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Recurrence, Rejection or Chronic Kidney Allograft Dysfunctions; Solving the Conundrum of Allograft Dysfunction

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ABSTRACT

Kidney transplantation offers the best modality of renal replacement therapy; however, requires overcoming the challenging task of maintaining long-term graft survival. Chronic allograft dysfunction (CAD) is a continuum of a process that eventually leads to graft loss. CAD has been previously viewed as a dilemma; however, it has now been found to be associated with a spectrum of aetiologies and with a careful search for the specific kidney lesion and possible causes with appropriate intervention, graft longevity could be achieved. In this review, we analyse the various potential contributory factors to chronic allograft dysfunction intending to update and suggest interventions that could improve outcome.

Keywords: Kidney transplantation, Chronic allograft dysfunction, Recurrence, Rejection

INTRODUCTION

Kidney transplantation offers the best choice for the treatment of patients with end-stage renal disease as compared with other modalities of renal replacement therapies. There is no gainsaying the fact that the ever-improving surgical techniques, peri-operative management, infection control, improved immunosuppressive medications and their pragmatic use have contributed significantly to short-term survival of kidney transplantation. Although patients with kidney transplant have higher 5 year survival than those who received other solid organs [1], there remains a herculean task of increasing long-term graft survival.

The paradigm change in the management and improved outcome of CAD was borne from the inquisitiveness of the members of the transplant community who have consistently questioned the seemingly dead-end diagnosis of chronic allograft nephropathy. This has now led to the discovery of some specific aetiologies; both immune and non-immunological components which are differentials to consider in patients with progressive kidney allograft dysfunction (CAD).

FACTORS ASSOCIATED WITH CAD

The aetiologies of CAD are both immunological and non-immunological-related as shown in **Table 1**. These factors are modifiable; however, there is a reduced chance of salvaging the graft once fibrosis and tubular atrophy are established. Therefore, the need for high index of suspicion, timely investigations and appropriate interventions to treat, prevent or delay progression.

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Table 1. Factors associated with chronic allograft dysfunction.

Immune-related	Non-immune related
HLA-mismatch or donor-specific antibodies Number and severity of rejection episodes Sub-clinical rejection <u>Rejections (Revised BANFF 2017 classification (2))</u> • Acute rejection Active ABMR: All 3 must be present 1 Histologic evidence; - Microvascular inflammation(g>0 and/or ptc>0v>0 - Acute TMA - Acute tubular injury 2 Evidence of current/recent interaction with endothelium -Linear C4d staining in peritubular capillaries - g+ptc ≥ 2 - increase expression of genetranspcripts associated with ABMR 3 Serologic evidence DSA to HLA and non-HLA antibodies • Chronic active ABMR; All 3 must be met 1) Morphologic evidence of chronic tissue injury including 1 of; Transplant glomerulopathy (cg>0) Peritubular capillary basement multilayering Arterial intimal fibrosis of new onset 2) Identical to acute ABMR criteria 2 3) Identical to acute ABMR criteria 3 Borderline changes, i.e., suspicious for acute TCMR -Foci of tubulitis (t>0) with minor interstitial inflammation (i0 or i1) or moderate to severe interstitial inflammation(i2 or i3) with tubulitis T-cell mediated rejection Type 1A: i2 or i3 and t2 Type 1B: i2 or i3 and t3 Type IIA: mild/moderate intimal arteritis v1 ± i2 or i3 or t2/3 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3 Chronic active T-cell rejection i-IFTA 0: No Interstitial inflammation <10% scarred cortical parenchyma i-IFTA 1: Inflammation 10-25% i-IFTA 2: Inflammation in 26-50% of scarred cortical parenchyma i-IFTA 3: Inflammation in >50% of scarred cortical parenchyma Other immunological changes not due to rejection	Recipient-related Age of the recipient Gender DM Obesity Hypertension Hyperlipidemia Non-compliance Genetic factors Donor-related Pre-existing age-related damage to the donated kidney Ischemia/reperfusion injury or brain death of the donor Inflammatory or proliferative processes in the arterial walls Interstitial fibrosis and tubular atrophy Recurrence of primary glomerulonephritis De novo glomerulonephritis Immunosuppressive medications; CNIs

IFTA: Interstitial Fibrosis and Tubular Atrophy; PTC: Peritubular Capillaritis; g: glomerulonephritis; TMA: Thrombotic Microangiopathy; DSA: Donor Specific Antigen; HLA: Human Leucocyte Antigen

DEFINITION OF CHRONIC ALLOGRAFT DYSFUNCTION

CAD is a progressive deterioration in the graft function resulting in loss of graft. It can occur anytime from a few months to years post kidney transplantation despite the patient being on immunosuppressive medications. Typically it presents as deterioration in kidney function as evidenced by progressively increasing serum creatinine and proteinuria.

MEDICAL HISTORY

Cardiovascular disease is the commonest cause of death in kidney transplant recipients and hypertension is one of the major risk factors. Hypertension is a significant modifiable risk factor for the development of atherosclerosis and a predictor of long term outcome of kidney transplantation. Opelz and Dohler [3], in a study of almost 24,000 transplant patients from 258 centres concluded that reducing blood pressure improves graft survival. Hypertension could arise from native kidney but this is expected to be reduced following successful implantation with improved glomerular filtration. Hypertension also can result from the use of an older donor kidney, using calcineurin inhibitors (cyclosporine more so than tacrolimus), from renal artery stenosis or as a consequence of antibody-mediated rejection. The use of steroid is not significantly associated with post-transplant hypertension as it usually tapers off following surgery. With every 10 mm Hg increase in blood pressure, there was a 5% increased risk of graft failure [4].

