Renal Failure in the Recipients of Nonrenal Solid Organ Transplants

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The increased success and availability of transplantation of solid organs other than kidneys has resulted in a large number of patients at risk for the usual medical complications of long-term immunosuppressive therapy. Acute and chronic renal failure play a critical role in the success of these procedures. By 10 yr after transplantation among these long-term survivors, approximately 12% of heart, 2 to 7% of lung, and 4% of liver patients will have developed severe renal insufficiency. About half of these will have end-stage renal failure (ESRD) and will either be on dialysis or have received a renal transplant. The analysis of renal function in patients who were previously diabetic and who received a pancreas transplant is confounded by the presence of pretransplant diabetic renal damage. However, in these patients, too, the subsequent loss of renal function is predominantly due to their immunosuppressive therapies.

The most important factor in the etiology of this renal failure is the chronic nephrotoxicity of the calcineurin inhibitor immunosuppressives (CNI), cyclosporine (CsA) (Neoral®, Sandimmune®, and tacrolimus (Prograf®). Paradoxically, it is the CNI that have made the transplantation of nonrenal organs successful. However, until we have adequate alternative immunosuppression, nephrotoxicity will remain a potential complication for patients currently receiving these transplants, and if this progresses to ESRD it will add to the number of patients waiting for kidney transplants. In nearly all patients in whom this has been studied, the pathologic findings are those of severe CNI toxicity. Cyclosporine nephrotoxicity was described soon after its introduction into clinical transplantation. One early report of clinical experience with CsA in renal, pancreas, and liver transplant recipients documented this potential nephrotoxicity (1). The most alarming reports and predictions of renal damage from the use of CsA were those of Myers et al., who in a number of reports documented the clinical course, pathology, and pathophysiology of CsA toxicity in cardiac transplant recipients (2–5).

Previously, it was presumed that the drug was most damaging in the setting of renal transplantation. Other authors have reported similar findings in patients treated with CsA for autoimmune diseases (6).

There have been many subsequent reports of renal failure in patients who have received nonrenal solid organ transplants (7–11). The frequency of perioperative renal failure is not surprising in view of the many factors that may affect renal function in these patients. These include the causes of renal failure associated with end-stage liver and heart disease, the complexity of these operations, the potential for postoperative graft dysfunction and sepsis, and the nephrotoxicity not only of the CNI, but also other therapeutic agents used to treat infection and rejection.

Chronic CsA toxicity is a well described, yet poorly understood, condition. Recent studies in renal transplantation describe findings that may differentiate it from other forms of chronic interstitial nephritis and chronic renal allograft nephropathy (12,13). This understanding of the nature of CsA toxicity may allow the introduction of less toxic CNI, or provide insight into how we can minimize the damage from those CNI already in clinical use.

Analysis of the impact of CsA on renal failure in these patients is complicated by a lack of good data. Most studies are descriptive and retrospective. CNI dosing and levels do not correlate well with renal damage, and reductions in dosage do not predictably halt the progression to renal failure. However, surrogate markers for acute episodes of significant toxicity and CsA exposure over time, such as trough levels and the daily dose (mg/kg) at various times after transplantation, have shown a weak correlation between higher drug exposures and the subsequent risk of a decline in renal function. In addition, most studies do not include any values, either by measurement or calculation, of the GFR or creatinine clearance (CCr). Instead, they rely on the serum creatinine concentration (SCr), which is notoriously unreliable in malnourished patients and in those with liver failure and heart failure (14). It is often not appreciated that a normal SCr does not necessarily correlate with normal renal function. Some of the apparent postoperative decline in renal function may merely reflect an increase in muscle mass in individuals who were previously severely malnourished. This is not to suggest that these patients do not have renal impairment, but rather that some of the loss of function may reflect damage already present before the introduction of cyclosporine.

In patients with liver disease, the analysis of their pre- and perioperative renal function is further complicated by the im-
pact of hepatorenal dysfunction. This is usually present to some degree by the time these patients require transplantation, even when it has not progressed to the full blown hepatorenal syndrome (HRS). None of the studies of long-term renal function in these patients has factored in the potential impact of posttransplant HRS from poor liver graft function. Only a few have segregated patients with recurrent hepatitis C or hepatitis B, who may additionally have hepatitis-associated glomerulonephritis.

The most commonly identified risk factors for the development of renal failure in recipients of nonrenal organs are impaired pre- and perioperative renal function. These patients also suffer from many of the other factors that are known to correlate with the progression of renal failure, such as hypertension, hyperlipidemia, and proteinuria.

