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Thrombotic microangiopathy after renal transplantation: Current insights in *de novo* and recurrent disease

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Abstract

Thrombotic microangiopathy (TMA) is one of the most devastating sequelae of kidney transplantation. A number of published articles have covered either *de novo* or recurrent TMA in an isolated manner. We have, hereby, in this article endeavored to address both types of TMA in a comparative mode. We appreciate that *de novo* TMA is more common and its prognosis is poorer than recurrent TMA; the latter has a genetic background, with mutations that impact disease behavior and, consequently, allograft and patient survival. Post-transplant TMA can occur as a recurrence of the disease involving the native kidney or as *de novo* disease with no evidence of previous involvement before transplant. While atypical hemolytic uremic syndrome is a rare disease that results from complement dysregulation with alternative pathway overactivity, *de novo* TMA is a heterogeneous set of various etiologies and constitutes the vast majority of post-transplant TMA cases. Management of both diseases varies from simple maneuvers, *e.g.*, plasmapheresis, drug withdrawal or dose modification, to lifelong complement blockade, which is rather costly. Careful donor selection and proper recipient preparation, including complete genetic screening, would be a pragmatic approach. Novel therapies, *e.g.*, purified

products of the deficient genes, though promising in theory, are not yet of proven value.

Key words: Kidney transplantation; *De novo* thrombotic microangiopathy; Thrombotic microangiopathy; Recurrent thrombotic microangiopathy; Atypical hemolytic uremic syndrome

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Core tip: Many articles in the literature have covered either *de novo* or recurrent thrombotic microangiopathy (TMA) in an isolated manner; we tried here in this article to gather the criteria of both types in one review for comparison. Contrary to what was believed in the past, *de novo* TMA is more common and its prognosis is poorer. On the other hand, recurrent TMA relies on a wide base of genetic backgrounds, with mutation errors differing in their impact on disease behavior and consequently on allograft and patient survival. This base for instance is rapidly expanding, and ultimately warrants a parallel robust work up regimen.

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INTRODUCTION

Thrombotic microangiopathy (TMA) is a debilitating complication of kidney transplantation that is associated with poor patient and graft outcomes. The incidence of post-transplant TMA has been reported to be 5.6 cases per 1000 renal transplant recipients per year with a 50% mortality rate three years after diagnosis^[1]. TMA after transplantation can be classified into either: (1) *De novo* TMA, *i.e.*, developed for the first time without any evidence of the disease before transplant; and (2) Recurrent TMA, *i.e.*, native kidneys failed as a result of TMA and it came back in renal transplantation. Since renal biopsy of native kidney is not performed in many patients with end stage renal disease (ESRD), missed diagnosis of TMA prior to kidney transplantation is likely. With the advent of the drug eculizumab, an anti C5 monoclonal antibody, that is highly effective in prevention as well as treatment of atypical hemolytic uremic syndrome (aHUS), it would be crucial to know the etiology of ESRD in order to differentiate *de novo* from recurrence. Such distinction will invariably have clear clinical and therapeutic implications. In this review, we shall try to discuss the main differences between the two categories in the pathophysiology, clinical course and available approaches of prevention and treatment.

DE NOVO TMA

In the presence of acquired or genetic dysregulation of the alternative complement pathway (AP), a number of precipitating factors have been identified in the context of renal transplantation that trigger the development of *de novo* TMA. These factors include the following: (1) Antibody mediated rejection (AMR); (2) Immunosuppressive-associated TMA: Calcineurin inhibitors (CNI) or mTOR inhibitors (mTORi), single or combined; (3) Other medications: *e.g.*, anti-vascular endothelial growth factor inhibitors (anti-VGFI); (4) Viral infection: *e.g.*, HCV, CMV, BK and parvovirus; (5) Genetic abnormalities in the complement cascade; (6) Phenotypical shift of C3 glomerulopathy (with ESRD), to an aHUS post transplantation; and (7) Missed diagnosis of TMA in the native kidney as a cause of ESRD (*i.e.*, recurrent TMA)^[2].

Which is more prevalent, *de novo* or recurrent TMA?

Reynolds *et al.*^[1], in a United States Renal Data System (USRDS)-based study, declared that the number of recurrent TMA cases was only 12 compared to 112 patients with *de novo* TMA, though the risk of post-transplant TMA recurrence was 36.5 times higher in kidney transplant recipients with ESRD due to hemolytic uremic syndrome (HUS) as compared to other etiologies (29.2% vs 0.8%)^[1]. Langer *et al.*^[3] reported the incidence of *de novo* TMA to be 1.5%. However, the incidence of *de novo* TMA is mentioned to be as high as 3%-14%^[4,5]. It is clear that *de novo* TMA is more prevalent after kidney transplantation and presumably underestimated. Graft loss rate of 40% is reported in *de novo* TMA within a couple of years of diagnosis^[5,6].

Etiopathogenesis of *de novo* TMA

AMR and medications are the two main causes of *de novo* TMA. In addition, the role of complement abnormalities is becoming more apparent with one study reporting an underlying complement mutational abnormality in one third of patients with *de novo* TMA^[7].

Calcineurin-induced TMA: The link between CNI (CyA and tacrolimus) administration and the evolution of *de novo* TMA is not a new concept. Three underlying mechanisms could explain the role of CNI in TMA development: (1) Loss of the normal balance between the vasodilator peptides (*e.g.*, prostaglandin (PG) E2 and prostacyclin (PGI₂)) and the vasoconstrictor peptides (*e.g.*, thromboxane A2 and endothelin), results in arteriolar vasoconstriction^[8,9], renal ischemia and establishment of endothelial injury^[10]; (2) CNI-induced platelet activation, pro-coagulant and anti-fibrinolytic activity have been shown to be involved in TMA evolution, particularly so, with an injured endothelium due to AMR, ischemia-reperfusion injury or any other etiology^[10-12]; and (3) Microparticle production from endothelial cells, a known effect of CyA that can result in activation of the AP, a well-known mechanism that is implicated in

TMA evolution^[13]. However, three trap points have been speculated to oppose the role of CNI: (1) Patients utilizing CNI to maintain immunosuppression represent more than 95% of kidney transplant recipients (KTR), and only a small percentage can develop TMA, which suggests the presence of another underlying predisposing factor (s)^[14]; (2) CNI withdrawal in *de novo* TMA does not always guarantee a favorable graft outcome^[6]; (3) A USRDS-based study demonstrates a significantly higher incidence of TMA in the group of KTR that was not under CNI maintenance therapy (11.9/1000/year), as compared to those on CNI maintenance (5.0/1000/year)^[1].

mTOR inhibitor-associated TMA: mTORi can inhibit cell cycle progression and proliferation. Both sirolimus and everolimus have been reported to be implicated in the pathogenesis of *de novo* TMA. The following explanations have been given: (1) mTORi has antiangiogenic properties, and can decrease renal expression of vascular endothelial growth factor (VEGF) with death of the endothelial progenitor cells. These effects are proven to be implicated in TMA pathogenesis^[15,16]; (2) The VEGF inhibition has been recently proven to be associated with reduced renal levels of complement factor H (CFH)^[17]. Patients with underlying CFH genetic mutations are more susceptible to develop *de novo* TMA, particularly with mTORi exposure^[7]; (3) Repair of endothelial injury could be hampered by mTORi use^[18-20]; and (4) Furthermore, the procoagulant and the antifibrinolytic activity of mTORi might play additional roles in *de novo* TMA development^[21,22].