Proteinuria, even in small amounts, independently predicts graft failure. By the end of the first-month post-transplant, protein excretion from the native kidney resolves. Increasing proteinuria after this period is from the kidney graft [5]. Increasing level of proteinuria is associated with a high risk of graft loss. Among patients with nephrotic proteinuria, when compared with those without, Amer and Cosio [6] reported 19 times increased risk of graft loss (41.2% vs. 3.9%) after a follow-up period of almost 4 years. The 2009 Kidney Disease Improved Global Outcome (KDIGO) [7] suggested annual measurement of protein excretion after the first year of kidney transplantation and to carry out kidney biopsies among those with new-onset or unexplained proteinuria in order to diagnose early treatable causes of graft dysfunction. Amer et al. [8] in another study reported that almost 60% of recipients with proteinuria have specific kidney graft lesions; allograft nephropathy, transplant glomerulopathy or acute rejection, as compared with 11% with glomerulonephritis. It was however emphasized by these authors that higher proteinuria (>2 g/day) is prevalent in glomerular lesions when compared with acute rejection or interstitial fibrosis (<0.6 g/day). Other histories to consider are the primary cause of kidney disease, delay graft function, previous rejection episodes, HLA incompatibility and immunosuppressive medications as listed in **Table 1**.

Transplant renal artery stenosis

Transplant renal artery stenosis (TRAS) is a recognized vascular complication of kidney transplantation. Its early diagnosis and treatment reduce the likelihood of graft loss. The incidence of TRAS ranges from 1-23%. As TRAS, in a similar way to native renal artery stenosis, activates the renin-angiotensin-aldosterone system (RAAS) it can present with poorly controlled hypertension, worsening kidney function, left ventricular failure, fluid retention and occasionally flash pulmonary edema. This may become more obvious with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Transplant ultrasound with Doppler is a non-invasive test to evaluate TRAS. It is diagnosed by the following criteria; increased acceleration time (renal and intra-renal) ≥ 0.1 s, peak systolic velocity in the graft renal artery >200 cm/s and the ratio >1.8 of peak systolic velocity in kidney graft to the external iliac artery is diagnostic of TRAS [9]. Low resistive index (RI) <0.5 may suggest preserved renal microcirculation and predicts benefit from vascularisation while elevated RI>0.8 shows compromised diastolic flow and risk of intrinsic parenchymal disease. Doppler USS is highly operator dependent. Angiography or preferably, digital subtraction angiography is still the gold standard in establishing the diagnosis of TRAS. The poor positive prediction of Doppler USS (sensitivity of 100% and specificity of 75%) supports the use of further imaging to confirm stenosis. Given the risk of contrast-induced nephropathy (CIN) with angiography, magnetic resonance angiography with gadolinium is a better option with low risk of CIN and it improves the diagnosis of renal artery stenosis. The risk of nephrogenic systemic fibrosis is reduced with newer agents like gadobenate dimeglumine [10,11]. However, it may become necessary to conduct a contrast study to achieve a standard of care for the diagnosis of TRAS. A systematic review by Abbas and other colleagues found no specific measures to prevent CIN in transplant patients but recommended universal precautions of adequate rehydration, use of low volume and low osmolar, non-ionic contrast, especially when serum creatinine is ≥ 1.5 mg/dl or eGFR <60 ml/min/1.73 m^2 [12].

Immunosuppressive medications related

New onset diabetes after transplant (NODAT) recipients predicts graft outcome. Kasiske et al. [13], in analysing United Renal data system reported that NODAT increased graft failure (1.63, 1.46-1.84, p<0.0001). Risk factors for the development of NODAT in their study were age, African or Hispanic ethnicity, male donor, high BMI, hepatitis C infection and induction with tacrolimus. On the contrary, a report by Kuo et al. [14] analysing the data of UNOS/OPTN failed to show the impact of NODAT on graft survival. And although it was a large data, the duration of follow up was short (548 days) and confident intervals were also wide.

Calcineurin inhibitors (CNIs) are double-edged medications. They are the cornerstone of the immunosuppressive regimen in kidney transplantation; however, their use is also associated with chronic allograft dysfunction and could reduce graft survival. In a recent systemic review of 2894 patients by Xia et al. [15], donor age, recipient arteriosclerosis and CYP3A5*3/*3 genotype were significantly associated with nephrotoxicity. In this study, subgroup analysis showed a statistically significant association between donor age and nephrotoxicity among European and Asian populations. There is a note of warning by these authors that therapeutic drug monitoring of CNIs does not accurately suggest dose exposure-nephrotoxicity and could distract from its non-linear relationship.

Nephrotoxicity is evidenced by a rise in serum creatinine, hemodynamic milieu changes, increasing blood pressure and reduced glomerular filtration rate (GFR). The nephrotoxicity of CNIs tends to follow acute and subsequently chronic phase of kidney damage. CNIs cause vasoconstriction of arterioles and disruption of the tubulointerstitial environment. In explaining the late allograft dysfunction, histopathological findings of de novo focal segmental glomerulosclerosis together with hyalinosis of the arterioles and tubular atrophy may point to CNIs nephrotoxicity [16,17]. This was later found to be non-specific for chronic CNI toxicity as Mazur et al. [18] reported that bladder-drained pancreas transplant possibly contributed to these features. And to further support this, Snanoudj et al. [19] reported similar lesions in a control group who did not receive CNIs. Attempts to minimise or avoid CNIs have also not consistently reduced the risk of CAD. While Elite-Symphony study [20] showed reduced acute rejections with low dose tacrolimus, CNI avoidance failed to demonstrate a significant benefit in another study [21]. Therefore, whether the CAD could be largely explained by CNI nephrotoxic effects remain controversial. In a multicenter Deterioration of kidney Allograft Function (DeKAF) study [22], low rate of graft loss was seen in C4d negative biopsies compared with biopsies that were positive for C4d suggesting a significant contribution from antibody-mediated rejection rather than nephrotoxicity. The hypothesis of CNIs and CAD is, however, further supported with chronic nephrotoxicity seen in non-kidney transplant patients [23] and those treated for auto-immune diseases with almost 50% reduction in glomerular filtration rate when compared with those not treated with CNIs [24].

