

CKJ REVIEW

Thrombotic microangiopathy after kidney transplantation: diagnosis and management strategies

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ABSTRACT

Thrombotic microangiopathy (TMA) is a pathological condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ dysfunction due to microvascular endothelial damage and thrombosis. It affects ~0.8%–14% of kidney transplant recipients, and may manifest as either a recurrent or *de novo* disease. While systemic manifestations are commonly anticipated, kidney-limited TMA can also occur and is not rare. Histopathologic examination of allograft biopsies shows morphologic features indicating endothelial injury, and repeated episodes of TMA may result in coexisting acute and chronic lesions within the same patient. In transplant recipients, multiple triggers contribute to endothelial damage, including ischemia-reperfusion injury, antibody-mediated rejection, immunosuppressive agents (calcineurin and mTOR inhibitors), and infections. The risk is particularly important in individuals with genetic variants that dysregulate the alternative complement pathway. In *de novo* TMA, environmental triggers and transplant-related stressors play a central role, whereas genetic predisposition is the primary factor in recurrent cases. Notably, these mechanisms often overlap and may act synergistically. Recurrent atypical hemolytic uremic syndrome can successfully be managed with terminal complement inhibitors, and prophylactic use of eculizumab in the peri-transplant period has significantly reduced recurrence rates. Management of *de novo* TMA begins with the identification and removal of precipitating factors. In cases where no clear trigger is found, or when the disease proves refractory to conventional therapy, terminal complement inhibition may be an effective therapeutic option.

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The prognosis of recurrent TMA has improved substantially with the advent of complement targeting therapies but research is still needed to optimize management strategies.

Keywords: alternative complement pathway, atypical hemolytic uremic syndrome, eculizumab, kidney transplantation, thrombotic microangiopathy

INTRODUCTION

Thrombotic microangiopathy (TMA) is a pathological condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ dysfunction due to microvascular endothelial damage and thrombosis, and/or evidence of TMA on pathological examination [1–3]. The etiology of TMA is quite heterogeneous and pathophysiology drives the classification [4]. Thrombotic thrombocytopenic purpura is characterized by an immune-mediated or inherited deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) enzyme. Hemolytic uremic syndrome (HUS) is usually triggered by Shiga toxin-producing *Escherichia coli* (STEC), while atypical HUS (aHUS) or complement-associated HUS is generally associated with genetic or acquired abnormalities that lead to dysregulation of the alternative complement pathway. Finally, secondary TMA is triggered by other underlying conditions such as hypertensive emergency, pregnancy, infections, autoimmune diseases, malignancies, and certain medications [3, 4].

In kidney transplant recipients, TMA often arises from the complex interplay between the immune activation, coagulation system abnormalities, and endothelial injury – all of which are frequently dysregulated in this population [5]. Post-transplant TMA is observed in 0.8%–14% of kidney transplants, and can develop as a *de novo* disease or recurrence of pre-transplant TMA, and each is predisposed by specific risk factors [6]. Heterogeneity in the diagnostic criteria may partially explain the large variation in the estimated incidence [1]. Notably, lack of a TMA diagnosis before transplantation might cause misclassification of some cases with recurrent TMA as *de novo* disease [1]. Although *de novo* TMA occurs more frequently than recurrent TMA after kidney transplantation, patients whose native kidney failure was caused by TMA face a particularly high risk of recurrence following the transplant [7].

Post-transplant TMA can culminate in kidney injury and graft loss in a short period of time and systemic manifestations have the potential to threaten various organs and systems if left untreated. Early diagnosis and treatment have the utmost significance to reverse the injury in time. Here we aim to provide a review of diagnostic and therapeutic strategies and to suggest an algorithm for the assessment of living-donor candidates and further measures to mitigate the risk of recurrence in patients with TMA.

DIAGNOSIS

Clinical manifestations

Clinical presentation of TMA after kidney transplantation exhibits significant variability and resembles that of both recurrent and *de novo* TMA. Diagnosis depends on clinical and laboratory findings, which include microangiopathic hemolytic anemia characterized by elevated serum lactate dehydrogenase and decreased haptoglobin levels, reticulocytosis, and the presence of schistocytes on peripheral blood smear, alongside thrombo-

cytopenia and acute kidney injury [8]. Notably, there is preferential activation of the alternative complement pathway in patients with aHUS, thus low serum C3 with normal C4 levels are expected. However, serum C3 levels are decreased in only 30%–50% of patients [9, 10]. Not all signs and symptoms are present in every patient, and a specific subset of kidney-limited TMA can occur without systemic hematologic abnormalities, further complicating the diagnosis [11–13]. Since diagnostic criteria for TMA vary widely in the literature, reported rates of systemic TMA in *de novo* cases range dramatically, from 0% to 100% [1]. Kidney-limited TMA presents with solely acute or progressive graft dysfunction and/or worsening hypertension, necessitating histological validation through allograft biopsy to confirm the diagnosis. Although early graft loss is more prevalent in systemic TMA, initial favorable survival trend in localized TMA diminishes over time [12]. Since the absence of systemic features may cause a delay in diagnosis, identification of specific signs of kidney injury and early biopsy are essential to avoid further delays. Protocol graft biopsies in the early post-transplant period might be useful, especially for recurrent disease. TMA can also present with extrarenal manifestations, including neurological (confusion, seizures, and paresthesia), cardiovascular (heart failure), and gastrointestinal (colitis, ischemic cholangitis, and jejunitis) symptoms [14].

Recurrent TMA typically manifests during the early period, developing within days to weeks following surgery [15, 16]. *De novo* TMA peaks within the first 3–6 months after transplantation, a time frame when the acquired risk factors are high, such as higher trough levels of calcineurin inhibitors (CNIs) [7]. However, the substantial risk of both recurrent and *de novo* TMA persists thereafter [7].

