SPECIAL ARTICLE

Report of the First International Liver Transplantation Society Expert Panel Consensus Conference on Renal Insufficiency in Liver Transplantation

Michael R. Charlton,[1] William J. Wall,[2] Akinlolu O. Ojo,[3] Pere Ginès,[4] Stephen Textor,[1] Fuad S. Shihab,[5] Paul Marotta,[6] Marcelo Cantarovich,[7] James D. Eason,[8] Russell H. Wiesner,[1] Michael A. Ramsay,[9] Juan C. Garcia-Valdecasas,[10] James M. Neuberger,[11] Sandy Feng,[12] Connie L. Davis,[13] Thomas A. Gonwa,[14] and the International Liver Transplantation Society Expert Panel

[1]Mayo Clinic, Rochester MN; [2]Department of General Surgery, London Health Science Center, London, Ontario, Canada; [3]Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI; [4]Liver Unit, Hospital Clinic, University of Barcelona School of Medicine, Barcelona, Spain; [5]Department of Nephrology, University of Utah School of Medicine, Salt Lake City, UT; [6]Medical School, University of Western Ontario, London, Ontario, Canada; [7]Department of Medicine, McGill University Health Center, Montreal, Quebec, Canada; [8]Transplant Institute, University of Tennessee, Memphis, TN; [9]Baylor University Medical Center, Dallas, TX; [10]Hospital Clinic I Provincial, Barcelona, Spain; [11]Queen Elizabeth Hospital, Birmingham, England; [12]Department of Transplant Surgery, University of California San Francisco Medical Center, San Francisco, CA; [13]Department of Medicine, University of Washington Medical Center, Seattle, WA; and [14]Mayo Clinic, Jacksonville, FL

Received March 30, 2009; accepted June 25, 2009.

This supplement is supported by an unrestricted educational grant from Bristol-Myers Squibb.

Scope of the Problem and Impact on Outcomes

Akinlolu O. Ojo

Both acute kidney injury (AKI) and chronic kidney disease (CKD) are highly prevalent in liver transplantation, affecting 25% to 50% and 30% to 90% of recipients, respectively. The risk of end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) ranges from 2% to 5% per year in the posttransplant period. Perioperative AKI with the need for RRT is associated with a 3- to 4-fold increase in the 30-day posttransplant mortality rate, and the 1-year survival rate in liver transplant recipients requiring perioperative dialysis support could be as low as 47% versus 92% for those recipients not requiring postoperative dialytic support. The etiology of AKI and CKD in liver transplant recipients is multifactorial, with pretransplant kidney disease and posttransplant immunosuppressant nephrotoxicity playing major etiogenic and aggravating roles. Preventative clinical management is frustrated by the gross imprecision or impracticality of the clinical methods available to diagnose kidney disease before and after liver transplantation. Borrowed therapeutic strategies such as calcineurin inhibitor minimization, substitution, and withdrawal are commonly employed to mitigate the progression of posttransplant kidney disease, but the evidence is scanty that these approaches prolong renal survival or mitigate the severity of CKD. The simultaneous implantation of a deceased donor kidney along with a liver allograft in patients with advanced renal insufficiency at the time of liver transplantation has gained substantial currency in a small number of liver transplant programs, but the criteria to determine the suitability of recipients of simultaneous liver-kidney transplantation are not standardized or rigorously formulated, and the survival benefits of the latter approach with respect to appropriate controls and alternative strategies have not been determined. Treatment of ESRD after liver transplantation with kidney transplantation appears to be overwhelmingly superior to long-term maintenance dialysis therapy with respect to recipient survival (10-year survival of 71% versus 20%, $P = 0.005$). Mechanistic and long-term clinical outcome studies specific to liver transplant populations are needed to better understand the etiology and mechanisms of the progression of kidney dysfunction. Such studies are necessary steps toward defining appropriate therapeutic targets and defining preventative strategies

RISK FACTORS

The calcineurin inhibitors tacrolimus and cyclosporine remain the cornerstone of maintenance immunosuppression in liver transplantation. Nephrotoxicity due to calcineurin inhibitors mediates several known clinical syndromes, including AKI and CKD. These well-recognized clinical syndromes and the nearly uniform findings of renal injury in patients exposed to long-term calcineurin inhibitors provide a strong basis for the presumption that calcineurin inhibition is the dominant cause of kidney dysfunction in liver transplant recipients (Fig. 1). Other risk factors known to predispose to renal insufficiency in liver transplant recipients include elevated pretransplant serum creatinine, pre-

Abbreviations: ACE, angiotensin-converting enzyme; ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; ATN, acute tubular necrosis; AUC, area under the concentration-time curve; bx pr, biopsy-proven; CKD, chronic kidney disease; CLKT, combined liver-kidney transplantation; CNI, calcineurin inhibitor; Cr, creatinine; CsA, cyclosporine A; CTLA4, cytotoxic T lymphocyte antigen 4; CYP, P450 cytochrome; ECM, extracellular matrix; ESRD, end-stage renal disease; ET, endothelin; Fc, fragment crystallizable; FFP, fresh frozen plasma; FSGS, focal segmental glomerulosclerosis; FTY-720, fingolimod; Fx, fractional; GFR, glomerular filtration rate; GI, gastrointestinal; GN, glomerulonephritis; Hb, hemoglobin; HCV, hepatitis C virus; HRS, hepatorenal syndrome; I/R, ischemia/reperfusion; IF/TA, interstitial fibrosis and chronic atrophy not otherwise specified; IgG, immunoglobulin G; IL2, interleukin 2; JAK3, Janus kinase 3; K_f, glomerular capillary ultrafiltration coefficient; LT, liver transplantation; MDRD, Modification of Diet in Renal Disease; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; ND, not determined; NS, not significant; NSAID, nonsteroidal anti-inflammatory drug; OLT, orthotopic liver transplantation; P-gp, P-glycoprotein; Q_A, single glomerular plasma flow rate; Rapa, rapamycin; RATG, rabbit antithymocyte globulin; RBC, red blood cell; retx, retransplanted; ROS, reactive oxygen species; RRT, renal replacement therapy; SNGFR, single nephron glomerular filtration rate; SRL, sirolimus; Tac, tacrolimus; TGF-β, transforming growth factor β; TIPS, transjugular intrahepatic portosystemic shunt; tx, transplant.

Address reprint requests to Michael R. Charlton, M.D., Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905. Telephone: 001-507-266-7054; FAX: 001-507-266-1856; E-mail: charlton.michael@mayo.edu

DOI 10.1002/lt.21877
Published online in Wiley InterScience (www.interscience.wiley.com).

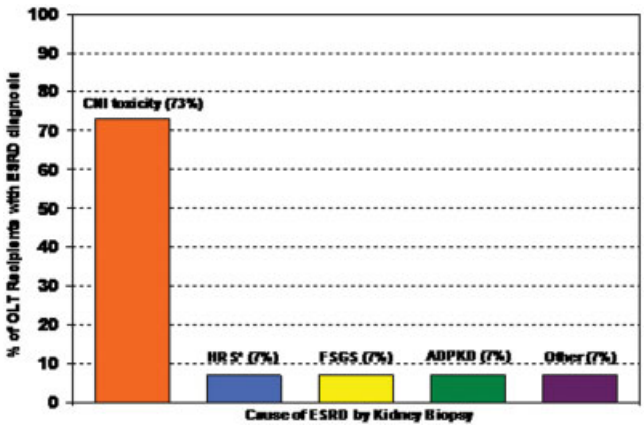

Figure 1. Biopsy-proven causes of ESRD in liver transplant recipients (some cases had multiple histological diagnoses). The asterisk indicates nonrecovery from pretransplant HRS. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CNI, calcineurin inhibitor; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HRS, hepatorenal syndrome; OLT, orthotopic liver transplantation. Adapted from Gonwa et al.[105]

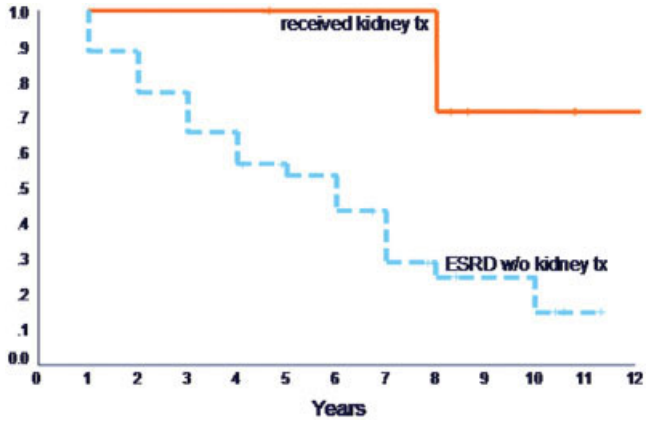

Figure 2. Patient survival: impact of subsequent kidney transplantation in orthotopic liver transplantation recipients (n = 1602). Abbreviations: ESRD, end-stage renal disease; tx, transplant. Adapted from Paramesh et al.[1]

transplant and posttransplant diabetes mellitus, and hypertension.[1-3] Hepatitis C infection is associated with multiple glomerular diseases, including membranous glomerulonephritis, mixed essential cryoglobulinemia, and membranoproliferative glomerulonephritis,[4-6] which may also contribute to the prevalence and severity of CKD before and after liver transplantation. Two series have shown a high prevalence of extensive glomerular abnormalities in renal biopsy tissue obtained at the time of liver transplantation from liver transplant recipients with and without hepatitis C.[7,8] Chronic liver failure itself causes renal insufficiency through a variety of mechanisms, including glomerular ischemia, hepatic glomerulosclerosis, and secondary immunoglobulin A nephropathy.

AKI

Acute deterioration in renal function is common in the period immediately before and after liver transplantation.[1,9-15] McCauley et al.[9] showed that 94.3% of recipients had acute renal failure, which was defined as a 50% increase in creatinine from preoperative levels. In a series from Spain, Gainza et al.[12] found acute renal failure (serum creatinine > 2.0 mg/dL or need for RRT) in 46% of orthotopic liver transplantation (OLT) recipients in the early postoperative period. Other series from Mount Sinai Medical Center (New York, NY) and Baylor College of Medicine (Dallas, TX) found postoperative RRT rates of 22% and 12% in 1602 and 724 liver transplant recipients, respectively.[1,15] The wide range of the reported rates of postoperative acute renal failure is partially due to the lack of a standard definition of acute renal failure prior to 2004.[16,17] The Acute Kidney Injury Network and the Acute Dialysis Quality Initiative[14] have developed a standard definition that can be applied in future studies. Most studies have consistently shown that postoperative renal failure has a significant impact on posttransplant outcomes, including mortality (Fig. 2).[1,9-15] In a study by O'Riordan et al.[14] in which the Acute Dialysis Quality Initiative definitions were employed, the 30-day mortality in subjects who had a 3-fold increase in serum creatinine or required RRT was 4 times greater than that in subjects with normal serum creatinine. Postoperative acute renal failure requiring RRT was also associated with a 2-fold increase in hospital stay (39 versus 73 days)[14] and a 5-fold increase in the duration of the postoperative intensive care unit stay (2 versus 10.5 days)[15] Finally, postoperative acute renal failure was a potent risk factor for CKD in the late posttransplant period.[3,18,19]

CKD

The majority of liver transplant recipients who survive beyond the first 6 months after liver transplantation develop CKD.[1-3,19-22] McCauley et al.[9] reported a CKD prevalence rate of 77.3% in OLT recipients. Gonwa et al.[3] showed that CKD (defined as serum creatinine > 2.5 mg/dL) developed in 4.9% and ESRD developed in 5.4% of OLT recipients (n = 834). In the Mount Sinai series, Paramesh et al.[1] found an incidence of ESRD of 23% at a median time of 46 months after liver transplantation. In a study of 1173 OLT procedures reported by Schmitz et al.[20] from Germany, CKD, defined as serum creatinine ≥1.8 mg/dL for ≥2 weeks, was observed in 11.7% of recipients. The wide range of reported incidence is partly due to the different thresholds used to define CKD. In a registry study of 36,849 OLT recipients in the United States in which the National Kidney Foundation Kidney Disease Quality Outcomes Initiative definition of CKD[23] was applied, investigators found a 5-year CKD stage IV-V incidence rate of 18.1% [stage IV CKD = estimated glomerular filtration rate of 15-29 mL/minute/1.73 m^2; stage V CKD = ESRD].[2] CKD in the liver transplant population is associated with a dramatically increased predisposition to cardiovascular events, an increased risk of hospitaliza-

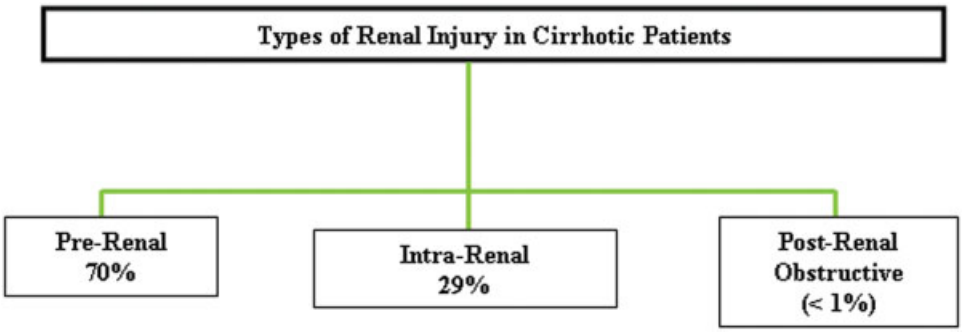

Figure 3.

tion, and a 4-fold excess mortality in comparison with recipients with preserved renal function.[19,24-26] Hepatic allograft dysfunction has been shown to occur more frequently in liver transplant recipients with chronic nephropathy.[27,28] Aside from a dramatic impact of ESRD on mortality (4- to 5-fold higher than that of recipients without CKD), even moderate CKD is associated with a significantly higher mortality rate. Finally, liver transplant recipients continue to experience a high rate of recurrent AKI during the late posttransplant period. In some series, the risk of AKI in the late posttransplant period has been as high as 25% per year, and recipients with CKD are also at a higher risk of intercurrent CKD.

Incidence, Diagnosis, Prevention, and Management of Acute Kidney Injury in Patients with Cirrhosis

Russell H. Wiesner

The development of acute kidney injury (AKI) in patients with cirrhosis is a frequent and ominous event. Indeed, renal dysfunction is a powerful predictor of death in patients with decompensated cirrhosis.[29] Serum creatinine is 1 of 3 variables used in the Model for End-Stage Liver Disease score, which is an excellent predictor of 3-month patient survival and is currently used for determining patient priorities for orthotopic liver transplantation in the United States and other countries.[30] In addition, pretransplant serum creatinine has been found to be one of the most powerful predictors of post–liver transplant survival.[31] Thus, preventing, identifying, and treating causes of renal dysfunction and preserving renal function in the patient with cirrhosis are important challenges for the liver transplant hepatologist.

CLASSIFICATION OF RENAL DYSFUNCTION

AKI occurs in approximately 20% of hepatorenal patients with cirrhosis.[32,33] In patients with cirrhosis, AKI can be classified as follows: (1) prerenal failure, (2) intrinsic renal disease (ie, glomerulonephritis and interstitial nephritis), and (3) postrenal injury related to a urinary obstruction (Fig. 3).[34,35] The most frequent cause of acute renal injury in patients with cirrhosis is prerenal azotemia; this occurs because of the progressive vasodilatory state of cirrhosis, which leads to relative hypovolemia and a decrease in renal blood flow, making patients with decompensated cirrhosis very susceptible to multiple insults to the kidney (Fig. 4). The most common causes of prerenal azotemia include the following: (1) sepsis, (2) gastrointestinal hemorrhage, (3) aggressive use of diuretics, and (4) diarrhea related to lactulose. All of these causes may result in additional hypovolemia resulting in further vasoconstriction and decreased renal blood flow. In addition, the use of nonsteroidal anti-inflammatory drugs, intravenous contrast, and aminoglycoside antibiotics (the latter having a direct toxic effect on renal tubules) is responsible for renal toxicity in a large number of patients with cirrhosis. Ultimately, hepatorenal syndrome (HRS; a functional type of prerenal acute injury) occurs in patients with cirrhosis who do not respond well to volume repletion. HRS can occur suddenly and spontaneously (type I HRS), and it often is precipitated by events that worsen vasodilatation, such as spontaneous bacterial peritonitis or a major esophageal variceal bleed. Type I HRS carries a very dismal prognosis.[36] The second type of HRS, type II, occurs more insidiously and has a better prognosis but can lead to type I HRS. Most often, however, acute renal failure in the patient with cirrhosis is related to multiple precipitating causes, including the presence of chronic kidney disease (CKD; eg, glomerular nephritis) and the development of AKI in the presence of type II HRS.

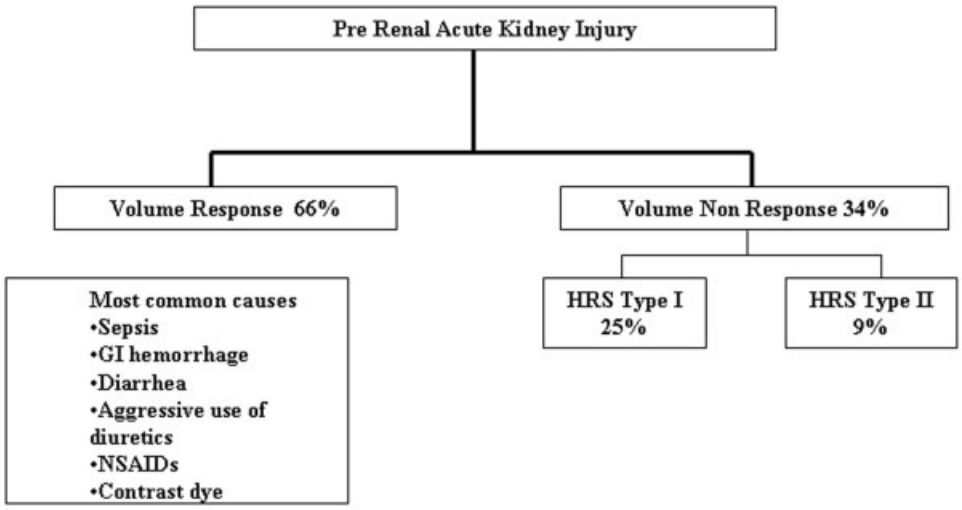

Figure 4. Abbreviations: GI, gastrointestinal; HRS, hepatorenal syndrome; NSAID, nonsteroidal anti-inflammatory drug.

	HRS	ATN	GN
Urine Na	<20 mEq	>40 mEq	>20 mEq
Fx Na Excretion	<1%	>2%	>2%
Osmolarity	>500	<350	-----
Urine Sediment	Bland	Epithelial casts	RBC casts, oval fat bodies – Proteinuria
Other markers		B-2 microglobulin	

Figure 5. Diagnosis of acute renal injury. Abbreviations: ATN, acute tubular necrosis; Fx, fractional; GN, glomerulonephritis; HRS, hepatorenal syndrome; RBC, red blood cell.

CKD occurs less often and may be secondary to glomerulonephritis, particularly immunoglobulin A nephropathy and diabetic nephropathy. Acute tubular necrosis is also common in patients who develop shock related to sepsis or who have experienced a major gastrointestinal bleed (Fig. 5). Interstitial nephritis related to drugs and toxins is also a common cause of CKD in patients with cirrhosis. Obstructive uropathy is a very uncommon cause in patients with cirrhosis.

In summary, AKI occurs in approximately 20% of hospitalized liver disease patients and is usually multifactorial, occurring in the context of a vasodilatory state related to portal hypertension. In general, AKI confers a poor prognosis, and the need for urgent liver transplantation should be considered.

DIAGNOSIS

Serum creatinine is the most established, simple, and inexpensive estimate of renal function and is the primary method of detection of all forms of renal failure. However, there are several limitations to the use of serum creatinine. First, serum creatinine is not helpful in distinguishing among various causes of renal injury. Second, serum creatinine lags behind renal injury and is therefore a delayed marker of decreased renal function. Third, significant renal disease can exist with minimal or no changes in serum creatinine because of renal reserves and enhanced tubular creatinine secretion. Lastly, serum creatinine is influenced by nonrenal factors such as body weight, muscle mass, race, age, gender, total body volume, and protein intake. The optimal method for measuring renal function is probably determination of the glomerular filtration rate with iothalamate or inulin clearance methods.

