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Complement-mediated renal diseases after kidney transplantation - current diagnostic and therapeutic options in *de novo* and recurrent diseases

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Abstract

For decades, kidney diseases related to inappropriate complement activity, such as atypical hemolytic uremic syndrome and C3 glomerulopathy (a subtype of membranoproliferative glomerulonephritis), have mostly been complicated by worsened prognoses and rapid progression to end-stage renal failure. Alternative complement pathway dysregulation, whether congenital or acquired, is well-recognized as the main driver of the disease process in these patients. The list of triggers include: surgery, infection, immunologic factors, pregnancy and medications. The advent of complement activation blockade, however, revolutionized the clinical course and outcome of these diseases, rendering transplantation a viable option for patients who were previously considered as non-transplantable cases.

Several less-costly therapeutic lines and likely better efficacy and safety profiles are currently underway. In view of the challenging nature of diagnosing these diseases and the long-term cost implications, a multidisciplinary approach including the nephrologist, renal pathologist and the genetic laboratory is required to help improve overall care of these patients and draw the optimum therapeutic plan.

Key words: Complement-related diseases; Kidney transplantation; *De novo*; Recurrent diseases

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Core tip: The recent progress in our understanding of the pathophysiology of complement-mediated diseases is gaining considerable popularity. Complement dysregulation due to inherited or acquired factors is currently the culprit mechanism. Several constitutional abnormalities usually trigger the process of recurrence, with a subsequent high rate of graft loss. The development of the terminal complement inhibitor “eculizumab” is a breakthrough in controlling abnormal complement activation. While diagnosing complement abnormalities is one challenge, treatment cost with this new agent is another major hurdle in any health care system. New lines of promising therapies are currently in the pipeline.

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INTRODUCTION

The complement components can be seen in biopsies of almost all types of glomerulonephritis, which can be broadly divided into two main groups: (1) “complement over-activation” includes IgA nephropathy (IgAN) and immune complex membranoproliferative glomerulonephritis (MPGN); and (2) “complement dysregulation” that encompasses atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G)^[1]. While complement activation is triggered by immune complex formation in the former group, genetic mutations are the driver of complement over-activation in the latter one. This explains why the disease process in the former class is potentially modifiable by immunosuppression in the post-transplantation period, which is not the case in the latter class. Our understanding of the biogenetic causes of C3G and aHUS/thrombotic microangiopathy (TMA) has been expanding. The mechanisms of these diseases not only affect their clinical history, but also affect the

recurrence rate^[2]. The role of complement in C3G evolution is now well-recognized^[3]. Recent progress in understanding the pathophysiology of MPGN led to newer classifications of MPGN into immune complex-mediated and complement-mediated subtypes. The hallmark of complement-mediated MPGN is the deposition of C3 and other complement products in glomerular tissues^[4]. This is caused by dysregulation and loss of control of the AP complement pathway^[5]. The AP is tightly regulated under physiological conditions. It can be disrupted through either inherited (mutations/polymorphisms) or acquired (autoantibodies) interferences to the regulating components. Histological staining using immunofluorescence (IF) is currently the best determinant technique, and C3G is defined by dominant C3 with dispersed, reduced or absent immunoglobulin (Ig). Based on electron microscopy (EM) examination, C3G subdivides into complement three glomerulonephritis (C3GN) and dense deposit disease (DDD). In C3GN, discrete deposits can be seen in the mesangium and capillary walls (subendothelial and subepithelial regions). On the contrary, DDD deposits are large in size, extremely dense (osmiophilic) and intramembranous, which leads to a characteristic thickening of the glomerular basement membrane (GBM)^[5]. The term aHUS is applied to a heterogenous group of diseases (Figure 1) that share TMA manifestations with an associated decline in renal function (classically, no IF staining of C3 or any other complement components). In aHUS, complement abnormalities (either genetic mutations or acquired autoantibodies) are well-recognized mechanisms with a clearly associated complement-mediated TMA^[1]. In this article, we will discuss various types of complement-mediated renal diseases after kidney transplantation and their current therapeutic options.

Methodology

In view of the lack of prospective controlled trials concerned with complement-mediated diseases post-kidney transplant, we tried to shed the light in this review on the most recent expert opinions, with regard to the best tools of management for these devastating diseases.

CLINICAL PRESENTATION

Salient features of C3G

DDD and C3GN share some salient features that include proteinuria, hematuria and increased serum creatinine concentration^[6,7]. Recurrence of C3G is typically encountered one to two years after transplant^[7]. C3G comprises a spectrum of diseases that result from aberrant control of complement activation, deposition and dysregulation, leading to C3 glomerular deposition with characteristic electron-dense deposits (EDD) in EM (Table 1).

Table 1 Morphological features of C3 glomerulopathy

Morphological features of C3G	
Light microscopy	<p>Active lesions</p> <p>Mesangial expansion with or without hypercellularity</p> <p>Endocapillary hypercellularity including monocytes and/or neutrophils</p> <p>Capillary wall thickening with double contours (combination of capillary wall thickening + mesangial increase is referred to as a membranoproliferative pattern)</p> <p>Fibrinoid necrosis</p> <p>Cellular/fibrocellular crescents</p> <p>Chronic lesions</p> <p>Segmental or global glomerulosclerosis</p> <p>Fibrous crescents</p>
IF microscopy	Typically dominant C3 staining
Electron microscopy	<p>DDD: Dense osmiophilic mesangial and intramembranous electron dense deposits.</p> <p>C3GN: Amorphous mesangial with or without capillary wall deposits including subendothelial, intramembranous and subepithelial EDD</p> <p>Subepithelial "humps" may be seen in both DDD and C3GN</p>

Adapted from Goodship *et al*^[12]. C3G: C3 glomerulopathy; DDD: Dense deposit disease; C3GN: C3 glomerulonephritis; EDD: Electron dense deposits, fibrinoid necrosis.

