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CKJ REVIEW

Kidney transplant in patients with C3 glomerulopathy

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ABSTRACT

Complement protein 3 (C3) glomerulopathy (C3G) is a rare and progressive kidney disease primarily affecting young individuals and frequently advancing to end-stage kidney disease (ESKD). For ESKD, kidney transplantation remains the optimal treatment option; however, C3G has a high recurrence rate post-transplantation, affecting over two-thirds of transplanted patients. Despite advances in our understanding of C3G, significant gaps persist regarding the optimal timing for transplantation and the best strategies for peri-transplant management. Currently, no clear evidence links functional complement levels to the risk of post-transplant recurrence. Genetic counseling is also complex, due to variable gene penetrance and weak genotype–phenotype correlations, which limit predictive accuracy.
Transplant-related factors are believed to significantly influence C3G recurrence, yet there are no established methods for preventing recurrence after transplantation. Eculizumab has shown inconsistent efficacy in managing recurrent C3G. However, new proximal complement inhibitors, such as factor B and C3 inhibitors, are under investigation in clinical trials and show promise. Some of these trials include kidney transplant patients with C3G, and their outcomes could potentially shape future treatment protocols.

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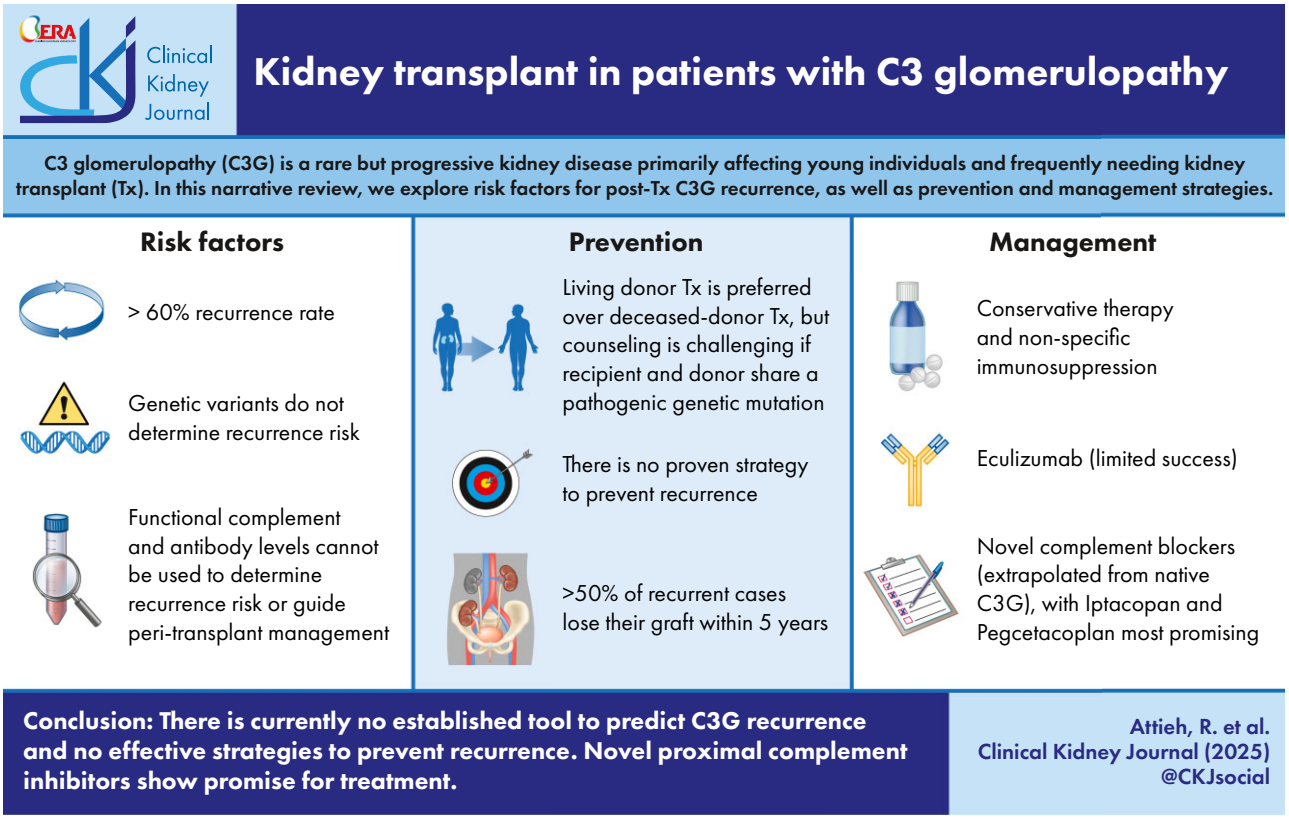
GRAPHICAL ABSTRACT



Keywords: alternative complement pathway, C3 glomerulopathy, eculizumab, kidney transplant, recurrent disease

INTRODUCTION

Complement protein 3 (C3) glomerulopathy (C3G) is a rare glomerular disease with an estimated incidence of 1–3 cases per million per year [1]. It presents with hematuria, varying degrees of proteinuria and renal failure. Over half of patients reach end-stage kidney disease (ESKD) within 10 years of diagnosis and recurrence rate following kidney transplantation is elevated, often leading to allograft loss [2, 3].

The pathophysiology of C3G is complex, involving dysregulation at multiple levels along the alternative complement pathway (ACP), leading to its constant uncontrolled activation [4]. These abnormalities of the ACP can be either inherited or acquired [5]. The degree of downstream dysregulation at the level of the C5 convertase is believed to drive differences in pathological expression, with C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) at the two ends of the phenotypic spectrum [6].