Careful preoperative management and preparation are important, as are attention to fluid management and renal function at the time of operation. Most studies correlate subsequent renal insufficiency with renal failure in this early period. The long-term management of all recipients of nonrenal transplants should include attention to the treatment of BP, using those agents most likely to reduce proteinuria, and of hyperlipidemia. When patients do reach ESRD, both cadaveric and living donor kidney transplantation have been used with successful outcomes.

Factors Common to Recipients of all Nonrenal Transplants

Despite the great differences between the factors leading to organ failure in the recipients of liver, heart, and lung transplantation, and the different clinical complications that result from failure of these organs, the postoperative clinical course of renal insufficiency in patients immunosuppressed with CNI is surprisingly uniform regardless of the organ transplanted. This allows a general description of renal failure in all of these groups. Subsequent sections highlight the findings peculiar to each organ group.

The Course of Renal Impairment

The selection process for transplantation excludes patients with severe and irreversible renal failure, unless they are accepted as candidates for combined organ transplantation. Therefore, those patients who receive nonrenal transplants usually have normal or only mildly impaired renal function at the time of transplantation. It is presumed that most of this mild renal dysfunction is reversible and that the kidneys have sufficient reserve to withstand the effects of the operation and the introduction of CNI. After the first administration of CNI, there is an acute reduction in renal perfusion caused by constriction of the afferent glomerular arteriole. However, for most patients, provided the BP and renal perfusion are well preserved, there is an immediate improvement in renal function in the postoperative period. Thereafter, there is frequently an early decline in renal function, and by 12 mo the GFR is reduced by about 50%. For most patients, renal function then stabilizes. However, Myers et al. (2–5) warned that even when the $S_{\text{Cr}}$ remains stable, or when significant proteinuria does not develop, it is probable that progressive and irreversible renal injury is occurring in the majority of these patients. It is probable that we will see a steady increase over time in the number of patients reaching ESRD. Data supporting this thesis were reported by Falkenhain et al. in heart and liver transplant recipients (15). A minority of patients progresses more rapidly to ESRD.

Common Risk Factors

The authors of many articles have analyzed the factors that predict an increased risk of renal failure in these patients (Table 1). It is not surprising that similar factors affect renal function no matter which organ is transplanted. In general, they are the same as those that predict renal failure in any patients undergoing major surgical procedures, and those in patients with intrinsic renal impairment, with the superimposed complication of CNI toxicity in the nonrenal transplant population.

Hypertension

Unlike patients with ESRD requiring renal transplantation, many patients who receive nonrenal transplants are not hypertensive in the preoperative period. However, patients treated with CNI, and most significantly CsA, have a high incidence of hypertension. Hypertension is present in as many as 90% of cardiac, 65 to 85% of liver, and 60 to 70% of lung transplant recipients. The onset of hypertension is usually early, at a time when both corticosteroid dose and CsA serum levels are high. Most patients who develop hypertension will do so within the first 6 mo, but the prevalence will continue to increase with time (16,17). Elevations in systolic, mean, or diastolic BP are all independent risk factors for the progression of renal failure in patients with intrinsic renal diseases, and it is highly probable that this is also true for transplant recipients. The Joint National Commission VI (JNC VI) report on the diagnosis and treatment of hypertension has guidelines for the aggressive management of hypertension in patients with renal disease, with and without proteinuria. These guidelines for target reductions in BP, and the recommended agents for treatment in these patients, should be followed in all transplant patients who have hypertension, in the hope of reducing the impact of hypertension on renal failure (18).

Proteinuria

Heavy proteinuria is not a usual feature of CNI nephrotoxicity, although there are reports of nephrotic range proteinuria in patients whose biopsies did not have any features of primary

<table>
<thead>
<tr>
<th>Table 1. Risk factors for developing progressive renal insufficiency</th>
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<tbody>
<tr>
<td>● Preoperative renal function</td>
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<tr>
<td>● Intraoperative renal function</td>
</tr>
<tr>
<td>● Perioperative events (sepsis, cytomegalovirus infection, hypotension, pressor agents)</td>
</tr>
<tr>
<td>● Cyclosporine/tacrolimus exposure</td>
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</table>
glomerulonephritis. In cases where proteinuria has been reported, it usually occurs several years after transplantation and is associated with advanced renal insufficiency (19). Lower levels of proteinuria are not infrequently observed, and because there is evidence correlating proteinuria with progressive renal failure, this is certainly an added risk factor in these patients. When nephrotic range proteinuria develops, at any time after transplantation, and particularly when renal function is better preserved, this is probably due to a primary glomerulonephritis and warrants further investigation. In recipients of liver transplantation, proteinuria may be a sign of hepatitis-associated glomerulonephritis.