Histopathology

Biopsies of allografts impacted by post-transplant TMA show morphologic features of tissue response to endothelial injury (Fig. 1), but histopathological evaluation alone is insufficient to determine the underlying etiology [17]. The morphological findings can be categorized into acute and chronic changes. In acute TMA, glomeruli show a bloodless appearance, mesangiolysis, endothelial swelling, and glomerulitis. Thrombi may be present in hilar/glomerular capillaries [13, 18]. Occasional cases demonstrate crescent formation. Tubulointerstitial changes include acute tubular injury and interstitial edema, with cortical necrosis in more severe cases. Endothelial swelling, luminal occlusion, and thrombi are commonly observed within the arterioles. Arteriolar intimal mucoid edema is also a feature of TMA [5]. Schistocytes may be observed entrapped within the thrombi, the glomeruli, or the arterioles. Fibrinoid necrosis can be present without an accompanying inflammatory infiltrate [17]. TMA lesions are typically focal, affecting <50% of glomeruli and/or arterioles. Ischemic necrosis is a rare finding [13]. Notably, the lack of thrombus formation does not preclude the presence of TMA [13]. In studies comparing TMA cases with and without thrombi, a slightly higher serum creatinine level was observed in patients

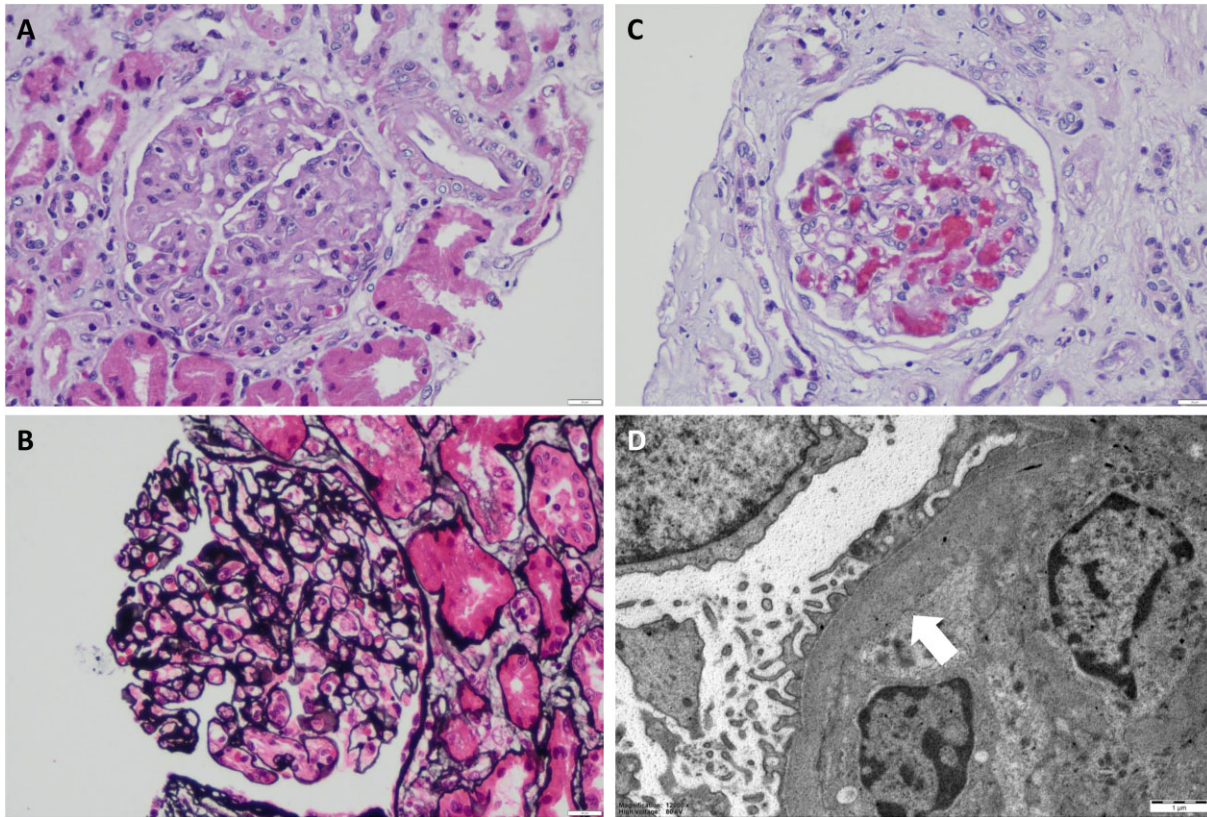


Figure 1: Histopathologic findings of thrombotic microangiopathy in a kidney allograft. (A) Glomerulus with mesangiolysis, endothelial swelling, and glomerulitis (hematoxylin and eosin). (B) Thrombus formation in glomerular capillaries (periodic acid methenamine silver stain). (C) Mesangial cell interposition and basement membrane duplication (hematoxylin and eosin). (D) Subendothelial space expansion, endothelial swelling and loss of fenestrations (transmission electron microscopy, uranyl acetate and lead citrate).

with thrombi, whereas a higher rate of prior rejection was reported in those without thrombi [13].

Chronic changes may appear within days following the acute onset. Glomerular findings include basement membrane duplication, mesangial cell interposition, and mesangial expansion with mesangiolysis. Focal segmental and global glomerulosclerosis, tubular atrophy, and interstitial fibrosis may be variably present. Chronic changes within the arterioles include intimal fibrosis, which may result in onion-skin appearance as a result of concentric multilayering [17]. Some studies reported vascular myxoid changes and onion-skin appearance, significantly more common in cases of clinical TMA, compared to subclinical or purely histologic TMA, suggesting that vascular occlusive features may be markers of clinically overt injury [19]. Repeated episodes of TMA can result in simultaneous presence of acute and chronic lesions in the same biopsy as well [5].

