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PERSPECTIVES IN RENAL MEDICINE

Posttransplantation chronic renal damage in nonrenal transplant recipients

Piero Stratta, Caterina Canavese, Marco Quaglia, Federico Balzola, Marco Bobbio, Alessandro Busca, Alessandro Franchello, Daniela Libertucci, and Gianna Mazzucco

Department of Nephro-Urology of the Avogadro University, Maggiore Hospital, Novara, Italy; Department of Internal Medicine, Section Gastroenterology, University of Torino, Torino, Italy; Department of Internal Medicine, Section of Cardiology, University of Torino, Torino, Italy; Department of Biological Science and Human Oncology, University of Torino, Torino, Italy; Bone Marrow Transplantation Unit, S. Giovanni Molinette, Hospital, Torino, Italy; Liver Transplantation Unit, S. Giovanni Molinette Hospital, Torino, Italy; and Lung Transplantation Unit, S. Giovanni Molinette Hospital, Torino, Italy

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Background. The growing problem of relentless deterioration of renal function in patients who undergo transplantation of nonrenal solid organs is bound to have an increasingly important impact as it may not only worsen patient morbidity and mortality but also increase transplantation costs.

Methods. We reviewed the literature in order to provide a sum of the most important data on the incidence, clinical picture, renal pathology pattern, damage mechanisms, and risk factors, along with strategies for prevention and treatment of chronic renal damage following nonrenal solid organ transplantation.

Results. Literature data report that 10% to 80% of transplanted patients have some degree of renal dysfunction and that they share a common clinical picture characterized by relentless asymptomatic progression, frequent hypertension, mild urinary abnormalities, and pathology features of vascular, glomerular, tubular, and interstitial involvement. These changes are very similar to those reported for chronic nephrotoxicity from calcineurin inhibitors. The occurrence of end-stage renal disease (ESRD) requiring chronic dialysis has been reported in up to 20% of nonrenal transplant recipients. Although there are some organ-specific differences, a group of common risk factors has been recognized, including the use of calcineurin inhibitors as immunosuppressive agents, age, pretransplantation renal function, intraoperative/perioperative factors, concomitant use of other nephrotoxic drugs, infections, and posttransplantation acute renal failure.

Conclusion. Calcineurin inhibitor–induced nephrotoxicity is a growing problem and, as the age of recipients of nonrenal organs is increasing, this problem is destined to increase. It would therefore be advisable for nephrologists to share their experiences in immunomodulation with other specialties, so as to favor the cautious extension of calcineurin inhibitor–sparing protocols to the area of life-saving transplants.

Key words: calcineurin inhibitors, nephrotoxicity, nonrenal transplantation, end-stage renal disease, calcineurin inhibitors-sparing protocols.

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The current "revolution" in the field of organ transplantation earmarks a new era for medicine. However, there is a growing awareness that chronic renal failure, eventually leading to end-stage renal disease (ESRD) requiring chronic dialysis, poses a serious threat to nonrenal organ transplant patients. Although previous data suggested a self-limited decrease in renal function in the absence of overt effects on patient outcomes [1], more recent studies performed on large samples of recipients of nonrenal transplants have shown that this is clearly not the case [2–5]. On the contrary, complications arising from nonrenal transplants significantly increase the risk of renal failure and rates of morbility and mortality in patients [4, 5]. Reports show that nonrenal transplant patients with chronic renal failure have a twofold higher risk of mortality than patients without chronic renal failure. Moreover, the presence of ESRD requiring chronic dialysis has been associated with an even higher risk of death (relative risk 4.55; 95% CI 4.38 to 4.74) ($P < 0.01$) [4]. Therefore, if we consider the potential impact on public health services of such complications in a large cross-section of patients, the need for strategies capable of preventing and minimizing renal damage after transplantation of nonrenal organs becomes clear.

This review analyzes the incidence of the problem, its clinical picture, renal pathology pattern, damage mechanisms and risk factors, along with strategies for prevention and treatment.

EPIDEMIOLOGIC DATA

It is estimated that more than 100,000 nonrenal solid organ transplants are carried out each year in the following order of frequency: liver (over 50%), heart, lung,

Table 1. Synopsis of the main epidemiologic studies on cumulative incidence of end-stage renal disease (ESRD) requiring maintenance dialysis in nonrenal organ transplant recipients, according to type of organ

Year	Author [reference]	Number of patients	Median follow-up *years*	ESRD incidence %
Liver				
1995	Naumann et al [6]	104	6.5	8.6
1998	Fisher et al [7]	883	4.3	1.4
2001	Gonwa et al [8]	834	13	5.4
2001	Lynn et al [9]	132	5	3.4
2002	Cohen et al [10]	353	10	10
2003	Pawarode et al [11]	172	6	7
2003	Moreno et al [12]	289	5.3	4.1
Heart				
1990	Greenberg et al [13]	228	7	2.2
1991	Lewis et al [14]	100	4	1
1992	Gonwa et al [15]	69	4	1.3
1994	Zietse et al [16]	187	5	3.2
1997	Tinawi et al [17]	133	5	0
1997	Goral et al [18]	39	6	4
1997	Goldstein et al [19]	293	10	6.5
1998	Van Gelder et al [20]	304	6.6	8
2000	Lindelow et al [21]	151	9	4
2002	Satchithananda et al [22]	697	6	5.8
2003	Garrido et al [23]	262	5	0.9
2004	Rubel et al [24]	370	10	20.3
Lung				
1999	Wilkinson et al [2]	126	8	1.6
2000	Tsimaratos et al [25]	19	5.3	5
Heart-lung				
1995	Pattison et al [1]	100	4	3

lung-heart, and intestine. A distinction must be made between low/mild degrees of renal damage, advanced chronic renal failure and ESRD patients requiring maintenance dialysis so as to correctly assess the incidence of renal impairment in these cases.

