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

Abbas F *et al*. Post-transplant complement-mediated diseases

Fedaey Abbas, Mohsen El Kossi, Jon Jin Kim, Ihab Sakr Shaheen, Ajay Sharma, Ahmed Halawa

**Fedaey Abbas,** Nephrology Department, Jaber El Ahmed Military Hospital, Safat 13005, Kuwait

**Fedaey Abbas, Mohsen El Kossi, Jon Jin Kim, Ihab Sakr Shaheen, Ajay Sharma, Ahmed Halawa,** Faculty of Health and Science, University of Liverpool, Institute of Learning and Teaching, School of Medicine, Liverpool L69 3GB, United Kingdom

**Mohsen El Kossi,** Doncaster Royal Infirmary, Doncaster DN2 5LT, United Kingdom

**Jon Jin Kim,** Nottingham Children Hospital, Nottingham NG7 2UH, United Kingdom

**Ihab Sakr Shaheen,** Royal Hospital for Children, Glasgow G51 4TF, United Kingdom

**Ajay Sharma,** Royal Liverpool University Hospitals, Liverpool L7 8XP, United Kingdom

**Ahmed Halawa,** Sheffield Teaching Hospitals, Sheffield S57AU, United Kingdom

**ORCID number:** Fedaey Abbas (0000-0001-8673-4344); Mohsen El Kossi ([0000-0002-2490-2784](http://orcid.org/0000-0002-2490-2784)); Jon Jin Kim ([0000-0003-4307-8513](http://orcid.org/0000-0003-4307-8513)); Ihab Sakr Shaheen ([0000-0002-4514-277X](https://orcid.org/0000-0002-4514-277X)); Ajay Sharma ([0000-0003-4050-6586](http://orcid.org/0000-0003-4050-6586)); Ahmed Halawa ([0000-0002-7305-446X](http://orcid.org/0000-0002-7305-446X)).

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**Correspondence to: Ahmed Halawa, FRSC, MD, Senior Lecturer, Consultant Transplant Surgeon,** Sheffield Teaching Hospitals, Herries Road, Sheffield S57AU, United Kingdom. [ahmed.halawa@sth.nhs.uk](mailto:Ahmed.Halawa@sth.nhs.uk)

**Telephone:** +44-778-7542128

**Fax:** +44-114-2714604

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**Abstract**

For decades, kidney diseases related to inappropriate complement activity such as atypical hemolytic uremic syndrome and C3 glomerulopathy, subtype of membranoproliferative glomerulonephritis have been mostly complicated by worse prognosis and rapidly progressing 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 considered non-transplantable cases previously. Several less costly therapeutic lines and probably better efficacy and safety profile are currently underway. In view of the challenging nature of diagnosis of these diseases and 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 much popularity. Complement dysregulation due to inherited or acquired factors is currently the culprit mechanism. Several constitutional abnormalities are usually triggering the process of recurrence with subsequent high rate of graft loss. The development of the terminal complement inhibitor, “eculizumab”, is a breakthrough in controlling the abnormal complement activation. Whilst diagnosing complement abnormalities is one of the challenges, treatment cost with this new agent is a major hurdle in any health care systems. New lines of promising therapies are currently in the pipelines.

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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]. Whilst 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 former class is potentially modifiable by immunosuppression in post-transplantation period, but that is not the case in the latter class. Our understanding of the bio-genetic 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]. The recent progress in understanding the pathophysiology of MPGN led to newer classification 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/polymorphism) or through an acquired (autoantibodies) interference to the regulating components. Histological staining using immunofluorescent (IF) is currently the best determinant technique, and C3G is defined by dominant C3 with disperse and reduced or absent immunoglobulin (Ig). Based on electron microscopy (EM) examination, C3G subdivides into complement 3 glomerulonephritis (C3GN) and dense deposit disease (DDD). In C3GN, deposits can be seen discrete in the mesangium and in capillary walls (subendothelial as well as subepithelial region). On contrary, DDD deposits are large in size, extremely dense (osmiophilic) and intramembranous, that leads to its characteristic thickening of glomerular basement membrane (GBM)[5]. The term aHUS is applied to a heterogenous group of diseases (Figure 1) that share TMA manifestations with associated decline in renal function (classically no IF staining of C3 or any other complement components). In aHUS, complement abnormality (either genetic mutation or acquired autoantibodies) is a well-recognized mechanism with a clearly associated complement-mediated TMA[1]. In this article, we shall discuss various types of complement mediated renal diseases after kidney transplantation with their current therapeutic options.

***Methodology***

In view of the lack of prospective controlled trials concerned with complement-mediated diseases post kidney transplant, we tried in this review to shed the light on the most recent experts’ opinions, as regard the best tools of management of 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, please see [Table 1](http://www.kidney-international.theisn.org/article/S0085-2538(16)30604-4/fulltext#tbl2).

***Pathology***

Renal biopsy is crucial for C3G diagnosis. LM is not helpful due to extremely diverse appearance. IF is the mainstay for diagnosis. A unique criterion on IF study is the presence of dominant C3 staining, with 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, they can be also encountered in C3G. However, the presence of double contours in the GBM raises the possibility of C3G diagnosis. To differentiate DDD from C3GN, EM study 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, refer to 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, it ranges 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](http://www.sciencedirect.com/topics/medicine-and-dentistry/haptoglobin) and appearance of schistocytes in peripheral blood smear. On the other hand, localized (renal-limited) TMA usually presents later in post-transplant course. In acute stage, evidence of endothelial injury with platelet aggregation (thrombosis), fibrinoid necrosis as well as 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, refer to Table 2[15]. As TMA is not always present with full blown systemic picture, 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 the antibody interaction with the endothelium. This is also a fundamental maneuver to differentiate *de novo* from recurrent (positive genetic testing) disease, 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, that represents an accumulation of lipids and complement-rich proteins between Bruch’s membrane and retinal pigmentary epithelium, is commonly reported in age-related macular degeneration but present in 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 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 can be attained through EM studies into C3GN and DDD[20]. Both subtypes are triggered through dysregulation of any parts of the AP. For example, patients may develop C3 convertase stabilizing factor called C3NeF leads to uncontrolled complement activation. Lost function of complement regulatory proteins (CFH or CFI)[20-23], or gain-of-function mutation in C3 leading to resistance to CFH regulation have been postulated as an underlying mechanism (Figure 3).

***Pathophysiology and recurrence of C3G***

Pathophysiology of the 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 due to the presence of autoantibodies can be seen. However, the presence of C3 nephritic factor (C3NeF) is by far the most common acquired complement defect. It has the ability to block CFH-mediated decay with stabilization of the C3 convertase[5,24]. Through binding to C3 convertase, C3NeF has the ability to trigger it about ten times[25,26]. C3 convertase can also block the action of CFH, CR1 as well as the decay accelerating factor (DAF).

C3NeF is prevalent as high as 50-80% in C3G patients[27]. Other autoantibodies have been also 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 protein or completely absent protein H. These mutations can be seen as homozygous or heterozygous forms[31,32]. C3NeF can be also encountered, which denotes clustering of different varieties of risk factors. More recently, genetic mutations involving the CFHR gene mutations have been reported in the C3G cohort of patients[33]. CFHR group genetic mutations[34], deletions[35], duplication[36] as well as hybrid genes[37], have also been observed in C3G patients either in isolated manner or in a familial cohort. Malik and his associates[38] reported that members of one family can develop C3G as an impact of aberrant copies of CFHR3 and CFHR1 loci. The presence of C3G in familiar distribution pays the attention to the genetic base of several C3G varieties and their relation to AP dysregulation.

To summarize, complement dysregulation is the specific etiology of C3G, it could be genetic or acquired. While genetic causes encompasses complement gene mutations, acquired causes include the C3NeFs, which has the ability to impede the normal complement regulation[1]. Moreover, genetic varieties constitute the pathophysiologic base of C3G or 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 been recently attained much popularity[39].

***TMA or C3G?***

Both TMA and C3G have a common underlying causation: The AP dysregulation. However, one question arises, which factors influence the evolution of one disease rather than the other[40]. Prevalence of the fluid phase complement activation dysregulation is in favor of C3G in animal models. On the other hand, complement activation involving capillary walls, can result in TMA evolution[41]. Furthermore, absolute deficiency of CFH is in favor of activation of the fluid phase of complement with subsequent C3G evolution, while the lack or aberrant binding region of CFH 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 mutation in CFHRs cannot inhibit CFH binding to endothelial cell surfaces[42]. Prevalence of C3G in a familial basis, is a robust indicator for the genetic base of its recurrence[1].

***Risk of DDD recurrence***

Despite the well-known microscopy of DDD variant of C3, its pathogenesis has recently only recognized. The 5 years graft survival rate was only 50% in one retrospective study of 75 children[6]. In adults, majority of the recipients developed recurrence in post-transplant period with 25% of them lost their allografts[43]. In another broader cohort included eighty adults and children with C3G, Medjeral-Thomas *et al*[44], reported histological recurrence in all six DDD recipients. Graft loss developed in 50% of his cases. For recipients who developed DDD recurrence, the 10 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, histological recurrence rate was reported to be more than 70%[46,47]. Recurrence may present spontaneously in post-transplant period, though it may take several years to be manifest[47]. This discrepancy raises some questions, *e.g*., impact of longevity of follow up, 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 trustable risk factor correlated to C3 recurrence is the presence of heavy proteinuria, with two thirds of C3 patients are vulnerable for recurrence and 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] failed to conclude a robust evidence for the risk of recurrence. This observation is partially explained by the heterogenicity 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 renal allografts had disease recurrence (50%), 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 months for the two remaining allografts, respectively)[51].

***Diagnosis* *of C3G recurrence***

Appearance of proteinuria, hematuria or eGFR decline 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 fulfilled before 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 WBCs MCP levels; (3) Screening for antibodies to CFH and C3NeFs; and (4) Mutation screening of CFH, CFI, CFB, C3, MCP. Furthermore, recombination in CFHR region should be tested[52].

***Prognosis of DDD/C3GN***

In both DDD/C3GN, recurrent disease is usually associated with allograft loss[6,44,53]. The one year allograft survival was reported to be 94%, 69% at 5 year, and 28% at 10 year. 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 time of first biopsy[44].

***Prognosis of TMA***

Compared to the recurrent TMA, prognosis of *de novo* TMA is quite poor. 50% may lose their graft within couple of years after diagnosis[54,55]. Many reports were in favor of this attitude[54-56]. Before the era of eculizumab (EZ), Schwimmer *et al*[54] reported that 54% of systemic TMA can develop dialysis-requiring AKI and about 38% have lost their allograft. However, no one patient with localized TMA have complicated with TMA-related allograft loss or need 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***

Therapeutic approach for *de novo* C3G therapy is similar to that in recurrent disease. Scarce of information is available about *de novo* C3G[58].

