An overview of thrombotic microangiopathy in kidney transplant patients

**Abstract**

Thrombotic microangiopathy (TMA) is one of the most severe complications consequent to kidney transplant that predominantly affects the renal microvasculature. It is a histological characteristic of antibody-mediated rejection (AMR) and can lead to graft failure, especially in highly sensitized, cross-match positive kidney transplant recipients. The clinical features of TMA include platelet thrombi and aggregation, thrombocytopenia, microangiopathic hemolytic anemia, and tissue ischemia with organ failure. The underlying mechanism is usually a sequalae of combined acute coagulopathy and complement activation. In kidney transplant patients, *de novo* TMA can develop without a prior history or recurrent TMA as a continuation of disease in the native kidney. Both types are associated with poor graft prognosis and patient outcomes post-transplant. Genetic testing, early diagnosis and treatment, as well as a thorough understanding of pathogenic pathways are crucial for its management. The treatment approach usually targets the causative factor, but some forms may require more aggressive or combined interventions. Plasma exchange and complement blockade with eculizumab are among the currently available therapies. Eculizumab is effective for both *de novo* and recurrent TMA post-transplant. But there is still a need to optimize the patient profile and duration of this therapy for its maximum benefits, along with exploring new alternate therapeutics. This review gives an overview of the types of TMA post-kidney transplant along with their pathophysiology, risk factors, incidence, and available treatment options.

**Keywords:** Thrombotic microangiopathy, kidney transplantation, mechanism, risk factors,

prevention, treatment

**Introduction**

Thrombotic microangiopathy (TMA) is a disorder of microvasculature with hallmark features of endothelial dysfunction due to injury, platelet aggregation, and thrombi forming in small blood vessels [1, 2]. The thrombi cause consumption of platelets and mechanical shearing of red blood cells, and ultimately thrombocytopenia and microangiopathic hemolytic anemia. The resulting occlusion of vessels primarily affect the kidneys but can damage other organs as well [3]. It may be triggered spontaneously due to several known factors like infections and genetic abnormalities, or develop secondary to solid organ transplantation, drugs, malignancy, pregnancy, and certain autoimmune diseases. Based on these mechanisms, TMA can be categorized as primary or secondary, respectively [3, 4].

When TMA develops post solid organ transplantation, it is potentially life-threatening and associated with poor patient and graft outcomes. Although initially considered rare, several studies over the years have highlighted a much higher TMA incidence than previously assumed [5, 6, 7]. In kidney transplant patients, it can develop systemically with the appearance of hemolytic microangiopathic anemia, thrombocytopenia, and renal failure. When locally limited, it can manifest as arterial hypertension, proteinuria, or gradual and continuous renal failure and is only diagnosed on kidney biopsy [3, 8]. After transplant, TMA can be categorized as *de novo* or recurrent types. *De novo* TMA develops without any signs or symptoms prior to transplant. Recurrent TMA is a continuation of the disease from the native kidney that is often missed or failed to be diagnosed. *De novo*, the more common form, has worse graft-related prognosis than recurrent [9].

TMA is a histological characteristic of antibody-mediated rejection (AMR) and can lead to graft failure, especially in highly sensitized patients with a cross-match positive kidney transplant [10]. Glomerular and/or vascular TMA can affect 6.4% of total renal allografts with pathologic AMR in 46.6% of the grafts, as seen via renal biopsies [11]. With reported graft failure rates of up to 40% within 2 years, TMA is associated with a poor prognosis of the overall graft function [5, 12].

For timely detection and management, TMA should be highly suspected and understood with respect to its underlying aetiologies [8]. In this review, we discuss the types of TMA in kidney transplant patients along with their risk factors, pathophysiologic mechanisms, and a brief overview of the interventions for their treatment.

**Clinical features of TMA**

Laboratory findings in TMA are distinguished by thrombocytopenia and microangiopathic hemolytic anemia (MAHA). Thrombocytopenia is a manifestation of platelet aggregation and consumption. MAHA is identified by observation of fragmented red blood cells via microscopic examination of the peripheral blood film. RBCs fragment due to turbulent flow in the microcirculation caused by platelet aggregate-mediated partial occlusion [13]. Other unusual laboratory findings include elevated lactate dehydrogenase, unconjugated hyperbilirubinemia, and low haptoglobin [14].

