AJKD
Core Curriculum in Nephrology

Kidney Disease in the Setting of Liver Failure: Core Curriculum 2013

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The nephrology consultant is often asked to evaluate patients who have both liver disease and kidney disease. The spectrum can involve diseases that cause both acute and chronic kidney and liver disease, drugs that are both hepatotoxic and nephrotoxic, and kidney diseases that occur in the setting of preexisting liver disease. Furthermore, nephrologists are often called upon to evaluate and manage kidney disease in patients being evaluated for liver transplantation, as well as manage kidney disease that occurs after liver transplantation. Finally, joint decision making as to whether to list a patient for simultaneous liver-kidney transplantation often is shared between the nephrologist, hepatologist, and transplant surgeon. This continuum is the subject of this core curriculum.

CONCOMITANT KIDNEY AND LIVER DISEASE

Kidney disease occurs in 20%-25% of patients with liver disease. One must first determine whether the patient is experiencing a process that affects both the kidney and the liver or has kidney disease as a result of liver disease. Table 1 lists the most common diseases that cause both liver and kidney disease, as well as primary liver diseases that are associated with intrinsic kidney disease. As can be seen, glomerulonephritis is common. Immunoglobulin A (IgA) deposition is an almost universal finding in patients with liver disease, particularly alcoholic cirrhosis, which may result in the full spectrum of IgA nephropathy. Management strategies are similar to those for the patient with idiopathic IgA nephropathy. Immunosuppressive therapy is not indicated in this setting. Membranous, membranoproliferative, and rapidly progressive crescentic glomerulonephritis are associated with both hepatitis B and C. Membranous is more common with hepatitis B, and membranoproliferative, particularly with cryoglobulinemia, with hepatitis C. Other diseases, such as focal segmental glomerulonephritis and antineutrophil cytoplasmic antibody–associated glomerulonephritis, also have been reported. A search for cryoglobulins is indicated in all patients presenting with proteinuria (protein excretion >0.5 g/24 h), low complement level, and typical purpuric rash. Treatment is targeted to the hepatitis virus, and remission of the kidney disease can occur with eradication. However, treatment itself may lead to further deterioration of kidney function. In cases of rapidly progressive kidney failure, plasma exchange with or without rituximab may be used.

Kidney biopsy may be necessary to determine the underlying cause of decreased kidney function, but carries an almost 12% risk of significant bleeding. Both percutaneous and transjugular approaches have been reported with similar complication rates, but transjugular biopsy is associated with smaller samples that are sometimes difficult to interpret. Biopsy information, when available, is useful not only to diagnose the underlying kidney disease, but also to estimate its chronicity and hence the chances of recovering kidney function after successful liver transplantation (discussed later). If not otherwise contraindicated, any patient with liver disease and proteinuria should be suspected of having an underlying glomerular lesion that can lead to end-stage renal disease (ESRD) and should be considered for a kidney biopsy.

There are several infectious diseases that are associated with concurrent hepatic damage and kidney disease. Varicella, cytomegalovirus, syphilis, leprosy, schistosomiasis, and salmonella all have been associated with liver disease and membranous glomerulonephritis. Toxoplasmosis, Epstein-Barr virus, leptospirosis, coccidiomycosis, and malaria can cause liver disease and variable renal pathologies. In addition to intrinsic glomerular disease, drug and toxin exposure can cause concomitant kidney and liver disease. The most common offenders are listed in Table 2. In addition to the drugs listed, toxins such as carbon tetrachloride, trichloroethylene, chloroform, *Amanita phalloides*, and arsenic can damage both organs. Treatment is supportive and removal of the offending agent is necessary. Dialysis or plasmapheresis (specifically for *Amanita* poisoning) to remove toxins may be indicated in some instances.

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Table 1. Disorders with Concomitant Kidney and Liver Disease

Primary Liver Disease Complicated by Kidney Disease

Liver Disease	Kidney Disease
Alcoholic cirrhosis	IgA nephropathy
Hepatitis B	Glomerulonephritis (IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, FSGS, crescentic glomerulonephritis); cryoglobulinemia
Hepatitis C	Glomerulonephritis; cryoglobulinemia
Obstructive jaundice	Acute kidney injury
Primary biliary cirrhosis	Renal tubular acidosis, interstitial nephritis
Wilson disease	Renal tubular acidosis, acute kidney injury

Systemic Diseases/Conditions That Affect the Liver and Kidney

Systemic Disease/Condition	Liver Disease	Kidney Disease
Pregnancy	HELLP syndrome; hepatic rupture	Preeclampsia
Ciliopathy	Polycystic liver disease	Polycystic kidney disease
Sarcoidosis	Liver granulomas; portal hypertension	Granulomatous interstitial nephritis; nephrolithiasis
Diabetes	Steatohepatitis	Diabetic nephropathy
Amyloidosis	Hepatomegaly	Nephrotic syndrome
Sickle cell disease	Hyperbilirubinemia; gallstones; cholecystitis; hepatitis C	Hematuria; renal infarct; proteinuria; FSGS
Paroxysmal nocturnal	Budd-Chiari syndrome	Hemoglobinuria
Hemoglobinuria	Portal vein thrombosis	Acute kidney injury
Shock	Ischemic hepatitis	Acute tubular necrosis

Abbreviations: FSGS, focal segmental glomerulosclerosis; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet count; IgA, immunoglobulin A.

Adapted from Wong F (*Clinics in Liver Disease*. 2002;2:981-1011) with permission of Elsevier.

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ASSESSMENT OF KIDNEY FUNCTION IN PATIENTS WITH LIVER DISEASE

In patients with cirrhosis, serum creatinine is an unreliable tool in assessing kidney function owing to the low production rate of creatine (the precursor of creatinine) by the liver with reduced muscle mass. Studies have shown that 37% and 31% of patients with cirrhosis and a serum creatinine level in the normal range have creatinine clearances <50 and 50-80 mL/min, respectively. Creatinine-based equations are unreliable for the same reason. The majority of the creatinine-based equations, including the MDRD (Modification of Diet in Renal Disease) Study equation and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation, overestimate glomerular filtration rate (GFR) in cirrhotic patients when inulin clearance is <70 mL/min. However, some