***Treatment of recurrent C3G***

In view of 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 degree of proteinuria and the magnitude of allograft dysfunction (Table 5): (1) Conservative measures, as with other glomerulotides include 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 control in a retrospective study[12,61]; and (3) EZ was firstly reported by Bomback *et al*[62], in treating 6 patients with C3G (3 with DDD and 3 with C3GN) in an open labelled trial. Dose of EZ 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, another patient showed better histological and laboratory findings[62]. Of note, elevated serum membrane attack complex (MAC) level was associated with clinical improvement[63]. Duration of therapy is not yet defined. 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 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 products levels), the impact of EZ therapy will be less impressive, and the process of uncontrolled complement dysregulation persists with consequent ongoing renal injury. Secondly, future application of “soluble C5b-9” as well as “C3 degradation products” 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 the 3 complement pathways activation; (2)CP 40 is a compstatin analog with a selective C3 inhibitor property. CP40 can prevent (*in vitro*) complement-mediated hemolysis induced by C3GN patients’ sera. Moreover, it can abort dysregulated AP activation induced by autoantibodies and genetic 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, and this agent may represent a breakthrough progress 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 antibody reported by Paixao-Cavalcante *et al*[71], anti-FB antibody as described by Subias[72], and anti-properdin antibody as professed by Pauly *et al*[73] targeting complement blockade are 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. Safety and efficacy of the soluble CR1 in normalizing complement activity in pediatric patient with ESRD have been reported. With its ability to breakdown the active C3b, soluble CR1 infusion can induce clinical improvement in C3GN as well as serum levels of MAC in patients with DDD recurrence[37].

The methods of achieving C3GN control are summarized in Table 5[34,75-86]. Until enough data from randomized controlled trials be available, the guideline related to complement blockade therapy of C3GN should be guided by that applied in aHUS (Table 6)[12].

***Renal transplantation for C3G***

Paucity of data is available for 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 may lose 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]. 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): Fresh frozen plasma (FFP) is advised as a reposition fluid, it must be type specific and needs to be 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 given early: (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 presence of underlying complement dysregulation, commencing PE therapy will be beneficial in also 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’s outcome[55,94]; (5) PE/IVIG therapy was successfully associated with a 100% response rate in 5 solid organ transplants complicated by systemic form of TMA. 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 co-stimulation blockade[95].

EZ, an anti-C5 agent that blocks lytic C5b-9 MAC generation, not only revolutionized aHUS therapy but also was effective in prevention of 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 agent has been also documented in 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](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Loupy%2C+A) *et al*[112] reported a similar graft survival (95.8% *vs* 89.7% at 2 year post-transplant, respectively) and estimated GFR (52.6 mL/min *vs* 46.7 mL/min) in comparing PE-treated recipients with 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) proved mutations (not combined with other gene defects) may be safe for kidney donation. Cases with documented TMA and with lack of definite genetic defects may proceed in kidney transplantation under umbrella of intensive PE therapy[114]. Polygenic pattern of TMA should be dealt 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 TMA evolution[116] are advised.PE therapy alone is not sufficient for TMA cure and prevention, the following explanation have been 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 declare that PE has no influence on complement activity.Prophylactic use of rituximab proved to be beneficial as anti-CFH-antibody[119], this effect can be augmented by adding PE therapy[120,121].The anti-C5 monoclonal antibody EZ has been reported to be successful in prevention of 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 to protect the patient by complement blockade, if not already instituted[127]. Unfortunately, this suggestion lacks the proper evidence[12].

## *Therapeutic protocols for aHUS recurrence*

## Given a clear role of complement blockade in management of TMA, two regimens have been suggested: (1) Minimal dosage to achieve complement blockade; and (2) dose withdrawal scheme, please refer to 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 no enough data supporting life-long therapy. However, holding EZ seems to be reasonable in certain situations. Figure 5 represents small guide meanwhile early biomarkers of disease recurrence and complement activation became available.

***Unanswered questions***

The lacunae in satisfactory data still present as regard 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 withdrawal of EZ[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 4 patients with high risk aHUS. Patients received living donor kidneys with therapeutic regimen consisted of: Basiliximab for induction, tacrolimus in low dosage, and prednisone and MMF for maintenance immunosuppression. A statin has been added. Further precautions include: lowering BP as much as tolerable, 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 the endothelial integrity[118].

#### Renal transplantation in TMA

#### Timing of transplant: 6 mo 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 the risk of recurrence may be used to evaluate recipient’s need for complement blockade, please refer to Table 9[1].

**CONCLUSION**

The role of complement cascade in evolution of kidney diseases either in the native kidney or post-transplant is well recognized. The prognosis of aHUS and 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 indicated 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 in the near future[139,140].

**REFERENCES**

1 **Salvadori M**, Bertoni E. Complement related kidney diseases: Recurrence after transplantation. *World J Transplant* 2016; **6**: 632-645 [PMID: 28058212 DOI: 10.5500/wjt.v6.i4.632]

2 **Nester CM**, Barbour T, de Cordoba SR, Dragon-Durey MA, Fremeaux-Bacchi V, Goodship TH, Kavanagh D, Noris M, Pickering M, Sanchez-Corral P, Skerka C, Zipfel P, Smith RJ. Atypical aHUS: State of the art. *Mol Immunol* 2015; **67**: 31-42 [PMID: 25843230 DOI: 10.1016/j.molimm.2015.03.246]

3 **Zipfel PF**, Skerka C, Chen Q, Wiech T, Goodship T, Johnson S, Fremeaux-Bacchi V, Nester C, de Córdoba SR, Noris M, Pickering M, Smith R. The role of complement in C3 glomerulopathy. *Mol Immunol* 2015; **67**: 21-30 [PMID: 25929733 DOI: 10.1016/j.molimm.2015.03.012]

4 **Sethi S**, Fervenza F C. Understanding MPGN in the Native and Transplanted Kidney. Kidney Week 2017. Available from: URL: http://www.kidneynews.org/kidney-news/special-sections/glomerular-disease/understanding-mpgn-in-the-native-and-transplanted-kidney

5 **Sethi S**, Fervenza FC, Zhang Y, Zand L, Vrana JA, Nasr SH, Theis JD, Dogan A, Smith RJ. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. *Kidney Int* 2012; **82**: 465-473 [PMID: 22673887 DOI: 10.1038/ki.2012.212]

6 **Braun MC**, Stablein DM, Hamiwka LA, Bell L, Bartosh SM, Strife CF. Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: The North American Pediatric Renal Transplant Cooperative Study experience. *J Am Soc Nephrol* 2005; **16**: 2225-2233 [PMID: 15888559 DOI: 10.1681/ASN.2005020175]

7 **Zand L**, Lorenz EC, Cosio FG, Fervenza FC, Nasr SH, Gandhi MJ, Smith RJ, Sethi S. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. *J Am Soc Nephrol* 2014; **25**: 1110-1117 [PMID: 24357668 DOI: 10.1681/ASN.2013070715]

8 **Hou J**, Markowitz GS, Bomback AS, Appel GB, Herlitz LC, Barry Stokes M, D'Agati VD. Toward a working definition of C3 glomerulopathy by immunofluorescence. *Kidney Int* 2014; **85**: 450-456 [PMID: 24067430 DOI: 10.1038/ki.2013.340]

9 **Larsen CP**, Ambuzs JM, Bonsib SM, Boils CL, Cossey LN, Messias NC, Silva FG, Wang YH, Gokden N, Walker PD. Membranous-like glomerulopathy with masked IgG kappa deposits. *Kidney Int* 2014; **86**: 154-161 [PMID: 24429395 DOI: 10.1038/ki.2013.548]

10 **Larsen CP**, Messias NC, Walker PD, Fidler ME, Cornell LD, Hernandez LH, Alexander MP, Sethi S, Nasr SH. Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. *Kidney Int* 2015; **88**: 867-873 [PMID: 26154922 DOI: 10.1038/ki.2015.195]

11 **Barbour TD**, Pickering MC, Terence Cook H. Dense deposit disease and C3 glomerulopathy. *Semin Nephrol* 2013; **33**: 493-507 [PMID: 24161036 DOI: 10.1016/j.semnephrol.2013.08.002]

12 **Goodship TH**, Cook HT, Fakhouri F, Fervenza FC, Frémeaux-Bacchi V, Kavanagh D, Nester CM, Noris M, Pickering MC, Rodríguez de Córdoba S, Roumenina LT, Sethi S, Smith RJ; Conference Participants. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* 2017; **91**: 539-551 [PMID: 27989322 DOI: 10.1016/j.kint.2016.10.005]

13 **Karthikeyan V**, Parasuraman R, Shah V, Vera E, Venkat KK. Outcome of plasma exchange therapy in thrombotic microangiopathy after renal transplantation. *Am J Transplant* 2003; **3**: 1289-1294 [PMID: 14510703 DOI: 10.1046/j.1600-6143.2003.00222.x]

14 **Nadasdy T**. Thrombotic microangiopathy in renal allografts: the diagnostic challenge. *Curr Opin Organ Transplant* 2014; **19**: 283-292 [PMID: 24811438 DOI: 10.1097/MOT.0000000000000074]

15 **Bouatou Y**, Bacchi VF, Villard J, Moll S, Martin PY, Hadaya K. Atypical Hemolytic Uremic Syndrome Recurrence after Renal Transplantation: C3-Glomerulonephritis as an Initial Presentation. *Transplant Direct* 2015; **1**: e9 [PMID: 27500215 DOI: 10.1097/TXD.0000000000000518]

16 **Matar D**, Naqvi F, Racusen LC, Carter-Monroe N, Montgomery RA, Alachkar N. Atypical hemolytic uremic syndrome recurrence after kidney transplantation. *Transplantation* 2014; **98**: 1205-1212 [PMID: 24933457 DOI: 10.1097/TP.0000000000000200]

17 **Recalde S**, Tortajada A, Subias M, Anter J, Blasco M, Maranta R, Coco R, Pinto S, Noris M, García-Layana A, Rodríguez de Córdoba S. Molecular Basis of Factor H R1210C Association with Ocular and Renal Diseases. *J Am Soc Nephrol* 2016; **27**: 1305-1311 [PMID: 26376859 DOI: 10.1681/ASN.2015050580]