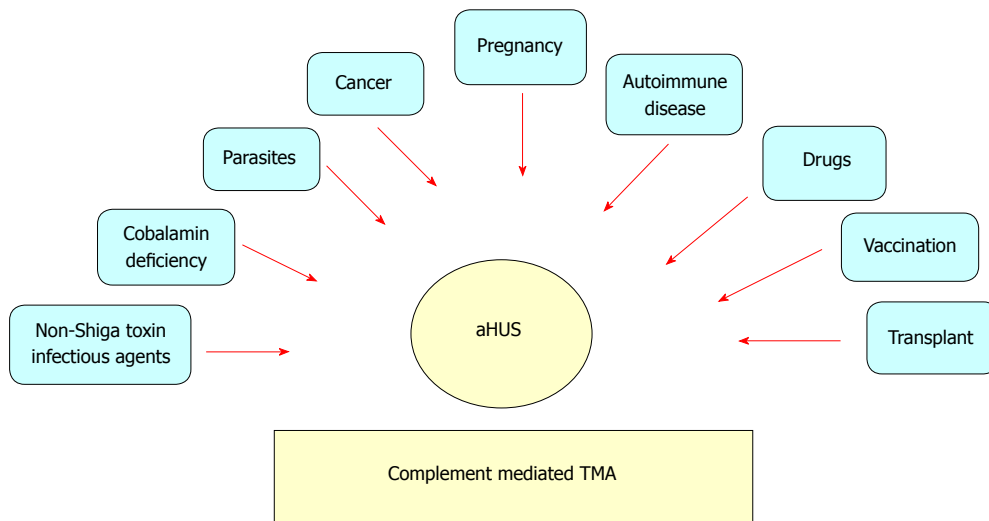


Figure 1 Heterogeneity of atypical hemolytic uremic syndrome. Adapted from Salvadori *et al*^[1]. TMA: Thrombotic microangiopathy; aHUS: Atypical hemolytic uremic syndrome.

Pathology

Renal biopsy is crucial for C3G diagnosis. LM is not helpful, due to its extremely diverse appearance. IF is the mainstay for diagnosis. A unique criterion in IF studies is the presence of dominant C3 staining, which is twice as intense as any other immunoreactant (IgG, IgM, IgA, and C1q)^[8]. Ninety percent of DDD patients, but fewer C3GN patients, can be diagnosed through applying this criterion^[8]. Repeated biopsy may be required to confirm the diagnosis. As C3G may present in acute infection, C3 can be observed with post-infectious GN. Humps are no longer pathognomonic criteria of post-infectious GN, however they can also be encountered in C3G. However, the presence of double contours in the GBM raises the possibility of C3G diagnosis. To differentiate DDD from C3GN, EM studies should be accomplished, as it has pivotal clinical implications. Moreover, staining for IgG as well as light

chains on pronase-digested paraffin should be applied for all cases of C3GN on standard IF, particularly in adults (Figure 2 and Table 1)^[9,10].

Salient features of TMA

TMA is mostly presented 3-6 mo post-transplant, but it can occur at any time after renal transplantation^[13]. Presentation of TMA is not universal, ranging from the renal-limited form up to a complete systemic picture with its classic triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and decline in renal function^[14]. MAHA is defined as increased LDH, decline in HB and haptoglobin, and appearance of schistocytes in peripheral blood smears. On the other hand, localized (renal-limited) TMA usually presents later in the post-transplant course. In the acute stage, evidence of endothelial injury with platelet aggregation (thrombosis), fibrinoid necrosis, as well as

Table 2 Morphological features in microangiopathy

Active lesions	Chronic lesions
Glomeruli: Thrombi - Endothelial swelling or denudation - Fragmented RBCs - Subendothelial flocculent material. EM: Mesangiolysis - Microaneurysms Arterioles: Thrombi - Endothelial swelling or denudation - Intramural fibrin - Fragmented red blood cells - Intimal swelling - Myocyte necrosis Arteries: Thrombi - Myxoid intimal swelling - Intramural fibrin - Fragmented red blood cells	Glomeruli: LM: Double contours of peripheral capillary walls, with variable mesangial interposition - EM: New subendothelial basement membrane - Widening of the subendothelial zone Arterioles: Hyaline deposits Arteries: Fibrous intimal thickening with concentric lamination (onion skin)

Adapted from Goodship *et al*^[12]. EM: Electron microscopy; LM: Light microscopy.