The exact role of mTORi in the evolution of *de novo* TMA is not fully understood^[3,18,23]. Some authors have suggested that the impact of these medications may exceed that of CNI in the development of *de novo* TMA^[1,24]. However, interpretation of these data may be limited by the fact that mTORi itself, *e.g.*, sirolimus, may be used as a rescue medication in the case of diagnosis of CNI-induced TMA^[1,24]. The risk of development of TMA with combined CNI and mTORi protocols is higher than using mTORi alone, an effect that has been documented in several studies. While Fortin *et al.*^[18] reported that the highest risk of *de novo* TMA was in the group using CNI and mTORi, Nava *et al.*^[20] studied 396 KTR, 36 (7.3%) developed TMA and 17 of them were drug-related. Not only were the drug levels of CNI and mTORi higher in the TMA group, but the sum of both drug levels in the TMA group was also higher^[18-20]. An explanation for this additive risk is that the repair of the endothelial injury induced by CNI is hampered by mTORi^[18-20]. Therefore, immunosuppression protocols using drug combinations should be planned cautiously, when high doses of these agents are usually used in the early post-transplant period^[7].

AMR-associated *de novo* TMA: The role of AMR in the development of post-transplant TMA is commonly reported and well-recognized^[1]. Endothelial cells are a well-known target of allo-immune response.

The peritubular capillary (PTC) C4d staining (a well-recognized surrogate marker of AMR) has been reported to be present in 16.2% of biopsied recipients with TMA^[1,25]. Moreover, Satoskar *et al.*^[6] reported an incidence of 55% of *de novo* TMA patients who express diffuse PTC C4d positivity. The observed prevalent administration of CyA in this study argued that it may have an augmenting effect on TMA prevalence. However, the observed difference between TMA in patients with C4d positive biopsy (13.6%) and that in C4d negative biopsies (3.6%) favors a postulated role of humoral rejection in the evolution of post-transplant TMA^[2]. Both studies, for instance, demonstrated that clustering of both AMR and TMA would predict much worse graft outcome^[6,26].

Other causes: Several less common etiologies have been reported to be involved in TMA pathogenesis and include: Viral infection, *e.g.*, CMV infection^[27,28], BK virus^[29], parvovirus^[30,31], chronic hepatitis C virus (with or without anti-cardiolipin seropositivity)^[32,33], and antiviral medications, *e.g.*, ribavirin and interferon^[34] and disseminated histoplasmosis^[35,36]. Ischemia-reperfusion injury can augment complement-associated injury through complement activation^[37]. An acquired disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency- another rare risk factor- has been shown in one case to represent post-transplant TMA^[38,39]. Unfortunately, the role of rare risk factors is rather difficult to evaluate in controlled studies. Living donation, on the other hand, has not been shown to guarantee any protection against graft dysfunction^[5]. Interestingly, a C3 glomerulopathy disease in a native kidney can undergo phenotypical shift and present after kidney transplantation as *de novo* TMA^[40].

Complement gene mutations: Chua *et al.*^[41] reported that renal complement activation is the common denominator in such a heterogeneous condition. They observed C4d deposits in more than 88% and C4d with localized C5b-9 in about 60% of 42 biopsy samples from patients with histologically confirmed diagnosis of TMA from a heterogeneous group of patients^[41]. Moreover, Le Quintrec *et al.*^[7] reported the presence of genetic mutations in CFH, Complement Factor I (CFI) or both in 29% of their studied *de novo* TMA patients, 25% showed low Complement Factor B (CFB) and/or low C3, suggesting an AP complement activation. No mutations have been found in healthy controls (100) or in TMA-free KTR controls^[7].

Relation to TMA evolution: The AP depends on two main regulators: CFH and CFI. CFH has the ability to inhibit the C3 cleaving enzyme C3bBb. Moreover, it can serve as co-factor for FI, and the latter has the ability to inactivate C3b. Consequently, inactivation of these proteins either due to genetic mutations or development of neutralizing antibodies, can trigger an uncontrolled AP activity, leading to endothelial injury, the pathogenetic

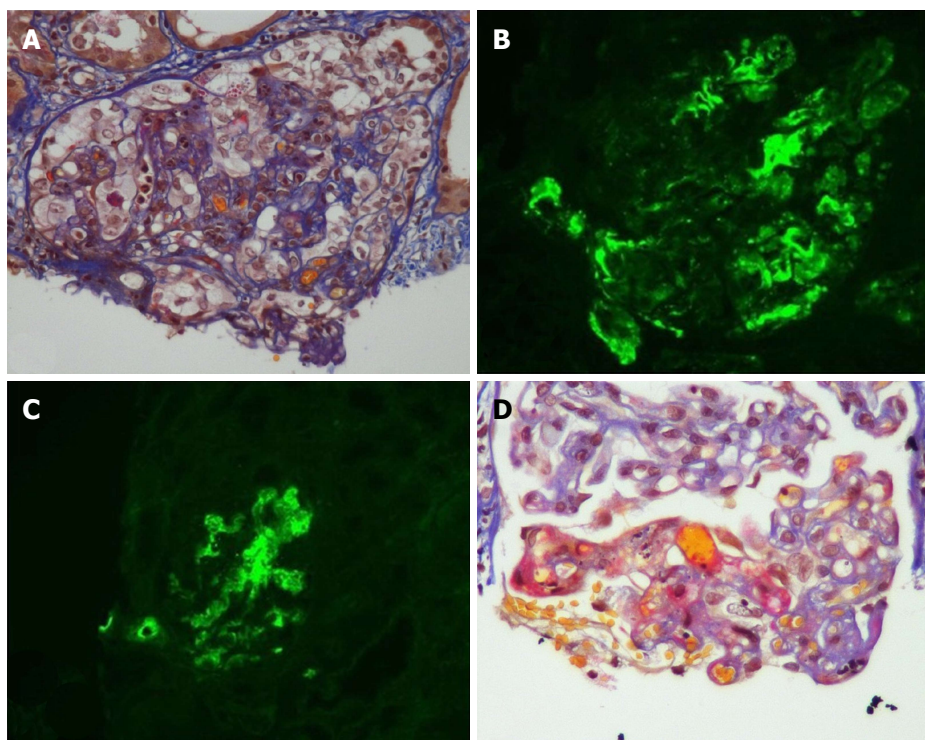


Figure 1 Acute and chronic thrombotic microangiopathy and calcineurin inhibitors-associated arteriolopathy with severe acute ischemic tubular lesions. A: Advanced interstitial inflammatory fibrosis (Masson trichrome stain); B: Immunofluorescence, diffuse and segmental C3; C: C1q deposits within glomerular capillary walls; D: Diffuse acute and chronic arteriolar and glomerular thrombotic microangiopathy lesions on light microscopy (LM). (Adapted from: Yassine *et al.*^[45]).

basis of TMA. Interpreting the results of the above study may suggest an overlap between aHUS and TMA. However, multiple mutational gene varieties related to complement and the coagulation-fibrinolysis cascades have been recently recognized in TMA patients^[42].

Clinical manifestations

Timing: TMA could develop at any time in the post transplantation course^[5,43], however this syndrome is mostly encountered in the first 3-6 mo post transplantation. This is probably when the CNI immunosuppressive trough levels are relatively higher^[1].