18 **Fritsche LG**, Chen W, Schu M, Yaspan BL, Yu Y, Thorleifsson G, Zack DJ, Arakawa S, Cipriani V, Ripke S, Igo RP Jr, Buitendijk GH, Sim X, Weeks DE, Guymer RH, Merriam JE, Francis PJ, Hannum G, Agarwal A, Armbrecht AM, Audo I, Aung T, Barile GR, Benchaboune M, Bird AC, Bishop PN, Branham KE, Brooks M, Brucker AJ, Cade WH, Cain MS, Campochiaro PA, Chan CC, Cheng CY, Chew EY, Chin KA, Chowers I, Clayton DG, Cojocaru R, Conley YP, Cornes BK, Daly MJ, Dhillon B, Edwards AO, Evangelou E, Fagerness J, Ferreyra HA, Friedman JS, Geirsdottir A, George RJ, Gieger C, Gupta N, Hagstrom SA, Harding SP, Haritoglou C, Heckenlively JR, Holz FG, Hughes G, Ioannidis JP, Ishibashi T, Joseph P, Jun G, Kamatani Y, Katsanis N, N Keilhauer C, Khan JC, Kim IK, Kiyohara Y, Klein BE, Klein R, Kovach JL, Kozak I, Lee CJ, Lee KE, Lichtner P, Lotery AJ, Meitinger T, Mitchell P, Mohand-Saïd S, Moore AT, Morgan DJ, Morrison MA, Myers CE, Naj AC, Nakamura Y, Okada Y, Orlin A, Ortube MC, Othman MI, Pappas C, Park KH, Pauer GJ, Peachey NS, Poch O, Priya RR, Reynolds R, Richardson AJ, Ripp R, Rudolph G, Ryu E, Sahel JA, Schaumberg DA, Scholl HP, Schwartz SG, Scott WK, Shahid H, Sigurdsson H, Silvestri G, Sivakumaran TA, Smith RT, Sobrin L, Souied EH, Stambolian DE, Stefansson H, Sturgill-Short GM, Takahashi A, Tosakulwong N, Truitt BJ, Tsironi EE, Uitterlinden AG, van Duijn CM, Vijaya L, Vingerling JR, Vithana EN, Webster AR, Wichmann HE, Winkler TW, Wong TY, Wright AF, Zelenika D, Zhang M, Zhao L, Zhang K, Klein ML, Hageman GS, Lathrop GM, Stefansson K, Allikmets R, Baird PN, Gorin MB, Wang JJ, Klaver CC, Seddon JM, Pericak-Vance MA, Iyengar SK, Yates JR, Swaroop A, Weber BH, Kubo M, Deangelis MM, Léveillard T, Thorsteinsdottir U, Haines JL, Farrer LA, Heid IM, Abecasis GR; AMD Gene Consortium. Seven new loci associated with age-related macular degeneration. *Nat Genet* 2013; **45**: 433-439, 439e1-439e2 [PMID: 23455636 DOI: 10.1038/ng.2578]

19 **Mathieson PW**, Würzner R, Oliveria DB, Lachmann PJ, Peters DK. Complement-mediated adipocyte lysis by nephritic factor sera. *J Exp Med* 1993; **177**: 1827-1831 [PMID: 8496694 DOI: 10.1084/jem.177.6.1827]

20 **Sethi S**, Fervenza FC, Zhang Y, Nasr SH, Leung N, Vrana J, Cramer C, Nester CM, Smith RJ. Proliferative glomerulonephritis secondary to dysfunction of the alternative pathway of complement. *Clin J Am Soc Nephrol* 2011; **6**: 1009-1017 [PMID: 21415311 DOI: 10.2215/CJN.07110810]

21 **Sethi S**, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. *Semin Nephrol* 2011; **31**: 341-348 [PMID: 21839367 DOI: 10.1016/j.semnephrol.2011.06.005]

22 **Rincón B**, Bernis C, Garcia A, Traver JA. Mesangiocapillary glomerulonephritis associated with hydatid disease. *Nephrol Dial Transplant* 1993; **8**: 783-784 [PMID: 8414165 DOI: 10.1093/ndt/8.8.783]

23 **Goules A**, Masouridi S, Tzioufas AG, Ioannidis JP, Skopouli FN, Moutsopoulos HM. Clinically significant and biopsy-documented renal involvement in primary Sjögren syndrome. *Medicine* (Baltimore) 2000; **79**: 241-249 [PMID: 10941353 DOI: 10.1097/00005792-200007000-00005]

24 **Servais A**, Noël LH, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey MA, Macher MA, Zuber J, Karras A, Provot F, Moulin B, Grünfeld JP, Niaudet P, Lesavre P, Frémeaux-Bacchi V. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int* 2012; **82**: 454-464 [PMID: 22456601 DOI: 10.1038/ki.2012.63]

25 **Dragon-Durey MA**, Blanc C, Marinozzi MC, van Schaarenburg RA, Trouw LA. Autoantibodies against complement components and functional consequences. *Mol Immunol* 2013; **56**: 213-221 [PMID: 23790637 DOI: 10.1016/j.molimm.2013.05.009]

26 **Smith RJ**, Harris CL, Pickering MC. Dense deposit disease. *Mol Immunol* 2011; **48**: 1604-1610 [PMID: 21601923 DOI: 10.1016/j.molimm.2011.04.005]

27 **Thomas S**, Ranganathan D, Francis L, Madhan K, John GT. Current concepts in C3 glomerulopathy. *Indian J Nephrol* 2014; **24**: 339-348 [PMID: 25484526 DOI: 10.4103/0971-4065.134089]

28 **Chen Q**, Müller D, Rudolph B, Hartmann A, Kuwertz-Bröking E, Wu K, Kirschfink M, Skerka C, Zipfel PF. Combined C3b and factor B autoantibodies and MPGN type II. *N Engl J Med* 2011; **365**: 2340-2342 [PMID: 22168663 DOI: 10.1056/NEJMc1107484]

29 **Goodship TH**, Pappworth IY, Toth T, Denton M, Houlberg K, McCormick F, Warland D, Moore I, Hunze EM, Staniforth SJ, Hayes C, Cavalcante DP, Kavanagh D, Strain L, Herbert AP, Schmidt CQ, Barlow PN, Harris CL, Marchbank KJ. Factor H autoantibodies in membranoproliferative glomerulonephritis. *Mol Immunol* 2012; **52**: 200-206 [PMID: 22721707 DOI: 10.1016/j.molimm.2012.05.009]

30 **Lorcy N**, Rioux-Leclercq N, Lombard ML, Le Pogamp P, Vigneau C. Three kidneys, two diseases, one antibody? *Nephrol Dial Transplant* 2011; **26**: 3811-3813 [PMID: 21813829 DOI: 10.1093/ndt/gfr436]

31 **Dragon-Durey MA**, Frémeaux-Bacchi V, Loirat C, Blouin J, Niaudet P, Deschenes G, Coppo P, Herman Fridman W, Weiss L. Heterozygous and homozygous factor h deficiencies associated with hemolytic uremic syndrome or membranoproliferative glomerulonephritis: report and genetic analysis of 16 cases. *J Am Soc Nephrol* 2004; **15**: 787-795 [PMID: 14978182 DOI: 10.1097/01.ASN.0000115702.28859.A7]

32 **Servais A**, Noël LH, Dragon-Durey MA, Gübler MC, Rémy P, Buob D, Cordonnier C, Makdassi R, Jaber W, Boulanger E, Lesavre P, Frémeaux-Bacchi V. Heterogeneous pattern of renal disease associated with homozygous factor H deficiency. *Hum Pathol* 2011; **42**: 1305-1311 [PMID: 21396679 DOI: 10.1016/j.humpath.2010.11.023]

33 **Skerka C**, Chen Q, Fremeaux-Bacchi V, Roumenina LT. Complement factor H related proteins (CFHRs). *Mol Immunol* 2013; **56**: 170-180 [PMID: 23830046 DOI: 10.1016/j.molimm.2013.06.001]

34 **Besbas N**, Gulhan B, Gucer S, Korkmaz E, Ozaltin F. A novel CFHR5 mutation associated with C3 glomerulonephritis in a Turkish girl. *J Nephrol* 2014; **27**: 457-460 [PMID: 24536001 DOI: 10.1007/s40620-013-0008-1]

35 **Chen Q**, Manzke M, Hartmann A, Büttner M, Amann K, Pauly D, Wiesener M, Skerka C, Zipfel PF. Complement Factor H-Related 5-Hybrid Proteins Anchor Properdin and Activate Complement at Self-Surfaces. *J Am Soc Nephrol* 2016; **27**: 1413-1425 [PMID: 26432903 DOI: 10.1681/ASN.2015020212]

36 **Gale DP**, de Jorge EG, Cook HT, Martinez-Barricarte R, Hadjisavvas A, McLean AG, Pusey CD, Pierides A, Kyriacou K, Athanasiou Y, Voskarides K, Deltas C, Palmer A, Frémeaux-Bacchi V, de Cordoba SR, Maxwell PH, Pickering MC. Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis. *Lancet* 2010; **376**: 794-801 [PMID: 20800271 DOI: 10.1016/S0140-6736(10)60670-8]

37 **Zhang Y**, Nester CM, Holanda DG, Marsh HC, Hammond RA, Thomas LJ, Meyer NC, Hunsicker LG, Sethi S, Smith RJ. Soluble CR1 therapy improves complement regulation in C3 glomerulopathy. *J Am Soc Nephrol* 2013; **24**: 1820-1829 [PMID: 23907509 DOI: 10.1681/ASN.2013010045]

38 **Malik TH**, Lavin PJ, Goicoechea de Jorge E, Vernon KA, Rose KL, Patel MP, de Leeuw M, Neary JJ, Conlon PJ, Winn MP, Pickering MC. A hybrid CFHR3-1 gene causes familial C3 glomerulopathy. *J Am Soc Nephrol* 2012; **23**: 1155-1160 [PMID: 22626820 DOI: 10.1681/ASN.2012020166]

39 **Tortajada A**, Garcìa SP, Gastoldi S, Fernandez JG, Martin Merinero H, Arjona E, Noris M, Rodriguez de Cordoba S. Prevalent FHR1 mutant protein generated by gene conversion reveals crucial role of factor H polymorhisms in atypical hemolytic uremic syndrome. *Immunobiology* 2016; **221**: 1199 [DOI: 10.1016/j.imbio.2016.06.166]

40 **Thurman JM**. Complement in kidney disease: core curriculum 2015. *Am J Kidney Dis* 2015; **65**: 156-168 [PMID: 25441433 DOI: 10.1053/j.ajkd.2014.06.035]

41 **Goicoechea de Jorge E**, Pickering MC. Atypical hemolytic uremic syndrome: telling the difference between H and Y. *Kidney Int* 2010; **78**: 721-723 [PMID: 20877372 DOI: 10.1038/ki.2010.222]

42 **Noris M**, Remuzzi G. Glomerular Diseases Dependent on Complement Activation, Including Atypical Hemolytic Uremic Syndrome, Membranoproliferative Glomerulonephritis, and C3 Glomerulopathy: Core Curriculum 2015. *Am J Kidney Dis* 2015; **66**: 359-375 [PMID: 26032627 DOI: 10.1053/j.ajkd.2015.03.040]

43 **Cochat P**, Fargue S, Mestrallet G, Jungraithmayr T, Koch-Nogueira P, Ranchin B, Zimmerhackl LB. Disease recurrence in paediatric renal transplantation. *Pediatr Nephrol* 2009; **24**: 2097-2108 [PMID: 19247694 DOI: 10.1007/s00467-009-1137-6]

44 **Medjeral-Thomas NR**, O'Shaughnessy MM, O'Regan JA, Traynor C, Flanagan M, Wong L, Teoh CW, Awan A, Waldron M, Cairns T, O'Kelly P, Dorman AM, Pickering MC, Conlon PJ, Cook HT. C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin J Am Soc Nephrol* 2014; **9**: 46-53 [PMID: 24178974 DOI: 10.2215/CJN.04700513]