This review explores the risk factors for recurrence of C3G following kidney transplantation, as well as prevention and management strategies. We also highlight key controversial areas surrounding kidney transplantation in patients with C3G.

RECURRENCE RATE IN RENAL ALLOGRAFTS

Recurrence of C3G after kidney transplantation is mostly described in small retrospective cohorts and case series, with fewer than 150 cases reported to date [2, 3, 7–12]. The presentation at recurrence can vary significantly, depending on the timing and indication for kidney allograft biopsy. Early recurrences may present as delayed graft function (DGF) with heavy proteinuria, while more typical recurrences are usually subacute, characterized by varying degrees of proteinuria, hematuria and gradually worsening allograft function [3]. C3G recurs in 60%–90% of patients, with similar recurrence rates in C3GN and DDD [3]. A summary of the reported literature is presented in Table 1.

There appears to be some variability in recurrence rates and timing across landmark studies. The shorter time-to-recurrence and higher recurrence rates observed in more recent series are likely attributable to the performance of surveillance biopsies and the use of more relaxed pathological criteria for diagnosing C3G, with an increased reliance on electron microscopy (EM) to detect histological recurrence at earlier stages. In the most recent series describing C3G post-transplant by Tarragon *et al.*, 18 patients were evaluated, including 12 with C3GN and 6 with DDD. Histologic recurrence was observed in 89% of patients at a median of 33 days post-transplant (range: 13–141 days) [12]. However, 38% of these recurrences were subclinical, identified only through protocol biopsies. Less than one-third of patients had proteinuria exceeding 300 mg/g at the time of recurrence. The time to recurrence was similar for both C3GN and DDD patients.

Table 1: Retrospective case series investigating recurrence of C3G post-transplant.

	Andresdottir *et al.* (1999) [7]	Zand *et al.* (2014) [3]	Regunathan-Shenk *et al.* (2019) [2]	Kumar *et al.* (2021) [15]	Caravaca-Fontán (2023) [8]	Tarragon *et al.* (2024) [12]
Number of patients	13 (all DDD)	21 (all C3GN)	19 (12 C3GN, 7 DDD)	21 (12 C3GN, 9 DDD)	34 (26 C3GN, 3 DDD, 5 unspecified C3G)	18 (12 C3GN, 6 DDD)
Date of kidney transplant	1983–1994	1996–2010	1999–2016	Unclear (biopsies performed 2012–2017)	1981–2021	2016–2023
Median age at transplant (years)	23	35.5	28	NR	47	31
Median follow-up duration (months)	29	73.9	76	50 (5–140)	53 (24–140)	37 (18–56)
Recurrence rate	62%	67%	84% (83% in C3GN and 86% in DDD)	67% DDD, 42% C3GN	62% (42% in C3GN and 100% in DDD)	89% (92% in C3GN and 83% in DDD)
Proportion of LRKTx	8%	Not specified	47%	81%	0%	50%
Autoantibodies (CFB Ab, CFH ab, C3Nef) detected (out of patients tested)	NR	NR	70%	0%, 11% and 44% of DDD cases, respectively, and in 17%, 17% and 33% of C3GN cases, respectively	12%	33%
Genetic complement mutations (out of patients tested)	NR	NR	30%	non-pathogenic CFH gene variants in 93%	29% with pathogenic variants and 3% VUS	50%
Paraproteins detected (out of patients tested)	NR	21%	43%	NR	0%	0%
Median time-to recurrence (months post-transplant)	2.9	28	14 in C3GN, 15 in DDD	16 in C3GN, 8 in DDD	14 (3–81)	1.1 (0.5–4.7)
Detection of recurrence	85% on for-cause biopsy	71% on for-cause biopsy	94% on for-cause biopsy	100% on for-cause biopsy	Most (unspecified) on for-cause biopsy	62% on for-cause biopsy
Median eGFR at recurrence (mL/min/1.73 m^2)	NR	NR	NR	NR	30 (16–44)	42
Patients with proteinuria at recurrence	100%	NR	31%	36%	67%	31%
Median proteinuria at recurrence	NR	799 mg/24 h (22–4288)	NR	1.75 g/day	3.5 g/day (1.5–6.8)	0.26 g/g
Hematuria at recurrence (out of patients tested)	NR	43%	25%	NR	33%	44%
Low C3 at recurrence (out of patients tested)	50%	45%	NR	100% in C3GN, 89% in DDD	?	36%
Transcriptomic analysis	N/A	Not performed	Not performed	Not performed	Not performed	No characteristic transcriptomic signals
Graft failure in patients with recurrent C3G	62%	50%	47% (25% in C3GN and 86% in DDD)	38% in C3GN and 56% in DDD	57%	0%
Median time from transplant to graft failure (months)	14	18	42	44 in C3GN, 10 in DDD	NR	N/A
Receipt of anti-complement therapy	None	None	37%	None	43%	25% in C3GN, 17% in DDD

For cause biopsy reasons: one or more of the following: acute kidney injury, proteinuria, hematuria, DGF, elevated serum creatinine of unclear cause.
LRKTx: transplant from living related kidney donor; NR, not reported; VUS: variant of undetermined significance.