Table 2. Drugs Causing Liver and Kidney Disease

Drug	Liver Disease	Kidney Disease
Acetaminophen	Liver failure	Acute or chronic kidney disease
Aspirin	Acute hepatitis; Reye syndrome	Papillary necrosis
NSAIDs	Acute hepatitis; cholestatic hepatitis; steatosis; granulomatosis	Acute and chronic kidney disease; minimal change disease; membranous nephropathy; allergic interstitial nephritis
Quinolones	Acute hepatitis	Interstitial nephritis
Sulfonamides	Acute hypersensitivity reaction causing granulomatous hepatitis	Crystalluria; interstitial nephritis
Rifampin	Acute hepatitis	Interstitial nephritis; glycosuria
Phenytoin	Acute hypersensitivity reaction causing granulomatous hepatitis	Interstitial nephritis
Allopurinol	Acute hypersensitivity reaction causing granulomatous hepatitis	Acute kidney injury
ACE inhibitors (sulfhydryl group, eg, captopril)	Cholestatic hepatitis	Membranous glomerulonephritis
Methotrexate	Fibrosis/cirrhosis	Acute obstruction/nephrotoxicity
Anesthetics (methoxyflurane, halothane)	Acute hepatic necrosis	Acute kidney injury

Abbreviations: ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug.
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equations perform better than others, and one study showed that 66% of GFR estimates were within 30% of iothalamate GFR when the 6-variable MDRD Study equation was used, which adds albumin and urea nitrogen levels, outperforming the 4-variable MDRD Study equation. The CKD-EPI creatinine equation offers no advantage compared to the MDRD Study equation in cirrhotic patients. Twenty-four–hour creatinine clearance is an acceptable tool in assessing kidney function, but is cumbersome and affected by increased tubular secretion of creatinine observed in cirrhotic patients. Iohexol or iothalamate clearance is the gold standard for measuring GFR in the general population, but has limitations in patients with ascites due to the variable volume of distribution and difficulties with urination. Cystatin C has been proposed as an alternative marker to assess kidney function because it is produced by all nucleated cells, is cleared primarily by glomerular filtration, and its blood level is not affected by age, sex, muscle mass, or bilirubin level. However, lack of widespread availability and concerns regarding assay variation with drugs such as calcineurin inhibitors (CNIs) and corticosteroids have limited the application of cystatin C measurement in assessing kidney function in cirrhotic patients. Using cystatin C–based formulas to assess kidney function in cirrhotic patients also has yielded mixed results.

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HYPONATREMIA IN THE SETTING OF LIVER DISEASE

Hyponatremia is common in patients with liver disease, and its prevalence increases with the progression of cirrhosis. Studies have demonstrated that in patients with advanced cirrhosis, serum sodium level is <135 mEq/L in 30%-50%, <130 mEq/L in 22%, and <125 mEq/L in 3%-6%. Hyponatremia most often is the result of nonosmotic release of vasopressin, but also can occur from overzealous diuretic use. Hyponatremia usually is asymptomatic but can manifest as nausea or vomiting or with serious central nervous system symptoms, such as lethargy, seizures, delirium, or coma. Central nervous system signs of hyponatremia may mimic those of hepatic encephalopathy, and serum sodium level should be checked in cirrhotic patients presenting with central nervous system manifestations. The mainstay of managing hyponatremia is free-water restriction and loop diuretic use. Vasopressin 2 receptor blockers have been shown to be effective in the treatment of hypervolemic hyponatremia in

cirrhotic patients, but concerns regarding associated hepatic toxicity with tolvaptan make this group of medication a less attractive option as an initial therapy and it should be reserved for resistant cases. Correction of hyponatremia should be gradual in asymptomatic patients, aiming not to exceed 8-10 mEq/L per day change in serum sodium level because more rapid correction is associated with devastating central pontine myelinosis. For this reason, serial monitoring of serum sodium level is crucial. For hyponatremic cirrhotic patients receiving hemodialysis (HD), dialysate sodium concentration should be within 10 mEq/L of the patient's serum sodium level to avoid rapid sodium correction and central pontine myelinosis. In symptomatic patients, rapid correction of hyponatremia to eliminate symptoms using hypertonic saline solution is the recommended treatment. Hyponatremia is an independent predictor of pre- and posttransplantation mortality, especially in those with low MELD (Model for End-Stage Liver Disease) scores. Whether correction of hyponatremia preoperatively improves outcomes posttransplantation is not clear, with one study showing liver transplant recipients with resolved or corrected hyponatremia more likely to be discharged at 3 weeks than those with uncorrected hyponatremia, although there were no differences in mortality or other complications at 180 days. A safe cutoff for preoperative sodium concentration has not been established, but serum sodium level <120 mEq/L is a reasonable cutoff.

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ACUTE KIDNEY INJURY IN THE SETTING OF LIVER DISEASE

Acute kidney injury (AKI) is common in patients with liver disease, and its prevalence increases with the progression of hepatic cirrhosis. Nearly 50% of cirrhotic patients who also have ascites develop AKI as well. Prerenal, renal, and postrenal factors can cause AKI, but the most common causes are volume depletion, acute tubular necrosis (ATN), and hepatorenal syndrome (HRS). These 3 causes alone comprise almost 80%-90% of all AKI observed in cirrhotic patients. HRS constitutes a small fraction of all AKI cases that develop in cirrhotic patients. In one study, HRS was responsible for only 7.6% of 129 instances of AKI that developed in cirrhotic patients with ascites. In another multicenter retrospective study that included 423 patients with cirrhosis and AKI, 65% of AKI was attributed to either ATN or prerenal causes, whereas type 1 and type 2 HRS were responsible for 20% and 6.6% of cases, respectively. The definitions of AKI used in these studies varied significantly, and it is difficult to determine the severity of AKI in these patients. A recent study used the AKI Network (AKIN) definition in 192 cirrhotic patients and demonstrated the prevalence of stage 1, stage 2, and stage 3 AKI at 26%, 24%, and 49%, respectively. It is important to mention that mortality increased with the progression of the AKI stage. Determining the cause of AKI is important not only for therapeutic purposes, but also

to assess prognosis because the outcome from HRS is much worse than AKI induced from either infection or hypovolemia.

Many factors in cirrhotic patients can lead to volume depletion and prerenal AKI. These include excessive diuretic use (especially in patients without evidence of peripheral edema), diarrhea related to lactulose use, and large-volume paracentesis without concomitant albumin infusion. Gastrointestinal bleeding also is associated with AKI, but most cases of massive blood loss lead to ATN rather than prerenal azotemia. Increased intra-abdominal pressure from tense ascites leads to abdominal compartmental syndrome and AKI. Increased intra-abdominal pressure can be confused with prerenal AKI due to its association with low urinary sodium excretion. The mechanism of GFR reduction in patients with abdominal compartmental syndrome is incompletely understood, but evidence suggests that the most important factor is the alteration in renal blood flow due to compression of the renal veins limiting renal venous return. Increases in plasma renin activity and serum aldosterone level occur in abdominal compartmental syndrome, indicating that the increased intra-abdominal pressure activates the renin-angiotensin-aldosterone system and explains the low urinary sodium excretion associated with this condition. Urinary sodium excretion increases after relieving the intra-abdominal pressure with paracentesis. Abdominal compartmental syndrome can be diagnosed by measuring an intrabladder pressure >20 mm Hg. Reduction of intra-abdominal pressure from 22 to 10 mm Hg with paracentesis leads to improvement in urine flow rate and creatinine clearance.