**Hyperlipidemia**

Transplant patients frequently develop hyperlipidemia. This should be treated to reduce the risk of cardiac and other vascular complications. However, hyperlipidemia is an associated risk factor for the progression of renal failure, and for this reason alone it is important to manage this complication aggressively. Early concerns that there would be an unacceptable incidence of myositis and rhabdomyolysis when hydroxymethylglutaryl CoA reductase inhibitors are used concurrently with CsA have not been confirmed by clinical experience. These agents may also reduce the risk of early graft rejection. It is recommended that these agents be used to correct both hypercholesterolemia and hypertriglyceridemia.

**Cyclosporine Exposure**

Virtually all of the studies describing renal dysfunction have included patients treated with CsA. Some of the more recent studies have also included patients on tacrolimus, and there appears to be little improvement following the introduction of the newer CNI. Exposure to CNI is the one feature common to all of these patients. The protocols used to immunosuppress these patients have varied by center and by time. No particular protocol has been reported to prevent the impact of CNI. Although CNI use is the most important risk factor in these patients, there are inconsistent data with regard to how this affects renal function. Neither daily dose nor trough levels correlate well with the exposure to area under the curve (AUC) for drug exposure. This was more pronounced in the majority of patients who were treated with Sandimmune™ than for those treated with either Neoral® or Prograf®. On the other hand, the improved absorption of Neoral® has probably resulted in a greater AUC for patients with equivalent trough levels. Using surrogates for AUC, such as blood concentrations of the drug or drug doses at variable times after transplantation, it is possible to show a weak correlation with overall exposure and the subsequent progression to renal failure. Most transplant centers set the dose of CNI to predetermined levels that are presumed to provide adequate immunosuppression without undue toxicity. However, there is no direct correlation between immunosuppression and toxicity, and when the serum creatinine rises it is usual for the CNI dose to be lowered to as low a level as possible, to minimize further nephrotoxicity.

**Pathology**

Renal biopsies performed on these patients demonstrate that CNI toxicity is the most common cause of proteinuria and the decline in kidney function. Pathologic changes were seen in all components of the kidney. There are glomerular, tubulointerstitial, and vascular abnormalities. The most common finding is that of interstitial fibrosis accompanied by tubular atrophy. This is often associated with an oblitative vasculopathy, characterized by arteriolar hyalinization, with myocyte necrosis, nodular hyaline deposits, and mucoid intimal edema. The glomeruli show changes suggestive of ischemia and collapse, with some global sclerosis. These changes were seldom described in patients in earlier studies presenting the histology in patients receiving only azathioprine and corticosteroids. These findings are identical to those described in patients receiving CsA for the treatment of autoimmune diseases (6,20). The only lesion seen more frequently in nonrenal transplant patients is that of focal segmental glomerulosclerosis (FSGS) (15,19). This is seen more frequently in patients with heavier proteinuria, and may rather reflect the coexistence of primary FSGS. The primary glomerular diseases, membranous nephropathy, IgA nephropathy, and membranoproliferative glomerulonephritis type 1, have been described in these patients, and probably reflect the incidental occurrence of nephritis.

**Organ-Specific Reports of Renal Insufficiency**

**Liver Transplantation**

The most important distinction in this population is the possible presence of the HRS and the high prevalence of glomerular abnormalities, most commonly IgA nephropathy, at the time of transplantation. Before the introduction of liver transplantation, the onset of ESRD due to HRS was universally fatal. There is still some confusion in the analysis of patients with liver disease and lesser degrees of renal failure, as not all practitioners recognize the progressive nature of the HRS. A large number of these patients will have episodes of renal dysfunction. The underlying cause in most of them is developing HRS aggravated by overzealous diuresis, by diarrhea induced by lactulose, or by gastrointestinal bleeding and renal hypoperfusion. In patients with ascites, paracentesis is less likely to lead to elevations of SCR than is the use of diuretics. It is now understood that renal function in the HRS is impaired by pathophysiologic abnormalities characterized by alterations in the secretion of prostaglandins, catecholamines, endothelin, angiotensin, and nitric oxide, which lead to an alteration in glomerular hemodynamics and a fall in the GFR.

Many studies have shown a strong correlation with preoperative renal dysfunction and both postoperative patient survival and long-term renal insufficiency. For example, one study documented abnormal renal function in 25% of patients before transplantation, and in 67% after transplantation (21). Improvements in the operative management of these patients have significantly reduced the incidence of postoperative acute renal failure. The effect of infusions of the calcium antagonist verapamil, to reverse some of the reduction in renal perfusion, has met with variable success (22,23). In a review of the National Institute of Diabetes and Digestive and Kidney Dis-
that only 23% of liver transplant recipients had a normal SCr by function of 40 to 50% by 6 mo (27,31,34). McCauley reported time of transplantation experience a mean decline in renal fraction in patients treated with tacrolimus (33).

