Renal Thrombotic Microangiopathy: A Review

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Abstract

Thrombotic microangiopathy (TMA) is a pathological lesion observed in a wide spectrum of diseases, triggered by endothelial injury and/or dysfunction. Although TMA lesions are often accompanied by clinical features of microangiopathic hemolytic anemia, thrombocytopenia and ischemic end organ injury, renal-limited forms of TMA are not infrequently encountered in clinical practice. The presence of renal-limited manifestations can be diagnostically challenging, often delaying initiation of targeted therapy. Prompt investigation and empiric treatment of TMA is warranted to reduce associated morbidity and mortality. Major advances have been made with respect to the pathophysiology of primary TMA entities, with the subsequent development of novel diagnostic tools and lifesaving therapies for diseases like thrombotic thrombocytopenic purpura and complement-mediated TMA. This article will review the clinical presentation and pathologic hallmarks of TMA involving the kidney, and the disease-specific mechanisms that contribute to the endothelial injury that characterizes TMA lesions. Diagnostic approach, and both empiric and disease-specific treatment strategies will be discussed, along with the potential role for emerging targeted disease-specific therapies.

Keywords: Thrombotic microangiopathy, acute kidney injury, anemia, thrombocytopenia, complement
Introduction

Thrombotic microangiopathy (TMA) is a pathologic lesion characterized clinically by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia and ischemic organ injury\(^1\). The kidney is the most frequently injured organ, however other systems including the central nervous system, the cardiovascular and respiratory systems and the gastrointestinal tract can be affected\(^2\).

The classification and nomenclature describing TMA continues to evolve in parallel with discoveries elucidating the molecular mechanisms responsible for the characteristic endothelial injury and microvascular thrombi formation\(^3\). For the nephrologist, an approach that facilitates timely identification of conditions requiring urgent targeted therapies is a priority. A practical schema outlining the differential diagnosis of the underlying causes of TMA is outlined in Figure 1, with a more exhaustive list of causes in Box 1.

This schema highlights fundamental mechanisms contributing to endothelial injury, including ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency in thrombotic thrombocytopenic purpura (TTP) and alternative pathway (AP) dysregulation in complement-mediated TMA (CM-TMA; also referred to as atypical, or complement-mediated, hemolytic uremic syndrome)\(^1,4\)\(^–\)\(^6\). This schema is helpful for generating a differential diagnosis, but may be simplistic with respect to molecular pathogenesis as it is increasingly recognized that the mechanisms contributing to the different TMA syndromes can overlap. Indeed, complement activation may be triggered at endothelial surfaces in the context
of ADAMTS13 mediated TMA, TTP\textsuperscript{7,8}. Furthermore, a trigger such as infection, is often identified at first presentation of CM-TMA, even in the presence of pathogenic complement mutations.

In this review, we will discuss the spectrum of conditions associated with TMA (Box 1), clinical and pathologic hallmarks, and provide a diagnostic approach to TMA. We will highlight the disease-specific mechanisms of endothelial injury of the commonly encountered TMA syndromes, treatment strategies (Table 1, Table S1) and investigational complement-directed therapies according to TMA etiology (Table 2).

**Clinical presentation and pathologic features**

Endothelial injury with associated platelet activation and consumption contribute to microvascular thrombosis formation, tissue ischemia and subsequently end-organ injury. As red blood cells (RBC) traverse the microvasculature laden with thromboses, they become fragmented, producing the hallmarks of MAHA including schistocytes and thrombocytopenia, with low haptoglobin and elevated indirect bilirubin reflecting RBC fragmentation. While LDH elevation is related to RBC destruction, marked elevations reflect tissue ischemia. Hematuria, proteinuria and hypertension are common with renal involvement.

Systemic findings of TMA (i.e. MAHA and thrombocytopenia) are not required for the diagnosis of TMA. Indeed, renal-limited TMA is not infrequently observed in clinical practice. For example, as discussed below, isolated renal TMA lesions with may be observed more often in the setting of glomerulonephritides (e.g. ANCA-associated vasculitis, IgA nephropathy), solid organ
transplantation (e.g. calcineurin inhibitor (CNI) or antibody-mediated rejection (ABMR)) and in drug-induced TMA. While endothelial injury is central in the development of TMA, a predilection for specific vascular beds, including the renal vasculature, is observed in many TMA syndromes and the pattern of organ involvement may be influenced by genetic factors underlying pathophysiology².

An example of pathologic features of TMA in scleroderma renal crisis (SRC) is illustrated in Figure 2. The histologic changes of TMA are protean and variably present⁹. Changes may be quite subtle and will evolve over time; while glomerular or arteriolar thrombi are pathognomonic, these may be missed with limited sampling. In addition to microthrombi, arterial intimal edema (mucoid / myxoid change) or fibrin, are also considered diagnostic. Within glomeruli, endotheliosis (particularly with pregnancy associated syndromes) and mesangiolysis, are also typical. Red blood cell fragments may be seen in any instance. It should be noted that while the type of histologic change is not specific for any etiology, glomerular thrombi are more frequent in CM-TMA and arteriolar changes are usually prominent in SRC and hypertension-related TMA.

In the chronic phase, glomerular capillary wall double contouring evolves from new subendothelial basement membrane formation, and arterial onion skinning from myointimal hyperplasia. With repeated cycles of acute and chronic disease activity, both acute and chronic lesions may be seen in a single sample. Of special note, the unusual appearance of marked segmental subendothelial expansion with loose and dense hyalinosis is specifically associated with VEGF antagonist-related TMA¹⁰.
Pathogenesis

End organ manifestations of TMA result from endothelial injury and/or dysfunction with subsequent intravascular thrombosis. Underlying endothelial health may affect susceptibility to organ dysfunction. Indeed, local intravascular production of nitric oxide by endothelial nitric oxide synthase (eNOS) promotes vasodilatation and reduces the risk of thrombosis formation\textsuperscript{11}. Vascular endothelial grow factor (VEGF) regulates eNOS expression and modulates complement activation via complement factor H (CFH)\textsuperscript{12,13}. Situations in which VEGF and/or nitric oxide are reduced therefore predispose to TMA.