Salient features: TMA manifestations are quite variable and can vary from a limited form confined to the kidney to a full blown systemic variant^[4,6,44]. The systemic form of TMA consists of the classic triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and acute kidney injury (AKI). Features of MAHA include raised lactic acid dehydrogenase (LDH), drop in hemoglobin (HB) and decreased haptoglobin with schistocytes on peripheral blood smear. Localized (limited) TMA is usually presented later in TMA course, as compared to the systemic form, which can be explained by the urgency of the systemic type, necessitating the diagnostic allograft biopsy^[4]. When a renal transplant recipient has significant renal dysfunction and the biopsy does not show any acute rejection, one must suspect two possibilities: (1) TMA or (2) Renal artery stenosis. The histopathologic changes are usually non-specific but vary in the acute

status to the chronic angiopathic changes. In the active stage, there is evidence of endothelial cell injury with platelet aggregation (thrombosis), fibrinoid necrosis and glomerular ischemia. In the chronic stage, the basement membranes undergo duplication and multilayering with increased matrix layers and vessel wall cells, which ultimately ends in the unique onion skin formation (Figure 1)^[2,45].

Once the diagnosis of TMA has been established, a prompt revision of the etiology of the native kidney ESRD should be instituted. In aHUS patients who do not show systemic manifestations, the diagnosis could be obscure. In the absence of renal biopsy, many cases can be misdiagnosed as hypertensive nephrosclerosis^[2]. Consequently, a prompt testing for genetic mutations should be accomplished to unmask an underlying complement dysregulation and avoid missing the diagnosis of a recurrent aHUS. This approach has key therapeutic implications, since *de novo* TMA has limited therapeutic options, in contrast to recurrent aHUS after transplantation, which has a better chance of C-5 blockade through the monoclonal antibody eculizumab, an effective therapeutic agent not only for treatment, but also for prevention of recurrence^[2,46].

Prognosis of *de novo* TMA: The prognosis of post-transplant *de novo* TMA is quite poor for the patient and as well as the allograft. About one half of the patients loses their graft within the first two years after diagnosis^[4,6]. This is supported by the USRDS-based

Table 1 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*^[38]. EM: Electron microscopy; LM: Light microscopy.

report presented by Reynolds *et al*^[1] that reported a patient mortality rate of 50% after three years of diagnosis. Many studies support these results^[4-6,18]. To compare systemic versus localized TMA, Schwimmer *et al*^[4] reported that 54% of systemic TMA develops dialysis-requiring AKI and 38% lost their grafts. On the other hand, none of the patients with localized TMA developed TMA-related early graft loss or required dialysis. Unfortunately, this variation in both types of behavior has not reflected on graft survival, as both types of TMA face poor long-term graft survival^[2,4].

RECURRENT TMA AFTER RENAL TRANSPLANTATION

Etiology of recurrent TMA

aHUS; thrombotic thrombocytopenic purpura (TTP); and autoimmune diseases: *e.g.*, scleroderma and systemic lupus erythematosus, with or without anti-phospholipid antibody syndrome^[2].

aHUS: Recurrence of TMA in the allograft depends on the underlying type involving the native kidney. Overactivation of the AP is known to be the underlying etiology of aHUS. By far, aHUS is the most common diagnosis in TMA associated with recurrence. Risk of recurrence is greatly dependent on the underlying associated abnormality^[47]. For example, mutational abnormality involving CFH and CFI, regulatory complement components produced by the liver, results in aberrant CFH and CFI. After transplant, CFH and CFI have a robust impact in the evolution of aHUS recurrence. The reported rate of aHUS recurrence approached 70%-90%^[47,48]. Membrane co-factor protein (MCP), a transmembrane complement regulatory component that is produced by kidney endothelial cells even in post-transplant period, keeps aHUS recurrence lower unless other mutational gene defects have been associated^[47-49]. Additional MCP mutations (> 22%), as reported by Bresin *et al*^[50], led to graft loss due to recurrence of aHUS in one third of patients. The global rate of recurrence in aHUS patients is reported to be as high as 60%. Untreated patients, however, ultimately develop graft loss at a rate of 90%, with 80% of them occurring in the first year^[50].

TTP: TTP is the second recognized etiology in TMA.

Genetic or acquired lack of ADAMTS13 has been recognized. For a long period, differentiation between TTP and HUS relied primarily on the presence of neurologic manifestation in TTP and renal dysfunction in HUS to settle the diagnosis. Serological evaluation of ADAMTS13 activity is now feasible. However, complete distinction between the two clinical entities is not always possible because of overlap in manifestations. Recently, Zafrani *et al*^[51] documented the presence of AKI in more than half of TTP patients (with low ADAMTS13 activity) and 50% progression of CKD and even ESRD. It is reasonable to expect TTP recurrence as long as the underlying defect is present after transplantation^[52]. The same explanation can be applied to the autoimmune diseases, *e.g.*, lupus nephritis, wherein patients can develop TMA in 5%-10% with documented recurrence after kidney transplantation^[53-57].

Pathology: aHUS is a variety of TMA that represents the tissue response to an ongoing endothelial injury. Thrombotic features, *e.g.*, fibrin/platelet plugging and intraluminal fibrin are not always seen in renal allograft biopsy. Non-thrombotic features can appear as denuded and swollen endothelium, mesangiolysis, glomerular basement membrane double contour, as well as accumulation of electrolucent material in the subendothelium. Arterial and arteriolar intraluminal fibrin, myxoid intimal thickening as well as concentric myointimal proliferation (onion skin appearance) have also been described^[58] (Table 1).

PATHOPHYSIOLOGY OF TMA RECURRENCE

The AP is constitutively active and is, therefore, fine-tuned. The regulatory components exist either in the serum (fluid phase) or attached onto cell membranes. CFH is the main inhibitor of the AP. CFH has the ability to work in fluid phase as well as on cell surfaces. Furthermore, CFH can act as a co-factor to CFI^[59,60]. Regulatory components on cell surfaces, or "membrane regulators" include the following: (1) Membrane cofactor protein (MCP/CD46); (2) Complement receptor 1 (CR1/CD35); (3) Decay accelerating factor (DAF/CD55); and (4) Protectin (CD59), which prohibits MAC formation^[61,62].