On immunofluorescence microscopy examination of TMA cases, no staining for immunoglobulins or complement proteins is typically observed, apart from nonspecific entrapment of IgM and C3, as well as fibrinogen staining within the thrombi [17]. Endothelial swelling, loss of fenestrations, and expansion of the subendothelial space by electron-lucent material are early and characteristic ultrastructural findings on electron microscopy. Ultrastructural correlates of chronic changes may include duplication of the glomerular basement membranes and mesangial cell interposition. Podocyte foot process effacement

is also commonly observed, reflecting a nonspecific response to injury [17].

Antibody-mediated rejection (ABMR) stands out as a common and essential cause of *de novo* TMA [20]. In both conditions, endothelial injury is a central pathogenic mechanism, leading to significant histopathological overlap. Shared features include glomerular microthrombi, endothelial cell swelling, and mesangiolysis [8]. Distinguishing TMA associated with ABMR and other etiologies is challenging and necessitates a comprehensive diagnostic approach, incorporating histological evaluation, C4d immunostaining, serological evaluation, and clinical context [21]. In biopsies with TMA associated with ABMR, the presence of glomerulitis and peritubular capillaritis has been reported to be more pronounced [6, 11]. In the absence of microvascular inflammation, ABMR-associated TMA can be diagnosed if at least two of the following features are present: positive C4d staining, donor-specific antibodies (DSA), or increased expression of ABMR-related transcripts [20]. Studies investigating peritubular capillary C4d staining in biopsies with TMA have reported variable findings, with positivity rates ranging from 16% to 55% [7, 11, 22]. In comparison, the presence of TMA in biopsies with peritubular capillary C4d staining was significantly lower, supporting the role of ABMR in TMA pathogenesis [7, 11, 22]. Notably, numerous studies have demonstrated that coexistence of TMA with ABMR and C4d positivity is associated with poorer graft survival [11, 13, 23].

C4d-negative ABMR occurs in up to half of cases; therefore, C4d negativity does not exclude ABMR, diagnosis must integrate clinical context, DSA, and microvascular injury (glomerulitis and peritubular capillaritis) rather than rely on C4d alone [24, 25]. DSA remain the most important discriminator as they are absent in aHUS. Electron microscopy, when available, may further support ABMR by demonstrating features of antibody-mediated endothelial injury [25, 26]. By contrast, aHUS is characterized by complement gene variants or anti-factor H antibodies, often with a prior history, and lacks both DSA and histologic evidence of rejection. Given the frequent multifactorial nature of post-transplant TMA, a composite assessment incorporating serology, histopathology (including electron microscopy), and complement evaluation is essential.

Transcriptome analysis has been incorporated into ABMR diagnostics, with MMDx and NanoString serving as the two principal platforms and providing reproducible gene-expression data that complement conventional histology. Although transcriptome analysis can support the diagnosis of ABMR, important diagnostic challenges still remain [27]. Current literature is insufficient to determine its utility in distinguishing TMA from ABMR or other related entities.

ETIOLOGIES

Many triggers can precipitate *de novo* TMA in kidney allografts, such as rejection, immunosuppressive medications, infections, and cancers, especially in patients with predisposing genetic abnormalities (Box 1). Some of these stressors can have simultaneous effects and it can be challenging to define the exact etiology [13]. Ischemia-reperfusion injury, which is an expected consequence of the transplantation process, has been shown to be associated with complement activation and amplification of complement-mediated injury [1, 28].

Box 1. Diagnostic work-up for thrombotic microangiopathy after transplantation (TMA).

In case of anemia and thrombocytopenia in a kidney transplant recipient,
Serum lactate dehydrogenase levels, haptoglobin and reticulocytes should be checked.
Peripheral blood smear should be examined for schistocytes.

- ✓ Increased lactate dehydrogenase
- ✓ Decreased haptoglobin
- ✓ Schistocytes on peripheral blood smear
- ✓ Reticulocytosis (>2.5% in adults)

→ TMA

Rule out thrombotic thrombocytopenic purpura (ADAMTS13 activity) and HUS (STEC)

Perform a graft biopsy in patients with graft dysfunction and/or proteinuria

💡 C4d staining for antibody-mediated rejection

What are the underlying etiologies?

- Viral infections (i.e. cytomegalovirus)
- Genetic or acquired complement abnormalities
- Medications (i.e. calcineurin inhibitors, mTOR inhibitors)
- Rejection
- Immune-mediated systemic diseases

Medications, including CNIs and mammalian target of rapamycin (mTOR) inhibitors, are among the most common causes of *de novo* TMA, comprising ~50% of the cases [13]. In general, exposure to one single culprit drug is insufficient to cause TMA, and a second hit is usually required. This is supported by the fact that they are commonly used in kidney transplant recipients, but only a minority develop TMA. CNIs increase the risk of TMA through multiple direct and indirect mechanisms, including arteriolar vasoconstriction with an imbalance of vasoconstrictor versus vasodilator molecules, platelet activation, and a procoagulant state, and alternative complement pathway activation [1, 29]. mTOR inhibitors reduce vascular endothelial growth factor and subsequently factor H levels, and generate a procoagulant state [30, 31]. Higher serum mTOR inhibitor and CNI concentrations are associated with a higher TMA risk, which supports distinct pathogenic impacts of these medications [32]. In addition, the combination of cyclosporine and sirolimus was associated with a higher risk of *de novo* TMA in kidney allografts compared to other regimens, such as cyclosporine and mycophenolate or sirolimus and mycophenolate [33, 34]. This combination exhibited pro-necrotic and anti-angiogenic activities on arterial endothelial cells in *in vitro* studies [33]. In addition to cyclosporine, tacrolimus can also cause *de novo* TMA [35]. Last, trimethoprim-sulfamethoxazole is implicated in rare cases of immune-mediated TMA in native kidneys, but data in kidney transplant recipients are lacking [36].