45 **Angelo JR**, Bell CS, Braun MC. Allograft failure in kidney transplant recipients with membranoproliferative glomerulonephritis. *Am J Kidney Dis* 2011; **57**: 291-299 [PMID: 21215503 DOI: 10.1053/j.ajkd.2010.09.021]

46 **McCaughan JA**, O'Rourke DM, Courtney AE. Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. *Am J Transplant* 2012; **12**: 1046-1051 [PMID: 22233157 DOI: 10.1111/j.1600-6143.2011.03923.x]

47 **Andresdottir MB**, Assmann KJ, Hoitsma AJ, Koene RA, Wetzels JF. Renal transplantation in patients with dense deposit disease: morphological characteristics of recurrent disease and clinical outcome. *Nephrol Dial Transplant* 1999; **14**: 1723-1731 [PMID: 10435883 DOI: 10.1093/ndt/14.7.1723]

48 **Ponticelli C**, Glassock RJ. Posttransplant recurrence of primary glomerulonephritis. *Clin J Am Soc Nephrol* 2010; **5**: 2363-2372 [PMID: 21030574 DOI: 10.2215/CJN.06720810]

49 **Andresdottir MB**, Assmann KJ, Hoitsma AJ, Koene RA, Wetzels JF. Recurrence of type I membranoproliferative glomerulonephritis after renal transplantation: analysis of the incidence, risk factors, and impact on graft survival. *Transplantation* 1997; **63**: 1628-1633 [PMID: 9197358 DOI: 10.1097/00007890-199706150-00016]

50 **Little MA**, Dupont P, Campbell E, Dorman A, Walshe JJ. Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk. *Kidney Int* 2006; **69**: 504-511 [PMID: 16395262 DOI: 10.1038/sj.ki.5000084]

51 **Wong L**, Moran S, Lavin PJ, Dorman AM, Conlon PJ. Kidney transplant outcomes in familial C3 glomerulopathy. *Clin Kidney J* 2016; **9**: 403-407 [PMID: 27274824 DOI: 10.1093/ckj/sfw020]

52 **Zuber J**, Le Quintrec M, Morris H, Frémeaux-Bacchi V, Loirat C, Legendre C. Targeted strategies in the prevention and management of atypical HUS recurrence after kidney transplantation. *Transplant Rev* (Orlando) 2013; **27**: 117-125 [PMID: 23937869 DOI: 10.1016/j.trre.2013.07.003]

53 **Pickering MC**, D'Agati VD, Nester CM, Smith RJ, Haas M, Appel GB, Alpers CE, Bajema IM, Bedrosian C, Braun M, Doyle M, Fakhouri F, Fervenza FC, Fogo AB, Frémeaux-Bacchi V, Gale DP, Goicoechea de Jorge E, Griffin G, Harris CL, Holers VM, Johnson S, Lavin PJ, Medjeral-Thomas N, Paul Morgan B, Nast CC, Noel LH, Peters DK, Rodríguez de Córdoba S, Servais A, Sethi S, Song WC, Tamburini P, Thurman JM, Zavros M, Cook HT. C3 glomerulopathy: consensus report. *Kidney Int* 2013; **84**: 1079-1089 [PMID: 24172683 DOI: 10.1038/ki.2013.377]

54 **Schwimmer J**, Nadasdy TA, Spitalnik PF, Kaplan KL, Zand MS. De novo thrombotic microangiopathy in renal transplant recipients: a comparison of hemolytic uremic syndrome with localized renal thrombotic microangiopathy. *Am J Kidney Dis* 2003; **41**: 471-479 [PMID: 12552512 DOI: 10.1053/ajkd.2003.50058]

55 **Satoskar AA**, Pelletier R, Adams P, Nadasdy GM, Brodsky S, Pesavento T, Henry M, Nadasdy T. De novo thrombotic microangiopathy in renal allograft biopsies-role of antibody-mediated rejection. *Am J Transplant* 2010; **10**: 1804-1811 [PMID: 20659088 DOI: 10.1111/j.1600-6143.2010.03178.x]

56 **Fortin MC**, Raymond MA, Madore F, Fugère JA, Pâquet M, St-Louis G, Hébert MJ. Increased risk of thrombotic microangiopathy in patients receiving a cyclosporin-sirolimus combination. *Am J Transplant* 2004; **4**: 946-952 [PMID: 15147429 DOI: 10.1111/j.1600-6143.2004.00428.x]

57 **Garg N**, Rennke HG, Pavlakis M, Zandi-Nejad K. De novo thrombotic microangiopathy after kidney transplantation. *Transplant Rev* (Orlando) 2018; **32**: 58-68 [PMID: 29157988 DOI: 10.1016/j.trre.2017.10.001]

58 **Java A**, Gaut JP, Brennan DC. De novo membranoproliferative glomerulonephritis III in a renal transplant patient: case report and review of the literature. *Transpl Int* 2012; **25**: e58-e61 [PMID: 22380572 DOI: 10.1111/j.1432-2277.2012.01452.x]

59 **Habbig S**, Mihatsch MJ, Heinen S, Beck B, Emmel M, Skerka C, Kirschfink M, Hoppe B, Zipfel PF, Licht C. C3 deposition glomerulopathy due to a functional factor H defect. *Kidney Int* 2009; **75**: 1230-1234 [PMID: 18633337 DOI: 10.1038/ki.2008.354]

60 **Nester CM**, Smith RJ. Treatment options for C3 glomerulopathy. *Curr Opin Nephrol Hypertens* 2013; **22**: 231-237 [PMID: 23318699 DOI: 10.1097/MNH.0b013e32835da24c]

61 **Rabasco C**, Cavero T, Román E, Rojas-Rivera J, Olea T, Espinosa M, Cabello V, Fernández-Juarez G, González F, Ávila A, Baltar JM, Díaz M, Alegre R, Elías S, Antón M, Frutos MA, Pobes A, Blasco M, Martín F, Bernis C, Macías M, Barroso S, de Lorenzo A, Ariceta G, López-Mendoza M, Rivas B, López-Revuelta K, Campistol JM, Mendizábal S, de Córdoba SR, Praga M; Spanish Group for the Study of Glomerular Diseases (GLOSEN). Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. *Kidney Int* 2015; **88**: 1153-1160 [PMID: 26221755 DOI: 10.1038/ki.2015.227]

62 **Bomback AS**, Smith RJ, Barile GR, Zhang Y, Heher EC, Herlitz L, Stokes MB, Markowitz GS, D'Agati VD, Canetta PA, Radhakrishnan J, Appel GB. Eculizumab for dense deposit disease and C3 glomerulonephritis. *Clin J Am Soc Nephrol* 2012; **7**: 748-756 [PMID: 22403278 DOI: 10.2215/CJN.12901211]

63 **Sanghera P**, Ghanta M, Ozay F, Ariyamuthu VK, Tanriover B. Kidney Diseases Associated With Alternative Complement Pathway Dysregulation and Potential Treatment Options. *Am J Med Sci* 2017; **354**: 533-538 [PMID: 29208248 DOI: 10.1016/j.amjms.2017.03.024]

64 **Gurkan S**, Fyfe B, Weiss L, Xiao X, Zhang Y, Smith RJ. Eculizumab and recurrent C3 glomerulonephritis. *Pediatr Nephrol* 2013; **28**: 1975-1981 [PMID: 23689905 DOI: 10.1007/s00467-013-2503-y]

65 **Herlitz LC**, Bomback AS, Markowitz GS, Stokes MB, Smith RN, Colvin RB, Appel GB, D'Agati VD. Pathology after eculizumab in dense deposit disease and C3 GN. *J Am Soc Nephrol* 2012; **23**: 1229-1237 [PMID: 22677550 DOI: 10.1681/ASN.2011121186]

66 **Garg N**, Zhang Y, Nicholson-Weller A, Khankin EV, Borsa NG, Meyer NC, McDermott S, Stillman IE, Rennke HG, Smith RJ, Pavlakis M. C3 glomerulonephritis secondary to mutations in factors H and I: rapid recurrence in deceased donor kidney transplant effectively treated with eculizumab. *Nephrol Dial Transplant* 2018 [PMID: 29370420 DOI: 10.1093/ndt/gfx369]

67 **Sethi S**, Nester CM, Smith RJ. Membranoproliferative glomerulonephritis and C3 glomerulopathy: resolving the confusion. *Kidney Int* 2012; **81**: 434-441 [PMID: 22157657 DOI: 10.1038/ki.2011.399]

68 **Rose KL**, Paixao-Cavalcante D, Fish J, Manderson AP, Malik TH, Bygrave AE, Lin T, Sacks SH, Walport MJ, Cook HT, Botto M, Pickering MC. Factor I is required for the development of membranoproliferative glomerulonephritis in factor H-deficient mice. *J Clin Invest* 2008; **118**: 608-618 [PMID: 18202746 DOI: 10.1172/JCI32525]

69 **Risitano AM**, Ricklin D, Huang Y, Reis ES, Chen H, Ricci P, Lin Z, Pascariello C, Raia M, Sica M, Del Vecchio L, Pane F, Lupu F, Notaro R, Resuello RR, DeAngelis RA, Lambris JD. Peptide inhibitors of C3 activation as a novel strategy of complement inhibition for the treatment of paroxysmal nocturnal hemoglobinuria. *Blood* 2014; **123**: 2094-2101 [PMID: 24497537 DOI: 10.1182/blood-2013-11-536573]

70 **Reis ES**, DeAngelis RA, Chen H, Resuello RR, Ricklin D, Lambris JD. Therapeutic C3 inhibitor Cp40 abrogates complement activation induced by modern hemodialysis filters. *Immunobiology* 2015; **220**: 476-482 [PMID: 25468722 DOI: 10.1016/j.imbio.2014.10.026]

71 **Paixão-Cavalcante D**, Torreira E, Lindorfer MA, Rodriguez de Cordoba S, Morgan BP, Taylor RP, Llorca O, Harris CL. A humanized antibody that regulates the alternative pathway convertase: potential for therapy of renal disease associated with nephritic factors. *J Immunol* 2014; **192**: 4844-4851 [PMID: 24729617 DOI: 10.4049/jimmunol.1303131]

72 **Subías M**, Tortajada A, Gastoldi S, Galbusera M, López-Perrote A, Lopez Lde J, González-Fernández FA, Villegas-Martínez A, Dominguez M, Llorca O, Noris M, Morgan BP, Rodríguez de Córdoba S. A novel antibody against human factor B that blocks formation of the C3bB proconvertase and inhibits complement activation in disease models. *J Immunol* 2014; **193**: 5567-5575 [PMID: 25355917 DOI: 10.4049/jimmunol.1402013]

73 **Pauly D**, Nagel BM, Reinders J, Killian T, Wulf M, Ackermann S, Ehrenstein B, Zipfel PF, Skerka C, Weber BH. A novel antibody against human properdin inhibits the alternative complement system and specifically detects properdin from blood samples. *PLoS One* 2014; **9**: e96371 [PMID: 24797388 DOI: 10.1371/journal.pone.0096371]

