Renal Disease in Recipients of Nonrenal Solid Organ Transplantation

Akinlolu O. Ojo, MD, PhD

Summary: Worldwide, more than 250,000 individuals who have received a liver, heart, lung, or intestinal transplant are living longer. Twenty percent to 25% of these recipients experience perioperative acute renal failure, with 10% to 15% requiring renal replacement therapy. Chronic kidney disease (CKD) is also highly prevalent, affecting 30% to 50% of the nonrenal organ transplant population with an annual end-stage renal disease risk of 1.5% to 2.0%. Both acute renal failure and CKD contribute to increased morbidity and premature mortality. The dominant causative factor for renal disorders seen in nonrenal transplant recipients are the calcineurin inhibitors (CNI) and rapamycin analogues, which singly or in combination lead to a variety of nephrotoxic injury. However, 25% to 30% of nonrenal transplant recipients with CKD have other conditions such as hypertension, focal segmental glomerulosclerosis, diabetes mellitus, and hepatitis C infection as the principal underlying cause. Management strategies for renal disease in the nonrenal transplant recipients include the following: (1) delayed introduction of CNI after graft implantation, (2) withdrawal or minimization of long-term CNI therapy, (3) timely use of an appropriate dialysis modality, and (4) expeditious introduction of supportive measures such as anemia management, phosphate binding therapy, and dietary modification. Compared with maintenance dialysis, kidney transplantation reduces long-term mortality by 60% to 70% in nonrenal transplant recipients with end-stage renal disease.

Keywords: Calcineurin inhibitors, nephrotoxicity, immunosuppressive drugs, liver transplantation, cardiac transplantation, lung transplantation

More than 250,000 individuals have received a nonrenal organ transplant worldwide. Compared with the 1980s, these organ transplant recipients are now enjoying improved longevity. In the United States alone, 70,000 individuals were alive with a heart, liver, lung, or intestinal transplant at the end of 2005. To put this in perspective, the number of individuals living with a kidney-only transplant (100,000 in 2005) exceeds those living with a nonrenal transplant by only 30,000. Because many more nonrenal transplant recipients survive well into the second and sometimes third decade of life, the time at risk for renal disease has lengthened so that many more cases of posttransplant renal dysfunction are now observed.1-4 Because of the broad spectrum of renal disorders that occurs in this population, nearly all nonrenal organ transplant recipients will require the service of a nephrologist in their posttransplant course. Indeed, the demand for nephrologic care in nonrenal organ transplant recipients almost equals that of the entire kidney-only transplant population.

This article aims to provide the nephrologist and other renal care providers with information on the descriptive epidemiology, pathogenesis, risk factors, and the clinical management of renal disease in nonrenal transplant recipients who invariably will be encountered in both the outpatient setting and the hospital environment. Typically, the nephrologic care of nonrenal transplant recipients is complicated by the presence of concurrent medical conditions that
may contribute to the worsening of renal disease and the need to manage an immunosuppressive regimen, which often is the primary offending agent underlying the renal disease in the majority of these recipients. Because of the critical need to maintain allograft function, without which survival is not possible, prudence of action and professional tact takes on extra value in dealing with the primary transplant providers to avoid precipitous withdrawal or minimization of specific immunosuppressive agents even when such agents are the glaringly obvious culprit in precipitating or worsening of the renal disease.

**EPIDEMIOLOGY**

Renal disease has been recognized as a serious and common complication of nonrenal solid-organ transplantation for several decades.\(^5,6\) Both acute and chronic renal failure occurs with a high frequency in nonrenal transplant recipients. Acute renal failure often is defined as 25% decline or 0.5 mg/dL increase in serum creatinine level above preoperative baseline or serum creatinine levels greater than 2.0 mg/dL.\(^7\)–\(^12\) The incidence of perioperative acute renal failure is 20% to 30% in heart transplant recipients, 46% to 61% in liver transplant recipients, and 5% to 60% in lung transplant recipients.\(^7\)–\(^12\) In the first 30 days after transplantation, renal replacement therapy (RRT) in the form of intermittent hemodialysis or continuous veno-venous hemodialysis is required in 10% to 15%, 20% to 25%, and 8% to 10% of heart, liver, and lung transplant recipients, respectively.\(^13\)–\(^16\) The occurrence of acute perioperative acute renal failure (ARF) requiring RRT is associated with a 1-year recipient survival rate of 40% to 50% in each type of nonrenal transplant compared with a 1-year survival rate of 92% in recipients without ARF.\(^13\)–\(^16\)

