most strongly linked to the development of membranous nephropathy and MPGN, respectively, and may occur in the absence of cirrhosis. Glomerular disease should be suspected in patients with hypertension, proteinuria, and glomerular hematuria (dysmorphic red blood cells and red blood cell casts), although in many cases glomerular changes are clinically silent.

**IgA Nephropathy**

Glomerular IgA deposits are frequently found in patients with cirrhosis, but clinically evident renal impairment is uncommon. In an autopsy series, predominant mesangial IgA deposits were found in 36% of 75 liver cirrhosis cases. In another study, 30 patients with HCV cirrhosis underwent intraoperative renal biopsies during liver transplantation. Seven of them had mesangial proliferation and IgA deposits, but only 2 had elevated serum creatinine levels with subnephrotic proteinuria, and only 1 patient had hematuria.

Pathogenesis of IgA nephropathy in cirrhosis remains poorly understood. Levels of circulating IgA are increased in the serum of patients with alcoholic liver disease compared with healthy controls. In vitro studies of lymphocytes from patients with alcoholic cirrhosis show that IgA synthesis may be increased. Circulating IgA levels are elevated in patients with cirrhosis, with increased fraction of polymeric IgA, decreased catabolism of polymeric IgA, and disproportionately higher rise in IgA2 compared with IgA1. IgA2 is cleared mainly through the hepatic asialoglycoprotein receptor, but only a small fraction of IgA1 is cleared through this pathway. This may account for the higher proportion of circulating IgA2 compared with IgA1 in patients with cirrhosis. IgA1 is the predominant form in renal deposits. IgA nephropathy in patients with cirrhosis can manifest as azotemia, hematuria, subnephrotic-range proteinuria, or overt nephrotic syndrome.
No study has specifically addressed the treatment of IgA nephropathy in cirrhosis. In several case reports of cirrhosis, portal hypertension, and IgA nephropathy, proteinuria decreased after treatment with propranolol was started, possibly due to a favorable effect on portal hypertension.\textsuperscript{52,53}

**Glomerulonephritis in Patients with Cirrhosis and Hepatitis B or C Infection**

**Hepatitis C virus infection**

Membranoproliferative glomerulonephritis with mixed essential cryoglobulinemia is most strongly, and likely causally, associated with HCV infection.\textsuperscript{55,56} Membranous nephropathy,\textsuperscript{57,58} focal segmental glomerulosclerosis,\textsuperscript{59} and IgA nephropathy\textsuperscript{45} have also been reported in the setting of HCV infection.

Glomerular changes were assessed in an autopsy series of 188 patients with HCV infection.\textsuperscript{54} A total of 83.5\% of cases had histologic evidence of liver cirrhosis. MPGN was found in 11.2\% of all autopsy cases, membranous nephropathy in 2.7\%, mesangio proliferative glomerulonephritis in 17.6\%, mesangial expansion without proliferation in 23.4\%, and normal glomeruli in the remaining 45.2\% of cases. In the presence of cirrhosis, glomerulonephritis was found in 59.2\% of the patients, in contrast to 32.3\% among the patients without cirrhosis. Overall, 12.2\% of patients had abnormal urinalysis findings (hematuria or proteinuria) within 1 year before death. Urinalysis findings were abnormal in 42\% of patients with MPGN.

In another report, 30 patients had intraoperative kidney biopsy during liver transplantation for cirrhosis due to HCV infection.\textsuperscript{45} Twenty-five of them had evidence of immune complex glomerulonephritis: 12 had MPGN type 1, 7 had IgA nephropathy, and 6 had mesangial glomerulonephritis. Fifteen of the 25 had normal urinalysis findings and no proteinuria by quantitative estimates.

Most patients with mixed essential cryoglobulinemia have evidence of HCV infection. HCV virions and immune complexes are found in high concentrations in the cryoprecipitates.\textsuperscript{56} Glomerular HCV protein deposits were detected in 67\% of cryoglobulinemic MPGN biopsy specimens, suggesting a possible causal role of HCV infection.\textsuperscript{60}

Mixed essential cryoglobulinemia is a systemic vasculitis that can present with systemic symptoms, palpable purpura, and kidney disease. Patients have detectable cryoglobulins and rheumatoid factor as well as low C3 and C4 levels. Renal involvement manifests as hypertension, azotemia, proteinuria, and nephritic sediment.