Once the endothelium becomes injured, there is activation of the coagulation system, mediated by tissue factor, inflammatory cytokines and lipopolysaccharide. There is growing evidence implicating neutrophil extracellular traps (NETs). Although NETs are released by activated neutrophils to help combat infection, they are also released in autoimmune diseases and may contribute to endothelial dysfunction and TMA\textsuperscript{14}. In addition to releasing antimicrobial proteins, they release scaffolding proteins which bind coagulation factors, platelets and RBC. Moreover, NETs contribute to thrombosis formation and can activate complement pathways\textsuperscript{15}.

Complement activation plays an important role in host defense by linking innate and adaptive immune responses, and maintaining homeostasis, by clearing immune complexes and damaged host cells\textsuperscript{16}. Three initiating pathways ultimately lead to terminal pathway (TP) activation. The classical pathway (CP) is activated by antibody-antigen complexes binding to the C1q complex. The lectin pathway (LP) becomes activated through the binding of mannose-binding lectin or
ficolins to mannose residues on microbial surfaces. Activation of the LP and CP result in proteolytic cleavage of C2 and C4 to form a C3 convertase. Conversely, the AP is constitutively active ("tick-over") whereby spontaneous hydrolysis of C3 binds factor B (FB) and ultimately leads to the production of the AP C3 convertase. The C3b produced by either the LP or CP can trigger the AP through proteolytic cleavage of C3 to C3b. The AP acts as an amplification loop to significantly increase downstream TP activation. Membrane-bound C3b triggers TP activation resulting in membrane attack complex formation and osmotic lysis of endothelial cells\textsuperscript{16}. C3a and C5a are complement activation by-products that are important for leucocyte recruitment at the site of injury and are involved in activating the coagulation cascade\textsuperscript{17}.

There exists cross-talk between the complement system and the coagulation cascade\textsuperscript{18,19}. The AP is tightly regulated by membrane-bound and soluble complement regulators to prevent widespread activation and host injury via C3b deposition on host cells. Complement overactivation leads to systemic endothelial injury and thrombosis. Conversely, endothelial injury, platelet activation and hemolysis can activate complement cascade\textsuperscript{20,21}. While targeting complement activation in this setting does not address the underlying disease-causing trigger for endothelial injury, it is not yet clear if modulation of complement activity may affect downstream injury pathways. The role of complement activation as a driving event or merely a secondary finding remains unclear in many other TMAs. Interestingly, the LP’s mannan-binding lectin-associated serine protease-2 (MASP-2) is also implicated in the coagulation cascade and clot formation by converting prothrombin into thrombin and activating factor XIII\textsuperscript{18,22}. 
Approach to common clinical syndromes associated with TMA

It is of critical importance to investigate the underlying TMA etiology to offer therapy directed towards the causal pathogenic process. A thorough “ideal” general diagnostic approach is provided in Figure 3, although it is recognized that in clinical practice the full spectrum of these tests is often not readily available. Furthermore, results of some of these tests may not be available for days to months. Prompt initiation of targeted therapies such as therapeutic plasma exchange (TPE) or eculizumab should not be delayed. While specific diagnostic tests are described in the sections below, in reality the priority is recognition of a clinical syndrome consistent with TMA, and verification of the presence of MAHA with review of a blood film. Once MAHA is confirmed, elimination of systemic causes such as infection, malignancy or autoimmune disease is of first importance; history and readily accessible clinical tests to exclude these causes are universally warranted early in diagnosis.

Although it is not typical for ADAMTS13-mediated TMA - TTP to present with renal-limited disease, early recognition is critical as mortality can reach 90% if left untreated\(^2\). Measurement of ADAMTS13 activity is now more widely available, and publicly funded drug access may require documentation of preserved ADAMTS13 activity prior to approval of eculizumab. Clinical risk scores (the French TMA Reference Center and PLASMIC scores) may be helpful tools to initially assess the likelihood of TTP, but do not eliminate the need for early consideration of lifesaving of plasma infusion or TPE\(^2\). These scores have limitations and thus do not replace the need for ADAMTS13 assessment.
Thrombotic thrombocytopenic purpura – ADAMTS13-mediated TMA

Although it is relatively unusual for TTP to present as a renal-limited TMA or with severe acute renal failure, familiarity with its diagnosis and therapy is critical as prompt initiation of TPE is associated with marked reduction in mortality\textsuperscript{23}.

Pathophysiology

TTP develops in the setting of ADAMTS13 deficiency (activity<10%). ADAMTS13 normally cleaves the highly thrombogenic von Willebrand factor (vWF). A deficiency in enzyme activity results in accumulation of ultralarge vWF multimers, followed by widespread platelet aggregation and thrombosis\textsuperscript{25}. TTP can either be congenital (cTTP), due to homozygous or compound heterozygous mutations in the \textit{ADAMTS13} gene, or immune-mediated (iTTP), due to inhibitory auto-antibodies against ADAMTS13 (majority of cases). Although cTTP normally presents during childhood, it can also present in early adulthood\textsuperscript{26}. Complement activation may be important in the development of clinical TTP manifestations. Elevated C3a and sC5b-9 levels have been observed in patients with TTP\textsuperscript{27}. Indeed, ultralarge vWF in the setting of ADAMTS13 deficiency activate the AP in \textit{ex vivo} models\textsuperscript{8}.