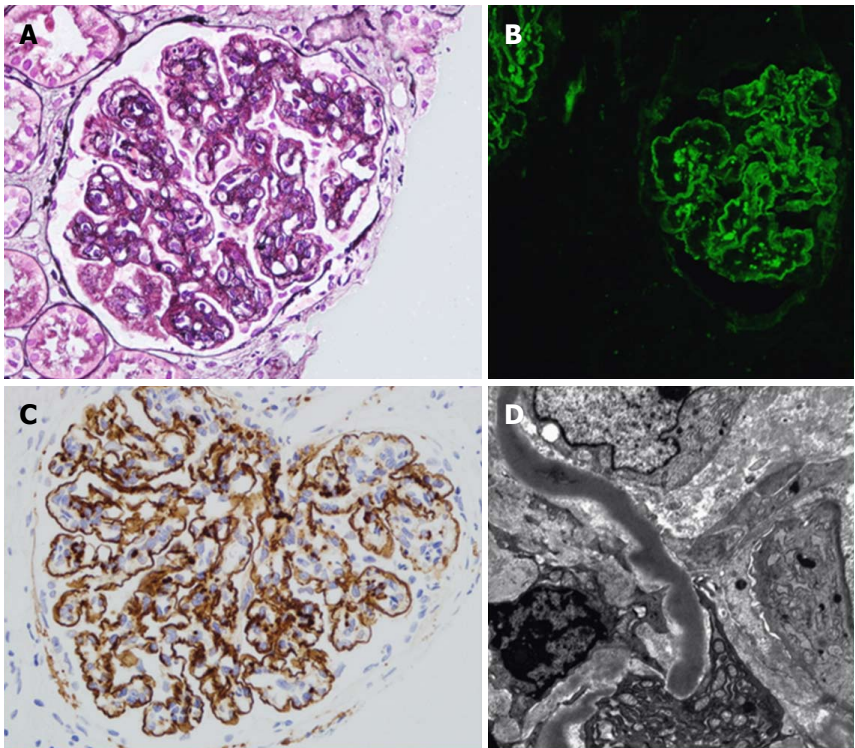


Figure 2 Renal histology in individuals with dense deposit disease. A: Light microscopy with silver stain showing a membranoproliferative glomerulonephritis pattern with double contours of the glomerular basement membrane; B: Immunofluorescence; C: Immunohistochemistry with immunoperoxidase showing strong capillary wall staining of C3 and some granular mesangial C3; D: Characteristic sausage-like, intramembranous, osmiophilic deposits on electron microscopy. Adapted from Barbour *et al*^[11].

glomerular ischemia can be seen. On the other hand, chronic lesions show duplication and multilayering of the GBM, with clustering of the matrix layers and vessel wall cells leading to the characteristic onion skin shape appearance (Table 2)^[15]. As TMA is not always present with full-blown systemic pictures, genetic studies to unmask the underlying complement defect are ultimately mandated, particularly if no other clear cause has been associated (*e.g.*, AMR-associated TMA). AMR can give a TMA-like picture, as it is an antibody interaction with the endothelium. This is also a fundamental maneuver to differentiate *de novo* from recurrent disease (positive genetic testing), with consequent clinical therapeutic implications^[16].

Extrarenal manifestations of aHUS and C3G

Twenty percent of aHUS patients express extrarenal

manifestations. Their relation to complement activation and TMA evolution is unclear. Drusen is rarely seen in TMA^[17]. Drusen formation, which represents an accumulation of lipids and complement-rich proteins between Bruch’s membrane and the retinal pigmentary epithelium, is commonly reported in age-related macular degeneration but present at a much earlier age with C3G^[18]. In C3G, retinal drusen and acquired partial lipodystrophy have been commonly reported. The latter is most commonly encountered with C3 nephritic factors. Factor D, an essential agent for C3 convertase formation, is highly concentrated in adipocytes that undergo C3 nephritic factor-induced complement-dependent lysis^[19] (Table 3).

Pathogenesis and classification of C3G

The new classification of MPGN encompasses two

Table 3 Extrarenal manifestations reported in atypical hemolytic uremic syndrome, dense deposit disease, and C3 glomerulonephritis

aHUS	DDD/C3GN
Digital gangrene, skin	Retinal drusen
Cerebral artery thrombosis/stenosis	Acquired partial lipodystrophy
Extracerebral artery stenosis	
Cardiac involvement/myocardial infarction	
Ocular involvement	
Neurologic involvement	
Pancreatic, gastrointestinal involvement	
Pulmonary involvement	
Intestinal involvement	

Adapted from Goodship *et al*^[12]. aHUS: Atypical hemolytic uremic syndrome; C3GN: C3 glomerulonephritis; DDD: Dense deposit disease.

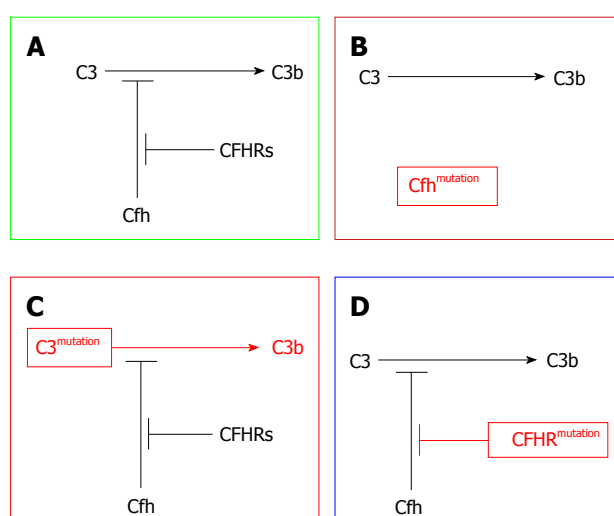


Figure 3 Disease mechanisms in C3 glomerulopathy, based on genetic defects identified in family studies. A: Physiological regulation of C3 activation to C3b via the alternative pathway is mediated by complement factor H (CFH) (Cfh). Competitive inhibition of CFH by CFHR proteins is termed CFH deregulation; B: Homozygous deficiency or dysfunction of CFH results in excessive C3 activation; C: Hyper-functional C3 produces excessive C3 activation despite normal CFH activity; D: Abnormal CFHR proteins enhance CFH deregulation, leading to excessive C3 activation. Adapted from Barbour *et al*^[11].

subtypes: the immune complex-mediated GN (ICGN) and complement-mediated GN (CGN), recently named (C3G). The former is characterized by both Ig as well as complement component deposition in kidney tissues as recognized by IF studies. The latter is characterized by dominant complement deposition with smaller amounts of Ig deposition. Further subdivision of C3G into C3GN and DDD can be attained through EM studies^[20]. Both subtypes are triggered through dysregulation of any part of the AP. For example, patients may develop the C3 convertase-stabilizing factor called C3NeF, which leads to uncontrolled complement activation. Loss-of-function mutations in complement regulatory proteins (CFH or CFI)^[20-23] or gain-of-function mutations in C3 leads to CFH resistance, which has been postulated as an underlying mechanism (Figure 3).

Pathophysiology and recurrence of C3G

Pathophysiology of AP activation in DDD and C3GN is nearly the same. In both disorders, disturbance

of the fluid phase is triggered as a result of aberrant gene mutations or the presence of autoantibodies. However, the presence of C3 nephritic factor (C3NeF) is by far the most commonly acquired complement defect. C3NeF has the ability to block CFH-mediated decay by stabilizing C3 convertase^[5,24]. By binding to C3 convertase, C3NeF has the ability to trigger it approximately ten times^[25,26]. C3 convertase can also block the action of CFH, CR1, as well as decay-accelerating factor (DAF).