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HEPATORENAL SYNDROME

HRS is a functional form of AKI that results from severe renal vasoconstriction without evidence of structural kidney damage. Multiple factors are involved in the pathogenesis of HRS, but the main underlying pathophysiologic change is intense renal vasoconstriction that results from imbalance between vasoconstricting and vasodilating substances. Renal vasoconstriction starts many months before changes in kidney function are clinically apparent and progresses gradually as the liver disease advances from diuretic-responsive ascites to diuretic-resistant ascites, then to HRS. Vasoconstriction also is evident in other vascular beds, including the brain and extremities, and the extent of extrarenal vasoconstriction parallels vasoconstriction of the renal vessels. Multiple systemic and local factors are responsible for the renal vasoconstriction. In cirrhotic patients, the accumulation of various vasodilator compounds, the most important of which is nitrous oxide, along with mechanical factors related to portal hypertension, leads to splanchnic vasodilatation and pooling of blood in the splanchnic circulation. This results in reduced effective circulating arterial blood volume (systemic underfilling). This relative hypovolemia leads to activation of the arterial baroreceptors in the aortic arch and carotid sinus, stimulating the sympathetic nervous system and release of vasoconstrictor peptides. Renal hypoperfusion activates the renin-angiotensin-aldosterone system with subsequent worsening of renal vasoconstriction and increases in salt and water retention. Nonosmotic release of vasopressin from the hypothalamus also contributes to the renal vasoconstriction and hyponatremia occurring in cirrhotic patients.

Figure 1 demonstrates the hemodynamic and neurohormonal changes occurring in patients with liver disease starting from the preascitic stage to HRS development. Box 1 highlights the major changes occurring in the splanchnic and systemic circulation in patients with liver disease. An increase in intrarenal production of vasodilating prostaglandins and kallikreins compensates for renal vasoconstriction. In patients who have cirrhosis and ascites, the excretion of vasodilating prostaglandins in urine is higher compared to that of healthy individuals, but it declines in patients with HRS, indicating imbalance between vasodilating and vasoconstrictor substances favoring renal vasoconstriction. Likewise, administering cyclooxygenase inhibitors to patients with cirrhosis and ascites leads to a syndrome that cannot be distinguished from HRS. Cardiac dysfunction, expressed as relative decline in cardiac output, begins before diagnosis of HRS and is

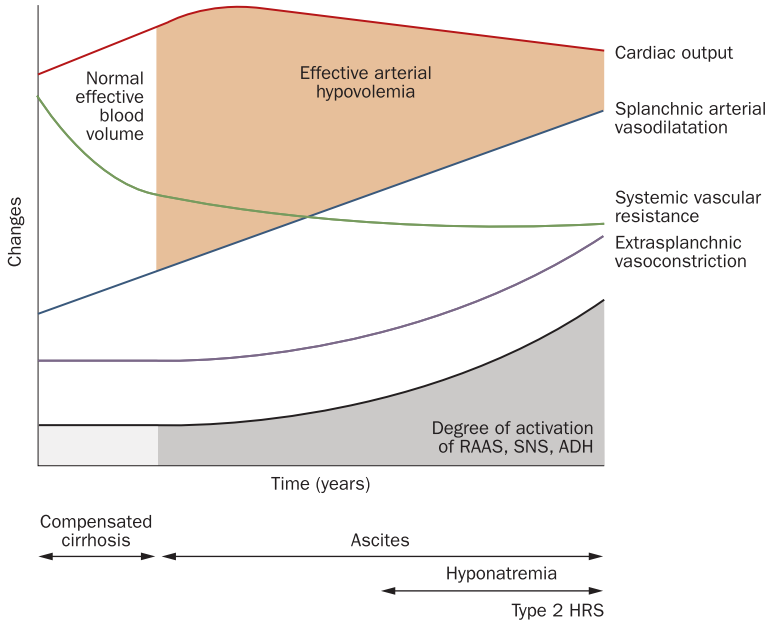

Figure 1. Mechanisms leading to circulatory and decreased kidney function in cirrhosis. The main mechanism is progressive splanchnic arterial vasodilatation due to overproduction of vasodilator molecules. During the initial phases of decompensated cirrhosis, when activation of vasoconstrictor systems is moderate, patients develop sodium retention and ascites. In subsequent stages, activation of antidiuretic hormone (ADH) leads to dilutional hyponatremia. Finally, in the most advanced phase, when circulatory dysfunction is extreme, renal vasodilatory systems are overcome and patients develop severe renal vasoconstriction and type 2 hepatorenal syndrome (HRS). Abbreviations: RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system. Reprinted from Arroyo et al (*Nature Reviews Nephrology*. 2011;7:517-526), with permission of Macmillan Publishers Ltd.

a contributor to renal vasoconstriction and renal hypoperfusion in these patients. Adrenal insufficiency also has been observed in 80% of patients with HRS, but in only 34% of patients with serum creatinine level <1.5 mg/dL, suggesting a role of adrenal insufficiency in HRS development.

Diagnostic Criteria for HRS

There are 2 types of HRS. Type 1 HRS is defined as doubling of serum creatinine to a level >2.5 mg/dL within 2 weeks, whereas in type 2 HRS, there is a gradual increase in serum creatinine level to ≥1.5 mg/dL. Type 1 HRS is more acute, often is associated with multiorgan failure, has a very grim prognosis, and can be confused with other causes of AKI, such as ATN. In type 1 HRS, a precipitating event is identified in 50%-70% of cases, and more than one event can occur in a single patient. Type 2 HRS represents the clinical expression of cirrhosis-induced vasoconstriction and is preceded by refractory ascites. Kidney failure in type 2 HRS progresses slowly, in step with the degree of decreases in liver function.