Diagnosis and Treatment

In the presence of TMA, it is imperative that physicians exclude ADAMTS13-mediated disease with activity assays. Limited access to timely results requires that physicians have a low threshold to initiate plasma therapy, pending test results; a clinical prediction score (see above) may be helpful in this regard.
Intermittent plasma infusion to replenish ADAMTS13 is required for exacerbations of cTTP triggered by stressors such as pregnancy or infection. A phase 1 study of recombinant ADAMTS13 suggests it is safe and effective\textsuperscript{28}. In iTTP, TPE and immunosuppression (steroids, rituximab) are required to remove the inhibitory auto-antibodies and prevent ongoing synthesis\textsuperscript{29}. Caplacizumab is a humanized monoclonal antibody that targets vWF and prevents its interaction with platelets. It is approved for the treatment of acute TTP following two multicenter, randomized controlled studies, demonstrating rapid hematological response, fewer exacerbations and shorter hospital stays\textsuperscript{30,31}. It does not however target antibody-production and consequently disease relapses occur without targeted B-cell depletion.

**Complement-mediated TMAs**

**Pathophysiology**

CM-TMA, also referred to as complement-mediated hemolytic uremic syndrome, is caused by AP dysregulation, resulting in persistent down-stream terminal pathway activation. The CP and LP have also been implicated in pathogenesis based on C4d and C1q staining on renal biopsies\textsuperscript{32}. Approximately 50-60% cases of CM-TMA are caused by Mendelian genetic variants (Table 3); however, the absence of a detectable mutation does not preclude a genetic form\textsuperscript{33-35}. More variants are emerging as genetic testing increases in quality and frequency, and as patient registries expand. The penetrance of familial CM-TMA is incomplete and may present with more advanced age, suggesting that a second hit is needed to unmask overt TMA\textsuperscript{34,35}. Triggers, when
identified, may be infection, pregnancy, vaccination or surgery\textsuperscript{34,35}. Age can help narrow the differential diagnosis, as the majority of patients who develop CM-TMA are less than 60 years\textsuperscript{36}.

Dysregulation of complement activation may also occur as a result of development of auto-antibodies that interfere with complement regulation. A prototypic example is patients documented to have auto-antibodies neutralizing factor H (FH), thereby interfering with FH-mediated downregulation of AP activity\textsuperscript{37}. The high degree of homology between gene encoding CFH and the CFH related proteins makes this area prone to gene rearrangement events. Auto-antibodies may then develop targeting the products of fusion genes or gene rearrangements (Table 3).

Referral for genetic screening is increasingly important as highly targeted complement-modulating therapies emerge. Functional assays and measures of complement cascade proteins are an important adjunct to genetic testing\textsuperscript{38}. While not yet widely available, functional assays are ideal for monitoring disease activity and treatment response.

\textit{Treatment}

Complement dysregulation is the predominant mechanism of endothelial injury in CM-TMA; treatment is directed towards restoring complement regulation. Initiation of therapy should not be delayed pending confirmation of complement dysregulation\textsuperscript{34}. Eculizumab, a humanized anti-C5 monoclonal antibody, is widely approved for CM-TMA\textsuperscript{6,39}. Duration of treatment with eculizumab remains unknown\textsuperscript{40,41}. Indeed, discontinuation of therapy is usually possible after a
6-12 months’ course of eculizumab, with the exception of patients with high risk mutations with severe disease manifestations (eg. CFH c-terminal mutation) or very high titers of anti-FH antibodies. TPE can be considered in patients with life threatening end-organ injury42. Patients with anti-FH antibodies may also benefit from TPE and immunosuppression (rituximab or cyclophosphamide) to clear circulating antibodies and prevent relapse43. Co-administration of eculizumab and immunosuppression is used to address downstream complement activation and production of anti-FH antibodies.

**Additional primary TMA syndromes**

Screening for genetic causes of TMA may reveal potentially pathogenic variants in genes encoding proteins involved in coagulation such as thrombomodulin, plasminogen as week as diacylglycerol kinase epsilon (DGKε). These are described in Tables 1-3. Mutations of DGKε have also been implicated in CM-TMA. The role of complement-inhibiting therapies in these instances is unknown. Similarly, rare hereditary disorders of B12 metabolism that may result in TMA arise due to mutations in the *MMACHC* gene (methylmalonic aciduria and homocystinuria type C). Targeted therapy focusing on restoring B12 metabolism is warranted in this instance; the involvement of complement in organ injury is not clear.

**Infection-associated TMA: Shigatoxin-mediated TMA and other infections**

**Pathophysiology**

Diverse pathogens, including bacteria, viruses and fungi, are associated with TMA (Box 1). Infections are the most common cause of pediatric TMA, the majority of which are in the setting
of Shiga toxin (Stx) producing *Escherichia coli*. Stx translocates from the intestines and binds globotriaosylceramide-3 (Gb3) in circulation, entering endothelial cells via the Gb3 receptor, which is highly expressed in the kidney\textsuperscript{44}. Within the cell, it inhibits protein synthesis resulting in endothelial injury, and an increase in tissue factor and vWF\textsuperscript{44}. Activation of the AP may be mediated by binding of STx to FH, thereby reducing its regulatory effects\textsuperscript{45}.

Systemic and renal TMA may also be observed in the context of infections as reviewed in Box 1. The SARS-CoV-2 virus is recently implicated in causing systemic TMA. Proposed mechanisms involved in systemic TMA include complement and coagulation dysregulation, and widespread cytokine storm resulting in systemic endothelial injury\textsuperscript{46}. However, in a series of patients biopsied for acute kidney injury or proteinuria with COVID-19, glomerular TMA was a rare finding compared to acute tubular necrosis or collapsing glomerulopathy\textsuperscript{47}.

*Treatment*

Management of infection-associated TMA is mainly supportive, including adequate hydration, transfusions and dialysis if needed\textsuperscript{44}. Per the American Society for Apheresis, there is insufficient evidence to support TPE in routine management of infection-associated HUS; however, it can be considered in severe cases\textsuperscript{48}. A favorable response to eculizumab in the setting of STEC-HUS has been reported, although it is not standard of care\textsuperscript{49,50}.

*Pregnancy-associated TMA*

*Pathophysiology*
Three distinct TMA etiologies are observed in pregnancy and the peri-partum period: CM-TMA, Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome and TTP. In addition, TMA syndromes not specifically associated with pregnancy (ex. catastrophic antiphospholipid syndrome) can also be triggered during gestation or the puerperium and should be ruled out in the appropriate clinical context. Another entity that may mimic TMA is pregnancy-associated renal cortical necrosis (RCN) in the setting of disseminated intravascular coagulation arising from postpartum hemorrhage and/or sepsis\textsuperscript{51}.