TMA primarily affects the renal microvasculature, but symptoms can also be observed in the central nervous system, cardiovascular system, lungs, skeletal muscle, gastrointestinal tract, and skin in 20% of patients [15]. Though rare, TMAs can be life-threatening and associated with significant morbidity and mortality. They also lead to poor patient and graft outcomes [7, 12, 16].

**TMA types based on pathogenic mechanism**

**Primary and secondary TMA:** TMA syndromes are classified as primary or secondary based on pathogenic mechanisms. Primary syndromes have known etiology. They include thrombotic thrombocytopenic purpura (TTP) [4], typical hemolytic uremic syndrome (HUS) [7], atypical HUS (aHUS) [3, 18], and pneumococcal-associated HUS. The secondary syndromes of TMA can be a result of multiple factors (Figure 1).

In many instances, an underlying cause like a complement mutation or ADAMTS13 deficiency (primary TMA), may express itself as an TMA episode only when triggered by surgery, pregnancy, or an inflammatory disorder (secondary TMA) [4].

**TMA types in kidney transplant patients**

***De novo* and Recurrent TMA:** Post-transplant TMA is categorized into *de novo* and recurrent TMA. *De novo* TMA post kidney transplantation can occur at any time point but is more likely to be detected in the initial 3-6 months [12, 20]. Its prevalence in renal transplant recipients has been shown to vary among studies—one study reporting higher prevalence in males, while another in females, especially younger patients [5, 21]. The cause-and-effect mechanisms in *de novo* TMA are still not completely known, but the two most common causes have been identified as AMR and medications. Twenty nine percent of patients presenting with *de novo* TMA were reported to have complement abnormalities at a genetic level to be an underlying cause [22]. A retrospective study identified preimplantation endothelial ultrastructural injury (identified by biopsy) along with abnormalities in alternate complement pathway to be associated with *de novo* posttransplant TMA [23]. Among the drugs, cyclosporin (CsA) therapy is linked to the majority of *de novo* instances [24]. Less common causes include viral infections, severe renal ischemia, and acute vascular rejection [21].

The probability of recurrent TMA is determined by the cause of primary TMA in the native kidneys. The most prevalent diagnosis with TMA recurring in allografts is aHUS, due to the impaired regulation and over-activation of the alternate pathway of complement system [9]. On an average, 60% of patients with aHUS develop recurrent TMA. Recurrent aHUS is associated with the graft failure in 90% of patients if left untreated, 80% within the first year of transplantation [25].

The prevalence of *de novo* TMA is significantly higher in post-transplant patients (90% vs 10% of all cases) and more diverse in etiology compared to patients with recurrent aHUS. However, patients with end stage renal disease (ESRD) and a history of aHUS have a 36.5 times higher probability of developing TMA post-transplant [5]. Though uncommon in itself, recurrent TMA is nearly always complement-mediated.

Schwimmer et al. describe TMA as systemic and localized with systemic extension being more aggressive and associated with a higher rate of graft loss compared to the localized TMA [16]. Aleš Rigler et al. correlate the severity of posttransplant TMA with the miRNA expression patterns in preimplantation kidney graft biopsies [23].

**Incidence of TMA in kidney transplant patients**

The chances of TMA remain high three months post-transplantation due to higher use of

immunosuppressants with one study reporting 10.5% cases of early renal allograft dysfunction [21]. Though one study found 1.5% cases of *de novo* TMA in kidney transplant recipients [26], it can easily range up to 14% [24]. Complement-mediated aHUS can recur with a rate of 25-50% in patients on dialysis [27, 28]. A study from the United States Renal Data System (USRDS) reported 5.6 cases of recurrent and 4.9 cases of de novo TMA per 1000 person-years in kidney transplant recipients with a 50% survival rate of three years post-TMA diagnosis [5].