Box 1. Hemodynamic Changes That Occur in Liver Cirrhosis

- Hepatic and the splanchnic circulation
  - ◇ Splanchnic vasodilatation
  - ◇ Hepatic vascular neoformation
  - ◇ Increased portal pressure with portosystemic collateral formation
- Systemic circulation
  - ◇ Increased cardiac output
  - ◇ Hyperdynamic circulation
  - ◇ Decreased arterial blood pressure
  - ◇ Increased plasma and total blood volumes
  - ◇ Reduced central blood volume
  - ◇ Vasoconstriction of the renal, femoral, and cerebral vascular beds

Diagnostic criteria for HRS were developed by the International Ascites Club (IAC) and modified in 2007. Serum creatinine level still needs to double to >2.5 mg/dL in less than 2 weeks in order to diagnose type 1 HRS. The new IAC criteria for type 2 HRS diagnosis are summarized in Box 2. However, the IAC criteria recently have been criticized for a number of reasons. First, these criteria are difficult to implement in clinical practice, as demonstrated in recent studies that showed that 36% of patients with serum creatinine level >1.5 mg/dL and suspected HRS did not meet one or more of the diagnostic criteria because of anuria, hematuria, and/or proteinuria. Second, the criteria for type 2 HRS diagnosis coincide with the definition of CKD. CKD is defined as having GFR < 60 mL/min/1.73 m^2 for at least 3 months. Consequently, patients with type 2 HRS who have a progressive increase in serum creatinine level for at least 3 months may be misdiagnosed as having CKD. Last, HRS is a form of AKI, but the IAC criteria deviate from the AKIN definition of AKI in the general population. The AKIN defines AKI as an absolute increase in serum creatinine level by 0.3 mg/dL within a 48-hour period and/or urine output <0.5 mL/kg/h for 6 hours. But according to the IAC criteria, patients with cirrhosis who develop AKI with an increase in serum creatinine level >0.3 mg/dL in less than 48 hours but do not have a creatinine level >1.5 mg/dL do not satisfy the definition of HRS. Recently, a working party was formed between members of the Acute Dialysis Quality Initiative and the International

Box 2. IAC Criteria for Type 2 HRS Diagnosis

- Cirrhosis with ascites
- Serum creatinine >1.5 mg/dL
- No improvement in serum creatinine (decrease <1.5 mg/dL) after 2 days off diuretics and volume expansion with albumin (1 g/kg body weight up to a maximum of 100 g/d)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of signs of parenchymal renal disease, as suggested by proteinuria (protein excretion >500 mg/d) or hematuria (>50 red blood cells/high-power field) and/or abnormal renal ultrasound

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: HRS, hepatorenal syndrome; IAC, International Ascites Club.

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Ascites Club to produce recommendations for prevention and treatment of AKI in cirrhotic patients. The working group proposal recommended using a definition of AKI in cirrhotic patients of an increase in serum creatinine level ≥0.3 mg/dL within a 48-hour period or an absolute 50% increase in serum creatinine level. Clearly, more work is needed to modify the current available criteria for HRS diagnosis so that they align better with the current AKIN staging system and to ensure that the criteria for type 2 HRS make it clearly distinguishable from CKD.

It is important to understand that HRS is a diagnosis of exclusion and should be made only when adequate volume resuscitation with a maximum of 100 g of albumin has been undertaken. Other causes of AKI also should be excluded, especially contrast nephropathy and ATN. HRS diagnosis should not be made in patients with evidence of structural kidney damage, such as proteinuria or hematuria, and in those without evidence of advanced liver disease or ascites. Persistent systemic hypertension may point to a different mechanism other than HRS as the cause of decreased kidney function. Although low fractional excretion of sodium (FeNa) has been advocated as consistent with HRS, kidney biopsy studies in cirrhotic patients demonstrate that almost 90% of these patients will have FeNa <1% despite biopsy evidence of ATN or glomerular pathology. For that reason, low FeNa is not always indicative of HRS and has been omitted from the HRS diagnostic criteria. A number of urinary biomarkers, including interleukin 18 and neutrophil gelatinase associated lipocalin (NGAL), currently are being investigated as potentially being of use to differentiate between type 1 HRS and ATN.

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Epidemiology, Precipitating Factors, Natural History, and Prognosis of HRS

Historically, the 1- and 5-year probability of HRS has been reported as 18% and 39%, respectively, in a pooled population of patients with cirrhosis. However, recent studies estimate the cumulative 5-year probability of HRS development at only 11.4%, reflecting lower HRS rates during the last 2 decades, probably as a result of better management of cirrhotic patients and the wide use of prophylactic antibiotics for spontaneous bacterial peritonitis prevention. The prevalence of HRS increases with the progression of liver disease. For patients who have advanced cirrhosis and are waiting for liver transplantation, the prevalence of HRS can be up to 48%.

Type 1 HRS has a grim prognosis; the 2-week mortality is as high as 80% in untreated patients and there is 10% survival at 3 months. The prognosis of type 2 HRS is marginally better, as its median survival is 6 months. However, recently, there has been some improvement in the prognosis for patients with HRS. As one example, in a multicenter study of 116 patients with HRS, in which some patients were given vasoconstrictor therapy and albumin, 3-month survival was 20% and 40% for type 1 and type 2 HRS, respectively. In a different study, there was 1-year survival of 38% for patients with type 2 HRS compared to mean survival of just 7 days for type 1 HRS. Figure 2 displays survival rates from recent studies for patients with type 1 and type 2 HRS.

Infection is the most important precipitating event that leads to HRS in cirrhotic patients. The most important implicated infections are spontaneous bacterial peritonitis, urinary tract infections, and, rarely, soft-tissue infections such as cellulitis. It has been shown that 20%-30% of patients who have spontaneous bacterial peritonitis develop HRS despite being given the necessary treatment and the infection resolving. Patients with spontaneous bacterial peritonitis who have elevated serum creatinine levels, preexisting hyponatremia, or high plasma and ascitic cytokine levels when diagnosed with spontaneous bacterial peritonitis also are more likely to develop HRS. Gastrointestinal hemorrhage, nonsteroidal