INFECTIONS AND CAD

Bacterial, viral and fungal infections could impact negatively on graft outcome. For example, the pro-inflammatory effects of the viral infection, with the release of cytokines (IL-1, 6, 8 and tumor necrosis factor), fibrotic and vasculopathy agents (TGF-β, platelet derived growth factor) contribute significantly to CAD and its progression. There are also reports of direct cytopathic effects. CMV infections can trigger acute rejection episodes and since its treatment and that of BK virus-associated nephropathy (BKVAN) come with a reduction in immunosuppression, it could be complicated by smoldering rejection with a resultant CAD. BK viremia is seen in 16 and 50% of patients and graft loss reported in 10-80% [25]. A subgroup analysis in a study by Giral et al. [26] and supported by a US data by Abbott et al. [27] also concluded that it has negative effects on graft survival.

Hepatitis C virus (HCV) infection is associated with poor allograft survival. The glomerular lesion in HCV infection is commonly membrano-proliferative GN. Less common are focal segmental glomerulosclerosis (FSGS), acute transplant glomerulopathy and renal thrombotic microangiopathy. It is also associated with development of diabetes mellitus in recipients which may contribute to CAD. Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) and cryoglobulinemia are uncommon causes of allograft dysfunction.

CELLULAR AND ANTIBODY MEDIATED REJECTION

Kidney grafts suffer from both early and late acute rejections. Antibody-mediated rejection is the main driver in CAD. More than 50% and almost all the participants in DeKAF study [22] and study by El-Zoghby et al. [28], respectively had background antibody-mediated immune process. Pre-transplant HLA-mismatches and the presence of donor-specific antibodies increased the risk of the immune cause of chronic allograft abnormality **(Table 1)**. In essence, more shreds of evidence for, than against, point to the significant contribution of the subtle immunological injury as being responsible for CAD rather the early suggestion of CNIs nephrotoxicity.

Kidney transplant biopsy becomes an important diagnostic tool here and using BANFF criteria **(Table 1)**, we can offer appropriate treatment for potentially treatable lesions based on classification [29]. Infections from CMV, polyoma BK virus or bacteria and drug non-compliance or complete stoppage of medications could also initiate rejection. Mullee et al. [30] reported a prevalence of 25% of non-compliant with a seven-fold increase in chronic graft loss.

CHRONIC ALLOGRAFT DYSFUNCTION (CAD)

Death with a functioning graft is the most frequent cause of graft loss and this is followed by CAD [31]. CAD replaced the initial chronic rejection of pre-Banff classification era. It is a diagnosis arrived at in the absence of nephrotoxicity, infections, acute rejection and other possible etiologies. It is a continuous deterioration in graft function and a histopathological diagnosis which represents not just the for-runner but the end of a continuum **(Figure 1)** of chronic graft loss with findings of hypertrophy of the glomeruli, focal glomerulosclerosis and increased lamellation of the basement membrane of peritubular capillaries, interstitial

fibrosis and tubular atrophy [32]. Risk factors are delayed graft function, prolonged cold ischemic time, donor age and vessels, CNI nephrotoxicity, untreated subclinical and vascular rejection and non-compliance.

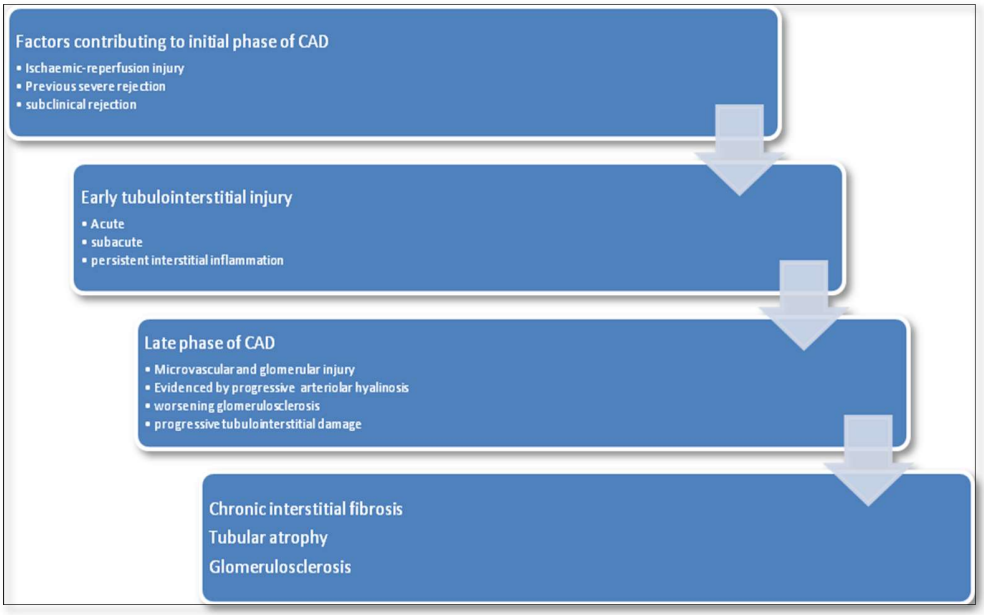

Figure 1. Time-dependent progressive injury in chronic allograft dysfunction.