The differentiation of types of AKI can be aided by the following parameters: (1) urinalysis and microscopy of urinary sediment, (2) urinary sodium, (3) fractional sodium excretion, (4) osmolarity, and (5) biological markers. The differentiation of HRS, acute tubular necrosis, and glomerulonephritis is outlined in Fig. 5.

PREVENTION AND TREATMENT

Specific therapies used to treat renal injury depend on the cause. Prophylaxis and prevention of acute renal injury play important roles in the management of patients with cirrhosis and particularly those patients on the liver transplantation waiting list. Prophylactic therapy to prevent variceal bleeding and spontaneous bacterial peritonitis is an important preventative measure. In addition, close monitoring of diuretic therapy and titration of the dose of lactulose to prevent severe diarrhea are also important preventative measures. The use of albumin with large-volume paracentesis and antibiotic treatment of spontaneous bacterial peritonitis are important therapeutic measures to prevent renal damage.[37-39] The avoidance of nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, and intravenous contrast are important measures to consider in the management of a decompensated patient with cirrhosis. Although not very well described, abdominal

compartment syndrome due to increased intra-abdominal pressure secondary to ascites should also be considered when AKI is being evaluated in patients with cirrhosis.

In patients developing prerenal azotemia, removal of the precipitating factors and volume replacement with albumin are important. Renal replacement therapy should be considered in those patients who develop hypovolemia, uremia, hyperkalemia, and acidosis. In patients developing HRS, the use of systemic vasoconstrictor therapy with terlipressin plus albumin or noradrenalin combined with albumin has been known to reverse HRS in some patients.[40-42] This can buy some time to find an acceptable donor for liver transplantation. The old myths regarding HRS, which state that the kidneys are normal, that recovery of renal function is immediate, and that complete recovery of renal function will occur, are not necessarily true in all patients with HRS; HRS may lead to permanent damage, particularly in patients with cirrhosis who experience prolonged renal dysfunction.[36] In these patients, a simultaneous kidney transplant may be indicated.[43] The use of systemic vasoconstrictor therapy associated with albumin is now undergoing testing in patients with non-HRS acute renal injury.[44] Furthermore, newer therapies such as transjugular intrahepatic portosystemic shunts and the use of a molecular absorbent recirculating system with albumin have also been shown to be of benefit in patients with prerenal azotemia and in patients with HRS.[45,46] The use of renal replacement therapy for acute tubular necrosis and the use of intermittent hemodialysis versus continuous venous filtration remain controversial at this time, and more data are needed.[47]

Hepatorenal Syndrome: Clinical Features, Management, and the Role of Liver Transplantation

Andrés Cárdenas and Pere Ginès

Hepatorenal syndrome (HRS) is a potentially reversible cause of renal impairment that occurs in patients with cirrhosis and ascites and in patients with acute liver failure or alcoholic hepatitis.[48,49] HRS is characterized by impaired renal function, marked alterations in cardiovascular function, and overactivity of the sympathetic nervous and renin-angiotensin systems, which lead to severe renal vasoconstriction with a significant decrease of the glomerular filtration rate (GFR) to <30 mL/minute.[48,49] HRS occurs in approximately 10% of hospitalized patients with cirrhosis and ascites.[50] In this section, we describe the clinical features, diagnosis, and management of HRS with a specific emphasis on the role of liver transplantation (LT) as a therapy for HRS.

CLINICAL FEATURES

There are no specific clinical findings in HRS. The majority of patients have features of very advanced liver disease with hyperbilirubinemia, an elevated prothrombin time, thrombocytopenia, hepatic encephalopathy, hypoalbuminemia, hyponatremia, and a large amount of ascites. In some patients, HRS develops spontaneously without any apparent triggering event, whereas in others, it occurs in close relationship with events that impair circulatory function, such as bacterial infection (particularly spontaneous bacterial peritonitis), which may precipitate HRS in approximately 40% of cases.[51,52] Renal failure is common in patients with cirrhosis and gastrointestinal bleeding, occurring in 11% of cases, but in this setting, renal failure is usually due to renal hypoperfusion with or without acute tubular necrosis related to hypovolemic shock and not to HRS.[53]

There are 2 different clinical types of HRS, type 1 and type 2, which have previously been defined by the International Ascites Club.[48,49] In type 1 HRS, renal function deteriorates rapidly with an increase in serum creatinine to a level higher than 2.5 mg/dL in less than 2 weeks. In these patients, GFR is very low, commonly below 20 mL/minute, and serum creatinine levels are high, with average values of 4 to 5 mg/dL at the time of diagnosis. This type of HRS, if not treated, is associated with a very poor prognosis with a median survival of 2 to 4 weeks.[50,54] In type 2 HRS, there is a steady decline in renal function, and serum creatinine levels usually range from 1.5 to 2.5 mg/dL. Survival in patients with type 1 HRS is not dependent on the Model for End-Stage Liver Disease (MELD) score; that is, patients have very poor survival regardless of the MELD score. Patients with type 2 HRS have a better prognosis than those with type 1 HRS, with a median survival of 6 months. In patients with type 2 HRS, survival is dependent on the MELD score: those with a score ≥ 20 have a poor outcome versus those patients with a MELD score < 20.[54] The diagnosis of HRS relies on the exclusion of other conditions that may cause renal failure in cirrhosis, particularly volume depletion, shock, treatment with nephrotoxic drugs, and parenchymal kidney diseases.[48,49] The diagnostic criteria recently revised by the International Ascites Club are shown in Table 1.[49]

TABLE 1. Diagnostic Criteria for Hepatorenal Syndrome in Cirrhosis

1. Cirrhosis with ascites
2. Serum creatinine > 1.5 mg/dL (133 μmol/L)
3. No improvement of serum creatinine [a decrease to <1.5 mg/dL (133 μmol/L)] after at least 2 days off diuretics and volume expansion with albumin (1 g/kg of body weight up to a maximum of 100 g/day)
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of signs of parenchymal renal disease, as suggested by proteinuria (>500 mg/day) or hematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasound

NOTE: This table was adapted from Salerno et al.[49]

MANAGEMENT

The most important aspect of providing care to patients with HRS is the assessment of candidacy for orthotopic LT. Currently available therapies other than LT for HRS include the use splanchnic vasoconstrictors and albumin and transjugular intrahepatic portosystemic shunt (TIPS).

Vasoconstrictors

The administration of vasoconstrictors is the best medical therapy currently available for the management of HRS. The rationale of this therapy is to improve circulatory function through vasoconstriction of the extremely dilated splanchnic arterial bed, which subsequently improves arterial underfilling, reduces the activity of the endogenous vasoconstrictor systems, and increases renal perfusion. The available vasoconstrictors used for HRS are vasopressin analogues (terlipressin) and α-adrenergic agonists (noradrenaline or midodrine), which act on V1 vasopressin receptors and α-1 adrenergic receptors, respectively, present in vascular smooth muscle cells. In most studies, vasoconstrictors have been given in combination with intravenous albumin to further improve the arterial underfilling. Most of the published data come from the use of intravenous terlipressin for type 1 HRS. Results from 2 recent randomized controlled studies indicate that treatment with terlipressin together with albumin is associated with marked improvement of renal function in approximately 40% of patients.[55,56] Previous uncontrolled studies suggested a higher response rate (50%-75%).[2] Although there are no dose-efficacy studies, treatment is usually started with 0.5 to 1 mg every 4 to 6 hours intravenously, and the dose is increased up to a maximum of 2 mg every 4 to 6 hours after 2 days if there is no response to therapy (response to therapy is defined as a reduction of serum creatinine > 25% of the pretreatment values). Response to therapy is considered when there is a marked reduction of the high serum creatinine levels, at least below 1.5 mg/dL, which is usually associated with increased urine output and improvement of hyponatremia. The incidence of ischemic side effects requiring the discontinuation of treatment is approximately 10%. Some patients may develop transient pulmonary edema during the first few days of therapy. The 2 aforementioned randomized studies[55,56] showed that the overall population of patients treated with terlipressin and albumin did not have improved survival in comparison with the population of patients treated with albumin alone. However, both studies showed that responders in terms of improvement of renal function after therapy had a significant (but moderate) increase in survival in comparison with nonresponders. In one study, patients that responded to therapy had a 3-month probability of survival of 58% versus 15% in those that did not respond to therapy (median survival greater than 90 days versus 13 days, respectively, $P = 0.03$).[56] However, it is important to highlight that the improvement in survival is subtle, and this means that responders still have a high risk of death while awaiting transplantation and, therefore, should continue as priority candidates, although their MELD score may decrease after therapy. Factors associated with poor response include a bilirubin level ≥10 mg/dL and a leukocyte count ≥ 9500/mm^3 before therapy.[57] α-Adrenergic agonists (noradrenaline and midodrine) represent an attractive alternative to terlipressin because of their low cost, wide availability, and apparently similar efficacy in comparison with terlipressin.[58-60] However, information on the efficacy and side effects of α-adrenergic agonists in patients with type 1 HRS is still very limited.

There are limited data on the use of vasoconstrictors plus albumin for patients with type 2 HRS. However, data from uncontrolled studies suggest that they are effective in decreasing serum creatinine levels in these patients. In 2 controlled studies, patients with type 2 HRS that received terlipressin plus albumin had a response rate between 67% and 88%; however, few were treated with this strategy in both studies (n = 13), and therefore more controlled studies are needed in order to better define the role of vasoconstrictors plus albumin in the management of type 2 HRS.[56,61]

TIPS

Two uncontrolled studies indicate that TIPS may improve renal function and GFR and reduce the activity of the renin-angiotensin-aldosterone system and the sympathetic nervous system in patients with type 1 HRS.[45,62] Improvement in renal function after TIPS placement alone is slow and successful in approximately 60% of patients.[45,62] Studies assessing TIPS for type 1 HRS have included only patients with moderate to severe liver failure and excluded those with a history of hepatic encephalopathy, Child-Pugh scores ≥ 12, or serum bilirubin > 5 mg/dL. The applicability of TIPS in patients with type 1 HRS is low because TIPS is considered contraindicated in patients with features of severe liver failure, which are common findings in the setting of type 1 HRS. The use of TIPS in type 2 HRS may improve renal function and reduce the risk of progres-

sion to type 1 HRS.[45,63,64] However, a subanalysis of patients with type 2 HRS included in a controlled study comparing TIPS and repeated paracentesis plus albumin in patients for refractory ascites showed that the use of TIPS was not associated with improved survival.[63]

Renal Replacement Therapy (RRT)

RRT, mainly hemodialysis, has been used in the management of patients with type 1 HRS, especially in patient candidates for LT, in an attempt to keep patients alive until LT is performed or a spontaneous improvement in renal function occurs.[65] Unfortunately, the potential beneficial effect of this approach has not been demonstrated. Most patients develop side effects during RRT, including severe arterial hypotension, bleeding, and infections, that may contribute to death during treatment. Additionally, indications for RRT (severe fluid overload, acidosis, or hyperkalemia) are uncommon in type 1 HRS, at least in the early stages.

LT

LT is the treatment of choice for patients with cirrhosis and HRS, either type 1 or type 2. However, a main limiting factor of LT for type 1 HRS is the high mortality rate on the waiting list due to the combination of short survival expectancy and prolonged waiting times in many transplant centers. This limitation can be overcome if these patients are assigned a high priority for transplantation. The short survival of patients with type 2 HRS (median of 6 months) should also be taken into account when these patients are assessed for LT.

There are 4 management approaches when LT is considered for patients with HRS. One is LT alone because when patients are transplanted with severe renal failure, they usually require more days in the intensive care unit and longer hospitalizations in comparison with patients without HRS. Moreover, RRT requirements are high during the first weeks after LT but decline thereafter, yet 10% of patients may need RRT after 6 weeks.[66,67] The second approach that has been advocated for patients with HRS is combined liver-kidney transplantation (CLKT). Since the introduction of the MELD score system for organ allocation in the United States, there has been an increase in the use of CLKT for patients with cirrhosis and renal failure, which has been associated with a decline in survival after CLKT in comparison with the preceding years.[67-70] Moreover, the outcome of patients with HRS treated with CLKT is not better than that of patients with HRS treated with LT alone.[68] In addition, this approach uses kidneys that could be used for patients with chronic renal failure without liver disease, who have prolonged waiting times for renal transplantation. All these factors, together with the fact that renal function in HRS patients usually recovers after LT alone, suggest that CLKT is not a good approach for the management of patients with HRS. The only exception may be patients with HRS who have been on RRT for more than 8 weeks.[70] The third strategy is the performance of LT alone followed by kidney transplantation if necessary. With this approach, kidney transplantation is performed in patients who undergo LT for HRS and require RRT more than 60 days after LT. Data on this approach are limited to only one study, and thus more studies are needed in order to consider this strategy acceptable.[71] The final strategy is the treatment of HRS with vasoconstrictors plus albumin while the patient is on the waiting list and subsequently LT. Because pretransplant renal failure is an independent risk factor for both short-term and long-term posttransplantation patient and graft survival, all efforts should be made to improve renal function in order to obtain a better outcome after transplantation.[72] The reversal of both type 1 and 2 HRS before transplantation may not only help patients reach transplantation but also reduce the relatively high morbidity and mortality after LT characteristic of HRS. Therapy of HRS with terlipressin before LT leads to similar and slightly better 3-year survival than therapy without HRS (100% versus 83%).[73] However, data are limited, only 40% of patients respond to terlipressin, MELD scores may decrease with therapy, and patients may experience side effects in 10% of cases; therefore, more studies and a longer follow-up period still are needed to determine whether pre-LT therapy of HRS actually will translate into better post-LT outcomes.

Mechanisms of Nephrotoxicity of Immunosuppressive Drugs

Fuad S. Shihab

The perfect immunosuppressive drug would be able to suppress the alloimmune response while avoiding toxicity. Unfortunately, none of the currently available drugs fit the bill, and most are characterized by a narrow therapeutic index in addition to broad interindividual variability. Cyclosporine A (CsA) is the perfect example of a drug that has revolutionized the field of transplantation by decreasing the incidence of acute rejection and improving short-term graft survival. However, its clinical use has been greatly limited by nephrotoxicity, which affects renal function and long-term renal graft survival. Most data in this field pertain to CsA, although the effects of tacrolimus (Tac) are thought to be similar. Two forms of calcineurin inhibitor (CNI) renal toxicity have been described: acute and chronic nephrotoxicity. In kidney transplantation, it is often difficult to dissociate nephrotoxicity mechanisms from other immune and non–immune-mediated events that lead to graft fibrosis. As a result, nephrotoxicity is best studied in nonrenal organ transplantation in addition to autoimmune diseases and animal models of nephrotoxicity.

CNI NEPHROTOXICITY

Reversible Hemodynamic Injury

CsA and Tac cause vasoconstriction of the afferent and efferent glomerular arterioles and reduce the renal blood flow and ultrafiltration coefficient and, as a result, the glomerular filtration rate. Acute CNI nephrotoxicity is usually reversible with cessation of therapy.

The precise mechanism of vasoconstriction is unclear, but we know that there is an imbalance in vasoactive substances leading to reduced production of vasodilators such as nitric oxide and prostaglandins and enhanced release of vasoconstrictors such as endothelin (ET), thromboxane, and angiotensin II (Fig. 6). Increased sympathetic tone is also present, although vasoconstriction occurs even in denervated kidneys. Increased vascular resistance is clinically reflected by elevated serum creatinine and hypertension. These complications are more likely to occur with prolonged ischemia and high CNI doses but can also be seen with therapeutic levels.

These functional abnormalities are associated with increased urinary ET excretion. Studies with ET-R antagonists suggest that ET mediates CNI-induced afferent arteriolar vasoconstriction.[74] Calcium channel blockers can prevent renal vasoconstriction but not ET excretion, and this suggests that vascular injury is still occurring. Rarely, idiosyncratic vascular lesions similar to hemolytic uremic syndrome are seen, presumably because of CNI-induced injury to endothelial cells.

Injury Manifested as Vasculopathy or Tubulotoxicity

The chronic form of CNI nephrotoxicity is characterized by the development of structural damage that is irreversible and may lead to end-stage renal disease. Histologically, there is an obliterative arteriolopathy, glomerular ischemic collapse and scarring, tubular vacuolization, and focal areas of tubular atrophy and interstitial fibrosis (striped fibrosis). These changes are seen with both low and higher dose CsA therapy, although they seem to occur earlier with higher doses. It has been proposed that the arterial lesion is the primary abnormality, with secondary ischemia being responsible for the tubular and interstitial lesions. This is supported by animal studies in which the vascular and interstitial findings can be dissociated.

The factors responsible for chronic CNI nephrotoxicity are not well understood (Fig. 7). The renin-angiotensin-aldosterone system is up-regulated in experimental models of chronic CNI nephrotoxicity, although there is no evidence that it is activated in humans. Angiotensin II, through activation of AT_1 receptors, not only participates in renal vasoconstriction but also promotes fibrosis either directly by up-regulating transforming growth factor β (TGF-β) or through other independent mechanisms.[75] Renal hypoxia, which results from renal vasoconstriction, leads to the formation of reactive oxygen species that cause cellular injury and promote cellular death by apoptosis. Increased apoptosis occurs in kidneys exposed to CNIs, and this potentially explains the loss of cells that accompanies fibrosis, which impairs the ability of the kidney to remodel effectively. The expression of apoptotic genes, such as p53 and Fas ligand, is enhanced in rats administered CsA in a manner favoring the induction of apoptosis.[76]

The development of interstitial fibrosis is also associated with increased expression of the macrophage chemoattractant osteopontin and a number of chemokines. However, it is the up-regulation of TGF-β expression that has taken center stage, and this is supported by considerable experimental evidence.[77] The profibrotic actions of TGF-β include stimulation of extracellular matrix (ECM) synthesis, inhibition of ECM degradation, and modulation of ECM receptor expression to facilitate cell-ECM interactions. The role of TGF-β in chronic CsA nephrotoxicity has been supported by experimental findings in which the lesion was significantly diminished with anti–TGF-β therapy.[78]

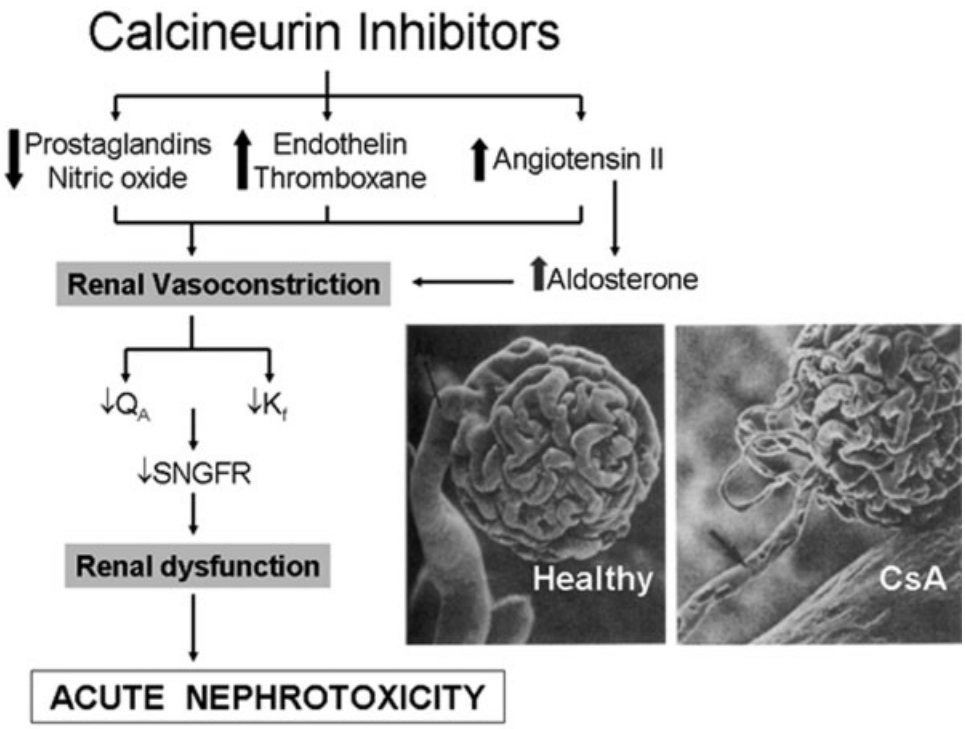

Figure 6. Abbreviations: CsA, cyclosporine A; K_f, glomerular capillary ultrafiltration coefficient; Q_A, single glomerular plasma flow rate; SNGFR, single nephron glomerular filtration rate.