Reports of the incidence of chronic renal disease range from 10% to 83%, but this marked difference is due to the different criteria used to define renal dysfunction [4].

Results in the largest most recent study of transplant patients, where severe chronic renal failure is defined as creatinine clearance equal to or below 29 mL/min per 1.73 m^2 of body surface area, are as follows: 16.5% (average value) liver (18%), heart (11%), lung (16%), heart-lung (7%), and intestine (21%) after a median follow-up of 36 months. The cumulative incidence of ESRD was 4.7% (3297/69,321 recipients) which is equal to 1% to 1.5% new cases per year [4].

Table 1 shows a synopsis of main studies on the rate of ESRD in the different types of nonrenal transplant recipients [2, 6–25]. ESRD cumulative incidence appears to range from 1.4% to 10% for liver transplants [8, 10, 12] and from 0% up to 23% for heart transplants [19, 20, 22, 24]. A lower incidence has been reported for lung transplants (1.6% to 5%) after a slightly shorter median follow-up [2]. We found only one large study on ESRD in heart-lung transplants, which reported severe chronic renal failure in 3% of transplant patients after 4 years [1]. No specific studies on ESRD in intestine transplants were available, probably due to the fact that patients belong to a lower age group and the relatively smaller number of cases.

Clinical picture

Patients who receive nonrenal transplantation usually have normal or only mildly impaired renal function at the time of transplantation, although serum creatinine levels can be misleading in malnourished patients with liver or heart failure. The clinical course from transplantation to ESRD ranges from rapid deterioration to slow progression with long periods of functional stability. However, the clinical picture in the recipients developing ESRD is similar [2], regardless of the type of organ transplant.

The most frequent pattern shows a biphasic curve, with a 50% decrease in the glomerular filtration rate (GFR) during the first 12 months after transplant, followed by stabilization and a subsequent slow but relentless decline until ESRD. Some authors warn that, during the second "stabilization" phase, renal function is preserved at the price of progressive hyperfiltration and irreversible structural renal damage progresses, even in the presence of stable serum creatinine values [26].

Even if increased proteinuria can occur as a consequence of this process, it is usually only about 1 g/day. When the increase is detected, it is usually associated with advanced chronic renal failure. It can also be a marker of other glomerular diseases, especially when it occurs with normal renal function. These include focal glomerular sclerosis after heart transplantation [2, 27] and IgA nephropathy, membranous and membranoproliferative glomerulonephritis after liver transplantation [2, 9]. The urinary sediment is usually unremarkable and abnormalities should again give rise to the suspicion of an associated glomerulonephritis; in liver transplantation hepatorenal syndrome is another differential diagnosis; indeed, kidney biopsy is advocated by some authors in these cases [2]. Hypertension accompanying the progression of renal dysfunction is common (65% to 85% in liver transplanted patients, 90% in heart, and 60% to 70% in lung) even if most patients were not hypertensive at the time of transplantation [2].

Hyperkalemic distal renal tubular acidosis (type IV) has been described with cyclosporine A (CsA) and tacrolimus therapy [28].Thrombotic microangiopathy is a less common expression of calcineurin inhibitor nephrotoxicity. The spectrum of thrombotic microangiopathy manifestations ranges from graft-limited forms, which can be diagnosed only through renal biopsy, to the full-blown picture of de novo hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura [29]. Prognosis of these systemic forms is poor, with nearly

