

# NEPHROLOGY

# Rounds™

## Late Allograft Dysfunction: An Ongoing Problem in Kidney Transplantation

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Renal allograft failure is the most common cause of end-stage renal disease in the renal transplant population beyond the early post-transplantation period<sup>1</sup> and accounts for nearly 20% of patients on the kidney waiting list. In fact, roughly 15% of kidney transplants performed with kidneys from deceased donors in the United States go to patients with  $\geq 1$  prior renal allografts. Despite recent advances in immunosuppressive therapy, improvements in the rates of long-term graft survival have not been commensurate with those observed at 1-year post-renal allograft.<sup>2</sup> As a major problem in renal transplantation, late allograft loss is arguably second in importance only to the shortage of available organs. The predominant causes of late renal allograft loss/dysfunction are death with a functioning graft, chronic allograft nephropathy (CAN), and recurrent disease. This issue of *Nephrology Rounds* elucidates the definition of "CAN" versus "chronic rejection," describes the histopathological features on biopsy that are suggestive of allograft failure, and provides an overview of factors that may contribute to renal allograft dysfunction and failure, including immunological, donor, preservation and implantation, recipient, and medical management factors.

### Definitions and terminology

Chronic allograft nephropathy is a poorly defined clinical-pathological entity manifested clinically by a gradual decrease in renal function over months to years after transplantation, coupled with hypertension (HTN) and variable degrees of proteinuria. CAN arose as a classification in the Banff schema of kidney-transplant diseases (discussed later) to include at least 4 entities that were not always differentiated on biopsy: chronic rejection, chronic toxic effects of cyclosporine (CsA), hypertensive vascular disease, and chronic infection or reflux.<sup>3</sup>

The term "CAN" was intended to supplant the more restrictive "chronic rejection," which obligated an immunologic mechanism of injury that was not detected in every biopsy. However, it was not intended to replace specific diagnostic categories if a particular entity could be identified. Some pathologists support the diagnosis only in biopsy specimens where pathological features are truly nonspecific (ie, CAN, not otherwise specified). Despite improvements in modern pathological techniques, distinctive features of various known renal diseases may not be accurately recognized. Even when these features can be recognized, coexisting and overlapping pathologic manifestations may be present, considering the multiple insults endured by most allografts. Furthermore, allograft biopsies often are not performed until late in the course of a particular disease process and, generally, without a baseline biopsy for comparison, making what might be a simple early diagnosis nearly impossible during the later stages. Finally, our understanding of the mechanisms of injury and methods for their detection continue to evolve. For instance, humoral rejection that was previously unrecognizable in graft biopsies is now routinely detected by staining for C4d,<sup>4</sup> a fragment of the C4 component of complement. Prior to routine immunostaining for polyomavirus (BK), pathological renal manifestations of BK virus were incorrectly categorized.<sup>5</sup>

Many immunologists have continued to cling to the term "chronic rejection," given the wealth of clinical and experimental data demonstrating minimal graft disease in the absence of an alloresponse.<sup>6</sup> Some contend a specific type of rejection exists to explain the more rapid deterioration of graft function in certain patients. However, convincing immunologic studies in humans lag behind those in animal models, which cannot be readily translated into

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clinical medicine. Others<sup>7</sup> have called for a moratorium on the use of “chronic rejection” and choose to describe allografts by a set of definable entities that include the presence and extent of:

- rejection (T cell- or antibody-mediated)
- allograft nephropathy (atrophy, fibrosis, and intimal thickening)
- transplant glomerulopathy
- specific diseases
- factors that could accelerate the progression of graft dysfunction.

Such an approach provides a framework to describe what is known about an allograft, but does not provide a convenient umbrella term for clinicians to describe a failing graft when the risk-to-benefit ratio argues against biopsy. The debate, therefore, continues over the ideal term for an incompletely understood process.