The optimal strategy for the treatment of glomerular disease associated with HCV infection in cirrhosis is unknown. Most treatment reports have focused on patients without cirrhosis.

A prospective study randomly assigned 52 patients with HCV-associated type II cryoglobulinemia either to receive interferon alfa or to a control group.\textsuperscript{61} Patients with decompensated liver disease were excluded. Fifteen of 25 patients in the treatment group, but none of the control subjects, had undetectable HCV viral loads at the end of the 24-week treatment period. Virologic response was associated with decreases in cryoglobulins, rheumatoid factor, and serum creatinine and an increase in complement levels.

Fourteen patients with MPGN and HCV infection (mostly chronic active hepatitis on liver biopsy) received interferon alfa for 6 to 12 months.\textsuperscript{62} Among virologic responders, there was a significant fall in proteinuria, but no improvement in serum creatinine values.

In another report, 18 patients with HCV infection, mixed cryoglobulinemia, nephrotic-range proteinuria, and biopsy-proven MPGN were treated with pegylated interferon alfa and ribavirin for a mean of 18 months.\textsuperscript{63} HCV viremia clearance was
achieved in 12 of 18 patients and was associated with a reduction in cryoglobulinemia and proteinuria, but serum creatinine levels remained stable regardless of virologic response.

Patients with decreased GFR are at risk for hemolytic anemia when taking ribavirin, and this drug should generally be avoided when creatinine clearance is less than 50 mL/min.

In a recent report, rituximab was successfully used to treat type II cryoglobulinemia and MPGN in patients with HCV infection.

**Hepatitis B virus infection**

Hepatitis B virus infection is associated with membranous nephropathy, MPGN, and polyarteritis nodosa. The frequency of HBV-associated glomerulonephritis is greater in endemic areas and may be related to more frequent HBV infection in childhood, leading to a chronic carrier state. Renal deposition of HBV antigens, including HBsAg and HBeAg, suggests an etiologic role of HBV infection in the development of glomerular disease.

Membranous nephropathy often presents as nephrotic-range proteinuria or nephrotic syndrome. Biopsy is required to make the diagnosis. Spontaneous remissions are frequent with HBV-associated membranous nephropathy in children, but the disease has a more progressive course in adults. In a report from China, 21 adult patients with HBV-associated membranous nephropathy were followed up for a mean of 60 months. Progressive renal failure was seen in 29% of the patients, and 10% required hemodialysis at the end of the follow-up.

No randomized clinical trials have been conducted on the treatment of HBV-associated renal disease. Several retrospective reports of antiviral therapy in this setting are presented here. There are no data specifically addressing treatment of HBV-associated glomerular disease in cirrhosis.

In one report, 15 patients with HBV infection and glomerulonephritis (membranous nephropathy or MPGN) were treated with interferon alfa for 6 weeks. Eight patients had a long-term virologic response including disappearance of HBeAg and HBV DNA. Of the responders, 7 showed a gradual improvement in proteinuria during follow-up. All responders had membranous nephropathy. In contrast, the 7 nonresponders continued to have signs of active renal disease; in 1 case there was progression to ESRD. Four of 7 nonresponders had MPGN.

In another report, 10 patients with HBV infection and membranous nephropathy were treated with lamivudine. Outcomes of this report were compared with outcomes in 12 historical controls that had not received antiviral therapy. Blood pressure was well controlled in both groups. Only 1 patient in the treatment group had sonographic evidence of cirrhosis. Lamivudine was associated with significant improvement in proteinuria and clearance of HBsAg. Three-year renal survival was 100% in the antiviral treatment group and 58% in the control group.