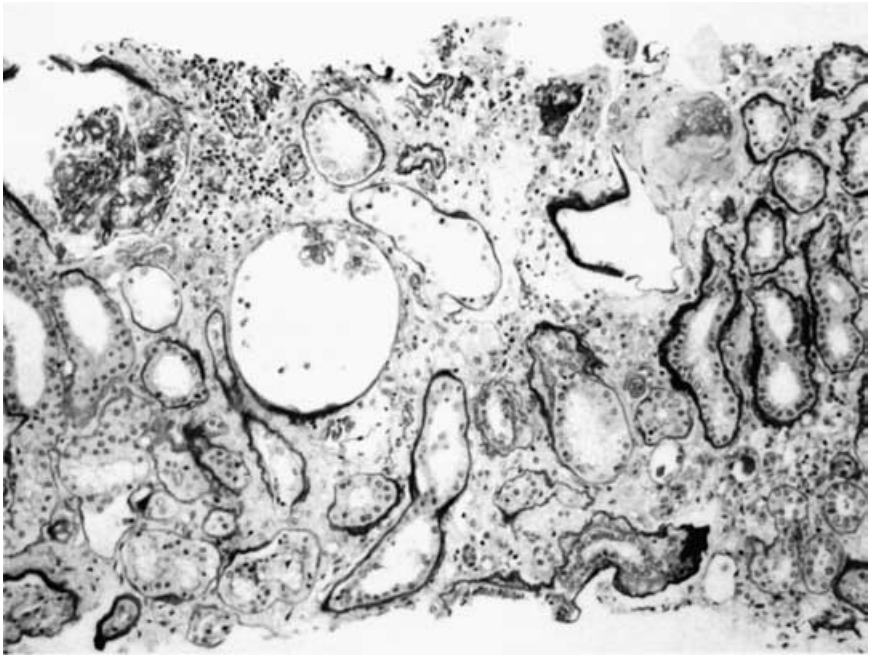

Fig. 1. Renal biopsy in a 48-year-old woman with liver transplant, who had been biopsied due to worsening of chronic renal failure 6 months after liver transplantation. Light microscopy [periodic acid-Schiff (PAS) 125×]. The morphologic feature was characterized by diffuse fibrosis with tubular atrophy and ischemic damage of glomeruli some with global sclerosis and some others showing collapsed tuft.

half of affected patients losing their transplanted kidney. CsA-induced HUS has also been described in association with hemorrhagic colitis [30].

All nephrotoxicity manifestations can occur even with very low CsA [31] and tacrolimus [32] levels and significant recovery of renal function can be achieved with calcineurin inhibitor discontinuation in these situations.

PATHOLOGY

Most data come from autopsy studies, as biopsies are more rarely reported. Pathologic damage has been observed in all portions of the nephron, including obliterative vasculopathy (characterized by arteriolar focal hyalinosis, myocyte necrosis, nodular hyaline deposits, and intimal edema). This primarily involves afferent arterioles and perhaps represents the most important lesion as it may result in irreversible damage affecting all the other nephron sectors causing ischemia, sclerosis, and collapse of glomeruli, tubular atrophy, and interstitial fibrosis. Globally, the picture closely resembles that observed in patients receiving CsA for the treatment of autoimmune diseases [33–35]. However, even if there are common features, renal damage in transplanted patients on CsA can vary significantly.

Organ-specific pictures

Liver. The aforementioned pathologic damage is common in liver transplant patients. Interstitial fibrosis is frequent and it increases progressively with exposure to CsA and the total dose administered [36, 37]. Our experience confirmed the presence of diffuse interstitial fibrosis in a 48-year-old woman with liver transplant, who had been biopsied due to a worsening of chronic renal failure 6 months after the transplantation. Although histology showed tubular and interstitial damage, the prominent feature was the ischemic damage of glomeruli (Fig. 1). Laboratory tests showed an increase in serum creatinine from a pretransplant value of 1.6 mg/dL to 3.5 mg/dL at the moment of renal biopsy. Maintenance immunosuppressive therapy was based on CsA, steroids, azathioprine; CsA had been substituted for tacrolimus a few weeks before biopsy.

Glomerular abnormalities were also found to be more frequent in liver transplant recipients than in other types of transplant patients. This depends on pretransplantation glomerular diseases such as IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, and focal segmental glomerulosclerosis [2, 36–38].

Heart. Pioneer studies demonstrated that heart transplant patients suffered from both a depression of the GFR and a variable degree of tubulointerstitial injury, accompanied by focal glomerular sclerosis. This was most commonly observed in patients treated with CsA than in those with azathioprine with equivalent cardiac output [39]. Bertani, Ferrazzi, and Schieppati [39] compared the histology of patients who died from congestive heart failure with that of cardiac transplant recipients, and demonstrated that the heart failure group showed none of the structural abnormalities found in the cardiac transplant group. This finding confirmed that most lesions in the renal biopsies of cardiac transplant recipients were caused by events occurring after transplantation and were therefore independent of cardiac factors.

Other studies suggested that early CsA damage is a form of thrombotic microangiopathy with focal glomerular and/or arteriolar thrombosis evolving into CsA arteriolopathy and subsequently interstitial fibrosis [40, 41], or an early preglomerular arteriolar involvement eventually leading to glomerular obliteration by a progressive increase in renal arteriolar hyalinosis and a higher number of glomeruli affected by global sclerosis, both correlated with the duration of exposure to CsA and the total dosage [42]. Furthermore, many cardiac transplant recipients develop a prominent segmental glomerulosclerosis which results in severe renal insufficiency and heavy proteinuria [27].

Lung. Zaltsman et al [43] and Paller et al [44] analyzed renal biopsies from a group of heart, lung, or heart and lung transplant recipients on CsA therapy and grouped their histopathologic findings into three categories: severe vascular and glomerular lesions due to thrombotic microangiopathy, a form of focal segmental glomerulosclerosis and glomerular ischemia. These alterations appeared to be part of the spectra of pathologies, all of which coexisted in some biopsies. In focal segmental glomerulosclerosis, monitoring of urinary protein proved useful because the onset of proteinuria usually precedes functional impairment.

PATHOPHYSIOLOGY, MECHANISMS OF DAMAGE, AND RISK FACTORS

All the studies reporting renal impairment after nonrenal transplantation included patients treated with CsA and tacrolimus, better known as calcineurin inhibitors. Their introduction into clinical practice, in the early 1980s, raised the 1-year survival rate for renal allografts from 60% to 80% to 90%. Besides the aforementioned benefits, the use of calcineurin inhibitors provided a cure for some autoimmune diseases. However, nephrotoxicity remains the main complication for patients treated with these drugs, as the same immunosuppression mechanism is also responsible for their nephrotoxicity. Records dating back to the pioneer studies carried out 20 years ago clearly show that the excess risk of chronic renal failure in nonrenal transplant recipients is mainly related to the adoption of calcineurin inhibitor immunosuppressive agents [45].