C3NeF is prevalent in 50%-80% C3G patients^[27]. Other autoantibodies have also been found (*e.g.*, autoantibodies against factor B^[28], CFH^[29,30] and C3 convertase)^[28]. In C3G, CFH mutations have been frequently reported. Different forms of mutations can be presented as defective or completely absent protein H. These mutations can be seen in homozygous or heterozygous forms^[31,32]. C3NeF can also be encountered, which denotes the clustering of different risk factor varieties. More recently, genetic mutations involving the CFHR gene have been reported in the C3G cohort of patients^[33]. CFHR group genetic mutations^[34], deletions^[35], duplications^[36], as well as hybrid genes^[37] have also been observed in C3G patients, either in an isolated manner or in a familial cohort. Malik and his associates^[38] reported that members of one family can develop C3G as an result of aberrant copies of CFHR3 and CFHR1 loci. The presence of familial C3G underscores the genetic basis of several C3G varieties and their relation to AP dysregulation.

To summarize, complement dysregulation is the specific etiology of C3G, which could be genetic or acquired. While genetic causes encompass complement gene mutations, acquired causes include the C3NeFs, which have the ability to impede normal complement regulation^[1]. Moreover, genetic varieties constitute the pathophysiologic basis of C3G and aHUS evolution (Table 4). Recently, a robust correlation between CFH-related proteins and a variety of complement-mediated diseases have been documented. Functional parameters (*e.g.*, complement regulators and CFH competitors) have recently attained significant popularity^[39].

TMA or C3G?

Both TMA and C3G have a common underlying

Table 4 Overview of mutations in complement factor H-related protein genes

Genetic defect	Phenotypic expression
Duplication in <i>CFHR5</i> gene	C3 glomerulopathy (CFHR5 nephropathy)
Duplication in <i>CFHR1</i> gene	C3 glomerulopathy
Hybrid <i>CFHR3/CFHR1</i>	C3 glomerulopathy
Hybrid <i>CFHR2/CFHR5</i>	C3 glomerulopathy
Hybrid <i>CFH/CFHR1</i>	aHUS
Hybrid <i>CFH/CFHR3</i>	aHUS

Adapted from Salvadori *et al*^[1]. aHUS: Atypical hemolytic uremic syndrome; CFH: Complement factor H.

causation: AP dysregulation. However, the question that arises is "which factors influence the evolution of one disease rather than the other?"^[40]. The prevalence of the fluid phase complement activation dysregulation in animal models suggests that C3G is the responsible factor. On the other hand, complement activation involving capillary walls can result in TMA evolution^[41]. Furthermore, absolute CFH deficiency is in favor of an activation of the fluid phase complement with subsequent C3G evolution, while the lack of an aberrant CFH binding region is in favor of TMA evolution^[41]. It has also been postulated that CFH and CFH/CFHR mutations induce aHUS to inhibit CFH-binding to many cell surfaces, while C3G-associated mutations in CFHRs cannot inhibit CFH binding to endothelial cell surfaces^[42]. The prevalence of familial C3G mutations serves as a robust indicator of the genetic base of C3G recurrence^[1].

Risk of DDD recurrence

Despite the well-known DDD variants of C3, its pathogenesis has only recently been recognized. The five-year graft survival rate was only 50% in one retrospective study of 75 children^[6]. In adults, a majority of the recipients developed recurrence in post-transplant periods, with 25% of them losing their allografts^[43]. In another broader cohort that included eighty adults and children with C3G, Medjeral-Thomas *et al*^[44], reported histological recurrence in all six DDD recipients. Graft loss had resulted in 50% of his cases. For recipients who developed DDD recurrence, the ten-year graft survival rate has been reported to be up to 57.5% in an UNOS review^[45]. Risk factors for DDD recurrent disease and graft loss are not well-recognized. However, the histological recurrence rate was reported to be more than 70%^[46,47]. Recurrence may present spontaneously in post-transplant periods, though it may take several years to manifest^[47]. This discrepancy raises some questions, such as the impact of the longevity of follow-ups, the need for tissue diagnosis, and the real rate of DDD recurrence.

Risk of C3GN recurrence

There is no documented relation between mode of presentation, C3 serum levels, or C3NeF levels and C3GN

recurrence^[48]. The only trustworthy risk factor correlated with C3 recurrence is the presence of heavy proteinuria, with two thirds of C3 patients showing vulnerability to recurrence and a high incidence of graft loss^[5,7,27]. All the available data about recurrence are based on case series, with the largest by Zand *et al*^[7] that failed to reveal robust evidence of recurrence risk. This observation is partially explained by the heterogeneity of complement defects implicated in C3GN evolution. Early reports postulated HLA-B8 DR3 and living related donation as possible risk factors for recurrence^[49]. However, the more recent reports suggested the following: (1) history of graft loss owing to recurrence^[50]; (2) aggressive histopathological alterations in native kidney biopsy; and (3) hybrid CFHR3 1 gene-related C3GN. Wong *et al*^[51] have recently reported a high rate of C3G recurrence (five patients received a total of eight kidney transplants). Four (50%) renal allografts had disease recurrence, of which three had biopsy-proven recurrence, with time to recurrence ranging from as early as 2 wk following living-related donor transplantation, to 93 and 101 mo for the two remaining allografts, respectively^[51].

Diagnosis of C3G recurrence

The declining appearance of proteinuria, hematuria or eGFR is a strong indicator of C3G recurrence. Final diagnosis is usually made through LM, IF, and EM studies of kidney biopsy. After histopathological examination, a thorough evaluation of any genetic mutation in the AP should be accomplished, especially if these studies were not previously fulfilled with the native kidney disease.

