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Thrombotic Thrombocytopenic Purpura: Pathogenesis, Diagnosis, and Potential Novel Therapeutics

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Summary

Thrombotic thrombocytopenic purpura (TTP), a potentially fatal clinical syndrome, is primarily caused by autoantibodies against the von Willebrand factor (VWF)-cleaving metalloprotease ADAMTS13. In general, severe deficiency of plasma ADAMTS13 activity (<10 IU/dL) with or without detectable inhibitory autoantibodies against ADAMTS13 supports the diagnosis of TTP if a patient presents with thrombocytopenia and microangiopathic hemolytic anemia (i.e. schistocytes, elevated serum lactate dehydrogenase, decreased hemoglobin and haptoglobin) without other known etiologies that cause thrombotic microangiopathy (TMA). Normal to moderately reduced plasma ADAMTS13 activity (>20 IU/dL) in a similar clinical context supports an alternative diagnosis such as atypical hemolytic uremic syndrome (aHUS) or other types of TMA. Prompt differentiation of TTP from other causes of TMA is crucial for the initiation of an appropriate therapy to reduce morbidity and mortality. While plasma infusion is often sufficient for prophylaxis or treatment of hereditary TTP due to *ADAMTS13* mutations, daily therapeutic plasma exchange remains the initial treatment of choice for acquired TTP with autoantibodies. Immunomodulatory therapies, including corticosteroids, rituximab, vincristine, cyclosporine, cyclophosphamide, and splenectomy, etc. should be considered to eliminate autoantibodies for sustained remission. Other emerging therapeutic modalities, including recombinant ADAMTS13, adeno-associated virus (AAV) 8-mediated gene therapy, platelet-delivered ADAMTS13, and antagonists targeting the interaction between platelet glycoprotein 1b and VWF are under investigation. This review highlights the recent progress in our understanding of the pathogenesis, diagnosis, and current and potential novel therapies for hereditary and acquired TTP.

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Addendum

M. Saha, J. K. McDaniel, and X. L. Zheng designed the manuscript, performed the literature search, critically analyzed the literatures, and wrote the manuscript.

Disclosure of Conflict of Interests

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Keywords

Thrombotic Microangiopathies; von Willebrand Factor; Therapeutics; Diagnosis; Pathology

Introduction

Thrombotic microangiopathies (TMA) are a group of heterogeneous disorders characterized by disseminated thrombus formation in arterioles and capillaries resulting in thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and potential end organ injury [1]. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two prototypes of TMA [2], although TMAs can also occur secondary to multiple other systemic disorders including malignant hypertension, infections, medications, malignancy, and HELLP (hemolysis, elevated liver enzyme, low platelets) syndrome, etc.

The estimated incidence of TTP ranges from 3 to 11 cases per million residents per year [3]. Prompt diagnosis and urgent initiation of plasma therapy are critical to reduce the mortality and morbidity rates. The estimated annual incidence of HUS ranges from 2 to 6 per 100,000 residents. The underlying pathophysiology of HUS was outlined in a recent review article, which includes infection with shigatoxin-producing *E. coli* (STEC) [4] and less commonly (0.5 to 2 per million population) non-infection associated etiologies such as complement dysregulation or activation of platelets. While plasma infusion or exchange is highly efficacious in treating TTP, it does not work for aHUS. Nearly 80% patients progressed to end-stage renal disease within 3 years of diagnosis despite plasma exchange therapy [5, 6]. Instead, anti-complement C5 (i.e. eculizumab) therapy is much more efficacious and should be the first-line therapy for patients with aHUS [7].

Differentiating TTP from other TMAs can be challenging given their significant overlap in clinical presentation but this distinction is critical for selecting an appropriate therapy for these patients. Herein, we review the current understanding of the pathogenesis, the diagnosis and differential diagnosis, and the current and potential novel therapeutics for TTP and other TMAs.

A brief history

TTP was first described by Dr. Eli Moschcowitz in 1924 [8] when a 16-yr-old girl came to hospital with fever, anemia, and weakness who subsequently developed paralysis and coma in the two weeks leading up to her death; autopsy revealed disseminated hyaline thrombi in the terminal arterioles and capillaries of heart, kidney and liver but the moderate size vessels were unaffected.