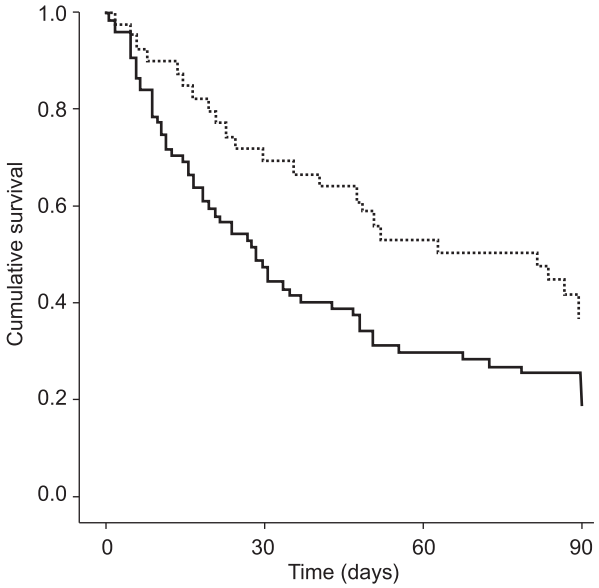

Figure 2. Probability of survival of a recent cohort of 116 patients who developed either type 1 (solid line) or type 2 (dotted line) hepatorenal syndrome between April 2007 and February 2009. Adapted from Salerno et al (*J Hepatol.* 2011;55:1241-1248), with permission of Elsevier.

anti-inflammatory drug use, and large-volume paracentesis without concomitant albumin infusion also can precipitate HRS. It is believed that a precipitating event leads to HRS by aggravating renal vasoconstriction or inducing further deterioration in cardiac function. The end results are worsening renal perfusion and HRS development.

Prevention of AKI and HRS in Cirrhotic Patients

Due to the adverse effect of AKI on mortality in cirrhotic patients, preventing AKI is of utmost importance. Diuretic use for ascites should be limited to a maximal dose of 400 mg of spironolactone and/or 160 mg of furosemide daily in divided doses. Caution should be used when administering diuretics to patients without peripheral edema and patients who have a history of decreased kidney function as a result of diuretic use. In patients with diuretic-resistant ascites, diuretics should be withdrawn if possible and ascites should be managed with paracentesis. Large-volume paracentesis (>5 L) should be followed by albumin infusion (8 g per liter of ascites fluid removed), and concomitant nonselective β-blockers should be used cautiously because these medications may increase the risk of paracentesis-induced circulatory dysfunction. Early paracentesis may avoid the effect of increased intra-abdominal pressure on renal hemodynamics. Nonsteroidal anti-inflammatory drugs should be avoided in patients with advanced cirrhosis, and the benefit of intravenous radiocontrast use must be balanced against the risk of kidney injury, particularly in patients with creatinine levels ≥1.5 mg/dL. Gastrointestinal bleeding must be managed aggressively to avoid detrimental effects on kidney function. Patients at risk of spontaneous bacterial peritonitis should receive antibiotic prophylaxis, and those with confirmed spontaneous bacterial peritonitis should receive intravenous albumin along with appropriate antibiotic treatment to decrease the risk of kidney injury. In a double-blind controlled study of pentoxyfylline, use for 28 days in patients with alcoholic hepatitis was associated with decreased risk of developing HRS and lower mortality. In patients who have already developed AKI, volume resuscitation and albumin infusion should be used aggressively before diagnosing HRS. If there are aggravating factors such as adrenal insufficiency or infections, they should be diagnosed and treated. In addition, the patient should be assessed promptly for possible liver transplantation. In patients with type 1 HRS who are not candidates for liver transplantation, setting realistic expectations and avoiding aggressive treatment modalities is recommended.

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Treatment of HRS

Pharmacological Therapy

The preferred treatment for patients with HRS in Europe is intravenous terlipressin and albumin infusion; however, terlipressin is not approved in the United States and Canada. Terlipressin uses vasoconstrictive action by binding to the vasopressin (V1) receptor, which is expressed preferentially on vascular smooth muscle cells within the splanchnic circulation. When terlipressin is metabolized through exopeptidases, it releases small quantities of lysine vasopressin over a continuous period, which means it can be administered as a bolus injection. Continuously infusing terlipressin is associated with a higher reversal rate of HRS in comparison to bolus injections. A number of studies have shown a beneficial effect on various clinical parameters, such as arterial

blood pressure, hyponatremia, and urine output, as well as amelioration in neurohormonal abnormalities in 50%-70% of patients with HRS after infusions of terlipressin and albumin. In addition, the median time to reversal of HRS is 7 days, and patients with lower serum creatinine levels at presentation recover more quickly. A positive response to terlipressin also is predicted by lower serum bilirubin level and a >5–mm Hg increase in mean arterial blood pressure after starting terlipressin therapy. Terlipressin has some side effects, but they are minimal; ischemic events occur in 5%-30% of patients, although most studies exclude patients who have a high risk of ischemic events. HRS recurs in as many as 50% of cases after terlipressin therapy is discontinued. It is unknown which factors are associated with recurrence of HRS, but reintroduction of terlipressin leads to improvement in kidney function in most cases. Terlipressin also is beneficial in type 2 HRS because the response rate is slightly improved and there is longer survival compared to type 1 HRS. Terlipressin also improves kidney function and induces natriuresis in patients with cirrhosis and refractory ascites without HRS.

Midodrine and norepinephrine are both α_1-adrenergic receptor agonists. They are each approved in the United States and have been shown to be effective in the treatment of HRS. The continuous infusion of norepinephrine, along with infusion of albumin and furosemide, has been shown to be beneficial in reversing HRS. Norepinephrine is provided through continuous intravenous infusion and requires monitoring in the intensive care unit. The drug is infused until either serum creatinine level decreases to <1.5 mg/dL or for a maximum of 15 days. Some studies titrated the dose to achieve a 10–mm Hg increase in mean arterial blood pressure. On average, mean norepinephrine dose was 0.8 mg/h and mean duration of infusion was 10 days. HRS reversal occurred in almost 80% of patients, including patients in whom terlipressin therapy previously failed. Compared to terlipressin, norepinephrine is less expensive and is associated with similar HRS reversal and ischemic event rates.

Midodrine is a prodrug that the liver metabolizes into an active metabolite, desglymidodrine, which then is excreted in urine. There have not been studies of the pharmacokinetics of midodrine and desglymidodrine in patients with HRS. Oral midodrine, when administered as monotherapy, provided a modest improvement in systemic hemodynamics, but did not improve kidney function in patients who had HRS or refractory ascites. When oral midodrine is administered in combination with the glucagon inhibitor octreotide (glucagon mediates splanchnic vasodilatation) and albumin infusion, studies have observed improved kidney function, mean arterial pressure, and plasma renin activity. The starting midodrine dose is 2.5 mg thrice daily, which can be increased to 15 mg thrice daily. Octreotide is injected subcutaneously at a starting dose of 100 μg thrice daily and can be uptitrated to 200 μg thrice daily. Nonrandomized studies that evaluated the effect of midodrine and octreotide on HRS reversal reported 50%-70% response rates, but randomized studies are lacking and these response rates seem to be much higher than experienced in clinical practice. However, a recent trial in 163 patients with HRS demonstrated improved survival and higher liver transplantation rates in patients receiving midodrine, octreotide, and albumin infusion compared with patients receiving no specific therapy for HRS. Midodrine/octreotide combination is safe overall, and no significant treatment-related side effects have been reported. Another advantage is that this combination therapy can be administered on an outpatient basis provided that the patient has been trained in subcutaneous injection.

