

## Management of chronic allograft nephropathy

Manejo da doença crônica do enxerto renal

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### ABSTRACT

Chronic renal allograft disease remains a leading cause of graft loss. Immunologic and non-immunologic risk factors are related to its development and may be present before or develop after transplantation. Histological evaluation of renal tissue has an important role in the management, especially for the evaluation of immune activity against the graft and toxicity of immunosuppressive drugs. Management of this condition is generally restricted to changes in the immunosuppressive regimen and the overall control of conditions related to the progression of chronic kidney disease.

**Keywords:** Kidney transplantation. Kidney failure, chronic. Biopsy. Graft rejection. Immunosuppression.

### RESUMO

A doença crônica do enxerto renal permanece sendo uma importante causa de perdas de enxertos. Ela está relacionada a fatores de risco imunológicos e não imunológicos que podem estar presentes antes do transplante ou que após ele se desenvolvam. A avaliação histológica do tecido renal tem papel importante no seu manejo, em especial para a avaliação de atividade imunológica contra o enxerto e toxicidade de drogas imunossupressoras. O manejo dessa condição está em geral restrito a alterações no regime imunossupressor e no manejo geral de condições relacionadas à progressão da doença renal crônica.

**Palavras-chave:** Transplante de rim. Falência renal crônica. Biópsia. Rejeição de enxerto. Imunossupressão.

Submitted on: 02/16/2011  
Approved on: 07/12/2011

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This study was undertaken at the Nephrology Service of the HCPA of the Faculdade de Medicina da Universidade Federal do Rio Grande do Sul – UFRGS.

The authors report no conflict of interest.

### INTRODUCTION

Significant advances in immunosuppressive therapy, mainly in the two last decades, have importantly reduced the rate of acute rejection and substantially increased short-term patient and graft survival in renal transplant recipients. Yet, chronic graft loss, due to chronic allograft nephropathy (CAN), has been hardly affected by such advances. CAN and death with a functioning graft remain the leading causes of renal graft loss, together accounting for 3-5% of annual kidney graft loss, after the first year posttransplantation.<sup>1, 2</sup> This is corroborated by a mere borderline increase of kidney graft half-lives in the past few years.<sup>3</sup>

CAN possibly results from different injuries to the graft, mediated by immunologic and non-immunologic mechanisms.

Clinical manifestations may be absent for some time, in spite of ongoing pathophysiological processes. Afterwards, generally some months or few years posttransplantation, there is gradual increase of the serum creatinine levels, with the development of hypertension and low-grade proteinuria, the three occurring simultaneously or in isolation. Diagnostic delay is in part due to the recognized low accuracy of serum creatinine as a marker of graft function, as this laboratory value fails to demonstrate progressive kidney function loss in this and other settings.<sup>2</sup>

Histologic findings are present in most grafts few years posttransplantation, and are practically universal after ten years.<sup>4</sup> The condition initially termed chronic allograft nephropathy (CAN) led to considerable confusion regarding the understanding and

management of kidney graft chronic disease, as it conveyed the notion that the condition was a specific nosologic entity. The expression interstitial fibrosis and tubular atrophy (IF-TA) is now used to describe conditions in which fibrosis and atrophy develop in the absence of defined etiologic factors, the term chronic allograft nephropathy (CAN) having been removed from pathology classification. What was previously termed CAN is now classified as chronic rejection, chronic hypertensive nephropathy, calcineurin-inhibitor nephrotoxicity, chronic obstruction, chronic pyelonephritis and viral infections.<sup>5</sup>