In 1966, Amorosi and Ultman [9] proposed the “pentad” for the diagnosis of TTP after reviewing over 270 cases. The “pentad” features include fever, hemolytic anemia, purpura or bleeding associated with thrombocytopenia, neurological signs, and renal disease presented with hematuria and/or proteinuria or elevated blood urea nitrogen. Over time, with increasing disease awareness, education, and advances in our understanding of the pathogenesis and diagnosis of TTP, the percentage of patients with a typical “pentad”

presentation has decreased [10, 11]. Currently, the presence of thrombocytopenia and microangiopathic anemia (increased lactate dehydrogenase (LDH), reduced hemoglobin and haptoglobin, and fragmentation of red blood cells, etc.) is sufficient for presumptive diagnosis of TTP.

Pathogenesis of TTP had been a mystery for nearly half a century until a seminal report by Moake *et al* [12]. They described the presence of "unusually large" (UL) multimers of von Willebrand factor (VWF) in plasma of patients with chronic relapsing TTP. The ULVWF could be detected in plasma during remission but disappeared in the acute episodes. They hypothesized that the lack of a VWF-depolymerase might be the cause of TTP in these patients. The deficiency of this mysterious VWF-depolymerase was first reported in patients with hereditary TTP by Furlan *et al* [13] and later in patients with acquired chronic relapsing TTP by Tsai [14]. Several groups in 2001 successfully purified this protease (Fig. 1), which was named ADAMTS13 (*A D*isintegrin *A*nd *M*etalloproteinase with *T*hrombo*S*pondin type I motif (ADAMTS), 13) [15–17]. Mutations in *ADAMTS13* were identified to be the causes of hereditary TTP [18].

Over the past decade and half, significant progress has been made in our understanding of the structure-function relationship and regulation of ADAMTS13 function [19, 20], the development of novel diagnostic tests [21, 22] and various therapeutic modalities [23–27], and the implication of ADAMTS13 deficiency in pathogenesis of hereditary and acquired autoimmune TTP. Additionally, further insight has been gained into the role of ADAMTS13 in other thrombotic and inflammatory disorders, including myocardial infarction, ischemic strokes, preeclampsia, and malignant malaria, etc. [28] (Fig. 1).

Terminology

A consensus on the standardization of terminology in TTP and related TMAs has recently been published on behalf of the International Working Group for TTP [29].

TMA is a pathological term, describing occlusive microvascular or macrovascular disease, often with intraluminal thrombus formation and endothelial swelling or damage. It is defined clinically by thrombocytopenia and microangiopathic hemolytic anemia (MAHA), although this does not specifically define a condition; therefore, further investigations are required to identify the underlying cause for TMAs, including TTP.

MAHA was initially described to result from intravascular coagulation that leads to mechanical destruction of red blood cells (i.e. anemia and fragmentation of red blood cells) as they traverse through platelet and/or fibrin rich thrombi. This process occurs in TTP but can also be seen in many other pathological conditions including HUS, disseminated malignancy, malignant hypertension, severe preeclampsia, cavernous hemangioma, disseminated intravascular coagulation (DIC), etc. Additionally, mechanical destruction of red blood cells can occur in patients with prosthetic heart valves, ventricular assisted devices, and extracorporeal membrane oxygenation in the absence of thrombosis and fibrin.

TTP is defined by the presence of MAHA and moderate to severe thrombocytopenia, with or without signs and symptoms of associated end organ dysfunction including neurologic,

cardiac, gastrointestinal, and renal involvement. Oliguric or anuric renal failure requiring renal replacement therapy is not a typical feature of TTP [30, 31]. Severe ADAMTS13 deficiency resulting from inherited mutations of *ADAMTS13* is the cause of hereditary TTP, whereas inhibitory antibodies against ADAMTS13 result in the more common acquired (autoimmune) TTP [14, 32] (Fig. 2).

In contrast, HUS is defined by the presence of MAHA and thrombocytopenia with predominant renal injury with plasma ADAMTS13 >10 IU/dL. Thrombocytopenia may not be as severe as in TTP and anemia at presentation can be variable [29] (Fig. 2). Infection-associated HUS is typically caused by toxins produced by certain bacteria (i.e. *E Coli* O157:H7 or other serotypes) [33, 34], primarily occurring in children less than 5 years old, while aHUS is caused by overwhelming activation of the complement system, resulting from a gain-of-function mutation of complement C3 or factor B or a loss-of-function mutation of complement factor H, factor I, membrane cofactor protein, thrombomodulin [35], or by platelet activation due to the mutations in diacylglycerol kinase epsilon (DGKE) [36]. However, only about 50% aHUS cases have identifiable genetic abnormalities and 1–2% of aHUS patients may have autoantibodies against CFH. The underlying etiologies for other 50% aHUS cases are yet to be identified [4].