Tight control of complement activation is necessary throughout pregnancy to ensure materno-foetal tolerance\textsuperscript{52}. Women with a genetic predisposition to complement dysregulation may develop overt CM-TMA during pregnancy or in the postpartum period, triggered by inflammation, infection and hemorrhagic complications\textsuperscript{53,54}. The underlying pathophysiology is identical to CM-TMA discussed earlier.

Preeclampsia and HELLP syndrome result from impaired spiral artery remodeling and placental ischemia resulting in an imbalance between the proangiogenic VEGF and placental growth factor (PlGF) and antiangiogenic circulating factors, including soluble Fms-like tyrosine kinase-1 (sFlt-1)\textsuperscript{55}. Aberrant complement activation is implicated in preeclampsia development\textsuperscript{56,57}. Abnormal uterine doppler analysis, low circulating PlGF, and elevated sFlt-1/PlGF ratio may aid in confirming the diagnosis\textsuperscript{58,59}. Finally, TTP may present during pregnancy, typically during the 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester; one quarter are congenital\textsuperscript{60}. 


Treatment

Distinguishing pregnancy associated TTP, CM-TMA and HELLP syndrome is necessary as treatments differ.

Similar to non-pregnant patients, cTTP and iTTP are treated with plasma infusions and TPE, respectively. Patients with cTTP may only require plasma infusions during this high-risk period\textsuperscript{61}. In the setting of iTTP, immunosuppression typically includes steroids and azathioprine or calcineurin inhibitor\textsuperscript{61}. Delivery is often required for refractory disease, with careful balance of pregnancy risk and foetal viability. In CM-TMA, TPE is frequently initiated pending the results of ADAMTS13 activity however optimal treatment is focused on complement blockade with eculizumab, which appears to be safe in pregnancy\textsuperscript{62}. Response to complement blockade, assessed via normalization of hemolytic and renal parameters should be monitored closely to ensure adequate eculizumab dosage\textsuperscript{63}.

In the situation of preeclampsia and/or HELLP syndrome, urgent placental delivery is required. Failure of resolution of MAHA following delivery should lead clinicians to suspect an alternate diagnosis from preeclampsia or HELLP such as an underlying CM-TMA\textsuperscript{64}.

Drug-induced TMA (DI-TMA)

Pathophysiology

Numerous drugs have been associated with TMA (See Box 1 for exhaustive list). Diagnosis of DI-TMA is further suspected when resolution or recurrence of disease occurs upon cessation and
retrial of the culprit drug, respectively. The exact mechanisms by which this occurs are not well established but include immune and non-immune-mediated mechanisms\textsuperscript{1,65}. Example of immune-mediated mechanisms include the development of auto-antibodies against ADAMTS13 (e.g. ticlopidine), platelets (e.g. quinine) or neutrophils. Non-immune-mediated mechanism result from direct endothelial toxicity, which can arise due to dose-related toxicity (e.g. gemcitabine) or aberrant angiogenesis (e.g. VEGF inhibitors).

**Treatment**

Cessation of the offending agent is the first, and usually only step required for resolution of TMA. Some patients develop iTTP following ticlopidine; TPE is warranted in this setting\textsuperscript{48}. TPE has otherwise no clear role in non-immune DI-TMA\textsuperscript{48}. The role of complement-targeted therapies in refractory cases is unclear.

**Transplant-associated TMA (TA-TMA)**

**Pathophysiology**

TMA can arise as a complication of solid organ transplantation or hematopoietic stem cell transplantation (HSCT). Some believe HSCT-TMA to be an endothelial variant of graft-versus-host disease\textsuperscript{66}.

Three hits likely contribute to HSCT-TMA: 1) endothelial dysfunction or predisposition to complement dysregulation; 2) a conditioning regimen causing endothelial injury; and 3) additional insults such as infection, medications and alloreactivity\textsuperscript{67}. In the setting of widespread
endothelial injury, there is subsequent complement and coagulation pathway activation. Interestingly, 65% of HSCT recipients with TMA are found to have a pathogenic complement variant.\(^\text{68}\)

Among solid organ recipients (especially, kidney), specific TMA causes include recurrent or de novo CM-TMA in the allograft, antibody-mediated rejection, drug-induced, and infections (Box 1).\(^\text{69}\) Up to 29% of kidney transplant recipients with de novo TMA have complement mutations.\(^\text{70}\) In the presence of donor-specific antibodies, TMA in antibody-mediated rejection is hypothesized to be mediated by CP activation.\(^\text{71}\) Despite this traditional belief, recent evidence suggests that TP activation may not be responsible for cytotoxicity in a significant portion of ABMR cases.\(^\text{72}\) The mechanisms implicated in drug-induced TMA in transplant include direct contributions to endothelial injury and complement dysregulation.\(^\text{73,74}\)

**Treatment**

In kidney transplantation, therapy is directed towards the underlying cause, including infection or rejection. Switching from one calcineurin inhibitor to another, or to an alternate agent is common. Use of TPE, intravenous immunoglobulin, belatacept and eculizumab in kidney transplant-associated TMA has recently been reviewed.\(^\text{75}\) The role of eculizumab in treatment or prevention of recurrent CM-TMA in the renal allograft is well established, although not available in all jurisdictions.\(^\text{75}\)
Management of HSCT-TMA, including the roles of TPE and eculizumab for refractory disease, has recently been reviewed. A recent phase 2 study investigating narsoplimab in patients with HSCT-TMA resulted in improvements in serological TMA markers and renal parameters in 60% of participants.