Any disturbance involving any of this protective

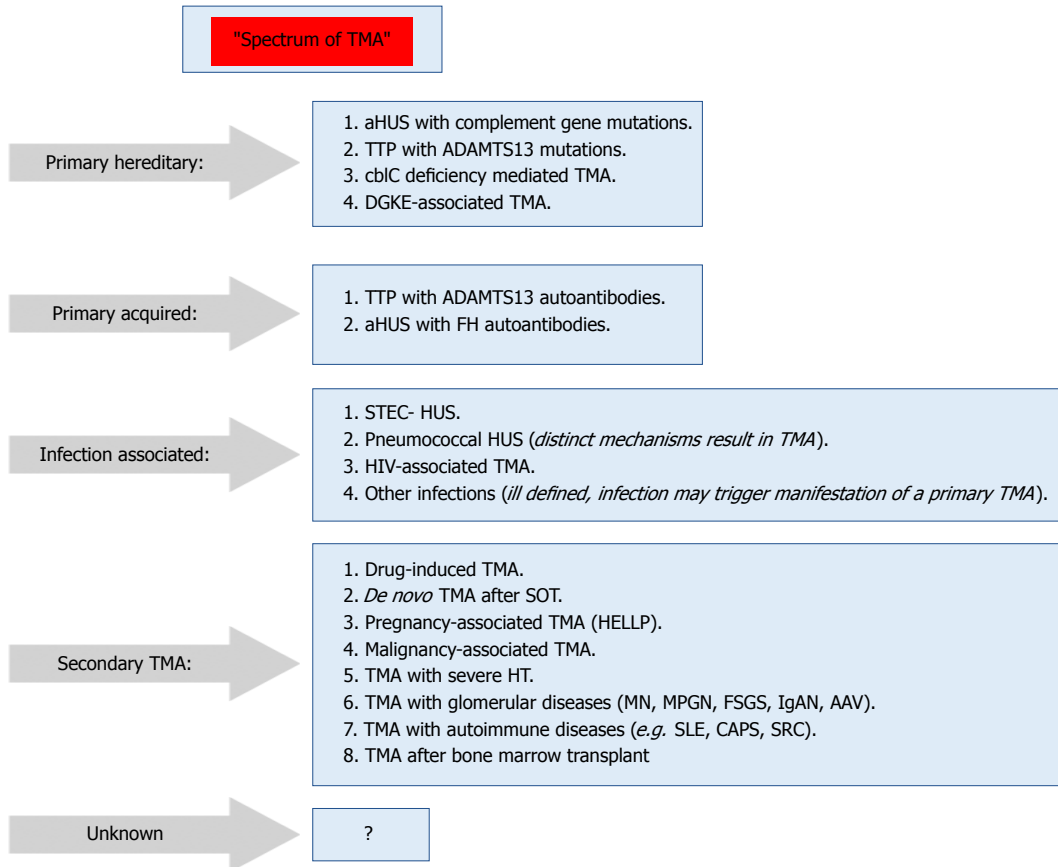


Figure 2 Spectrum of thrombotic microangiopathy^[64]. AAV: ANCA-associated vasculitis; ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS: Atypical hemolytic uremic syndrome; C3G: C3 glomerulopathy; CAPS: Catastrophic antiphospholipid syndrome; cblC: Cobalamin C type; DGKE: Gene encoding diacylglycerol kinase ϵ ; FH: Factor H; HELLP: Syndrome of hemolysis, elevated liver enzymes, and low platelets; HUS: Hemolytic uremic syndrome; IgAN: IgA nephropathy; MN: Membranous nephropathy; MPGN: Membranoproliferative GN; SRC: Scleroderma renal crisis; STEC: Shiga toxin-producing *Escherichia coli*; TMA: Thrombotic microangiopathy; TTP: Thrombotic thrombocytopenic purpura.

shield will ultimately lead to complement activation with subsequent endothelial cell derangement^[63]. It is increasingly recognized that complement dysregulation is the fundamental etiology involved in TMA evolution. Both genetic aberrations as well as autoantibodies can be involved in this process. Usually, there is (are) an inciting environmental trigger factor(s).

Current classification of TMA includes the following

Primary hereditary TMA: Includes mutations in ADAMTS13, MMACHC (cb1c deficiency), or in genes encoding complement components.

Primary acquired TMA: Autoantibodies to ADAMTS13 or to CFH, which occurs with homozygous CFHR3/1 deletion.

Infection-associated TMA: Shiga toxin-producing *Escherichia coli*-HUS (STEC-HUS) and pneumococcal HUS have distinct mechanisms that result in TMA; in other infections, the processes are ill-defined and sometimes can trigger manifestations of the primary TMA.

Secondary TMA: Presents in a variety of conditions, and

in many conditions the culprit mechanisms are usually multifactorial or unknown. The shown classification (Figure 2) is not unequivocal, *i.e.*, in some secondary forms of TMA, *e.g.*, pregnancy-associated TMA or *de novo* TMA after transplantation, a significant percentage of cases may be associated with genetic predisposition (Figure 2)^[64].

The most common complement mutation in aHUS is CFH, with 40% of cases inherited and 25% sporadic^[65,66]. Furthermore, not only CFH has its impact on TMA evolution, but the CFH-related genes (CFHR1-5) have additional roles. Through deletion, hybrid protein formation and duplication^[67] of these genes, the endothelial cell surface becomes denuded from its protective shield, and consequently aHUS may supervene^[65,68].

The risk of aHUS recurrence could be four times higher with CFH mutations or with the carriers of CFH/CFHR1 hybrid genes^[24]. On the other hand, the impact of CFI mutations is controversial. While early reports about CFI mutations documented a high rate of recurrence and graft loss^[69-71], Bienaime *et al.*^[72] denied any risk of recurrence associated with CFI mutations. Le Quintrec *et al.*^[24] were in agreement with them. As MCP can normally be expressed by the endothelial cell surface of

Table 2 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-CFH AB)	NA

Adapted from Salvadori *et al*^[74]. NA: Not available; CFH: Complement factor H; CFI: Complement factor I; CFB: Complement factor B; C3: Complement component 3; MCP: Membrane cofactor protein; THBD: Thrombomodulin.

the allograft, aHUS recurrence is seldom influenced by MCP gene mutations. No more than three cases of MCP-associated recurrence have been reported^[73,74], where recurrence was attributed either to combined gene mutations^[49] or microchimerism related to the recipient's endothelium^[74] (Table 2).

There is a paucity of data on the role of thrombomodulin (THBD) gene mutations in aHUS. Like MCP, THBD is membrane-anchored, so the possibility of recurrence is rarely seen. Only a few cases have been reported^[75,76]. Gain of function mutation (C3 and CFB) is vulnerable for recurrence. Recurrent aHUS with subsequent graft loss have been reported in up to four cases of CFB carriers^[77,78]. On the other hand, data related to C3-associated recurrence are conflicting. While Le Quintrec *et al*^[24] documented recurrence in four of five allografts, Noris *et al*^[79] reported only two cases out of seven transplants with C3 mutations. Zuber *et al*^[80] postulated that normal C3 supplied by the graft tissues might have a protective effect.

Role of diacylglycerol kinase- ϵ (DGKE) mutations:

Until recently, the vast majority of aHUS patients were thought to be associated with AP dysregulation. On the contrary, most patients with DGKE mutations exhibit no evidence of complement overactivity. Homozygous mutations in the gene encoding for DGKE and DGKE-associated nephropathy have been recently uncovered. Complete loss of function is associated with acute renal failure, thrombocytopenia and hemolytic anemia. Consequently, it has been postulated that the DGKE protein may play a fundamental role in regulating thrombosis in renal tissues, a robust fact that urged expert renal clinicians to include DGKE mutations in the pathophysiology of aHUS^[81,82] (see treatment below).

Environmental triggers: The process of aHUS recurrence can be triggered by anti-HLA antibodies^[6], viral infection, ischemia-reperfusion injury and immunosuppressive medications^[83], either isolated or in clusters, which can initiate the cascade of complement activation in susceptible patients.

Clinical assessment of aHUS: Any HUS that is not due to STEC-HUS has been called aHUS^[75]. The recent

progress in understanding the pathophysiology and the underlying genetic factors led to the current classification of aHUS^[84]. Consequently, the term "primary HUS" has been addressed by some clinicians when there is underlying abnormality in the AP. However, patients with underlying complement abnormality need a trigger factor, *e.g.*, infection, including pneumococcal infection (T-antigen associated TMA), surgery, medications, pregnancy, so that aHUS can clinically manifest^[85,86].

Acute vs chronic lesion?

Timing of an aHUS episode is not easily predictable. Many patients are at persistent risk of recurrence. In medical genetics, penetrance of any disease-causing mutation means the percentage of subjects with genetic mutations who can express clinical symptoms^[87]. Penetrance in aHUS is age-related, by age 70, penetrance reaches 64%^[88], which supports the presence of disease modifiers by the aging process. The fact that certain patients (3%-5%) may express more than one genetic variant supports the postulation that mutation burden determines the magnitude of disease penetrance. The late presentation of aHUS reflects the impact of the environmental triggers. However, dissociation between the pathological entities and the clinical presentation have been reported. For example, TMA can be diagnosed in tissue biopsy without simultaneous decline in platelet count. Moreover, the current use of eculizumab has its impact on the natural history of aHUS^[89]. Complement inhibition can improve glomerular perfusion enough to maintain kidney function. Once this biological agent is withdrawn, the renal endothelium may interact with the complement system through an unknown mechanism. More studies are obviously warranted to declare these alterations^[58].