Diagnosis

Clinical features

TTP presentations vary significantly and thus clinicians must maintain a high index of suspicion for diagnosis; in the early stages, symptoms may be non-specific including weakness, confusion, headache, nausea, vomiting and diarrhea. With progression of the disease, specific signs and symptoms of organ injury may evolve. Neurological symptoms such as ischemic stroke, coma, and seizures may be developed in approximately 10% of cases. Chest pain and elevated serum troponin I may be present in acute TTP, but ST-elevation or non-ST elevation myocardial infarction is rare [37]. Recent study shows that acute renal failure may occur in more than 50% of TTP cases [38].

Laboratory tests

The blood specimen for evidence of thrombocytopenia, microangiopathic hemolysis, ADAMTS13 activity, and end organ injury must be drawn prior to initiation of plasma therapy. TTP patients present with severe thrombocytopenia (platelet count usually $<30\times10^9$/L), decreased hemoglobin and hematocrit, significantly elevated lactate dehydrogenase (LDH), low haptoglobin, increased indirect bilirubin, and presence of schistocytes on peripheral blood smear [10, 39]. Schistocytes are formed when red blood cells travel through the VWF-platelet or fibrin network, resulting in mechanical destruction. The International Council for Standardization in Haematology (ICSH) recommends that schistocytes should be reported as the percentage after counting at least 1,000 red blood cells on a peripheral smear. A value of >1% schistocytes is suggestive of TMA in the absence of an alternative diagnosis [40]. A higher percentage (>4%) of schistocytes may be required to diagnose TMA associated with hematopoietic progenitor cell transplant (HPCT), as the fragmentation of red blood cells is a common finding in patients after whole body irradiation

and chemotherapy [41]. Schistocytes may be absent in the early disease course but can persist despite clinical remission (i.e. normalization of platelet counts and LDH) after plasma exchange therapy [42].

Plasma ADAMTS13 activity is a key laboratory parameter for differential diagnosis. Plasma ADAMTS13 activity (<10 IU/dL) is highly specific for TTP [14, 32]. However, normal or mildly reduced plasma ADAMTS13 activity may be seen in a variety of hematological or non-hematological disorders, as well as other types of TMA [32, 43]. A recent study demonstrates that if a cut-off of ADAMTS13 activity <20 IU/dL is used to diagnose TTP, ADAMTS13 test has a sensitivity and specificity of 100% and 99%, respectively, with a positive predictive value of 91% and negative predictive value of 100% after excluding interfering conditions like infection, HPCT, and DIC [44].

ADAMTS13 assay for diagnostic purpose is mostly a FRETS-based [21], followed by ELISA [45, 46], mass spectrometry [47], and coagulation analyzer-based [48] assays. Each has its advantages and disadvantages, but will produce ADAMTS13 activity results within an hour to several hours. If ADAMTS13 activity is less than 30%, the laboratory will perform the mixing study to identify the anti-ADAMTS13 inhibitor levels. Interpretation of the test results should be performed in conjunction with evaluation of the clinical information, as pre-analytical variables such as overt hemolysis and increased bilirubin may result in a falsely low ADAMTS13 activity in many FRETS-based assays [49, 50], Such interference has less effect on the ELISA-, mass spectrometry-, or coagulation analyzer-based assay or some other newer FRETS-based assays using different labels [50].

Scoring systems

In the acute setting if ADAMTS13 results are not readily available, there are scoring systems that can be used to predict whether a patient has severe ADAMTS13 deficiency. Coppo et al [51] proposed three criteria at presentation, including creatinine <2.2 mg/dl, platelet count$<30\times10^9$/L, and positive antinuclear antibody; this scoring system has a positive predictive value of ~99% with specificity of ~98%, but a low sensitivity of 46%. These two criteria: creatinine and platelet count, are sufficient to predict severe ADAMTS13 deficiency (<10 IU/dL) with adjusted Odds ratios of >20 and 9, respectively [51]. Another recently developed scoring system, the PLASMIC score, uses seven criteria: platelet count $<30\times10^9$/L, hemolysis variable, no active cancer, no history of transplant, MCV $<9\times10^{-14}$ L, INR<1.5, and creatinine <2 mg/dL[52]. The PLASMIC score has similar predictive values as the Coppo's scoring system but is better at predicting severe ADAMTS13 deficiency in low-risk patients [52].