There are only a few studies that compare terlipressin with other vasoconstrictor agents in a head-to-head fashion. Still, the existing studies have not found that one vasoconstrictor agent has an advantage over another for reversal of HRS. In one study, patients treated with terlipressin had an improved HRS recovery rate and survival and an increased likelihood of receiving a liver transplant compared with patients who received the octreotide/midodrine combination. However, this study was not randomized and it is possible that selection bias affected the results. A recently published meta-analysis did not observe a difference between the different vasoconstrictors in terms of patient survival.

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) insertion has been evaluated in patients with type 1 HRS and type 2 HRS with preserved liver function. Reversal of HRS occurred in almost 50% of type 1 HRS cases and nearly all type 2 HRS cases within 3 months of TIPS insertion. These clinical changes were associated with improved hemodynamics in the kidney and lowered plasma levels of the different mediators of vasoconstriction. An important observation is that kidney function recovery often is delayed after TIPS insertion (within 2-4 weeks), whereas kidney function recovers faster after vasoconstrictor therapy. Uncontrolled hepatic encephalopathy and advanced liver disease are the main contraindications to TIPS insertion. Importantly, a recent study showed that TIPS insertion improved liver transplantation outcomes, likely through improved kidney function. In 2 studies, vasoconstrictor therapy

was evaluated in conjunction with TIPS. However, because there are only a small number of cases and TIPS has limited applicability in patients with advanced cirrhosis, it is difficult to generalize this combination therapy for a large number of patients.

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RENAL REPLACEMENT THERAPY IN THE SETTING OF CIRRHOSIS

Renal replacement therapy (RRT) may be indicated in patients with cirrhosis. Some patients with stable compensated cirrhosis who are not yet candidates for liver transplantation may develop ESRD. Similarly, patients with ESRD may develop cirrhosis. These patients can undergo long term RRT with either intermittent HD or peritoneal dialysis (PD). Therapy may be challenging depending on the severity of the underlying kidney disease. One of the hallmarks of cirrhosis is low mean arterial pressure, and there may be a lack of cardiac reserve due to the presence of cirrhotic cardiomyopathy. This makes HD challenging, and maneuvers to change the sodium concentration and temperature of the dialysate may be indicated. PD also may be difficult, particularly in patients with ascites. Risk of infection, overzealous fluid removal, and protein depletion can be significant. However, PD in cirrhotic patients has been used successfully while avoiding these complications. It probably is indicated only in patients who are being dialyzed long term and not those waiting for a liver transplant with well-compensated cirrhosis. Candidates for liver transplantation receiving PD risk the development of peritonitis, which jeopardizes their receiving a liver transplant.

Another situation in which RRT is indicated is for cirrhotic patients who develop AKI. If patients are candidates for liver transplantation or are undergoing evaluation for liver transplantation, RRT is indicated as a bridge to transplantation. Patients who are on RRT prior to liver transplantation have higher 90-day

mortality and worse 1-year survival. If patients are not candidates for liver transplantation, RRT may still be indicated to determine whether kidney function will return. If patients are not candidates for liver transplantation and are not expected to survive for any length of time due to decompensated liver disease, RRT may not be indicated.

The choice of RRT in patients awaiting liver transplantation depends on the clinical status of the patient. A comparison of HD versus continuous RRT (CRRT) shows that patients receiving CRRT have worse survival to transplantation. However, these are not comparable groups because CRRT usually is chosen for sicker patients. RRT prior to transplantation leads to worse 90-day survival compared with patients not receiving RRT, which ranges from 50%-80% in those receiving RRT compared to >92% in patients not on pretransplantation RRT.

There is one clear-cut choice for patients who have hepatic encephalopathy. The major cause of death in patients with hepatic encephalopathy is increased intracranial pressure leading to brainstem herniation. CRRT does not increase intracranial pressure as HD may. Furthermore, brain perfusion pressure is maintained with CRRT. All patients with hepatic encephalopathy requiring RRT should receive CRRT. There are a variety of other techniques that combine detoxification of the hepatic encephalopathy combined with a CRRT modality. The main 2 are the molecular adsorbent recirculating system and the Prometheus system. Both rely on removing albumin-bound toxins and regenerating the albumin combined with CRRT. The molecular adsorbent recirculating system now is available in the United States, whereas the Prometheus system is not. The molecular adsorbent recirculating system has been shown to improve hepatic encephalopathy, but its clinical usefulness for this indication is open for debate. Details of the systems can be found in the additional reading selections. They are supportive but not curative of HRS and may be useful bridging maneuvers in patients awaiting transplantation or patients with reversible fulminant hepatic failure, in other words, drug overdose or acute hepatitis.

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COMBINED LIVER-KIDNEY TRANSPLANTATION

In 2002, the MELD system was introduced for the allocation of livers for transplantation in the United States. Calculation of MELD is influenced heavily by the recipient's serum creatinine level, so that patients with worse kidney function have higher MELD scores and therefore a better chance of receiving a liver transplant. Prior to the introduction of the MELD, total simultaneous liver-kidney transplantations never exceeded 135 a year, or 2.5% of the total deceased donor liver transplantations performed in the United States. Since the introduction of MELD, the kidney function of patients listed for transplantation has worsened and simultaneous liver-kidney transplantations in 2012 were 7.4% of the liver transplantations performed in the United States (462 transplants). Analysis of the Organ Procurement and Transplantation Network (OPTN) database has demonstrated that patients receiving a simultaneous liver-kidney transplant have better long-term survival than patients with serum creatinine levels >2 mg/dL or who are on dialysis therapy who receive only a liver transplant. However, there are subpopulations of these groups of patients who may recover their kidney function posttransplantation, making the selection of patients for simultaneous liver-kidney transplantation problematic. With the stress of surgery and the planned use of nephrotoxic immunosuppressants anticipated posttransplantation, many transplantation programs opt for simultaneous liver-kidney transplants in patients with poor kidney function (eg, serum creatinine >2 mg/dL or estimated GFR <20 mL/min/1.73 m^2). Therefore, the number of simultaneous liver-kidney transplantations has increased in