### Histopathological findings

The renal allograft biopsy should ideally provide answers to at least three important clinical questions:

1. the cause of graft dysfunction
2. the current activity of the process
3. the degree of irreversible damage that has already occurred, which has significant implications for therapy.

Standardization of renal allograft biopsy interpretation is necessary to guide therapy and establish an objective endpoint for clinical trials in renal transplantation. The Banff Working Classification of Renal Allograft Pathology is an international schema published originally in 1993 to meet this need. Table 1 outlines the current overall Banff grading scheme for chronic/sclerosing allograft nephropathy, which has been divided into three grades based on the severity of the changes<sup>7</sup> Figure 1 contains representative photographs of the characteristic histopathological findings in CAN, which are discussed in more detail below.

**Tubular atrophy/ interstitial fibrosis:** Chronic/sclerosing changes can develop in the glomeruli, interstitium, tubules, and vessels of renal allografts subjected to ischemia, HTN, drug toxicity, infection, increased ureteral pressure, de novo or recurrent glomerular disease, non-immune inflammation, and chronic or recurring allo-immune responses. Grading of only the tubules and interstitium, however, serves as the basis for the severity of CAN in the Banff schema, since there is less sampling error of these structures. In fact, the most recent grading of chronic interstitial fibrosis and tubular atrophy/loss (Banff 97) has remained unchanged from Banff 93-95.

**Glomerulopathy:** The grading of chronic glomerular changes related to rejection involves the presence of “double contours” in capillary loops created by mesangial interposition (ie, transplant glomerulopathy) and mesangial matrix increase. Severity of chronic glomerulopathy is now graded by the extent of “double contours” in the most severely affected glomerulus, while increased mesangial matrix is graded by the percentage of nonsclerotic glomeruli with at least moderate mesangial matrix

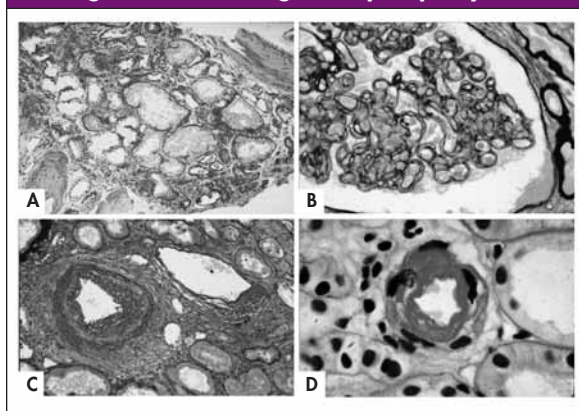
**Table 1: Chronic/sclerosing allograft nephropathy (Banff '97)**

Grade	Histopathological findings
<b>Grade I (mild)</b>	Mild interstitial fibrosis and tubular atrophy without (a), or with (b), specific changes suggesting chronic rejection
<b>Grade II (moderate)</b>	Moderate interstitial fibrosis and tubular atrophy (a) or (b)
<b>Grade III (severe)</b>	Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b)

increase. Transplant glomerulopathy may be difficult to distinguish from membrano-proliferative glomerulonephritis or focal segmental glomerulosclerosis. Duplication of capillary lamina densa in peritubular capillaries (PTC) has been associated with chronic allograft glomerulopathy.<sup>8</sup> However, this potential distinguishing feature is only reliably detectable by electron microscopy and, hence, not available to all clinicians.

**Fibrous intimal thickening:** Vascular changes potentially enable identification of chronic/sclerosing changes due specifically to an immune response (ie, chronic rejection). These changes include disruptions of the elastica and inflammatory cells in the fibrotic intima, as well as proliferation of myofibroblasts in the expanded intima and the formation of a neointima. Chronic vascular changes are graded, based on the extent of occlusion (percentage) of the most severely affected vessel. Scoring of arteriolar hyalinosis remains unchanged from previous schema and is graded by the severity of hyaline thickening, as well as the number of arterioles involved. Those changes that are nodular and new-onset may represent calcineurin inhibitor (CNI) toxicity and are scored separately in the overall schema. When present, arteriolitis is designated by an asterisk added to the arterial hyalinosis score. In the overall grading scheme (Table 1), chronic/sclerosing nephropathy grades 1-3 may be modified by “a” (no changes strongly suggestive of chronic rejection in