Table 2: Major transplant-related differences between C3G and aHUS.

	aHUS	C3G
Risk of recurrence [3, 62]	6%–78%	60%–90%
Frequency of genetic mutation or complement abnormality [2, 62, 63]	CFH: 24%–46% MCP: 5.5%–7% THBD: 0%–5% C3: 4%–7% CFI: 4%–16% CFB: 1.8% Combined: 3%–7%	C3Nef: 11%–56% CFHR5: 10%–11% CFH: 9%–10% CFI: 2%–11% CD46: 11% MCP: 1%
Recurrence of disease with or without pre-emptive eculizumab [64–66]	6.3% -11% vs 53%–89%	No evidence to support pre-emptive use of eculizumab
Time to recurrence [12, 67]	Bimodal: Early: median 3 months (0.3–8.8) Late: median 46 months (18–69)	Median: 13–41 days (13–141 days)
Available treatments for recurrence of disease [2, 12, 47, 67, 68]	Eculizumab Plasma exchange Rituximab Plasma exchange	Glucocorticoid Mycophenolate mofetil Calcineurin inhibitors Eculizumab Plasma exchange Rituximab Corticotropin
Outcomes after use of eculizumab for recurrent disease [2, 67]	Improvement or stabilization of kidney function: 91%–93%	Improvement or stabilization of kidney function: 33%–57%

HISTOLOGIC FEATURES OF RECURRENCE

There is significant overlap in the histologic features of recurrent C3GN and DDD, and no distinct transcriptomic signatures specific to C3G recurrence compared with other glomerular diseases. Recurrent C3G post-transplant can manifest with a spectrum of histologic findings on light microscopy, including mesangial hypercellularity, mesangial or endocapillary proliferation, membranoproliferative glomerulonephritis (MPGN), crescentic GN or sclerosing lesions. In some cases, especially when diagnosed early through protocol biopsies, patients may even show normal glomerular cellularity. These patients typically have normal renal function and minimal proteinuria, suggesting that histologic recurrence may precede clinical recurrence. As recurrence evolves, mesangial hypercellularity becomes the most common pattern, followed by progression to MPGN in 20%–30% of patients [12].

A dominant C3 on immunofluorescence (IF) is a diagnostic pre-requisite, similar to native kidney C3G. However, in recurrent C3G, C3 staining tends to be more subtle in intensity and may appear focal and segmental, rather than diffuse and global as seen in native C3G. In about half of the cases, C3 staining is isolated, while in the other half, C3 is dominant, accompanied by immunoglobulin G (IgG) staining. Importantly, C3 staining is typically at least two orders of magnitude more intense than the other immune reactants [8, 12]. C1q is typically negative.

EM can have deposits in subendothelial, mesangial or subepithelial spaces. In C3GN, there is isolated C3 fragment deposition in the mesangium, whereas, in DDD, dense deposits are mainly present in the lamina densa of the glomerular basement membrane [1]. However, significant overlap exists between both conditions [6, 13]. Unlike the highly dense sausage-shaped deposits in native DDD, recurrent DDD cases have “waxy” and ill-defined deposits (similar to C3GN) which persist in all patients on protocol biopsies performed at 1 and 2 years after transplant.

More recently, immunohistochemical staining for Apolipoprotein E (ApoE) has been found to mirror C3 deposits in over 80% of DDD cases, but not in C3GN. Therefore, ApoE staining has been proposed as an adjunct tool to help differentiate C3GN from DDD, especially when EM is unavailable [14]. However, as these findings were mostly in native kidney C3G, it remains to be determined whether ApoE staining is also useful in renal allografts.

Thrombotic microangiopathy (TMA) with C3 dominant or codominant staining on IF has also been reported in some patients with native kidney C3G and recurrence post-transplant [2, 15]. Regunathan-Shenk *et al.* described two patients with C3G recurrence manifesting as TMA on allograft biopsy. Both had concurrent monoclonal gammopathy (MG) indicating the potential for monoclonal proteins in triggering the ACP [2].

RISK FACTORS FOR C3G RECURRENCE IN RENAL ALLOGRAFTS

Risk factors for C3G recurrence include the type of genetic mutation(s) in the recipient, the degree of functional complement activation at the time of kidney transplantation, donor-derived factors, factors related to transplant surgery itself or a combination of these elements. Additionally, young age at diagnosis of native kidney, an aggressive course of disease in the native kidneys (e.g. crescentic GN with rapid progression) [16, 17], male sex [18] and pre-emptive transplantation [19] are associated with a higher risk of recurrence. While these factors can sometimes help guide clinical decisions and patient counseling, there is currently no reliable tool for predicting C3G recurrence. The main differences in transplant considerations between TMA and C3G are summarized in Table 2.

Genetic factors

The genes involved in the ACP include C3, complement factor B (CFB), complement factor I (CFI), complement factor H (CFH), CD46 (Membrane Cofactor Protein), diacylglycerol kinase epsilon (DGKE), thrombomodulin (THBD), properdin and complement

factor H receptors (CFHRs 1, 2, 3, 4A, 4B and 5) [20]. CFH acts as a cofactor for CFI to inactivate the C3 convertase. A pathogenic complement mutation is identified in only 20%–29% of cases of recurrent C3G [8, 16]. In addition, patients with C3G often carry multiple genetic mutations, complicating the analysis of recurrence rates associated with specific mutations. For example, Garg *et al*. described a patient with both CFH and CFI mutations who experienced early C3G recurrence, presenting as prolonged DGF [21]. Some patients with recurrence may also carry variants of uncertain significance.

CFHR gene abnormalities leading to fusion proteins are the most common genetic alterations in C3G and can be inherited in families. For instance, Cypriot family nephritis, also known as CFHR5 nephropathy, results from exon duplication in the *CFHR5* gene leading to activation of the ACP [22, 23]. Familial C3G has also been associated with a hybrid *CFHR3-1* gene, which is linked to a high rate of recurrence [24]. *CFHR1-5* copy number variations should be tested using multiplex ligation-dependent probe amplification (MLPA) [25].