A comparative study of heart transplant patients treated with azathioprine or CsA was carried out by Myers, Newton, and Boshkos [46] in 1988. It was demonstrated that, although both groups had the same cardiac output, both the GFR and renal plasma flow were depressed in the CsA group, which showed a trend toward a restricted transglomerular transport of neutral dextrans. This suggested an intrinsic loss of ultrafiltration capacity by glomerular capillaries rather than a simple hemodynamic mechanism [46].

Even if most studies on calcineurin inhibitors dosing and levels do not predict renal damage, rather suggesting independent individual susceptibility traits, when trough levels and daily dose (mg/kg) at various times after transplantation are considered, a weak correlation does emerge between increased exposure and the risk of impaired renal function [2].

So, the negative calcineurin inhibitor influence has been implicated as being largely responsible for chronic renal failure also in nonrenal transplant recipients, although peculiar mechanisms and organ-specific risk factors must be taken into account.

An in-depth review of the mechanisms leading to calcineurin inhibitor–mediated nephrotoxicity is beyond the scope of this review.

In summary, calcineurin inhibitor–mediated nephrotoxicity is the result of hemodynamic and direct cellular effects on vascular endothelium and tubular epithelium. Indeed, functional nephrotoxicity is essentially due to a vasoconstriction of preglomerular afferent arterioles and is triggered by an increased sympathetic tone, activation of the renin-angiotensin system, an altered balance between thromboxane and prostaglandins, an increased production of endothelin-1, and a decreased production of nitric oxide by endothelial cells. Calcineurin inhibitors also exert a direct toxic effect on endothelial and tubular cells, which may contribute to the release of various vasoactive compounds. Calcineurin inhibitor–induced vasoconstriction is dose-related and determines chronic renal ischemia, which consequently triggers activation of the renin-angiotensin system and an increased transforming growth factor-β (TGF-β) synthesis as well as other fibrogenic mediators. This process results in interstitial fibrosis leading to chronic renal failure [47, 48].

Calcineurin inhibitor-nephrotoxicity in native kidneys versus renal allografts

What are the main potential differences between calcineurin inhibitor-nephrotoxicity in native kidneys and in renal allografts? The comparison between the impact of nephrotoxicity on nonrenal and renal transplant patients is a difficult task, as the factors to be considered are many and varied [2, 3, 49, 50].

From a pathogenetic point of view, the most intriguing aspect is that transplanted kidneys lack the sympathetic innervation, whereas native kidneys of nonrenal transplant recipients have to pay for sympathetic stimulation, which is one of the main mechanisms involved in calcineurin inhibitor–induced renal vasoconstriction. On the other hand, they are not prone to the immune-mediated components of chronic rejection, which compound the effects of nephrotoxicity [47] (Fig. 2).

From a morphologic point of view, some subtle differences in renal pathology may be observed at the matrix

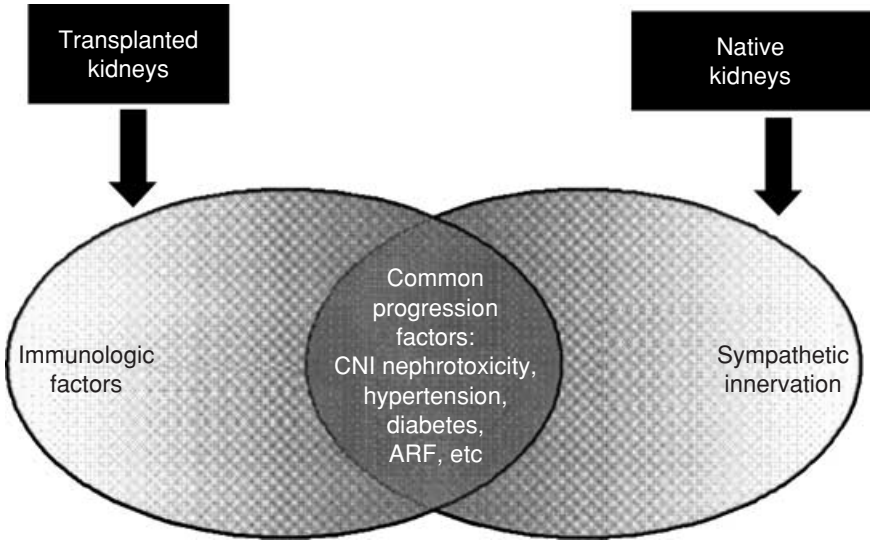

Fig. 2. Mechanisms of damage for transplanted and native kidneys in renal transplanted and nonrenal transplanted patients. Calcineurin inhibitor (CNI)-nephrotoxicity is shared as the same insult on different targets. ARF is acute renal failure.

protein level [51]. A prevalence of ischemic damage over interstitial lesions has also been observed and may be the consequence of some of the pathogenic differences. It is tempting to speculate that the noxious hemodynamic calcineurin inhibitor effects might be enhanced by a normal sympathetic innervation and aggravate ischemic damage in native kidneys [51].

Risk factors other than calcineurin inhibitor-nephrotoxicity

There are other variables that could contribute to renal dysfunction (Table 2).