Chronic kidney disease (CKD) also is a pervasive problem in nonrenal transplant recipients. Although definitions vary, CKD is clinically evident in 80% to 100% of nonrenal transplant recipients who have survived 36 months after transplantation.\(^6,17\) By using the harmonized definition of CKD produced by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation,\(^18\) an analysis of approximately 70,000 nonrenal organ transplant recipients in the US Scientific Registry of Transplant Recipients\(^19\) found an adjusted risk of stages IV to V CKD of 20% to 25% at 60 months in nonrenal transplant recipients. Table 1 shows the adjusted cumulative risk of stages IV to V CKD at 12, 36, and 60 months in 5 different groups of nonrenal transplant recipients.\(^19\) The risk levels summarized in Table 1 are consistent with the results from several other studies from single transplant centers.\(^8,20\)–\(^27\) In this unique population, CKD leads to serious medical complications and escalates the use of health care resources. First, poor renal function may require complete avoidance of potentially useful drugs or drastic alteration of immunosuppressants, anti-infectives, and other indicated therapeutic agents. Second, CKD has been associated with an increased frequency of hospitalizations and infectious complications.\(^8\) Third, CKD is associated with a 2- to 4-fold excess risk of mortality among affected recipients.\(^12,20,25,28\) Last, dysfunction of the transplanted liver, heart, or lung allograft may ensue in association with CKD.\(^12,26\)

<table>
<thead>
<tr>
<th>Time Since Transplantation, mo</th>
<th>Percentage of Recipients With Stages IV to V CKD</th>
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<tbody>
<tr>
<td></td>
<td>Heart</td>
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<tr>
<td>12</td>
<td>1.9</td>
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<tr>
<td>36</td>
<td>6.8</td>
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<td>60</td>
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RISK FACTORS AND PATHOGENESIS

As with the general population, the major traditional risk factors for renal disease (systemic hypertension, atherosclerotic cardiovascular disease, diabetes mellitus, and advancing age) have been shown to be strong independent predictors of CKD after nonrenal organ transplantation.\(^{19,23,26,28-30}\) Nonrenal organ transplant recipients often are exposed to a variety of nonimmunomodulating nephrotoxic agents that may initiate or worsen existing renal dysfunction.\(^{16,31}\) Most commonly, contrast agents and antimicrobial drugs contribute to renal failure in these populations.\(^{16,31}\) As a result, intermittent episodes of ARF with incomplete recovery are common in otherwise stable nonrenal recipients long after transplantation. ARF at anytime, even when not requiring RRT, contributes to the long-term risk of chronic kidney disease in heart, lung, and liver transplant recipients.\(^{8,19,32-34}\) The levels of renal function at the time of transplantation and need for perioperative RRT are associated with an increased risk of CKD.\(^{8,19,28}\) Fig. 1 shows the prevalence of different causes of CKD in heart and liver transplant recipients who underwent renal biopsy.

A list of global risk factors and organ-specific predisposing factors for renal disease are shown in Table 2. The nonrenal transplant recipient may be predisposed to renal disease consequent to the nature and cause of the underlying disease that led to end-stage organ failure. Among liver transplant recipients, chronic

![Figure 1](image-url)

**Figure 1.** Histologic renal diagnosis in solid organ transplant recipients with ESRD. Some cases have multiple histologic diagnoses. (A) Orthotopic heart recipients with ESRD (n = 24). Adapted and reprinted with permission, Copyright National Kidney Foundation 1987.\(^{6,93}\) (B) Orthotopic liver recipients with ESRD (n = 45). *Nonrecovery from pretransplant hepatorenal syndrome. Adapted and reprinted with permission from Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy. Risk of development and treatment. Transplantation. 2001;72:1934-9 (http://lww.com).\(^{8}\)