**Figure 1: Characteristic histopathological findings in chronic allograft nephropathy**



A. Tubular atrophy/interstitial fibrosis; B. Transplant glomerulopathy; C. Fibrous intimal thickening; D. Arteriolar hyalinosis.

glomeruli and/or vessels present) or “b” (changes strongly suggestive of chronic rejection present).

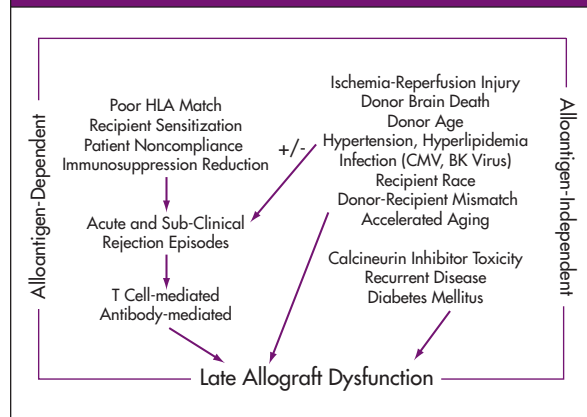
Another grading system that focuses on chronic changes is the Chronic Allograft Damage Index (CADI).<sup>9</sup> In contrast to the Banff criteria, the CADI severity score also takes into account vascular and glomerular changes. Using protocol biopsies, the CADI at 2 years was shown to correlate significantly with transplant function at 6 years and accurately identified those recipients who developed progressive graft dysfunction 4 years later.<sup>10</sup> In this study, incipient histological changes compatible with CAN were present at 2 years in >50% of allografts, including nearly half of those with stable graft function. The phenomenon has been confirmed by several other single-center studies, including 4 using Banff criteria and, more recently, as part of 2 pivotal mycophenolate mofetil (MMF) multi-center trials.<sup>11</sup> The ability to predict graft survival, despite normal graft function, makes it possible to use the Banff and CADI schema as surrogate endpoints in primary prevention trials and to reduce the number of patients required to adequately power secondary interventional trials.

In an effort to provide new insights into the “natural” history of CAN, a recent prospective study evaluated 961 protocol kidney transplant biopsies. These were taken on a regular basis, from the time of transplantation to 10 years thereafter, from 120 recipients with type 1 diabetes, all but one of whom had received a kidney-pancreas transplant.<sup>12</sup> Two distinctive phases of injury were evident as CAN evolved. An initial phase of early tubulointerstitial damage was present in 94% of patients by 1 year. Beyond 1 year, a later phase of CAN was characterized by microvascular and glomerular injury. Although subclinical rejection was present at multiple timepoints, chronic rejection (defined as persistent subclinical rejection for  $\geq 2$  years) was uncommon (5.8%). By 10 years, severe CAN was present in 58.4% of patients, with sclerosis in 37.3% of glomeruli. Tubulointerstitial and glomerular damage, once established, was irreversible, resulting in declining renal function and graft failure. CNI nephrotoxicity was virtually universal by 10 years after transplantation despite mild-to-moderate reductions in doses, making it the chief cause of late histologic injury and ongoing decline in renal function. The study was notable for the pristine condition of the transplanted kidneys, which avoided confounding influences of preexisting organ damage. Although a general applicability to kidney transplants alone may be limited – given that all but one were kidney-pancreas transplants – a similar study of living donor kidney transplants with shorter follow-up confirmed many of the early findings.<sup>13</sup>

### Risk factors and mechanisms

Despite extensive research in the area of CAN and the known associations of various factors and cells with development of the condition, the precise mechanism(s) responsible for the characteristic histopathological findings still remains unknown. It is clear from a wealth of animal studies<sup>6</sup> that both alloantigen-dependent and