Another antifibrotic agent, pirfenidone, which is thought to inhibit TGF-β actions, has been shown to significantly inhibit fibrosis by approximately 50% in CsA-treated rats.[79] TGF-β appears to be induced in part by decreased secretion of nitric oxide as well as increased local concentrations of angiotensin II, and this possibly explains the beneficial effects observed with angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists.[80] Blockade of aldosterone receptors has also been successful in ameliorating CsA nephropathy, at least partly by decreasing TGF-β.[81]

In addition, mycophenolate mofetil was capable of improving arteriolopathy in CsA-treated rats and decreased TGF-β but did not affect renal function.[82] A list of pharmacological treatments used to reduce or prevent chronic CNI nephrotoxicity is shown in Table 2. It is to be noted that none of the interventions are entirely successful in improving renal function or reducing fibrosis, and this suggests that a number of mechanisms are likely to be involved.

NEPHROTOXICITY OF mTOR INHIBITORS

In the absence of concomitant CNIs, mammalian target of rapamycin (mTOR) inhibitors do not seem to have significant nephrotoxicity in most animal and human studies. However, when they are combined with a CNI, serum creatinine levels often increase. Furthermore, clinical data have shown that the administration of sirolimus (SRL) after renal transplantation impairs recovery from delayed graft function, possibly because of inhibition of renal tubular cell proliferation, which normally occurs in tubular repair. A characteristic cast nephropathy lesion has also been reported. Proteinuria has been shown to occur with long-term use of SRL and may be related to a decrease in tubular reabsorption and/or podocyte dysregulation. Vascular endothelial growth factor is increased in this setting, and a lesion of collapsing focal segmental glomerulosclerosis has also been reported. In addition to a pharmacokinetic interaction raising CsA blood trough levels, there seems to be a CsA-SRL interaction occurring at the cellular level and resulting in enhanced nephrotoxicity. Both CsA and SRL are P-glycoprotein (P-gp) substrates (discussed later), and in human renal epithelial cells, inhibition of P-gp–mediated efflux by SRL leads to increased cellular concentrations of CsA that could explain, at least partly, the exacerbation of CsA nephrotoxicity.[83] In addition, SRL has been shown to increase TGF-β expression in experimental CsA nephrotoxicity.[84] The experience with the new mTOR inhibitor everolimus is limited, but similar increases in serum creatinine when it is used in conjunction with a CNI and proteinuria have been observed.

FACTORS INFLUENCING THE NEPHROTOXICITY OF IMMUNOSUPPRESSIVE DRUGS

Therapeutic drug monitoring is widely applied for the management of immunosuppressive drugs. It allows for individualized dose administration in an attempt to optimize safety and efficacy. Drug pharmacokinetics are affected by processes such as bioavailability, volume of distribution, binding, and elimination. Most of the time, drug exposure is best studied by the determination of the area under the concentration-time curve (AUC). In the case of CsA, an $AUC_{0\text{-}4}$ of 4400 to 5500 mg h/L or

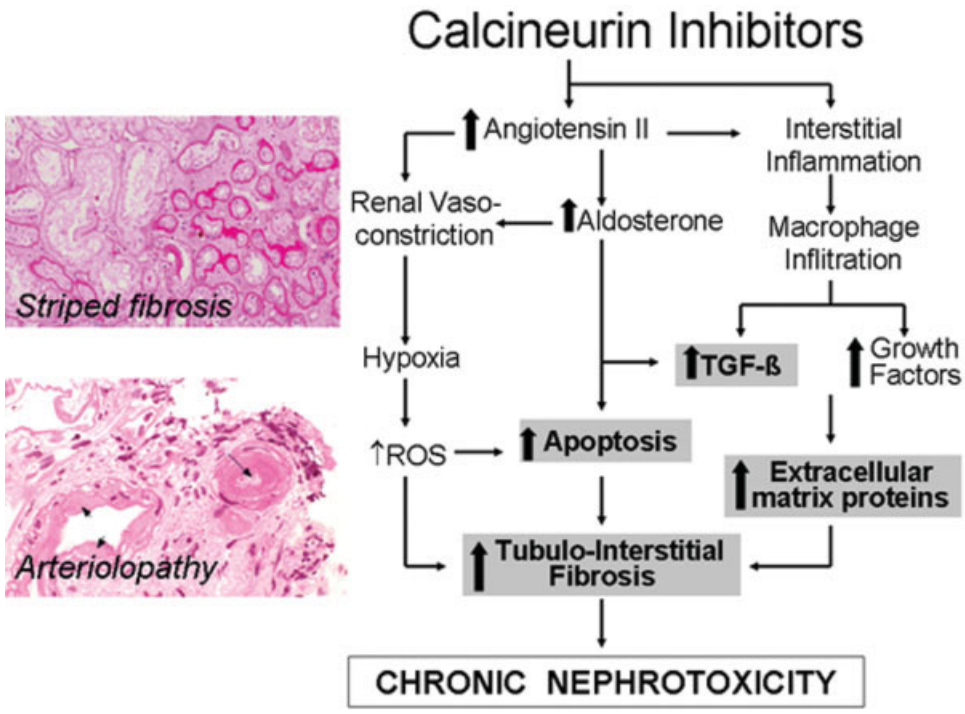

Figure 7. Abbreviations: ROS, reactive oxygen species; TGF-β, transforming growth factor β.

TABLE 2. Select Pharmacological Interventions for Cyclosporine A Nephrotoxicity

Treatment	Improvement of Renal Function	Reduction of Renal Fibrosis
Nifedipine	No	ND
Thromboxane synthase inhibitor	No	ND
ET-A/B-R blocker	30%	No
Fish oil	No	No
Pentoxifylline	No	ND
Losartan/enalapril	50%	50%
Losartan	No	50%
Pentosan polysulfate	No	45%
Leukotriene receptor antagonist	65%	ND
Oral magnesium	No	ND
Magnesium supplementation	80%	80%
Pirfenidone	20%	50%
l-Arginine	70%	50%
Spironolactone	100%	50%
Mycophenolate mofetil	No	↓ Arteriolopathy
Anti–TGF-β	ND	40%
TGF-βRII/IgG Fc	ND	60%
Sirolimus	Worse	Worse
Pravastatin	75%	55%
Hepatocyte growth factor	No	25%

Abbreviations: ET, endothelin; Fc, fragment crystallizable; IgG, immunoglobulin G; ND, not determined; TGF-β, transforming growth factor β.

an $AUC_{0\text{-}12}$ of 9500 to 11,500 mg h/L best defines the therapeutic window below which the risk of rejection is increased and above which the risk of nephrotoxicity is increased.[85] Unfortunately, CsA trough levels do not correlate well with AUC. This correlation is better with Tac but is not perfect. Because routine AUC measurements are cumbersome, clinicians continue to use the imperfect measure of CNI blood trough levels. Built into this is a major assumption: the concentration of the drug in the blood or serum is related to the concentration of free drug at its effector site in the tissue. However, this may not always be true, as shown in routine hepatic biopsies performed in 146 liver transplant recipients: tissue levels displayed an excellent correlation with liver histological Banff rejection scores ($R^2 = 0.98$), whereas blood levels did not.[86]

In addition, some patients seem to be particularly susceptible to CNI nephrotoxicity. CNIs are substrates for P-gp, an efflux pump that protects cells from environmental toxins. There is some evidence that decreased expression of P-gp may contribute to increased CsA tissue levels, leading to nephrotoxicity. In addition, there may also be an intrinsic renal susceptibility to CsA-induced renal vasoconstriction. Experimental support for this hypothesis is derived from a study of 8 pairs of stable, unrelated renal transplant recipients receiving a deceased donor kidney from the same donor. Although there was a parallel response to increasing CsA dose, 4 pairs showed an elevation in plasma creatinine, whereas 3 pairs showed no change ($P < 0.05$).

Pharmacogenomics could also explain 20% to 95% of the variability encountered not only in drug disposition and targets but also in side effects. This applies, for example, to the adenosine triphosphate–binding cassette B1 gene that encodes for the P-gp protein.[87,88] In addition, the P450 cytochromes (CYPs) play a key role in the metabolism of CNIs and mTOR inhibitors and are expressed in the liver and intestine. Although the influence of genetic polymorphism on CsA pharmacokinetics remains a source of contention, CYP3A5 polymorphism is undoubtedly closely associated with Tac disposition.

CONCLUSIONS

The mechanisms involved in the nephrotoxicity of immunosuppressive drugs remain poorly understood, and numerous mediators are likely to be involved. In addition, the success of transplantation remains largely dependent on the use of CNIs because the success of CNI-free regimens has been very limited. However, identification of elements that predispose patients to drug-related nephrotoxicity constitutes a major improvement and may offer a promising new approach to assess individual risk and select treatment according to patient parameters. Finally, studies of the genetic basis of interindividual variability in the pharmacokinetics and effects of immunosuppressive agents may optimize dosing strategies for immunosuppressive drugs after organ transplantation in the future.

APPROACHES TO THE MANAGEMENT OF RENAL INSUFFICIENCY IN LIVER TRANSPLANT RECIPIENTS

Evaluation and Pharmacotherapy of Calcineurin Inhibitor Toxicity

Stephen Textor

Calcineurin inhibitors (CNIs), including cyclosporine and tacrolimus, have been a fundamental component of immunosuppression for solid organ transplantation for more than 25 years. These agents regularly induce renal vasoconstriction and reduce the glomerular filtration rate (GFR). GFR typically falls 30% to 35% during the first weeks after CNI therapy is started in nonrenal transplantation. Cyclosporine has been most widely studied, but the effects of tacrolimus are similar, albeit less rapid and less severe.

EARLY AFTER TRANSPLANTATION (1-6 MONTHS)

CNIs rapidly alter hemodynamic factors within both systemic and renal circulations. These effects include a reduction in vasodilation (eg, prostacyclin and nitric oxide) and enhanced vasoconstriction (thromboxane A2 and endothelin).[89,90] Studies in human subjects using cyclosporine have indicated that this effect develops in a dose-dependent and time-dependent fashion within hours after each dose.[91] In some experimental models, sympatho-adrenergic activity is increased.[92] The net vasoconstrictor effect raises systemic vascular resistance, producing a rise in arterial pressure, and reduces renal blood flow and filtration. These early vascular changes are dose-dependent and reversible if the CNI is reduced or withdrawn. Clinicians recognize that preexisting hemodynamic compromise and/or intrinsic renal disease may magnify the nephrotoxic effects of CNIs. The evaluation of reduced renal function in this period focuses on the identification and removal of these additional factors when possible. These include identification of drug-drug interactions that change CNI levels. Drug interactions leading to elevated CNI levels are particularly common with antifungal therapy (ketoconazole, voriconazole, and itraconazole) and highly active antiretroviral therapy. Importantly, conditions producing relative volume depletion, hypotension, sepsis, and other nephrotoxic drugs magnify CNI nephrotoxicity. Chronic conditions predisposing to intravascular volume depletion, such as an ileostomy, chronic diarrheal states, and bladder-drained pancreas allografts, routinely reduce GFR, sometimes accelerating

the need for renal replacement or kidney transplantation. The aggressive administration of diuretic therapy after organ transplantation may accelerate this process.

Many patients treated with CNIs demonstrate moderate tubular dysfunction reflected by impaired acidification (renal tubular acidosis), magnesium wasting, and impaired potassium secretion (hyperkalemia). These are usually self-limited. During the early period after transplantation, a predilection for hyperkalemia can limit the use of trimethoprim-sulfa and/or agents that block the renin-angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers. In view of the multiple factors affecting both potassium and creatinine early after kidney transplantation, our practice is to avoid the routine use of ACE inhibitors and angiotensin receptor blockers for the first several months.

LATE AFTER TRANSPLANTATION (BEYOND 6 MONTHS)

Continued administration of CNIs eventually produces changes in glomerular filtration that no longer reverse after withdrawal of the drugs. Identification of irreversible nephrotoxicity depends on a biopsy demonstration of hyaline accumulation, vascular obliteration, and regional ischemia (striped fibrosis) and the exclusion of other lesions. Follow-up studies indicate that up to 17% of nonrenal solid organ transplant recipients (liver, heart, lung, and intestine) eventually develop stage 4 chronic kidney disease (CKD; estimated GFR < 29 mL/minute/1.73 m^2) during a mean follow-up of 37 months.[2] About 30% of these eventually progress to the need for renal replacement therapy, including kidney transplantation or dialysis. How best to identify individuals predisposed to developing ongoing renal injury that will accelerate during CNI exposure after transplantation remains problematic.[93,94] When GFR is reduced on the basis of hemodynamic changes primarily associated with organ failure, such as congestive heart failure or liver failure, it may improve substantially after hemodynamics recover with successful transplantation.[93] Many of these patients do not require combined liver-kidney or heart-kidney transplants.[95] It should be recognized that other forms of parenchymal renal injury may also coexist with advanced organ failure. Such intrinsic kidney pathology likely will affect the nephrotoxicity of CNIs and accelerate the loss of GFR after organ transplantation. Many patients with hepatitis C, for example, have evident immune complex deposition on kidney biopsy at the time of liver transplantation.[8] Over the long term, reduced GFR during CNI administration can develop for many reasons. Important causes include vascular occlusive disease, primary parenchymal diseases, including posttransplant diabetic nephropathy, immune complex diseases, and BK nephropathy. The last remains a significant problem (with a reported rate of 2%-5%) in kidney transplantation, but it also can occur in nonrenal transplants. Progressive loss of GFR primarily related to CNI use can be observed. Reduced GFR 1 year after solid organ transplantation remains a strong predictor of long-term nephrotoxicity and the development of progressive CKD. An evaluation should include studies to evaluate the renal circulation and the magnitude of proteinuria and to exclude outflow tract obstruction. Kidney biopsy should be considered when the explanation is unclear and/or significant proteinuria is detected.

PHARMACOTHERAPY OF CNI NEPHROTOXICITY

CNI dose reduction remains the mainstay of avoiding major progression. Dihydropyridine calcium channel blocking drugs effectively reduce systemic vasoconstriction (and therefore arterial pressure) but do not consistently increase renal blood flow or GFR. During early phases of vasoconstriction, blockade of the renin-angiotensin system (with ACE inhibition or angiotensin receptor blockers) has little effect in human studies, although long-term activation of this system increases their effectiveness for antihypertensive therapy after the first year. Animal models of CNI toxicity indicate that renin-angiotensin blockade reduces kidney fibrosis.[96] Although these agents lower proteinuria in subjects with glomerular disease, no specific benefits have been demonstrated in humans with respect to kidney function after nonrenal transplantation. Although human data are limited to uncontrolled observations, the use of ACE inhibition in conjunction with CNIs as a means of avoiding nephrotoxicity may provide immunological protection while mitigating toxicity and, in the long term, may be a more durable strategy than minimizing immunosuppression. Some studies suggest that amplification of vasodilator systems such as endogenous nitric oxide by the provision of excess substrate (L-arginine) can reverse the effects of cyclosporine.[97] Whether this strategy has clinically beneficial effects in patients with CNI nephrotoxicity is not yet known.

Complete withdrawal of CNIs has been undertaken, sometimes with substitution using alternative non-CNI immunosuppression such as sirolimus. Reports of cardiac transplant recipients with a measured GFR of 36 ± 2 mL/minute indicated that follow-up GFR rose to 48.7 ± 4 mL/minute after 12 months.[98] In some centers, long-term GFR is somewhat improved when a transition away from a CNI (cyclosporine) is achieved 3 to 6 months after the initial transplant.[99] Other experience with sirolimus has been mixed. A long-term, prospective, randomized comparison of tacrolimus-based and sirolimus-based regimens (CNI-free at all times) achieved similar levels of GFR, similar graft outcomes, and similar levels of hypertension with the 2 regimens.[100,101] Sirolimus has been associated with nephrotoxicity in its own right and often worsens proteinuria in patients with developing parenchymal kidney disease.[102,103] Hence, this agent should not be used in patients with worsening proteinuria.

Recent trends suggest that requirements for kidney transplantation after other solid organ transplants may be stabilizing despite the migration to solid organ trans-

plantation with more advanced kidney disease.[25,104] Careful avoidance of transient episodes of volume depletion or high blood levels can allow the safe use of CNIs for many years. Nonetheless, the "therapeutic window" of CNIs remains distressingly narrow. Improved methods for monitoring and minimizing nephrotoxic and vascular effects of these agents on the kidney are sorely needed.

Renal-Sparing Protocols in Liver Transplantation

Paul J. Marotta

Renal dysfunction is an exceedingly common and significant problem after liver transplantation. Renal impairment may start or already preexist in the early posttransplant period and may then progress as the years from transplantation march on. The renal impairment suffered by liver transplant recipients has only recently become increasingly apparent and has a clear impact on transplant recipients' overall quality of life, in addition to the evidence revealing a significant insult to these patients' overall morbidity and potential mortality. The cumulative incidence of chronic kidney disease (CKD) in the post–liver transplant recipient has been made evident by several authors, and no report has been more sobering than the one by Ojo et al.,[2] who not only detailed an alarming 18.1% incidence of CKD only 5 years after liver transplantation but additionally reported that renal dysfunction is a progressive and cumulative complication in all organ transplant recipients. The impact is significant, such that the presence of chronic renal failure in nonrenal transplant recipients is associated with a risk of death increased by a factor of more than 4.

Immunosuppressive therapy given after liver transplantation typically includes a calcineurin inhibitor (CNI). These agents have been used widely for several decades in the field of liver transplantation and have been responsible for the impressive increments in both patient and graft long-term survival. Despite the tremendous gains provided by CNIs, it has become increasingly clear that these agents are linked intrinsically to nephrotoxicity through vasoconstriction mechanisms and through other potential renal damaging adverse effects, namely hypertension, hyperlipidemia, and diabetes mellitus. This combined adverse effect profile has been implicated as the principle cause of progressive renal impairment after solid organ transplantation.[105] The nephrotoxicity related to the use of CNIs is not related to either the overall dosage or the trough blood levels produced.[106,107] Questions remain about whether the degree of chronic renal impairment or its progression can be either prevented or potentially reversed with the manipulation of CNI agents. Worldwide, liver transplant programs have struggled to identify immunosuppressive protocols that continue to have the benefit of low rejection rates, excellent patient and graft survival, and limited short-term and long-term toxicity. Several other immunosuppressive agents have been developed in an attempt to "spare" the kidney from toxicity. These agents have been used increasingly to overcome CNI toxicity.[108,109] They include mycophenolate mofetil (MMF) and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) and have proven efficacy in the field of liver transplantation.[110] Hence, despite the importance of the CNI class of immunosuppressive agents, combinations of other immunosuppressants are being used in an attempt to affect and potentially reverse renal impairment.

Although there is clear recognition that the etiology of chronic renal failure is multifactorial, the renal effect of CNIs does remain the key component. Immunosuppressive protocols have been developed and studied, with the main outcome measure being the impact on renal function. These renal-sparing strategies include the following:

1. The reduction or complete withdrawal of the CNI. This is typically accomplished with the introduction of an adjuvant agent such as MMF or azathioprine or, alternatively, the complete discontinuation of the CNI with the use of MMF monotherapy.
2. The conversion of primary CNI-based therapy to a non–CNI-based therapy such as one using sirolimus with MMF.
3. The use of antibody induction therapy in an attempt to delay the initiation of CNI-based therapy.

Renal impairment unfortunately is not easy to recognize in the early stages. Despite the poor correlation of serum creatinine to underlying renal function, this marker is often the only value on which physicians act, often well after the onset of true renal impairment.[111-113] Given the importance of long-term renal function in liver transplant recipients, it is not surprising that many clinical studies are now focused on accurately measuring renal function longitudinally. The challenge has been in selecting the most appropriate outcome measure and an adequate period of follow-up. Given the limitation of longitudinally measuring the glomerular filtration rate (GFR) in patients, the calculated GFR has been a reasonable surrogate marker and is most often the main outcome measure followed in clinical trials focused on the impact of various immunosuppression strategies on long-term renal function.[111]

The following strategies aim to halt the progression of renal impairment or reverse it. This is not meant to be

an exhaustive literature review but rather is meant to provide supporting evidence for several acceptable approaches to the management of post–liver transplant renal impairment.