<table>
<thead>
<tr>
<th>Table 2. Risk Factors for Renal Disease in Nonrenal Transplant Recipients</th>
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<tr>
<td>Risk factors common to all organ types</td>
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<tr>
<td>Age at transplantation</td>
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<tr>
<td>Systemic hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Drug-induced nephrotoxicity (nonimmunomodulating agents)</td>
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<td>Perioperative ARF</td>
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<td>Cardiac transplantation</td>
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<tr>
<td>Systemic atherosclerosis</td>
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<td>Renal hypoperfusion caused by congestive heart failure</td>
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<tr>
<td>Cyanotic congenital heart disease</td>
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<td>Lung transplantation</td>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Pulmonary hypertension</td>
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<tr>
<td>FSGS secondary to chronic hypoxia</td>
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<tr>
<td>Liver transplantation</td>
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<tr>
<td>Secondary Immunoglobulin A nephropathy</td>
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<tr>
<td>Hepatitis B– or C–associated glomerulonephritides</td>
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<tr>
<td>Hepatorenal syndrome</td>
</tr>
<tr>
<td>Oxalosis</td>
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<td>Repeat liver transplantation MELD score ≥ 21</td>
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viral hepatitides independently cause kidney disease and a large proportion of liver transplant recipients show significant glomerular disease on renal histology before liver transplantation even when clinical features of kidney disease are absent.³⁵ Prolonged hepatorenal syndrome may not resolve completely after liver transplantation.³⁶ Heart transplant recipients most often suffer from systemic atherosclerosis involving small and large renal vessels.³⁷–³⁹ Pretransplant histology in cardiac transplant candidates showed advanced arteriolar hyalinosis and obsolescent glomeruli in a large percentage of patients before transplantation or to exposure to calcineurin inhibitors (CNIs).³⁹ Chronic glomerular hypoxia associated with cyanotic congenital cardiac disorders and chronic lung disease has been associated with secondary focal segmental glomerulosclerosis (FSGS). In one study of lung transplant recipients, cystic fibrosis was accompanied by an increased risk of posttransplant renal failure.⁴⁰

CNIs (cyclosporine and tacrolimus) are essential posttransplant immunosuppressive agents with inherent nephrotoxicity that often lead to a number of distinct renal syndromes including oligoanuric acute renal failure, chronic kidney disease, type IV renal tubular acidosis, hyperkalemia, and thrombotic microangiopathy.⁴¹–⁴⁴ In comparison studies in which clinical features are evaluated, cyclosporine and tacrolimus generally have similar acute and chronic nephrotoxic effects. Acute CNI nephrotoxicity is caused by intense vasoconstriction of the renal microcirculation, particularly the afferent arteriole, resulting in an acute reversible decrease in glomerular perfusion and glomerular filtration rate (GFR). This acute hemodynamic insult is not immediately associated with damage to the renal parenchyma—hence, it is a functional prerenal effect. The chemical mediators of CNI-mediated renal vasoconstriction are thought to include arachidonic acid metabolites (especially thromboxane) and endothelin. Local activation of the sympathetic nervous system and effects on nitric oxide metabolism also play a role. More severe acute CNI toxicity may be associated with signs of damage (such as vacuolization) to renal tubular cells—these changes are not specific. In general, there is some correlation between trough blood concentrations and acute nephrotoxicity.⁴⁵

There is a large body of evidence indicating that the chronic nephrotoxic effect of CNIs is mediated by angiotensin II (ang II).⁴⁶,⁴⁷ Cyclosporine-induced arteriolopathy develops only in the afferent arteriole where renin is localized abundantly.⁴⁸ Chronic cyclosporine administration in human beings stimulates both plasma renin and prorenin activity with concurrent hyperplasia of the juxtaglomerular apparatus.⁴⁹–⁵¹ Increased synthesis of the pluripotent fibrogenic cytokine transforming growth factor β (TGF-β) appears to be a central pathophysiological process by which CNIs cause chronic renal injury.⁵² TGF-β1–induced gene product is expressed prominently in the renal tissue of CNI-treated heart, lung, and renal transplant recipients.⁴⁶,⁵²–⁵⁴ Angiotensin-converting enzyme inhibitor–mediated reductions in TGF-β1 concentrations correlated directly with preservation of renal function in patients with diabetic nephropathy.⁵⁵ Although serum levels of TGF-β are not reliable indicators of prosclerotic cytokine activity,⁵⁶,⁵⁷ the correlation between TGF-β1 and renal function deterioration support the role of TGF-β1 as a downstream effector cytokine of angiotensin II (ang II) in the face of CNI exposure.