**Cancer-associated TMA**

**Pathophysiology**

TMA can arise in the setting of cancer or as a consequence of its treatment, and has been reported in nearly all solid malignancies and lymphoproliferative cancers. TMA has also been observed in patients with monoclonal gammopathies, warranting investigations directed towards underlying monoclonal proteins in adults above 50 years of age. Proposed mechanisms involved in solid cancer-associated TMA include direct endothelial injury from mucin-producing adenocarcinomas, tumor embolization and, activation of the coagulation and complement systems.

**Treatment**

Distinguishing cancer, chemotherapy, infection and complement-dysregulation as possible causes of TMA is challenging. Treatment is directed towards the underlying TMA driver (solid cancer, lymphoproliferative disorder, monoclonal protein, medication or infection). There is no proven evidence supporting TPE or eculizumab for cancer-associated TMA. Although eculizumab may be considered in malignancy-triggered CM-TMA, consideration the patient’s overall
prognosis should be factored into the decision, and often funding of medication costs is not supported by payers in this clinical context.\textsuperscript{85}.

**Autoimmune diseases**

**Catastrophic antiphospholipid syndrome (CAPS)**

*Pathophysiology*

CAPS is a rare manifestation of antiphospholipid syndrome (APS), characterized by multiorgan injury from disseminated micro- and macrovascular thrombosis within 1 week\textsuperscript{86}. In the presence of a trigger (infection, pregnancy, surgery), binding of circulating antibodies on endothelial cells, platelets and leucocytes results in their activation, with subsequent endothelial injury, uncontrolled coagulation and complement activation\textsuperscript{87,88}. Patients with CAPS are more likely to have genetic complement abnormalities compared to those with SLE and APS without catastrophic features, further supporting complement dysregulation in disease development\textsuperscript{89}.

*Treatment*

The cornerstones of therapy are anticoagulation, immunosuppression and, either IVlg or plasmapheresis\textsuperscript{90,91}. In refractory disease, use of rituximab or eculizumab are described\textsuperscript{92,93}.

**Scleroderma renal crisis**

*Pathophysiology*

Endothelial injury and subsequent arterial intimal thickening and proliferation of the arcuate and interlobar arteries characterize SRC\textsuperscript{94}. Immune complexes comprised of scleroderma-specific
auto-antibodies may be involved in mediating endothelial activation\textsuperscript{95}. Vessel narrowing and vasospasm results in reduced renal blood flow and activation of the renin-angiotensin-aldosterone system\textsuperscript{96}. Despite activation of the renin-angiotensin system, up to 10\% of patients will be normotensive at presentation\textsuperscript{97}. Presence of endothelin-1 (ET-1) and C3b on renal biopsies, along with elevated serum C4d and sC5b-9, is potentially suggestive of a role for endothelin and complement activation in mediating renovascular injury\textsuperscript{98,99}.

Treatment

Treatment is focused on angiotensin converting enzyme inhibitors\textsuperscript{100}. The role of ET-1 receptor antagonists is not well established in SRC\textsuperscript{101}. Patients who develop SRC are at high risk of requiring renal replacement therapy. Peritoneal dialysis may be the preferred modality given better preservation of residual renal function, as renal recovery can be delayed in SRC up to a year.

Systemic lupus erythematosus and other autoimmune diseases

Pathophysiology

TMA is an infrequent complication of SLE; however, its incidence is up to 24\% in patients with lupus nephritis, as it may be identified on renal biopsy\textsuperscript{102}. Acquired CM-TMA, iTTP, APS and hypertensive emergency are identified in a third of cases with lupus-associated TMA\textsuperscript{103}. Immune complex deposition and complement activation are the likely culprits in the development of otherwise unexplained TMA in the setting of SLE\textsuperscript{104,105}. 
TMA can also be observed in patients with dermatomyositis/polymyositis and rheumatoid arthritis, and can be observed in biopsies of patients with severe glomerulonephritis including vasculitis.

_Treatment_

Immunosuppression is the mainstay of treatment of TMA in autoimmune diseases. Plasma exchange is frequently initiated pending results of ADAMTS13 activity in patients with MAHA. The American Society for Apheresis supports its use in severe cases of SLE. Eculizumab has been associated with favorable outcomes in patients with refractory TMA and SLE.

_Hypertensive emergency_

_Pathophysiology_

Hypertensive emergency is a recognized cause of renal TMA; it is believed to arise from mechanical shear stress to the renal microcirculation. Cases of hypertension-associated TMA may in fact represent undiagnosed CM-TMA. In a recent study of 26 participants with hypertensive emergency and TMA, 69% had massive _ex vivo_ endothelial C5b-9 formation. Among these, 50% had pathogenic variants in complement genes. Endothelial C5b-9 formation was a risk factor for kidney failure. This supports the importance of complement testing in TMA attributed to “hypertensive emergency” to unmask complement dysregulation. If accessible, evaluation of sC5b-9 may help identify patients who should undergo genetic testing. Ongoing systemic hemolysis despite adequate blood pressure control warrants further testing.
**Treatment**

Aggressive blood pressure control is the cornerstone of treatment. As complement inhibitors become more widely available, these may be trialed in the future in patients with elevated complement cleavage products (without a complement mutation)\textsuperscript{108}.

**Conclusion**

In summary, TMA is pathologic lesion identified in a spectrum of life-threatening diseases. While much remains to be learned about the disease-specific mechanisms causing TMA, endothelial injury is a central feature of patients with TMA involving the kidney. Complement dysregulation is a causative or maladaptive feature of many syndromes associated with TMA and a potential role for cross-talk between coagulation and complement pathways is an area of active investigation. The availability of highly targeted therapies mandates rapid and accurate diagnosis; timely genetic and functional testing are increasingly essential to make therapeutic decisions and broader access to these tests would assist in personalizing care. Future attention and discussion should focus on overcoming financial and diagnostic barriers to equitable access to highly-targeted therapies.

**Supplementary Material**

**Table S1.** Epidemiology, pathophysiology, treatment including investigational therapies according to TMA etiology.

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Figure Legend

Figure 1. Schema illustrating a practical approach to the classification of thrombotic microangiopathy.