Alloimmune responses against kidney allografts increase the risk of post-transplant *de novo* TMA, especially in patients with higher DSA and longer cold ischemia times [37]. ABMR comprises the second most common cause of *de novo* TMA, occurring in ~30%–50% of cases [11]. Alloantibodies bind to the endothelium and activate the complement system, which leads to endothelial damage and TMA. Although TMA from hyperacute rejection (within a few hours to days after transplantation) due to the high titer of preformed DSA was more common historically, this complication is very rare in the current era with the availability of enhanced crossmatch techniques and the use of induction immunosuppression [38]. Notably, early TMA is not uncommon after ABO-incompatible kidney transplantation, despite prophylactic use of plasma exchange and biologic agents [39]. In some cases, it can be difficult to determine whether *de novo* TMA is primarily driven by ABMR or medications. Diagnosis may rely on sequential therapeutic interventions, such as escalating immunosuppression or removing potential offending agents, a process that can be challenging. Interestingly, in a case series by Satoskar et al., 56 of 59 cases with ABMR and *de novo* TMA were on cyclosporine during diagnosis; however, the outcomes were not different between the patients who stopped, temporarily held, or continued the agent [11]. This observation might postulate a more predominant role of ABMR in most patients.

The other etiologies of *de novo* TMA are less common and resemble processes in native kidney disease. HUS caused by STEC has been reported in kidney transplant patients [40, 41]. Viral infections like cytomegalovirus (CMV), Epstein-Barr virus, BK virus, parvovirus B19, and hepatitis C virus, and bacterial infections including non-STEC, Gram-negative bacilli, *Streptococcus*, and *Staphylococcus*, are common causes of *de novo* TMA that are unexplained by medications or ABMR [13, 42]. Other rare etiologies may include cancers, conventional chemotherapeutic agents such as gemcitabine, new agents used in oncology practice (i.e. anti-VEGF therapies, tyrosine kinase inhibitors, immune checkpoint inhibitors), and thrombophilia [13, 43, 44]. Although data are limited, thrombotic thrombocytopenic purpura,

lupus nephritis, scleroderma, and anti-phospholipid syndrome-induced TMA can recur after a kidney transplant [6].

Genetics

Among patients with a history for kidney failure caused by aHUS, the risk of disease recurrence after transplantation is high, and influenced by the presence of pathogenic variants in complement genes, anti-factor H antibodies and/or history of disease recurrence/loss of a kidney allograft [45]. Different underlying specific gene variants pose varying levels of recurrence risk. Patients with complement gene variants in *CFH* or hybrid *CFH/CFHR* rearrangements, gain-of-function variants (*C3* and *CFB*), and/or history of (early) recurrence, are classified as high risk, with a recurrence rate of 50%–100% [46]. Isolated *CD46* variants and absence of detectable anti-factor H antibodies before transplantation is classified as low risk (<10%). Other scenarios, including isolated *CFI* variants, variants of unknown significance in complement genes, absence of detectable variants, or persistent low-titer anti-factor H antibodies, are defined as moderate risk (10%–50%) [10]. Notably, it was also suggested that risk stratification could be further improved based on the presence or absence of a homozygous at-risk *CFH* haplotype (*CFH-H3*) [47]. However, it has not been implemented into the consensus reports [10]. When there is concomitant presence of multiple gene variants, the recurrence risk is usually driven by the higher-risk gene. Missed diagnosis of aHUS in the native kidneys could categorize some of these patients falsely into the *de novo* TMA category, highlighting the importance of broad investigation in these patients, including genetic testing. Another rare entity is a phenotypic shift from *C3* glomerulopathy in native kidneys to aHUS after transplantation, as these two diseases share overlapping underlying genetic variants [48].

Genetic variants in metabolic and coagulation pathways can also cause TMA; however, the data regarding their implications for kidney transplant recipients are scarce. Biallelic variants in *MMACHC*, *MTR*, and *MTHFD1* are responsible for cobalamin metabolism-related disorders. TMA has been reported in these rare entities [49]. The exact mechanism underlying TMA in this context remains unclear, and lack of response to eculizumab suggests a pathology unrelated to the complement pathway [50]. Hyperhomocysteinemia-induced endothelial toxicity has been proposed as the most likely mechanism [51]. Notably, a case of recurrent disease was reported in a patient with *MMACHC*-associated TMA who did not receive hydroxycobalamin therapy [51]. Similarly, diacylglycerol kinase ϵ (*DGKE*) variants have been identified as a pathophysiologic mechanism leading to HUS and/or a membranoproliferative glomerulonephritis pattern of injury particularly in infants presenting before 2 years of age [52]. *DGKE* deficiency results in decreased levels of phosphatidylinositol bisphosphate, which regulates the vascular endothelial growth factor receptor 2 pathway. This dysregulation leads to increased prostaglandin E2 production via induction of cyclooxygenase-2 activity. The resulting prothrombotic state is thought to underlie the pathogenesis of TMA in *DGKE*-associated cases [53]. However, none of five kidney transplant recipients with these variants developed recurrent TMA in a case series [54], supporting the hypothesis of a non-complement pathway-associated TMA [55]. While initial reports suggested a link between thrombomodulin (*THBD*) variants and complement-associated HUS [56], this has not been validated in larger cohorts [49, 57] or enrichment analyses [58–60]. Accordingly, identifying rare *THBD* variants is not considered clinically relevant for management [10]. Notably, in a study of patients with *THBD* gene variants, none of the 12 patients experi-

enced recurrence of the disease, including four patients who received a kidney graft without preemptive eculizumab [58]. An overview of genes associated with TMA in the setting of kidney transplantation is presented in Table 1. Genetic screening is recommended for kidney transplant candidates with a history of TMA or a family history of TMA before transplantation [61, 62]. In addition, genetic testing may be considered in recipients with a history of chronic kidney disease of unknown etiology [63].