While recognizing the existence of familial C3G is important, a recent consensus document from the American Society of Transplantation Kidney-Pancreas Community of Practice and the Pediatric Community of Practice emphasized that genetic variants do not determine the risk of disease recurrence in C3G. The workgroup stressed that genetic testing is not a diagnostic tool for C3G and does not provide sufficient prognostic information to guide decisions regarding candidacy for kidney transplant [26]. This perspective aligns with recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which note that there is insufficient evidence to reliably assess recurrence risk based on genetic testing due to variability in gene penetrance and phenotypic expression, even in monogenic forms of the disease [27].

In addition to complement mutations, certain recipient HLA haplotypes have been associated with an increased risk of recurrence in type 1 MPGN. A large-scale whole-genome sequencing study identified the HLA loci DQA1*05:01, DQB1*02:01 and DRB1*03:01 as being associated with primary MPGN, including C3G [10]. The HLA haplotype B8DR3 has also been linked to a higher risk of recurrence in these patients [28].

Functional complement activation (acquired factors)

C3G is driven by circulating factors, particularly acquired autoantibodies (nephritic factors) targeting complement proteins and C3 or C5 convertases [1, 29]. Pre-transplant autoantibody testing includes anti-CFH antibodies (CFH-Ab), C3 nephritic factor (C3Nef), C5 nephritic factor (C5Nef) and anti-CFB antibodies. Baseline functional complement testing includes serum levels of C3, C4, CFB, CFI, CFH, serum membrane attack complex (sMAC), membrane cofactor protein (MCP), CH50 (total complement activity test), AP50 (alternative complement pathway activity test), properdin and decay-accelerating factor (DAF). Low serum C3 levels have been reported as a risk factor for recurrent disease [17, 30]. However, a normal serum C3 level does not negate the risk of recurrence.

Most studies evaluating CFH-Ab have been conducted in patients with atypical hemolytic uremic syndrome (aHUS) [7, 25, 31, 32], with only a few examining its role in C3G. Kumar *et al*. found CFH-Ab in 17% of recurrent DDD patients and 25% of recurrent C3GN patients, with cases showing low CFH levels [15]. On the other hand, C3Nef, an autoantibody that stabilizes the C3 convertase, is found in over half of native C3G cases [29], and 11%–37% of recurrent cases [2, 8]. High levels of C3Nef and/or C5Nef have been linked to low C3 levels and increased sMAC levels [31]. However, serum levels of C3Nef and C5Nef do not reliably predict the risk of recurrence of DDD in renal allografts [32].

It is important to note that there is currently insufficient evidence to support a consistent association between functional complement levels or antibody levels and the risk of recurrence after transplant. Therefore, baseline testing can only serve as reference in case better-targeted therapies become available in the future. In other words, complement protein and autoantibody levels available to date cannot be used to guide decisions regarding the timing of transplantation or peri-transplant management.

Monoclonal gammopathy

C3G patients presenting after age 50 years should be screened for MG [27]. MG-related C3GN has a very high rate of recurrence [8], and can recur as early as 9 days post-transplant [3]. Recurrence after transplantation tends to be more aggressive when associated with MG [3, 16, 30]. One hypothesis explaining this finding is that monoclonal immunoglobulins inhibit the function of complement regulatory proteins by acting as an autoantibody [33]. Excess circulating lambda light chains, for example, can function as CFH autoantibodies, triggering uncontrolled activation of the ACP [34]. Monoclonal immunoglobulins can also act as C3NeF [11]. When MG is suspected as the underlying cause of C3G, pronase digestion of biopsy specimens should be performed to unmask any hidden paraproteins. However, MG-related C3G can still occur despite the absence of monoclonal deposits on the biopsy. It is crucial to make this distinction, as treating the underlying B-cell disorder can significantly improve renal outcomes in these patients [35].

Factors related to transplant

Despite the lack of robust evidence specific to C3G, some experts advise against transplantation during periods of active inflammation and acute renal loss [36]. However, C3G recurrence is influenced not only by recipient-related factors, but also by donor and graft factors. Activation of the ACP in the donor or graft, whether before, during or after transplantation, can inflict significant damage on the allograft, leading to a gradual decline in functional mass [18, 37, 38].

Ischemia–reperfusion injury is an important trigger of ACP activation at the time of transplant [39], as hypoxia can increase local production of C3 and properdin [16]. Complement activation can also occur post-transplant, often due to infections, potentially triggering a recurrence.

Other factors such as cold ischemia time, degree of HLA mismatch antigen, the use of induction therapy, the choice of maintenance therapy and occurrence of rejection episodes were not found to be associated with increased risk of MPGN (including C3G) recurrence on univariate analysis in a large retrospective study [8].

Donor selection

There is insufficient evidence to suggest that the potential risk of C3G recurrence with living donor kidney transplant negates its substantial benefits over deceased donor transplant. Therefore, it is not currently recommended to advise kidney transplant candidates with C3G to wait for a deceased donor transplant if living donor options are available.

Although some reports have indicated an increased tendency towards C3G recurrence with living donors [16, 30],

this association has not been consistently replicated in other studies [8, 17]. In fact, living-related donor organs have been shown to offer significantly better 5-year survival compared with cadaveric donor organs among DDD patients (66 ± 11% vs 34 ± 10% respectively; $P = .004$) [40]. Furthermore, a propensity score-matched analysis of 28 living donors (not all related) evaluating long-term outcomes of kidney donation to patients with alternative complement pathway diseases found no increased risk of *de novo* C3G or aHUS [41]. This may be due to the fact that receiving a living donor kidney causes significantly less ischemia–reperfusion injury and less elevation of sMAC levels compared with deceased donor kidney transplants [42].