A 'time-lag' association exists between serum creatinine and chronic allograft dysfunction (CAD). Evolution of the renal function by monitoring changes in GFR rather than an absolute >10% increase in serum creatinine is recommended. **Figure 1** summarises the factors and consequences in a time-dependent flow. Prompt intervention is required as once tubule-interstitial fibrosis and glomerulosclerosis are established, the injury is no longer reversible. Minimization and addition of other immunosuppressive agents such as everolimus [33] to low dose CNIs or total removal of CNIs and replacement with others to mitigate nephrotoxicity and vascular hyalinosis improve kidney function. However, we must strike a balance to ensure both treatments of smoldering acute rejection and prevention of its development. These modalities of minimization, withdrawal, conversion or complete avoidance of CNIs are reported to be beneficial in the early stage of CAD [34]. However, in the presence of severe proteinuria, conversion from CNIs to proliferative signal inhibitors (PSIs) such as everolimus or sirolimus is discouraged. In the same vein, high serum creatinine with concomitant low clearance predicts poor outcome [35]. Effectively, early conversion from CNIs is advisable when the chronic allograft nephropathy is not yet established or is early. The combination of everolimus and a lower dose of CNI also reduced the incidence of acute rejections [36-38].

Diekmann et al. [37] therefore advised that proteinuria greater than 800 mg/day and baseline creatinine clearance less than 40 ml/min in kidney recipients should preclude changing of CNIs to the PSIs as it could cause further deterioration in proteinuria, a significant predictor for rapid progression of kidney damage.

TRANSPLANT GLOMERULOPATHY

Transplant glomerulopathy (TG) was first described four decades ago. Baid-Agrawal et al. [39] recognized in their study of biopsies of 25 kidney grafts that TG is common in, but not only associated with chronic antibody mediated rejection (AMR). TG was also reported in T-cell-mediated rejection, thrombotic microangiopathy (TMA), an adverse effect of cyclosporine, hepatitis C virus infection and membrano-proliferative glomerulonephritis. In a study, TG causes chronic allograft dysfunction with two-thirds having nephrotic range proteinuria and usually no hematuria with or without hypertension and it is associated with reduced graft survival [40].

Age, medication non-compliance [41] and *de novo* donor specific antibody (DSA) [37] post-transplant increased the risk of TG. Kidney transplant biopsy is required to establish its diagnosis. Histology findings are; double contouring of the glomerular basement membrane, swelling of the endothelial and mesangial cells, mesangial matrix expansion and widening of the sub-endothelial zone.

Both glomerular and peritubular C4d may be present in TG suggesting the severity. The finding or absence of C4d has poor correlation with the presence of HLA antibodies. Non-HLA antibodies also contribute to the development and progression of TG as some of the patients failed to demonstrate C4d or HLA antibodies [42]. Early diagnosis of TG is again very important as not much could be achieved if

the intervention comes late. Unfortunately, there are no randomized trials conducted in the treatment of TG, but close surveillance of DSA, encouraging compliance and avoidance of rejections have been suggested by experts. Management of proteinuria with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is advocated. Plasma exchange in combination with immunoglobulin and rituximab reduce the risk of chronic AMR [43,44]. In the clinical trial by Eskandary et al. [45], bortezomib fails to improve chronic AMR and prevent graft loss while eculizumab shows some promise [46].

Recurrence of primary kidney disease or *de novo* glomerulonephritis

In patients with glomerulonephritis (GN) as the primary disease, 10-20% will have recurrence after initial treatment of GN and half of them will lose their graft [47]. In **Table 2**, the various primary diseases and graft loss is shown and in **Figure 3**, MPGN recurrence is the main factor responsible for graft loss once it recurs.

Table 2. Risk of primary kidney disease and graft loss.

Type of glomerulonephritis	Risk of recurrence (%)	Associated risk of graft loss (%)	References
FSGS	20-50	12.7-50	[48,49]
Membranous nephropathy	10-48	10-45.4	[50]
IgA Nephropathy	20-60	45-70	[51,52]
MPGN	27-65	16-88	[53-57]
Type I*	20-48	88	
Type II*	50-100	14.7	
New classification			
ICGN	43		
Polyclonal	30-35	10	
Monoclonal	66	50	
C-MPGN(NICE)	>70	>50	
C3GN	18-100	30-50	
DDD	80-90	25-50	
HUS			[58]
Non-infection-related	60	>90	
Factor H mutation	73.7	77.8	

FSGS: Focal Segmental Glomerulonephritis; CGN: Complement Mediated Membranoproliferative Glomerulonephritis; C3GN: C3 Glomerulonephritis; DDD: Dense Deposit Disease; HUS: Hemolytic Uremic Syndrome
** based on old classification*

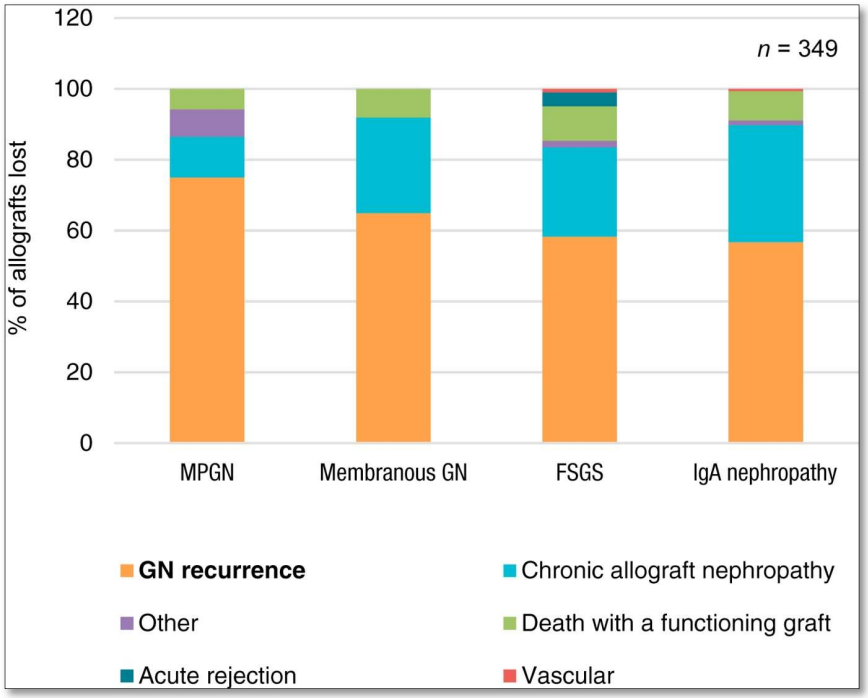

Figure 3. Etiology of allograft loss among recipients with recurrent glomerulonephritis.
Adapted from Allen et al. [66]