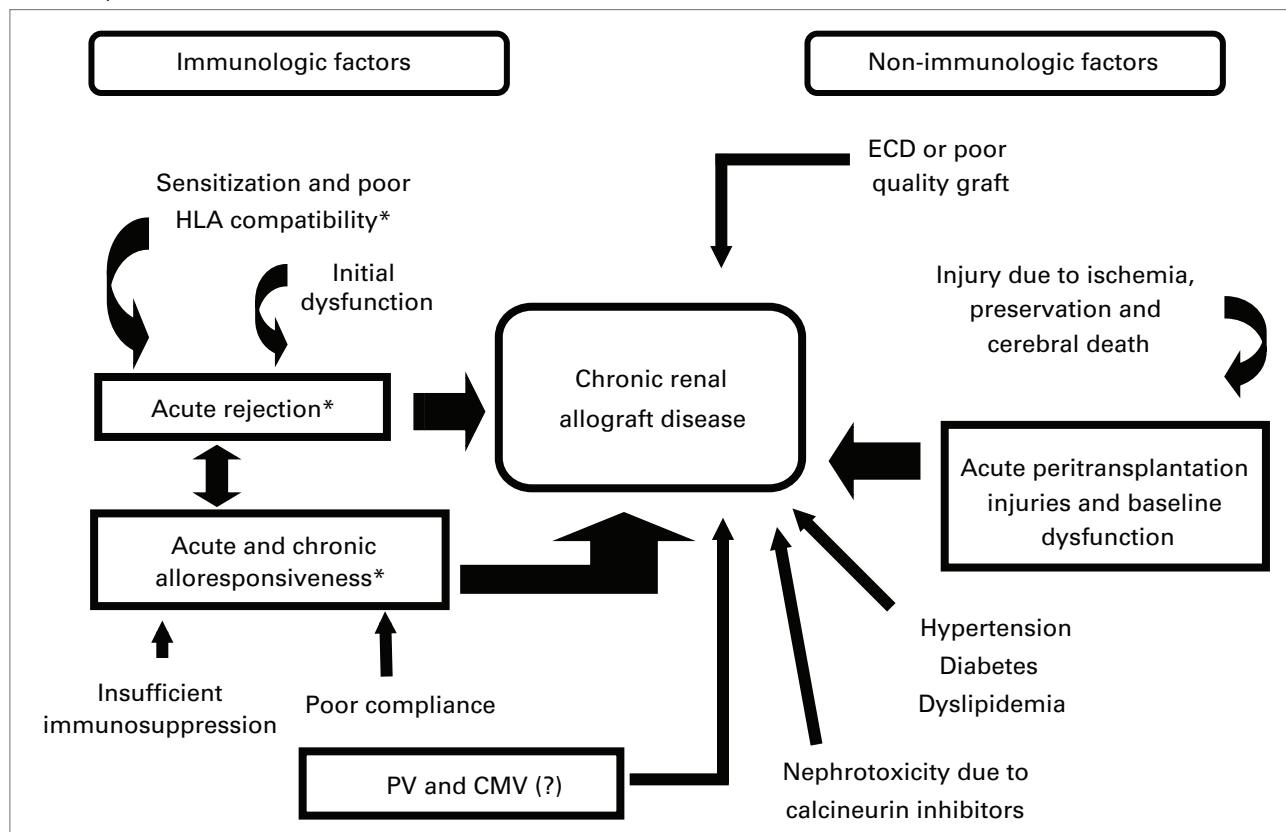
Although the term chronic allograft injury has recently been proposed to be a correlate of IF-TA, it has not been incorporated into the jargon of the specialty.<sup>6</sup> On the other hand, the term chronic allograft nephropathy (CAN) remains in widespread use in the clinical setting, to refer to a chronic, progressive disease of the kidney graft, of undetermined etiology, and generally with an onset within three months post-transplantation.<sup>6</sup>

This study is an update on the management of chronic allograft disease. I will use the term chronic renal allograft disease (CRAD) instead of chronic allograft nephropathy (CAN), as the latter tends to be abandoned.