Nonetheless, the presence of a pathogenic genetic mutation in an asymptomatic living-related donor candidate should still prompt extensive discussions before approving the donor. The recipient is typically phenotyped first, followed by donor testing for the corresponding variant [43]. Counseling becomes even more challenging if the donor and recipient share variants of undetermined significance [44], which are commonly found in the general population, such as copy number variations in the CFH and CFHR genes [25]. In these patients, accepting a potential living related donor is more debatable.

STRATEGIES FOR PREVENTION OF C3G RECURRENCE

There is no proven optimal strategy for the prevention of C3G recurrence, and the evidence supporting the prophylactic use of complement blockade in C3G is limited. However, it is generally accepted that patients with C3G related to MG should be treated with clone-directed therapies prior to transplantation for the best outcomes. In cases of C3G with concurrent TMA but without MG, the prophylactic use of eculizumab to prevent recurrence may be considered, despite the lack of strong supporting evidence.

Although the choice of post-transplant induction and/or maintenance immunosuppression regimen has not been shown to be effective in preventing C3G recurrence, one might consider switching to alternative "endothelial-protective" maintenance immunosuppression (such as belatacept or mammalian target of rapamycin inhibitors) in place of calcineurin inhibitors, to avoid the combined effect of calcineurin inhibitors (CNIs) and complement mutations on complement pathway activation [45]. There is also insufficient evidence to recommend protocol biopsies in the absence of definitive therapy targeting the precise pathogenic mechanism [16]. Identifying recurrence at the preclinical stage may not alter patient prognosis without an effective treatment for C3G.

MANAGEMENT OF RECURRENT C3G

The management of C3G in an allograft is largely based on our understanding of the disease's pathophysiology in the native kidney. When possible, efforts should be made to identify any genetic abnormalities or pathogenic antibodies as this may potentially guide future therapies or enrollment in clinical trials. Figure 1 illustrates our suggested algorithm to guide therapy of recurrent C3G.

Conservative management

All patients should receive conservative therapy with renin–angiotensin–aldosterone system inhibition (RASi) for proteinuria reduction, strict blood pressure control and individual cardiovascular risk–based lipid management. This recommendation is extrapolated from the management of native proteinuric kidney disease. While proteinuria reduction aligns with that in native kidney disease, available data do not indicate kidney failure reduction in proteinuric kidney transplant recipients treated with RASi compared with placebo [46]. Therefore, individualized decisions should be made weighing benefits and risks when prescribing RASi in kidney transplant recipients. Adding sodium-glucose co-transporter 2 inhibitors to control proteinuria is reasonable although these agents are not specifically studied in C3G.

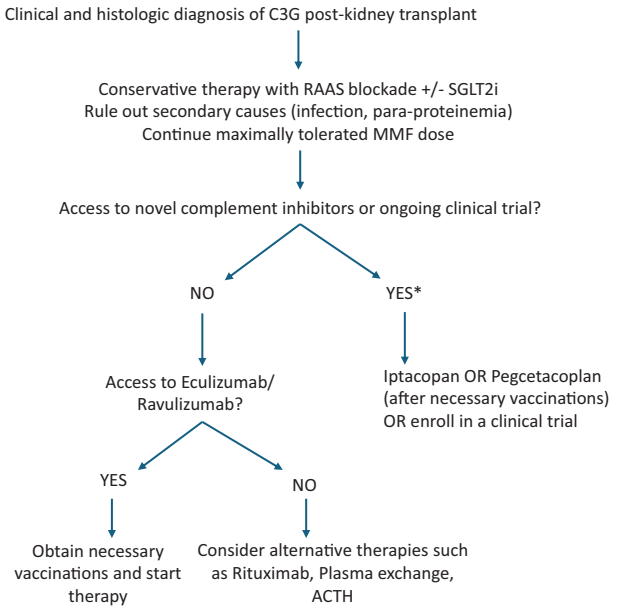


Figure 1: Proposed algorithm for the management of C3G post-kidney transplant in adults aged ≥18 years. Given the lack of randomized controlled trials, this algorithm is largely based on available evidence from case series and expert opinion. *In patients with rapidly progressive kidney failure or advanced histopathological chronicity, treatment must be individualized as they were typically excluded from clinical trials. Most centers would use other therapies as well, such as prompt plasma exchange or eculizumab, based on case reports.

Non-specific immunosuppression

In addition to CNIs, most kidney transplant patients who experience recurrence are already on mycophenolate mofetil (MMF) and prednisone, both of which are well-studied in the treatment on native C3G [12]. The proposed mechanism of action of MMF in C3G is a reduction of intraglomerular inflammation although this has not been proven. It is unclear why patients recur despite being on an effective regimen for native kidney C3G. One explanation is that post-transplant recurrent disease represents a more aggressive phenotype of C3G that has not responded to therapy in the native kidney. In a study of 60 pediatric C3G patients, patients with an identified genetic mutation were not different in terms of MMF treatment response and kidney survival from patients without an identified mutation [47].

In patients with moderate disease [defined as slowly declining estimated glomerular filtration rate (eGFR) and proteinuria >1.5–3.5 g/day] or severe disease (marked by rapidly worsening eGFR or proteinuria >3.5 g/day), intensification of maintenance immunosuppression can be considered by increasing MMF and steroids. This is typically followed by rituximab or plasma

exchange in individual cases based on physician discretion. However, available evidence does not support this approach as it has not been proven to prolong allograft survival and carries a risk of opportunistic infections such as BK nephropathy [2]. In this respect, Caravaca-Fontán *et al*. found that treatment with either an increased dose of corticosteroids or MMF did not change the risk of progression [hazard ratio (HR) 0.44, 95% confidence interval (CI) 0.15–1.29, $P = .14$ and HR 0.72, 95% CI 0.20–2.65, $P = .47$ respectively] [8].