Early studies also identified variants in *CFH* and *CFI* in kidney transplant recipients with *de novo* TMA [64]. In a large series by Dessaix *et al.*, pathogenic complement gene variants were found to be more common in these patients when compared to healthy controls [13]. Various insults causing endothelial injury can be the triggers of TMA in patients harboring variations that cause dysregulation of the alternative complement pathway. Environmental factors and the aforementioned triggers play significant roles in *de novo* disease, whereas genetic factors are the major culprits in recurrent cases. Donor genetic background also contributes to the process, but the data for *de novo* TMA are scarce [65].

Genetic risk assessment of living donors

Evaluation of living-related kidney donors is particularly critical in complement-associated HUS. Unlike deceased or unrelated living kidney donors, related donors share genetic risks and may develop TMA during or after donation [66]. Therefore, genetic testing is routinely recommended for both recipient and related donor candidates. An algorithm for donor evaluation is provided in Fig. 2. Initial genetic testing to identify complement pathway-associated genetic variants in the recipient candidate is essential. Pathogenic and likely pathogenic variants in genes associated with the complement system can increase susceptibility to aHUS, and any identified variant in the recipient must prompt donor screening to reduce the risk of post-donation kidney failure or aHUS [66, 67]. If a donor candidate carries the same pathogenic causal variant as the recipient, donor candidates should not proceed with donation [61, 62]. For related donors with different genetic variants, the decision should be guided by the pathogenicity of the identified variant; in cases involving variants of uncertain significance (VUS), functional studies or additional genetic evaluation may be required. Functional assays used to clarify the pathogenicity of complement gene VUS include serum-induced *C5b-9* deposition assays, hemolytic assays (CH50/AH50), and protein expression or binding studies [68–72]. Among these, the serum-induced *C5b-9* formation assay on activated endothelial cells has become one of the most informative rapid tests, with high sensitivity for distinguishing pathogenic from benign variants. Standard hemolytic assays (CH50/AH50) remain useful screening tools for detecting classical and alternative pathway dysfunction, even when individual protein levels are normal. Additional variant-specific studies including cofactor activity, *C3b*-binding assays, and surface protection assays may be required for genes such as *CFH* or *CD46* [72]. These functional assays can be helpful not only in evaluating potential living donors but also in patients on the transplant waiting list, particularly when genetic results include VUS that may influence recurrence risk and transplant decision-making. Genetic testing should always be coupled with counseling to explain risks and implications. When no causal variant is detected in the recipient, donor evaluation is more challenging. In such cases, related donors should be assessed cautiously by a multidisciplinary team, with counseling and a low threshold for declining donation.

Table 1: An overview of genes associated with TMA and outcomes after kidney transplantation.

Genes	Graft outcomes after kidney transplantation
CFH (Factor H)	3-year graft survival without eculizumab was 35%. Only one recurrence in 16 patients was reported under eculizumab treatment [80].
CFI (Factor I)	3-year graft survival without eculizumab was 60% [80].
CD46	3-year graft survival without eculizumab was 75% [80].
C3	3-year graft survival without eculizumab was 45% [80].
CFB (Factor B)	A single case report of post-transplant TMA has been published [120].
ADAMTS13	Biallelic ADAMTS13 variants cause congenital TTP (Upshaw–Schülman syndrome). Data on kidney transplantation outcomes in these patients are limited. Post-transplant TMA has been reported in a patient with previously undiagnosed Upshaw–Schülman syndrome who underwent living-donor kidney transplantation. With twice-monthly plasma infusions, kidney function was preserved over 2 years of follow-up [121].
MMACHC and other genes of cobalamin metabolism	Biallelic variants in MMACHC, MTR, and MTHFD1 are responsible for cobalamin metabolism-related disorders. Data on post-kidney transplantation outcomes in such patients are limited. A case of recurrent disease was reported in a patient with MMACHC-associated TMA who did not receive hydroxycobalamin therapy [51].
DGKE	No recurrence was observed after kidney transplantation in 5 reported cases [54], supporting the hypothesis of a non-complement pathway-associated TMA [52, 55]. Kidney transplantation may serve as a therapeutic option by correcting the dysregulated prothrombotic pathways.
TSEN2	Biallelic TSEN2 variants cause TRACK syndrome, which is characterized by growth retardation, intellectual disability, microcephaly, and TMA. TSEN2 encodes a subunit of the tRNA splicing endonuclease [122]. These patients develop progressive kidney failure that is unresponsive to eculizumab. In addition, TMA relapse was observed in one patient while on eculizumab therapy prior to kidney transplantation. Two patients underwent kidney transplantation: one experienced early-onset TMA 3 days post-transplant, which was treated with eculizumab, whereas the other had an uneventful post-transplant course [49, 122].
TREX1	Heterozygous C-terminal frameshift variants of TREX1 are associated with kidney-limited TMA. Data on kidney transplantation outcomes in these patients are limited. One reported patient underwent kidney transplantation and had an uneventful post-transplant course [123].