**SUMMARY OF THE PATHOGENESIS OF CHRONIC RENAL ALLOGRAFT DISEASE (CRAD)**

Several mechanisms may be related to the development of CRAD. Classically, immunologic and non-immunologic factors have been implicated in its pathogenesis, and can be seen in Figure 1. Alloimmunity-related immunologic factors have been demonstrated through several clinical observations, such as good HLA-antigen compatibility (protective factor), and the occurrence of clinical or subclinical acute cellular rejection, antibody-mediated rejection and poor pharmacological compliance (risk factors). Relapsing, severe, late-onset (> 90 dias posttransplantation) rejections, with a vascular component, and those steroid-resistant ones, are especially predictive of CRAD. Recent evidence points to a predominant

**Figure 1.** Pathogenesis of chronic renal allograft disease (CRAD). Immunologic and non-immunologic factors contribute to the development of CRAD. HLA: human leukocyte antigens; ECD: expanded criteria donor; PV: polyoma virus; CMV: cytomegalovirus; (?): There is experimental evidence that CMV may play a role in the genesis of CRAD, but this is not certain. Modified from Pascual *et al.*<sup>1</sup>



role of antibody-mediated rejections in the pathogenesis of late kidney graft loss.<sup>7,8</sup> Viral infections, especially with the polyoma virus (PV),<sup>9</sup> are factors which involve the immune system but are alloantigen-independent. Although cytomegalovirus (CMV) infection is involved in chronic heart and liver graft diseases, its role in the development of CRAD remains uncertain.<sup>10</sup>

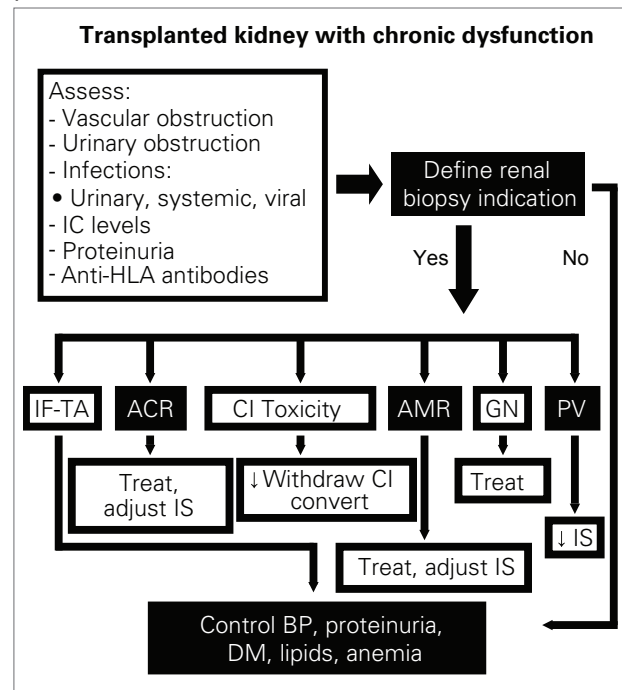
Non-immunologic factors are more directly concerned with: (a) quality of the transplanted organ, which is directly related to donor's age, through the mechanisms of renal senescence, nephron dose, putative greater immunogenicity and the presence of comorbidities (*e.g.* Hypertension); (b) pretransplantation injury to the organ (cause of death and management of the deceased donor), organ retrieval and storage process (warm and cold ischemia and possibly the type of preservation); (c) posttransplantation injuries, such as the use of nephrotoxic drugs, chiefly calcineurin inhibitors (CI);<sup>11-13</sup> and (d) receptor-related factors which were present before the transplantation or which developed posttransplantation, such as relapse of the underlying disease, diabetes mellitus (DM), dyslipidemia and vascular or urinary obstruction.

#### MANAGEMENT OF CHRONIC RENAL ALLOGRAFT DISEASE (CRAD)

Management of CRAD is now limited to the so-called modifiable conditions, consisting of: handling of the immunosuppressive regimen to control alloimmunity and minimize or eliminate its nephrotoxicity; treatment of hypertension, DM, proteinuria, dyslipidemia and infections; and possibly the management of anemia and of bivalent ion metabolism. An algorithm with management measures can be seen in Figure 2.