Differential diagnosis

TTP must be distinguished from aHUS (Fig. 2) and other TMAs (Table 1), including certain medications, occult malignancy, malignant hypertension, HELLP syndrome, and DIC. An initial platelet count $\geq30\times10^9$/L and serum creatinine ≥2.3 mg/dL almost eliminate TTP and severe deficiency of plasma ADAMTS13 activity [51], therefore, other causes of TMAs should be actively sought because the treatment and long-term outcome are quite different.

a. Therapeutic drug-associated TMA

Ticlopidine and clopidogrel are anti-platelet agents with similar chemical structures, the derivatives of thienopyridine. Ticlopidine-associated TMA occurs in the first few weeks after initiation of treatment. These patients usually exhibit severe deficiency of ADAMTS13 activity resulting from autoantibodies against ADAMTS13, and respond to plasma exchange therapy [53]. Clopidogrel-associated TTP occurs during the first week and does not seem to be associated with severe ADAMTS13 deficiency or detectable inhibitors [54]; therefore, plasma exchange is usually not effective. Treatment in these cases relies on the discontinuation of the drug. Similarly, quinine can cause immune-mediated TMA with acute kidney injury and may also cause liver toxicity or DIC [55, 56]. All patients improved with plasma exchange and prednisone. Calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus, used as immunosuppressive drugs after solid organ transplantation, are also known to cause TMA more resembling aHUS. The estimated incidence ranges from 1.1% to 3.6% of kidney transplant recipients [57]. The TMA occurs at a median of 7 days post-transplant and presents with worsening renal function after acute rejection is excluded [58]; histological analysis may reveal capillary thrombosis, subendothelial cell swelling, and inflammatory infiltrate. CNI may cause TMA by various different mechanisms: decrease in thrombomodulin activity, endothelial injury, enhanced VWF release by cremophor (CNI-vehicle) by increasing cytosolic calcium, and changes in thromboxane A2-prostacyclin ratio. Karthikeyan reported a graft salvage rate of 80% when CNIs were stopped and plasma exchange was performed [59]. Treatment with reducing or stopping CNIs alone could result in significant graft loss (40–57%) [59–61].

b. Chemotherapy-induced TMA

Some of these occur due to cumulative toxicity as with mitomycin and gemcitabine and tend to cause renal injury and uncontrolled blood pressure [62]. The mechanism is unclear but endothelial injury or endotheliopathy is likely the underlying mechanism [63]. TMA secondary to anti-VEGF therapy tends to present as hypertension, proteinuria, and rarely renal failure. This may due to blockade of the interaction of VEGF secreted by podocytes and its interaction with VEGFR2 receptor on glomerular endothelial cells that is important for endothelial function. ADAMTS13 is usually normal or mildly low (>20 IU/dL or 20%) in such cases [64]. Withdrawal of the mitomycin and gemcitabine should be the first measure in a suspected case of TMA. There have been reports of use of rituximab and eculizumab in refractory cases of chemotherapy-induced TMA while the role of plasma exchange is unclear[65].

c. Transplant-associated TMA

Patients with solid-organ and bone marrow transplantation may present with TMAs, likely caused by infections, graft-versus-host disease, humoral rejection, and medication. TMA associated with transplantation most commonly affects the kidneys but can manifest with gastrointestinal, pulmonary, neurologic, or cardiac involvementand typically has normal or mildly low ADAMTS13 activity., There are rare case reports of severe deficiency of ADAMTS13 activity in the presence of an inhibitor in lung- [66] and kidney-transplant

patients [67]. Medications, including CNIs, anti-VEGF bevacizumab, and sirolimus have been implicated to cause TMA in this population [68].