Diagnosis of C3G/TMA recurrence

A robust work-up of analytic studies including genetic, biochemical and pathological evaluation should be instituted, including the following: (1) complement components and complement regulatory protein levels; (2) peripheral WBC MCP levels; (3) screening for antibodies to CFH and C3NeFs; and (4) mutation screening of CFH, CFI, CFB, C3, and MCP. Furthermore, recombination in the CFHR region should be tested^[52].

Prognosis of DDD/C3GN

In both DDD and C3GN, recurrent disease is usually associated with allograft loss^[6,44,53]. The one-year allograft survival was reported to be 94%, with 69% at five years, and 28% at ten years. Three predictive criteria for progression to ESRD were recognized: (1) crescentic GN; (2) severe arteriolar sclerosis by LM; and (3) decline of renal function at the time of first biopsy^[44].

Prognosis of TMA

Compared to recurrent TMA, the prognosis of *de novo* TMA is quite poor. Fifty percent of patients may lose their graft within a couple of years after diagnosis^[54,55]. Many reports were in favor of this attitude^[54-56]. Before

Table 5 Recommended therapy approach for C3 glomerulopathy based on small prospective trial, case reports, and expert opinion

All patients	Moderate disease	Severe disease
Lipid control	Urine protein > 500 mg/24 h despite supportive therapy, or	Urine protein > 2000 mg/24 h despite immunosuppression and supportive therapy or
Optimal BP control (< 90% in children and ≤ 120/80 mm Hg in adults)	Moderate inflammation on renal biopsy or	Severe inflammation represented by marked endo- or extracapillary proliferation with/without crescent formation despite immunosuppression and supportive therapy or
Optimal nutrition for both normal growth in children and healthy weight in adults	Recent increase in serum creatinine suggesting risk for progressive disease	Increased S. Cr suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy
	Recommendation Prednisone	Recommendations Methylprednisolone pulse-dosing as well as other anti-cellular immune suppressants have had limited success in rapidly progressive disease
	Mycophenolate mofetil	Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease

Adapted from Goodship *et al*^[12].

the era of eculizumab (EZ), Schwimmer *et al*^[54] reported that 54% of systemic TMA can develop dialysis requiring AKI, and about 38% lost their allograft. However, no one patient with localized TMA has complicated with TMA-related allograft loss or a need for dialysis. Nevertheless, both systemic and localized forms may experience unfavorable long-term graft survival^[54,57].

THERAPY OF COMPLEMENT DYSREGULATION-RELATED DISEASES

Treatment of *de novo* C3G

The therapeutic approach for *de novo* C3G therapy is similar to that of recurrent disease. Very minimal information is available regarding *de novo* C3G^[58].

Treatment of recurrent C3G

In light of the paucity of data from controlled studies, some experts have suggested an approach that depends on disease severity (*i.e.*, mild, moderate and severe) based on the degree of proteinuria and the magnitude of allograft dysfunction (Table 5): (1) conservative measures, as with other glomerulotides, including RAS blockade and lipid-lowering agents; (2) glucocorticoids, MMF, rituximab and PE have been used with variable success^[59,60]. In selected patients, MMF has been reported to be effective in C3GN controls in a retrospective study^[12,61]; and (3) EZ was firstly reported by Bomback *et al*^[62], in treating six patients with C3G (three with DDD and three with C3GN) in an open-labelled trial. EZ dose is guided by previous experience in aHUS and used for one year. Improved kidney function was observed in two patients; one patient showed partially improved proteinuria, while another patient showed better histological and laboratory findings^[62]. Notably, elevated serum membrane attack complex (MAC) levels were associated with clinical

improvement^[63]. Duration of therapy is not yet defined. The beneficial effects of EZ in DDD recurrence^[46] and C3GN recurrence^[64] have been shown in case reports^[65]. However, histopathological evidence of disease progression has been observed in subsequent biopsies. This highlights the fact that there is no standard accepted biomarker for disease monitoring, which can be used to assess the patient's response to treatment and predict better renal function.

In 2018, Garg *et al*^[66] described the spectrum of C3 pathophysiology and its clinical implications. The observed variability of the degrees of upstream (site of C3 convertase) and downstream (site of C5 convertase) complement dysregulation may result in variable phenotypic differences^[67,68]. Consequently, the nature of this spectrum will be reflected clinically on disease progress in two ways: firstly, the variability in response to EZ therapy (Figure 4)^[66]. In C3G, if the dominant process focused on activation of C5 convertase (resulting in increased soluble C5b-9 levels), EZ will be of therapeutic benefit. On the other hand, patients with the dominant process focused on dysregulation at the level of C3 convertase (increased C3 split product levels), the impact of EZ therapy will be less impressive, and the process of uncontrolled complement dysregulation will persist with consequent ongoing renal injury. Secondly, future application of "soluble C5b-9" as well as "C3 degradation product" measurements will be feasible in monitoring EZ therapy (and other newly introduced C3 convertase inhibitors agents) and, thereby, will help in predicting its response^[66]: (1) compstatin is a C3 inhibitory peptide that can block C3 and its convertase interaction, so that all of the three complement pathways are activated; (2) CP40 is a compstatin analog with a selective C3 inhibitor property. CP40 can prevent *in vitro* complement-mediated hemolysis induced by C3GN patient sera. Moreover, it can abort dysregulated AP activation induced by autoantibodies and genetic

A

Underlying defect	Lab response		Tissue response (histopathology)	Reference
	SCr	PCR		
None	○	●	●	Bomback <i>et al</i> , 2012 ^[62]
C3Nef	●	●	Not performed	McCaughan <i>et al</i> , 2012 ^[46]
C3Nef	●	●	●	Sánchez-Moreno <i>et al</i> , 2014 ^[85]
None	●	●	●	Le Quintrec <i>et al</i> , 2015 ^[80]