Biopsy of the kidney graft plays a pivotal role in the management of CRAD. In spite of its limitations, histologic assessment is, to date, the only way to differentiate situations whose identification can be crucial for CRAD management. Detection of an active immune component (interstitial infiltrate, tubulitis), complement fraction (C4d) deposits, polyoma virus-related inclusions, nephrotoxicity-associated interstitial fibrosis and tubular atrophy are some of the examples. Furthermore, in spite of the several pathophysiological possibilities, the most important prognostic factor is demonstration of an active immune component, even in grafts with stable function, in which histology

**Figure 2.** Management of chronic renal allograft disease (CRAD). Non-invasive assessment of putative pathophysiological factors, indication of renal biopsy, management according to renal biopsy results. IF-TA: interstitial fibrosis and tubular atrophy; ACR: acute cellular rejection; CI: calcineurin inhibitors; AMR: antibody-mediated rejection; GN: glomerulonephritis; PV: polyoma virus; IS: immunosuppression; BP: blood pressure; DM: diabetes mellitus.



detects immunologic activity.<sup>14,15</sup> New non-invasive methods might substitute for graft biopsy for this and other finalities.<sup>8,16-18</sup>

CRAD may be seen as a variant of chronic renal disease (CRD) occurring only in renal transplant recipients. Thus, the principles guiding CRD management may and, in general, must be applied to the modifiable conditions mentioned above. It must be considered that these conditions are also cardiovascular risk factors, and that cardiovascular diseases are the main cause of death in renal transplant recipients during the first year posttransplantation. From this point onwards, I will focus this review on the modifiable factors that may impact the establishment and progression of CRAD.<sup>19</sup>

#### NEPHROTOXICITY OF CALCINEURIN INHIBITORS (CI)

CI are the most efficient immunosuppressive drugs at present, being used in most protocols.<sup>20</sup> Detection of an immune component, whether through renal biopsy findings or detection of antibodies against the donor's HLA, in the setting of

graft dysfunction, points to the need for review of the immunosuppressive regimen, which must include an assessment of the patient's pharmacological compliance.

Conversely, CI-related nephrotoxicity is considered the main cause of renal graft dysfunction, also being an important cause of renal dysfunction in recipients of other grafts.<sup>4,12</sup> This paradigm, however, has been recently disputed, with the emerging concept that anti-HLA antibody-related damage to the graft microcirculation is the mechanism underlying the chronic loss of renal grafts.<sup>8</sup>

Established CI-related nephrotoxicity may be managed with dose reduction or withdrawal of these drugs, with replacement with other efficient immunosuppressive drugs. A small sample randomized study suggested that substitution of tacrolimus for cyclosporine may lead to improvement of graft function.<sup>21</sup>

Strategies involving the use of mycophenolic acid derivatives, sirolimus, everolimus and belatacept, the latter under ongoing phase-III studies, have been proposed with this finality and will soon be reviewed. In a randomized study involving patients with progressive deterioration of the renal function, substitution or mycophenolate mofetil (MMF) for azathioprine, with subsequent cyclosporine withdrawal, resulted in stabilization of the renal function in a larger number of patients in the MMF group, compared with those who remained on azathioprine and cyclosporine.<sup>22</sup> In another approach, the cyclosporine dose was halved after the addition of MMF, which also resulted in stabilization of the renal function in the group with the reduced cyclosporine dose, whereas those on the full dose experienced progressive worsening.<sup>23</sup>

Strategies with mTOR inhibitors have been published.<sup>13,24-26</sup> To date, the most robust study demonstrated that patients with glomerular filtration rates (GFR) > 40 mL/min had improvement of renal function and lower rate of neoplastic diseases 24 months after conversion to sirolimus, compared with controls. Nevertheless, there was a significant increase in the proteinuria. The study arm in which the patients had baseline GFR between 20-40 mL/min was prematurely closed due to a high number of subjects reaching the primary outcome.<sup>25</sup> Similar findings had been previously described in a systematic review of a substantial number of patients, although including randomized and non-randomized trials.<sup>24</sup>