Extrarenal manifestation: Twenty percent of aHUS patients can express extrarenal manifestations in the form of digital gangrene, cerebral artery thrombosis, myocardial infarction, in addition to ocular, GIT, pulmonary and neurologic involvement^[42,90-98]. Drusen formation is not common in aHUS^[99].

Laboratory investigations and differential diagnosis: Once the diagnosis of aHUS is suspected,

Table 3 Complement studies for atypical hemolytic uremic syndrome (aHUS)

Complement test	aHUS
Complement protein levels	C3, C4, FB ¹ , C5 ¹
Complement regulatory protein levels	FH, FI, Properdin ¹ , CD46 ²
Complement split products	C3c ¹ , C3d ¹ , Bb ¹ , sC5b-9 ¹
Complement functional assays	CH50, AH50, hemolytic assays, FH assays ¹
Autoantibodies	Anti-FH
Genetic screening	CFH, CFI, C3, CD46, CFB Genomic rearrangements across the FH-FHR locus (<i>e.g.</i> , by MLPA) Sequencing of coding regions and assessment of CNV Non-complement genetic screening includes THBD and DGKE

¹Currently available only at specific laboratories; they are research and not clinically validated assays; ²CD46 is also known as MCP. Adapted from: Goodship *et al.*^[58]. AH50: Alternative pathway hemolytic assay; C3: Complement component 3; C4: Complement component 4; C5: Complement component 5; CFB: Complement factor B gene; CFH: Complement factor H gene; CFHR: Complement factor H related genes; CFI: Complement factor I gene; CH50: Classical pathway hemolytic assay; CNV: Copy number variation; DGKE gene: Diacylglycerol kinase epsilon gene; FB: Complement factor B; FH: Complement factor H; FI: Complement factor I; MLPA: Multiplex ligation-dependent probe amplification; sC5b-9: Soluble C5b-9; THBD: Thrombomodulin; aHUS: Atypical hemolytic uremic syndrome.

exclusion of ADAMTS13 activity is urgently mandated to exclude TTP diagnosis. In children, TTP is less common; therefore, eculizumab therapy should be instituted early without waiting for the results of ADAMTS13 activity. In addition, 5% of STEC-HUS patients have no prodromal diarrhea and 30% of complement-mediated aHUS patients can present with a diarrheal prodrome^[100].

Complement assessment in aHUS: Before commencing plasma therapy, serum complement component should be thoroughly evaluated. C3 is low in 30% of aHUS patients and, therefore cannot be used as a screening criteria for aHUS^[97,101]. CD46 surface expression should be assessed by flow cytometry. Functional parameters as well as activation markers should be also determined. Whether these biological markers can be used to guide therapy requires further investigation^[102] (Table 3).

Panel of genetic testing: The diagnostic list of genes of aHUS should include at least CFH, CFI, C3, CFB, THBD, CFHR1, CFHR5 and DGKE^[48,65,75,103-105]. Genotyping workup should also include CFH-H3 and MCP ggaac haplotypes^[106]. Recent advances in genetic surveys addressed the use of copy number variation (CNV), hybrid genes, and the complex genomic rearrangements of CFH/CFHRs genomic region^[68,107-111]. The full-detailed genetic mapping, however, allows proper diagnosis and therapeutic plans, and helps in genetic counseling, particularly in living related-donation^[112]. The role of living-related kidney donor transplantation in aHUS is that the culprit agent(s), either acquired or genetic, should be well-recognized, and the donor should be free of this factor(s) at the same time. Consequently, the presence of CFH or MCP mutations in the donor is not per se- a contraindication for donation^[58].

Rationale for genetic screening: The current progress in understanding the underlying genetic background of aHUS and its molecular basis makes it paramount to

provide a full detailed genetic map before transplant, and the following explanations have been given: (1) Determination of the actual cause of the disease that allows for correct genetic counseling; (2) Drawing the plan of disease management; (3) Evaluating the expected response for therapy; and (4) Defining the prognostic course as well as patient and allograft survival. These studies, however, did not hamper the progress in clinical diagnosis and therapy institution before irreversible sequelae have been established^[113]. A schematic presentation for the "genetic drivers" of aHUS is supplied in Figure 3^[58].

Interpretation of the genetic variants: Genetic mutations can be interpreted as: (1) Benign; (2) Likely benign; (3) Variant of uncertain significance; (4) Likely pathogenic; or (5) Pathogenic, according to the international guidelines^[114].

The pathogenic mutations in aHUS have the ability to hamper the capacity to protect the endothelial lining and the platelet from the devastating effect of complement or its activation^[78,115-121]. It is well-documented now that pathogenic variant combinations as well as clustering of risk factors facilitate the evolution of aHUS^[49,88,122-125]. Genetic designation also has its impact on therapeutic plans, response to therapy as well as the chance for aHUS recurrence^[79,126] (Table 4).

Acquired drivers of aHUS: The FH autoantibodies are the best reported example. It is typically characterized by homozygosity for delCFHR3-CFHR1. Test results need to be confirmed after two weeks if the initial results were positive. According to the consensus guidelines in pediatrics, CFH autoantibodies assessment should be confirmed, if positive, on a regular basis^[84]. About a quarter of patients with anti-CFH-associated HUS are vulnerable for relapse.

Diagnosis of aHUS recurrence: A full detailed clinical history is usually warranted. A proven tissue diagnosis

Table 4 Genotype-phenotype correlations in atypical hemolytic uremic syndrome (data refer to the period before introduction of eculizumab)

Gene	Risk of death or ESRD at onset or first yr	Risk of recurrence	Risk of death or ESRD after 3-5 yr	Risk of recurrence in allograft
CFH or CFH-CFHR1/3 hybrid genes	50%-70%	50%	75%	75%-90%
CFI	50%	10%-30%	50%-60%	45%-80%
MCP single	0%-6%	70%-90%	6%-38%	< 20%
MCP combined ¹	30%-40%	50%	50%	50%-60%
C3	60%	50%	75%	40%-70%
CFB	50%	100%	75%	100%
THBD	50%	30%	54%	?
Anti-FH	30%-40%	40%-60%	35%-60%	Depends on antibody titers

¹Combined with CFH or CFI or C3 mutations. Adapted from: Goodship *et al*^[58]. CFB: Complement factor B gene; CFH: Complement factor H gene; CFHR: Complement factor H-related genes; CFI: Complement factor I gene; FH: Factor H protein; THBD: Thrombomodulin gene.