REDUCTION OR COMPLETE WITHDRAWAL OF CNIs

Several studies have looked at a reduction in the overall dose and subsequent trough levels of CNIs; others have attempted the complete withdrawal of CNIs in an attempt to intervene in those patients with established renal impairment. CNI reduction has been accomplished with the addition of adjuvant agents such as MMF and azathioprine.[114,115] The few CNI withdrawal studies have placed patients on MMF monotherapy.[114]

Pageaux et al.[116] performed a prospective, randomized study in patients with established chronic renal impairment (serum creatinine > 140 μmol/L). One study arm had their CNI dose reduced by more than 50% of the initial dose with the addition of MMF (2-3 g/day), and the other study arm maintained CNI monotherapy without MMF (however, the patients were allowed to have a maximum CNI dose reduction of 25%). There was a significant reduction in serum creatinine at 1 year (171 versus143 μmol/L) and an improvement in creatinine clearance favoring the dose-reduced group, without any risk for rejection. This controlled study was able to show that in recipients with established renal impairment years after liver transplantation, the introduction of MMF combined with a significant reduction of the baseline CNI dose (>50%) leads to a significant improvement in GFR. Additionally, this study reveals that there is a strong reversible component of renal impairment.

We have shown similar results in a consecutive group of stable post–liver transplant recipients on CNI monotherapy who were evaluated longitudinally with an accurate, "measured" GFR after a protocol of CNI reduction to 75% of the baseline with the addition of MMF.[117] This strategy led to substantial improvement in the measured GFR from a mean baseline of 59.5 mL/minute to 69.3 mL/minute 1 year later. Of significant interest, the patients with more advanced renal impairment (GFR < 60 mL/minute) achieved the most improvement in GFR over time with this combination of CNI reduction with MMF. This adds further support to the fact that intervening, even when advanced renal impairment is present, can affect overall renal function, allowing us to speculate that we may be altering the natural history of this life-threatening complication.

Several other authors have shown similar results, with reductions of CNI dosing and the addition of MMF leading to substantial improvements in calculated creatinine clearance, estimated GFR, and measured GFR with no appreciable increase in the incidence of acute rejection.[114,118-120] There have been only a few reports of complete withdrawal of CNIs and the addition of MMF monotherapy, as this strategy has shown not only improvements in creatinine clearance but perhaps an undesirable increased risk of acute rejection.[119,121]

CONVERSION TO A NON–CNI-BASED THERAPY

The expansion of immunosuppressant agents has increased the opportunity for transplant physicians to tailor therapy to the individual patient. Effective immunosuppression with minimal toxicity remains the challenge; however, we are clearly approaching these goals. In those recipients with established renal impairment, mTOR inhibitors such as sirolimus have been used in an attempt to avoid CNI therapy completely. Sirolimus-based therapies have shown mixed results in terms of the potential for renal improvement. Watson et al.[122] was not able to show any appreciable change in the calculated GFR 1 year after converting a cohort of patients from CNI-based therapy to sirolimus. There are indeed many reports of significant improvements in GFR in cohorts converted from CNI-based therapy to sirolimus monotherapy or sirolimus with MMF; unfortunately, several of these studies also reveal that adverse events are relatively common. Side effects such as proteinuria, hyperlipidemia, and oral ulcers have limited the widespread use of sirolimus and erase any benefit to renal function that may exist. Several large-scale studies with a uniform patient population are in progress, and early reports do reveal an improvement in renal function in those randomized to sirolimus therapy versus CNI-based therapy. There may continue to be a cost to pay with sirolimus, however, as more severe rejection episodes are noted in addition to other adverse effects that affect patient morbidity.[123-127]

INITIAL INDUCTION THERAPY WITH THE DELAYED USE OF CNIs

In an attempt to delay the introduction of CNIs, induction therapy can be used, particularly in those individuals with abnormal renal function at the time of transplantation. The use of a potent induction therapy followed by a delayed introduction of CNIs has been shown to produce improvements in GFR.[128] A recent publication of the first prospective, randomized study evaluating renal function with induction therapy revealed that only a short delay in CNI introduction (4-10 days), in conjunction with daclizumab and MMF, preserved early renal function 1 and 6 months after liver transplantation without increasing the risk for acute rejection.[129] Others have also shown improvements in both short-term and long-term calculated GFR with the use of the induction agents daclizumab and antithymocyte globulin in combination with MMF.[130]

SUMMARY

Chronic renal impairment is exceedingly common after liver transplantation. Several strategies have been

employed to reduce or avoid CNIs with a goal of reducing CNI nephrotoxicity. Significant reductions or withdrawal of CNIs with the addition of adjuvant agents such as MMF have proven effective in improving estimated and measured GFR. Several studies support the idea that significant reductions in the CNI dose with the addition of MMF can lead to improved renal function without added toxicity or costs. However, the complete withdrawal of CNIs seems to lead to higher rejection rates and should be avoided. The substitution or conversion from CNI-based therapy to novel mTOR agents such as sirolimus has shown an inconsistent benefit in renal function yet a clear increase in various adverse events, so this strategy is limited to a select group of patients. Strategies that employ the use of induction agents at the time of transplantation seem to halt the early onset of renal dysfunction. Thus, induction therapy may be appropriate for recipients with preexisting renal impairment. In these patients, under the cover of a potent induction agent, corticosteroids, and MMF, one can delay the use of CNIs with the proven benefit of a reduction in short-term renal impairment.

The optimum immunosuppressive strategy for improving the long-term costs and complications associated with renal impairment remains unclear; however, until more prospective, randomized studies are performed, an individualized approach to immunosuppression is recommended in which ideally renal function remains a critical variable.

Renal Protection Strategies: Lessons from Renal Transplantation

Marcelo Cantarovich

Renal transplantation is the treatment of choice for patients experiencing end-stage renal disease. Over the past 2 decades, we have observed a reduction in the incidence of acute rejection from 30% to 55% to <15%.[101,131-133] However, long-term graft survival has not improved. The main causes of graft loss include death with a functioning graft[134] and chronic allograft nephropathy, which is presently known as interstitial fibrosis and chronic atrophy not otherwise specified (IF/TA).[135] The causes of IF/TA are multifactorial and include immunological and nonimmunological factors.[136-139] The currently used calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus (Tac), have been associated with the development of IF/TA. Protocol biopsies showed a >50% incidence of severe chronic changes in patients receiving CsA at 10 years' follow-up.[140] More recently, a progression of chronic changes was observed in 6-month protocol biopsies in 20.5% and 38% of patients treated with Tac.[141]

The present review analyzes current immunosuppressive strategies used to either treat renal transplant patients with renal dysfunction or prevent its development. Some of the studies have addressed the development and/or progression of IF/TA. Nonimmunosuppressive strategies such as the use of pulsatile machine perfusion for kidney preservation, the use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, the treatment of hypercholesterolemia, prophylaxis for cytomegalovirus infection, and the prevention and treatment of polyomavirus nephropathy and cigarette use are not discussed in the present review. The following strategies are summarized: avoidance of nephrotoxic combinations, CNI avoidance, use of low-dose CNIs, and early and late CNI withdrawal.

AVOID NEPHROTOXIC COMBINATIONS

Meier-Kriesche et al.[142] described decreased graft survival in patients receiving a combination of either CsA or Tac and rapamycin (Rapa). The authors analyzed 23,016 patients from the Scientific Registry of Transplant Recipients between January 1998 and July 2003. Patients receiving CsA and Rapa had decreased graft survival at 4 years post-transplant in comparison with patients receiving CsA and mycophenolate mofetil (MMF; 74.6% versus 79.3%, $P = 0.002$) as well as decreased death-censored graft survival (83.7% versus 87.2%, $P = 0.003$). The same authors analyzed 44,915 patients on Tac-based immunosuppression from the Scientific Registry of Transplant Recipients between 2000 and 2004. The combination of Tac with Rapa resulted in decreased death-censored graft survival at 3 years in patients on Tac and Rapa in comparison with patients on Tac and MMF (83.6% versus 90.4%, $P < 0.001$) as well as decreased graft survival in recipients of expanded criteria donor organs (74.5% versus 57.5%, $P < 0.001$).[143]

USE OF LOW-DOSE CNIs

In a randomized controlled trial including 1645 patients (the SYMPHONY trial), Ekberg et al.[101] compared low-dose Tac (trough level = 3-7 ng/mL), low-dose Rapa (trough level = 4-8 ng/mL), and low-dose CsA (trough level = 50-100 ng/mL) in combination with daclizumab, MMF, and corticosteroids and standard-dose CsA (trough level = 150-250 ng/mL) in combination with MMF and corticosteroids. At 1 year, the low-dose Tac group had a lower rate of acute rejection [12.3%

versus 24% (low-dose CsA), 37.2% (low-dose Rapa), and 25.8% (standard-dose CsA)] and a higher glomerular filtration rate (GFR; 69.6 versus 65.3, 64.4, and 63.5 mL/minute, respectively) in comparison with the other treatment groups.

CNI AVOIDANCE

Flechner et al.[144] compared Rapa (n = 31) and CsA (n = 30) in combination with basiliximab induction, prednisone, and MMF. There was no significant difference in the incidence of acute rejection in Rapa-treated patients (6.4%) and CsA-treated patients (16.6%). The 5-year death-censored graft survival rate was higher with Rapa versus CsA (96.4% versus 76.7%, $P = 0.02$). Moreover, patients on Rapa had a higher estimated GFR.[145]

In a randomized controlled trial, Larson et al.[100] compared Tac to Rapa in combination with prednisone and MMF in 165 renal transplant patients. The incidence of acute rejection was 10% in patients receiving Tac and 13% in those treated with Rapa. At 1 year post-transplant, protocol biopsies showed no difference in interstitial fibrosis, tubular atrophy, or glomerulopathy. However, chronic vascular lesions were more frequent with Tac versus Rapa (43% versus 26%, $P = 0.03$). The iothalamate GFR was higher with Rapa at 1 month, but there was no significant difference at 12 and 24 months post-transplant. Asberg et al.[146] compared daclizumab induction (5 doses), MMF (1.5 g twice daily), and prednisone to CsA, MMF (1.0 g twice daily), and prednisone in 54 low-risk renal transplant recipients (0% panel reactive antibodies and human leukocyte antigen DR–identical). The incidence of acute rejection was higher in the CsA avoidance group (70.4% versus 29.6%, $P = 0.006$). However, graft survival and the radionuclide GFR were similar at the 12-month follow-up.

In a single-arm, multicenter study, Vincenti et al.[147] evaluated the combination of daclizumab (5 doses), MMF (1.5 g twice daily for 6 months followed by 1.0 g twice daily), and prednisone in 98 renal transplant recipients with low immunological risk. The incidence of acute rejection was 48%. Acute rejection episodes were reversible. CNIs were initiated in 62% of the patients.

In a prospective, randomized controlled trial (n = 218), Vincenti et al.[148] compared costimulatory pathway blockade with belatacept (intensive and less intensive groups) and CsA. All the patients received prednisone and MMF. The incidence of acute rejection did not differ in the 3 treatment groups (7%, 6%, and 8%). However, patients receiving belatacept (intensive and less intensive groups) had a higher GFR (66 and 62 mL/minute/1.73 m^2) than CsA-treated patients (53.5 mL/minute/1.73 m^2). Moreover, patients receiving belatacept experienced a lower incidence of chronic allograft nephropathy at 1 year (29% and 20% versus 44% in CsA-treated patients).

EARLY CNI WITHDRAWAL

Kreis et al.[99] studied 525 renal transplant patients on Rapa, CsA, and prednisone. At 3 months, 430 patients were randomized to continue on the same regimen or discontinue CsA and continue on Rapa (trough levels were increased from 5 to 20-30 ng/mL) in combination with prednisone. There was no difference in 3-year patient survival (94.4% versus 96.3%) or graft survival (91.2% versus 93.5%). The incidence of acute rejection was 9.3% versus 10.2% pre-randomization and 5.6% versus 10.2% post-randomization in CsA-treated and Rapa-treated patients, respectively. At the 3-year follow-up, the GFR was >65 mL/minute in Rapa-treated patients versus 55 mL/minute in CsA-treated patients. Conversion to Rapa resulted in an improvement in renal function in patients with a GFR < 67 mL/minute versus a decline in patients on CsA.

Ekberg et al.[149] (the CAESAR study) randomized 536 patients into 3 groups:

Group 1: Daclizumab, MMF, steroids, and low-dose CsA (trough level = 50-100 ng/mL), with weaning begun in month 4 and discontinuation by month 6.

Group 2: Daclizumab, MMF, steroids, and low-dose CsA.

Group 3: MMF, steroids and standard-dose CsA.

The incidence of acute rejection was significantly higher in group 1 (38%) versus group 2 (25.4%, $P = 0.027$) and group 3 (27.5%, $P = 0.04$).

Flechner et al.[150] (the Orion trial) randomized 451 renal transplant patients into 3 groups:

Group 1: Rapa (8-15 ng/mL and then 12-20 ng/mL after week 13) and Tac (6-15 ng/mL), with discontinuation at 13 weeks.

Group 2: Rapa (10-15 ng/mL until week 26 and then 8-15 ng/mL) and MMF.

Group 3: Tac (8-15 ng/mL until week 26 and then 5-15 ng/mL) and MMF.

All the patients received corticosteroids and daclizumab. The incidence of acute rejection was significantly higher ($P < 0.01$) in group 2 (28.3%) versus group 1 (14.5%) and group 3 (9.4%). This resulted in an early termination of group 2.

Pearson et al.[151] (the Spare the Nephron trial) randomized 298 patients between 30 and 180 days post–renal transplant to either continue on a CNI (81% of the patients were on Tac) or convert from a CNI to Rapa (trough level = 5-10 ng/mL) in combination with MMF. Induction therapy and steroid use were based on center practice. The incidence of acute rejection was 7% in all groups. One year after randomization, the GFR increased by 27.9% in patients converted to Rapa versus 11% in those who remained on a CNI ($P = 0.052$) and 6.1% in those who remained on Tac ($P = 0.02$). There was a higher incidence of peripheral edema, oral ulcers, back pain, hypertension, hyperlipidemia, hypokalemia, and proteinuria in patients on Rapa.

LATE CNI WITHDRAWAL

Birnbaum et al.[152] reported a systematic review of 12 randomized controlled trials including 635 patients with chronic allograft dysfunction or chronic allograft

nephropathy (the term used before IF/TA). All patients were on a CNI, most often CsA, and were >6 months post-transplant at the time of randomization. The patients were converted to MMF, Tac or Rapa, or azathioprine, MMF or Rapa was added to their immunosuppressive regimen. The follow-up time ranged from 6 to 36 months. The results suggested that conversion from a CNI to MMF or Rapa may be beneficial with respect to renal function. Moreover, one trial showed a decreased incidence of chronic lesions in patients on MMF/Rapa compared to patients who continued on a CNI.[153] The incidence of graft loss ranged from 0% to 19%. On the other hand, the incidence of side effects was reported to be up to 50% with MMF and up to 68% with Rapa, and these side effects led to MMF or Rapa withdrawal in 0% to 24% of patients.[152]

CONCLUSIONS

The combination of a CNI and Rapa is associated with inferior long-term graft survival in comparison with a CNI and MMF.[142,143] The use of low Tac trough levels (3-7 ng/mL) in combination with MMF and prednisone results in a lower acute rejection rate and a higher GFR in comparison with standard-dose and low-dose CsA and low-dose Rapa.[101]

There are controversial results regarding the incidence of acute rejection in CNI avoidance protocols using MMF and Rapa and anti-CD25 monoclonal antibody induction.[100,144,146,147] Strategies using Rapa, MMF, and prednisone as well as belatacept, MMF, and prednisone have resulted in a lower incidence of chronic lesions without increasing acute rejection rates versus CNIs.[100,145,148]

Early CNI discontinuation has resulted in a variable incidence of acute rejection. A higher acute rejection rate has been observed after the discontinuation of CsA,[99,149] whereas no difference has been observed in other trials in which a majority of the patients discontinued Tac.[150,151] However, acute rejection does not seem to influence graft survival during the early follow-up. Conversion to Rapa resulted in an improvement in renal function in patients with a GFR < 67 mL/minute versus a decline in patients on CsA.[99] The drawback remains the higher incidence of side effects in patients receiving the MMF/Rapa combination.[151] The late conversion from a CNI to MMF and/or Rapa results in an improvement in renal function versus continuation on a CNI, a reduced-dose CNI, or a reduced-dose CNI and Rapa.[152] There is a potential for decreased progression of IF/TA,[153] and the incidence of graft loss ranges from 0% to 19%.[152] There is an increased incidence of side effects secondary to MMF and Rapa that need to be balanced with the benefits of this combination. Future strategies should focus on the optimization of the presently used renal protective strategies and the development of new immunosuppressive combinations with a lower side-effect profile.

New Immunosuppressive Agents and New Protocols: Impact on Renal Function in Liver Transplantation

James D. Eason

Many new immunosuppressive agents are being tested in investigative trials trying to decrease the reliance on calcineurin inhibitors (CNIs) in liver transplantation. One of the primary incentives for developing these new agents is to decrease the impact of immunosuppression on renal dysfunction following transplantation. There is limited experience with these new agents in liver transplantation. This report summarizes new immunosuppressive agents under investigation and their possible role in preserving renal function in liver transplantation. Experience using rabbit antithymocyte globulin (RATG) in a CNI-sparing protocol is summarized as well.

Current clinical trials of the effects of immunosuppression on renal function in liver transplantation from ClinicalTrials.gov[154] are as follows:

1. AEB071: pharmacokinetics with tacrolimus (Europe).
2. Everolimus with basiliximab versus cyclosporine (Europe).
3. Everolimus: tacrolimus withdrawal (United States).
4. Belatacept versus tacrolimus (United States).
5. Thymoglobulin: delayed tacrolimus (Nebraska).
6. Sirolimus with mycophenolate mofetil (MMF) and anti-CD25 induction.
7. Spare the Nephron: sirolimus with MMF versus CNI with MMF.

New agents under investigation in transplantation fall into the 4 main categories listed here:

1. Costimulatory blockade: belatacept,[155-157] efalizumab,[156-158] and alefacept.[156,157,159]
2. Inhibitors of proliferation signals: everolimus.[160]
3. Janus kinase 3 (JAK3) inhibitors: CP690550 9.[156,157]
4. Protein kinase C inhibitor: AEB071.[156,157]
5. Inhibitors of nucleotide synthesis: FK778.[156,157,160]

6. Inhibitors of lymphocyte trafficking: fingolimod (FTY-720).[156,157]
7. Potentially less nephrotoxic CNIs: ISA-247.

Belatacept and alefacept are examples of costimulatory blocking agents. Belatacept (LEA29Y) is a second-generation cytotoxic T lymphocyte antigen 4 (CTLA4)–immunoglobulin that blocks the CD28/CTLA4-CD80/CD86 binding interactions. Blockade of this interaction inhibits T cell proliferation. Belatacept has been investigated in a phase II kidney transplantation trial against cyclosporine. This trial consisted of belatacept injections every 2 weeks for 1 year. There was an improvement in the glomerular filtration rate in the belatacept-treated group over cyclosporine, but there was no difference in biopsy-proven acute rejection.[155-157] Belatacept is now being investigated in a phase II clinical trial in liver transplantation.

Efalizumab is a humanized monoclonal antibody to CD11a that interferes with lymphocyte function–associated molecule 1/intercellular cell adhesion molecule interaction. Efalizumab has been investigated in phase II and III clinical trials in renal transplantation in conjunction with full-dose or half-dose cyclosporine, MMF, and steroids. The efalizumab arms had decreased rejection and no identified nephrotoxicity.[156-158] There are no liver transplant data at this time.

Everolimus is a mammalian target of rapamycin inhibitor that inhibits proliferation signals. It has been used successfully in CNI conversion trials in liver transplantation in Europe. Conversion from a CNI to everolimus was feasible in 75% of the cases and was associated with improvements in renal function for patients with higher baseline calculated creatinine clearance. It is currently under investigation in the United States in a tacrolimus-withdrawal trial.[160]

Alefacept is an anti-CD2 antibody consisting of a lymphocyte function–associated molecule 3/immunoglobulin G fusion protein. Alefacept blocks CD2, causing apoptosis of effector memory cells. It has been approved for psoriasis and has no known nephrotoxicity. There are no transplant data on alefacept at this time, except for the treatment of graft-versus-host disease in bone marrow transplantation.[156,157,159]

JAK3 inhibitors block signal 3 of the immune response and are lymphoid-specific. These agents interfere with JAK3-dependent interleukin 2 (IL2) proliferation of T cells. CP690550 is a JAK3 inhibitor that has been used in phase II trials comparing JAK3 to tacrolimus with IL2 receptor antibody, MMF, and steroids in renal transplants. There was no difference in biopsy-proven acute rejection or the estimated glomerular filtration rate at 6 months.[156,157] There are other JAK3 inhibitors in early trials.