## HYPERTENSION

This condition affects approximately 80% of renal transplant recipients on CI.<sup>19,27,28</sup> Data from analysis of thousands of patients from the Collaborative Transplant Study (CTS) clearly show that poor hypertension control, with a systolic blood pressure (SBP) over 130 mmHg, is deleterious to graft function in the long run, and that gradual BP increase is associated with progressively increased graft loss.<sup>27</sup> Because BP is a modifiable risk factor for graft loss, the same authors tested the impact of BP control on this outcome, having found that reduction of the SBP is associated with better graft survival indices.<sup>28</sup>

Several drugs have been used for BP control in renal transplant recipients. Dihydropyridine calcium-channel blockers effectively control BP and, through dilatation of the afferent arterioles, has led to a higher improvement of the GFR, compared with an angiotensin-converting enzyme (ACE) inhibitor,<sup>29</sup> although this finding may not be consistent.<sup>30</sup> Drugs active on the renin-angiotensin system (RAS), ACE-inhibitors and angiotensin type 1 receptor-1 blockers (ARB), because of their possible renal protective effects, are indicated for management of patients with proteinuria greater than 1.0 g/24 hours, as recommended by the KDIGO guidelines for renal transplant recipients. However, these guideline do not recommend any particular antihypertensive drug class, except in situations with significant proteinuria.<sup>31</sup>

Experimental data demonstrate that RAS activation is involved in the development of fibrosis, and that its blockade is associated with slower CRAD progression, due to inhibition of fibrogenic factors (reviewed in reference 10). Finally, it is worth remembering that CRAD patients may have significant loss of glomerular filtration, a situation in which diuretics are frequently necessary for BP control.

## DYSLIPIDEMIAS

Dyslipidemias are frequent in renal transplant recipients, occurring in approximately 60% of the patients within the first year posttransplantation, with the suggestion that they may be related with the development of CRAD.<sup>32</sup> In this setting, the pathogeny is multifactorial and includes pretransplant dyslipidemia, weight gain, proteinuria, graft function loss, and the use of steroids, cyclosporine and sirolimus. Observational studies and a randomized clinical trial showed that high total cholesterol and high LDL-cholesterol

are independently associated with cardiovascular events in renal transplant recipients.<sup>33</sup>

Proteinuria reduction and diabetes and hypothyroidism control may improve serum lipid levels. In some cases, modification of the immunosuppressive regimen may be necessary for control of the dyslipidemia. Treatment follows a two-step approach. Initially, the possible causes are removed, and changes to the lifestyle, including diet, weight reduction and physical exercises, are implemented. Afterwards, pharmacological treatment with statins and, at times, fenofibrate for patients with severely increased triglycerides are implemented, with rigorous monitoring of graft function. According to the present guidelines, adult renal transplant recipients are at high risk of atherosclerotic coronary disease, and should be maintained on a statin, with the goal of keeping their LDL-cholesterol below 100 mg/dL.<sup>5,34</sup> Likewise, triglyceride levels over 500 mg/dL must be treated. In a robust study, fluvastatin led to a 38% reduction of the cardiovascular mortality of renal transplant recipients. Yet, there is no clinical evidence supporting a beneficial effect of statins on graft function or on protection against the development of CRAD.<sup>34</sup> Additionally, a recent meta-analysis assessed statin use in CRD patients, including renal transplant recipients. There were significant reductions of total cholesterol, LDL-cholesterol and proteinuria. However, renal transplant recipients did not have any reduction in their rates of cardiovascular events, global mortality and cardiovascular mortality.<sup>35</sup>

#### DIABETES MELLITUS

Renal transplantation in diabetic recipients has become more frequent. The incidence of posttransplantation diabetes mellitus (PTDM) is known to have significantly increased with use of CI, chiefly tacrolimus, early steroid withdrawal and lower dose regimens being associated with a reduction of DM rates.<sup>36</sup> It has also been suggested that mTOR inhibitors may be involved in the development of PTMD.<sup>37</sup>

It has been well demonstrated that PTDM decreases patient and graft survival, mainly due to cardiovascular and infectious complications. PTDM is chiefly managed with diet, changes to lifestyle, weight reduction, and pharmacological treatment with insulin or oral antidiabetic agents. The latter may metabolically interact with the immunosuppressive drugs, there being limited information on

their safety and efficacy in renal transplant recipients. Besides, some of these drugs may be contraindicated in patients with significant loss of their renal function.<sup>38</sup>