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; anti-FH, Factor H auto-antibody; CFH, complement factor H; CM-TMA, complement-mediated thrombotic microangiopathy; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Figure 2. Kidney histopathologic findings in acute thrombotic microangiopathy with mild chronic changes.

Light and electron microscopic findings of acute thrombotic microangiopathy with early features of chronicity in a patient with systemic sclerosis and normotensive scleroderma renal crisis. A. Segmental thrombus (*) and capillary wall thickening with double contouring (arrow head) (hematoxylin phloxine saffron (HPS), 40X); B. Arteriolar intimal fibrin (*) and edema with adjacent mildly shrunken glomerulus and congestion (HPS, 40X); C. Glomerular capillary subendothelial expansion with mild lucency and loose new basement membrane formation (arrow) (4000X).

Figure 3. Complete diagnostic algorithm for thrombotic microangiopathy.

This is an example of an ‘ideal’ thorough diagnostic algorithm. Many of the tests are not widely clinically available and some results may only be returned days to months after presentation. Further, the list of tests continues to evolve with new discoveries about pathophysiology.
Abbreviations: ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif member 13; ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; anti-GBM, anti-glomerular basement membrane antibody; APLA, anti-phospholipid antibody; CFB/H/I, complement factor B/H/I; CFHR1-5, complement factor H receptor 1-5; CM-TMA, complement-mediated thrombotic microangiopathy; CMV, cytomegalovirus; DGKε, diacylglycerol kinase epsilon; dsDNA, anti-double-stranded DNA antibody; ENA, extractable nuclear antigen antibodies; FB, factor B; FH, factor H; FI, factor I; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; MCP, membrane cofactor protein; MMA, methylmalonic acid; PCR, polymerase chain reaction; PLG, plasminogen; RF, rheumatoid factor; THBD, thrombomodulin; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; *; coagulation-mediated TMA; #, research-based assays.
Box 1. Conditions associated with thrombotic microangiopathy

| ADAMTS13-mediated TMA - Thrombotic thrombocytopenic purpura – congenital or immune  |
| Complement-mediated thrombotic microangiopathy – congenital or immune  |
| Coagulation-mediated TMA - pathogenic variants in thrombomodulin, plasminogen and diacylglycerol kinase epsilon  |
| Metabolic - Defects of cobalamin metabolism  |
| Infection  |
| - Bacterial: Shiga-toxin producing *Escherichia coli*, *Streptococcus pneumoniae*, *Campylobacter jejuni*, *Klebsiella pneumoniae*  |
| - Viral: Influenza, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, BK virus, parvovirus B19, SARS-CoV-2  |
| - Fungal: Histoplasmosis  |
| Pregnancy  |
| - Preeclampsia, HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome  |
| - Trigger of thrombotic thrombocytopenic pupura, atypical hemolytic uremic syndrome, catastrophic antiphospholipid syndrome  |
| Drug-induced  |
| - Immune-mediated via drug-triggered antibodies against platelets/neutrophils: gemcitabine, oxaliplatin, trimethoprim-sulfamethoxazole, quinine, vancomycin  |
| - Immune mediated via auto-antibodies against ADAMTS13: Ticlopidine  |
| - Non-immune mediated: Chemotherapy: Alemtuzumab, gemcitabine, mitomycin C, vincristine, doxorubicin, pentostatin, vascular endothelial growth factor inhibitors, tyrosine kinase inhibitors, proteasome and checkpoint inhibitors  |
| - Immunosuppressive therapy: Calcineurin inhibitor, sirolimus, interferon beta  |
| - Antibiotics: Ciprofloxacin, levofloxacin, metronidazole, nitrofurantoin, penicillin  |
| Other: Cocaine, ecstasy, estrogen/progesterone, anti-inflammatory, oxymorphone, simvastatin  |
| Transplant  |
| - Solid organ, hematopoietic stem cell transplant  |
| Malignancy  |
| - Solid: Breast, gastric, lung, ovarian, prostate and urothelial cancers  |
| - Hematologic: Myelo and lymphoproliferative, monoclonal gammopathies (myeloma, smouldering myeloma, monoclonal gammopathy of renal significance and POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes)  |
| Autoimmune diseases  |
| - Antiphospholipid syndrome  |
| - Scleroderma (renal crisis)  |
| - Systemic lupus erythematosus  |
| - Primary glomerulonephritis and vasculitis (observed on biopsy)  |
| - Sjögren’s syndrome, rheumatoid arthritis, dermatomyositis  |
| Hypertensive emergency  |
| Other  |
- Hemophagocytic lymphohistiocytosis, Sickle cell disease, Castleman disease and variants
Table 1. Pathophysiology and treatment according to TMA etiology.

<table>
<thead>
<tr>
<th>Disease causing TMA</th>
<th>Pathophysiology</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTTP</td>
<td>Congenital ADAMTS13 deficiency</td>
<td>Plasma infusion</td>
</tr>
<tr>
<td></td>
<td>Complement activation potentially involved</td>
<td></td>
</tr>
<tr>
<td>iTTP</td>
<td>Acquired ADAMTS13 deficiency through circulating ADAMTS13 auto-antibodies</td>
<td>TPE</td>
</tr>
<tr>
<td></td>
<td>Complement activation potentially involved</td>
<td>Caplacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroids/RTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bortezomib if refractory</td>
</tr>
<tr>
<td>Hereditary CM-TMA</td>
<td>Pathogenic variant(s) in complement gene(s) (Table 3)</td>
<td>Eculizumab or ravulizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPE vs. plasma infusions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver transplant (CFH, CFI, CFB)</td>
</tr>
<tr>
<td>Acquired CM-TMA</td>
<td>Complement dysregulation through circulating auto-antibodies</td>
<td>Eculizumab or ravulizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RTX or cyclophosphamide</td>
</tr>
<tr>
<td>Coagulation-mediated TMA (PLG, THBD and DGKε)</td>
<td>Endothelial cell dysregulation</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Role of complement therapies unclear</td>
</tr>
<tr>
<td>Metabolic - Cobalamin deficiency</td>
<td>Endothelial dysfunction mediated by hyperhomocysteinemia suspected(^{109})</td>
<td>Cobalamin</td>
</tr>
</tbody>
</table>