Another study also observed TMA in 14% (26 of 188) of kidney transplant recipients, of which 24 were on CsA [24]. Higher doses of CsA are associated with 4-15% of *de novo* cases with a graft survival of 43% [29, 30]. Calcineurin inhibitor (CNI) tacrolimus on the other hand contributes to around 1% of TMA cases in kidney transplant patients [31]. Among the genetic mutations, that of complement factor H (CFH) and complement factor I (CFI) cause *de novo* TMA in 29% of patients [32]. Their implication is much higher in recurrent TMA with CFH and CFI mutations contributing to recurrence rates of 50-100% in transplant patients [33]. The recurrence rate is much lower (15-20%) in patients with mutations in membrane cofactor protein (MCP) as it is rapidly expressed in the transplanted kidney [28, 33].

The primary forms of TMA, TTP and HUS, have been reported to be incident in about 3 per 1000000 (adults) [34] and 3 per 100000 (in children), respectively [35]. Childhood onset HUS has a recurrence rate of <1% in kidney transplant patients and is a consequence of Shiga-toxin producing *Escherichia coli* in >90% of patients [19, 36]. According to a retrospective study of 17 patients with post-transplant TMA proven by biopsy in the nephrology transplant unit of a tertiary care referral hospital in the northern part of India between 1989 and 2015, CNI-associated TMA constitutes the majority of post-transplant TMA (70%). TMA associated with rejection was not only resistant to conventional treatment, but also resulted in poor graft outcomes [6]. In a retrospective observational study among 1210 renal transplants conducted from 2005 to 2018, 12 patients developed post-transplant thrombotic complications, out of which acute rejection was linked to 58.3% of the cases, whereas calcineurin toxicity was linked to 16.6% of the cases. Graft loss was seen in 50% of patients within the 1st year [37].

The chronic activation of immune cells by coronavirus disease 2019 (COVID-19) infection is associated with endothelial injury and microthrombotic pathway, among others. Bascunana et al. have reported a COVID-19 infected kidney transplant recipient who developed TMA along with acute infection, low platelet count, anemia and acute kidney injury that worsened with the COVID-19 infection [39].

**Pathophysiology of TMA syndromes post kidney transplant**

Ischemic tissue injury in TMA is a triad of microangiopathic hemolytic anemia, thrombocytopenia, and microthrombi [14]. TMA is not a common complication in highly sensitized kidney transplant recipients. But it develops fast with no distinguishable early signs and can cause severe kidney injury and even graft loss as a result. Immunosuppressive medicines such as CsA, CNI, and sirolimus; AMR; and recurrent and *de novo* HUS are all linked to new TMA manifestations in the transplanted kidney [10, 39, 40]. To reverse TMA in a timely manner, it is critical to detect and treat it early, with an accurate understanding of the underlying pathogenic mechanisms.

TMA is mediated by a combination of acute coagulopathy and complement activation, both in response to human leukocyte antigen (HLA) antibodies [10].

**Complement system and TMA:** With a network of more than 40 soluble proteins and membrane receptors, the complement system performs multifaceted functions and coordinates with both native and adaptive immune systems. Apart from the direct lysis of the bacterial membrane via membrane attack complex (MAC), complement also opsonizes the pathogens for phagocytosis, plays a critical role in inflammatory pathways, regulates T- and B-cell activity, and helps in the clearance of host cells after apoptosis [41, 42].

The complement gets activated through one of the three different pathways—classical, alternate, and lectin—that ultimately converge to the release of anaphylatoxins and MAC formation. The classical and lectin pathways have distinct target recognition molecules. The alternate pathway, on the other hand, has no specific target recognition molecule and is activated spontaneously. Regulator proteins protect damage to the healthy host cells from such triggers. Subsequently, the C3 convertase assembles in all the three pathways. The C3 convertase further leads to the assembly of the C5 convertase that contributes to the formation of MAC along with other complement proteins [42, 43].

After renal transplantation, renal ischemia along with reperfusion injury is marked by complement activation and enhanced expression of its component molecules in the allograft. Combined with inflammatory mediators and other immune-related processes involving increased antibody production and T-cell infiltration, the chances of allograft success and long-term outcomes are negatively affected [43].