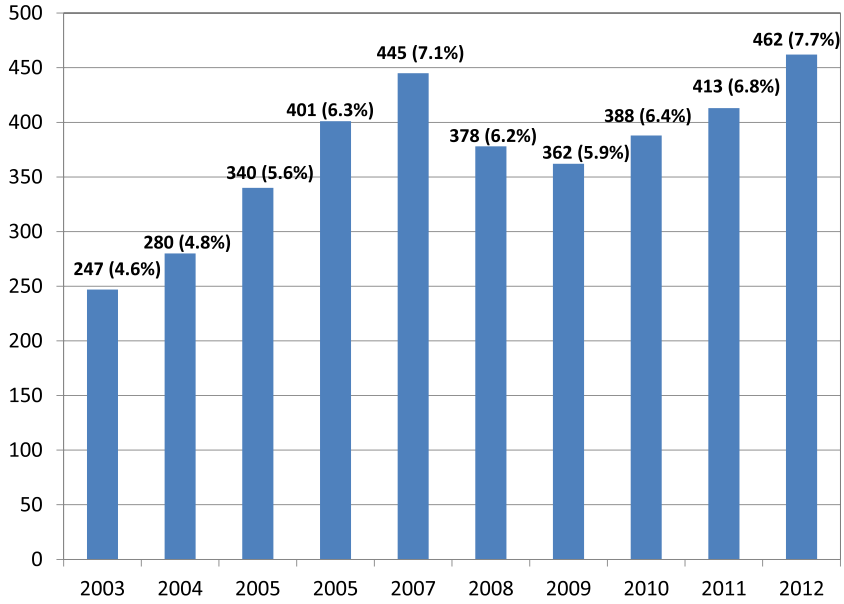

Figure 3. Number of simultaneous liver-kidney transplantations in the United States by year and their percentage of total deceased donor liver transplantations. Health Resources and Services Administration/Organ Procurement and Transplantation Network data as of December 31, 2012. Source www.optn.transplant.hrsa.gov.

both total numbers and as a percentage of transplantations done (Fig 3). This does not appear to have decreased overall patient survival, but has raised concerns, particularly in the nephrology community, about the proper use of deceased donor kidneys. With the increasing waiting list for kidney transplantation and increasing mortality on the kidney transplant wait lists, it is problematic to many nephrologists to watch the number of kidneys being used for simultaneous liver-kidney transplantations increasing.

Great scrutiny has been applied to this problem, with an examination of the utility of performing the procedure on the terms of outcome and mortality. This has resulted in 3 separate national consensus conferences being held. Each has arrived at similar conclusions regarding the appropriateness of performing simultaneous liver-kidney transplantation in various patient populations. In addition, the United Network for Organ Sharing (UNOS) has published guidelines for the simultaneous allocation of kidneys to liver recipients. Box 3 lists the recommendations from the last 2 consensus conferences and the OPTN guidelines. The OPTN guidelines have yet to be adopted. Furthermore, when these guidelines were used to determine if they could accurately predict which patients would not recover kidney function (ie, appropriate patients for simultaneous liver-kidney transplants), sensitivity was only 53%. Thus, there continues to be controversy in this area. One potentially useful diagnostic tool is percutaneous kidney biopsy to predict who would benefit from simultaneous liver-kidney versus liver transplantation alone. The degree of glomerulosclerosis and interstitial fibrosis may predict who will not recover following liver transplantation. Although kidney biopsy in cirrhotic patients is difficult and results in slightly higher complication rates, the approach has shown promise and is included as one of the criteria in both of the last 2 national consensus conferences. In general, a biopsy specimen with >30% interstitial fibrosis or >30% glomerulosclerosis is considered to show advanced and irreversible kidney disease, and in these cases, it may be best to consider combined liver-kidney transplantation. It is important to mention that these cutoff points for interstitial fibrosis and glomerulosclerosis were derived from studies that correlated histology with long-term kidney survival in other forms of kidney diseases not related to the liver. At the present time, there is no consensus and further improvement is necessary to accurately predict which patient to select for this procedure. There is some evidence that critically ill patients with multiorgan failure in the critical care unit prior to the procedure are not well suited for simultaneous liver-kidney transplantation.

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Box 3. Published Guidelines and OPTN Proposed Policy on Simultaneous Liver-Kidney Transplantation

- Eason et al (2008)

Simultaneous liver-kidney transplantation recommended for:

a. Patients with end-stage renal disease
b. Patients with CKD with GFR $\leq$ 30 mL/min/1.73 m^2
c. Patients with AKI/HRS with serum creatinine $\geq$2 mg/dL or dialysis $\geq$8 wk
d. Patients with evidence of CKD and kidney biopsy demonstrating >30% glomerulosclerosis or 30% fibrosis

Other criteria recommended are the presence of comorbid conditions such as diabetes, hypertension, age >65 y, other preexisting renal disease along with proteinuria, renal size, and duration of elevated serum creatinine.

- OPTN Kidney Transplantation Committee and the Liver and Intestinal Organ Transplantation Committee Policy 3.5.10 (2009)

Simultaneous liver-kidney transplantation recommended for:

a. Patients with CKD requiring dialysis with documentation of the CMS form 2728[a]
b. Patients with CKD (GFR $\leq$ 30 mL/min/1.73 m^2 by MDRD Study 6-variable equation or iothalamate measurement and proteinuria $\geq$3 g/d)
c. Patients with sustained AKI requiring dialysis for $\geq$6 wk (defined as dialysis at least twice per week for 6 consecutive wk)
d. Patients with sustained AKI (GFR $\leq$ 25 mL/min/1.73 m^2 for $\geq$6 wk by MDRD Study 6-variable equation or direct measurement) not requiring dialysis
e. Patients with sustained AKI: patients also may qualify for simultaneous liver-kidney transplantation listing with a combination of time in categories (c) and (d) for a total of 6 weeks (eg, patients with GFR < 25 mL/min/1.73 m^2 for 3 wk followed by dialysis for 3 wk).
f. Patients with metabolic disease

- Nadim et al (2012)

Simultaneous liver-kidney transplantation recommended for:

1. Candidates with persistent AKI for $\geq$4 wk with one of the following:
   a. Stage 3 AKI as defined by the modified RIFLE, ie, 3-fold increase in serum creatinine from baseline, serum creatinine $\geq$4 mg/dL with acute increase $\geq$0.5 mg/dL, or renal replacement therapy
   b. eGFR $\leq$ 35 mL/min/1.73 m^2 (MDRD Study 6-variable equation) or GFR $\leq$ 25 mL/min/1.73 m^2 (iothalamate clearance)
2. Candidates with CKD as defined by the National Kidney Foundation for 3 mo with one of the following:
   a. eGFR $\leq$ 40 mL/min/1.73 m^2 (MDRD Study 6-variable equation) or GFR $\leq$ 30 mL/min/1.73 m^2 (iothalamate clearance)
   b. Proteinuria $\geq$2 g/d
   c. Kidney biopsy showing $\geq$30% global glomerulosclerosis or $\geq$30% interstitial fibrosis
   d. Metabolic disease

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CMS, Centers for Medicare & Medicaid Services; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; MDRD, Modification of Diet in Renal Disease; OPTN, Organ Procurement and Transplantation Network; RIFLE, risk, injury, failure, loss, end-stage disease.