AEB-071 is a protein kinase C inhibitor with inhibition of both lymphocyte proliferation and IL2 messenger RNA expression. This inhibition abolishes the production of several cytokines by activated human T cells. AEB-071 has been used in CNI-free protocols for kidneys, but these trials were stopped because of an increased incidence of acute rejection in the AEB-071 arm. There is an ongoing CNI-free kidney trial as well as pharmacokinetic trials in liver transplantation in Europe. AEB-071 has no known nephrotoxicity.

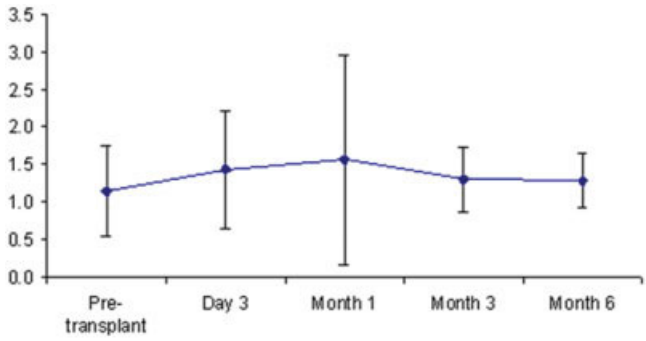

Figure 8. Serum creatinine in rabbit antithymocyte globulin induction with calcineurin inhibitor delay and reduction.

FTY-720 is an immunomodulator, that is, an agonist of sphingosine 1–phosphate receptor 1 on thymocytes and lymphocytes that regulates egress from the thymus and peripheral lymphoid organs. FTY-720 causes internalization of the receptor, rendering cells unresponsive to signals to egress from lymphoid organs. Clinical trials of FTY-720 in kidney transplantation with reduced-dose cyclosporine A demonstrated increased acute rejection macular edema in some subjects, and this caused further transplant studies to be discontinued.[156,157] There was no direct nephrotoxicity. FTY-720 is currently being evaluated for multiple sclerosis.

ISA-247 is a novel, potent CNI. In interim results of a phase 2b study in kidney transplant recipients (n = 116), ISA-247 was associated with a frequency of acute cellular rejection that is similar to that observed in the control, tacrolimus-based arm.

In an ongoing single-center study of RATG induction as a CNI-sparing protocol in steroid-free liver transplantation,[161] 315 patients were induced with RATG (1.5 mg/kg) in the anhepatic phase and on posttransplant day 2 for a total of 3 mg/kg. Maintenance therapy with MMF was started on day 1 and continued for 3 months. Tacrolimus was delayed a minimum of 3 days or when serum creatinine fell below 2 mg/dL. Primary sirolimus was initiated in 35 patients with serum creatinine > 2.5 by day 14. Mean tacrolimus levels were 7.2, 7.4, 7.1, and 5.8 at 1 month, 3 months, 6 months, and 1 year, respectively. The serum creatinine level and estimated glomerular filtration rate assessed in 180 patients who were at least 1 year out from transplant showed a slight worsening at 1 month post-transplant with a slow and steady improvement at 6 months and 1 year post-transplant (Figs. 8 and 9). Patient survival and graft survival at 1 year were 90% and 87%, respectively, with a 10% incidence of steroid-requiring rejection. Conclusions at this time from this experience are that tacrolimus can be safely delayed up to 14 days with RATG induction in the absence of steroids with excellent patient and graft survival and a low incidence of rejection. Delaying and decreasing tacrolimus dosing may

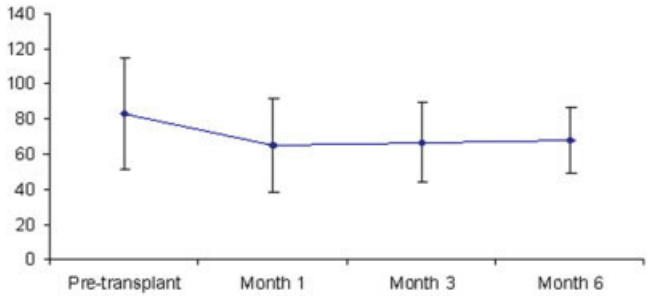

Figure 9. Estimated glomerular filtration rate in rabbit antithymocyte globulin induction with calcineurin inhibitor delay and reduction.

provide long-term protection against further declines in renal function.

SUMMARY AND CONCLUSIONS

Although there are many new agents on the horizon, several agents that were thought to be promising have been discontinued because of inferior results or prohibitive side effects. The most promising new strategies are costimulatory blockade with belatacept, alefacept, or efalizumab and JAK3 and protein kinase C inhibition. Antibody induction with CNI delay and even avoidance shows promising early results.

Intraoperative Renal Protection: Anesthesia Approaches

Michael A.E. Ramsay and Juan Carlos García-Valdecasas

The strategy for intraoperative renal protection during liver transplantation is the prevention of injury or, in many patients, further injury to the kidney. Renal ischemia, inflammation, and exposure to nephrotoxins are the main reasons that renal dysfunction or failure can develop during liver transplantation.[2] Liver recipients are at increased risk in the intraoperative period for renal deterioration because they frequently present with preexisting renal dysfunction, often as a result of hepatorenal syndrome. Intraoperatively, severe hemodynamic and volume changes occur, and at reperfusion of the liver graft, the new organ, the kidneys, and other major organs are exposed to inflammatory cytokines. The vascular endothelium is particularly at risk during the ischemia/reperfusion (I/R) period.[162] The glomeruli are an extension of this vascular endothelium. The exposure to potential nephrotoxic drugs may occur intraoperatively with the administration of agents such as vancomycin and calcineurin immunosuppressants. Blood flow to the kidneys is autoregulated to maintain a stable glomerular filtration rate with an arterial pressure of approximately 80 to 160 mm Hg. This autoregulation maintains fluid and salt balance and preserves the glomerular structure. Azotemia and oliguria can represent specific diseases, but they may also be manifestations of a normal response of the kidneys to volume depletion or a reduction in renal blood flow.

Hemorrhaging and the need for large-volume red blood cell and plasma transfusions are detrimental to renal perfusion and contribute to the risk of postoperative renal failure. Measures during the operation should be aimed at avoiding hemorrhaging and, by doing so, reducing the risk of renal compromise. As general principles, maintenance of adequate blood pressure (tissue perfusion) and avoiding the need for a massive transfusion are desirable in liver transplantation, as they are in all operations.[163]

During the procedure, the aim is to maintain the coagulation profile, which will enhance hemostasis, and minimize the requirement for transfusion of blood products, including plasma and red blood cells.[164,165] American Society of Anesthesiologists guidelines suggest that the threshold for a red blood cell transfusion is a hemoglobin level within 60 to 100 g/L, the threshold for plasma is an international normalized ratio greater than 1.5, and the threshold for a platelet transfusion is a platelet count less than 50×10^9/L.[166] By a combination of isovolemic hemodilution and maintenance of a low central venous pressure (keeping the patient "dry"), Massicotte et al.[167] showed that the need for a red blood cell transfusion during the procedure is significantly reduced, and this consequently decreases the number of postoperative complications, including renal failure.[168]

Using a similar approach that also preserves the vena cava (piggyback technique) and uses a portocaval shunt during the anhepatic phase, we can significantly reduce blood product requirements while maintaining adequate diuresis[168] (Table 3). This technique also employs a continuous infusion of norepinephrine to maintain a mean arterial pressure above 65 mm Hg.

Venovenous bypass, the piggyback technique, and temporary portocaval shunts share the same objective of maintaining hemodynamic stability during the anhepatic period. A prospective, randomized trial of venovenous bypass showed that, although renal function was adequately preserved during the anhepatic phase, the effect did not last for more than 24 hours.[169] The beneficial effect (as measured by inulin clearance, urinary β_2-microglobulin, and *N*-acetyl-β-D-glusaminidase) was evident only during the operation. It has been shown that the piggyback technique does not compro-

TABLE 3. Analysis Comparing 2006 and 2007 with Respect to Blood Cell Component Requirements and Renal Function

	2006 (n = 69)	2007 (n = 78)	*P*
Plasma-Lyte (mL)	2328 + 941	1887 + 632	0.001
FFP (mL)	1884 + 1910	1240 + 1014	0.01
RBC (U)	5.6 + 7.2	3.3 + 3.1	0.014
Diuresis	1406 + 895	1056 + 622	0.006
Balance (mL)	−785 + 2309	−812 + 1296	NS
Final Hb (g/L)	94 + 9	97 + 2	NS
Cr (baseline) (mg/dL)	0.99 + 0.3	0.91 + 0.3	NS
Cr (24 hours) (mg/dL)	0.99 + 0.4	0.95 + 0.4	NS

NOTE: Significant differences were found with respect to blood products and Plasma-Lyte, whereas similar renal function was maintained. This table is reprinted with permission from Beltran et al.[168]
Abbreviations: Cr, creatinine; FFP, fresh frozen plasma; Hb, hemoglobin; NS, not significant; RBC, red blood cell.

mise renal outflow at any time, maintaining normal kidney function.[170] The anastomosis of the donor liver to the vena cava is performed at the junction of the 3 hepatic veins, with care taken to avoid compromising vena cava flow.[171,172] It has been argued that preserving the vena cava is the most "physiological" method of removing the diseased liver. A massive transfusion of fluid to maintain hemodynamic stability is avoided during the anhepatic phase.

In a recent randomized trial of temporary portocaval shunting during the anhepatic phase, Figueras et al.[173] showed that the technique can decrease blood transfusion requirements, but there was no significant improvement in postoperative renal function. The use of apronitin to reduce bleeding has been common, but a recent report of diminished survival and worse serum creatinine levels in cardiac surgery patients who received aprotinin has limited its use in liver transplantation.[174]

Pharmacological agents are used in combination with volume replacement to maintain a mean arterial pressure above 65 mm Hg.[175] Norepinephrine appears to be the vasopressor of choice.[176,177] The use of loop diuretics and "renal-dose" dopamine, although common, does not prevent renal injury.[178-183] Pretransplant use of vasoconstrictors, such as terlipressin, has demonstrated some promise in the management of hepatorenal syndrome, but to date, no data exist about the intraoperative use of vasopressin analogues.[184] Fenoldopam has been demonstrated to reduce the need for renal replacement therapy in cardiovascular surgery, but its efficacy in the liver transplant recipient is still controversial.[185-189] Abdominal compartment syndrome, causing compression on the kidneys, can be a significant cause of renal dysfunction following liver transplantation.[190]

The vascular endothelium is activated by both the ischemia and reperfusion stages of liver transplantation. This results in the activation of polymorph neutrophils and platelets causing adhesion to the endothelium, creating a proinflammatory and prothrombotic surface and a loss of local vasoactive mechanisms. This process is facilitated by increased permeability of the endothelium, cell adhesion molecules, and inflammatory cytokines. The endothelial dysfunction is further enhanced by a depletion of nitric oxide resulting in a vasoconstrictive state. Oxidative stress results in an increase in reactive oxygen species that include superoxide, hydrogen peroxide, and hydroxyl ions. These free radicals also cause extensive cellular damage. The cytoprotective effects of antioxidants are inactivated by the massive oxidant load caused by the I/R syndrome. The vascular dysfunction caused by this cascade of events may result in a systemic inflammatory response causing multiorgan dysfunction, including renal failure.

Many therapeutic approaches have been tried in an effort to reduce the injuries caused by reperfusion. They include the use of free-radical scavengers, vasodilators such as inhaled nitric oxide, prostaglandin E1, and various antioxidants. Ischemic preconditioning is being investigated as a method of preventing I/R-induced injury. Because oxidative stress and associated inflammation are potential mechanisms for renal injury during surgery, strategies to reduce inflammation include the administration of *N*-acetyl cysteine. *N*-Acetyl cysteine, a scavenger of oxygen free radicals, potentially can stimulate endothelium-derived relaxing factor, thereby improving microvascular blood flow. The data for perioperative renal protection are not yet convincing, but it warrants further trials.[191-194] In a small human study, inhaled nitric oxide at 80 ppm intraoperatively was demonstrated to attenuate the I/R injury and improve liver graft function.[195] This should have a positive downstream effect on the other major organs, including the kidneys, and warrants further study.

Summary of Posttransplant Strategies

James Neuberger

The improved outcomes after liver transplantation over the last 3 decades are due primarily to a reduction in early mortality and graft loss in the first 6 to 12 months.[196] The lack of improvement in patient and graft survival over the longer term is likely due to a combination of many factors, some of which are associated with the need for chronic immunosuppression.

There are several approaches to minimizing calcineurin inhibitor (CNI) nephrotoxicity, and the first is to prevent and/or treat other causes of nephrotoxicity such as hypertension and diabetes mellitus. Unnecessary damage to the kidneys should be avoided by limiting the use of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs.

Deliberate modifications in the use of CNIs to avoid nephrotoxicity are common. They include avoiding them entirely, delaying their introduction, and minimizing their dose. Several studies have shown that late CNI-associated nephrotoxicity is predicted by pretransplant renal function and the level and dose of the CNI in the first 6 to 12 months post-transplant.[19,93] Thus, the risk of renal failure is determined, at least in part, by early events; therefore, especially in those at risk, strategies should be aimed at minimizing high concentrations of CNIs in the first year. However, the use of both cyclosporine and tacrolimus has been associated with better graft and patient survival,[197] so most clinicians will still use these agents. Sirolimus is usually not used in the first 6 months because of its impact on wound healing and possible thrombotic tendency, which may result in graft loss from hepatic artery thrombosis. One approach is to use induction therapy (such as interleukin 2 receptor blocking, campath-1, or thymoglobulin) with corticosteroids and an antimetabolite such as mycophenolate.

There are now a few studies that have used delayed introduction of CNIs (until days 5-7) and shown that, at least in the short term, this approach is associated with less nephrotoxicity at 1 year.[129,198] Whether this will be extrapolated to less renal failure in the longer term is uncertain, and whether this immunosuppression regimen will be associated with other problems, such as more aggressive hepatitis C disease, again remains to be shown.

It is popular to aim for lower blood levels of CNIs, usually in conjunction with the use of other nonnephrotoxic immunosuppressants. The target levels of CNIs are derived from both the experience of renal transplantation and clinical experience. However, there is no strong reason to believe that blood concentrations of either tacrolimus or cyclosporine will fully reflect the completeness of the reduction of the antigraft immune response or that nephrotoxicity may not develop at a concentration similar to (or indeed below) that which is immune-effective. Thus, one strategy in the development of renal impairment will be to reduce the CNI dose and monitor the recipient for signs of early rejection. The reduction in the CNI dose can be done either with monotherapy or with the addition of other immunosuppressive agents, such as mycophenolate and/or corticosteroids.

When patients manifest evidence of CNI nephrotoxicity, the clinician has several options, including reducing the CNI without altering other immunosuppressive drugs; reducing the CNI with an increase in or addition of other agents; and switching to alternative non-CNI regimens, such as mycophenolate monotherapy, mycophenolate with steroids, steroids and azathioprine, or sirolimus. Mycophenolate monotherapy has been associated with acute rejection, ductopenic rejection, and graft loss.[199] Switching to sirolimus may be helpful in selected cases, but the agent itself is associated with other toxicities and should be avoided when there is significant proteinuria. Improvement in renal function does not always occur.[200] There are no strong data to tell the clinician at what level of renal impairment switching should start or above what level of impairment the change is futile.

Immunosuppression Withdrawal: A Strategy to Improve the Renal Function of Liver Transplant Recipients?

Sandy Feng

To a tremendous degree, the everyday success of liver transplantation has been attributed to the emergence of calcineurin inhibitors as the primary axis of immunosuppression. However, the main toxicity of calcineurin inhibitors is well known to be nephrotoxicity. For adult liver transplant recipients, the cumulative incidence of chronic renal failure has been reported to be 8.0% ± 0.1% at 1 year, 13.9% ± 0.2% at 3 years, and 18.1% ± 0.2% at 5 years after liver transplantation.[2] Of children who are, on average, 7.6 ± 3.4 years after liver transplantation (range = 3-14.6 years), 32% suffer from renal dysfunction, which is defined as a measured glomerular filtration rate of less than 70 mL/minute/1.73 m^2.[201] Calcineurin inhibitor withdrawal, in the context of tolerance trials, has obvious implications for renal function in liver recipients.

Several single-center experiences have demonstrated that prospective immunosuppression withdrawal can be successful for both adult and pediatric liver transplant patients.[202-213] Table 4 summarizes the published experience for adults. Of 316 adult patients for whom immunosuppression withdrawal was attempted, 57 (18%) were successful; 168 (53%) developed clinically suspected and/or biopsy-proven acute rejection, and 9 (3%) experienced chronic rejection with 2 resultant deaths and 2 patients undergoing retransplantation. Unfortunately, the subgroups of recipients in which withdrawal was attempted were often poorly defined and differed from center to center, yielding imprecise information concerning the prevalence of functional tolerance either in the overall group or in a well-defined subset of the adult transplant population. For pediatric liver transplant recipients, the outcome of immunosuppression withdrawal may be better. The University of Pittsburgh has provided updated information regarding the subset of pediatric liver transplant recipients for whom withdrawal has been attempted. Of 64 children, 22 (34%) appeared to be functionally tolerant, 9 (14%) experienced acute rejection, and none experienced chronic rejection[203,204] (G. Mazariegos, personal communication, 2009). The Kyoto group initially reported on a cohort of 63 pediatric liver transplant recipients[206,207]; 24 (38%) were successfully withdrawn from immunosuppression for a median of 23.5 months (range = 3-69 months), whereas 16 (25%) experienced acute rejection, and a single patient developed chronic rejection, which was successfully managed with triple immunosuppression (corticosteroids, tacrolimus, and mycophenolate mofetil). More recently, however, the same group has reported that 87 of 581 children or 15% of their entire cohort of pediatric liver transplant recipients have been withdrawn from all maintenance immunosuppression.[214] Detailed information on how many children have attempted, are undergoing, or have failed withdrawal is unknown.

Although the benefit of immunosuppression withdrawal may be deeply intuitive, few withdrawal experiences have yielded proof as their focus has, heretofore, primarily been to document success and failure rates. Thus far, the only published reports examining potential benefits have come from Tor Vergata (Italy) and have been based on the hypothesis that restoration of

TABLE 4. Summary of Published Single-Center Immunosuppression Withdrawal Experiences in Adult Liver Transplant Recipients

Year	Center	Number of Patients Attempted	Number of Tolerant Patients	Rejection	
				Acute	Chronic
1994	Mayo[3]	12	0	6	3 (2 deaths)
1997	Pittsburgh[4,5]	95	18 (19%)	21	3
1998	King's[6]	18	5 (17%)	13 (4 bx pr)	1 (1 retx)
2003	Spain[9]	9	3 (33%)	6 (2 bx pr)	0
2005	Miamai[10]	104	20 (19%)	70 (30 bx pr)	2 (1 retx)
2005	Ochsner[11]	18	1 (6%)	11	0
2006	Tor Vergata[12]	34	8 (23%)	26	0
2007	Ontario[13]	26	2 (8%)	15	0
Total	316	57 (18%)	168 (53%)	9 (3%)	

Abbreviations: bx pr, biopsy-proven; retx, retransplanted.

immune competence might favorably affect posttransplant hepatitis C virus (HCV) outcomes.[211] Of the 34 enrolled patients, all on cyclosporine monotherapy, 8 succeeded in withdrawing from and remaining off all immunosuppression. Initially, they reported that complete withdrawal stabilized the progression of posttransplant HCV, but longer follow-up, at 78 months after withdrawal, appeared to erode this advantage.[211,215] Of the 8 tolerant recipients, 1 died of severe HCV recurrence 6 years after withdrawal, but 7 remained off immunosuppression without any evidence of rejection. Four of 26 intolerant patients died: 2 of HCV recurrence, 1 of lung cancer, and 1 of acute myocardial infarction. Liver graft pathology was comparable between the tolerant and intolerant recipients for necroinflammatory grade, fibrosis stage, and fibrosis progression rate. Notably, however, none of the tolerant subgroup developed diabetes, whereas 11 of 22 intolerant recipients required treatment for new onset diabetes mellitus ($P = 0.03$). Moreover, significantly fewer tolerant patients versus intolerant patients experienced cardiovascular (0/7 versus 14/22, $P = 0.01$) and infectious (0/7 versus 13/22, $P = 0.01$) morbidity.