74 **Zhang Y**, Shao D, Ricklin D, Hilkin BM, Nester CM, Lambris JD, Smith RJ. Compstatin analog Cp40 inhibits complement dysregulation in vitro in C3 glomerulopathy. *Immunobiology* 2015; **220**: 993-998 [PMID: 25982307 DOI: 10.1016/j.imbio.2015.04.001]

75 **Bonucchi D**, Leonelli M, Damiano F, Granito M, Ghiandai G, De Amicis S, Americo C, Ligabue G, Albertazzi V, Cappelli G. [Post-transplant recurrence of glomerulonephritis: a complex clinical case]. *G Ital Nefrol* 2010; **27** Suppl 52: S82-S84 [PMID: 21132668]

76 **Daina E**, Noris M, Remuzzi G. Eculizumab in a patient with dense-deposit disease. *N Engl J Med* 2012; **366**: 1161-1163 [PMID: 22435382 DOI: 10.1056/NEJMc1112273]

77 **Garnier AS**, Augusto JF, Pellier I, Subra JF, Sayegh J. Successful long-term outcome of kidney transplantation in a patient with X-linked thrombocytopenia: 9-year follow-up. *Transplantation* 2014; **98**: e57-e58 [PMID: 25221901 DOI: 10.1097/TP.0000000000000338]

78 **Inman M**, Prater G, Fatima H, Wallace E. Eculizumab-induced reversal of dialysis-dependent kidney failure from C3 glomerulonephritis. *Clin Kidney J* 2015; **8**: 445-448 [PMID: 26251714 DOI: 10.1093/ckj/sfv044]

79 **Kerns E**, Rozansky D, Troxell ML. Evolution of immunoglobulin deposition in C3-dominant membranoproliferative glomerulopathy. *Pediatr Nephrol* 2013; **28**: 2227-2231 [PMID: 23892798 DOI: 10.1007/s00467-013-2565-x]

80 **Le Quintrec M**, Lionet A, Kandel C, Bourdon F, Gnemmi V, Colombat M, Goujon JM, Frémeaux-Bacchi V, Fakhouri F. Eculizumab for treatment of rapidly progressive C3 glomerulopathy. *Am J Kidney Dis* 2015; **65**: 484-489 [PMID: 25530108 DOI: 10.1053/j.ajkd.2014.09.025]

81 **Oosterveld MJ**, Garrelfs MR, Hoppe B, Florquin S, Roelofs JJ, van den Heuvel LP, Amann K, Davin JC, Bouts AH, Schriemer PJ, Groothoff JW. Eculizumab in Pediatric Dense Deposit Disease. *Clin J Am Soc Nephrol* 2015; **10**: 1773-1782 [PMID: 26316621 DOI: 10.2215/CJN.01360215]

82 **Ozkaya O**, Nalcacioglu H, Tekcan D, Genc G, Meydan BC, Ozdemir BH, Baysal MK, Keceligil HT. Eculizumab therapy in a patient with dense-deposit disease associated with partial lipodystropy. *Pediatr Nephrol* 2014; **29**: 1283-1287 [PMID: 24464478 DOI: 10.1007/s00467-013-2748-5]

83 **Radhakrishnan S**, Lunn A, Kirschfink M, Thorner P, Hebert D, Langlois V, Pluthero F, Licht C. Eculizumab and refractory membranoproliferative glomerulonephritis. *N Engl J Med* 2012; **366**: 1165-1166 [PMID: 22435384 DOI: 10.1056/NEJMc1106619]

84 **Rousset-Rouvière C**, Cailliez M, Garaix F, Bruno D, Laurent D, Tsimaratos M. Rituximab fails where eculizumab restores renal function in C3nef-related DDD. *Pediatr Nephrol* 2014; **29**: 1107-1111 [PMID: 24408225 DOI: 10.1007/s00467-013-2711-5]

85 **Sánchez-Moreno A**, De la Cerda F, Cabrera R, Fijo J, López-Trascasa M, Bedoya R, Rodríguez de Córdoba S, Ybot-González P. Eculizumab in dense-deposit disease after renal transplantation. *Pediatr Nephrol* 2014; **29**: 2055-2059 [PMID: 24908321 DOI: 10.1007/s00467-014-2839-y]

86 **Vivarelli M**, Pasini A, Emma F. Eculizumab for the treatment of dense-deposit disease. *N Engl J Med* 2012; **366**: 1163-1165 [PMID: 22435383 DOI: 10.1056/NEJMc1111953]

87 **Lu DF**, Moon M, Lanning LD, McCarthy AM, Smith RJ. Clinical features and outcomes of 98 children and adults with dense deposit disease. *Pediatr Nephrol* 2012; **27**: 773-781 [PMID: 22105967 DOI: 10.1007/s00467-011-2059-7]

88 **Czubkowski P**, Pawłowska J, Jankowska I, Teisseyre M, Kamińska D, Markiewicz M, Ryżko J. Successful sirolimus rescue in tacrolimus-induced thrombotic microangiopathy after living-related liver transplantation. *Pediatr Transplant* 2012; **16**: E261-E264 [PMID: 22066835 DOI: 10.1111/j.1399-3046.2011.01601.x]

89 **Franco A**, Hernandez D, Capdevilla L, Errasti P, Gonzalez M, Ruiz JC, Sanchez J; HUS-Sirolimus Spanish Study Group. De novo hemolytic-uremic syndrome/thrombotic microangiopathy in renal transplant patients receiving calcineurin inhibitors: role of sirolimus. *Transplant Proc* 2003; **35**: 1764-1766 [PMID: 12962787 DOI: 10.1016/S0041-1345(03)00614-6]

90 **Epperla N**, Hemauer K, Hamadani M, Friedman KD, Kreuziger LB. Impact of treatment and outcomes for patients with posttransplant drug-associated thrombotic microangiopathy. *Transfusion* 2017; **57**: 2775-2781 [PMID: 28836275 DOI: 10.1111/trf.14263]

91 **McLeod BC**. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. *Best Pract Res Clin Haematol* 2006; **19**: 157-167 [PMID: 16377548 DOI: 10.1016/j.beha.2005.01.004]

92 **Bell WR**, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. *N Engl J Med* 1991; **325**: 398-403 [PMID: 2062331 DOI: 10.1056/NEJM199108083250605]

93 **Le Quintrec M**, Lionet A, Kamar N, Karras A, Barbier S, Buchler M, Fakhouri F, Provost F, Fridman WH, Thervet E, Legendre C, Zuber J, Frémeaux-Bacchi V. Complement mutation-associated de novo thrombotic microangiopathy following kidney transplantation. *Am J Transplant* 2008; **8**: 1694-1701 [PMID: 18557729 DOI: 10.1111/j.1600-6143.2008.02297.x]

94 **Djamali A**, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M. Diagnosis and management of antibody-mediated rejection: current status and novel approaches. *Am J Transplant* 2014; **14**: 255-271 [PMID: 24401076 DOI: 10.1111/ajt.12589]

95 **Masson P**, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev* 2014; **(11)**: CD010699 [PMID: 25416857 DOI: 10.1002/14651858.CD010699.pub2]

96 **Legendre CM**, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nürnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, Sheerin NS, Trivelli A, Zimmerhackl LB, Goodship T, Loirat C. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; **368**: 2169-2181 [PMID: 23738544 DOI: 10.1056/NEJMoa1208981]

97 **Chua JS**, Baelde HJ, Zandbergen M, Wilhelmus S, van Es LA, de Fijter JW, Bruijn JA, Bajema IM, Cohen D. Complement Factor C4d Is a Common Denominator in Thrombotic Microangiopathy. *J Am Soc Nephrol* 2015; **26**: 2239-2247 [PMID: 25573909 DOI: 10.1681/ASN.2014050429]

98 **Shochet L**, Kanellis J, Simpson I, Ta J, Mulley W. De novo thrombotic microangiopathy following simultaneous pancreas and kidney transplantation managed with eculizumab. *Nephrology* (Carlton) 2017; **22** Suppl 1: 23-27 [PMID: 28176480 DOI: 10.1111/nep.12936]

99 **Dedhia P**, Govil A, Mogilishetty G, Alloway RR, Woodle ES, Abu Jawdeh BG. Eculizumab and Belatacept for De Novo Atypical Hemolytic Uremic Syndrome Associated With CFHR3-CFHR1 Deletion in a Kidney Transplant Recipient: A Case Report. *Transplant Proc* 2017; **49**: 188-192 [PMID: 28104134 DOI: 10.1016/j.transproceed.2016.11.008]

100 **Ikeda T**, Okumi M, Unagami K, Kanzawa T, Sawada A, Kawanishi K, Omoto K, Ishida H, Tanabe K. Two cases of kidney transplantation-associated thrombotic microangiopathy successfully treated with eculizumab. *Nephrology* (Carlton) 2016; **21** Suppl 1: 35-40 [PMID: 26970541 DOI: 10.1111/nep.12768]

101 **Safa K**, Logan MS, Batal I, Gabardi S, Rennke HG, Abdi R. Eculizumab for drug-induced de novo posttransplantation thrombotic microangiopathy: A case report. *Clin Nephrol* 2015; **83**: 125-129 [PMID: 24495904 DOI: 10.5414/CN108163]

102 **Loirat C**, Babu S, Furman R, Sheerin N, Cohen D, Gaber O. Eculizumab Efficacy and Safety in Patients With Atypical Hemolytic Uremic Syndrome (aHUS) Resistant to Plasma Exchange/Infusion. Poster presented at the 16th Congress of European Hematology Association (EHA); 2011 June 9-12; London, UK: Abstract 0979

103 **Loirat C**, Muus P, Legendre C, Douglas K, Hourmant M, Delmas Y. A Phase II Study of Eculizumab in Patients with Atypical Hemolytic Uremic Syndrome Receiving Chronic Plasma Exchange/Infusion. Poster presented at the 16th Congress of European Hematology Association (EHA); 2011 June 9-12; London, UK: Abstract 0979

104 **Stegall MD**, Diwan T, Raghavaiah S, Cornell LD, Burns J, Dean PG, Cosio FG, Gandhi MJ, Kremers W, Gloor JM. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. *Am J Transplant* 2011; **11**: 2405-2413 [PMID: 21942930 DOI: 10.1111/j.1600-6143.2011.03757.x]

105 **González-Roncero F**, Suñer M, Bernal G, Cabello V, Toro M, Pereira P, Angel Gentil M. Eculizumab treatment of acute antibody-mediated rejection in renal transplantation: case reports. *Transplant Proc* 2012; **44**: 2690-2694 [PMID: 23146495 DOI: 10.1016/j.transproceed.2012.09.038]

106 **Chehade H**, Rotman S, Matter M, Girardin E, Aubert V, Pascual M. Eculizumab to treat antibody-mediated rejection in a 7-year-old kidney transplant recipient. *Pediatrics* 2015; **135**: e551-e555 [PMID: 25624380 DOI: 10.1542/peds.2014-2275]

107 **Locke JE**, Magro CM, Singer AL, Segev DL, Haas M, Hillel AT, King KE, Kraus E, Lees LM, Melancon JK, Stewart ZA, Warren DS, Zachary AA, Montgomery RA. The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. *Am J Transplant* 2009; **9**: 231-235 [PMID: 18976298 DOI: 10.1111/j.1600-6143.2008.02451.x]