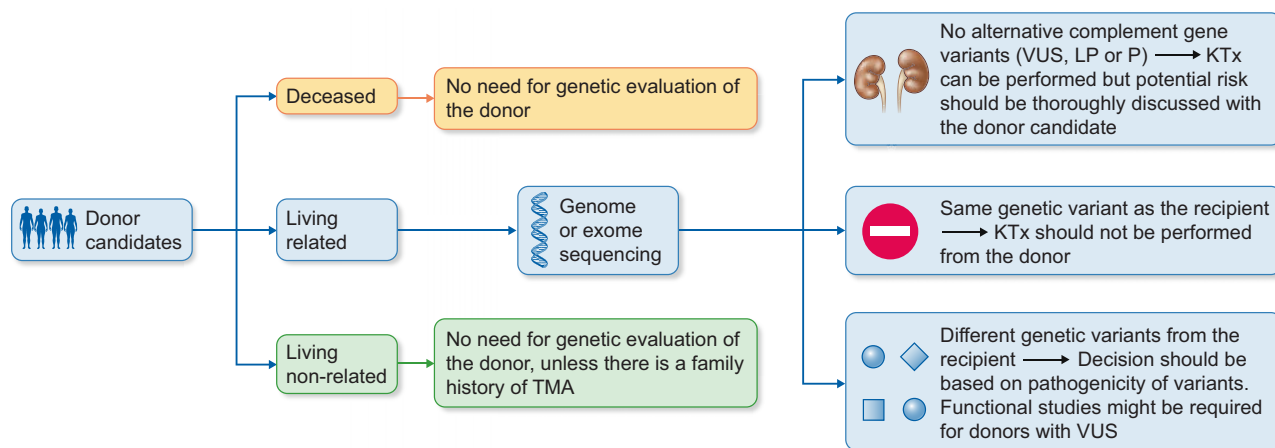


Figure 2: A donor evaluation algorithm for kidney transplantation in the setting of complement-associated thrombotic microangiopathy. KT_x, kidney transplantation; LP, likely pathogenic; P, pathogenic. According to the guidance of American College of Medical Genetics and Genomics, a standard terminology including “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” is in use to describe genetic variants [124]. Likely pathogenic and likely benign should be used to mean ≥90% certainty of a variant either being disease-causing or benign [124].

Table 2: Risk of aHUS recurrence after kidney transplantation and proposed management. Adapted from references [10, 73].

Risk classification	Criteria	Prevention of recurrence
High (>50%–80%)	• Previous recurrence on a kidney allograft • Pathogenic/likely pathogenic variant in <i>CFH</i>, <i>C3</i>, <i>CFB</i>, <i>CFHR1</i>; <i>CFH/CFHR</i> hybrid genes • High titer of anti-factor H autoantibodies	• Prophylactic eculizumab (prolonged duration, lifelong?) • Potential alternatives: living-donor transplantation combined with a protocol to reduce endothelial injury, or combined liver and kidney transplantation in selected cases
Moderate (10%–50%)	• Pathogenic/likely pathogenic <i>CFI</i> variant (isolated) • Variant of unknown significance or absence of pathogenic/likely pathogenic variant • Low-titer anti-factor H autoantibodies	• Prophylactic eculizumab (3–6 months?) • Potential alternatives: living-donor transplantation combined with a protocol to reduce endothelial injury, or combined liver and kidney transplantation in selected cases
Low (<10%)	• Pathogenic/likely pathogenic <i>MCP</i> variant (isolated) • Persistently negative anti-factor H autoantibodies	None

TREATMENT

Key therapeutic challenges include preventing disease recurrence in recipients with a history of aHUS-related kidney failure and managing *de novo* TMA.

Mitigating the risk of aHUS recurrence

aHUS resulting from genetic or acquired dysregulation of the alternative complement pathway is associated with a high risk of recurrence following kidney transplantation. Among patients at moderate or high risk, prevention of disease recurrence after kidney transplantation can be successfully achieved using prophylactic terminal complement inhibition. The introduction of eculizumab and ravulizumab—humanized monoclonal antibodies targeting complement protein C5, a critical component of the terminal complement pathway—has transformed the management and prognosis of patients with complement-associated TMA [10, 73]. In patients with aHUS affecting native kidneys or kidney allografts, terminal complement inhibitors have demonstrated remarkable efficacy in controlling TMA activity, significantly reducing the risk of progression to kidney failure or death [74–78]. In a seminal case report, prophylactic administration of eculizumab successfully prevented disease recurrence and preserved allograft function in a 9-year-old child with kidney failure due to aHUS associated with a pathogenic *CFH* variant who underwent deceased donor kidney transplantation [79]. Subsequent registry studies have confirmed the substantial benefits of peri-transplant eculizumab prophylaxis, showing a marked reduction in the risk of disease recurrence and significant improvement in graft survival among patients at moderate to high risk of relapse [47, 80]. These findings have supported the development of a personalized, risk-stratified approach to managing aHUS in the context of kidney transplantation (Table 2) [10, 73]. Emerging reports suggest that ravulizumab may offer similar efficacy to eculizumab in preventing disease recurrence and graft loss in patients with aHUS [81]. Prophylactic eculizumab can probably be safely discontinued after kidney transplantation in selected patients, particularly those at moderate risk for disease recurrence [47, 82]. Notably, SETS-aHUS trial showed that withdrawal of eculizumab with monitoring of disease activity was not associated with an increased risk of harm compared

to continuation of the agent [83], and substantially reduced the costs [84]. However, the trial excluded some high-risk patients. Optimal duration of complement inhibition in high-risk individuals remains undefined and warrants further investigation. The decision to withdraw eculizumab should be individualized, with a careful evaluation of potential risks and benefits (Box 2). Caution is especially advised in patients with reduced kidney function (e.g. estimated glomerular filtration rate <30 ml/min per 1.73 m²) or in those with a recent history of ABMR or infection (e.g. CMV or BK virus), as these factors may trigger disease recurrence.