First, complications arising from the transplantation procedure itself may play a decisive role in a subsequent development of ESRD. A particularly significant risk factor is the early occurrence of acute renal failure following transplantation. This may be due to a variety of factors that can be classified into three categories: preoperative, intraoperative, and perioperative settings. Preoperative renal status includes intrarenal hemodynamic changes, such as hepatorenal syndrome in liver transplant recipients and severe hypoperfusion from cardiac failure in heart transplant recipients; the intraoperative conditions include hypotension, hemorrhage, and hemolysis due to extracorporeal circulation in heart transplants; and perioperative factors include hemodynamic instability, infection (cytomegalovirus), sepsis, or effects of pressure agents or other drugs, such as nephrotoxic antibiotics or continuous intravenous CsA [2].

Second, organ-specific peculiarities, including pretransplantation renal status, also play an important role. Liver transplant recipients, for instance, tend to have preexisting glomerular diseases, due to inadequate clearance of immunocomplexes caused by liver disease [2, 9, 10].

Table 2. General risk factors for developing progressive renal insufficiency in nonrenal transplanted patients

Setting	Risk factor
Preoperative	Age
	Gender
	Race
	Genetic factors
	Pretransplant renal status
	Preexisting renal diseases due to subcategories of organ-specific transplants
	Chronic renal failure [glomerular filtratration rate (GFR) <90 mL/min]
	Dialysis treatment before transplantation
	Hypertension
	Hyperlipidemia
	Diabetes mellitus
	Hepatitis C virus positivity
	Retransplantation
Intraoperative	Acute renal failure
	Need for dialysis
	Hypotension
	Use of pressor agents
Postoperative	Acute renal failure
	Sepsis
	Cytomegalovirus infection
	Calcineurin inhibitor exposure
Long-term	Renal function at 1 year
	Hypertension
	Proteinuria
	Hyperlipidemia
	Infections
	Calcineurin inhibitor exposure

Furthermore, other contributing factors may be due to subcategories of diseases within organ-specific transplants. For example, in the setting of liver disease hepatitis C infection can be associated with various glomerulonephritides [52]. This form of immune-mediated damage will not be present if the cause of end-stage liver disease is, for example, Caroli disease [2]. According to the study by Ojo et al [4], a positive serologic

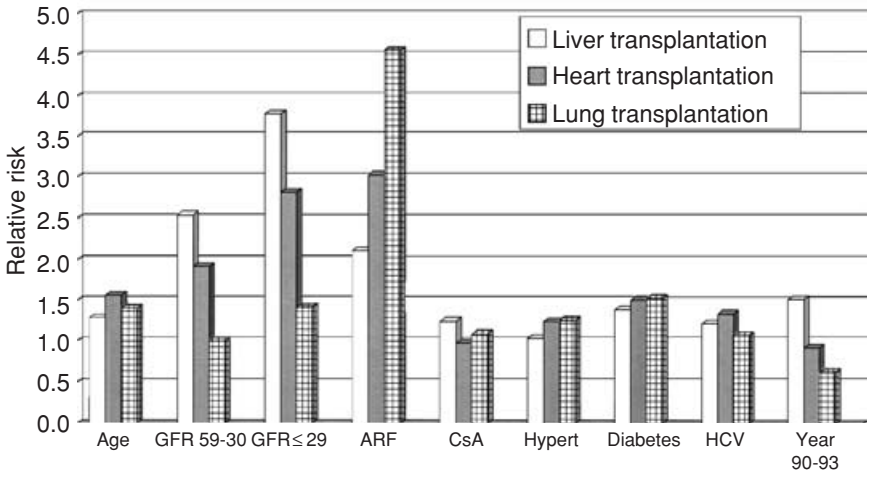

Fig. 3. Relative risks of chronic renal failure in different nonrenal transplanted patients according to the presence of different risk factors (modified from [4]). Risk factors are: age categorized as per 10-year increments, pretransplantation glomerular filtration rate (GFR) between 59 and 30 mL/min and ≤29 mL/min as compared to ≥90 mL/min as reference group, postoperative acute renal failure (ARF) defined as 50% reduction from baseline in the GFR or a need for dialysis treatment during the initial hospitalization for transplantation, cyclosporine used during initial hospitalization, hypertension (hyper) categorized as previous diagnosis before transplantation, diabetes before transplantation, hepatitis C virus (HCV) seropositivity before transplantation, 1990 to 1993 as the period during which transplantation was performed as compared to 1998 to 2000 as reference group.

result for hepatitis C before transplantation was closely associated with an increased risk of chronic renal failure, except for recipients of lung transplants.

There are factors in the heart transplant patients, such as an underlying diagnosis of ischemic cardiomyopathy at the time of transplantation, which seem to contribute to the development of chronic renal failure, as this manifestation of atherosclerotic vascular disease usually parallels ischemic renal status [2, 19].

Lung transplant patients at risk include those with pulmonary hypertension and chronic obstructive pulmonary disease, who have a significantly better prognosis than patients with cystic fibrosis, despite normal pretransplant renal function. The increased risk for this subgroup is explained by several factors, including the fact that most cystic fibrosis patients have usually had previous exposure to aminoglycoside antibiotics and have experienced preexistent renal tubular function disorders or microcalcinosis, secondary amyloidosis, and diabetes mellitus [53].