Ang II and aldosterone have central roles in the development of tubulointerstitial fibrosis and glomerulosclerosis, which are the hallmarks of CNI-induced CKD (Fig. 2). Ang II, adrenocorticotropic hormone (ACTH), and potassium stimulate the synthesis and secretion of aldosterone from the zona glomerulosa of the adrenal gland.⁵⁸ Acting synergistically and independently, ang II and aldosterone participate directly in renal vascular injury and vascular thrombosis.⁵⁹–⁶⁷ In the presence of ang II, experimental infusion of aldosterone increases the expression of plasminogen activator inhibitor-1 (PAI-1) in a concentration-dependent fashion.⁶⁸ PAI-1 is a SERPIN family cytokine that promotes extracellular matrix protein deposition by mesangial cells.⁶⁸ Renal histology in cyclosporine-treated organ transplant recipients showed hyperplastic juxtaglomerular apparatus.⁴⁹,⁵¹,⁶⁹ Although there are extrarenal
sites of ang II synthesis, the intrarenal renin angiotensin aldosterone system (RAAS) is, by far, physiologically dominant because the concentration of ang II in the peritubular capillaries and proximal tubules is approximately 1,000 times higher than in the systemic circulation.\textsuperscript{70} TGF-\(\beta\) is essential to the immunosuppressive effect of CNI. Ang II stimulates the synthesis of TGF-\(\beta\), platelet-derived growth factor, and nuclear factor \(\kappa B\), hence leading to exuberant fibroblast proliferation, collagen deposition, and inflammation.\textsuperscript{74} In an experimental model of CNI nephropathy, cyclosporine produced arteriolopathy in the renal tissue together with increased renal cortical expression of messenger RNA for TGF-\(\beta\), collagen I, collagen IV, fibronectin, and epidermal growth factor.\textsuperscript{74} The counterbalancing effects of tissue inhibitors of metalloproteinases and plasmin on excessive extracellular matrix deposition is abrogated by ang II through its up-regulation of PAI-1 and decreased synthesis of tissue inhibitors of metalloproteinases. In summary, human and experimental evidence empirically supports the construct that CNI-induced stimulation of ang II and aldosterone production act synergistically to promote intrarenal fibrosis and glomerulosclerosis, which manifest as CKD on chronic exposure to CNI.\textsuperscript{71,73,75}

Other immunosuppressive agents that may be risk factors for renal disease are the mammalian target of rapamycin (mToR) agents (sirolimus and everolimus), which are being used increasingly as CNI-sparing agents in organ transplant recipients. These agents may potentiate the nephrotoxic effects of CNI when used in combination with standard doses of CNI.\textsuperscript{76–78} Used without CNI, the mToR have not been shown to cause deterioration of the GFR,\textsuperscript{79} but many recent reports have implicated these agents in the development of new-onset proteinuria in both renal and nonrenal transplant recipients.\textsuperscript{80,81}

**DIAGNOSIS AND MANAGEMENT**

**ARF**

A normal serum creatinine measurement is an insensitive marker of ARF in the nonrenal transplant population, particularly in the perioperative period when creatinine generation may be compromised by end-organ failure–induced muscle atrophy and malnutrition. Typical clinical features of isolated CNI nephrotoxicity include an increasing creatinine level over hours to days and a bland urinalysis. Signs of extrarenal toxicity such as tremor may be present. The fractional excretion of sodium may be low.
(<1%), in keeping with the functional prerenal effects of CNI. Rarely, there are signs of an acute thrombotic microangiopathy: increased plasma lactate dehydrogenase (LDH) levels, decreased hemoglobin and platelet levels, hemoconcentration, and low serum haptoglobin levels. In the immediate posttransplant period, a kidney biopsy almost never is performed and the diagnosis relies almost exclusively on clinical findings. The presence of multiple nephrotoxic insults should lead to frequent screening for ARF before telltale signs of increased serum creatinine concentration and/or oligoanuria supervenes. Recipients with a higher risk of ARF include those with a newly transplanted heart who show temporary right heart failure (because of recipient pulmonary hypertension) or a newly transplanted liver recipient with prolonged intraoperative hypotension or initial nonfunction of the liver allograft resulting in hepatorenal syndrome. Bleeding, acute myocardial infarction, or sepsis with associated hypovolemic, cardiogenic, or distributive shock, respectively, or amphotericin and other nephrotoxic agents should alert the renal provider to imminent ARF.

The management of ARF in the immediate or early posttransplant period is largely supportive. Standard measures to optimize the mean arterial pressure and optimize renal perfusion should be used. When possible, nephrotoxic drugs should be stopped. Nonnephrotoxic alternatives to amphotericin now are available and should be considered when antifungal therapy is required. In instances in which the initial renal function is poor, antilymphocyte antibody preparations (such as interleukin-2-receptor blockers or thymoglobulin [Genzyme, Cambridge, MA]) can be used to delay introduction of the CNI without an increased risk of rejection. This strategy is being tested in 3 ongoing randomized controlled trials sponsored by Roche (Basel, Switzerland) and Genzyme.