Box 2. Practical approach to a kidney transplant recipient treated with prophylactic terminal complement inhibition (eculizumab or ravulizumab) with regard to vaccination and treatment withdrawal. Treatment withdrawal and monitoring may be a cost-effective option [84].

Vaccination	Vaccination for encapsulated microorganisms (meningococcus, pneumococcus and <i>H. influenza</i>) 2 weeks before the initiation In urgent cases, prophylactic antibiotics concurrent with the terminal complement inhibitor until 2 weeks after vaccination
Treatment withdrawal	In patients with moderate risk of recurrence*, withdrawal of prophylactic eculizumab or ravulizumab can be attempted after 3 to 6 months provided that there is no residual activity of thrombotic microangiopathy
Monitoring after withdrawal	Serum creatinine, urinalysis, serum lactate dehydrogenase, haptoglobin, schistocytes on peripheral blood smear
Recurrence after withdrawal	Rescue therapy

*Risk groups and treatment strategy are summarized in Table 2 and Fig. 3, respectively.

An alternative approach to prophylactic eculizumab involves the use of living-donor transplantation combined with a protocol to reduce endothelial injury [85, 86]. Living-donor kidney transplantation reduces the extent of ischemia-reperfusion injury, a known trigger for recurrence. In addition, maintaining lower than standard tacrolimus blood levels, strict blood pressure control, and the use of statins and renin-angiotensin system blockers may provide further endothelial protection. A prospective study evaluating this strategy reported a recurrence rate of ~20%, substantially lower than the historically reported estimates in high-risk patients [86]. However, many recurrences occurred late, with a median onset of 46 months post-transplantation. These late recurrences often presented subtly, with isolated rises in serum creatinine and without classical hematologic features of TMA, such as thrombocytopenia or microangiopathic hemolytic anemia, therefore requiring a kidney biopsy for diagnosis. Despite the administration of eculizumab as a rescue therapy, patients who experienced recurrence had poor outcomes, likely due to delayed recognition and treatment. Retrospective studies suggest that eculizumab rescue therapy might preserve allograft function if treatment is started within 7 days of TMA onset [10].

There are no randomized controlled trials directly comparing prophylactic versus rescue eculizumab to prevent aHUS recurrence and allograft loss after kidney transplantation. The available evidence for prophylactic C5 inhibition derives from retrospective cohort studies, whereas the rescue approach has primarily been proposed by a few centers in the Netherlands. In a recent retrospective comparison of prophylaxis versus rescue therapy, death-censored graft survival appeared similar between groups [87]. However, baseline differences limit the interpretation of these findings. In particular, the prevalence of very high-risk complement abnormalities (CFH SCR20 mutations or hybrid genes) was significantly higher in the prophylaxis group (31% vs 5%, $P < 0.01$), while living-donor transplantation was more common in the rescue cohort (20% vs 66%, $P < 0.001$). These imbalances preclude any firm conclusions regarding comparative efficacy. [Supplementary Table 2](#) compares these two main approaches in kidney transplant recipients with aHUS.

Combined liver-kidney transplantation offers the potential for a definitive cure of aHUS caused by pathogenic variants in CFH, CFB, or C3, which encode liver-derived complement factors [88]. However, this approach carries a significantly higher risk of perioperative and postoperative complications compared to kidney transplantation with prophylactic eculizumab. Therefore, it should be reserved for carefully selected, well-informed patients who explicitly request the procedure with the goal of improving their quality of life [89]. Further studies are needed to refine patient selection criteria and accurately balance the risks and benefits of the available therapeutic strategies [10, 87].

Additional strategies to minimize the risk of recurrence following kidney transplantation include reducing cold ischemia time to the shortest duration possible and avoiding the use of donors after circulatory death, donors with a high risk of ischemia-reperfusion injury, or ABO-incompatible transplants. Furthermore, toxic levels of CNIs and the use of mTOR inhibitors should be avoided [7, 33, 89]. Belatacept, a selective blocker of T cell co-stimulation via CTLA-4, may be considered as an alternative to CNIs in patients with recurrent disease [90].

Management of *de novo* TMA

Initial management of *de novo* TMA focuses on identifying and correcting the precipitating factor(s) including reduction

or discontinuation of CNIs, and treating concurrent infections or episodes of rejection. Given the potential role of complement dysregulation, early initiation of complement inhibition should be considered, at least in selected patients. Although well-designed, randomized controlled trials to assess the safety and efficacy of terminal complement inhibitors in patients with *de novo* TMA after kidney transplantation are currently lacking, case reports and case series are accumulating. More than 80 cases treated with eculizumab have been reported to date, of which ~80% showed a significant improvement in allograft function ([Supplementary Table 1](#)) [13, 91–110]. While acknowledging the inherent limitations of data from selected cases, these observations support considering terminal complement inhibition, particularly when no clear trigger is identified (e.g. CMV infection, elevated blood levels of CNIs, or ABMR), or when the TMA is severe, persistent, or unresponsive to conventional treatments [3, 73]. Re-evaluation based on complement genetic testing and clinical response is recommended [3, 73]. As in patients with aHUS on native kidneys, early recognition and prompt initiation of terminal complement inhibition is key to improve outcomes in post-transplant *de novo* TMA [96]. There are no additional safety concerns about terminal inhibition in kidney transplant recipients compared with non-transplanted patients with aHUS. In selected cases, switching from CNIs to belatacept may be considered as part of the immunosuppressive strategy, alone or in combination with terminal complement inhibition [103, 104, 111]. Patients who exhibit TMA features despite low trough levels of CNIs without high immunological risk can be ideal candidates for the switch if belatacept is available [111]. Nevertheless, risks of post-transplant lymphoproliferative disorders and CMV reactivation should be considered [112]. Preventive measures for *de novo* TMA include minimizing ischemia time, close therapeutic drug monitoring, infection prevention and treatment, maintaining optimal blood pressure control, and effective management of rejection episodes (Fig. 3). Novel complement inhibitors—including iptacopan (an oral factor B inhibitor), crovalimab (a recycling anti-C5 monoclonal antibody administered subcutaneously), and pegcetacoplan (a subcutaneous C3/C3b inhibitor)—have demonstrated efficacy in paroxysmal nocturnal hemoglobinuria and complement-mediated kidney diseases [113–115]. Phase 3 trials are currently evaluating iptacopan and crovalimab in patients with aHUS, including kidney transplant recipients (NCT04889430, NCT04861259, NCT04958265).