CsA toxicity is associated with further alterations in renal hemodynamics, producing an acute fall in GFR. This fall in the GFR has been documented in liver transplant recipients, in whom it falls immediately after the introduction of CsA. This effect is exaggerated by intravenous administration of CNI. The change in GFR was documented in more than 260 patients with the use of isothalamate (Glofil) clearance studies. The GFR fell by 40% within 6 wk of transplantation, but thereafter remained stable for more than 4 yr (26). Gonwa (Table 2) has documented long-term data in 300 liver transplant recipients. A comparable decline with respect to the preoperative GFR was documented in other studies in patients with eventual stable, albeit impaired, long-term renal function (27–32).

The effect of early CNI administration in these patients is exacerbated by the pathophysiologic abnormalities that characterize the HRS. The results of a number of studies in which the primary immunosuppressive agent was tacrolimus, first introduced for use in liver transplantation, show no clear reduction in nephotoxicity (24,31,32). Tauxe et al. compared the use of CsA and tacrolimus and found significantly less impairment in effective renal plasma flow, GFR, and filtration fraction in patients treated with tacrolimus (33).

Liver transplant patients with preserved renal function at the time of transplantation experience a mean decline in renal function of 40 to 50% by 6 mo (27,31,34). McCauley reported that only 23% of liver transplant recipients had a normal SCr by 39 mo after transplantation (34). In longer-term follow-up, Fisher et al. found that nearly 80% of patients had reduced renal function (SCr > 125 μM/L) at 5 yr (9). The median SCr rose from 135 μM/L at 1 yr to 157 μM/L at 5 yr. In patients surviving at least 1 yr, 4% developed ESRD. The mean time to the onset of ESRD was about 5 yr. Patient survival after the onset of ESRD was reduced to a median of 1.2 yr. Half of the patients with severe renal insufficiency had proteinuria >3 g/24 h. Renal biopsies confirmed CsA nephrotoxicity in all but one patient who had IgA nephropathy. In two patients, there were changes compatible with a CsA-induced microangiopathy. The clinical and histologic features of patients on CsA and tacrolimus were indistinguishable in this study and that of Platz et al. (9,35). Univariate risk factor analysis for the development of severe renal insufficiency at 5 yr identified an elevated SCr at 3 mo and at 1 yr as significant. However, the predictive value of an elevated SCr value was poor. There was a weak association between higher CsA trough levels at 1 mo and subsequent severe renal insufficiency when the data were analyzed by multivariate analysis. Patients with severe renal insufficiency at 5 yr were divided into two groups, the first with early and the second with late renal failure, depending on whether the SCr was more than 200 μM/L at 1 yr. The risk factors for early dysfunction included older age, cytomegalovirus infection, a requirement for renal replacement therapy during surgery, and retransplantation of the liver. CsA levels were not a factor. In those in whom renal dysfunction developed later than 1 yr, risk factors were a higher daily CsA dose at annual intervals, and a higher cumulative CsA dose at 5 yr. A retrospective analysis showed no benefit of a reduction in CsA dose at the time that renal dysfunction was diagnosed (9).

**Outcome in Patients with the HRS.** One of the most difficult decisions for physicians is whether to perform a combined kidney-liver transplant in patients with dual organ failure. There is no adequate way to assess the extent to which renal impairment is only a consequence of the HRS or acute tubular necrosis (ATN), or whether in addition there is intrinsic renal disease. The usual tests of renal function such as the Ccr and SCr and urinary electrolyte determinations are all unreliable in this setting. The presence of a systemic disease associated with nephritis, a primary renal disease such as polycystic kidney disease, and the presence of proteinuria raise the possibility of intrinsic renal failure. The presence of hematuria may be a sign of IgA nephropathy, or may result from bleeding secondary to impaired coagulation. It is important to obtain information about renal function before the decline in liver function and to use ultrasound and computerized tomography. Renal biopsy data should be obtained when possible. By optimizing the intravascular volume status, it is sometimes possible to show that renal failure is reversible.