Infection-Associated

1. STEC-HUS | Coagulation and complement activation via Shiga toxin | Supportive |

2. S. pneumonia; viral | Complement dysregulation implicated | Supportive, including antibiotics |

3. SARS-CoV-2 | Complement dysregulation Cytokine storm iTTP | Supportive treatment Steroids Remdesivir Tocilizumab, Baricitinib |

Pregnancy-Associated (note other entities ex. CAPS may be triggered during pregnancy)

1. TTP | Triggered by pregnancy See cTTP and iTTP above | Plasma infusion TPE IS |

2. CM-TMA | Triggered by pregnancy See CM-TMA above and Table 3 | Eculizumab TPE if circulating auto-antibodies |
<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. PET/HELLP syndrome</td>
<td>Anti-angiogenic imbalance, Complement dysregulation</td>
<td>Supportive care, including delivery</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Immune-mediated and non-immune mediated mechanisms</td>
<td>Cessation of causal drug TPE in iTTP</td>
</tr>
<tr>
<td>Transplant-Associated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Hematopoietic stem cell transplant</td>
<td>Multiples hits required (genetic predisposition, conditioning regimen and trigger(s))</td>
<td>Supportive treatment Modification of IS/chemotherapy</td>
</tr>
<tr>
<td>2. Kidney transplant</td>
<td>Multiple causes/multifactorial (recurrent or de novo disease, drug-induced, antibody mediated rejection, infection)</td>
<td>Directed towards underlying cause: Antibiotics/anti-viral Modification of immunosuppression Eculizumab/TPE</td>
</tr>
<tr>
<td>Cancer-associated</td>
<td>Endothelial dysfunction, Intravascular tumor emboli, Coagulation and complement pathway activation</td>
<td>Cancer-directed therapy</td>
</tr>
<tr>
<td>Auto-immune associated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. CAPS</td>
<td>Unclear but may involve genetic predisposition and circulating antibodies</td>
<td>Anticoagulation IS and IVIg or TPE If refractory, consider RTX or eculizumab</td>
</tr>
<tr>
<td>2. SRC</td>
<td>Unclear but involves renal ischemia, activation of the RAAS and hypertension-mediated mechanical stress</td>
<td>ACE inhibitors Unclear role for endothelin receptor antagonist, TPE and eculizumab</td>
</tr>
<tr>
<td>3. SLE</td>
<td>Unclear but complement activation implicated</td>
<td>IS TPE for severe cases If refractory, consider eculizumab</td>
</tr>
<tr>
<td>Hypertensive emergency</td>
<td>Mechanical shear stress</td>
<td>Blood pressure control</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin converting enzyme; ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif member 13; CAPS, catastrophic antiphospholipid syndrome; CM-TMA, complement-mediated thrombotic microangiopathy; cTTP, congenital TTP; DGKe, diacylglycerol kinase epsilon; HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets; IS, immunosuppression; iTTP, immune-mediated TTP; IVIg, intravenous immunoglobulin; PET, preeclampsia toxemia; PLG, plasminogen; RAAS, renin-
angiotensin-aldosterone system; RTX, rituximab; SLE, systemic lupus erythematosus; SRC, scleroderma renal crisis; STEC-HUS, Shiga toxin-producing Escherichia coli hemolytic uremic syndrome; THBD, thrombomodulin; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.
Table 2. Complement-directed investigational therapies according to TMA etiology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Investigational therapy (target)</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTTP</td>
<td>Recombinant ADAMTS13</td>
<td>NCT03393975 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td>Narsoplimab (MASP-2)</td>
<td>NCT04683003 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT02222545 (Phase 2)</td>
</tr>
<tr>
<td>iTTP</td>
<td>Recombinant ADAMTS13</td>
<td>NCT03922308 (Phase 2)</td>
</tr>
<tr>
<td></td>
<td>Narsoplimab (MASP-2)</td>
<td>NCT02222545 (Phase 2)</td>
</tr>
<tr>
<td>Hereditary and acquired CM-TMA</td>
<td>Narsoplimab (MASP-2)</td>
<td>NCT03205995 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td>Iptacopan (Factor B)</td>
<td>NCT02222545 (Phase 2)</td>
</tr>
<tr>
<td></td>
<td>Crovalimab (C5)</td>
<td>NCT04889430 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT04958265 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT04861259 (Phase 3)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>No registered clinical trial</td>
<td></td>
</tr>
<tr>
<td>Metabolic- including cobalamin deficiency</td>
<td>No registered clinical trial</td>
<td></td>
</tr>
<tr>
<td>Infection-associated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. STEC-HUS</td>
<td>Eculizumab (C5)</td>
<td>NCT02205541 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EUCTR2016-000997-39</td>
</tr>
<tr>
<td>2. SARS-CoV-2</td>
<td>Ruconest (C1)</td>
<td>NCT04705831 (Phase 4)</td>
</tr>
<tr>
<td></td>
<td>Narsoplimab (MASP-2)</td>
<td>NCT04530136 (Phase 2)</td>
</tr>
<tr>
<td></td>
<td>Danicopan (Factor D)</td>
<td>NCT04488081 (Phase 2)</td>
</tr>
<tr>
<td></td>
<td>AMY-101 (C3)</td>
<td>NCT04395456 (Phase 2)</td>
</tr>
<tr>
<td></td>
<td>Eculizumab (C5)</td>
<td>NCT04288713</td>
</tr>
<tr>
<td></td>
<td>Ravulizumab (C5)</td>
<td>NCT04346797 (Phase 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT04570397 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT04369469 (Phase 3)</td>
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<td></td>
<td>NCT04369469 (Phase 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT04333420 (Phase 2/3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT04382755 (Phase 2)</td>
</tr>
<tr>
<td>3. Other</td>
<td>Eculizumab (C5)</td>
<td>NCT04743804 (Phase 3)</td>
</tr>
<tr>
<td>Pregnancy-associated PET/HELLP syndrome</td>
<td>Eculizumab (C5)</td>
<td>NCT04103489 (Phase 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT04725812 (Phase 2)</td>
</tr>
<tr>
<td>Drug-induced TMA</td>
<td>Ravulizumab (C5)</td>
<td>NCT04743804 (Phase 3)</td>
</tr>
<tr>
<td>Transplant-associated 1. HSCT</td>
<td>Narsoplimab (MASP-2)</td>
<td>NCT04247906 NCT02222545 (Phase 2) NCT05148299 (Phase 2) NCT03518203 (Phase 2) NCT04543591 (Phase 3) NCT04557735 (Phase 3) NCT04784455 (Phase 3)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Solid Organ</td>
<td>Pegcetacoplan (C3)</td>
<td>NCT04743804 (Phase 3)</td>
</tr>
<tr>
<td>Autoimmune-associated TMA, excluding primary CAPS</td>
<td>Eculizumab (C5)</td>
<td>Ravulizumab (C5)</td>
</tr>
<tr>
<td>Cancer-associated TMA</td>
<td>No registered clinical trial</td>
<td></td>
</tr>
<tr>
<td>Hypertension emergency</td>
<td>Ravulizumab (C5)</td>
<td>NCT04743804 (Phase 3)</td>
</tr>
</tbody>
</table>