Gene mutations in complement proteins such as CFH, CFI, MCP, C3 and others have been recognized in cases of recurrent TMA. Since the genetic evaluation is complex, many complement genetic mutations risk haplotypes remain undetected and contribute to post transplant TMA and graft failures [2, 44].

Other than the genetic causes, many TMA cases develop due to AMR and positive C4d as enabled by detection of donor-specific HLA antibodies. The HLA antibodies are known to activate the complement system through the innate pathway [10].

It has been suggested that all patients with *de novo* TMA should also undergo genetic testing for complement mutations [45]. In many cases, the genetic variants are silent in the native kidney but become evident when they lead to the development of TMA post transplantation.

**Acute coagulopathy and TMA:** Thrombin makes up the central component of the coagulation cascade, which in turn is similar to the complement pathway [46, 10]. But in the coagulation pathway, thrombin activation leads to platelet aggregation in primary hemostasis, and fibrin monomers due to dissolution of soluble fibrinogen in secondary hemostasis [10]. In a pig-to-baboon liver xenotransplant model, administration of coagulation factors led to thrombosis of the graft and large vessels with contemporaneous development of TMA. Further studies on the same model also highlighted the key contribution of thrombin to platelet activation in TMA [47].

**Endothelial cell activation:** HLA antibodies have been shown to activate endothelial cells (ECs) through multiple mechanisms including enhanced expression of cell adhesion molecules to promote leucocyte migration and monocyte adhesion. The activated ECs in turn activate the complement as well as the coagulation pathways. HLA antibodies induce EC exocytosis, which leads to an enhanced expression of von Willebrand Factor (vWF), a multimeric glycoprotein and key factor involved in both primary and secondary hemostasis [48]. Additionally, it initiates thrombus formation by stimulating adherence of platelets to thrombogenic surfaces and their cohesion. It also reduces the clearance of Factor VIII indirectly [49]. Genetically driven increase in vWF plasma levels has been linked to an increased risk of arterial thrombosis [50]. A significant connection with TMA comes from the enzyme ADAMTS-13 that regulates the vWF multimer size and is deficient in TTP, a systemic form of primary TMA [51]. *In vitro*, the ECs activated by HLA antibodies lead to the production of C4, a complement cascade member locally [52].

**Complement and coagulation cascade cross-talk:** Mannose-binding lectins (MBL) or other lectins bind to various membrane-bound glycoproteins or glycolipids in the lectin pathway. MBL-associated serine protease 1 (MASP-1) generates thrombin via activation of prothrombin, FXIII, and thrombin-activatable fibrinolysis inhibitor [53, 54]. MASP-2 directly leads to formation of clot, comparable to the one formed by thrombin [55]. Consequently, increased production of lectin pathway proteases (MASP-1 and MASP-2) both initiates and amplifies the coagulation cascade [56]. Thus, the cross-talk between complement and coagulation pathways converges to TMA at some point.

**Risk factors associated with TMA development**

***De novo* TMA**: The underlying causes form the basis of therapeutic management of TMA. *De novo* TMA occurs more commonly and the factors responsible for its development include single or combined CNI or mammalian target of rapamycin inhibitor (mTORi), abnormalities in complement system, AMR, any kind of viral infection (hepatitis C, cytomegalovirus (CMV), BK, influenza A, human herpesvirus-6 (HHV-6) and parvovirus), associated TMA, use of anti-vascular endothelial growth factor inhibitors, and missed diagnosis of recurrent TMA [57]. Genetic mutations in complement factors CFH, CFI, and CFH/CFI combination are also prominent risk factors for *de novo* TMA [22].

Figure 2 summarizes the major risk factors associated with *de novo* TMA. Drug induced TMA is observed as a sudden onset acute kidney injury that develops soon after the drug exposure. Though more than one mechanism exists, they both lead to TMA development predominantly through their pro-thrombotic effects [58]. CsA can have toxic effects on ECs directly or reduce the production of activated protein C from them indirectly that causes endothelial damage and thrombosis.