Complement inhibition with eculizumab

Eculizumab is a recombinant, fully humanized IgG2/IgG4 monoclonal antibody, targeted against the human C5 complement protein. It thereby prevents C5a and C5b formation with their downstream effects. Eculizumab is the standard of care in managing TMA characterized by excess terminal complement pathway activation. However, in C3G, the complement abnormality starts higher up in the complement cascade at the level of the C3 convertase. Eculizumab does not inhibit C3 convertase activity or glomerular C3 deposition, allowing persistent inflammation through C3a (an anaphylatoxin) and C3b (an opsonin). Therefore, eculizumab has not been shown to be consistently effective [48].

A meta-analysis and systematic review by the Mayo Group [49] encompassed 12 studies of 122 patients. For treated patients, the pooled rate of allograft loss was 33% with eculizumab, 42% with therapeutic plasma exchange and 81% with rituximab. When stratified by disease subgroup, eculizumab was associated with lower rates of graft loss in C3GN (22% versus 56% for TPE and 70% for rituximab), with limited data in dense deposit disease (53% rate of allograft loss with eculizumab). The pooled risk of allograft loss for those not receiving treatment was 32%. Data on the soluble membrane attack complex (sMAC) was available for only seven patients. In total, 80% of those with elevated sMAC levels responded to eculizumab, and all responders normalized sMAC levels after treatment. Prompt initiation of eculizumab before the development of chronicity on biopsy, may be necessary to halt disease progression. Evidence on the use of eculizumab in recurrent C3G is summarized in Table 3.

Alternative therapies

Rituximab and plasma exchange or infusions are alternative immunosuppressive therapies used off-label for recurrent C3G. The rationale for B-cell depletion with rituximab use is based on the presence of pathogenic complement factor autoantibodies in some cases. Outcomes with rituximab in recurrent C3G have been variable, with one study showing no benefit [2], while in another series, one out of three patients treated showed improvement of renal function, with the remaining two patients not responding [3]. Plasma exchange was used in four recurrent C3G patients in the series by Regunathan-Shenk *et al*., with varying outcomes [2]. The rationale for using plasma exchange is to remove pathogenic autoantibodies, replace them with normal immunoglobulins, and/or to replace mutated/depleted complement proteins with normal complement proteins.

Repository corticotropin (ACTH injections) 80 units subcutaneous twice weekly was used in a patient with post-transplant C3GN with partial remission of nephrotic range proteinuria in 2 months [50]. This patient was also treated with eculizumab later leading to complete remission. The mechanism of action of ACTH injections is unknown. Finally, autologous stem cell transplant and targeted therapies such as bortezomib are used in C3G associated with MG [51, 52].

Table 3: Studies investigating allograft outcomes after the use of eculizumab in recurrent C3G.

	Number of recurrent C3G patients treated with ecu	Median time from diagnosis to start of ecu (months)	Median duration of ecu treatment (months)	Median follow-up duration (months)	Number of patients with autoantibodies to complement proteins	Number of patients with genetic mutations	Outcomes
Mirioglu *et al*. (2024) [69]	8	NR	NR	27 (12–75)	NR	NR	4 patients (50%) with complete remission, 3 with allograft loss
Welte *et al*. (2023) [70]	6	45 (1–144)	10 (5–46)	36 (17–95)	3 (2 to C3Bb and 1 to FH)	3 (CFHR1-3 in 2 and 1 potentially pathogenic mutation in C3 gene)	2 (33%) with stable eGFR, 0 with improved eGFR, the rest had worsening eGFR
Regunathan-Shenk *et al*. (2019) [2]	7	3 (0.5–39)	>6 months (3–>12)	76	1 (C5Nef), 3 C3Nef,	1 (CD46 mutation), 1 (CFI deficiency, heterozygous CFI mutation)	4 grafts responded with improvement in eGFR and proteinuria. 3 grafts initiated on ecu >6 months post-diagnosis failed
Bomback *et al*. (2012) [48]	3	2 (0.5–8)	12	12 months	2 C3Nef	1 MCP mutation	Renal function stable in 1, AKI with stopping ecu in 1 (resolved with restarting ecu), crt improved in 1 patient
Moog *et al*. (2018) [51]	1	3	28	28			Ecu used in conjunction with bortezomib for MG-C3G Improvement in creat and proteinuria
Garg *et al*. (2018) [21]	1	0.3	36	36		CFH + CFI mutation	Normalization of allograft function and resolution of proteinuria
Gurkan *et al*. (2013) [71]	1	9	12	12	CNef	None	Stable serum creat or proteinuria

AKI, acute kidney injury; creat, creatinine; ecu, eculizumab; NR: not reported.