In patients with HRS, renal function generally recovers rapidly after liver transplantation, and these patients should receive only a liver transplant. Up to 4 yr after transplantation, the long-term patient and graft survival is usually reported as being similar in patients with and without HRS. However, in one study, up to 10% of patients with HRS progressed to ESRD, compared with only 0.8% of recipients without HRS (36). In a report of patients transplanted at UCLA, 46% of an initial cohort required dialysis after transplantation, and an additional 20% developed reversible episodes of renal dysfunction. The survival of patients with HRS requiring preoperative dialysis was greater than that of the group as a whole, which

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**Table 2. Long-term renal function in liver transplant patients treated with cyclosporine**

<table>
<thead>
<tr>
<th>Period</th>
<th>Creatinine (mg/dl)</th>
<th>GFR (ml/min per m^2)</th>
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<tbody>
<tr>
<td>Before transplantation</td>
<td>1.1 ± 0.03</td>
<td>94.1 ± 1.8</td>
</tr>
<tr>
<td>6 to 8 wk after surgery</td>
<td>1.3 ± 0.03</td>
<td>57.1 ± 2.2</td>
</tr>
<tr>
<td>1 yr after surgery</td>
<td>1.5 ± 0.03</td>
<td>59.8 ± 1.6</td>
</tr>
<tr>
<td>2 yr after surgery</td>
<td>1.6 ± 0.06</td>
<td>58.9 ± 2.1</td>
</tr>
<tr>
<td>3 yr after surgery</td>
<td>1.6 ± 0.05</td>
<td>57.0 ± 5.4</td>
</tr>
<tr>
<td>4 yr after surgery</td>
<td>1.6 ± 0.01</td>
<td>56.7 ± 4.5</td>
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</table>

* Modified from reference 27.
emphasizes the excellent prognosis possible for these patients when they undergo liver transplantation. When patients presumed to have HRS or ATN require dialysis for more than 4 wk before liver transplantation, it is likely that they will develop renal cortical fibrosis and that their renal function will not recover. Under these circumstances, we recommend a dual kidney-liver transplant (37,38).

**Combined Kidney-Liver Transplantation**

The impact of renal failure on the morbidity and cost of liver transplantation has encouraged combined kidney-liver transplantation. There is an acute shortage of organs for kidney transplantation, and this should only be done when there is a strong expectation that kidney function is irreversible and impaired by something other than HRS or ATN. The rate at which combined kidney-liver transplants are performed as a function of all liver transplants ranges from about 2% to as high as 10% at different liver transplant programs. In two reports (Table 3) on 35 combined kidney-liver transplant patients, the causes of renal failure in the combined series included primary renal diseases, drug-induced nephropathies, and patients with renal failure from CNI (39,40). The patient and graft survival in this combined procedure is excellent except when the patients are critically ill before transplantation. Markowitz et al. reviewed 32 patients who received combined kidney-liver transplants at UCLA. One-year actuarial patient and graft survival was 78% for United Network of Organ Sharing (UNOS) status 2 patients, and 89% for UNOS status 3 patients, but for the critically ill UNOS status 1 patients survival at 1 yr was only 25%. This emphasizes that this procedure is not necessarily indicated in patients with severe multiorgan failure (41). Although organ distribution does not take this variable into account, consideration should be given to allocating livers more quickly to patients with HRS who require dialysis, to avoid the need for kidney-liver transplantation.

A significant number of patients with liver failure secondary to hepatitis B or C develop recurrence of hepatitis in the liver graft. By the time this group of patients reaches the point at which they are evaluated for a second liver transplant, many will have mild urinary abnormalities and an elevation in the S_{Cr}. These abnormalities can result both from CNI treatment and in some patients from membranoproliferative glomerulonephritis or membranous nephropathy. However, they may only have HRS, and a kidney biopsy may help resolve this diagnostic dilemma. The value of repeat liver transplantation with or without simultaneous kidney transplantation is still under evaluation. There is currently no effective treatment for hepatitis C, but in patients with hepatitis B, treatment with lamivudine has been shown to decrease the risk of recurrence.

**Pancreas Transplantation**

A majority of diabetic patients receives simultaneous pancreas-kidney transplants, while a small number of patients receive pancreas-alone transplants. The group from the University of Minnesota has compared renal function in the pancreas-alone patients and a control group of patients that was not transplanted (42,43). Their first article described the findings at 5 yr. At the time of listing for transplantation, both groups had similar, normal baseline renal function. Interestingly, those patients who remained diabetic, neither transplanted nor receiving CNI, maintained excellent renal function and did not develop hypertension. The baseline C_{Cr} was 102 ± 21 ml/min per 1.73 m^2, and that at 5 yr was 91 ± 26 ml/min per 1.73 m^2. Those patients with functioning pancreas allografts, but on CsA therapy, experienced a decline in the C_{Cr} from a similar baseline to 68 ± 24 ml/min per 1.73 m^2. This decline occurred over the first 12 mo. In these patients, the magnitude of the decline in renal function correlated significantly with the mean daily CsA dose during month 12 after transplantation. Nine of the 13 pancreas transplant recipients developed hypertension, compared to three of 10 control subjects. In biopsies of the kidneys of the pancreas recipients, there were changes of CNI toxicity. Two of the transplanted patients had a sequential kidney transplant when they developed ESRD. This same group reported on the 10 yr follow-up data of eight of the original 13 patients. Overall, the diabetic glomerular histologic abnormalities diminished, while the S_{Cr} remained stable.