Abbreviations: ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif member 13; CAPS, catastrophic antiphospholipid syndrome; CM-TMA, complement-mediated thrombotic microangiopathy; cTTP, congenital TTP; HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets; HSCT, hematopoietic stem cell transplantation; iTTP, immune-mediated TTP; MASP-2, Mannan-binding lectin serine protease 2; PET, preeclampsia toxemia; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.
Table 3. Frequent genetic mutations implicated in thrombotic microangiopathy.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Incidence (^{33,110})</th>
<th>Transplant recurrence (^{35})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Inactivating</td>
<td>20-30%</td>
<td>High risk of recurrence; prophylactic eculizumab recommended</td>
</tr>
<tr>
<td>CFI</td>
<td>Inactivating</td>
<td>4-8%</td>
<td>Moderate risk of recurrence after transplant; prophylactic eculizumab recommended</td>
</tr>
<tr>
<td>MCP/CD46</td>
<td>Inactivating</td>
<td>10-15%</td>
<td>Moderate to high risk recurrence post-transplant</td>
</tr>
<tr>
<td>C3</td>
<td>Activating; increased activity or resistance to FI regulation</td>
<td>2-10%</td>
<td>Moderate risk of recurrence after transplant; prophylactic eculizumab recommended</td>
</tr>
<tr>
<td>CFB</td>
<td>Activating; increased activity or resistance to FH regulation</td>
<td>1-2%</td>
<td>High risk of recurrence after transplant; prophylactic eculizumab recommended</td>
</tr>
<tr>
<td>CFH-CFHR rearrangements resulting in CNVs, including deletions (CFHR1, possibly associated with auto-FH)</td>
<td>Auto-antibody; inhibition of FH C-terminal function (i.e. surface and C3b binding)</td>
<td>Varies by cohort; Austrian cohort 25%; Indian cohort up to 50%</td>
<td>High risk of recurrence in the first 2 years if ongoing high auto-FH titres</td>
</tr>
<tr>
<td>THBD</td>
<td>Inactivating</td>
<td>Rare</td>
<td>True risk of recurrence after transplant unknown</td>
</tr>
<tr>
<td>DGK(\varepsilon)</td>
<td>Inactivating</td>
<td>Rare</td>
<td>Risk of recurrence after transplant unknown</td>
</tr>
</tbody>
</table>

Abbreviations: *CFB/H/I*, complement factor B/H/I; CNV, copy number variation; FH/I, factor H/I; *DGK\(\varepsilon\)*, diacylglycerol kinase epsilon; *MCP*, membrane cofactor protein; *THBD*, thrombomodulin.
Pathologic evidence of TMA

TTP

- Congenital: *ADAMTS13* mutation
- Immune: *ADAMTS13* autoantibody

CM-TMA

- Variants in complement-associated genes (eg, *CFH*)
- Antibody-mediated complement dysregulation (eg, anti-CFH autoantibodies)

- Variants in non-complement genes
- Role of complement under investigation

- Infection-associated TMA – Shiga toxin and Other (see Box 1)

- Secondary to systemic disease or exposure (see Box 1)
| TMA | • MAHA: anemia, thrombocytopenia, reticulocytosis, elevated LDH and bilirubin, low haptoglobin, and/or schistocytes  
• Exclude alternate diagnosis: autoimmune hemolytic anemia (direct antiglobulin test), disseminated intravascular coagulopathy (coagulation parameters, d-dimer, fibrinogen)  
• Assess renal and extrarenal end-organ involvement |
| Exclude TTP | • Evaluate ADAMTS13 activity  
• If ADAMTS13 activity < 10% → Evaluate the presence of autoantibodies against ADAMTS13 |
| Exclude infection | • Stool toxin, cultures, imaging  
• Viral testing, including HIV  
• According to clinical presentation: viral PCR (Influenza A/B, COVID-19, BK virus, CMV) |
| Exclude secondary | • Autoimmune screen: ANA, dsDNA, ENA, APLA, RF, ANCA, anti-GBM  
• Metabolic: Vitamin B₁₂, MMA and homocysteine  
• Pregnancy test, transplant rejection markers |
| CM-TMA | • Functional assays: CH50, AH50, hemolytic assay#, CFH assay#  
• Genetic testing: CFI, CFI, CFB, MCP, CFHR1-5, C3, THBD*, DGKe*, PLG*  
• Complement proteins: CFB, CFH, CFI, C5, MCP#, properdin#, C3c, C3d, Bb, sC5b-9  
• Autoantibodies: anti-CFH |