Finally, another aspect which must not be forgotten is that of patient-specific factors which contribute to a worsening of renal damage, whether genetic (TGF-β genetic polymorphisms seem to contribute to the development of ESRD in heart transplant recipients) [54], or acquired (hypertension, dyslipemia, or hyperuricemia).

Summing up, apart from patient-specific and organ-specific susceptibility traits, there is a common group of risk factors which lead to ESRD in recipients of any type of nonrenal transplant (Table 2). Common potential contributors to the progression of chronic renal failure in patients who have received any type of transplantation are age, gender, year of transplantation, diabetes mellitus, hypertension, creatinine clearance of 29 mL/min prior to renal transplantation or preexisting renal diseases, hepatitis C infection, postoperative acute renal failure, hyperlipidemia, and nephrotoxic drugs [2, 4, 7, 55]. Although their prevalence and importance appears to vary according to the type of transplanted organ (Fig. 3), they are all independent variables which increase the risk of progression to ESRD. In Figure 3, according to the corresponding reference, risk factors are age, categorized as per 10 years' increment, pretransplantation GFR between 59 and 30 mL/min and ≤29 mL/min as compared to ≥90 mL/min as reference group, postoperative acute renal failure, defined as 50% reduction from baseline in the GFR or a need for dialysis treatment during the initial hospitalization for transplantation, CsA used during initial hospitalization, hypertension, categorized as previous diagnosis before transplantation, diabetes before transplantation, hepatitis C virus seropositivity before transplantation, 1990 to 1993 as the period during which transplantation was performed as compared to 1998 to 2000 as a reference group.

The role of calcineurin inhibitors cannot be evaluated by comparing it with other immunosuppressive protocols, as no comprehensive alternative schedules are available. One such example may be seen in the study by Ojo et al [4] where less than 1% of recipients of all extrarenal organs received sirolimus, with or without calcineurin inhibitors, during pretransplant hospitalization. However, it is worth noting that in this study patients with insufficient or incomplete medical picture on such treatment (data not being available at the time of initial hospitalization for transplantation) are indicated as having a lower risk of developing chronic renal failure (relative risk = 0.87) ($P < 0.001$). And there was no association between sirolimus therapy and chronic renal failure in the subgroup of liver transplants. Another important exponent for gauging the likelihood of renal complications is longevity. The risk of developing chronic renal failure appears to correlate with age. This relationship, confirmed in single-center studies performed on patients receiving liver and heart transplants [2, 4], is in agreement with current knowledge on renal transplantation. Kidneys from older donors seem to be more susceptible to calcineurin inhibitor toxicity [2].

In conclusion, mechanisms of ESRD in nonrenal transplant recipients share some common denominators (first, calcineurin inhibitor–mediated nephrotoxicity) to which procedure-specific, organ-specific, and patient-specific factors have to be added.

A primary source of kidney damage in nonrenal transplant recipients is calcineurin inhibitor–mediated nephrotoxicity, as in renal allografts, minus the local damage mediated by chronic rejection, plus the additional damage mediated by local innervation and other organ-specific factors (Fig. 2).

At present, it is impossible to assess to what extent calcineurin inhibitor–mediated nephrotoxicity aggravates the deterioration of renal function in renal versus nonrenal transplant recipients. Moreover, it is difficult to stratify patients into risk factor groups of one type of nonrenal transplant versus the others. However, a better understanding of analogies and differences in damaging calcineurin inhibitor mechanisms within different subsets of patients is important in order to implement "organ-specific" strategies for both prevention and therapy.

PREVENTION AND THERAPY STRATEGIES

Prevention of renal function loss after nonrenal solid organ transplantation should start from a careful evaluation of several preoperative, intraoperative, and postoperative components (Table 3), before considering any change in the immunosuppressive regimen [2, 3].

Indeed, in the presence of pretransplantation renal function impairment it is essential to achieve an adequate renal perfusion by the adoption of careful anesthetic and operative techniques. Concomitant nephrotoxic drugs or intravenous calcineurin inhibitors should also be avoided, and early-phase calcineurin inhibitor peak levels should be closely monitored [2, 3].

Dihydropyridine calcium antagonist and drugs blocking the renin-angiotensin system (both ACE inhibitors and angiotensin II receptor antagonists) should be considered. A combination of these two categories could in theory provide protection from both the acute hemodynamic component of nephrotoxicity (through calcium antagonist–mediated reduction of afferent arteriole vasoconstriction [56]) and chronic vascular and tubulointerstitial injury (through inhibition of angiotensin II effects with consequent reduction of TGF-β and other profibrotic mediators) [57, 58].

Enalapril and valsartan have been proved to be effective in restoring physiologic vasoconstriction of renal arteries in response to noradrenalin and angiotensin II, as well as relaxation response to acetylcoline and sodium nitroprusside, after the administration of CsA in spontaneously hypertensive rats [59].

The role of angiotensin II–induced oxidative stress in CsA nephrotoxicity is also emerging. Angiotensin II receptor antagonist candesartan cilexetil has been shown to reduce tissue lipid peroxidation and morphologic changes in CsA-treated rats [60].