Although a report has not yet been published, the Miami group recently presented at the 2008 American Transplant Congress long-term follow-up of functionally tolerant adult liver transplant recipients.[216] Three years previously, in 2005, they reported on withdrawing immunosuppression from 104 liver transplant recipients, 45 of whom had received donor bone marrow infusions shortly after transplantation.[209] At trial entry, all participants were at least 3 years post-transplant, and immunosuppression was withdrawn over 3 years. The functionally tolerant recipients (n = 20) were compared to the intolerant recipients (n = 73) with respect to renal function and de novo malignancy. Tolerant patients exhibited lower serum creatinine levels, and they had fewer cancers during long-term follow-up.

Currently, 1 of the 2 immunosuppression withdrawal trials for adult liver transplant recipients sponsored by the Immune Tolerance Network has, as an integral part of its design and aims, the goal of defining the clinical benefit of transplantation. The trial (A Phase II Trial to Assess the Safety of Immunosuppression Withdrawal in Liver Transplant Recipients; see http://www.clinicaltrials.gov/ct2/show/NCT00135694) is a prospective, multicenter, open-label randomized trial that aims to enroll 275 candidates who will undergo liver transplantation for HCV or nonimmune, nonviral causes. Participants will receive standard immunosuppression composed of corticosteroids and a calcineurin inhibitor in the absence of any induction agents. Between 1 and 2 years after transplant, recipients will be randomized to withdraw from or stay on maintenance immunosuppression in a 3 to 1 ratio. Those randomized to weaning will withdraw from immunosuppression over approximately 56 weeks. Two years following random assignment, the withdrawal and maintenance immunosuppression groups will be compared for total immunosuppression exposure as the primary endpoint and incidence of immunosuppression-related complications as one of the secondary endpoints. Specific complications that will be assessed include quality of renal function (glomerular filtration rate), severity of hypertension and metabolic abnormalities (hypercholesterolemia and diabetes), and rates of opportunistic infections and secondary malignancies. Therefore, it is very likely that there will soon be data quantifying clinical benefits associated with attempted and/or successful immunosuppression withdrawal.

Although immunosuppression withdrawal experiences date back over a decade, only recently have any glimpses into a profile of functional tolerance begun to emerge. Two groups, one studying children and the other studying adults, have reported that functionally tolerant recipients have increased proportions and absolute numbers of circulating γδ T cells and a predominance of Vγδ1+ cells over Vγδ2+ cells.[213,214,217,218] One group has also suggested that the expression patterns of as few as 22 genes can accurately predict the outcome of immunosuppression withdrawal for adult recipients.[217,218] They have suggested that the combination of peripheral blood cell phenotypic markers and a characteristic gene expression profile compose a highly discriminative signature of functional tolerance for adult liver recipients. In Europe, there is an ongoing trial (Search for the Immunological Signature of Operational Tolerance in Liver Transplantation) that aims to prospectively validate the accuracy of this signature to predict successful withdrawal (http://clinicaltrials.gov/ct2/show/NCT00647283). Sponsored by a multinational project [Reprogramming the Immune System for Establishment of Tolerance (RISET)], the trial will enroll 60 eligible adult liver transplant recipients, subject them to gradual immunosuppression weaning, and correlate the immunological and gene expression characteristics with clinical outcome.

The 3 immunosuppression withdrawal trials that are underway in the United States (2 adult trials and 1 pediatric trial) all include vigorous longitudinal collection of peripheral blood and liver tissue specimens to support a parallel search for biomarkers of functional tolerance. There is substantial hope that these invaluable specimens will not only elucidate or confirm a predictive signature of functional tolerance but also suggest the mechanisms responsible for establishing and maintaining the tolerant state.

Clearly, immunosuppression withdrawal as a strategy to mitigate the development of chronic kidney disease in liver transplant recipients is a concept in its infancy. The clinical focus of both past and current trials has centered on understanding whether withdrawal is safe, rather than whether it is advantageous. Intuition and common sense suggest that foregoing lifelong immunosuppression would be highly desirable and beneficial to patients. This concept, however, remains entirely unproven. The realistic horizon of a predictive profile for functional tolerance signals the emergence of an entirely new landscape. The ability to identify liver transplant recipients who are likely to be tolerant of their liver allograft will tremendously facilitate larger clinical trials powered to determine the optimal timing, effi-

cacy, and benefit of immunosuppression withdrawal. Moreover, a deeper understanding of the tolerance signature with respect to when it emerges relative to transplantation and whether it is universal for all liver transplant recipients will be critical to future tolerance induction trials that will likely reduce exposure to immunosuppressive regimens centered on nephrotoxic agents.

CONSENSUS REPORT

Evaluation and Management of Pretransplant Renal Insufficiency and Criteria for Simultaneous Liver-Kidney Transplantation

Thomas A. Gonwa and Connie Davis

Every patient undergoing a liver transplant evaluation should have a renal evaluation consisting at least of the following:

1. Serum creatinine.
2. Urinalysis.
3. Urine protein creatinine ratio or 24-hour urine for protein.
4. Serum sodium.

The group reviewed the value of predictive equations for the measurement of the glomerular filtration rate (GFR) and also looked at the results of using cystatin C to measure GFR. Neither of these methods was recommended. A true GFR measurement was recommended if possible. It was noted that unpublished data demonstrated that using a measured GFR to replace creatinine in the Model for End-Stage Liver Disease (MELD) calculations improved the accuracy of MELD to predict mortality in cirrhosis to the same degree as adding serum sodium to the MELD calculation.[219] However, it is clear that there is a need to develop standardized protocols for GFR measurement, particularly when patients are receiving extra fluid or albumin or have a Foley catheter. Given the inability of the GFR prediction equations to accurately predict the true GFR in patients with cirrhosis,[3] greater attention should be paid to developing a tool to measure GFR that is easy to use and reproducible. Further renal evaluations should be done in all patients with a serum creatinine greater than 1 mg/dL, urinalysis showing increased white blood cells, red blood cells, or casts, or urinalysis showing proteinuria with increased albuminuria. Further evaluation should include a measurement of urinary electrolytes, imaging studies, appropriate immunological tests, nephrology consultation and, potentially, renal biopsy. It is unclear whether the fractional excretion of sodium or chloride is consistently useful as it might be dependent on the recent administration of diuretics. There should be an anatomic evaluation by sonogram, computed tomography scan, or magnetic resonance imaging, with the choice depending on the clinical setting and the assessed risks of contrast agents. Any imaging abnormality should prompt a true GFR measurement, preferably one that is non–creatinine-based. If proteinuria or active urinary sediment is present, appropriate serologies should be obtained, such as anti-neutrophil cytoplasmic antibodies and anti-nuclear antibodies, as well as the measurement of cryoglobulins presenting in hepatitis C–infected patients. Complement levels should be evaluated; however, low levels may be seen in severe liver disease and may not be discriminatory.[220,221] A measurement of renal blood flow by Doppler examination is a useful gauge of resistance to intrarenal blood flow (ie, ischemia) in those regions in which there is an experienced sonographer. The degree of sonographically determined resistance has been correlated with the development of hepatorenal syndrome.[222,223] Finally, renal biopsy should be considered if the urine is abnormal, there is unexplained renal dysfunction, or there is prolonged renal dysfunction.[224] The group discussed the results of using kidney biopsy, particularly in determining the need for combined kidney-liver transplantation (discussed later).

The group then discussed the criteria for combined kidney-liver transplantation. The United Network for Organ Sharing Liver and Kidney Committees are examining criteria for simultaneous liver-kidney transplantation, and their preliminary proposal served as the basis for the discussion. The group agreed with the suggestion that there should be criteria that make the patient eligible for listing and that patients falling outside these criteria should be reviewed by the regional review board (Table 5).

The first group of patients deemed to be candidates for simultaneous liver-kidney transplantation includes those with end-stage renal disease on dialysis. Docu-

TABLE 5. Criteria for Simultaneous Liver-Kidney Transplantation

End-stage renal disease and dialysis
No dialysis but a glomerular filtration rate < 30 mL/minute and proteinuria > 3 g/day with a 24-hour urine protein/creatinine ratio > 3
Acute kidney injury and a requirement for dialysis at least 2 times per week for more than 6 weeks

mentation of the dates of the initiation of dialysis and the cause of end-stage renal disease, as reported on Centers for Medicare and Medicaid Services form 2728, would be required for candidacy. The second group includes patients with chronic kidney disease not on dialysis but having either a documented GFR of less than 30 mL/minute by the Modification of Diet in Renal Disease 6 (MDRD6) equation or a direct measurement of GFR of less than 30 mL/minute and proteinuria greater than 3 g per day with a 24-hour protein measurement or a urine protein creatinine ratio greater than 3. The third group consists of patients with sustained acute renal failure and documentation of dialysis at least 2 times per week for greater than 6 weeks. Patients who are not on dialysis for more than 6 weeks with sustained acute renal failure and a GFR of less of 25 by MDRD6 or a direct measurement of GFR would also qualify for listing. Patients with sustained acute renal failure with a combination of the aforementioned 2 factors for at least 6 weeks would be acceptable (eg, patients with a GFR of less than 25 for 3 weeks followed by dialysis for 3 weeks). Criteria for the initiation of dialysis are discussed later. The fourth group consists of patients with metabolic or other genetic diseases and documentation from a nephrologist specifying the reason for the kidney transplant. This, for example, would include patients with hyperoxaluria and polycystic liver and kidney disease.[225] These recommendations appeared appropriate, and the group agreed with them, recommending that the International Liver Transplantation Society support the proposals. They did recommend that caution should be used if the MDRD equation is used, given its documented inaccuracy in this group of patients. These panel recommendations incorporate metrics and durations of kidney disease that are somewhat different than those recommended by the National Kidney Foundation Disease Outcomes Quality Initiative, which defines chronic kidney disease as kidney damage for ≥3 months as defined by structural or functional abnormalities of the kidneys with or without decreased GFR as manifested by either pathological abnormalities of urine, blood, or imaging or by a GFR > 60 mL/minute/1.73 m^2 for ≥3 months. This reflects the high prevalence and very poor prognosis associated with hepatorenal syndrome, a common cause of renal disease in patients with liver failure.

The work group felt that these criteria for liver-kidney transplantation are similar to the ones produced by the American Society of Transplantation, American Society of Transplant Surgeons, American Society of Nephrology, and United Network for Organ Sharing Consensus Conference a year ago and recently published in the *American Journal of Transplantation*.[70] Some of this work was based on the University of California Los Angeles liver-kidney transplant experience, which determined that patients who have been dialyzed for 30 days or less prior to liver transplantation do just as well as patients receiving a combined liver-kidney transplant.[67] The workgroup reviewed the results of a recent article on kidney biopsy in liver transplant candidates to determine whether or not this would be useful in allocating patients to receive a liver transplant alone or a simultaneous liver-kidney transplant. The procedure allowed this group to avoid a simultaneous liver-kidney transplant in two-thirds of the patients who underwent renal biopsy.[94] This is similar to the results presented in preliminary form from the group at the University of Washington. This group looked at 34 transplant biopsies; 18 were listed for liver transplantation alone, and 10 were listed for simultaneous liver-kidney transplantation.[226] Although the work group felt that these data were interesting, the use of kidney biopsy in this setting was felt to need further study. The group did not recommend that biopsy data be used to allocate kidneys at this time, given the small data set and risks of the procedure, but it highly recommended that further data be collected.

The United Network for Organ Sharing committees may also propose criteria for priority kidney allocation after liver transplantation in patients still on dialysis. It is clear that some patients have been given a liver only when they might have qualified for a liver-kidney transplant. Previous publications have suggested that patients who do not recover renal function and who require prolonged hemodialysis after liver transplantation have worse posttransplant survival.[71] It was felt by the group that these patients might be given priority for a kidney after liver transplantation, but there was no consensus. Other groups who might qualify for priority listing for kidney transplantation include certain patients receiving a liver only who did not initially qualify for a simultaneous liver-kidney transplant. Patients who had been on dialysis pre–liver transplant for at least 2 weeks and continued on dialysis for 6 weeks post-transplant were suggested to receive priority for kidney transplantation. Finally, patients who had not been on dialysis pre-transplant but had renal dysfunction for at least 4 weeks pre-transplant with documented intrinsic kidney disease pre–liver transplant with a GFR between 30 and 40 would be considered for a priority kidney transplant if they remained on dialysis for 90 days post–liver transplant. It was proposed that these patients who fulfill 1 of the aforementioned requirements could qualify for priority points on the kidney transplant waiting list. The working group felt that points should be determined on the basis of the average waiting time per disease specific activity (DSA) with the intent that these candidates will appear on the match list just below highly sensitized candidates. The feasibility of calculating DSA-specific points should be explored with the United Network for Organ Sharing IT Committee. It

was recognized that the impact of these recommendations may change in the setting of the new proposed kidney allocation system based on life years after transplant gained.[227] It was felt that the International Liver Transplantation Society should support the aforementioned priorities for kidney transplantation in liver allograft recipients. Finally, it was felt that all efforts should be made to encourage living kidney donation.

Every attempt should be made to improve the patient's renal function prior to transplantation, particularly given the preliminary results of using terlipressin to improve posttransplant outcome.[73] It was felt that the prophylactic measures that are most important are the use of terlipressin (not yet approved in the United States), transjugular intrahepatic portosystemic shunt, albumin, and midodrine. The group also discussed the marked importance of adequate spontaneous bacterial peritonitis prophylaxis, volume management, and avoidance of nephrotoxins in all patients waiting liver transplantation to prevent deterioration of renal function. A precautionary word was mentioned regarding the impact of treatment on allocation by MELD. If the patient's renal function improves with the aforementioned measures, the MELD score may actually decrease, and this would prolong the waiting time for receiving a liver transplant. There was no consensus on changing the MELD score for those who respond to treatment strategies at this point, but it was felt that this required further discussion. The group felt that treatment for liver-related kidney disease should be started for hepatorenal syndrome when the creatinine level is greater than 2 mg/dL. It was clear that further studies are needed to determine exactly when to start treatment and what effect this would have on the waiting time for liver transplantation. It was felt that the timing of dialysis and ultrafiltration is still quite center-specific, being determined by a center's experience with ease of operative management. The timing and selection criteria for this treatment need to be studied. Potential criteria discussed by the group included a creatinine level greater than 2 mg/dL, massive ascites, severe oliguria, severe hyponatremia, and marginal potassium levels. The group did not arrive at a consensus concerning when to use intraoperative renal replacement therapy. Overall, the group supported aggressive treatment of hepatorenal syndrome and all forms of kidney dysfunction by whatever means a center finds appropriate. This should be accomplished by improvements in the pretransplant kidney function to improve the posttransplant outcome. There are not enough data yet to recommend one form of hepatorenal syndrome treatment, although there are more patients currently reported to have received vasoconstrictor therapy.

Recommendations for the Management of Immunosuppression in Patients with Preoperative and Postoperative Renal Dysfunction

Florence Wong, Michael Charlton, and William Wall

The group felt strongly that more randomized controlled trials are needed to determine optimal strategies for posttransplant renal preservation. Given the impact of posttransplant renal dysfunction on important outcomes, it was felt that a low threshold should be used for employing renal-sparing immunosuppressive protocols. The available data presented and discussed were synthesized into the following recommendations regarding the management of immunosuppression in the liver transplant recipient with renal dysfunction. Patients with pretransplant renal dysfunction, defined minimally as a glomerular filtration rate (GFR) < 60 mL/minute, should be considered for a posttransplant renal-sparing immunosuppressive protocol. Based on the interpretation of the available data from published clinical trials reviewed by the group, renal-sparing immunosuppression protocols might include the following:

1. Induction with interleukin 2 receptor antibodies (basiliximab or daclizumab) or antithymocyte globulin.
2. Mycophenolate mofetil from day 0 and, if needed, as maintenance.
3. Induction and maintenance of corticosteroids (tapering over 3-6 months).
4. Delay of tacrolimus dosing for 5 to 7 days, with target 12-hour trough levels of 4 to 6 ng/mL.

RECOMMENDATIONS FOR THE MANAGEMENT OF IMMUNOSUPPRESSION IN PATIENTS WITH POSTOPERATIVE RENAL DYSFUNCTION

Because of the high incidence and prevalence of posttransplant renal insufficiency, the group felt that renal function should be measured at regular intervals posttransplantation. If GFR is $\leq$60 mL/minute or if there is

a 20% reduction in GFR, the evaluation and management of renal dysfunction described in a preceding section of this report (Evaluation and Pharmacotherapy of Calcineurin Inhibitor Toxicity) should be initiated. Once calcineurin inhibitor nephrotoxicity has been diagnosed, the consensus recommendation is to reduce tacrolimus or cyclosporine dosing, regardless of trough levels at the time of onset of renal dysfunction. The optimal schedule for dose reduction of tacrolimus/cyclosporine is not known. However, initial dose reductions of approximately 30% appear safe in the context of close biochemical follow-up. Further dose reductions (0.5-1 mg/dose for tacrolimus and 25-50 mg/dose for cyclosporine) until the GFR stabilizes or improves or until doses of 0.5 to 1 mg (tacrolimus) or 25 to 50 mg (cyclosporine) twice daily are achieved can be considered. For patients on tacrolimus or cyclosporine monotherapy who develop evidence of rejection, the addition of mycophenolate mofetil and/or prednisone may facilitate continued calcineurin inhibitor dose reduction. The role, if any, of sirolimus in renal preservation strategies is unclear.

Concomitant medical conditions that may contribute to or exacerbate renal dysfunction should be aggressively managed (eg, dehydration and hypertension). As always, drug-drug interactions should be considered.