**Figure 2: Mechanisms contributing to chronic allograft nephropathy (CAN)**



alloantigen-independent factors contribute to the pathophysiology of CAN, although these factors need not be considered mutually exclusive. Several recent, well-executed, large-scale retrospective database analyses have identified key risk factors important for long-term graft survival.<sup>4</sup> It appears from such studies that, despite more intense immunosuppression in recent years, long-term graft survival, at least for deceased donor grafts, may actually be worsening.<sup>14</sup> These findings underscore the importance of non-immunologic factors and their contribution to CAN. In the next section, factors important for long-term graft survival and the development of CAN will be reviewed, along with any specific mechanisms (Figure 2).

### Immunologic factors

**Acute rejection:** Confirmed by numerous clinical studies, acute rejection (AR) remains one of the strongest risk factors for the development of CAN and ultimate long-term graft loss.<sup>6</sup> The risk is highest in AR episodes that are late,<sup>15</sup> recurrent,<sup>16</sup> or exhibit a vascular component<sup>17</sup> and, most important, those that result in impaired renal function at the time of diagnosis<sup>18</sup> and following treatment.<sup>19</sup> These findings have been duplicated using surrogate markers for graft survival, including both Banff<sup>12</sup> and CADI<sup>11</sup> schema. In the protocol biopsy/CAN “natural” history study mentioned previously,<sup>12</sup> AR not requiring anti-lymphocyte therapy had no direct effect on the development of CAN. The 3-month risk of subclinical rejection, however, was increased by a previous episode of severe AR and, interestingly, with CsA therapy as compared with tacrolimus (TAC) therapy. Patients who had acute and borderline sub-clinical rejection had subsequent biopsy specimens showing higher grades of CAN, as compared with those without such rejection, especially between 3 and 12 months. TAC and MMF, individually, and in combination, reduced the prevalence of subclinical rejection. These findings suggest that after successful treatment of severe AR episodes, subclinical rejection may be responsible for CAN and ultimate graft failure. However, since most patients are now on MMF, it is still not clear why overall graft survival should be worsening.<sup>14</sup>

The presence of C4d, a marker for antibody deposition, in biopsy specimens with chronic rejection (transplant glomerulopathy or arteriopathy) correlates well with serum anti-donor antibodies and reduced graft survival, implicating a role for antibody-mediated responses in at least certain subsets of CAN.<sup>4</sup>

**Inadequate immunosuppression:** Long identified as a risk factor for AR, inadequate immunosuppression is also associated with a reduction in long-term graft survival and the development of CAN. In clinical practice, such “underdosing” of immunosuppressive medications is generally due to patient noncompliance<sup>16</sup> or attempts by physicians to reduce immunosuppression. Even in the more recent trials using MMF,<sup>20</sup> protocol steroid withdrawal appears to increase the risk of AR, although follow-up was too short to determine the effects on long-term graft survival. Attempts have been made to minimize or withdraw CsA from the standard immunosuppressive regimen. A recent meta-analysis in the MMF era<sup>21</sup> confirms a small, but significant increase in AR after CsA withdrawal, with most of the episodes occurring in patients not achieving ideal MMF and steroid doses.

### Donor quality and related factors

Also confirmed by numerous clinical studies, advanced donor age is a major risk factor for poor long-term renal allograft survival. Kidneys from older donors show an increased frequency of adverse events, including delayed graft function (DGF) and a reduced baseline glomerular filtration rate (GFR).<sup>22</sup> Although the reason is not entirely clear, decreased functional reserve due to age and age-related diseases such as HTN and vascular disease likely explains the phenomenon. Transplanted kidneys may also exhibit accelerated aging after transplantation, making older kidneys more susceptible than their younger counterparts to late injury and subsequent nephron loss.<sup>23</sup>