[a]CMS Form 2728: form required by Medicare and Medicaid stating that a dialysis patient has end-stage renal disease with no chance of renal recovery.

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TREATMENT OF KIDNEY FAILURE FOLLOWING LIVER TRANSPLANTATION

There was early recognition that CNIs had great success in prolonging transplant survival, and their introduction ushered in the modern era of solid-organ transplantation. However, it soon was realized that this class of drug also exhibited nephrotoxicity when used in nonkidney solid-organ transplantation. Several studies have examined the incidence of CKD (GFR < 30 mL/min/1.73 m^2) and eventually ESRD in liver transplant recipients treated long-term with CNIs. Most of the early experience was with the use of cyclosporine, but tacrolimus also is nephrotoxic. There is a suggestion that tacrolimus may be less nephrotoxic, but there have been no direct comparisons of the nephrotoxicity between the drugs. The incidence of CKD (defined variously as serum creatinine >2 mg/dL or estimated GFR < 30 mL/min/1.73 m^2) has varied from 25%-65% of patients treated with CNIs for 5-10 years. The development of CKD is very important in that long-term observational studies have demonstrated that GFR reduction posttransplantation is a significant risk factor for cardiac death posttransplantation and identifies patients at highest risk for poor survival.

Rates of ESRD approach 5%-20% at 10 years posttransplantation, depending on the study. Pretransplantation factors that identify patients at risk for long-term decreased kidney function including ESRD are HRS, pretransplantation dialysis, pretransplantation AKI, hepatitis C, pretransplantation diabetes, and persistent estimated GFR $\leq$ 30 mL/min/1.73 m^2 for 6 weeks. Patients with HRS have among the highest rates at 10%-25%, depending on the study. The development of ESRD has a significant impact on long-term survival in these patients, and treatment is discussed next. Interestingly, a recent article investigated the development of ESRD in the MELD era and determined that the development of ESRD in long-term patients has not increased substantially in the period of 6 months to 5 years posttransplantation. However, the development of ESRD in the first 6 months posttransplantation has increased dramatically from an incidence of 21.8 events/1,000 patient-years to 36.3 events/1,000 patient-years. This has led to an overall increase in ESRD in patients receiving liver transplants in the MELD era. That

same study developed equations using pretransplantation variables (including donor organ quality) to predict the development of ESRD in liver transplant recipients. Although not developed for allocation of simultaneous liver-kidney transplants, these equations may help guide appropriate donor selection and potentially decrease the number of simultaneous liver-kidney transplantations performed.

Identification of decreased kidney function early after liver transplantation is important because one of the factors that determines the risk of ESRD is kidney function at 1 year. Up to that point, much of the decreased kidney function due to CNI use may be reversible. One also must be cognizant that not all decreased kidney function is due to CNI toxicity because kidney biopsy studies in the post–liver transplantation patient have demonstrated a wide range of pathologies. Before consideration is given to changing immunosuppression, one should be certain of the diagnosis.

Several approaches to mitigate CNI nephrotoxicity have been used. Delayed introduction of CNIs with the use of induction therapy in one large study demonstrated excellent early results. Longer term follow-up is not available yet. Use of mycophenolate mofetil (MMF) with reduced CNIs has been shown to be efficacious in some patients, but total withdrawal of the CNI may lead to rejection. Mammalian target of rapamycin (mTOR) inhibitor (sirolimus and everolimus) use is controversial. Sirolimus carries a black box warning from the US Food and Drug Administration for use in liver transplantation. This applies to the early use as a primary immunosuppressant agent. A recently published study looked at liver transplant recipients randomly assigned at 4-12 weeks to continue CNI and MMF or switch to sirolimus and MMF (Spare the Nephron Trial). The sirolimus/MMF combination resulted in better kidney function at 1 year with a slight but nonsignificant increase in rejections. There was no difference in patient survival. Another trial randomly assigned patients at 30 days to standard CNI therapy, everolimus with reduced CNI therapy, or everolimus and no CNI therapy. The last arm was terminated prematurely due to adverse events. The everolimus/low-dose CNI arm had superior kidney function with equal survival compared to the standard CNI arm at 24 months. Studies performed later after transplantation have shown no advantage, whereas most have shown stabilization or improvement in kidney function after conversion from CNI to sirolimus therapy. However, sirolimus can cause proteinuria, and use of this drug in patients with preexisting proteinuria probably is not indicated. In that setting, worsening of proteinuria and kidney function has occurred. Therapy should be individualized and patients should be monitored carefully for potential rejection and worsening of kidney function. Doses used vary according to the study, and the reader is referred to the additional readings section for details. Regardless of the method chosen, therapy should start early because patients with severe CKD usually do not benefit from changes in therapy. Use of the lowest dose of CNI necessary to prevent rejection is the first step.

Sometimes therapy fails and the patient progresses to ESRD. Choice of therapy is individualized. There are very few reports of PD in post–liver transplantation patients, and many are reluctant to attempt this type of RRT. Given the history of extensive abdominal surgery and ongoing need for immunosuppression, PD may not be the best choice due to peritoneal membrane transport issues and the increase risk of infection. HD has been used, but survival seems poor compared to standard ESRD patients. This is to be expected given the comorbid conditions seen in these patients because ESRD usually results 5-10 years posttransplantation. As in nonliver transplant recipients, the treatment of choice remains kidney transplantation. Kidney transplantation after liver transplantation represents $\sim$1% of the total kidney transplantations done in the United States. Median time from liver transplantation to kidney transplantation is about 8 years. Although overall patient survival is low (again probably due to the comorbid conditions associated with long-term immunosuppression), death-censored transplant survival is no different for either living or deceased donor kidney transplantation compared to nonliver transplant recipients. In 2008, about two-thirds of the 120 kidney transplantations after liver transplantation done were from deceased donors. That number had been stable for several years.

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