REFERENCES

1. Paramesh AS, Roayaie S, Doan Y, Schwartz ME, Emre S, Fishbein T, et al. Post-liver transplant acute renal failure: factors predicting development of end-stage renal disease. Clin Transplant 2004;18:94-99.
2. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-940.
3. Gonwa TA, Jennings L, Mai ML, Stark PC, Levey AS, Klintmalm GB. Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. Liver Transpl 2004;10:301-309.
4. Kendrick EA, McVicar JP, Kowdley KV, Bronner MP, Emond MJ, Alpers CE, et al. Renal disease in hepatitis C-positive liver transplant recipients. Transplantation 1997;63:1287-1293.
5. Morales JM, Campistol JM, Andres A, Rodicio JL. Glomerular diseases in patients with hepatitis C virus infection after renal transplantation. Curr Opin Nephrol Hypertens 1997;6:511-515.
6. Nochy D, Callard P, Bellon B, Bariety J, Druet P. Association of overt glomerulonephritis and liver disease: a study of 34 patients. Clin Nephrol 1976;6:422-427.
7. Crawford DH, Endre ZH, Axelsen RA, Lynch SV, Balderson GA, Strong RW, et al. Universal occurrence of glomerular abnormalities in patients receiving liver transplants. Am J Kidney Dis 1992;19:339-344.
8. McGuire BM, Julian BA, Bynon JS Jr, Cook WJ, King SJ, Curtis JJ, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. Ann Intern Med 2006;144:735-741.
9. McCauley J, Van Thiel DH, Starzl TE, Puschett JB. Acute and chronic renal failure in liver transplantation. Nephron 1990;55:121-128.
10. Rimola A, Gavaler JS, Schade RR, el-Lankany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. Gastroenterology 1987;93:148-156.
11. Cabezuelo JB, Ramirez P, Rios A, Acosta F, Torres D, Sansano T, et al. Risk factors of acute renal failure after liver transplantation. Kidney Int 2006;69:1073-1080.
12. Gainza FJ, Valdivieso A, Quintanilla N, Errazti G, Gastaca M, Campo M, et al. Evaluation of acute renal failure in the liver transplantation perioperative period: incidence and impact. Transplant Proc 2002;34:250-251.
13. Lima EQ, Zanetta DM, Castro I, Massarollo PC, Mies S, Machado MM, Yu L. Risk factors for development of acute renal failure after liver transplantation. Ren Fail 2003; 25:553-560.
14. O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. Am J Transplant 2007;7:168-176.
15. Sanchez EQ, Gonwa TA, Levy MF, Goldstein RM, Mai ML, Hays SR, et al. Preoperative and perioperative predictors of the need for renal replacement therapy after orthotopic liver transplantation. Transplantation 2004;78:1048-1054.
16. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–R212.
17. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
18. Zaltzman JS, Pei Y, Maurer J, Patterson A, Cattran DC. Cyclosporine nephrotoxicity in lung transplant recipients. Transplantation 1992;54:875-878.
19. Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM. Chronic renal failure following liver transplantation: a retrospective analysis. Transplantation 1998;66:59-66.
20. Schmitz V, Laudi S, Moeckel F, Puhl G, Stockmann M, Tran ZV, et al. Chronic renal dysfunction following liver transplantation. Clin Transplant 2008;22:333-340.
21. Neau-Cransac M, Morel D, Bernard PH, Merville P, Revel P, Potaux L, Saric J. Renal failure after liver transplantation: outcome after calcineurin inhibitor withdrawal. Clin Transplant 2002;16:368-373.
22. Poplawski S, Gonwa T, Goldstein R, Husberg B, Klintmalm G. Long term nephrotoxicity in liver transplantation. Transplant Proc 1989;21:2469-2471.
23. National Kidney Foundation Kidney Disease Outcome Quality Initiative Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation. Am J Kidney Dis 2002;34:S1–S266.
24. Griffiths MH, Crowe AV, Papadaki L, Banner NR, Yacoub MH, Thompson FD, Neild GH. Cyclosporin nephrotoxicity in heart and lung transplant patients. QJM 1996;89: 751-763.
25. Pawarode A, Fine DM, Thuluvath PJ. Independent risk factors and natural history of renal dysfunction in liver transplant recipients. Liver Transpl 2003;9:741-747.
26. Platz KP, Mueller AR, Blumhardt G, Bachmann S, Bechstein WO, Kahl A, Neuhaus P. Nephrotoxicity following orthotopic liver transplantation. A comparison between cyclosporine and FK506. Transplantation 1994;58:170-178.
27. Satchithananda DK, Parameshwar J, Sharples L, Taylor GJ, McNeil K, Wallwork J, Large SR. The incidence of end-stage renal failure in 17 years of heart transplantation: a single center experience. J Heart Lung Transplant 2002;21:651-657.
28. Veillon S, Caillard S, Epailly E, Eisenmann B, Hannedouche T, Moulin B. Chronic renal failure after cardiac transplanta-

tion: predictive factors and influence on mortality—results of a monocenter study in 141 patients. Transplant Proc 2002; 34:2819-2820.

29. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-231.
30. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for End-Stage Liver Disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-96.
31. Weismuller TJ, Prokein J, Becker T, Barg-Hock H, Klempnauer J, Manns MP, Strassburg CP. Prediction of survival after liver transplantation by pre-transplant parameters. Scand J Gastroenterol 2008;43:736-746.
32. Hampel H, Bynum GD, Zamora E, El-Serag HB. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. Am J Gastroenterol 2001;96:2206-2210.
33. Wu CC, Yeung LK, Tsai WS, Tseng CF, Chu P, Huang TY, et al. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. Clin Nephrol 2006;65:28-33.
34. Betrosian AP, Agarwal B, Douzinas EE. Acute renal dysfunction in liver diseases. World J Gastroenterol 2007; 13:5552-5559.
35. Moreau R, Labrec D. Diagnosis and treatment of acute renal failure in patients with cirrhosis. Best Pract Res Clin Gastroenterol 2007;21:111-123.
36. Munoz SJ. The hepatorenal syndrome. Med Clin North Am 2008;92:813-837, viii-ix.
37. Gines P, Tito L, Arroyo V, Planas R, Panes J, Viver J, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493-1502.
38. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341:403-409.
39. Fernandez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007; 133:818-824.
40. Uriz J, Gines P, Cardenas A, Sort P, Jiminez W, Salmeron JM. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 2001; 33:43-48.
41. Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras D, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002;36:941-948.
42. Lim JK, Groszmann RJ. Vasoconstrictor therapy for the hepatorenal syndrome. Gastroenterology 2008;134: 1608-1611.
43. Davis CL. Impact of pretransplant renal failure: when is listing for kidney-liver indicated? Liver Transpl 2005;11: S35–S44.
44. Krag A, Moller S, Henriksen JH, Holstein-Rathlou NH, Larsen FS, Bendtsen F. Terlipressin improves renal function in patients with cirrhosis and ascites without hepatorenal syndrome. Hepatology 2007;46:1863-1871.
45. Brensing KA, Textor J, Perz J, Schiedermaier P, Raab P, Strunk H, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000;47:288-295.
46. Mitzner S, Stange J, Klammt S, Risler T, Erley C, Bader B. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective randomized, controlled clinical trial. Liver Transpl 2000; 6:277-286.
47. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MT, Farkas A, Kaplan RM. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int 2001;60:1154-1163.
48. Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23:164-176.
49. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310-1318.
50. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229-236.
51. Terra C, Guevara M, Torre A, Gilabert R, Fernandez J, Martin-Llahi M, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology 2005; 129:1944-1953.
52. Fasolato S, Angeli P, Dallagnese L, Maresio G, Zola E, Mazza E, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology 2007;45:223-229.
53. Cardenas A, Gines P, Uriz J, Bessa X, Salmeron JM, Mas A, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology 2001;34:671-676.
54. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jimenez W, Arroyo V, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology 2005;41:1282-1289.
55. Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008; 134:1360-1368.
56. Martin-Llahi M, Pepin MN, Guevara M, Diaz F, Torre A, Monescillo A, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology 2008;134:1352-1359.
57. Nazar A, Guevara M, Marinelli M. Predictive factors of response to therapy in patients with cirrhosis and hepatorenal syndrome treated with terlipressin and albumin. Hepatology 2008;48:1682A.
58. Angeli P, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29:1690-1697.
59. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004;40:55-64.
60. Duvoux C, Zanditenas D, Hezode C, Chauvat A, Monin JL, Roudot-Thoraval F, et al. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. Hepatology 2002;36:374-380.
61. Alessandria C, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol 2007; 47:499-505.
62. Guevara M, Gines P, Bandi JC, Gilabert R, Sort P, Jimenez W, et al. Transjugular intrahepatic portosystemic

shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 1998;28:416-422.
63. Gines P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Del Arbol LR, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123: 1839-1847.
64. Sanyal AJ, Genning C, Reddy KR, Wong F, Kowdley KV, Benner K, McCashland T. The North American Study for the Treatment of Refractory Ascites. Gastroenterology 2003;124:634-641.
65. Wong LP, Blackley MP, Andreoni KA, Chin H, Falk RJ, Klemmer PJ. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. Kidney Int 2005;68:362-370.
66. Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. Transplantation 1995;59:361-365.
67. Ruiz R, Kunitake H, Wilkinson AH, Danovitch GM, Farmer DG, Ghobrial RM, et al. Long-term analysis of combined liver and kidney transplantation at a single center. Arch Surg 2006;141:735-741; discussion 741-732.
68. Jeyarajah DR, Gonwa TA, McBride M, Testa G, Abbasoglu O, Husberg BS, et al. Hepatorenal syndrome: combined liver kidney transplants versus isolated liver transplant. Transplantation 1997;64:1760-1765.
69. Locke JE, Warren DS, Singer AL, Segev DL, Simpkins CE, Maley WR, et al. Declining outcomes in simultaneous liver-kidney transplantation in the MELD era: ineffective usage of renal allografts. Transplantation 2008;85:935-942.
70. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). Am J Transplant 2008;8:2243-2251.
71. Ruiz R, Barri YM, Jennings LW, Chinnakotla S, Goldstein RM, Levy MF, et al. Hepatorenal syndrome: a proposal for kidney after liver transplantation (KALT). Liver Transpl 2007;13:838-843.
72. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35:1179-1185.
73. Restuccia T, Ortega R, Guevara M, Gines P, Alessandria C, Ozdogan O, et al. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. J Hepatol 2004;40:140-146.
74. Lanese DM, Conger JD. Effects of endothelin receptor antagonist on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. J Clin Invest 1993;91:2144-2149.
75. Wolf G. Renal injury due to renin-angiotensin-aldosterone system activation of the transforming growth factor-beta pathway. Kidney Int 2006;70:1914-1919.
76. Shihab FS, Andoh TF, Tanner AM, Yi H, Bennett WM. Expression of apoptosis regulatory genes in chronic cyclosporine nephrotoxicity favors apoptosis. Kidney Int 1999;56:2147-2159.
77. Shihab FS, Andoh TF, Tanner AM, Noble NA, Border WA, Franceschini N, Bennett WM. Role of transforming growth factor-beta 1 in experimental chronic cyclosporine nephropathy. Kidney Int 1996;49:1141-1151.
78. Xin J, Homma T, Matsusaka T, Ma J, Isaka Y, Imai E, Ichikawa I. Suppression of cyclosporine a nephrotoxicity in vivo by transforming growth factor beta receptor-immunoglobulin G chimeric protein. Transplantation 2004; 77:1433-1442.
79. Shihab FS, Bennett WM, Yi H, Andoh TF. Pirfenidone treatment decreases transforming growth factor-beta1 and matrix proteins and ameliorates fibrosis in chronic cyclosporine nephrotoxicity. Am J Transplant 2002;2: 111-119.
80. Shihab FS, Bennett WM, Tanner AM, Andoh TF. Angiotensin II blockade decreases TGF-beta1 and matrix proteins in cyclosporine nephropathy. Kidney Int 1997;52: 660-673.
81. Bobadilla NA, Gamba G. New insights into the pathophysiology of cyclosporine nephrotoxicity: a role of aldosterone. Am J Physiol Renal Physiol 2007;293:F2–F9.
82. Shihab FS, Bennett WM, Yi H, Choi SO, Andoh TF. Mycophenolate mofetil ameliorates arteriolopathy and decreases transforming growth factor-beta1 in chronic cyclosporine nephrotoxicity. Am J Transplant 2003;3:1550-1559.
83. Anglicheau D, Pallet N, Rabant M, Marquet P, Cassinat B, Meria P, et al. Role of P-glycoprotein in cyclosporine cytotoxicity in the cyclosporine-sirolimus interaction. Kidney Int 2006;70:1019-1025.
84. Shihab FS, Bennett WM, Yi H, Choi SO, Andoh TF. Sirolimus increases transforming growth factor-beta1 expression and potentiates chronic cyclosporine nephrotoxicity. Kidney Int 2004;65:1262-1271.
85. Mahalati K, Belitsky P, Sketris I, West K, Panek R. Neoral monitoring by simplified sparse sampling area under the concentration-time curve: its relationship to acute rejection and cyclosporine nephrotoxicity early after kidney transplantation. Transplantation 1999;68:55-62.
86. Capron A, Lerut J, Verbaandert C, Mathys J, Ciccarelli O, Vanbinst R, et al. Validation of a liquid chromatography-mass spectrometric assay for tacrolimus in liver biopsies after hepatic transplantation: correlation with histopathologic staging of rejection. Ther Drug Monit 2007; 29:340-348.
87. Hebert MF, Dowling AL, Gierwatowski C, Lin YS, Edwards KL, Davis CL, et al. Association between ABCB1 (multidrug resistance transporter) genotype and post-liver transplantation renal dysfunction in patients receiving calcineurin inhibitors. Pharmacogenetics 2003;13: 661-674.
88. Hauser IA, Schaeffeler E, Gauer S, Scheuermann EH, Wegner B, Gossmann J, et al. ABCB1 genotype of the donor but not of the recipient is a major risk factor for cyclosporine-related nephrotoxicity after renal transplantation. J Am Soc Nephrol 2005;16:1501-1511.
89. Textor SC, Wilson DJ, Lerman A, Romero JC, Burnett JC Jr, Wiesner R, et al. Renal hemodynamics, urinary eicosanoids, and endothelin after liver transplantation. Transplantation 1992;54:74-80.
90. Textor SC, Burnett JC Jr, Romero JC, Canzanello VJ, Taler SJ, Wiesner R, et al. Urinary endothelin and renal vasoconstriction with cyclosporine or FK506 after liver transplantation. Kidney Int 1995;47:1426-1433.
91. Perico N, Ruggenenti P, Gaspari F, Mosconi L, Benigni A, Amuchastegui CS, et al. Daily renal hypoperfusion induced by cyclosporine in patients with renal transplantation. Transplantation 1992;54:56-60.
92. Sander M, Victor RG. Hypertension after cardiac transplantation: pathophysiology and management. Curr Opin Nephrol Hypertens 1995;4:443-451.
93. Cohen AJ, Stegall MD, Rosen CB, Wiesner RH, Leung N, Kremers WK, Zein NN. Chronic renal dysfunction late after liver transplantation. Liver Transpl 2002;8:916-921.
94. Wadei HM, Geiger XJ, Cortese C, Mai ML, Kramer DJ, Rosser BG, et al. Kidney allocation to liver transplant candidates with renal failure of undetermined etiology: role of percutaneous renal biopsy. Am J Transplant 2008;8:2618-2626.

95. Campbell MS, Kotlyar DS, Brensinger CM, Lewis JD, Shetty K, Bloom RD, et al. Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. Liver Transpl 2005;11: 1048-1055.
96. Elzinga LW, Rosen S, Bennett WM. Dissociation of glomerular filtration rate from tubulointerstitial fibrosis in experimental chronic cyclosporine nephropathy: role of sodium intake. J Am Soc Nephrol 1993;4:214-221.
97. De Nicola L, Thomson SC, Wead LM, Brown MR, Gabbai FB. Arginine feeding modifies cyclosporine nephrotoxicity in rats. J Clin Invest 1993;92:1859-1865.
98. Kushwaha SS, Khalpey Z, Frantz RP, Rodeheffer RJ, Clavell AL, Daly RC, et al. Sirolimus in cardiac transplantation: use as a primary immunosuppressant in calcineurin inhibitor-induced nephrotoxicity. J Heart Lung Transplant 2005;24:2129-2136.
99. Kreis H, Oberbauer R, Campistol JM, Mathew T, Daloze P, Schena FP, et al. Long-term benefits with sirolimus-based therapy after early cyclosporine withdrawal. J Am Soc Nephrol 2004;15:809-817.
100. Larson TS, Dean PG, Stegall MD, Griffin MD, Textor SC, Schwab TR, et al. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. Am J Transplant 2006;6:514-522.
101. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007; 357:2562-2575.
102. Abramowicz D, Hadaya K, Hazzan M, Broeders N, Hoang AD, Ghisdal L, et al. Conversion to sirolimus for chronic renal allograft dysfunction: risk factors for graft loss and severe side effects. Nephrol Dial Transplant 2008;23: 3727-3729.
103. Aliabadi AZ, Pohanka E, Seebacher G, Dunkler D, Kammerstatter D, Wolner E, et al. Development of proteinuria after switch to sirolimus-based immunosuppression in long-term cardiac transplant patients. Am J Transplant 2008;8:854-861.
104. Gonwa TA, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us? Am J Transplant 2006;6:2651-2659.
105. Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, Klintmalm GB. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. Transplantation 2001;72:1934-1939.
106. Feutren G, Miller C. Low predictive value of cyclosporine level for efficacy or renal dysfunction in psoriasis and idiopathic nephrotic syndrome. Transplant Proc 1990; 22:1299-1302.
107. Bach JF, Feutren G, Noel LH, Hannedouche T, Landais P, Timsit J, et al. Factors predictive of cyclosporine-induced nephrotoxicity: the role of cyclosporine blood levels. Transplant Proc 1990;22:1296-1298.
108. Farkas SA, Schnitzbauer AA, Kirchner G, Obed A, Banas B, Schlitt HJ. Calcineurin inhibitor minimization protocols in liver transplantation. Transpl Int 2009;22:49-60.
109. Alexander JW, Goodman HR, Cardi M, Austin J, Goel S, Safdar S, et al. Simultaneous corticosteroid avoidance and calcineurin inhibitor minimization in renal transplantation. Transpl Int 2006;19:295-302.
110. Fisher RA, Stone JJ, Wolfe LG, Rodgers CM, Anderson ML, Sterling RK, et al. Four-year follow-up of a prospective randomized trial of mycophenolate mofetil with cyclosporine microemulsion or tacrolimus following liver transplantation. Clin Transplant 2004;18:463-472.
111. Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver-kidney transplantation: part II. Liver Transpl 2002;8:193-211.
112. Brown RS Jr, Lombardero M, Lake JR. Outcome of patients with renal insufficiency undergoing liver or liver-kidney transplantation. Transplantation 1996;62:1788-1793.
113. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 2003;41:269-278.
114. Herrero JI, Quiroga J, Sangro B, Girala M, Gomez-Manero N, Pardo F, et al. Conversion of liver transplant recipients on cyclosporine with renal impairment to mycophenolate mofetil. Liver Transpl Surg 1999;5:414-420.
115. Chan CY, DasGupta K, Baker AL. Cyclosporin A: drug discontinuation for the management of long-term toxicity after liver transplantation. Hepatology 1996;24:1085-1089.
116. Pageaux GP, Rostaing L, Calmus Y, Duvoux C, Vanlemmens C, Hardgwissen J, et al. Mycophenolate mofetil in combination with reduction of calcineurin inhibitors for chronic renal dysfunction after liver transplantation. Liver Transpl 2006;12:1755-1760.
117. Dale C, Marotta P. Continuous improvement in measured GFR with tapering CNI and the introduction of MMF in liver transplant recipients. Can J Gastroenterol 2008;22:44-45.
118. Orlando G, Baiocchi L, Cardillo A, Iaria G, De Liguori Carino N, De Luca L, et al. Switch to 1.5 g MMF monotherapy for CNI-related toxicity in liver transplantation is safe and improves renal function, dyslipidemia, and hypertension. Liver Transpl 2007;13:46-54.
119. Bilbao I, Castells L, Rojas L, Cancino J, Dopazo C, Castro E, et al. Immunosuppression based on mycophenolate mofetil in stable liver transplanted patients. Int Immunopharmacol 2006;6:1977-1983.
120. Creput C, Blandin F, Deroure B, Roche B, Saliba F, Charpentier B, et al. Long-term effects of calcineurin inhibitor conversion to mycophenolate mofetil on renal function after liver transplantation. Liver Transpl 2007; 13:1004-1010.
121. Schlitt HJ, Barkmann A, Boker KH, Schmidt HH, Emmanouilidis N, Rosenau J, et al. Replacement of calcineurin inhibitors with mycophenolate mofetil in liver-transplant patients with renal dysfunction: a randomised controlled study. Lancet 2001;357:587-591.
122. Watson CJ, Gimson AE, Alexander GJ, Allison ME, Gibbs P, Smith JC, et al. A randomized controlled trial of late conversion from calcineurin inhibitor (CNI)-based to sirolimus-based immunosuppression in liver transplant recipients with impaired renal function. Liver Transpl 2007;13:1694-1702.
123. Fairbanks KD, Eustace JA, Fine D, Thuluvath PJ. Renal function improves in liver transplant recipients when switched from a calcineurin inhibitor to sirolimus. Liver Transpl 2003;9:1079-1085.
124. Nair S, Eason J, Loss G. Sirolimus monotherapy in nephrotoxicity due to calcineurin inhibitors in liver transplant recipients. Liver Transpl 2003;9:126-129.
125. Izzedine H, Brocheriou I, Frances C. Post-transplantation proteinuria and sirolimus. N Engl J Med 2005;353: 2088-2089.
126. Morard I, Dumortier J, Spahr L, Hadengue A, Majno P, Morel P, et al. Conversion to sirolimus-based immunosuppression in maintenance liver transplantation patients. Liver Transpl 2007;13:658-664.
127. Sher L, Marotta P, Teperman A. Spare-the-Nephron trial in liver transplant recipients: interim efficacy and safety of mycophenolate mofetil/sirolimus maintenance ther-

apy after CNI withdrawal [abstract]. Am J Transplant 2008;8:867-871.