Table 3. Preventive strategies for calcineurin inhibitor–induced nephrotoxicity in nonrenal transplanted patients

Setting	Strategy
Preoperative	Thoroughly evaluate renal function
	Try to identify and reduce, when possible, main pathogenic causes of renal failure
Intraoperative	Avoid renal hypoperfusion through careful fluid management
	Reduce use of catecholamines
Postoperative	Treat infections and sepsis with a full and aggressive schedule
	Carefully use aminoglycosides, always monitoring serum levels
	If dialysis is needed, optimize tolerance by avoiding hypotension and excessive ultrafiltration, especially in patients already on calcineurin inhibitor
	When possible, delay introduction of calcineurin inhibitor, especially in patients with acute tubular necrosis or heart failure
	Avoid intravenous administration of calcineurin inhibitor
	Monitor peak cyclosporine A levels
Long-term	Treat hypertension [angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists should be employed especially if proteinuria is present Dihydropyridine calcium antagonist may be useful
	Treat hyperlipidemia
	Limit calcineurin exposure
	Consider reduction of calcineurin levels or even its withdrawal through introduction of alternative immunosuppressors.

In animal models endothelin antagonists have proved capable of counteracting calcineurin inhibitor–induced hemodynamic changes, but even though they can prevent the decline in GFR they seem to offer no protection against the morphologic injury [58]. Adequate control of calcineurin inhibitor–induced hypertension is probably as important as in native kidney disease and renal transplantation [47]. However, whether or not these preventive measures will also be able to offer clinically relevant renal protection in nonrenal transplant recipients is something which requires further study.

The priority should therefore be to minimize or completely avoid the use of calcineurin inhibitors. This section will focus on immunosuppressive options which are employed with ever increasing frequency to this aim. Several protocols first tested in the setting of kidney transplants, where organ rejection is not usually a life-threatening event, were then applied to the area of life-saving transplants, where a greater degree of caution has to be respected. We will now review the state of the art of these approaches both in kidney and in nonrenal organ transplants.

Lessons from calcineurin inhibitor minimization in kidney transplants

The goal of minimizing calcineurin inhibitor nephrotoxicity led to three approaches being attempted: calcineurin inhibitor elimination, avoidance, or substitution [61]. Every approach was based on either sirolimus or mycophenolate mofetil (MMF) or on an association of these two drugs [62, 63].

Elimination of CsA was achieved in an early phase (3 months after transplantation) within a protocol, including sirolimus, CsA, and steroids. A marked improvement of renal function was observed in the subgroup of patients that had been randomly chosen to continue a maintenance therapy of only sirolimus and steroids at 1 year (mean calculated GFR of 57 mL/min vs. 63 mL/min) ($P < 0.001$), with no significant difference in the transplant outcome [64].

Both MMF [65] and sirolimus [66] were used to either reduce or discontinue calcineurin inhibitor drugs in chronic allograft nephropathy. Significant improvements in renal function were observed in about 30% of patients. The antiproliferative properties of both drugs (especially rapamycin) and their specific inhibitory effect on fibrogenesis make them good candidates to counteract calcineurin inhibitor–induced nephrotoxicity [67, 68].

Avoidance of calcineurin inhibitor was obtained in induction protocols with monoclonal antibodies, based on the use of daclizumab, MMF, and steroids [69] or alemtuzumab and sirolimus monotherapy [70]. Although renal function was excellent in both cases (serum creatinine = 1.2 mg/dL at 1 year), proving the remarkable impact of a nonnephrotoxic therapy in the initial posttransplant phase, high rejection rates were reported.

Another way of avoiding calcineurin inhibitors can be defined as calcineurin inhibitor substitution [71, 72]. Sirolimus can be used instead of CsA in a three-drug maintenance regimen with an antiproliferative agent (azathioprine or MMF) and steroids.

The prototype of this protocol was first tested by Groth et al [71] (using azathioprine) and Kreis et al [72] (using MMF), with excellent results in terms of renal function (serum creatinine = 1.3 mg/dL and 1.4 mg/dL). But, once again, elevated rejection rates were recorded (41% and 30%, respectively).

In an attempt to improve the safety of this protocol, Flechner et al [73] developed a similar one, reinforced with basiliximab induction (followed by sirolimus, MMF, and steroids). When compared to a traditional protocol with CsA, MMF, and steroids, no difference in transplant outcome emerged after an average follow-up of 18 months (acute rejection rate at 1 year = 6.4% with sirolimus and 6.7% with CsA). There was, however, a dramatic improvement in renal function in the calcineurin inhibitor–free patients after the first few months, which increased steadily over time. Samples taken at 6, 12, and 18 months showed average creatinine levels (mg/dL) for the sirolimus patients to be 1.29, 1.32, and 1.30 while those for CsA patients measured 1.74, 1.78, and 1.89, respectively ($P = 0.005$).

In conclusion, on the one hand induction therapy based on calcineurin inhibitor–sparing or calcineurin inhibitor–free protocols with MMF and/or sirolimus contributes to a better renal function level after 1 year, which is a powerful predictor of long-term graft survival [74]. On the other, both drugs appear to be effective in allowing some degree of renal function recovery in chronic allograft nephropathy. In this setting, besides having positive effects on nephrotoxicity, due to the reduction or discontinuation of calcineurin inhibitor, their immunosuppressive properties have an impact on chronic rejection, the alloantigen-dependent process of chronic allograft nephropathy. Therefore, they interact with both the nonimmune and the immune component of chronic allograft nephropathy in kidney transplant recipients. Obviously, their effects on renal function in nonrenal transplant recipients only allow us to cut down the use of calcineurin inhibitors.