B

Underlying defect	Lab response		Tissue response (histopathology)	Reference
	SCr	PCR		
C3Nef	○	○	●	Bomback <i>et al</i> , 2012 ^[62]
C3Nef, CD46 mutation	●	Non-proteinuric throughout	○	Bomback <i>et al</i> , 2012 ^[62]
C3Nef, CFH mutations	○	● > ●	● (Increased fibrosis and continuously active C3GN)	Gurkan <i>et al</i> , 2013 ^[64]
CFH and CFI mutations	●	●	● Improved tubulointerstitial injury, recovered ischemic injury; persistent 2-3 C3 deposition	Garg N <i>et al</i> , 2018 ^[66]

● = Improved ○ = No change ● = Worsened ● > ● = Improved, then worsened

Figure 4 Response of complement 3 glomerulopathy subtypes to eculizumab therapy based on laboratory parameters and tissue (histopathological) response. A: Dense deposit disease response to eculizumab therapy^[66]; B: Complement 3 glomerulonephritis response to eculizumab therapy^[66]. CFH: Complement factor H; CFI: Complement factor I; C3Nef: C3 nephritic factor.

mutations^[63]. Since C3d is the major complement fragment deposited in C3GN and DDD, CP40 represents a promising therapeutic agent. CP40 has been evaluated in paroxysmal nocturnal hemoglobinuria and hemodialysis-induced inflammation^[69,70]. If CP40 is able to offer a disease-specific targeted therapy, this agent may represent a breakthrough in C3G control; (3) other novel therapeutics: antibody-based agents targeting complement function by blocking particular components of C3 convertase to hamper its formation and/or function (e.g., anti-C3b monoclonal antibodies reported by Paixao-Cavalcante *et al*^[71], anti-FB antibodies as described by Subias^[72], and anti-properdin antibodies as professed by Pauly *et al*^[73] targeting complement blockade are all under thorough evaluation^[74]). Soluble complement receptor1 (CR1): a robust regulator of complement activity *in vitro*, soluble CR1 can prevent dysregulation of the AP C3 convertase. The safety and efficacy of the soluble CR1 in normalizing complement activity in pediatric patients with ESRD have been reported. With its ability to breakdown active C3b, soluble CR1 infusion can induce clinical improvement in C3GN as well as in the serum levels of MAC in patients with DDD recurrence^[37].

Methods of achieving C3GN control are summarized in Table 5^[34,75-86]. Until enough data from randomized control trials become available, the guidelines related to complement blockade therapy of C3GN should be based on those applied in aHUS (Table 6)^[12].

Renal transplantation for C3G

Minimal data is available concerning renal transplantation for C3G. The available recommendations (Table 7) are currently based on expert opinion. Recurrence post-transplant is common, with about half of the patients with C3G at risk of losing their grafts^[12].

TREATMENT OF POST-TRANSPLANT TMA

For cases of TMA secondary to medication, switching of the culprit drug to another agent (mTOR or CNI) is associated with a better response^[88-90]. The first line of therapy of *de novo* TMA should encompass withdrawal of the offending drug, an essential step that is usually associated with correction of the hematological profile^[57].

Plasmapheresis (PE) and intravenous immunoglobulins (IVIG) (particularly with AMR-associated TMA):

Table 6 Monitoring eculizumab therapy

CH50 (total complement activity)	AH50 (alternative pathway hemolytic activity)	Eculizumab trough	Alternative assays
Measures the combined activity of all of the complement pathways Tests the functional capability of serum complement components to lyse 50 % of sheep erythrocytes in a reaction mixture Low in congenital complement deficiency (C1-8) or during complement blockade Normal range: Assay dependent	Measures combined activity of alternative and terminal complement pathways Tests functional capability of alternate or terminal pathway complement components to lyse 50% of rabbit erythrocytes in a Mg ²⁺ -EGTA buffer Will be low in congenital C3, FI, FB, properdin, FH, and FD deficiencies or during terminal complement blockade Normal range is assay-dependent.	May be a free or bound level ELISA: using C5-coated plates, patient sera, and an anti-human IgG detection system Not affected by complement deficiencies Recommended trough level during complement blockade: 50-100 µg/mL	The following assays are under investigation Free C5 <i>In vitro</i> human microvascular endothelial cell test SC5b-9 (also referred to as sMAC and TCC) remain detectable in aHUS remission, so not recommended as a monitoring tool
Recommended goal during therapeutic complement blockade: < 10% of normal	Recommended goal during complement blockade: < 10% of normal		

Adapted from Goodship *et al*^[12]. aHUS: Atypical hemolytic uremic syndrome; C3: Complement component 3; C5: Complement component 5; EGTA: Ethyleneglycol tetraacetic acid; ELISA: Enzyme-linked immunosorbent assay; FB: Complement factor B; FD: Complement factor D; FH: Complement factor H; FI: Complement factor I; sC5b-9: Soluble C5b-9; sMAC: Soluble membrane attack complex; TCC: Terminal complement complex.

Table 7 Transplant considerations in C3 glomerulopathy¹

Timing	Donor selection	Risk reduction
Avoid transplantation during acute period of renal loss Avoid transplantation during acute inflammation No data supporting whether specific complement abnormalities (<i>e.g.</i> , high titer C3Nef, low C3 or high soluble C5b-9) predict increased risk for relapse	No specific recommendation can be made on donor choice. When considering living donors, high risk of recurrence should be weighed against presumed risk of waiting on cadaveric donor list	C3G histological recurrence is as high as 90% ^[7,87] Limited data suggest: rapid progression to ESRD in native kidneys increases recurrence risk ^[87] There are no known strategies to reduce recurrence risk of C3G Clinical recurrence should drive decision to treat ^[7] In absence of clinical trials, use of anti-complement therapy is based solely on a small open-label trial and positive case reports ^[62] (the impact of publication bias is unknown) C3G associated with monoclonal gammopathy has a high rate of recurrence ^[7]