108 **Lonze BE**, Dagher NN, Simpkins CE, Locke JE, Singer AL, Segev DL, Zachary AA, Montgomery RA. Eculizumab, bortezomib and kidney paired donation facilitate transplantation of a highly sensitized patient without vascular access. *Am J Transplant* 2010; **10**: 2154-2160 [PMID: 20636451 DOI: 10.1111/j.1600-6143.2010.03191.x]

109 **Stewart ZA**, Collins TE, Schlueter AJ, Raife TI, Holanda DG, Nair R, Reed AI, Thomas CP. Case report: Eculizumab rescue of severe accelerated antibody-mediated rejection after ABO-incompatible kidney transplant. *Transplant Proc* 2012; **44**: 3033-3036 [PMID: 23195021 DOI: 10.1016/j.transproceed.2012.03.053]

110 **Tran D**, Boucher A, Collette S, Payette A, Royal V, Senécal L. Eculizumab for the Treatment of Severe Antibody-Mediated Rejection: A Case Report and Review of the Literature. *Case Rep Transplant* 2016; **2016**: 9874261 [PMID: 27478676 DOI: 10.1155/2016/9874261]

111 **Orandi BJ**, Zachary AA, Dagher NN, Bagnasco SM, Garonzik-Wang JM, Van Arendonk KJ, Gupta N, Lonze BE, Alachkar N, Kraus ES, Desai NM, Locke JE, Racusen LC, Segev DL, Montgomery RA. Eculizumab and splenectomy as salvage therapy for severe antibody-mediated rejection after HLA-incompatible kidney transplantation. *Transplantation* 2014; **98**: 857-863 [PMID: 25121475 DOI: 10.1097/TP.0000000000000298]

112 **Loupy A**, Viglietti D, Mengel M. Complement inhibition in HLA-incompatible kidney transplants: persisting antibody-mediated injury despite marked decrease of clinical ABMR. *Am J Transplant* 2015; **15**: 1139-1140 [PMID: 25731892 DOI: 10.1111/ajt.13172]

113 **Vernon KA**, Gale DP, de Jorge EG, McLean AG, Galliford J, Pierides A, Maxwell PH, Taube D, Pickering MC, Cook HT. Recurrence of complement factor H-related protein 5 nephropathy in a renal transplant. *Am J Transplant* 2011; **11**: 152-155 [PMID: 21114651 DOI: 10.1111/j.1600-6143.2010.03333.x]

114 **Loirat C**, Fremeaux-Bacchi V. Hemolytic uremic syndrome recurrence after renal transplantation. *Pediatr Transplant* 2008; **12**: 619-629 [PMID: 18482212 DOI: 10.1111/j.1399-3046.2008.00910.x]

115 **Zuber J**, Le Quintrec M, Sberro-Soussan R, Loirat C, Frémeaux-Bacchi V, Legendre C. New insights into postrenal transplant hemolytic uremic syndrome. *Nat Rev Nephrol* 2011; **7**: 23-35 [PMID: 21102542 DOI: 10.1038/nrneph.2010.155]

116 **Noris M**, Remuzzi G. Overview of complement activation and regulation. *Semin Nephrol* 2013; **33**: 479-492 [PMID: 24161035 DOI: 10.1016/j.semnephrol.2013.08.001]

117 **Zuber J**, Le Quintrec M, Krid S, Bertoye C, Gueutin V, Lahoche A, Heyne N, Ardissino G, Chatelet V, Noël LH, Hourmant M, Niaudet P, Frémeaux-Bacchi V, Rondeau E, Legendre C, Loirat C; French Study Group for Atypical HUS. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. *Am J Transplant* 2012; **12**: 3337-3354 [PMID: 22958221 DOI: 10.1111/j.1600-6143.2012.04252.x]

118 **Verhave JC**, Westra D, van Hamersvelt HW, van Helden M, van de Kar NC, Wetzels JF. Living kidney transplantation in adult patients with atypical haemolytic uraemic syndrome. *Neth J Med* 2013; **71**: 342-347 [PMID: 24038559]

119 **Goicoechea de Jorge E**, Caesar JJ, Malik TH, Patel M, Colledge M, Johnson S, Hakobyan S, Morgan BP, Harris CL, Pickering MC, Lea SM. Dimerization of complement factor H-related proteins modulates complement activation in vivo. *Proc Natl Acad Sci USA* 2013; **110**: 4685-4690 [PMID: 23487775 DOI: 10.1073/pnas.1219260110]

120 **Kwon T**, Dragon-Durey MA, Macher MA, Baudouin V, Maisin A, Peuchmaur M, Fremeaux-Bacchi V, Loirat C. Successful pre-transplant management of a patient with anti-factor H autoantibodies-associated haemolytic uraemic syndrome. *Nephrol Dial Transplant* 2008; **23**: 2088-2090 [PMID: 18326881 DOI: 10.1093/ndt/gfn063]

121 **Waters AM**, Pappworth I, Marchbank K, Bockenhauer D, Tullus K, Pickering MC, Strain L, Sebire N, Shroff R, Marks SD, Goodship TH, Rees L. Successful renal transplantation in factor H autoantibody associated HUS with CFHR1 and 3 deficiency and CFH variant G2850T. *Am J Transplant* 2010; **10**: 168-172 [PMID: 19951285 DOI: 10.1111/j.1600-6143.2009.02870.x]

122 **Zimmerhackl LB**, Hofer J, Cortina G, Mark W, Würzner R, Jungraithmayr TC, Khursigara G, Kliche KO, Radauer W. Prophylactic eculizumab after renal transplantation in atypical hemolytic-uremic syndrome. *N Engl J Med* 2010; **362**: 1746-1748 [PMID: 20445192 DOI: 10.1056/NEJMc1001060]

123 **Román-Ortiz E**, Mendizabal Oteiza S, Pinto S, López-Trascasa M, Sánchez-Corral P, Rodríguez de Cordoba S. Eculizumab long-term therapy for pediatric renal transplant in aHUS with CFH/CFHR1 hybrid gene. *Pediatr Nephrol* 2014; **29**: 149-153 [PMID: 23982707 DOI: 10.1007/s00467-013-2591-8]

124 **Nester C**, Stewart Z, Myers D, Jetton J, Nair R, Reed A, Thomas C, Smith R, Brophy P. Pre-emptive eculizumab and plasmapheresis for renal transplant in atypical hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2011; **6**: 1488-1494 [PMID: 21617085 DOI: 10.2215/CJN.10181110]

125 **Krid S**, Roumenina LT, Beury D, Charbit M, Boyer O, Frémeaux-Bacchi V, Niaudet P. Renal transplantation under prophylactic eculizumab in atypical hemolytic uremic syndrome with CFH/CFHR1 hybrid protein. *Am J Transplant* 2012; **12**: 1938-1944 [PMID: 22494769 DOI: 10.1111/j.1600-6143.2012.04051.x]

126 **Pérez-Caballero D**, González-Rubio C, Gallardo ME, Vera M, López-Trascasa M, Rodríguez de Córdoba S, Sánchez-Corral P. Clustering of missense mutations in the C-terminal region of factor H in atypical hemolytic uremic syndrome. *Am J Hum Genet* 2001; **68**: 478-484 [PMID: 11170895 DOI: 10.1086/318201]

127 **Licht C**, Heinen S, Józsi M, Löschmann I, Saunders RE, Perkins SJ, Waldherr R, Skerka C, Kirschfink M, Hoppe B, Zipfel PF. Deletion of Lys224 in regulatory domain 4 of Factor H reveals a novel pathomechanism for dense deposit disease (MPGN II). *Kidney Int* 2006; **70**: 42-50 [PMID: 16612335 DOI: 10.1038/sj.ki.5000269]

128 **West CD**, Witte DP, McAdams AJ. Composition of nephritic factor-generated glomerular deposits in membranoproliferative glomerulonephritis type 2. *Am J Kidney Dis* 2001; **37**: 1120-1130 [PMID: 11382679 DOI: 10.1053/ajkd.2001.24511]

129 **Dragon-Durey MA**, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B, André JL, Takagi N, Cheong HI, Hari P, Le Quintrec M, Niaudet P, Loirat C, Fridman WH, Frémeaux-Bacchi V. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. *J Am Soc Nephrol* 2010; **21**: 2180-2187 [PMID: 21051740 DOI: 10.1681/ASN.2010030315]

130 **Khandelwal P**, Gupta A, Sinha A, Saini S, Hari P, Dragon Durey MA, Bagga A. Effect of plasma exchange and immunosuppressive medications on antibody titers and outcome in anti-complement factor H antibody-associated hemolytic uremic syndrome. *Pediatr Nephrol* 2015; **30**: 451-457 [PMID: 25217328 DOI: 10.1007/s00467-014-2948-7]

131 **Noris M**, Galbusera M, Gastoldi S, Macor P, Banterla F, Bresin E, Tripodo C, Bettoni S, Donadelli R, Valoti E, Tedesco F, Amore A, Coppo R, Ruggenenti P, Gotti E, Remuzzi G. Dynamics of complement activation in aHUS and how to monitor eculizumab therapy. *Blood* 2014; **124**: 1715-1726 [PMID: 25037630 DOI: 10.1182/blood-2014-02-558296]

132 **Tanimoto T**, Oshima Y, Kami M. Eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; **369**: 1378-1379 [PMID: 24088109 DOI: 10.1056/NEJMc1308826]

133 **Zuber J**, Fakhouri F, Roumenina LT, Loirat C, Frémeaux-Bacchi V; French Study Group for aHUS/C3G. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat Rev Nephrol* 2012; **8**: 643-657 [PMID: 23026949 DOI: 10.1038/nrneph.2012.214]

134 **Sheerin NS**, Kavanagh D, Goodship TH, Johnson S. A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. *QJM* 2016; **109**: 27-33 [PMID: 25899302 DOI: 10.1093/qjmed/hcv082]

135 **Wetzels JF**, van de Kar NC. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome. *Am J Kidney Dis* 2015; **65**: 342 [PMID: 25616634 DOI: 10.1053/j.ajkd.2014.04.039]

136 **Ardissino G**, Possenti I, Tel F, Testa S, Salardi S, Ladisa V. Discontinuation of eculizumab treatment in atypical hemolytic uremic syndrome: an update. *Am J Kidney Dis* 2015; **66**: 172-173 [PMID: 26111906 DOI: 10.1053/j.ajkd.2015.04.010]

137 **Povey H**, Vundru R, Junglee N, Jibani M. Renal recovery with eculizumab in atypical hemolytic uremic syndrome following prolonged dialysis. *Clin Nephrol* 2014; **82**: 326-331 [PMID: 23557793 DOI: 10.5414/CN107958]

138 **Licht C**, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, Delmas Y, Douglas K, Furman RR, Gaber OA, Goodship T, Herthelius M, Hourmant M, Legendre CM, Remuzzi G, Sheerin N, Trivelli A, Loirat C. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. *Kidney Int* 2015; **87**: 1061-1073 [PMID: 25651368 DOI: 10.1038/ki.2014.423]