Calcineurin inhibitor minimization in nonrenal organ transplants

Minimization strategies in this context rely on the same strategies described for kidney transplants, although their application has unique peculiarities depending on the type of transplanted organ.

Comparison between CsA and tacrolimus has not yet produced any sound evidence of a less nephrotoxic impact of the latter [75, 76], and available data are so far conflicting. Indeed, in pediatric heart transplant recipients [77], exposure to tacrolimus was found to increase the independent risk of renal dysfunction, whereas in the study by Ojo et al [4], the excess risk of chronic renal failure in liver transplant recipients was greater with CsA therapy than with tacrolimus.

Similarly, many experiences on small samples of nonrenal organ recipients suggest that a cautious shift from the use of calcineurin inhibitors to alternative immunosuppressive agents may prove a potentially advantageous and safer approach.

Organ-specific reports

Liver. Prospective studies demonstrated that both GFR and renal plasma flow (measured with ^{125}I-iothalamate and ^{131}I-hippuran, respectively), considerably improved after CsA withdrawal and stimulation with dopamine and amino acid infusion (from 74 to 90 mL/min) ($P < 0.04$) and from 310 to 380 mL min/min ($P < 0.03$), even after more than 2 years of CsA treatment [78].

Sirolimus has been used as the primary immunosuppressive agent to replace calcineurin inhibitors in cases

of nephrotoxicity, making the reduction or complete withdrawal of calcineurin inhibitors possible. Conversion to sirolimus led to an improvement in renal function in about a half of the patients, on average more than 6 months after the switch [79]. It has been used either as a monotherapy [80] or together with low-dose tacrolimus, resulting in exceptionally low rates of acute rejection, and continued, excellent renal function [81–83]. In several experiences MMF and azathioprine both made safe withdrawal of CsA or tacrolimus possible [84–86]. In a recent report by Cantarovich, Tzimas, and Barkun [84] a gradual reduction of CsA (up to 25 mg twice daily) combined with an introduction of MMF (1 g twice daily) determined a significant improvement of renal function, even in long-term transplant patients (46 ± 22 months), although a 12-month follow-up was needed to confirm these results. Acute rejection occurred in 29% of these patients and was steroid-responsive in all but one (the patient died because of liver necrosis due to acute rejection caused by noncompliance).

Heart. The first attempt to prevent calcineurin inhibitor–induced nephrotoxicity involved the once daily administration of CsA [87] or a concomitant treatment with pentoxifylline [88]. In more recent studies, a strategy of switching from azathioprine to MMF as well as a reduction of CsA dosage determined a short-term improvement in renal function in most patients, although both acute rejection and infections were reported within the first 12 months after the switch [89, 90]. A study performed on pediatric heart transplant recipients shows that the nephrotoxic effect of tacrolimus and CsA are comparable over a long term [91], while other authors report positive effects after conversion from CsA to tacrolimus in small samples of patients [92].

Lung. Conversion from azathioprine to MMF and a decrease in calcineurin inhibitor doses, with subsequent improvement of renal function (increase of GFR by 20% after a mean follow-up of 16 ± 4 months), has been described in lung transplant patients [93]. When sirolimus was used on this population, a substantial decrease or even withdrawal of calcineurin inhibitors was possible. It is worth noting that the direction of creatinine after 30 days predicted long-term creatinine, whereas the starting creatinine did not predict the 30-day or long-term value [94].

Intestine. A protocol-based on tacrolimus, daclizumab, sacrolimus, and budesonide has been used after small bowel transplantation to reduce nephrotoxicity [95].

CONCLUSION

Not only does chronic renal failure and ESRD significantly worsen the prognosis of nonrenal transplant patients, they are also very expensive. The risk of chronic renal failure and the need for long-term renal replacement therapy will increase, as improvements in general care allow transplant recipients to live longer.

As these complications are relatively common, it is essential that patients receive thorough counseling before transplantation. Preventive measures should be encouraged, these include a careful assessment of preexisting renal disease and chronic renal failure, improvements in the operative and perioperative management to minimize the risk of acute renal failure, and the identification and correction of modifiable cardiovascular risk factors. Once nephrotoxicity occurs, the role of the nephrologist should not be limited to diagnosing it as the cause of posttransplant chronic renal failure and of monitoring its follow-up through periodical controls; this "wait and see" attitude often merely results in the passive registration of a relentless progression of renal damage. The nephrologists' experience in immunosuppressive therapy should rather be cautiously applied to the other solid organs and tissue transplant recipients. Active strategies for optimizing calcineurin inhibitor treatment should concentrate on the association of nonnephrotoxic drugs (such as MMF and rapamycin) and even on new induction protocols for the delayed introduction of calcineurin inhibitors (through the employment of monoclonal antibodies). Avoiding their effects at an early phase can reduce the detrimental outcome caused by concomitant factors such as hemodynamic instability. In the near future calcineurin inhibitor–sparing protocols might even be considered as a primary immunosuppressive therapy, before the onset of an established renal damage.

Their widespread use may have the potential to significantly reduce renal morbidity in the area of life-saving transplants.

Reprint requests to Professor Piero Stratta, Transplantation and Nephrology, Department of Nephro-Urology, Amedeo Avogadro University, Novara Ospedale Maggiore della Carità, Corso Mazzini 18, 28100 Novara, Italy.
E-mail: strattanefro@hotmail.com

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