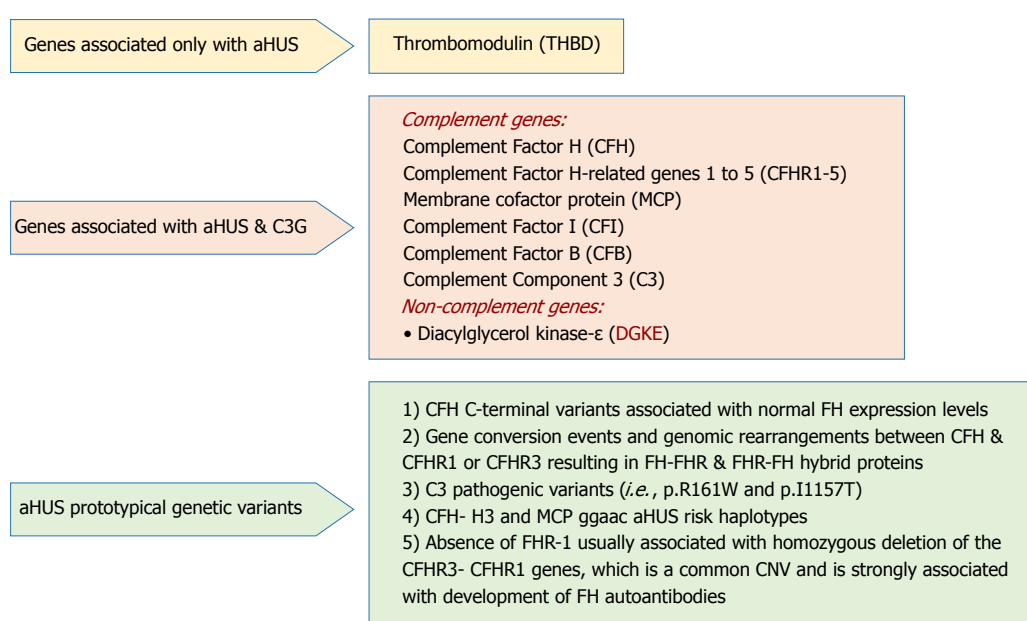


Figure 3 Genetic drivers in atypical hemolytic uremic syndrome (Adapted from: Goodship *et al*^[58]). aHUS: Atypical hemolytic uremic syndrome; C3G: C3 glomerulopathy; CNV: Copy number variation; SCR: Short consensus repeat.

with light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) studies supporting the diagnosis of aHUS in the native kidney should be available. However, once diagnosis of aHUS is suspected, a full battery of biochemical, genetic as well as pathological investigations of the AP should be accomplished^[127], including the following: (1) Estimation of the anti-CFH AB; (2) MCP screening on the peripheral blood WBCs; (3) Examination of the recombination in CFHR region; and (4) Screening of the genetic mutations related to CFH, CFI, CFB, C3, and MCP.

The impact of various genetic mutations on allograft survival is not universally quantifiable. Not all of the genetic mutations share the same magnitude of risk on allograft survival. Despite the fact that genetic screening is difficult and complex and the spectrum of gene mutation is a continuously expanding field^[102], performing such studies is fundamental to determining the possible outcome of the kidney transplant in the set

of aHUS recurrence^[128].

THERAPY OF POST-TRANSPLANT TMA

Treatment of *de novo* TMA

In view of the extreme heterogeneity of the mechanisms related to variable etiologies of TMA, therapeutic maneuvers should be individualized for each patient. Institution of therapeutic options is highly dependent on diagnosis as well as the patient's response. The following approaches have been suggested: (1) Immunosuppressive medication management: the role of immunosuppressive medications (*e.g.*, CNI or mTORi) has been reported in the literature, with a documented better response after switching from one CNI member to another or to an mTORi^[5,129-134]. However, this was not agreed by Satoskar *et al*^[6], who denied any difference in outcomes between temporary discontinuation, dose modulation, withdrawal or continuation of CyA in man-

agement of *de novo* TMA. Whatever the situation would be, the withdrawal of the offending agent should be the first line in treating *de novo* TMA, a fundamental step that ultimately results in correction of the hematological profile^[2]; (2) Plasmapheresis (PE) and intravenous immunoglobulins (IVIG): The following rationales have been addressed in favor of PE/IVIG therapy: Depending on its efficacy in treating patients with TTP^[135,136], and previous choice as a first line therapy for aHUS (replaced now by eculizumab), PE with IVIG has been extrapolated to be used early in treating *de novo* TMA patients. In 2003, Karthikeyan *et al.*^[43] reported a graft salvage rate with PE approaching 80%. Two benefits have been postulated for this type of therapy: Removal of the platelet aggregation factors, *e.g.*, thromboxane A2 and the simultaneous replenishment of the deficient factors, *e.g.*, PGI2-stimulating factor^[43]. With the possibility of the presence of underlying complement dysregulation in patients undergoing kidney transplantation due to systemic TMA^[7], in the same manner, it is reasonable to speculate that PE can be beneficial for two reasons: Removal of the abnormal mutant complement proteins and supplying normally functioning complement components^[7]. In AMR-associated TMA, an improved outcome has been reported, which was attributed to removal of the anti-HLA antibodies^[6,137]. A 100% response has been reported to be associated with PE/IVIG therapy in five solid organ transplantation with systemic TMA with no evidence of relapse after withdrawal of the culprit agent (*e.g.*, tacrolimus) in a recent study^[2]; (3) Belatacept: A promising alternate option that allows withdrawal of the offending drug incriminated in TMA evolution. Belatacept is an immunosuppressive co-stimulatory blocker against CD80 and CD86 surface ligands and CD28 on T cells. The first case report in 2009 documented TMA resolution after belatacept therapy used for immunosuppression in post-transplantation TMA due to CNI-induced endothelial toxicity^[138]. Two case series have followed, thereafter documenting fair graft outcome due to resolution of the CNI-induced TMA^[139,140]. Of note, belatacept has nothing to do with the underlying endothelial derangement, its role is only to replace/displace the culprit drug^[2]; and (4) Complement inhibition: Eculizumab, an anti-C5 agent, blocks the lytic C5b-9 membrane attack complex generation. This recombinant monoclonal antibody addressed a breakthrough in the management of aHUS, as it was proven to be effective in treatment as well as in prevention of recurrent aHUS after renal transplantation^[141]. A large percentage of patients with diagnosed TMA express complement activation, including those patients with unrecognized complement genes^[2]. For example, Chua *et al.*^[41] reported C4d renal deposition in all histologically documented cases with post-transplantation TMA. These data delineate that complement overactivation can be considered as one of the final common pathways incriminated in TMA evolution^[2]. Consequently, anti-complement therapy has been suggested to have a fundamental role in the management of *de novo* post-transplantation TMA.

Efficacy of eculizumab has been documented in several case reports and case series in management of resistant cases of medication-associated TMA, including cases with unrecognized genetic defects^[142-147]. This efficacy has been also documented in patients with refractory AMR with TMA^[147-156].

On the other hand, Cornell *et al.*^[157] reported no difference in death-censored graft survival or biopsy finding at one year when they compared the outcome of eculizumab-treated patients with positive cross matching with controls, even though the incidence of acute AMR was less in the eculizumab group. So, in view of these conflicting results as well as considering the high cost of the drug, the use of this vital biological agent should be confined to a specified subset of *de novo* TMA patients, presumably: (1) AMR-associated TMA; (2) Patients who became PE-dependent; and (3) Refractory hemolysis persists despite maximum doses of PE therapy. However, more efforts are still warranted to declare the best way to utilize this unique agent and which subset of TMA patients are the best candidates for this costly drug. An urgent need for new biomarkers is also warranted for early detection of complement overactivity^[2] (see kidney transplantation without eculizumab prophylaxis below).

Treatment of recurrent TMA

Recommendations for recurrent TMA: First of all, it is worthy to remember that most of the recommendations about recurrence and therapeutic advices relied primarily on case reports (level 4 evidence) as well as experts' opinions (level 5 evidence) rather than on randomized controlled trials (level 1b evidence). (1) The minimal list of genetic screening should include: CFH, CFI, CFHR, CFB, MCP and C3^[158]; (2) All patients with primary or suspected aHUS, should be surveyed for all complement components and its related proteins; (3) Patients with isolated MCP associated mutations (not combined with other mutations) may be safe for kidney donation; (4) Patients with documented aHUS and with lack of definite genetic mutations can proceed in renal transplantation under the umbrella of intensive plasma exchange therapy^[159]; and (5) Polygenic pattern for aHUS patients should be handled with extreme caution in case of living donation^[80].