The primary source for solid organ transplantation is a deceased donor who has suffered extensive and irreversible central nervous system damage secondary to hemorrhage, infarction, or trauma. Clinically, brain death (BD) involves a syndrome that includes rapid swings in blood pressure, coagulopathy, pulmonary changes, hypothermia, and electrolyte abnormalities. Experimentally, this catastrophic central injury has been shown to cause rapid and massive upregulation of a variety of inflammatory mediators and other acute-phase proteins in peripheral organs.<sup>24</sup> Furthermore, the tempo of AR in kidney allografts from these donors is accelerated,<sup>25</sup> probably because inflamed organs increase host alloresponsiveness. Even in models of gradual-onset BD, in which donor animals remain normotensive before organ removal and engraftment, accelerated deterioration of renal function occurs.<sup>26</sup> BD in the donor, therefore, appears to explain, at least in part, the observations that living donated kidneys perform

consistently superior than those from deceased donors, despite increased HLA mismatching.<sup>27</sup>

### Preservation and implantation injury

Total ischemia of an allograft is the sum of the transient warm ischemic interval before, or during, actual removal from the donor, cold ischemia associated with preservation and storage, and ischemia occurring during the period of revascularization. Both the ischemic insult and the events of post-ischemic reperfusion contribute to tissue injury. Although the mechanisms of the insults that may contribute to graft demise are still not entirely clear, as with kidneys from BD donors, evidence is growing that events surrounding organ removal, storage, and engraftment may increase graft immunogenicity by upregulating major histocompatibility complex (MHC) antigens and triggering the cytokine adhesion molecule cascade to influence the eventual development of chronic interstitial fibrosis and tubular atrophy/loss.<sup>28</sup> These mechanisms probably contribute to the worse outcomes observed with deceased versus living donated donor kidneys, which experience longer periods of ischemia. Despite minimal periods of ischemia and a low incidence of DGF in the “natural” history study previously mentioned,<sup>12</sup> acute tubular necrosis (ATN) was nevertheless present in 23% of biopsy specimens at the time of transplantation and was subsequently associated with an increased prevalence of CAN and fibrointimal vascular thickening at 1 month. Furthermore, a generalized estimating equation revealed ATN to be a predictor of the CAN grade, 1 to 12 months after transplantation.

### Recipient factors

Retrospective analysis of registry data has identified several recipient risk factors important for long-term graft survival, although due to the known limitations of this approach, the precise mechanisms for such graft loss are not always clearly elucidated.

**Recipient sensitization:** It is clear that recipient sensitization (PRA >20%) has a major impact on graft survival.<sup>29</sup> Whether therapies designed to lessen the degree of sensitization (plasmapheresis, intravenous immunoglobulin) result in significant improvement is the subject of ongoing studies.

**Recipient age:** The elderly are the fastest growing segment of the ESRD population and as renal transplant recipients, experience fewer AR episodes than younger recipients. However, despite the lower immunologic graft loss rate, several analyses have identified advanced recipient age as an independent risk factor for death-censored graft loss.<sup>29</sup>

**Recipient size:** Recipient obesity, as defined by body mass index (BMI) measurement, has been shown to be an independent risk factor for long-term graft failure in some,<sup>30</sup> but not all analyses.<sup>31</sup> Several inves-

tigators have suggested that hyperfiltration injury from “inadequate nephron dosing” may cause progressive injury in transplanted kidneys.<sup>32</sup> In a recent analysis using body surface area (BSA) measurements,<sup>31</sup> the adjusted risk for graft failure was increased by 43% for large recipients (high BSA) of kidneys from smaller donors (low BSA), suggesting that donor-recipient size disparity may be a true risk factor for late allograft failure. However, a recent report showing no accelerated loss of creatinine clearance (CrCl) in transplant recipients in the absence of intervening insults, even at very low levels of renal function, argues against this hypothesis.<sup>22</sup>