PROGNOSIS

Prognosis is influenced by etiology, timing of diagnosis, underlying complement dysregulation or genetic predisposition, and the availability of eculizumab therapy, when appropriate. *De novo* TMA demonstrates variable outcomes, with graft survival rates between 50% and 70% in 2–5 years after diagnosis, depending on the timely identification and management of precipitating factors [11–13, 116]. In contrast, recurrent TMA, especially in the context of aHUS, has been associated with a significant risk of graft loss, with pre-eculizumab data showing graft failure rates exceeding 80% in 5 years [15, 16]. Following the introduction of eculizumab, early initiation has been linked to significant decreases in TMA recurrence, stabilization or enhancement of kidney function, and improved graft survival [47, 96, 117–119]. A meta-analysis of 18 studies found that in patients receiving prophylactic eculizumab, the incidence of allograft loss due to TMA was 5.5%, whereas in those treated with eculizumab for post-transplant aHUS recurrence, the rate of allograft loss due to TMA

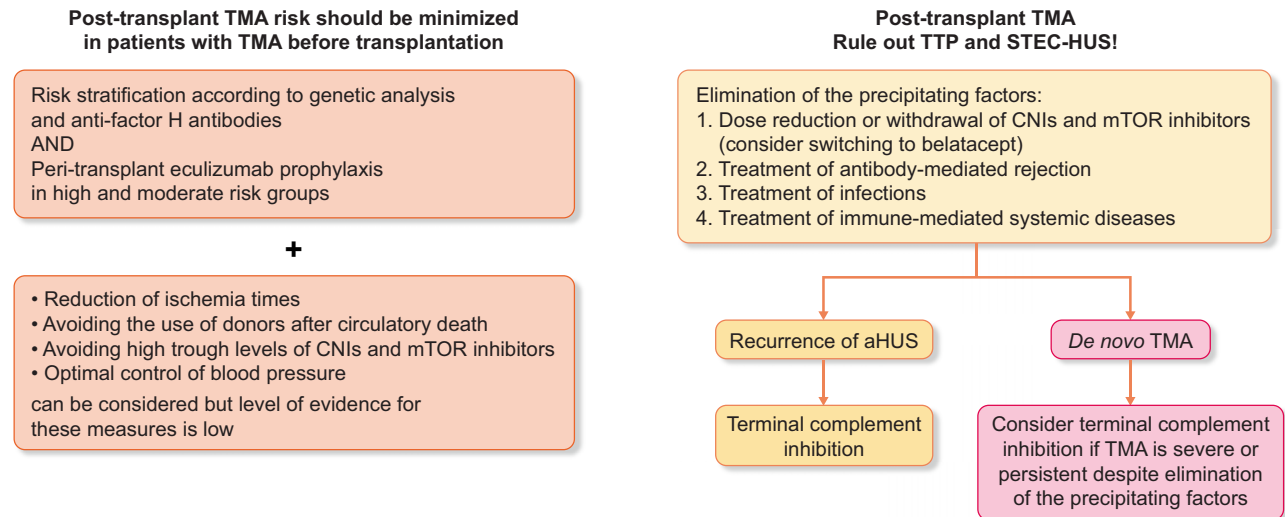


Figure 3: Therapeutic approach to patients with TMA before and after kidney transplantation. TTP, thrombotic thrombocytopenic purpura.

was 22.5% [119]. A summary of key studies examining the incidence and outcomes of recurrent and *de novo* TMA is presented in [Supplementary Table 3](#).

CONCLUSIONS

TMA after kidney transplantation is not rare, observed in up to 14% of patients over the life of the allograft. The disease may present either with classical hematological manifestations of microangiopathic hemolytic anemia and thrombocytopenia, or as a kidney-limited TMA. Post-transplant TMA result from a complex interplay between genetic predisposition factors and environmental triggers. Genetic factors are the major triggers in recurrent disease, while environmental factors and the aforementioned secondary insults play significant roles in *de novo* TMA. aHUS recurrence can successfully be managed with terminal complement inhibition. Notably, peri-transplant eculizumab prophylaxis dramatically reduced the recurrence rates. Eliminating the precipitating factor(s) is the first approach in *de novo* TMA, and terminal complement inhibition can be of use when no clear trigger is identified or when the disease is persistent and unresponsive to conventional treatments. Prognosis of recurrent TMA has considerably changed with better outcomes after eculizumab was introduced into clinical practice. If or when to discontinue terminal complement inhibition is still undecided. Ongoing research is needed to optimize management strategies to improve outcomes of this challenging complication in kidney transplant patients.

SUPPLEMENTARY DATA

Supplementary data are available at [Clinical Kidney Journal](#) online.

AUTHORS' CONTRIBUTIONS

S.M. designed the article. S.M., J.M., O.E., O.H., A.B.D., and G.K. prepared the first draft. K.L.L. and Y.C. led the critical revisions. All authors read and approved the final version to be submitted.

CONFLICT OF INTEREST STATEMENT

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