Prevention of aHUS: The following strategies are suggested to decrease/prevent aHUS: (1) Complement activity incited by an injury to endothelium, *e.g.*, ischemia-reperfusion injury, viral infection and immunosuppressive medications^[127], should be avoided; (2) Certain relations have been reported between CNI use and aHUS recurrence^[160], which is not confirmed by other authors^[15,112], even the usual substitute in such a case (an mTOR) is not innocent and can induce recurrence^[15,112]; (3) We cannot depend solely on PE therapy in management of aHUS recurrence for several reasons: PE failed to prevent aHUS recurrence in many cases^[161]; PE cannot guarantee prevention of aHUS recurrence after cessation of therapy; Many cases under PE therapy were

Table 5 Eculizumab dosing in atypical hemolytic uremic syndrome based on dosing goal, one additional monitoring may be required during intercurrent events (*e.g.*, infection, surgery, vaccination) to detect unblocked complement activity

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

Adapted from: Goodship *et al.*^[58]. AH50: Alternative pathway hemolytic activity; CH50: Total complement activity.

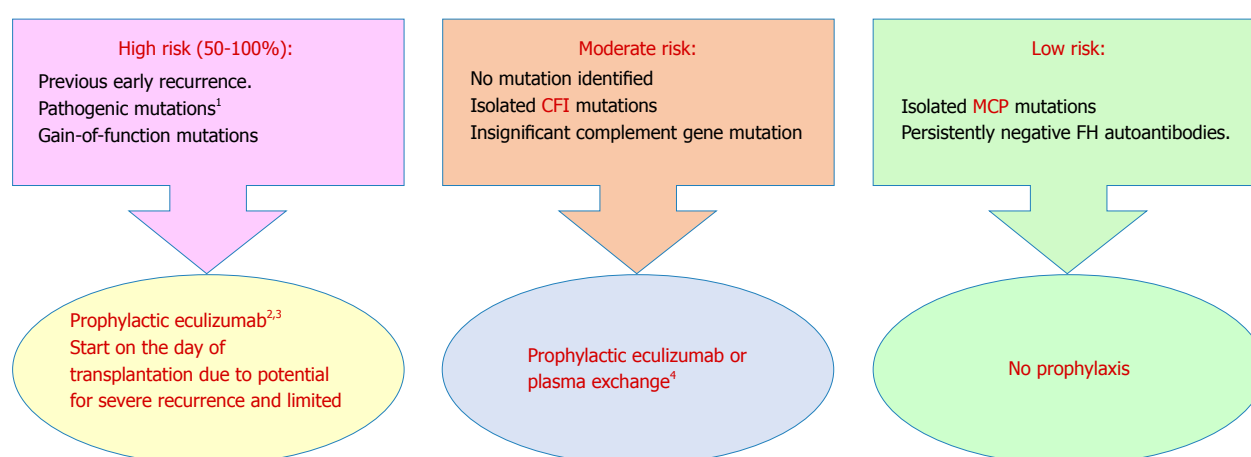


Figure 4 Prophylaxis against atypical hemolytic uremic syndrome recurrence in allograft based on a risk-assessment strategy^[96] (Adapted from: Goodship *et al.*^[58]). ¹Requires complete screening of all genes implicated in atypical hemolytic uremic syndrome; ²Prophylactic regimens are based on local center protocols; no trial data exist to support superiority of one protocol over another; ³Liver transplantation can be considered for renal transplant recipients with liver-derived complement protein abnormalities, uncontrolled disease activity despite eculizumab therapy or financial considerations regarding cost of long-term eculizumab therapy; ⁴Decision to perform or not to perform prophylactic plasma exchange or complement inhibition is left to the discretion of the clinician. aHUS: Atypical hemolytic uremic syndrome; CFI: Complement factor I gene; FH: Complement factor H protein; MCP: Membrane cofactor protein gene.

proved to develop “subclinical” aHUS recurrence, which means that PE therapy cannot influence complement activity; Prophylactic use of rituximab proved to be efficacious as anti-CFH-antibodies^[162], the beneficial effect of rituximab can be enhanced by adding PE therapy^[163,164]; and (4) The anti-C5 monoclonal antibody eculizumab has been reported to be used successfully to prevent aHUS recurrence in patients with CFH, CFH/CFHR1 hybrid genes as well as with C3 gene mutations^[165-168] (see below).

Prophylactic complement blockade: Gene abnormalities have been reported to be associated with aHUS recurrence in 80% of patients^[112]. In light of robust evidence of increased complement activity during aHUS episodes^[169,170] after exposure to a trigger, *e.g.*, surgery or infection, clinical indication of complement blockade is suggested^[171]. However, this explanation lacks enough evidence (Figure 4^[58]).

Therapeutic protocols for aHUS recurrence: Once the diagnosis of primary aHUS has been established, complement blockade therapy should be instituted. The available data points to two strategies: (1) Minimal dosage to establish complement blockade; and (2)

Dose withdrawal scheme^[142]. Both options, however, lack enough evidence and require precise monitoring of complement blockade (Table 5).

FH autoantibody-driven aHUS: Anti-cellular therapy is recommended, with close monitoring of the antibody titer (Figure 5). How to monitor complement blockade? Detailed description is shown in Table 6.

Duration of therapy: There is not enough data supporting life-long therapy for aHUS. Cessation of therapy appears to be plausible in certain situations (Figure 6). Enough time, however, should be permitted to optimize renal recovery and satisfy TMA resolution. Early biomarkers of disease relapse due to complement activation or endothelial derangement as well as their inciting triggers should be thoroughly investigated in the future.

Unanswered questions: There is paucity of information about this biological agent, *e.g.*, what is the most optimal dose? What are the ideal dose-intervals? For how long should this kind of costly therapy be continued?^[175] What impact does this agent have on the spectrum of renal transplantation^[113]?

Table 6 Monitoring eculizumab therapy

Description	
CH50 (total complement activity)	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 is assay dependent
AH50 (alternative pathway hemolytic activity)	Recommended goal during therapeutic complement blockade: < 10% of normal Measures combined activity of alternative and terminal complement pathways Tests the 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
Eculizumab trough	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 complement deficiencies
Alternative assays	Recommended trough level during complement blockade: 50-100 µg/mL The following assays are under investigation (or awaiting to be replicated in different laboratories) ^[83] as a means to monitor therapeutic complement blockade Free C5 <i>In vitro</i> human microvascular endothelial cell test sC5b-9 (also referred to as sMAC and TCC) may remain detectable in aHUS patients in remission and therefore is not recommended as a monitoring tool

Adapted from: Goodship *et al*^[58]. 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.