**Acute Tubular Necrosis**

ATN develops in response to nephrotoxic exposures (eg, aminoglycosides, radiocontrast media exposure) or ischemic insult (eg, septic or hemorrhagic shock). Classically, ATN is characterized by acute renal failure following insult, decreased tubular sodium avidity (FeNa > 2%), and muddy-brown casts on microscopic examination of urinary sediment. However, occasionally patients with HRS may have elevated urinary Na⁺, and conversely, as a result of high sodium avidity, cirrhotic patients with ATN may have low urinary Na⁺.
**Postrenal Causes**

Common causes of obstructive uropathy include benign prostatic hypertrophy, neurogenic bladder, and kidney stones. In some reports, renal papillary necrosis was associated with alcoholic liver disease. Renal imaging (ultrasound, CT scanning) can help detect hydronephrosis or urinary retention. Treatment of renal failure should focus on relieving obstruction.

**Medications**

**Nonsteroidal antiinflammatory drugs**

Renal perfusion in patients with liver cirrhosis is highly dependent on vasodilatory effects of prostaglandins, especially prostaglandin E2 and prostacyclin. NSAIDs inhibit synthesis of prostaglandins and may cause a transient decrease in GFR and impairment in sodium and water excretion in patients with cirrhosis. NSAIDs can also cause ascites to become resistant to diuretics. For these reasons, the use of NSAIDs should generally be avoided in patients with liver cirrhosis.

**Inhibitors of the renin-angiotensin-aldosterone system**

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be used with caution in patients with cirrhosis and are rarely used in patients with advanced liver disease because they may cause hypotension. Angiotensin II helps maintain GFR in cirrhotic patients with decreased renal perfusion by mediating efferent arteriolar constriction. ACE inhibitors or angiotensin receptor blockers, even at low doses that have no effect on systemic blood pressure, may cause a significant reduction in GFR and worsening of sodium retention in patients with cirrhosis.

**Aminoglycosides**

Aminoglycoside antibiotics are a well-known cause of toxic tubular injury. Clinical records of 214 patients receiving gentamicin or tobramycin were reviewed, and liver disease was found to be one of the risk factors of renal failure with aminoglycoside use. In another retrospective case-control study of US veterans with cirrhosis, aminoglycoside use was strongly associated with acute renal failure.

**RENAL REPLACEMENT THERAPY IN CIRRHOSIS**

Patients with advanced cirrhosis and renal failure undergoing hemodialysis are prone to intradialytic hypotension due to decreased EABV and higher risk of bleeding with anticoagulation. Despite difficulties and high patient mortality, RRT is an important bridge to liver transplantation. According to 1 retrospective review of 102 liver transplant candidates undergoing acute RRT, 35% survived to receive liver transplant. The 1-year mortality of patients requiring RRT before liver transplantation, however, was 30%, compared with 9.7% for other liver recipients.

Peritoneal dialysis may be better tolerated hemodynamically and no anticoagulation is required. In addition, ascites fluid may be directly removed via peritoneal dialysis catheter, obviating the need for LVP. Potential concerns include higher incidence of peritonitis, protein loss, and bleeding during catheter insertion. In 1 report, 9 patients with ESRD, chronic liver disease, and ascites were initiated on peritoneal dialysis. No complications occurred from catheter insertion, peritonitis rates were similar to patients on peritoneal dialysis without cirrhosis, and serum albumin levels remained stable in most patients. Another report comparing peritoneal dialysis outcomes in 21 cirrhotic patients and 41 patients without cirrhosis did not show a significant
difference in the rate of peritonitis. Serum albumin remained steady in patients with cirrhosis. Five-year patient and technique survival rates were similar in both groups.

**Simultaneous Liver-Kidney Transplantation**

Pretransplant renal function is a strong predictor of both short- and long-term survival in liver transplant recipients. To improve prognosis in patients with dual organ failure, simultaneous liver-kidney transplantation (SLK) should be considered. A recent consensus conference addressed the complex issue of SLK. The following groups are granted automatic approval for SLK transplantation:

- Patients with ESRD who have cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure with gradient of 10 mm Hg or more
- Patients who have end-stage liver disease (ESLD) and chronic kidney disease with GFR of 30 mL/min or less
- Patients who have acute kidney injury (including HRS) with creatinine 2 mg/dL or more that have been on dialysis for 8 weeks or more
- Patients with ESLD and chronic kidney disease who have greater than 30% glomerulosclerosis or 30% fibrosis on kidney biopsy

Online registry for SLK has been established to monitor patient outcomes and help further redefine the criteria for SLK transplantation.

**REFERENCES**