139 **Thurman JM**, Le Quintrec M. Targeting the complement cascade: novel treatments coming down the pike. *Kidney Int* 2016; **90**: 746-752 [PMID: 27325183 DOI: 10.1016/j.kint.2016.04.018]

140 **Le KN**, Gibiansky L, van Lookeren Campagne M, Good J, Davancaze T, Loyet KM, Morimoto A, Strauss EC, Jin JY. Population Pharmacokinetics and Pharmacodynamics of Lampalizumab Administered Intravitreally to Patients With Geographic Atrophy. *CPT Pharmacometrics Syst Pharmacol* 2015; **4**: 595-604 [PMID: 26535160 DOI: 10.1002/psp4.12031]

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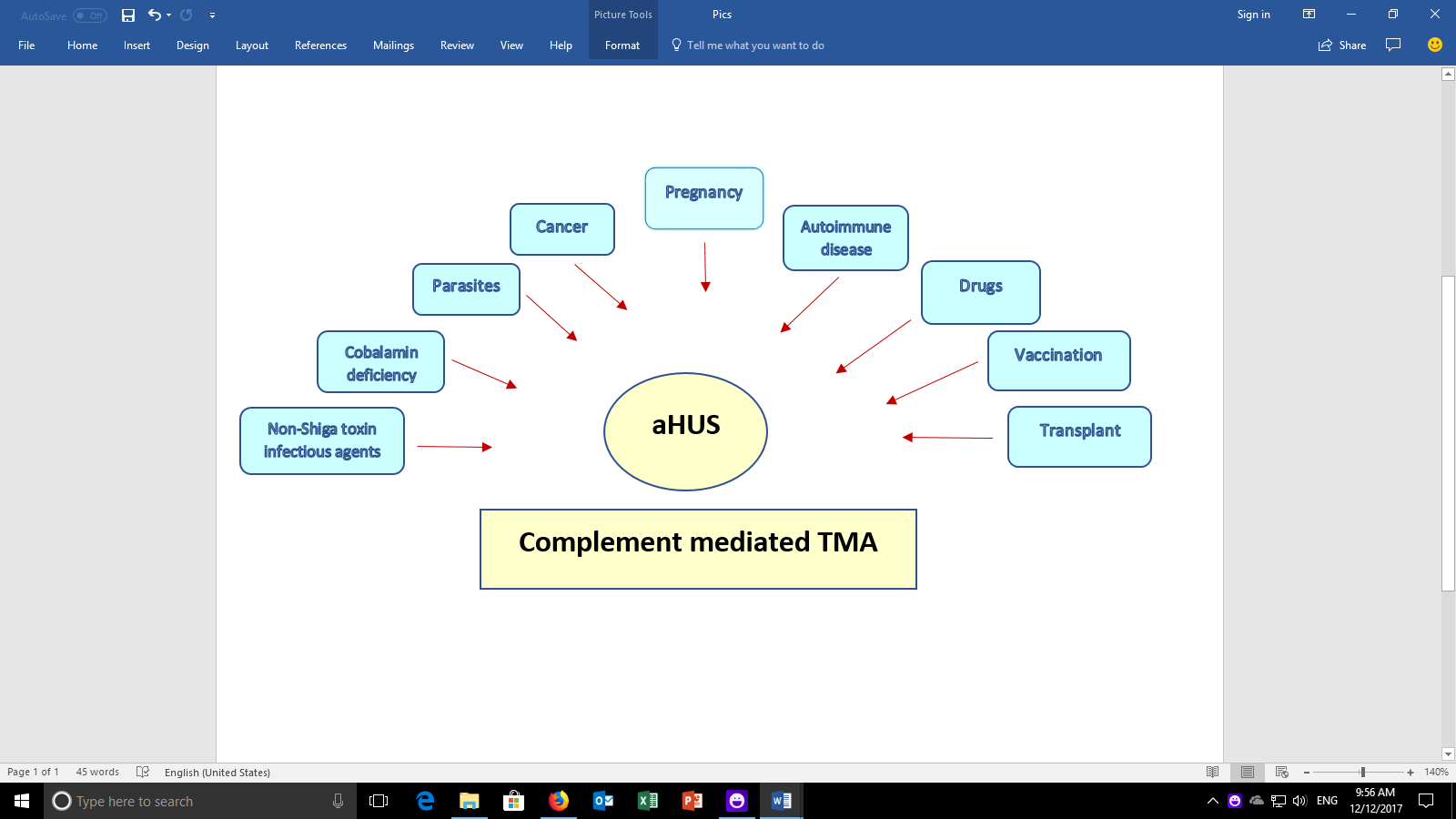
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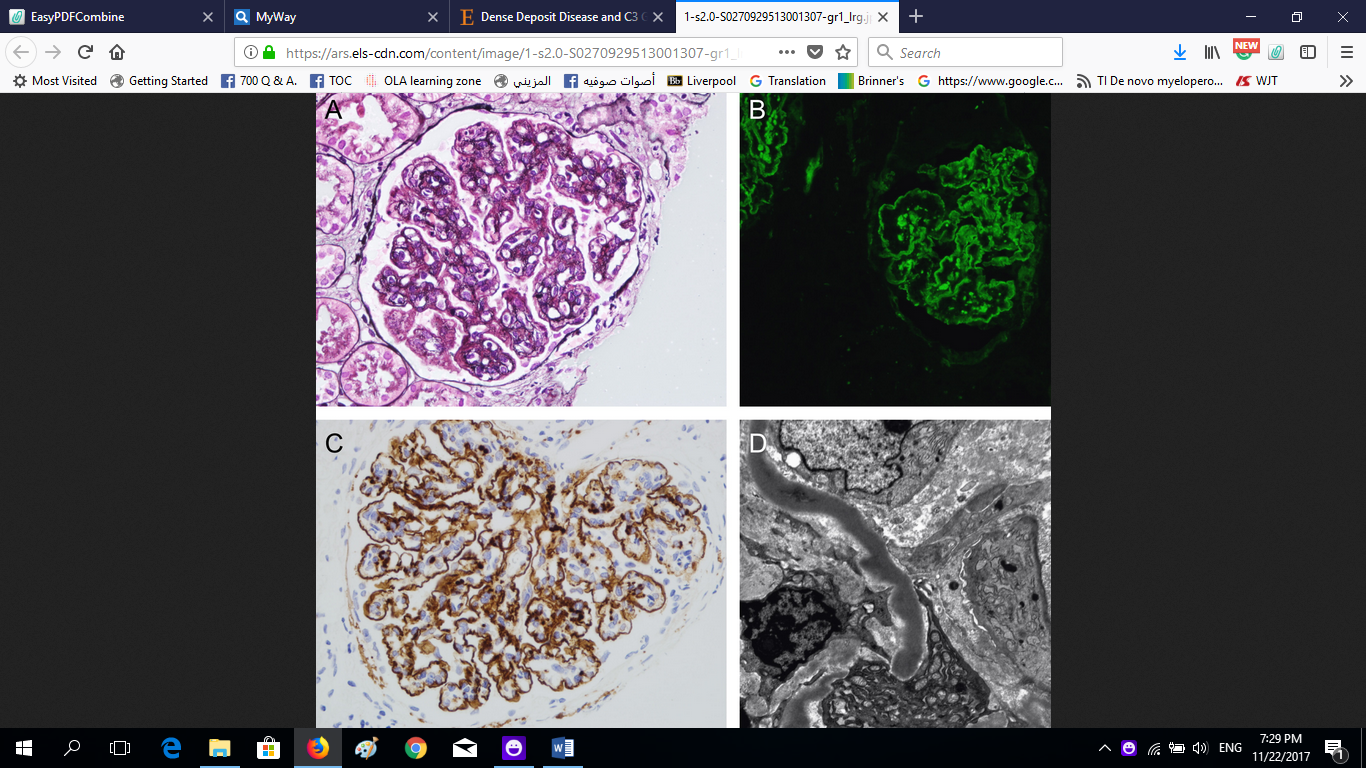
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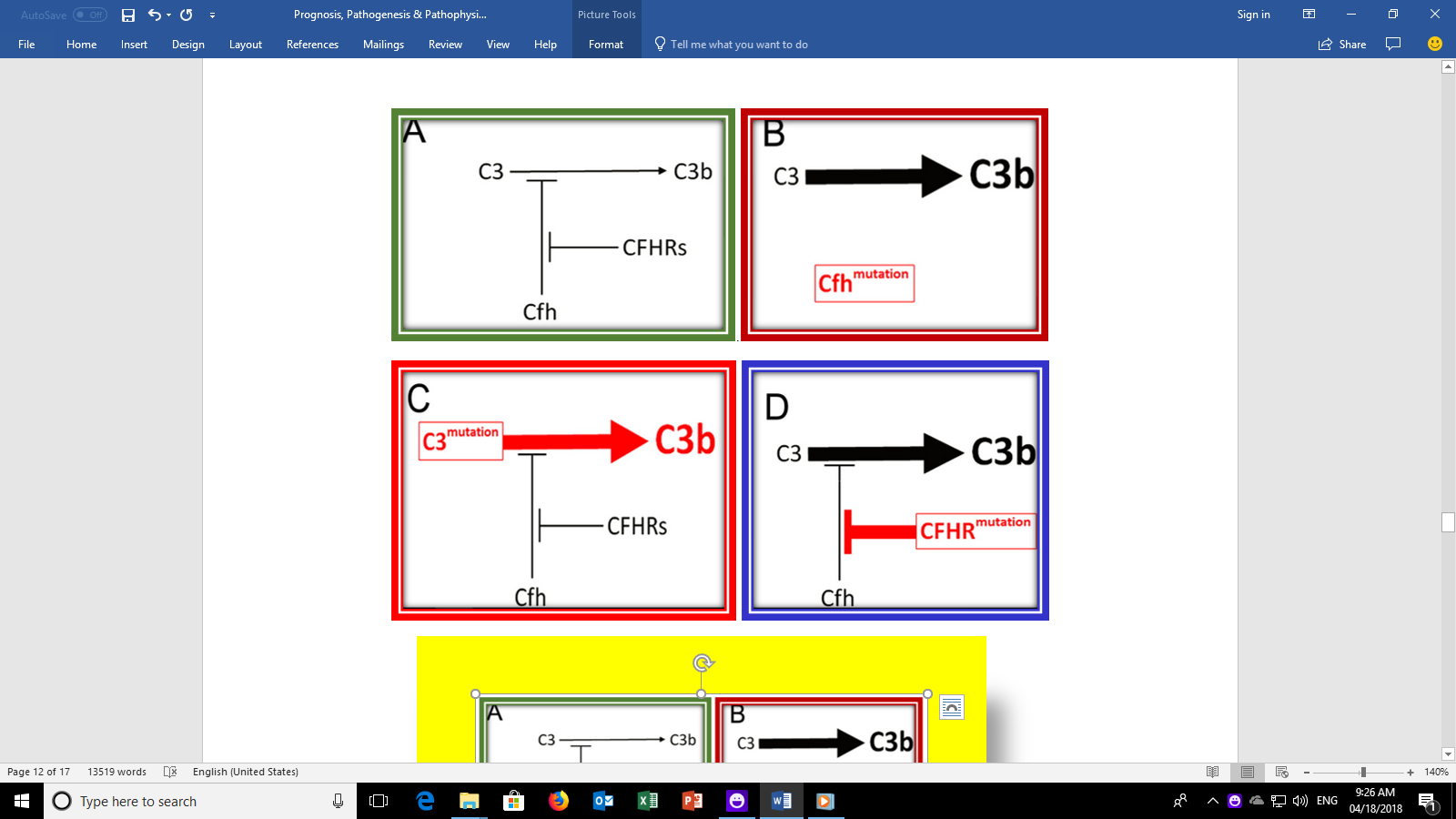
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[**Figure 1**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5175220/figure/F3/) **Heterogeneity of atypical hemolytic uremic syndrome.** Adapted from Salvadori *et al*[1]. TMA: Thrombotic microangiopathy; aHUS: Atypical hemolytic uremic syndrome.