Complement system has a significant role in AMR as the antibodies specific to the donor bind to leukocyte antigens on allograft endothelium. This activates both the classical and alternate complement pathway by generating MAC to cause cell lysis and inflammatory infiltration [59]. Patients with concurrent AMR and TMA show poor graft survival compared to patients with AMR alone [60]. A study conducted over a period of 5 years in India revealed pathologic AMR to be the most common cause of TMA [11]. Early activation of complement system in the absence of a previous aHUS can depend on the donor type *viz.* in donors after brain or circulatory death [3]. A state of increased pro-coagulants and reduced fibrinolysis can also cause post-transplantation TMA [61, 62].

Among other drugs, anti-cancer medications, like pazopanib can sometimes be involved in TMA appearance. A renal transplant recipient with a history of metastatic renal carcinoma showed indications of *de novo* kidney limited TMA, due to treatment with pazopanib and CNI [63]. Other studies have also reported pazopanib-associated TMA development, along with kidney injury and hyperbilirubinaemia [64, 65].

Deposition of viruses in endothelial cells along with activation of adhesion molecules and release of vWF are some other risk factors [66]. Even though the reported cases are few, CMV is the most frequently implicated virus [3]. In an interesting instance, *de novo* TMA was induced in a 45-year-old Caucasian male, 25 years after renal transplantation. In this case and several others, the hemolysis associated with TMA disappeared after the CMV-DNAemia was negated [67]. Other instances of post-transplant TMA due to infection with parvovirus B-19, hepatitis C virus, HIV, HHV-6, and histoplamosis (fungal) have also been reported [3, 68, 69, 70, 71].

**Recurrent TMA:** The risk of recurrence of aHUS after kidney transplant depends on recurrence in previous transplants and the genetic mutations in the complement proteins (Table 1). The presence of anti-CFH autoantibodies, MCP mutations, and thrombomodulin mutations have shown better outcomes [22, 30]. Cases with combined mutations are rare and their outcomes are difficult to decipher [19]. The management strategy for post-transplant aHUS should be based on the risk stratification of these mutations [72].

**Interventions for treatment of TMA in kidney transplant recipients**

Some forms like TTP can be managed well by plasmapheresis while others like recurrent aHUS that are associated with low graft survival and risk of mortality, require more aggressive interventions [19].

***De novo* post-transplant TMA:** In cases where TMA develops secondary to immunosuppressive drugs, the offending agent should be reduced or stopped and switched to another CNI or mTORi. Patients receiving CsA can be switched to tacrolimus [19, 28].

Plasma exchange can remove platelet-aggregating factors while providing the depleted ones and is beneficial in patients with disease progression despite withdrawal of CNI/mTOR inhibitor [19, 73]. For patients resistant to plasma exchange and positive for CFH and CFI mutations, eculizumab (recombinant monoclonal antibody against human complement protein C5) is the recommended treatment [3].

Plasmapheresis therapy is the mainstay in treatment of AMR associated TMA with eculizumab as a rescue therapy only when hemolysis is observed even after maximal management with plasma exchange [3]. For CMV-mediated TMA, intravenous ganciclovir and plasma exchange has been shown to resolve hemolysis. In cases where this therapy failed and the TMA recurred, valganciclovir and eculizumab have been used to treat it

successfully [66].

**Recurrent aHUS:** Eculizumab has proved to be an excellent therapy for recurrent aHUS. Its first dose is used an hour prior to reperfusion followed by a second dose one day subsequent to transplantation to reduce secondary activation of complement [3, 20]. Administration of eculizumab reduced the recurrent TMA from 49% to 12% in post-transplant patients with aHUS along with improved graft function [74]. In a retrospective multicenter study, the prophylactic as well as post kidney transplant treatment with eculizumab was associated with a much lower percentage of patients losing the graft due to aHUS compared to patients receiving no eculizumab (10% and 5.9% vs 91%, respectively). The same study also showed acute rejection in 67% of patients receiving no eculizumab compared to 0% and 35% in the prophylaxis and post-transplant treatment groups. All these findings further strengthen the need for eculizumab to treat aHUS in kidney transplant patients [7]. There is no definite duration of therapy, but response to eculizumab should be measured before each dose for the first 4 doses by total hemolytic complement (CH50) level or with markers like thrombomodulin to decide the best therapeutic strategy for the patients [19, 72] However, eculizumab is associated with meningococcal infection and vaccination against *Neisseria meningitides* serogroups is necessary, 2 weeks prior to eculizumab administration [3].