The Australia New Zealand Dialysis Transplant Data System (ANZDATA) [48] of 30 years-registry reported 10% prevalence of recurrent glomerulonephritis among almost 5000 patients followed up for a mean duration of 7.7 years with 50% losing their graft. Both ANZDATA and Renal Allograft Disease Registry (RADR) [48] showed an increasing prevalence of recurrence with post-transplant duration (2.9%, 9.8% and 18.5% at 2, 5 and 8 years, respectively in RADR). In ANZDATA study, only one-third with recurrent membrano-proliferative GN (MPGN) sustained their graft for 5 years while almost 60% who had a recurrence of focal segmental glomerulosclerosis (FSGS), IgA nephropathy and membranous nephropathy had graft survival for same 5 years. Recipients with any form of recurrence of GN are 2 times likely to lose their graft (HR 2.04 CI 1.81-2.31). Older recipient age (0.96 95% CI 0.94-0.97), use of steroid at baseline (0.54 95% CI 0.37-0.76) and increased total ischemic time (0.97 95% CI 0.96-0.99) reduced the risk of recurrence of IgAN but not FSGS. Young age of the recipient was independently predictive of IgA and FSGS recurrence.

The risk of recurrence with the second graft in FSGS is almost 100% if the first graft was lost from an FSGS recurrence. The recurrence in FSGS could be early (hours to days after transplantation) or late (months to years). Recurrence of idiopathic membranous nephropathy is usually detected around the second or third-year post-transplant and it could sometimes be earlier or later.

Membrano-proliferative GN has a variable rate of recurrence [60]. It is a common cause of recurrent disease depending on the type with dense deposit disease having the highest risk. There is immune-complex (ICGN) (monoclonal, oligoclonal or polyclonal) and complement-mediated (CGN) types (C3 glomerulopathy/dense deposit disease) [61]. The ICGN contains immunoglobulin and complement while CGN has only complement deposition. The ICGN has a higher rate of recurrence than the CGN, which could transform into another type of MPGN.

In true recurrence **(Table 3)** both the native and histological graft lesions would appear the same whereas, in *de novo* GN, it would show a new pathology with a different type of immunoglobulin for instance, in *de novo* membranous GN(MGN) which sometimes has a higher occurrence than recurrence MGN.

Table 3. Clinical and histological phenotypes of recurrent glomerular diseases [59].

Clinical classification	Histologic classification
1. True recurrence: Native and recurrence is the same 2. Transplant glomerulopathy with unknown primary disease **3.** The de novo disease which is the presence of new pathology in the kidney graft	1. Recurrent FSGS, MPGN, IgAN, MN, etc. 2. Recurrence of secondary glomerulonephritis, e.g. SLE, HSP, HUS/TTP, anti-GBM 3. Recurrence of metabolic or systemic disease, e.g. diabetic nephropathy, Fabry disease, scleroderma 4. *De novo* diseases, e.g. anti GBM disease in Alport syndrome, MN in a patient with ADPKD

HSP: Henoch-Scholein Purpura; SLE: Systemic Lupus Erythematosus; HUS: Hemolytic Uremic Syndrome; TTP: Thrombotic Thrombocytopenic Purpuria

The presence of crescents in the immune complex is a poor prognostic feature for the outcome of recurrence GN. Recurrence of MPGN is increased in high proteinuria, hypocomplementemia, the presence of monoclonal immunoglobulin, HLA B8, DR3, B49 and DR4. In a single centre study, more than 50% of recurrence of MPGN occurred during the first-year post-transplantation with 16%-88% losing their graft [62].

The risk of de novo MPGN, on the other hand, is associated with hepatitis C infection in almost half of the patients. In a French cohort [63], only 3.25% developed de novo ICGN type of MPGN. Only a few cases have been reported in CGN. Other factors are an active autoimmune disease or monoclonal gammopathy. These should be managed before the patient can be re-transplanted.

The treatment of recurrent MPGN is determined by the underlying cause. Eculizumab is found useful in C3 glomerulopathy and dense deposit disease [64]. Rituximab has been successfully used in idiopathic MPGN [65]. Steroids and/or plasma electrophoresis with cyclophosphamide had no breakthrough apart from immune-mediated MPGN.

MANAGEMENT

A transplant kidney biopsy, according to the committee in Banff 2013, is important to allocate a degree of fibrosis and tubular atrophy as a score with a view to acting in potentially treatable kidney lesions. Presence of interstitial fibrosis and tubular atrophy are associated with graft loss. Mannon et al. [67] reported that inflammation in areas of tubular atrophy is strongly correlated with graft loss. The recognition and suggestion by revised Banff classification **(Table 1)** on the use of surrogate markers to diagnose antibody-mediated rejection in the absence of detectable DSA, the description of chronic active ABMR and quantification of i-IFTA increased the predictive value of the new criteria [68]. In order to comprehensively uncover immunologic injury, HLA-C, HLA-DP and non-HLA antibodies should form part of the panel of tests. Further molecular testing could also be considered.