Antibody-mediated rejection in a renal allograft can have similar histological features to TMA. Predominant endarteritis, presence of C4d staining of peritubular capillaries, and donor-specific antibody may favor the diagnosis of humoral rejection [69]. It is also important to rule out infections as a cause of TMA in a transplant recipient including bacterial, viral, and fungal pathogens.

d. Malignancy-associated TMA

The estimated incidence is between 0.25 and 0.45 cases per million residents [70], lower than that of autoimmune TTP. The mechanism underlying TMA may be multifactorial: the obstruction of microcirculation by invading cancer cells, microvascular thrombosis, DIC, and chemotherapeutic agents. Lechner et al [70] reviewed 154 cases of malignancy-associated TMA, more than 90% of the cases showed metastatic cancer when TMA was diagnosed; 24% of patients had renal or neurological involvement, 36% had leukoerthyroblastic presentation on peripheral smear, and 36% had low fibrinogen with elevated fibrin degradation products or dimer, suggestive of DIC. A majority of cancers were gastric, breast, prostate, or lung in origin and about 30% of patients had pulmonary symptoms/involvement. Therefore, in TMA patients with pulmonary involvement an occult malignancy should be aggressively sought. Plasma ADAMTS13 activity in malignancy-associated TMA is usually normal or modestly reduced (35–84 IU/dL) [71]. Severe deficiency of ADAMTS13 activity (<10 IU/dL) with IgG antibody was reported in a few cases [72]. Therefore, the presence of TMA with any of the following clinical features including elderly age, prior history of cancer, involvement of the lungs (i.e. pleural effusion and interstitial infiltrate), extreme elevation of serum LDH, laboratory features of DIC (i.e. reduced levels of fibrinogen and increased D-dimer), and symptoms of progressive cancer should prompt a thorough search for an occult malignancy [72].

e. Malignant hypertension-associated TMA

Severely elevated blood pressure with associated retinal changes (i.e. flame-shape hemorrhage, cotton wool spots and papilledema) is a characteristic feature of malignant hypertension [73, 74]. Patients with malignant hypertension may present with MAHA, thrombocytopenia, and renal failure; conversely, patients with TMA sometimes can also present with severe hypertension, especially those with renal involvement. The hypertension-associated TMA improves after aggressive control of blood pressure. Patients with malignant hypertension presented with schistocytes, a mean systolic blood pressure of 159 mm Hg, renal failure (mean creatinine 5.3 mg/dL), and a modest reduction of platelet count (mean 60×10^9/L) with plasma ADAMTS13 activity usually >10 IU/dL [75, 76]. The reduced ADAMTS13 activity might be caused by consumption related to endothelial activation and increased levels of plasma VWF. A significantly inversed correlation between plasma VWF and ADAMTS13 activity ($r=-0.34$, $p=0.03$) was observed in patients with malignant hypertension [76]. Aggressive blood pressure control therapy is warranted to mitigate the organ damage.

f. Pregnancy-associated TMA

Between 1:25,000 and 1: 100,000 pregnant women develop signs and symptoms of TMA [77], 3–10 times higher than idiopathic TTP. Both TTP and aHUS can occur during pregnancy and after delivery. Immediate delivery of the fetus is sometimes the only effective treatment for TMA patients during pregnancy; additional therapy such as plasma infusion, plasma exchange, and anti-complement therapy may be necessary, depending on the underlying diagnosis. While severe ADAMTS13 deficiency or complement dysregulation alone is often not sufficient to cause acute TTP or aHUS, respectively, pregnancy may be a precipitating factor for these diseases.. In the French registry of 42 pregnancy-associated TTP cases, 23 patients had autoantibodies against ADAMTS13 and were diagnosed as acquired TTP while 19 patients did not have autoantibodies and were confirmed to have hereditary TTP after sequencing analysis of *ADAMTS13* gene. The most common mutation found in these patients was p. Arg1060Trp and most patients were compound heterozygotes. The associated conditions along with pregnancy were: ovarian stimulation, viral infection, thyroiditis, HIV, lupus, or anti-phospholipid syndrome (APS) [77].