**CKD**

The typical presentation of CKD in nonrenal transplant recipients is a large decrease in the GFR in the first 6 months posttransplant, often 30% to 50%. Thereafter, the GFR usually stabilizes or decreases more slowly. However, a significant percentage of patients ultimately progress to end-stage renal disease (ESRD). Other clinical features include hypertension. Despite the antiproteinuric effect of the CNI, proteinuria may be present if secondary FSGS develops, particularly in patients with congenital heart disease or in liver recipients with secondary Immunoglobulin A nephropathy as a result of poor liver allograft function. Laboratory features of a low-grade thrombotic microangiopathy also are present. In advanced cases, renal ultrasonography shows normal- or reduced-size kidneys unless there is concomitant diabetic nephropathy or other kidney diseases associated with nephromegaly.

Renal biopsy is not performed frequently in nonrenal transplant recipients with CKD mainly because at the time of clinical presentation or referral to the nephrologist most patients already have contraindications that mitigate against safely performing a diagnostic renal biopsy (small kidneys, acquired bleeding disorders, severe orthopnea, inability to lie prone for an extended period of time, and inability to cooperate with respiratory maneuvers). In the series in which renal biopsy was performed and a histologic diagnosis was established, arteriolopathy, stripped interstitial fibrosis, and obsolescent glomeruli were the typical findings. Histopathologic findings consistent with but not pathognomonic of CNI-induced chronic nephrotoxicity include stripped atrophy and fibrosis of the tubulointerstitium, hylanization of arterioles and glomeruli at various stages of ischemic collapse, and sclerosis. In 26 liver transplant recipients who underwent renal biopsy, Pillebout et al found the predominant histologic lesions to be CNI arteriolopathy in 46%, diabetic nephropathy in 34%, and FSGS in 34%. Gonwa et al reported on 45 liver recipients with ESRD who had undergone renal biopsy and found CNI-induced changes in 73%, FSGS in 7%, cystic kidney disease in 7%, and other diagnoses in 7%. In a series of 24 heart transplant recipients, Cooperstein et al found hypertensive nephrosclerosis in 30%, FSGS in 16%, diabetic nephropathy in 6%, and CNI-mediated lesions in 60%.

The clinical management of CKD in nonrenal transplant recipients is based on a combination
of the specific measures such as manipulation of CNI therapy (the dominant causative factor) and the application of consensus guidelines for the management of CKD in the nontransplant population. Appropriate and early treatment of hypertension, diabetes mellitus, and hepatitis C will limit renal damage from these conditions. There is a modicum of evidence that calcium channel blockers improve GFR if added to a CNI-immunosuppressive regimen based on the rationale that calcium channel blockers reduce the degree of afferent arteriole vasoconstriction.\textsuperscript{51} Because of the central efficacy role of CNI in posttransplant immunosuppression, there has been reluctance to pursue protocols without CNI in recipients of nonrenal transplants. Moreover, immunologic events such as acute rejection of nonrenal organs have potentially catastrophic consequences because a back-up analogous to dialysis in renal transplantation is not available. Safe reduction in CNI dosage, at least in patients with a low likelihood of acute rejection, has been shown to slow the rate of CKD progression.\textsuperscript{86–88} Protocols that incorporate mycophenolate mofetil or mTOR can be used to reduce CNI dosage. Sirolimus or everolimus should be used with great caution in the immediate posttransplant period because of wound healing complications caused by the antiproliferative effect of this class of agents.\textsuperscript{89}

Treatment of ESRD in nonrenal transplant recipients with hemodialysis or peritoneal dialysis is feasible and 3% to 5% of the chronic hemodialysis population are nonrenal transplant recipients. Maintenance dialysis is associated with a prohibitively high risk of premature mortality in this population. Many series have found that kidney transplantation confer significant survival benefits in nonrenal transplant recipient with ESRD.\textsuperscript{8,9,36} Kuo et al\textsuperscript{90} found improved survival in a series of 9 cardiac recipients who underwent deceased donor renal transplantation. Coopersmith et al\textsuperscript{86} also showed survival benefits of kidney transplantation in a series of heart, lung, and liver transplant recipients with ESRD. Gonwa et al\textsuperscript{8} found a 6-year survival rate of 71.4% in liver transplant recipients who received kidney transplantation after the onset of ESRD compared with 27% for their dialysis-treated counterparts. Molmenti et al\textsuperscript{91} reported an equally large survival advantage of kidney transplantation in liver transplant recipients. Although kidney transplantation was associated with an increased risk of death in the early postoperative period after kidney transplantation, the surgical risk dissipated by 6 months after transplantation and, in the long term, recipients see a 40% to 70% lower risk of death compared with wait-listed, dialysis-treated, nonrenal transplant recipients.\textsuperscript{90–92}

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