Simultaneous liver and kidney transplant has also been investigated to restore kidney function as well as avert aHUS recurrence in patients with mutations in CFH and presumably other genes that encode for liver-derived complement proteins [75, 76]. After complications in initial cases that included premature liver failure, extensive microvascular thrombosis, and complement deposition due to functional CFH deficiency, a modified approach was applied. It employed substantial plasma exchange prior to the transplant to ensure normal CFH till graft stabilization. Heparin and low-dose aspirin mitigated any associated risks of enhanced thrombogenicity. Six patients with CFH mutations and one with mixed CFH/CFI had successful results with this altered procedure but one child with CFH mutations exhibited a life-threatening encephalopathy and extensive hepatic thrombosis [76]. However, the positive outcomes of the combined liver-kidney transplant support its continued use in individual patients [75].

Use of prophylaxis-based plasmapheresis treatment is ineffective in recurrent aHUS treatment in moderate-to-high risk patients and can potentially activate the complement pathway [3, 20].

Guidelines recommend a direct approach to address *de novo* disease with a potential to develop into aHUS in a related donor. For recurrent disease, the risk needs to be alleviated through the regulated approval and use of a complement activation inhibitor, *i.e.,* eculizumab, in current practice. Patients at low risk of recurrence do not require eculizumab prophylaxis but should be closely monitored. It is also recommended to perform genetic testing for complement abnormalities in patients and donors to avoid similar genetic mutations. Even if the mutation is not identified, living related kidney transplantation is not suggested in aHUS as the disease can occur in the donor [77].

**Conclusion**

TMA can severely affect graft survival and outcomes in kidney transplant patients. The treatment ranges from simple procedures like plasmapheresis, withdrawal or dose modification of the offending drug, to more complex therapies like lifelong complement blocking. Plasma exchange as one of the primary treatments for TMA is limited by its response rate. Eculizumab minimizes the occurrence of recurrent TMA in post-transplant patients and is also effective in *de novo* disease. Alternative immunosuppressive drugs like belatacept and other anti-complement treatments are also emerging as treatment options. But these therapies may have to be continued indefinitely, leading to a significant cost burden [7]. There is a need to search for alternate therapeutic agents that are simpler and cost-effective. The starting point, however, should be to identify and avoid any risk factors for HUS at the pre-transplantation level itself. A pragmatic approach would include careful selection of donors and thorough preparation of recipients. Complete genetic screening should be the norm. Identifying early markers to diagnose and control TMA in a timely manner can further ensure optimum graft outcomes in patients.

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Table [1]: Risk stratification of recurrent aHUS based on mutations in complement proteins and others (Source: Avila et al., 2021 [3]; Abbas et al., 2022 [19]

|  |  |
| --- | --- |
| **Mutation in complement or other proteins** | **Risk stratification of aHUS recurrence** |
| * Genetic variants of CFH/CFB/CFH that are pathogenic: Rearrangements in CFHR1/TBHD
* C3 mutations
 | High |
| * Carriers of CFI variants/C3/anti-FH antibodies/homozygous for haplotypes CFH-H3/absence of variants
 | Moderate |
| * Isolated MCP/DGKε variants
* Negative anti-FH antibodies during transplantation
* MCP mutations
* Thrombomodulin mutations
 | Low |

CFH: Complement factor H; CFHR1: Complement factor H related protein 1; CFB: Complement factor B; TBHD: Thrombomodulin; CFI: Complement factor I; MCP: Membrane cofactor protein; DGKε: Diacylglycerol kinase epsilon

Figure 1: The primary and secondary syndromes of TMA (Sources: Abbas et al., 2022 [19]; Avila et al., 2021 [3]



Figure 2: Risk factors for *de novo* HUS (Sources: Abbas et al., 2018 [9]; Garg et al., 2018 [57]; Abbas et al., 2022 [19]