The level of VWF increases during pregnancy with a concomitant decrease in ADAMTS13 activity, mainly due to consumption or related to estrogen, in the second and third trimester that persists for few weeks postpartum [30]. Some clinical and laboratory features may provide a hint towards a specific diagnosis. TTP may occur at any point in pregnancy or in post-partum period while acute fatty liver (AFL) and HELLP syndrome typically occur in second and third trimesters; additionally, the presence of severe renal injury may be more suggestive of aHUS or HELLP syndrome than TTP. Acute renal injury in HELLP syndrome is usually associated with acute tubular necrosis without thrombosis, which may improve with conservative management [78]. Symptoms of abdominal pain, headache, fever, and nausea may be seen in many different TMAs, but hypoglycemia is not a presenting feature of TTP or aHUS and may be more suggestive of AFL or HELLP syndrome. It is critical to obtain an ADAMTS13 level on the first day of presentation prior to initiation of plasma therapy. An ADAMTS13 activity (<10 IU/dL) with or without an autoantibody is diagnostic for TTP. Other clues towards TTP include platelet count ($\leq 30\times10^9$/L) or other signs and symptoms that do not improve after delivery of a fetus. Plasma infusion or exchange therapy should be started immediately when the index of suspicion for hereditary or acquired TTP, respectively, is high or a presumptive diagnosis of TTP has been made.

h. DIC-associated TMA

Patients with DIC may exhibit features of TMA with underlying causes, including severe trauma, sepsis, malignancy, preeclampsia/HELLP syndrome, etc. Because of the consumptive coagulopathy, patients with DIC have prolonged prothrombin time and activated partial thromboplastin time, elevated fibrin degradation products or D-dimer, reduced fibrinogen, and increased thrombin time. Fibrinogen is also an acute phase reactant, and therefore normal values do not exclude ongoing consumptive coagulopathy. Thrombocytopenia is a common feature of DIC although an extremely low count ($\leq 20\times10^9$/L) is rare. Various scoring systems are available for diagnosis of DIC, including one developed by ISTH [79]. This scoring system should only be used in patients with an underlying disorder that is known to cause DIC; prospective studies in an intensive care unit

setting showed that the ISTH scoring system had a sensitivity and specificity of 91% and 97%, respectively, for the diagnosis of DIC. Thus, in appropriate clinical situations, DIC should be ruled out given that a significantly low ADAMTS13 activity (<10 IU/dL) may occur.

g. Infection-associated

Systemic bacterial, viral, or fungal infections can cause MAHA and thrombocytopenia and therefore should always be considered during evaluation of such patients. This is more relevant for elderly patients who have fever or chills associated with features of TTP. An infection can also trigger an acute episode of TTP and it may be difficult to differentiate whether the infection is the cause or a trigger. The ADAMTS13 activity in patients with infection-associated TMA is usually low normal (>20 IU/dL). Severe sepsis, Dengue, endocarditis, and sepsis-induced DIC have been reported to cause severe ADAMTS13 deficiency in the absence of an inhibitor [80, 81]. The underlying mechanism is multifactorial but unified by: endothelial damage leading to increased VWF release and increased consumption of ADAMTS13, bacterial enzymes leading to ADAMTS13 proteolysis, and cytokine mediated protease inhibition [80]. Also, neutrophil extracellular traps (NETs), chromatin fibers (containing histones and antimicrobial proteins) released from neutrophils during infection/inflammation, may result in thrombosis due to their ability to cause platelet aggregation and adhesion. Elevated markers of NETs have been demonstrated in patient plasma during acute TMA episodes [82]. Plasma DNAse1 is required to degrade NETs and prevent thrombosis and this may be lacking in some patients with an acute TMA episode [83].

In a HIV-infected patient, features of TMA may be due to multiple causes including coexisting TTP. These include advanced disease with opportunistic infections (HHV-8 and CMV), malignancies (Kaposi sarcoma), and anti-viral medications. In addition, during immune reconstitution with initiation of highly active antiretroviral therapy (HAART) therapy, elevated levels of cytokines (IL-6 and IL-8) may inhibit ADAMTS13 activity and result in features of TMA [68, 84]. In a large study of HIV-infected patients, two subsets of TMA were described: those with <5 IU/dL ADAMTS13 activity had higher CD4 count, fewer AIDS-related complications, and better prognosis in contrast to those with >5 IU/dL ADAMTS13 activity. There was no difference in platelet count, renal function, or neurologic symptoms in those 2 groups. This was attributed to higher levels of serum VWF and moderately low ADAMTS13 activity, a result of endothelial activation/injury in advanced disease either due to direct endothelial effects of HIV or other opportunistic infections. Patients with higher CD4 cell count and less severe disease may encounter an autoimmune process of TTP [84]. Plasma apheresis should be considered in a HIV-patient who has features of TMA in the presence of severe ADAMTS13 deficiency provided other opportunistic infections, malignancies, and other causes have been ruled out. HAART should be considered in patients with HIV-related TMA with severe ADAMTS13 activity along with plasma exchange, remaining cognizant that immune reconstitution during HAART may precipitate an acute flare. In addition, HHV-6 and CMV can cause vascular endothelial injury and have features of TMA [85].