**Recipient race:** Numerous reports have confirmed a higher incidence of AR and worse long-term outcomes in black recipients. With more potent immunosuppression, this gap has narrowed for short-term graft survival.<sup>33</sup> However, long-term survival is still reduced in comparison to that in white recipients, although there is some evidence that new immunosuppressive agents and treatment strategies have started to improve this outcome in black recipients.<sup>1</sup>

**Hypertension and hyperlipidemia:** The prevalence of these 2 conditions in the renal transplant population approaches 80%. The causal role of HTN in the development and progression of chronic native renal disease is well-established, although the phenomenon is not as well-studied in recipients of renal allografts. Likewise, studies linking hyperlipidemia with worsened long-term graft survival have yielded conflicting results.<sup>6</sup>

**Infection:** Animal models have confirmed that cytomegalovirus (CMV) infection induces transplant vasculopathy.<sup>6</sup> Recent analyses, however, have failed to demonstrate a strong association between CMV infection and CAN using biopsy surrogate endpoints<sup>11</sup> or decline in the loss of CrCl.<sup>22</sup> Although considered a separate entity, BK virus nephropathy has many of the features seen in CAN, including tubular atrophy and interstitial fibrosis.<sup>5</sup>

### Medical management

It can be said that therapeutic intervention in late allograft dysfunction is currently at a crossroads. Some clinical investigators advocate maintaining higher levels of immunosuppression for the entire life of the transplant, while others suggest that immunologic causes of graft demise are probably less important late after transplantation and favor a switch from potent, but nephrotoxic CNI-based regimens. Studies in patients on conventional regimens with declining renal function and CAN showed that graft function stabilized or improved more in those whose CNI was eliminated rather than reduced (90% vs 60%).<sup>34</sup> Withdrawal of CsA from a sirolimus (SRL)-CsA-steroid (ST) regimen at 3 months attenuated the progression of histologic damage (by CADI) at 36 months and, ultimately, resulted in better graft

survival at 48 months.<sup>35</sup> Unfortunately, these reports lacked a conventional CsA-based, but SRL-free, treatment group for comparison. It is becoming clear that the combination of CsA with SRL is particularly nephrotoxic. In fact, withdrawal of SRL from patients on a SRL-CNI regimen who had deteriorating graft function also resulted in improvement in renal function in the majority.<sup>36</sup> Multi-center trials comparing CsA versus SRL regimens, including treatment arms that substitute SRL for CsA after the early post-transplantation period, are forthcoming.

Given recent improvements in pathological diagnostic techniques, an argument can be made for a more aggressive biopsy practice with any new decrement in graft function. Although this approach may uncover specific features of CAN, until proven therapeutic avenues become available, many clinicians will be reluctant to subject patients routinely to biopsy. Agreed upon by most clinicians despite a lack of definitive trials in transplant recipients, a comprehensive treatment plan to manage accelerating factors, including control of HTN, reduction of proteinuria, aggressive treatment of hyperlipidemia, strict glycemic control and infection prophylaxis seems prudent.<sup>37</sup>

Such interventions will likely impact on patient death, the other major cause of late allograft loss. Future strategies to block T cell co-stimulatory pathways and/or target B cells and alloantibodies are under development. Finally, the “holy grail” for most immunologists is the induction of transplantation tolerance, but whether tolerance will offer a cure for the problem of late allograft dysfunction in humans remains to be determined.<sup>38,39</sup>

### Conclusions

Late renal allograft dysfunction continues to be a vexing issue in transplant nephrology. Numerous animal and clinical studies have attempted to elucidate the mechanisms involved in the complex pathogenesis of this condition to allow design of specific therapies that prevent or interrupt the process. Although several clinical approaches have shown promise, the large number of variables responsible for the process will necessitate that large multi-centered trials be performed to obtain truly meaningful answers. To make such trials feasible, a coordinated approach involving the scientific community, federal agencies, private foundations, and the pharmaceutical/biotechnology industry will be essential.

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