**Cardiac Transplantation**

Similar to the findings in liver transplantation, there are a number of reports examining the incidence, etiology, pathology, and clinical course of renal dysfunction following cardiac transplantation. In many patients, there is a marked deterioration in renal function over the first 6 mo. By 5 yr after transplantation, Greenberg et al. found that very few patients will have a normal GFR (44,45). Several groups have reported a period of stabilization, at least by measurement of the S_{Cr}, beginning about 1 yr after transplantation and continuing in most patients for many years (46–49). Myers et al. in a series of reports suggest that this apparent stabilization is maintained by progressive hyperfiltration of fewer and fewer nephrons, and that structural damage will continue in patients treated continuously with CNI (2–5). Adler et al. have provided support for this thesis in studies that measured renal functional reserve following amino acid infusion (50). They found that even in cardiac transplant patients with a mean GFR of 71 ml/min per 1.73 m^2, the renal functional reserve was only 59%.

<table>
<thead>
<tr>
<th>Table 3. Causes of renal failure in patients receiving kidney-liver transplants*</th>
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<tbody>
<tr>
<td>Glomerulonephritis</td>
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<tr>
<td>CsA nephrotoxicity (previous transplant)</td>
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<tr>
<td>Adult polycystic kidney disease</td>
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<tr>
<td>Diabetic nephropathy</td>
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<tr>
<td>Primary oxalosis</td>
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<tr>
<td>Chronic interstitial nephritis</td>
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<tr>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>Protracted acute tubular necrosis</td>
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<tr>
<td>Total</td>
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*Modified from references 39 and 40.
of that of control subjects. The group at Columbia-Presbyterian in New York has found that of patients surviving 3 yr or more, 6.5% will develop ESRD, and another 5.5% already had a $S_{Cr}$ > 4.0 mg%. These results are comparable to those reported from other centers (51,52).

In contrast to patients receiving liver transplants, it has been more difficult to identify risk factors that predict a poor renal outcome. At Columbia-Presbyterian Medical Center, in an analysis of several hundred cardiac transplant recipients, the factors that correlated best with subsequently developing renal insufficiency were age and renal function at the time of transplantation. In addition, this group of patients had more severe hypertension, higher triglyceride levels, and lower HDL cholesterol levels. This association with age is important, as it is known from renal transplantation that kidneys from older donors do less well after transplantation, possibly because they tolerate the effects of CNI less well. In this group of recipients, it will be important to develop immunosuppressive strategies that minimize exposure to CNI. The correlation with CNI exposure in this group of transplant recipients is no better than in any other group receiving nonrenal transplants. Some authors have found that decreasing the CNI dose in patients with renal failure increases the risk of rejection (53–56).

Goldstein et al. have examined the extent to which abnormalities of cardiac function, and renal hypoperfusion, could account for this decline in renal function (52). They found that the cardiac output remained stable even in patients with deteriorating renal function. They further examined whether the use of a left ventricular assist device (LVAD) would, by improving renal perfusion before transplantation, reduce the incidence of renal failure in the immediate postoperative period. Use of an LAVD was associated with a significantly lower preoperative $S_{Cr}$ compared with patients not on an LAVD (1.07 ± 0.34 versus 1.33 ± 0.43 mg/dl). This improvement had no impact on long-term renal function, and by 6 mo after transplantation the two groups had an equivalent $S_{Cr}$. This equivalence was still present at 2 yr (57).

The histology of kidneys in patients dying from severe congestive heart failure has been compared with that of cardiac transplant recipients who had been transplanted for at least 2 yr. The heart failure group had no structural abnormalities by light microscopy, confirming that the majority of renal structural abnormalities in the cardiac transplant recipients’ renal biopsies were caused by events occurring after transplantation (58). The transplant patients’ biopsies showed extensive obliterative arteriolopathy, widespread glomerular ischemic changes, and segmental or global sclerosis in 40% of glomeruli. These are typical findings of cyclosporine toxicity (59). It is of interest that many cardiac transplant recipients with severe and progressive renal insufficiency develop a heavy proteinuria and prominent FSGS as renal insufficiency advances (19).