¹Based on limited retrospective cohort data. Adapted from Goodship *et al*^[12]. C3: Complement component 3; C3G: C3 glomerulopathy; C3Nef: C3 nephritic factor; ESRD: End-stage renal disease.

fresh-frozen plasma (FFP) is advised as a reposition fluid, which must be type-specific, ordered in advance and thawed before use, despite the high risk of reactions; however, it replaces all plasma constituents and is appropriate for patients with TMA^[91]. Before the era of EZ, the following supportive explanations have been provided: (1) proven efficacy in TTP^[92]; (2) a graft salvage rate of more than 80%, as reported by Karthikeyan *et al*^[13]. He addressed two possible benefits for this type of therapy: clearance of the platelet aggregation factors (*e.g.*, thromboxane A2) and replenishment of the deficient agents (*e.g.*, PGI2-stimulating factor)^[13]; (3) with frequent possibility of the presence of underlying complement dysregulation, commencing PE therapy will also be beneficial in two ways: clearance of the aberrant complement components, and replacement with normally functioning complement proteins^[93]; (4) clearance of the anti-HLA

antibodies in AMR-associated aHUS improved patient outcome^[55,94]; (5) PE/IVIG therapy was successfully associated with a 100% response rate in five solid organ transplants complicated by a systemic form of TMA. There was no evidence of relapse after cessation of the culprit drug (*e.g.*, tacrolimus) in a recent report^[57].

Belatacept, a fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), selectively inhibits T cell activation through a co-stimulatory blockade^[95].

EZ, an anti-C5 agent that blocks lytic C5b-9 MAC generation, not only revolutionized aHUS therapy but was also effective in preventing its recurrence^[96]. The role of complement activation in TMA evolution has been recognized in a majority of *de novo* TMA patients. Chua *et al*^[97], for example, reported deposition of C4d in all biopsies of post-transplant TMA. Efficacy of this

Table 8 Eculizumab dosing in atypical hemolytic uremic syndrome based on dosing goal

Minimal dose	Discontinuation
Desire to continue dosing with the minimal dose required to achieve a pre-identified level of complement blockade ¹	Desire to discontinue complement blockade
Dose reduction or interval extension	No consensus exists regarding tapering of dose
Goal CH50 < 10% (recommended)	
Goal AH50 < 10% (recommended)	
Goal eculizumab trough >100 µg/mL	

¹Additional monitoring may be required during intercurrent events (e.g., infection, surgery, vaccination) to detect unblocked complement activity. Adapted from Goodship *et al*^[12]. AH50: Alternative pathway hemolytic activity; CH50: Total complement activity.

agent has also been documented in the management of resistant cases of medication-associated *de novo* TMA, including those with unidentified genetic mutations^[98-103]. Moreover, efficacy of EZ has been also shown in some cases of resistant AMR-associated TMA^[103-111]. However, Loupy *et al*^[112] reported a similar graft survival (95.8% vs 89.7% at two years post-transplant, respectively) and estimated GFR (52.6 mL/min vs 46.7 mL/min) in comparing PE-treated recipients with the EZ-treated group. Considering the high cost of this drug, utilization of this agent is better confined to PE-dependent patients, AMR-associated TMA and to cases with refractory hemolysis.

Treatment of recurrent TMA

Minimal work-up of genetic studies should include: CFH, CFI, CFHR, CFB, MCP and C3^[113]. All cases with suspected TMA should be screened for all complement components and its related proteins. Cases with isolated membrane cofactor protein (MCP) mutations (not combined with other gene defects) may be safe for kidney donation. Cases with documented TMA and with a lack of definitive genetic defects may proceed with kidney transplantation under the umbrella of intensive PE therapy^[114]. Polygenic patterns of TMA should be dealt with cautiously in case of living donation^[115].

Prevention of aHUS

Avoid trigger factors that stimulate complement activity (e.g., ischemia-reperfusion injury, viral infection and culprit medications)^[52]. Immunosuppressive regimens devoid of medications related to TMA evolution^[116] are advised. PE therapy alone is not sufficient for TMA cure and prevention, with the following explanations postulated: (1) PE alone frequently failed to prevent TMA recurrence^[117]; (2) TMA regression cannot be preserved after cessation of therapy; and (3) recipients treated with PE showed an evidence of "subclinical" disease^[118], which declares that PE has no influence on complement activity. Prophylactic use of rituximab proved to be beneficial as an anti-CFH-antibody^[119], and this effect can be augmented with the addition of PE therapy^[120,121]. The anti-C5 monoclonal antibody EZ has been reported to be successful in preventing TMA recurrence in recipients with CFH, CFH/CFHR1 hybrid gene mutations as well as in C3 gene mutations^[122-125].

Prophylactic complement blockade

Eighty percent of kidney transplantation recipients with TMA proved to be associated with genetic mutations^[126]. Based on the fact that a TMA episode is suspected with trigger factor (e.g., surgery), a robust suggestion is to protect the patient with complement blockade, if not already instituted^[127]. Unfortunately, this suggestion lacks appropriate evidence^[12].

Therapeutic protocols for aHUS recurrence

Given a clear role of complement blockade in the management of TMA, two regimens have been suggested: (1) minimal dosage to achieve complement blockade; and (2) a dose withdrawal scheme (Table 8)^[84]. EZ monitoring, however, is mandated for better response (Table 6)^[128-131].

HOW TO MONITOR COMPLEMENT BLOCKADE - TABLE 6 DESCRIBES EZ THERAPY MONITORING

Duration of therapy

There is not enough data supporting life-long therapy. However, sustaining EZ seems to be reasonable in certain situations. Figure 5 represents a small guide, meanwhile early biomarkers of disease recurrence and complement activation became available.

Unanswered questions

The lacunae in satisfactory data still present as proper dosage, dose intervals, and duration of therapy^[132], as well as the impact of this type of therapy on transplant spectrum^[133].