#### PROTEINURIA

Proteinuria is highly prevalent after renal transplantation, occurring in up to 45% of the patients, when a stricter definition is used. Besides relapsing and *de novo* glomerulonephritides, proteinuria in renal transplant recipients is commonly associated with specific diagnoses of chronic transplant nephropathy, transplant glomerulopathy and acute rejection. Proteinuria is associated with reduced graft survival, with an estimated two to fivefold increase in the risk of graft loss and increased risk of cardiovascular events.

In non-transplanted CRD patients with proteinuria, randomized clinical trials have confirmed that RAS blockade is associated with improved clinical outcomes. Although in renal transplant recipients reduction of dietary protein and the use of ACE inhibitors or ARB reduce proteinuria, to date there is no evidence from robust randomized studies that these strategies lead to improved survival or better graft function preservation.<sup>39</sup> A small randomized trial with 47 patients showed that lisinopril led to a 30% proteinuria reduction, in spite of a greater, albeit not statistically significant, fall in the GFR in the group on lisinopril.<sup>40</sup> Observational studies have led to conflicting results regarding the usefulness of ACE inhibitors and ARB to modify graft survival or mortality outcomes.<sup>41,42</sup>

#### ANEMIA

The prevalence of anemia after renal transplantation ranges from 20 to 40%. Its etiology is multifactorial and includes graft function (and associated erythropoietin production), iron deficiency, blood loss, concomitance of neoplastic disorders, infections and commonly used drugs. Among the latter, some immunosuppressive drugs (azathioprine, mycophenolic acid derivatives, sirolimus and everolimus), ACE inhibitors and ARB should be included.<sup>43,44</sup> It has been suggested that renal transplant recipients may have higher than expected anemia levels for a given graft function, without a specific cause being determined.<sup>45</sup> The impact of posttransplantation anemia on patient and graft survival has been recently assessed, with the observation that the presence of anemia after 12 months



posttransplantation negatively impacts patient and graft survival. It seems, however, that the authors of the aforementioned study did not control the results for baseline graft function.<sup>45</sup> Another study, with a larger sample, confirmed these findings, and also reported a higher incidence of acute rejection in anemic patients.<sup>46</sup>

Anemia should be investigated in those in which active bleeding was ruled out and who attained stable graft function. Treatment must target the cause, iron administration sometimes being necessary. Around 20% of renal transplant recipients now receive erythropoiesis stimulators.<sup>47</sup> However, there are no randomized trials assessing the effect of anemia correction with erythropoietin in renal transplant recipients. The most robust study, a recently published retrospective cohort, confirmed that anemia is associated with a higher risk of death in these patients.<sup>41</sup> Yet, there have been recent reports, subject to confirmation by randomized clinical trials, that anemia correction with erythropoietin is beneficial up to a hemoglobin level of 12.5 mg/dL, with increased mortality over this value, which becomes significant when the values reach 14.0 mg/dL.<sup>47</sup>

Anemia management in renal transplant recipients may make it necessary to withdraw or replace an immunosuppressive. In this setting, the risk this may represent to the graft must be taken into account.

## CONCLUSIONS

CRAD is now the main cause of graft loss. Immunologic and non-immunologic factors contribute to its development and lead to fibrosis, whose etiology is not always clear. Renal biopsy is essential for the detection of modifiable factors which may lead to adjustments to the immunosuppressive therapy. As it is recommended for CRD patients not on dialysis, adequate management of the conditions related to CRD progression may be useful to prolong patient survival and delay the progression of graft loss.<sup>48</sup> However, there are no robust data, at present, to support these recommendations for the population of renal transplant recipients. Greater knowledge of the pathogenesis of the different causes of CRAD and of the fibrogenesis mechanisms may afford individualized therapeutic options to stop or delay damage to the renal graft.

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