128. Tzakis AG, Tryphonopoulos P, Kato T, Nishida S, Levi DM, Madariaga JR, et al. Preliminary experience with alemtuzumab (Campath-1H) and low-dose tacrolimus immunosuppression in adult liver transplantation. Transplantation 2004;77:1209-1214.
129. Yoshida EM, Marotta PJ, Greig PD, Kneteman NM, Marleau D, Cantarovich M, et al. Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial. Liver Transpl 2005;11:1064-1072.
130. Soliman T, Hetz H, Burghuber C, Gyori G, Silberhumer G, Steininger R, et al. Short-term induction therapy with anti-thymocyte globulin and delayed use of calcineurin inhibitors in orthotopic liver transplantation. Liver Transpl 2007;13:1039-1044.
131. Kootte AM, Lensen LM, van Bockel JH, van Es LA, Paul LC. High- and low-dose regimens of cyclosporin in renal transplantation: immunosuppressive efficacy and side-effects. Nephrol Dial Transplant 1988;3:666-670.
132. Vincenti F, Laskow DA, Neylan JF, Mendez R, Matas AJ. One-year follow-up of an open-label trial of FK506 for primary kidney transplantation. A report of the U.S. Multicenter FK506 Kidney Transplant Group. Transplantation 1996;61:1576-1581.
133. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. Transplantation 1997;63:39-47.
134. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. Kidney Int 2000;57:307-313.
135. Solez K, Colvin RB, Racusen LC, Sis B, Halloran PF, Birk PE, et al. Banff '05 meeting report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). Am J Transplant 2007;7:518-526.
136. Womer KL, Vella JP, Sayegh MH. Chronic allograft dysfunction: mechanisms and new approaches to therapy. Semin Nephrol 2000;20:126-147.
137. Nankivell BJ, Chapman JR. Chronic allograft nephropathy: current concepts and future directions. Transplantation 2006;81:643-654.
138. Chapman JR, O'Connell PJ, Nankivell BJ. Chronic renal allograft dysfunction. J Am Soc Nephrol 2005;16:3015-3026.
139. Yates PJ, Nicholson ML. The aetiology and pathogenesis of chronic allograft nephropathy. Transpl Immunol 2006;16:148-157.
140. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med 2003;349:2326-2333.
141. Rush D, Arlen D, Boucher A, Busque S, Cockfield SM, Girardin C, et al. Lack of benefit of early protocol biopsies in renal transplant patients receiving TAC and MMF: a randomized study. Am J Transplant 2007;7:2538-2545.
142. Meier-Kriesche HU, Steffen BJ, Chu AH, Loveland JJ, Gordon RD, Morris JA, Kaplan B. Sirolimus with neoral versus mycophenolate mofetil with neoral is associated with decreased renal allograft survival. Am J Transplant 2004;4:2058-2066.
143. Meier-Kriesche HU, Schold JD, Srinivas TR, Howard RJ, Fujita S, Kaplan B. Sirolimus in combination with tacrolimus is associated with worse renal allograft survival compared to mycophenolate mofetil combined with tacrolimus. Am J Transplant 2005;5:2273-2280.
144. Flechner SM, Goldfarb D, Modlin C, Feng J, Krishnamurthi V, Mastroianni B, et al. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. Transplantation 2002;74:1070-1076.
145. Flechner SM, Goldfarb D, Solez K, Modlin CS, Mastroianni B, Savas K, et al. Kidney transplantation with sirolimus and mycophenolate mofetil-based immunosuppression: 5-year results of a randomized prospective trial compared to calcineurin inhibitor drugs. Transplantation 2007;83:883-892.
146. Asberg A, Midtvedt K, Line PD, Narverud J, Holdaas H, Jenssen T, et al. Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. Transplantation 2006;82:62-68.
147. Vincenti F, Ramos E, Brattstrom C, Cho S, Ekberg H, Grinyo J, et al. Multicenter trial exploring calcineurin inhibitors avoidance in renal transplantation. Transplantation 2001;71:1282-1287.
148. Vincenti F, Larsen C, Durrbach A, Wekerle T, Nashan B, Blancho G, et al. Costimulation blockade with belatacept in renal transplantation. N Engl J Med 2005;353:770-781.
149. Ekberg H, Grinyo J, Nashan B, Vanrenterghem Y, Vincenti F, Voulgari A, et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. Am J Transplant 2007;7:560-570.
150. Flechner S, Cockfield S, Grinyo J. A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with tacrolimus (TAC) + mycophenolate mofetil (MMF) in de novo renal allograft recipients: preliminary 2-year safety results from the ORION trial. Am J Transplant 2008;9:254.
151. Pearson T, Mulgaonkar S, Patel A. Efficacy and safety of mycophenolate mofetil (MMF)/sirolimus (SRL) maintenance therapy after calcineurin inhibitor (CNI) withdrawal in renal transplant recipients: final results of the Spare-the-Nephron (STN) trial. Am J Transplant 2008;8:213.
152. Birnbaum L, Limpan M, Paraskevas S. Management of chronic allograft nephropathy: a systematic review. Clin J Am Soc Nephrol 2009;4:860-865.
153. Stallone G, Infante B, Schena A, Battaglia M, Ditonno P, Loverre A, et al. Rapamycin for treatment of chronic allograft nephropathy in renal transplant patients. J Am Soc Nephrol 2005;16:3755-3762.
154. ClinicalTrials.gov. Available at: http://clinicaltrials.gov. Accessed June 2009.
155. Larsen CP, Knechtle SJ, Adams A, Pearson T, Kirk AD. A new look at blockade of T-cell costimulation: a therapeutic strategy for long-term maintenance immunosuppression. Am J Transplant 2006;6:876-883.
156. Vincenti F, Kirk AD. What's next in the pipeline. Am J Transplant 2008;8:1972-1981.
157. Hirose R, Vincenti F. Immunosuppression: today, tomorrow, and withdrawal. Semin Liver Dis 2006;26:201-210.
158. Vincenti F, Mendez R, Pescovitz M, Rajagopalan PR, Wilkinson AH, Butt K, et al. A phase I/II randomized open-label multicenter trial of efalizumab, a humanized anti-CD11a, anti-LFA-1 in renal transplantation. Am J Transplant 2007;7:1770-1777.
159. Shapira MY, Abdul-Hai A, Resnick IB, Bitan M, Tsirigotis P, Aker M, et al. Alefacept treatment for refractory chronic extensive GVHD. Bone Marrow Transplant 2009;43:339-343.
160. De Simone P, Carrai P, Precisi A, Petruccelli S, Baldoni L,

Balzano E, et al. Conversion to everolimus monotherapy in maintenance liver transplantation: feasibility, safety, and impact on renal function. Transpl Int 2009;22:279-286.

161. Eason JD, Nair S, Cohen AJ, Blazek JL, Loss GE Jr. Steroid-free liver transplantation using rabbit antithymocyte globulin and early tacrolimus monotherapy. Transplantation 2003;75:1396-1399.
162. Bonventre JV, Weinberg JM. Recent advances in the pathophysiology of ischemic acute renal failure. J Am Soc Nephrol 2003;14:2199-2210.
163. Byrick RJ, Rose DK. Pathophysiology and prevention of acute renal failure: the role of the anaesthetist. Can J Anaesth 1990;37:457-467.
164. Dupont J, Messiant F, Declerck N, Tavernier B, Jude B, Durinck L, et al. Liver transplantation without the use of fresh frozen plasma. Anesth Analg 1996;83:681-686.
165. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41:553-558.
166. Massicotte L, Lenis S, Thibeault L, Sassine MP, Seal RF, Roy A. Reduction of blood product transfusions during liver transplantation. Can J Anaesth 2005;52:545-546.
167. Massicotte L, Lenis S, Thibeault L, Sassine MP, Seal RF, Roy A. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantations. Liver Transpl 2006;12:117-123.
168. Beltran J, et al. Paper presented at: 14th Congress of International Liver Transplantation Society; 2008; Paris, France.
169. Grande L, Rimola A, Cugat E, Alvarez L, Garcia-Valdecasas JC, Taura P, et al. Effect of venovenous bypass on perioperative renal function in liver transplantation: results of a randomized, controlled trial. Hepatology 1996; 23:1418-1428.
170. Gonzalez FX, Garcia-Valdecasas JC, Grande L, Pacheco JL, Cugat E, Fuster J, et al. Vena cava vascular reconstruction during orthotopic liver transplantation: a comparative study. Liver Transpl Surg 1998;4:133-140.
171. Parrilla P, Sanchez-Bueno F, Figueras J, Jaurrieta E, Mir J, Margarit C, et al. Analysis of the complications of the piggy-back technique in 1,112 liver transplants. Transplantation 1999;67:1214-1217.
172. Cirera I, Navasa M, Rimola A, Garcia-Pagan JC, Grande L, Garcia-Valdecasas JC, et al. Ascites after liver transplantation. Liver Transpl 2000;6:157-162.
173. Figueras J, Llado L, Ramos E, Jaurrieta E, Rafecas A, Fabregat J, et al. Temporary portocaval shunt during liver transplantation with vena cava preservation. Results of a prospective randomized study. Liver Transpl 2001;7:904-911.
174. Shaw AD, Stafford-Smith M, White WD, Phillips-Bute B, Swaminathan M, Milano C, et al. The effect of aprotinin on outcome after coronary-artery bypass grafting. N Engl J Med 2008;358:784-793.
175. Ruggeberg A, Boehm S, Napieralski A. Development of a risk stratification model for predicting acute renal failure in orthotopic liver transplantation recipients. Anesthesia 2008;63:174-1180.
176. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. Crit Care Med 2008;36:S179–S186.
177. Zaky A, Pretto EA Jr, Earle SA, Piraccini E, Zuccarelli JE, Arheart KL, Proctor KG. Hemodynamic and metabolic efficacy of dopamine versus norepinephrine in a brain-dead swine model. Liver Transpl 2008;14:1266-1272.
178. Zacharias M, Gilmore IC, Herbison GP, Sivalingam P, Walker RJ. Interventions for protecting renal function in the perioperative period. Cochrane Database Syst Rev 2005:CD003590.
179. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med 2005;142:510-524.
180. Swygert TH, Roberts LC, Valek TR, Brajtbord D, Brown MR, Gunning TC, et al. Effect of intraoperative low-dose dopamine on renal function in liver transplant recipients. Anesthesiology 1991;75:571-576.
181. Marik PE. Low-dose dopamine: a systematic review. Intensive Care Med 2002;28:877-883.
182. Bagshaw SM, Delaney A, Haase M, Ghali WA, Bellomo R. Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. Crit Care Resusc 2007;9:60-68.
183. Polson RJ, Park GR, Lindop MJ, Farman JV, Calne RY, Williams R. The prevention of renal impairment in patients undergoing orthotopic liver grafting by infusion of low dose dopamine. Anaesthesia 1987;42:15-19.
184. Dohler KD, Meyer M. Vasopressin analogues in the treatment of hepatorenal syndrome and gastrointestinal haemorrhage. Best Pract Res Clin Anaesthesiol 2008;22: 335-350.
185. Landoni G, Biondi-Zoccai GG, Marino G, Bove T, Fochi O, Maj G, et al. Fenoldopam reduces the need for renal replacement therapy and in-hospital death in cardiovascular surgery: a meta-analysis. J Cardiothorac Vasc Anesth 2008;22:27-33.
186. Biancofiore G, Della Rocca G, Bindi L, Romanelli A, Esposito M, Meacci L, et al. Use of fenoldopam to control renal dysfunction early after liver transplantation. Liver Transpl 2004;10:986-992.
187. Hadengue A, Moreau R, Bacq Y, Gaudin C, Braillon A, Lebrec D. Selective dopamine DA1 stimulation with fenoldopam in cirrhotic patients with ascites: a systemic, splanchnic and renal hemodynamic study. Hepatology 1991;13:111-116.
188. Tumlin JA, Finkel K, Murray P. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. Am J Kidney Dis 2007;49:56-68.
189. Fontana I, Germi MR, Beatini M, Fontana S, Bertocchi M, Porcile E, et al. Dopamine "renal dose" versus fenoldopam mesylate to prevent ischemia-reperfusion injury in renal transplantation. Transplant Proc 2005;37:2474-2475.
190. Maerz L, Kaplan LJ. Abdominal compartment syndrome. Crit Care Med 2008;36:S212–S215.
191. Hynninen MS, Niemi TT, Poyhia R, Raininko EI, Salmenpera MT, Lepantalo MJ, et al. N-acetylcysteine for the prevention of kidney injury in abdominal aortic surgery: a randomized, double-blind, placebo-controlled trial. Anesth Analg 2006;102:1638-1645.
192. Haase M, Haase-Fielitz A, Bagshaw SM, Reade MC, Morgera S, Seevenayagam S, et al. Phase II, randomized, controlled trial of high-dose N-acetylcysteine in high-risk cardiac surgery patients. Crit Care Med 2007;35:1324-1331.
193. Burns KE, Chu MW, Novick RJ, Fox SA, Gallo K, Martin CM, et al. Perioperative N-acetylcysteine to prevent renal dysfunction in high-risk patients undergoing CABG surgery: a randomized controlled trial. JAMA 2005;294:342-350.
194. de Araujo M, Andrade L, Coimbra TM, Rodrigues AC Jr, Seguro AC. Magnesium supplementation combined with N-acetylcysteine protects against postischemic acute renal failure. J Am Soc Nephrol 2005;16:3339-3349.
195. Lang JD Jr, Teng X, Chumley P, Crawford JH, Isbell TS, Chacko BK, et al. Inhaled NO accelerates restoration of

liver function in adults following orthotopic liver transplantation. J Clin Invest 2007;117:2583-2591.
196. Barber K, Blackwell J, Collett D, Neuberger J. Life expectancy of adult liver allograft recipients in the UK. Gut 2007;56:279-282.
197. Starzl TE, Iwatsuki S, Shaw BW Jr, Gordon RD, Esquivel CO. Immunosuppression and other nonsurgical factors in the improved results of liver transplantation. Semin Liver Dis 1985;5:334-343.
198. Neuberger JM, Mamelok RD, Neuhaus P, Pirenne J, Samuel D, Isoniemi H, et al. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. Am J Transplant 2009;9:327-336.
199. Stewart SF, Hudson M, Talbot D, Manas D, Day CP. Mycophenolate mofetil monotherapy in liver transplantation. Lancet 2001;357:609-610.
200. DuBay D, Smith RJ, Qiu KG, Levy GA, Lilly L, Therapondos G. Sirolimus in liver transplant recipients with renal dysfunction offers no advantage over low-dose calcineurin inhibitor regimens. Liver Transpl 2008;14:651-659.
201. Campbell KM, Yazigi N, Ryckman FC, Alonso M, Tiao G, Balistreri WF, et al. High prevalence of renal dysfunction in long-term survivors after pediatric liver transplantation. J Pediatr 2006;148:475-480.
202. Sandborn WJ, Hay JE, Porayko MK, Gores GJ, Steers JL, Krom RA, Wiesner RH. Cyclosporine withdrawal for nephrotoxicity in liver transplant recipients does not result in sustained improvement in kidney function and causes cellular and ductopenic rejection. Hepatology 1994;19:925-932.
203. Ramos HC, Reyes J, Abu-Elmagd K, Zeevi A, Reinsmoen N, Tzakis A, et al. Weaning of immunosuppression in long-term liver transplant recipients. Transplantation 1995;59:212-217.
204. Mazariegos GV, Reyes J, Marino IR, Demetris AJ, Flynn B, Irish W, et al. Weaning of immunosuppression in liver transplant recipients. Transplantation 1997;63:243-249.
205. Devlin J, Doherty D, Thomson L, Wong T, Donaldson P, Portmann B, Williams R. Defining the outcome of immunosuppression withdrawal after liver transplantation. Hepatology 1998;27:926-933.
206. Takatsuki M, Uemoto S, Inomata Y, Egawa H, Kiuchi T, Fujita S, et al. Weaning of immunosuppression in living donor liver transplant recipients. Transplantation 2001; 72:449-454.
207. Oike F, Yokoi A, Nishimura E, Ogura Y, Fujimoto Y, Kasahara M, et al. Complete withdrawal of immunosuppression in living donor liver transplantation. Transplant Proc 2002;34:1521.
208. Pons JA, Yelamos J, Ramirez P, Oliver-Bonet M, Sanchez A, Rodriguez-Gago M, et al. Endothelial cell chimerism does not influence allograft tolerance in liver transplant patients after withdrawal of immunosuppression. Transplantation 2003;75:1045-1047.
209. Tryphonopoulos P, Tzakis AG, Weppler D, Garcia-Morales R, Kato T, Madariaga JR, et al. The role of donor bone marrow infusions in withdrawal of immunosuppression in adult liver allotransplantation. Am J Transplant 2005;5:608-613.
210. Eason JD, Cohen AJ, Nair S, Alcantera T, Loss GE. Tolerance: is it worth the risk? Transplantation 2005;79: 1157-1159.
211. Tisone G, Orlando G, Cardillo A, Palmieri G, Manzia TM, Baiocchi L, et al. Complete weaning off immunosuppression in HCV liver transplant recipients is feasible and favourably impacts on the progression of disease recurrence. J Hepatol 2006;44:702-709.
212. Assy N, Adams PC, Myers P, Simon V, Minuk GY, Wall W, Ghent CN. Randomized controlled trial of total immunosuppression withdrawal in liver transplant recipients: role of ursodeoxycholic acid. Transplantation 2007;83: 1571-1576.
213. Li Y, Koshiba T, Yoshizawa A, Yonekawa Y, Masuda K, Ito A, et al. Analyses of peripheral blood mononuclear cells in operational tolerance after pediatric living donor liver transplantation. Am J Transplant 2004;4:2118-2125.
214. Koshiba T, Li Y, Takemura M, Wu Y, Sakaguchi S, Minato N, et al. Clinical, immunological, and pathological aspects of operational tolerance after pediatric living-donor liver transplantation. Transpl Immunol 2007;17:94-97.
215. Orlando G, Manzia T, Baiocchi L, Sanchez-Fueyo A, Angelico M, Tisone G. The Tor Vergata weaning off immunosuppression protocol in stable HCV liver transplant patients: the updated follow up at 78 months. Transpl Immunol 2008;20:43-47.
216. Tzakis A, Tryphonopoulos P, Weppler D, Garcia-Morales R, Cirocco R. Operational tolerance: long term observations after complete withdrawal of immunosuppression (ISP) in liver transplant recipients. Am J Transplant 2008;8(suppl 2):542.
217. Martinez-Llordella M, Puig-Pey I, Orlando G, Ramoni M, Tisone G, Rimola A, et al. Multiparameter immune profiling of operational tolerance in liver transplantation. Am J Transplant 2007;7:309-319.
218. Martinez-Llordella M, Lozano JJ, Puig-Pey I, Orlando G, Tisone G, Lerut J, et al. Using transcriptional profiling to develop a diagnostic test of operational tolerance in liver transplant recipients. J Clin Invest 2008;118:2845-2857.
219. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-1026.
220. Carbone J, Micheloud D, Salcedo M, Rincon D, Banares R, Clemente G, et al. Humoral and cellular immune monitoring might be useful to identify liver transplant recipients at risk for development of infection. Transpl Infect Dis 2008;10:396-402.
221. Propst-Graham KL, Preheim LC, Vander Top EA, Snitily MU, Gentry-Nielsen MJ. Cirrhosis-induced defects in innate pulmonary defenses against *Streptococcus pneumoniae*. BMC Microbiol 2007;7:94.
222. Platt JF, Ellis JH, Rubin JM, Merion RM, Lucey MR. Renal duplex Doppler ultrasonography: a noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. Hepatology 1994;20:362-369.
223. Kastelan S, Ljubicic N, Kastelan Z, Ostojic R, Uravic M. The role of duplex-Doppler ultrasonography in the diagnosis of renal dysfunction and hepatorenal syndrome in patients with liver cirrhosis. Hepatogastroenterology 2004;51:1408-1412.
224. Davis CL, Feng S, Sung R, Wong F, Goodrich NP, Melton LB, et al. Simultaneous liver-kidney transplantation: evaluation to decision making. Am J Transplant 2007;7: 1702-1709.
225. Ueno T, Barri YM, Netto GJ, Martin A, Onaca N, Sanchez EQ, et al. Liver and kidney transplantation for polycystic liver and kidney-renal function and outcome. Transplantation 2006;82:501-507.
226. Pichler R, Dittrich M, Anderson A, Kendrick E, Crithers R, Larson A. Prediction of benefit from simultaneous liver kidney transplantation versus liver alone transplantation: potential role for native kidney biopsy. J Am Soc Nephrol 2006;17:795A.
227. Wolfe RA, McCullough KP, Schaubel DE, Kalbfleisch JD, Murray S, Stegall MD, Leichtman AB. Calculating life years from transplant (LYFT): methods for kidney and kidney-pancreas candidates. Am J Transplant 2008;8: 997-1011.