### Lung Transplantation

The renal function of patients transplanted by the Lung Transplant Program at the Columbia-Presbyterian Medical Center from 1989 through the end of 1997 was assessed in all patients transplanted for more than 1 yr (Table 4). Of these 126 patients, 75 received a double, and 51 a single lung transplant. In 19 patients followed for more than 5 yr, the mean $S_{Cr}$ was 2.16 mg/dl. Two patients had reached ESRD, one of whom had received a successful living donor kidney transplant.

In another study, Zaltzman et al. reported an analysis of the renal function of 30 lung transplant recipients followed for a mean of 39 mo, with a minimum follow-up of 6 mo after transplantation. The mean $S_{Cr}$ increased from a baseline of 75 $\mu$M/L at the time of transplantation to 144 $\mu$M/L at 6 mo and 182 $\mu$M/L at last follow-up after transplantation (60). Of this group, nine patients had $S_{Cr}$ > 200 $\mu$M/L and two had reached ESRD. There was no relationship between CsA dosage and changes in renal function even though patients with $S_{Cr}$ > 200 $\mu$M/L had a slightly higher mean CsA dose at 6 mo. In these nine patients, renal function continued to decline even after the CsA doses were reduced. In two patients who had a renal biopsy, the findings were those of CNI nephrotoxicity. Others have described reductions in the mean GFR of 36 to 60% within 2 yr of lung transplantation (61,62).

Broekroelofs et al. (62) analyzed the factors predictive of a long-term decline in renal function. There were two factors that correlated with a decline in GFR from 101 ml/min per 1.73 m$^2$ before transplantation to 80 ml/min per 1.73 m$^2$, and to 54 ml/min per 1.73 m$^2$ by 30 mo. These were the causes of pulmonary disease and perioperative renal function. Patients with pulmonary hypertension or chronic obstructive pulmonary disease did significantly better than those with cystic fibrosis, in whom renal function declined more rapidly. In those whose $S_{Cr}$ rose more rapidly, the decline in renal function has been attributed to preexisting renal arteriolar constriction at the time of transplantation (61). Other investigators found that 66% of lung transplant patients developed hypertension within the first year. No data were supplied to correlate the degree of hypertension with the severity of renal failure (17). The histologic findings in two reports of the changes seen in recipients of lung transplants are similar to those described for other groups (19,63).

### Table 4. Renal function after lung transplantation$^a$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
<th>36 mo</th>
<th>Last Follow-Up (4.7 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_{Cr}$ (mg/dl)</td>
<td>0.8 ± 0.26</td>
<td>1.2 ± 0.45</td>
<td>1.5 ± 0.59</td>
<td>1.6 ± 0.67</td>
<td>1.7 ± 0.86</td>
<td>1.7 ± 0.97</td>
<td>1.9 ± 1.5</td>
</tr>
<tr>
<td>No. of patients</td>
<td>124</td>
<td>126</td>
<td>117</td>
<td>103</td>
<td>73</td>
<td>45</td>
<td>44</td>
</tr>
</tbody>
</table>

$^a$ Columbia-Presbyterian Medical Center. Data are mean ± SD.
Heart-Lung Transplantation

As described for all other organs, the decline in renal function is biphasic. Pattison et al. from Stanford University reported on 100 consecutive heart-lung transplant recipients (64). There was a rapid decline over the first 6 mo, with a 60% increase in the mean $S_Cr$ from 0.96 mg/dl to 1.55 mg/dl. Thereafter, there was a slower decline, and by 60 mo the mean $S_Cr$ was 1.80 mg/dl. Of these patients, 9% had $S_Cr > 2.25$ mg/dl, and 3% reached ESRD. The mean time to ESRD was 73.3 mo, similar to the rate of progression seen in other organ groups. In this study, there was no correlation with patient age, CsA dose, or CsA levels and the decline in renal function.

Sequential Renal Transplantation in Patients with Nonrenal Transplants

Many of the articles that discuss renal function in the recipients of nonrenal organ transplants describe the use of sequential renal transplantation in patients who develop ESRD. This has generally been described as being as successful as primary renal transplantation (11). The prevalence of renal failure in these groups has not been systematically collected for the UNOS database. To gain some impression of the extent of this problem, a request was submitted to UNOS for data relating to patients who received a renal transplant after they had received any other solid organ transplant. The data obtained included the type of initial transplant, the dates of the primary and the renal transplant, and the date of renal allograft failure. The data covered the period from 1984 to 1997 (Table 5). These data probably under-report the number of kidney transplants that have failed. Our individual experience at UCLA, and that at the Columbia-Presbyterian Medical Center, supports the finding that renal transplantation is a successful form of treatment for ESRD after nonrenal transplantation.