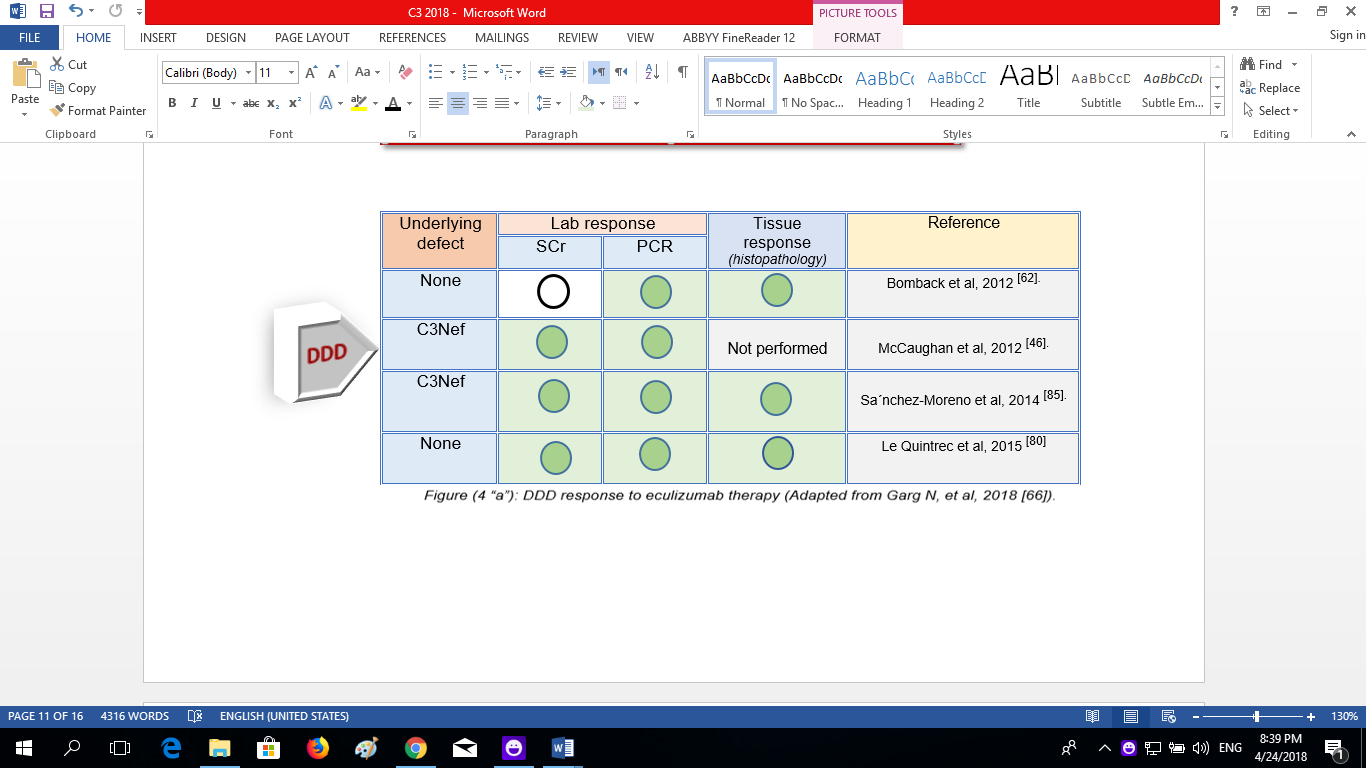


**Figure 2 Renal histology in individuals with dense deposit disease.** A: Light microscopy with silver stain showing a membranoproliferative glomerulonephritis pattern with double contours of the glomerular basement membrane; B: Immunofluorescence; C: Immunohistochemistry with immunoperoxidase showing 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].

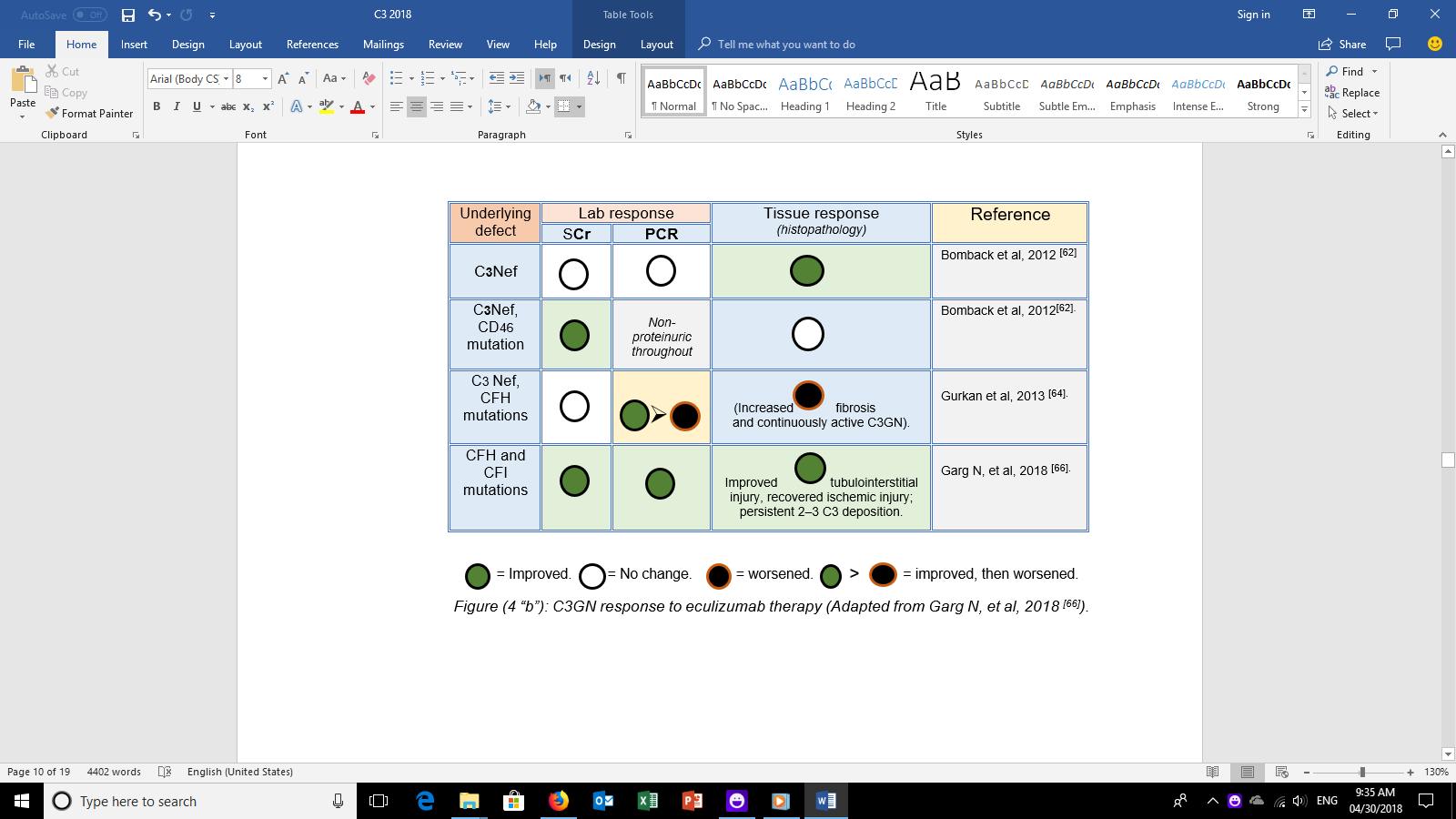


**Figure 3 Disease mechanisms in C3 glomerulopathy, based on genetic defects identified in family studies.** A: Physiological regulation of C3 activation to C3b via the alternative pathway is mediated by complement factor H (CFH) (Cfh). Competitive inhibition of CFH by CFHR proteins is termed CFH deregulation; 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].

A



B

(B)

**Figure 4 Response of complement 3 glomerulopathy subtypes to eculizumab therapy as regard 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.

**Clinical diagnosis of aHUS**

**Minimal period of treatment and absence of extrarenal disease**

Transplant

Adult

Child

Complete recovery of renal function in children > 3 years of age

Transplant patients especially those who have lost previous allograft, are not good candidate for treatment cessation

*If eculizumab is to be discontinued close periodic monitoring of renal function and hematological parameters is mandatory. There are NO data to inform the frequency of testing.*

**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, 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].

**Table 1 Morphological features of C3 glomerulopathy**

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

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

**Table 2 Morphological features in microangiopathy**

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

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

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

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

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

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

|  |  |
| --- | --- |
| **Genetic defect** | **Phenotypical expression** |
| Duplication in *CFHR5* gene | C3 glomerulopathy  (CFHR5 nephropathy) |
| Duplication in *CFHR1* gene | C3 glomerulopathy |
| Hybrid *CFHR3/CFHR1* | C3 glomerulopathy |
| Hybrid *CFHR2/CFHR5* | C3 glomerulopathy |
| Hybrid *CFH/CFHR1* | aHUS |
| Hybrid *CFH/CFHR3* | aHUS |

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

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

Adapted from Goodship *et al*[12].

**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  **Recommended goal during therapeutic complement blockade: < 10%** of normal | 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 Mg2+-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.  **Recommended goal during complement blockade: < 10**% of normal | May be a free or bound level  ELISA: Using C5 coated plates, patient sera, and an anti-human IgG detection system  Not affected by comp-lement deficiencies  **Recommended trough level during compleme-nt blockade:** 50-100 μg/mL | **The following assays are under investigation**  Free C5  In vitro human microvascular endothelial cell test  SC5b-9 (also referred to as sMAC and TCC) remain detectable in aHUS remission and so, not recommended as a monitoring tool |

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 (*e.g*., 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’re 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.

**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 blockade1  Dose reduction or interval extension  Goal CH50 < 10% (recommended)  Goal AH50 < 10% (recommended)  Goal eculizumab trough >100 μg/mL | Desire to discontinue complement blockade  No consensus exists regarding tapering of dose |

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.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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.