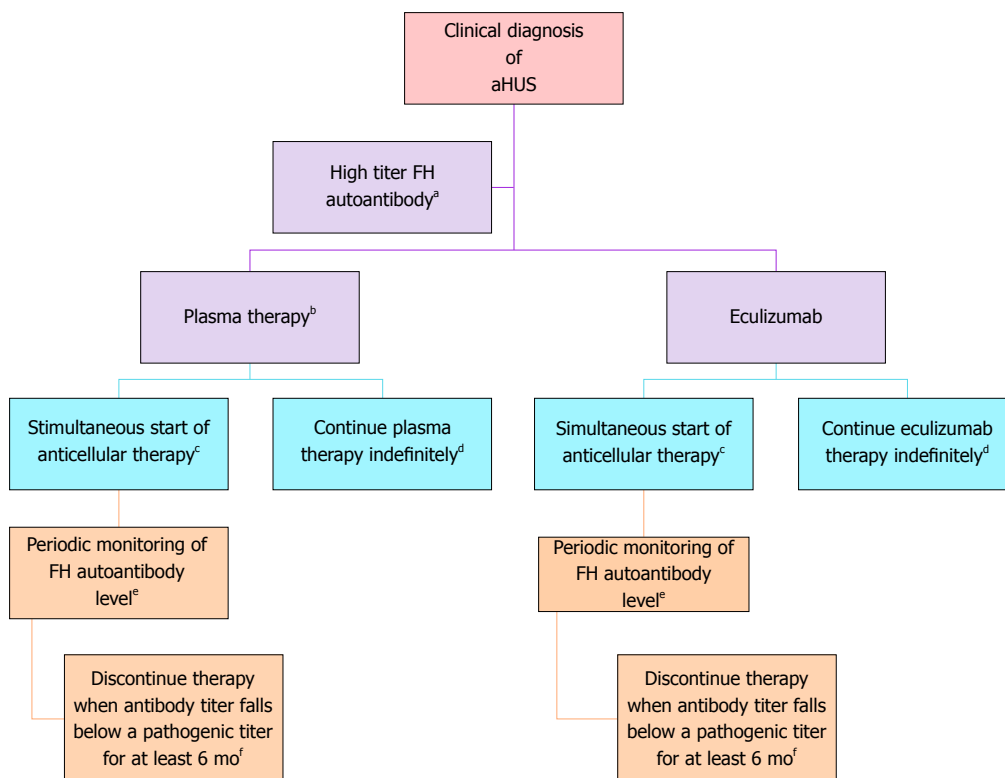


Figure 5 Treatment of complement factor H autoantibody-mediated atypical hemolytic uremic syndrome. There are no prospective controlled studies in patients with atypical hemolytic uremic syndrome (aHUS) due to anti-factor H protein (FH) antibodies, and thus the proposed management is based on a pediatric consensus^[84] (Adapted from: Goodship *et al*^[58]). ^aAbnormal titer depends on the testing laboratory; ^bThe decision to use plasma therapy versus eculizumab will be based on patient age and local resource availability; ^cCyclophosphamide, rituximab, or mycophenolate mofetil; ^dThe decision to continue anticomplement therapy indefinitely is not informed by data; ^eThe interval may be monthly or quarterly and is based on local resources; ^fThis recommendation is based on limited retrospective case reviews^[172-174].

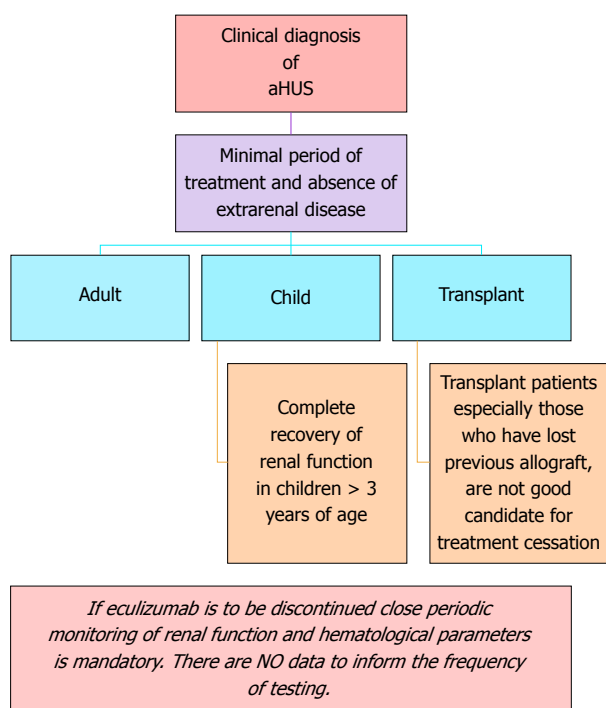


Figure 6 Recommendations for cessation of treatment with complement inhibitors. There are no prospective controlled studies in patients with atypical hemolytic uremic syndrome (aHUS) to define criteria for discontinuation of eculizumab therapy. This flow diagram is based on expert opinion^[176-178]. 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 CKD) of kidney function. Earlier cessation (at 3 mo) may be considered in patients (especially children) with pathogenic variants in MCP 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*^[58]. aHUS: Atypical hemolytic uremic syndrome.

Cessation of therapy: The following scheme is suggested for withdrawal of complement blockade therapy (Figure 6).

Kidney transplantation without eculizumab prophylaxis: A case series presented by Verhave *et al*^[179] described successful kidney transplantation without recurrence in four high risk aHUS patients. They received living donor kidney with therapeutic protocol consisted of: Basiliximab for induction, tacrolimus in low dose, and prednisone and mycophenolate mofetil as immunosuppressive in addition to a statin. Additional precautions include lowering the blood pressure and minimizing the cold ischemic time. No recurrence or rejection has been observed after 16-21 mo. This case series heralds the possibility of successful kidney transplantation in recurrent aHUS without the need for prophylactic eculizumab through minimizing cold ischemic time, decreasing the risk of rejection and, thereby, providing endothelial protection^[179].

Treatment of DGKE mutation associated TMA: The role of complement blockade here is questionable.

Many cases experienced disease remission with no specific therapy. Azukaitis^[82] and colleagues reported the feasibility of kidney transplantation in five patients with no recurrence after transplantation.

RENAL TRANSPLANTATION

Timing

Renal transplantation should be postponed six months after institution of dialysis, as limited kidney recovery can occur several months after commencing eculizumab therapy^[170,180]. Disappearance of the extrarenal manifestations as well as resolution of TMA hematological parameters are the prerequisite for kidney transplantation. The magnitude of risk of recurrence can be utilized to guide the necessity of anti-complement blockade (Table 2).

Risk of kidney donation

Two risks have been reported to be associated with living-related kidney donation: (1) Recurrent disease in the recipient; and (2) *De novo* disease in the donor, if he/she is a genetic mutation carrier^[169]. Any potential donor proved to exhibit alternative pathway dysregulation should be excluded. On the other hand, any potential living-related donor devoid of complement gene abnormalities can be permitted^[113]. "Liver transplantation" may be reserved for patients with liver-derived complement protein aberrations, particularly in patients poorly responding to complement blockade^[181].

Future therapy

The following future therapeutic agents have been addressed: (1) Purified products of the deficient genes; and (2) C3 convertase inhibitors^[182].

Research targets

The following agents are under investigation: (1) The anti-C3b blocker, compstatin analog Cp40^[183]; and (2) The anti-C3 convertase monoclonal antibodies^[184].

CONCLUSION

The impact of TMA, either *de novo* or recurrent, on allograft longevity is underestimated. The spectrum of the culprit genes implicated in the evolution of TMA is currently expanding. Despite the landmark breakthrough of immense efficacy of complement blockade therapy, the outlook of this devastating syndrome remains poor if the diagnosis is delayed. In contrast, the recurrent TMA is much more optimistic if there is timely intervention by complement blockade before permanent damage sets in. More efforts targeting genetic mutation management as well as the advent of early predictors of TMA recurrence are warranted for better disease control and, thereby, better patient and allograft outcome.

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