There is no specific consensus by the transplant community of how to manage CAD. Optimization and modification of the immunosuppressive medications are the current practice with many studies showing good outcomes. In a systematic review of randomized studies by Birnbaum and others [69], renal function improved in the Mycophenolate Mofetil (MMF) cohorts compared to CNI in four studies. Conversion of CNI to rapamycin showed better kidney function and histology in favor of rapamycin in two of four studies. Few single-centre studies showed improved kidney function; there was no significant positive outcome in four RCTs when cyclosporine was changed to tacrolimus [70,71]. Renal function improved significantly when MMF was added to CNI-based therapy with the latter later discontinued. Kidney function improved or stabilized in more than half of the patients when cyclosporine was withdrawn and replaced with mycophenolate mofetil. This group also had no loss of their kidney grafts [72].

Ji et al. [73] showed a significant reduction in lipid levels, proteinuria and hypertension when cyclosporine was converted to tacrolimus with trough levels of 5 and 10 µg/L. The kidney graft survived longer by ameliorating protein excretion, hypertension and the renin-angiotensin-aldosterone system inhibition. Renin-angiotensin-aldosterone system blockade improved kidney graft survival when compared with those without its use (6.3 vs. 1.8 years) [74].

Other co-morbidities such as hypertension, diabetes and hyperlipidemia should be managed and monitored. Sub-clinical and acute rejections should be avoided during the course of adjusting or conversion of immunosuppressive medications. Blood for CMV PCR and urine or blood for BKV are required for detection and monitoring of treatment. The presence of large T-antigen for SV40 in kidney biopsy is the gold standard of diagnosis of BKVAN. Reduction of

immunosuppression is still the basis of treatment of BKVAN.

PROGNOSIS

The poor prognostic factors are elevated creatinine, proteinuria and high DSA. The result of the biopsy, when reviewed, will further guide the prognosis or give assurance to the managing clinicians if the patient would benefit from any treatment depending on the histological findings and BANFF classification. Preventive measures with avoidance of or use of low dose CNIs, early detection, transplant biopsy and prompt intervention with modification of immunosuppressant are important determinants of the outcome of CAD.

CONCLUSION

Chronic allograft dysfunction is not a 'dead-end' nor 'one-size-fits-all' clinical scenario. As it shortens graft survival, efforts to investigate the specific etiology or contributing risk factors is a worthwhile endeavor in order to extend graft survival thus allowing patients to have a better quality of life considering the superiority of kidney transplant compared with any other modalities of renal replacement therapy.

REFERENCES

1. Scientific Registry of Transplant Recipients (2012) Annual Data Report. Available at: http://www.srtr.transplant.hrsa.gov
2. Solez K, Colvin RB, Racusen LC, Haas M, Sis B, et al. (2008) Banff '07 classification of renal allograft pathology: Updates and future directions. Am J Transplant 8: 753-760.
3. Opelz G, Dohler B (2005) Improved long-term outcomes after renal transplantation associated with blood pressure control. Am J Transplant 5: 2725-2731.
4. Kasiske BL, Anjum S, Shah R, Skogen J, Kandaswamy C, et al. (2004) Hypertension after kidney transplantation. Am J Kidney Dis 43: 1071-1081.
5. Myslak M, Amer H, Morales P, Fidler ME, Gloor JM, et al. (2006) Interpreting post-transplant proteinuria in patients with proteinuria pretransplant. Am J Transplant 6: 1660-1665.
6. Amer H, Cosio FG (2009) Significance and management of proteinuria in kidney transplant recipients. J Am Soc Nephrol 20: 2490-2492.
7. KDIGO (2009) Clinical practice guidlines for the care of kidney transplant recipients. Am J Transplant 9: S1-S157.
8. Amer H, Fidler ME, Myslak M, Morales P, Kremers WK, et al. (2007) Proteinuria after kidney transplantation, relationship to allograft histology and survival. Am J Transplant 7: 2748-2756.
9. Chen W, Kayler LK, Zand MS, Muttana R, Chernyak V, et al. (2015) Transplant renal artery stenosis: Clinical manifestations, diagnosis and therapy. Clin Kidney J 8: 71-78.
10. De Morais RH, Muglia VF, Mamere AE, Garcia Pisi T, Saber LT, et al. (2003) Duplex Doppler sonography of transplant renal artery stenosis. J Clin Ultrasound 31: 135-141.
11. Soyer P, Dohan A, Patkar D, Gottschalk A (2017) Observational study on the safety profile of gadoterate meglumine in 35,499 patients: The SECURE study. J Magn Reson Imaging 45: 988-997.
12. Abbas FM, Julie BM, Sharma A, Halawa A (2016) "Contrast nephropathy" in renal transplantation: Is it real? World J Transplant 6: 682-688.
13. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ (2003) Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 3: 178-185.
14. Kuo HT, Sampaio MS, Vincenti F, Bunnapradist S (2010) Associations of pretransplant diabetes mellitus, new-onset diabetes mellitus after transplantation and acute rejection with transplant outcomes: An analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. Am J Kidney Dis 56: 1026-1028.
15. Xia T, Zhu S, Wen Y, Gao S, Li M, et al. (2018) Risk factors for calcineurin inhibitor nephrotoxicity after renal transplantation: A systemic review and meta-analysis. Drug Des Devel Ther 12: 417-428.
16. Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, et al. (2018) Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. Clin Pharmacol Ther 98: 19-24.
17. Mihatsch MJ, Thiel G, Basler V, Ryffel B, Landmann J, et al. (1985) Morphological patterns in cyclosporine-treated renal transplant recipients. Transplant Proc 17: 101-116.
18. Mazur MJ, Rea DJ, Griffin MD, Larson TS, Prieto M, et al. (2004) Decline in native renal function early after bladder-drained pancreas transplantation alone. Transplantation 77: 844-849.
19. Snanoudj R, Royal V, Elie C, Rabant M, Girardin C, et al. (2011) Specificity of histological markers of long-term CNI nephrotoxicity in kidney transplant patients under low-dose cyclosporine therapy. Am J Transplant 11: 2635-2646.
20. Cosio FG, Frankel WL, Pelletier RP, Pesavento TE, Henry ML, et al. (1999) Focal segmental glomerulosclerosis in renal allografts with chronic

nephropathy: Implications for graft survival. Am J Kid Dis 34: 731-738.