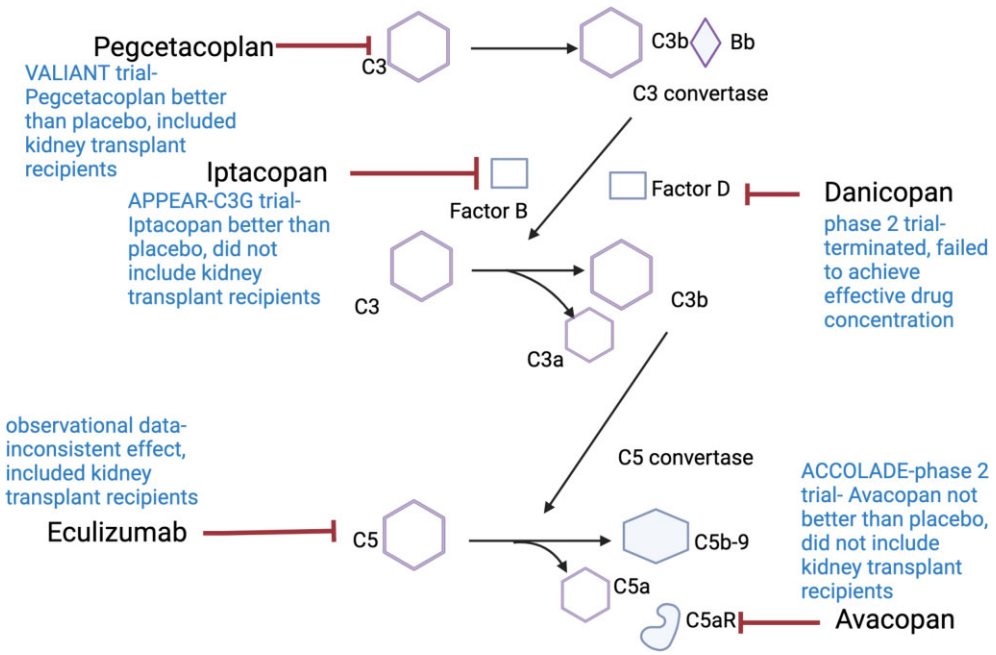


Figure 2: Novel complement blockers used to treat C3G.

Novel complement blockers

Complement-targeted therapies show promise in treating C3G. The mechanism of action and evidence behind the use of these novel agents is summarized in Fig. 2. Avacopan, a C5a receptor antagonist, has shown efficacy in maintaining remission in native kidney C3G in isolated reports. A phase II (ACCOLADE) trial which included patients with recurrent C3G failed to show superior efficacy of avacopan compared with placebo [53]. Promising treatments in the pipeline for recurrent C3G include proximal complement inhibitors such as pegcetacoplan and iptacopan. By targeting early steps in disease pathogenesis, these agents may offer greater benefit than therapies that inhibit only the terminal complement pathway.

Iptacopan is an oral complement inhibitor that binds CFB (cofactor for C3 activation), thereby inhibiting the activation of the ACP at an upstream level. This inhibition prevents the activity of both the C3 and C5 convertases, key components in C3G pathogenesis. In a phase 2 study, 11 adult kidney transplant recipients with biopsy-proven C3G recurrence (73% C3GN) received iptacopan 200 mg twice daily for 12 weeks [54]. These patients were at least 3 months post-transplant, on stable immunosuppression and with no evidence of rejection on biopsy. Repeat kidney biopsies showed a statistically significant decrease in the median C3 deposit score by 2.5 (scale: 0–12) on Day 84 versus baseline [54]. Serum C3 levels also improved while eGFR remained stable (mean eGFR 52.6 mL/min/1.73 m^2 at baseline to 50.6 mL/min/1.73 m^2 on Day 84). Proteinuria levels, which were mainly normal at baseline in the recurrence cohort, remained stable during the trial. Iptacopan was well tolerated. An open-label extension study (NCT03955445) is now ongoing to evaluate the longer-term efficacy and safety of iptacopan. Iptacopan is now the first and only Food and Drug Administration-approved treatment for C3G after the phase 3 APPEAR-C3G trial showed a 35% sustained proteinuria reduction at 12 months [55, 56]. Longer-term studies will be crucial in determining their value in real life clinical scenarios.

Pegcetacoplan, a PEGylated compstatin derivative, is another promising factor 3 inhibitor that prevents activation of C3 and C3b. In the phase 2 trial (DISCOVERY; NCT03453619) evaluating eight patients with native kidney biopsy diagnosis of C3G, pegcetacoplan reduced mean proteinuria by 51% from baseline at 48 weeks. No serious treatment-emergent adverse events were observed, and none of the mild adverse events led to study discontinuation. Additionally, mean serum C3 levels increased, while mean soluble C5b-9 levels decreased over the course of the study [57]. In the phase 2 prospective trial (NOBLE; NCT04572854) investigating pegcetacoplan in post-transplant recurrent immune-complex MPGN (two patients) and C3G (eight patients), C3c staining on the kidney allograft was reduced in 80% of patients after 12 weeks. All patients in this study were adults (>18 years) with an eGFR >15 mL/min/1.73 m^2 and no biopsy evidence of rejection. Proteinuria was reduced by approximately 54% in patients who had higher baseline proteinuria (≥1 g/day), and eGFR remained stable in the pegcetacoplan group. No serious treatment-emergent adverse events were reported [58]. The phase 3 study VALIANT (NCT05067127) randomized 124 participants with native or recurrent C3G or immune-complex MPGN and showed significant proteinuria reduction in the treatment arm compared with placebo at 26 weeks. Patients in the intervention arm received pegcetacoplan at 1080 mg twice weekly for 26 weeks [59]. The extension phase of the VALIANT trial, known as the VALE study, will evaluate the long-term safety and efficacy of pegcetacoplan.

Narsoplimab (OMS721) is a monoclonal antibody targeting MASP-2, a key enzyme in the lectin complement pathway, and is currently being tested in a phase II trial (NCT02682407) for patients with native C3G. Danicopan, an orally administered Factor D inhibitor, was evaluated in patients with native kidney C3G but failed to achieve the optimal concentration needed for effective ACP inhibition, resulting in clinical inefficacy. Similarly, BCX9930, another Factor D inhibitor in native C3G patients in the phase II open label RENEW trial (NCT05162066), has also been terminated [60].

Table 4: Studies examining outcomes of kidney re-transplantation in patients with C3 glomerulopathy.