Cessation of therapy

Figure 5 represents a guiding scheme suggested for EZ withdrawal^[12].

Is EZ therapy the end of the road?

In 2013, Verhave *et al*^[118] reported the feasibility of successful kidney transplantation without EZ therapy in four patients with high-risk aHUS. Patients received living donor kidneys with a therapeutic regimen consisting of: Basiliximab for induction, tacrolimus in low dosage, prednisone, and MMF for maintenance

Table 9 Risk of atypical hemolytic uremic syndrome recurrence according to the implicated genetic abnormalities

Gene mutation	Location	Functional Impact	Mutation frequency in aHUS (%)	Recurrence after transplantation (%)
CFH	Plasma	Loss	20-30	75-90
CFI	Plasma	Loss	2-12	45-80
CFB	Plasma	Gain	1-2	100
C3	Plasma	Gain	5-10	40-70
MCP	Membrane	Loss	10-15	15-20
THBD	Membrane	Loss	5	One case
Homozygous CFHR1 del (3%-8%)	Circulating	Undetermined	14-23 (> 90% with anti-CHF AB)	NA

Adapted from Salvadori *et al*^[1]. aHUS: Atypical hemolytic uremic syndrome; NA: Not available; CFH: Complement factor H; CFI: Complement factor I; CFB: Complement factor B; C3: Complement 3; MCP: Membrane cofactor protein; THBD: Thrombomodulin.

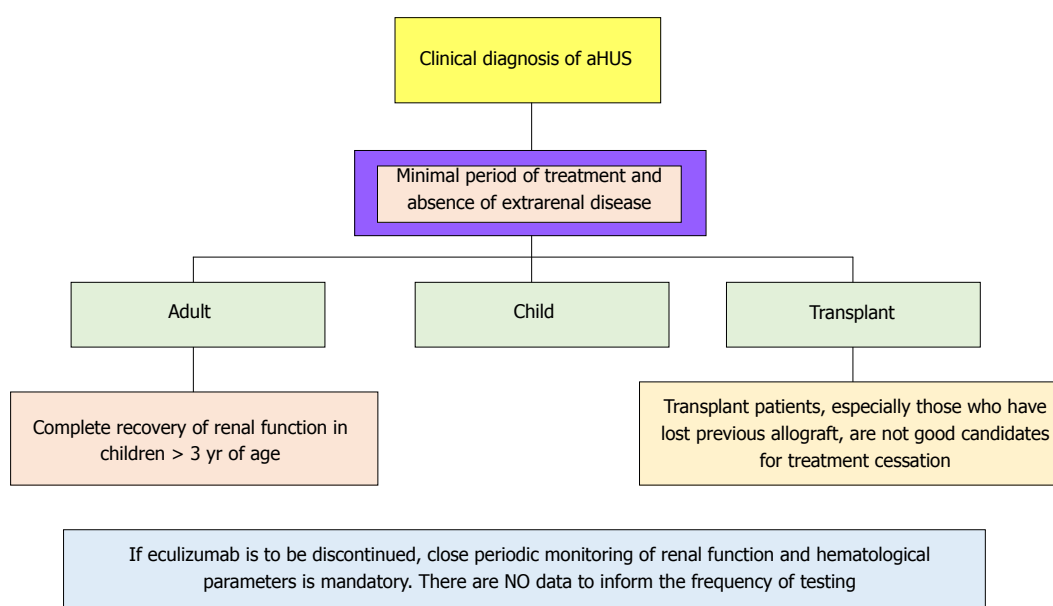


Figure 5 Recommendations for cessation of treatment with complement inhibitors. There are no prospective controlled studies in patients with atypical hemolytic uremic syndrome (aHUS) to define criteria for discontinuation of eculizumab therapy. This flow diagram is based on expert opinion^[134-137]. Discontinuation can be considered on a case-by-case basis in patients after at least 6-12 mo of treatment and at least 3 mo of normalization (or stabilization in the case of residual chronic kidney disease) of kidney function. Earlier cessation (at 3 mo) may be considered in patients (especially children) with pathogenic variants in membrane cofactor protein if there has been rapid remission and recovery of renal function. Patients on dialysis or eculizumab should be maintained for at least 4 to 6 mo before discontinuation. In this setting, assessment of fibrotic changes in kidney biopsy may be helpful. In transplant patients, especially patients who have lost previous allografts, discontinuation is not recommended. Adapted from Goodship *et al*^[12].

immunosuppression. A statin has also been added. Further precautions include: lowering BP as much as tolerable and minimizing the cold ischemic time. For the next 16-21 mo, no recurrence or rejection events have been reported^[118]. The following conclusion has been addressed: successful kidney transplantation in recurrent aHUS patients can be achieved with an EZ-free regimen through: (1) decreasing cold ischemic time; (2) minimizing the risk of rejection; and (3) preserving endothelial integrity^[118].

Renal transplantation in TMA

Timing of transplant: six months after commencing, dialysis should elapse before proceeding in transplant, as renal recovery can be observed several months after initiation of EZ therapy^[137,138]. Two prerequisites should be fulfilled before commencing renal transplantation: (1) resolution of the extrarenal manifestations of TMA;

and (2) recovery of TMA hematological parameters. The magnitude of recurrence risk may be used to evaluate the recipient's need for complement blockade (Table 9)^[1].

CONCLUSION

The role of complement cascade in the evolution of kidney diseases either in the native kidney or post-transplant is well recognized. The prognosis of aHUS and, in some cases, C3G is greatly improved after commencing complement blockade. These agents are not only curative, but also successful in preventing post-transplant disease recurrence. Owing to the inherited nature of most of these diseases, the maintenance of this therapy is recommended despite cost burden. Consequently, the need for regimens allowing safe withdrawal of these agents is urgently required. However, newer therapies (*e.g.*, new monoclonal

antibodies, recombinant proteins, and small interfering RNA (siRNA) agents) hold promise for the near future^[139,140].

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