21. Ekberg H, Tedesco-Silva H, Demirbas A, Vítko Š, Nashan B, et al. (2007) Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 357: 2562-2575.
22. Dean PG, Grande JP, Sethi S, Park WD, Griffin MD, et al. (2008) Kidney transplant histology after one year of continuous therapy with sirolimus compared with tacrolimus. Transplantation 85: 1212-1215.
23. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB (2003) Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 349: 931-940.
24. Vercauteren SB, Bosmans J, Elsevirs MM, Verpooten GA, De Broe ME (1998) A metaanalysis and morphological review of cyclosporine-induced nephrotoxicity in auto-immune diseases. Kidney Int 54: 536-545.
25. Dupont PJ, Manuel O, Pascual M (2010) Infection and chronic allograft dysfunction. Kidney Int 78: S47-S53.
26. Giral M, Pascuariello G, Karam G, Hourmant M, Cantarovich D, et al. (2002) Acute pyelonephritis and long-term kidney allograft outcome. Kidney Int 61: 1880-1886.
27. Abbott KC, Swanson SJ, Richter ER, Bohen EM, Agodoa LY, et al. (2004) Late urinary tract infection after renal transplantation in the United States. Am J Kidney Dis 44: 353-362.
28. Hardinger K (2018) Cyclosporine and tacrolimus nephrotoxicity.
29. Gaston RS, Cecka JM, Kasiske BL, Fieberg AM, Leduc R, et al. (2010) Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation 90: 68-74.
30. El-Zoghby ZM, Stegall MD, Lager DJ, Kremers WK, Amer H, et al. (2009) Identifying specific causes of kidney allograft loss. Am J Transplant 9: 527-535.
31. Mullee M, Mason JC, Peveler RC (2004) Frequency and impact of non-adherence to immunosuppressants following renal transplantation: A systematic review. Transplantation 77: 769-776.
32. ANZDATA (2004) Registry Report. Edited by McDonald S, Excell L. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia.
33. Chapman JR, O'Conell PJ, Nankivell BJ (2005) Chronic renal allograft dysfunction. JASN 16: 3015-3026.
34. Seron D, Arns W, Chapman JR (2008) Chronic allograft nephropathy- clinical guidance for early detection and early intervention strategies. Nephrol Dialys Transpl 23: 2467-2473.
35. Pascual J (2005) Concentration-controlled everolimus (Certican): Combination with reduced dose calcineurin inhibitors. Transplantation 79: S76-S79.
36. Diekmann F, Budde K, Oppenheimer F, Fritsche L, Neumayer HH, et al. (2004) Predictors of success in the conversion from calcineurin inhibitor to sirolimus in chronic allograft dysfunction. Am J Transplant 4: 1869-1875.
37. Diekmann F, Campistol JM (2006) Conversion from calcineurin inhibitors to sirolimus in chronic allograft nephropathy: Benefits and risks. Nephrol Dial Transplant 21: 562-568.
38. Tedesco H, Vitko S, Pascual J, Eris J, Magee JC, et al. (2007) 12 month safety and efficacy of everolimus with reduced exposure cyclosporine in *de novo* renal transplant recipients. Transplant Int 20: 27-36.
39. Baid-Agrawal S, Farris AB, Pascual M, Mauiyyedi S, Farrell ML, et al. (2011) Overlapping pathways to transplant glomerulopathy: Chronic humoral rejection, hepatitis C infection and thrombotic microangiopathy. Kidney Int 80: 879-885.
40. Eng HS, Bennett G, Chang SH, Dent H, McDonald SP, et al. (2011) Donor human leukocyte antigen-specific antibodies predict development and define prognosis in transplant glomerulopathy. Hum Immunol 72: 386-391.
41. Allen PJ, Chadban SJ, Craig JC, Lim WH, Allen RDM, et al. (2017) Recurrent glomerulonephritis after kidney transplantation: Risk factors and allograft outcomes. Kidney Int 92: 461-469.
42. Dinavahi R, George A, Tretin A, Akalin E, Ames S, et al. (2011) Antibodies reactive to non-HLA antigens in transplant glomerulopathy. J Am Soc Nephrol 22: 1168-1178.
43. Lefaucheur R, Nochy D, Andrade J, Verine J, Gautreau C, et al. (2009) Comparison of combination plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. Am J Transpl 9: 1099-1107.
44. Sellarés J, de Freitas DG, Mengel M, Reeve J, Einecke G, et al. (2012) Understanding the causes of kidney transplant failure: The dominant role of antibody-mediated rejection and non-adherence. Am J Transplant 12: 388-399.
45. Eskandary F, Regele H, Baumann L, Bond G, Kozakowski N, et al. (2018) A randomized trial of bortezomib in late antibody-mediated kidney transplant rejection. JASN 29: 591-605.

46. Stegall MD, Chedid MF, Cornell LD (2012) The role of complement in antibody-mediated rejection in kidney transplantation. Nat Rev Nephrol 8: 670-678.

47. Salvadori M, Tsalouchos A (2019) Recurrence of primary glomerulonephritis after renal transplantation. Junipers Publishers.

48. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ (2002) Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 347: 103-109.