Study	Number of retransplanted patients	Outcomes
Caravaca-Fontán *et al.* (2023) [8]	6	– Disease recurrence in 50% (N = 3) of retransplanted patients – Only 1 patient lost his 2nd graft due to recurrence – Disease recurred in 4 grafts in 1 patient with *CFHR1* mutation
Regunathan-Shenk *et al.* (2019) [2]	3	– No recurrence in 2 patients (never biopsied) – Disease recurrence in 3 allografts in 1 patient with C3Nef
Zand *et al.* (2014) [3]	3	– Recurrence in 3 allografts in 1 patient with MG (shorter time to recurrence with every transplant)
Andresdottir *et al.* (1999) [7]	1 (DDD)	– No recurrence or proteinuria at 7 years post-transplant
TOTAL	13	– Disease recurrence in 12 allografts (5 patients)

As intra-renal complement activation is very important in the pathogenesis of C3G, targeted therapies and/or pretreatment of donor organs such as *ex vivo* machine perfusion, during organ procurement and preservation may potentially allow increased efficiency while limiting systemic side effects [16].

In summary, recurrent C3G post-kidney transplant is typically treated with intensification of maintenance immunosuppression particularly MMF and steroids in addition to consideration of early use of eculizumab in some cases. With emerging favorable evidence on novel complement inhibitors such as iptacopan and pegcetacoplan, the treatment arsenal for recurrent C3G is expanding.

PROGNOSIS OF RECURRENT DISEASE

Among those with recurrence, 11%–77% experience graft failure, with most studies reporting rates over 50% [2, 3, 7, 8, 61]. Graft loss is more common and occurs sooner in DDD compared with C3GN, with an 83% vs 30% incidence, respectively, and median time to failure of 41 months for DDD and 59 months for C3GN [2, 3, 7]. Approximately 50%–57% lose their allograft within 5 years of recurrence in Western populations [3, 8]. However, in an Indian cohort, progression to graft failure was observed in <1 year post-transplant for both DDD and C3GN patients [15]. These studies were all conducted in the era of complement blockade highlighting the need for more effective therapies.

The prognosis of recurrent disease may vary based on its underlying etiology. In a series of 17 patients with C3G caused by a *CFHR5* gene mutation, the disease recurred (classified as "likely" or "confirmed" recurrence) in two-thirds of cases; however, the outlook was favorable, with 76.5% of patients retaining a functional allograft at 10 years [9].

Differences in prognosis between studies, as noted in Table 1, are likely due to variations in disease detection timing—some studies identified recurrence early via protocol biopsy, while others waited for clinical signs. Differences in follow-up duration may also contribute to variations in outcomes. Key predictors of poor response included early recurrence (<15 months post-transplant), an eGFR <30 mL/min/1.73 m², and serum albumin levels <3.5 g/dL at the time of recurrence [8].

RE-TRANSPLANTATION AFTER ALLOGRAFT FAILURE DUE TO RECURRENT C3G

C3G often affects younger patients, and given the high risk of recurrence post-transplant, repeat kidney transplants are relatively common. Similar to the initial transplant evaluation, it is essential to rule out MG which can significantly increase recurrence risk if left untreated. If graft failure is due to recurrence, delaying a repeat transplant may be advisable, as active inflammation and renal loss could predispose to further recurrence.

In cases of allograft failure from recurrent C3G, using a living donor for a repeat kidney transplant is generally discouraged due to the high likelihood of recurrence, which could jeopardize the donor organ and risk its premature failure. A summary of studies discussing outcomes of kidney re-transplantation in patients with C3G is presented in Table 4. The absence of recurrence in the second allograft for many patients supports the notion that genetic mutations or autoantibodies are not the sole determinants of recurrence. As noted above, donor and transplant-related factors, as well as the post-transplant course, may also contribute to modulating the risk of C3G recurrence.

CONCLUSIONS

Despite advances in understanding the pathogenesis of C3G, much remains to be discovered. There is currently no established tool to predict C3G recurrence, nor are there proven agents or strategies to prevent recurrence. Progress in therapeutics has been slow, and no therapy has yet been approved for recurrent C3G after transplantation. Newer proximal complement pathway inhibitors are currently being studied in phase III trials. Diagnostic tests that can identify biomarkers reflecting the exact points of complement pathway dysregulation in individual patients are essential for advancing therapeutics. Widespread global availability of these diagnostic tests is urgently needed. Finally, increased awareness among both physicians and patients will promote international collaboration and participation in clinical trials, ultimately facilitating the integration of new treatments into clinical practice.

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R.M.A., G.A. and J.Bharati . participated in the review of available evidence and drafting of the manuscript. P.S. and G.N. participated in reviewing and providing critical input to the paper.

K.D.J. was responsible for supervision of the project, editing and finalization of the manuscript.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzsed in support of this research.

CONFLICT OF INTEREST STATEMENT

K.D.J. reports consultancy agreements with Novartis, Otsuka, Calliditas, Appelis, George Clinicals, Vera therapeutics, Citrus Oncology, Decipher, GSK, PMV pharmaceutics and Travere; reports honoraria from the American Society of Nephrology and the International Society of Nephrology; is a paid contributor to UpToDate.com and is section editor for Onconephrology for *Nephrology Dialysis Transplantation*; serves on the editorial boards of *American Journal of Kidney Diseases*, *CJASN*, *Clinical Kidney Journal*, *Frontiers in Nephrology*, *Journal of Onco-Nephrology* and *Kidney International*; serves as the Editor-in-Chief of ASN Kidney News; and serves as Co-President of the American Society of Onco-Nephrology. P.S. reports consulting agreements with Appelis, Travere, Otsuka and Vera therapeutics. G.A. is the Galdi fellow in Glomerular Diseases and Onconephrology at Northwell with grant support from Greg and Linda Galdi. The remaining authors have no relevant disclosures.

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