Prevention of Renal Failure

The decline in renal function in these patients is the result of the initial perioperative insults to renal function, and subsequent CNI therapy. In the preoperative phase, the management of these patients must be similar to that of patients with known renal dysfunction, and all potentially harmful factors should be avoided or corrected. The importance of maintaining adequate hydration and renal perfusion cannot be overstated. Improvements in anesthetic and operative techniques have already reduced the incidence of early postoperative renal failure and the need for dialysis. When possible, CNI should be withheld until renal function has improved, particularly in patients with ATN or renal hypoperfusion from heart failure or HRS. The use of intravenous CNI should be avoided. When dialysis is prescribed, care must be taken to avoid hypotension and excessive ultrafiltration, especially in patients already on CNI.

It is inevitable that some patients will develop early renal dysfunction. All will be exposed to long-term CNI therapy and be at risk for chronic renal injury. The factors that correlate with progression of renal failure in patients with intrinsic renal disease have been described in detail in recent reviews (65,66). It is highly likely that attention to similar risk factors will reduce the rate of decline in the function of the native kidneys of patients immunosuppressed with CNI for solid organs other than kidneys. However, the use of the dihydropyridine calcium antagonists, which do not appear to reduce proteinuria to the same degree as other calcium antagonists in patients not on CNI, may be beneficial in these patients (67). They may be useful in reducing the afferent arteriolar vasoconstriction caused by CNI. Bunke and Ganzel have reported an improvement in the CCl in a group of heart transplant recipients whose antihypertensive treatment was converted from angiotensin-converting enzyme inhibitors (ACEI) to calcium antagonists (68). Chan et al. also reported a possible benefit of the use of calcium antagonists in heart and lung transplant recipients (69). Other studies have documented benefits from the use of ACEI (70). Treatment with ACEI and angiotensin receptor blockers has been shown to benefit all patients with renal insufficiency and should be considered for use in these patients as well. The pathophysiology of CNI toxicity and the fibrosis caused by proteinuria both appear to involve growth factors that may be downregulated by blocking angiotensin activity (12,65,66). Care should be taken when using diltiazem or verapamil, as these drugs can cause an elevation in CsA levels by inhibition of CsA metabolism. The treatment of hyperlipidemia was discussed in the section on risk factors.

It is possible that with the introduction of mycophenolate (Cellcept®) and the anti-interleukin-2 (IL-2) receptor antagonists daclizumab (Zenapax®) and basiliximab (Simulect®), it will be possible to avoid or significantly reduce the use of CNI in the immediate postoperative period. The anti-IL-2 receptor antagonists do not have the severe side effects, including the risk of renal dysfunction and infections, seen with OKT3 and other antilymphocyte antibodies. In the immediate postoperative period, some transplant centers withhold CNI in patients with HRS who receive liver transplants, until the hemody-

<table>
<thead>
<tr>
<th>Initial Transplant Type</th>
<th>No. of Patients Receiving Renal Transplants</th>
<th>Time from Initial Transplant to Renal Transplant: mean days (yr)</th>
<th>No. of Renal Grafts Reported as Failed</th>
<th>Duration of Follow-Up after Renal Transplant: mean days (yr)</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>220</td>
<td>1417 (3.9)</td>
<td>33</td>
<td>2899 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>142</td>
<td>2173 (5.9)</td>
<td>14</td>
<td>3479 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>23</td>
<td>1690 (4.6)</td>
<td>1</td>
<td>1705 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Heart/lung</td>
<td>12</td>
<td>2315 (6.3)</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>


b These data may not reflect all of the cases in which the renal allograft has failed. NA, not available.
dynamic abnormalities appear to have reversed, and renal function is improving. Advice about the use of low-dose CNI protocols must allow for the potential increase in graft loss from rejection as a consequence of inadequate immunosuppression.

Conclusions
Over the past two decades, the introduction of CNI has allowed a rapid increase in nonrenal transplantation. This success has been bought at the price of a number of complications seen in all transplant recipients. These include hypertension, hypercholesterolemia, and diabetes mellitus. Many, if not all, patients treated with CNI will show a reduction in renal function. Some of this reduction in GFR is reversible if the CNI are stopped early enough. However, this is seldom possible, and for most patients it is imperative to minimize the pre- and perioperative factors known to increase the risk of renal insufficiency. A small percentage, more often in heart and lung transplant recipients than in those receiving a liver, will progress to ESRD and require dialysis or sequential kidney transplantation. As time passes, more of these patients may develop ESRD from chronic CNI nephrotoxicity. The UNOS and other reported data support sequential transplantation as an effective treatment for ESRD.

References
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