49. Amaral S, Neu A (2016) Recurrent FSGS post-kidney transplant: Moving the needle forward. CJASN 11: 1932-1934.

50. Ponticelli C, Traversi L, Banfi G (2004) Renal transplantation in patients with IgA mesangial glomerulonephritis. Pediatr Transplant 8: 334-338.

51. Soler MJ, Mir M, Rodriguez E, Orfila A, Munne A, et al. (2005) Recurrence of IgA nephropathy and Henoch-Schönlein purpura after transplantation: Risk factors and graft survival. Transplant Proc 37: 3705-3709.

52. Green H, Rahamimov R, Rozen-Zvi B, Pertzov B, Tobar A, et al. (2015) Recurrent membranoproliferative glomerulonephritis type I after kidney transplantation: A 17-year single centre experience. Transplantation 99: 1172.

53. Andresdottir MB, Assmann KJ, Hoitsma AJ, Koene RA, Wetzels JF (1997) Recurrence of type I membranoproliferative glomerulonephritis after renal transplantation: Analysis of the incidence, risk factors and impact on graft survival. Transplantation 63: 1628.

54. Braun MC, Stablein DM, Hamiwka LA, Bell L, Bartosh SM, et al. (2005) Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: The North American Pediatric Renal Transplant Cooperative Study experience. J Am Soc Nephrol 16: 2225-2233.

55. (2019) Prevention of recurrence of C3 glomerulopathy post-transplant: Eculizumab. NICE Evidence summary. Published 2015. Available at http://www.nice.org.uk/guidance/esuom44

56. Zand L, Lorenz EC, Cosio FG, Fervenza FC, Nasr SH, et al. (2014) Clinical findings, pathology and outcomes of C3GN after kidney transplantation. J Am Soc Nephrol 5: 1110-1117.

57. Bresin E, Daina E, Noris M, Castelletti F, Stefanov R, et al. (2006) International Registry of Recurrent and Familial HUS/TTP: Outcome of renal transplantation in patients with non-Shiga toxin-associated hemolytic uremic syndrome: Prognostic significance of genetic background. Clin J Am Soc Nephrol 1: 88-99.

58. (2006) Australia and New Zealand Dialysis and Transplant Registry: The 29th Annual Report. Available at: http://www.anzdata.org.au

59. Golgert W, Appel GB, Hariharan S (2008) Recurrent glomerulonephritis after renal transplantation: An unresolved Problem. Clin J Am Soc Nephrol 3: 800-807.

60. Hariharan S, Peddi VR, Savin VJ, Johnson CP, First MR, et al. (1998) Recurrent and *de novo* renal diseases after renal transplantation: A report from the renal allograft disease registry. Am J Kidney Dis 31: 928-931.

61. Abbas F, El Kossi M, Jin JK, Sharma A, Halawa A (2017) *De novo* glomerular diseases after renal transplantation: How is it different from recurrent glomerular diseases? World J Transplant 24: 285-300.

62. Alasfar S, Carter-Monroe N, Rosenberg AZ, Montgomery RA, Alachkar N, et al. (2016) Membranoproliferative glomerulonephritis recurrence after kidney transplantation: Using new classification. BMC Nephrol 17: 7.

63. Roth D, Cirocco R, Zucker K, Ruiz P, Viciana A, et al. (1995) *De novo* membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. Transplantation 59: 1676-1682.

64. Gurkan S, Fle B, Weiss L, Xiao X, Zhang Y, et al. (2013) Eculizumab and recurrent C3 glomerulonephritis. Pediatr Nephrol 28: 1975-1981.

65. Guiard E, Karras A, Plaiser E, Huyen JPDV, Fakhouri F, et al. (2011) Patterns of non-cryoglobulinaemic glomerulonephritis with monoclonal Ig deposits: Correlation with IgG subclass and response to rituximab. Clin J Am Soc Nephrol 6: 1609-1616.

66. Mannon RB, Matas AJ, Grande J, Leduc R, Connett J, et al. (2010) Inflammation in areas of tubular atrophy in kidney allograft biopsies: A potent predictor of allograft failure. Am J Transplant 10: 2066-2073.

67. De Serres, Noel R, Cote I, Lapointe I, Wagner E, et al. (2016) Comparison of predictive value of Banff 2013 vs. Banff 2007 criteria for chronic, active ABMR. Am J Transplant 16: 1515-1525.

68. Loupy A, Haas M, Solez K (2017) The Banff 2015 kidney meeting report: Current challenges in rejection classification and prospects for adopting molecular pathology. AJT 17: 28-41.

69. Birnbaum LM, Lipman M, Paraskevas S, Chaudhury P, Tchervenkov J, et al. (2009) Management of chronic allograft nephropathy: A systematic review. CJASN 4: 860-865.

70. Cantarovich D, Renou M, Megnigbeto A, Giral-Classe M, Hourmant M, et al. (2005) Switching from

cyclosporine to tacrolimus in patients with chronic transplant dysfunction or cyclosporine-induced adverse events. Transplantation 79: 72-78.

71. Dudley C, Pohanka E, Riad H, Dedochova J, Wijngaard P, et al. (2005) Mycophenolate mofetil substitution for cyclosporine A in renal transplant recipients with chronic progressive allograft dysfunction: The "Creeping Creatinine" study. Transplantation 79: 466-475.

72. Ji SM, Li LS, Sha GZ, Chen JS, Liu ZH (2007) Conversion from cyclosporine to tacrolimus for chronic allograft nephropathy. Transplant Proc 5: 1402-1405.

73. Artz MA, Hilbrands LB, Borm G, Assmann KJM, Wetzels JFM (2004) Blockade of the renin-angiotensin system increases graft survival in patients with chronic allograft nephropathy. Nephrol Dial Transplant 19: 2852-2857.