Therapies

Current therapies

To date, prophylactic plasma infusion remains the mainstay for treatment of hereditary TTP resulting from mutations in *ADAMTS13*. Based on the study described by Furlan et al [86], the half-life of infused plasma ADAMTS13 was between 2–3 days. For prophylactic purpose, 5 ml/kg bi-weekly fresh frozen plasma seemed to be sufficient to prevent acute episodes. However, when acute TTP has developed, 10 ml/kg every 1–2 weeks may be necessary for treatment [87]. Hopefully recombinant ADAMTS13 will soon become the standard of care for treating hereditary TTP [88].

Therapeutic plasma exchange (TPE) is the treatment of choice for acquired TTP due to autoantibodies against ADAMTS13. The first reported success of using plasma as part of treatment for acquired TTP was reported in 1977; more than 60% of acquired TTP patients responded to plasma treatment [89]. Randomized trial demonstrated the superiority of plasma exchange over plasma infusion in survival [39]. Other immunosuppressive therapies, including corticosteroids, vincristine, cyclophosphamide, cyclosporine, and rituximab (a humanized monoclonal antibody against B-cell surface antigen CD20), and bortezomib (a proteasome inhibitor that targets plasma cells) [90, 91], may be prescribed in patients with acquired TTP to eliminate antibody formation and sustain a long-term remission. Since TTP results in platelet-rich thrombus in microcirculation, physicians treating TTP patients are sometimes reluctant to use platelet transfusion. Swisher et al. suggests based on their cohort that platelet transfusion should be minimized but can be considered in patients with overt bleeding and also during invasive procedures in patients with severe thrombocytopenia [92].

Potential novel therapies

Various novel therapies have been tested in preclinical animal models. AAV8-based gene therapy expressing a murine C-terminal truncated ADAMTS13 (i.e. mMDTCS) in the liver appears to be highly successful in a murine model of hereditary TTP [23]. A single injection of AAV8-hAAT-mMDTCS vector at a dose >2.6×10^{11} vector genome per kilogram body weight resulted in a long-term expression of functional ADAMTS13 at therapeutic levels, which prevented shigatoxin-induced TTP in *Adamts13*$^{-/-}$ mice [23]. Other gene therapy approaches include the transplantation of hematopoietic progenitor cells transduced with lentiviral vector encoding a full-length ADAMTS13 [93] and the liver expression of a full-length ADAMTS13 by sleeping beauty transposon SBX100 system [94]. In addition, ectopic expression of a full-length recombinant ADAMTS13 in megakaryocytes and platelets in *Adamts13*$^{-/-}$ mice also showed protection against TTP after VWF or shigatoxin challenge in the presence of anti-ADAMTS13 antibody [24]. N-acetylcysteine, which contains free thiols and is therefore able to reduce disulfide bonds, has been shown to be efficacious in preventing recombinant VWF-induced TTP in *Adamts13*$^{-/-}$ mice. However, N-acetylcysteine was not effective in reversing TTP signs in *Adamts13*$^{-/-}$ mice or baboon models despite a reduction in VWF multimer size [95]. More recently, Zheng et al demonstrated that the blockade of VWF-platelet glycoprotein 1b (GP1b) interaction by anfibatide, isolated from snake venom, was also efficacious for preventing or treating spontaneous and shigatoxin-induced TTP in *Adamts13*$^{-/-}$ mice [96]. Similar results were

obtained in a baboon model with caplacizumab, a nanobody targeted at the VWF-A1 domain, thereby blocking VWF-platelet GP1b interactions [97]. The therapeutic efficacy of the VWF-GP1b blockage has been recently demonstrated in a phase II clinical trial for acquired TTP [27]. Patients with acquired TTP received subcutaneous injection of caplacizumab (10 mg) daily or placebo during plasma exchange and for 30 days afterward. The time to a response was significantly reduced with caplacizumab as compared with placebo (39% reduction in median time, p=0.005).

In summary, recent progress in ADAMTS13 testing has allowed us to distinguish TTP from other TMAs with great confidence. However, the potential triggers for acute TTP in light of severe ADAMTS13 deficiency remain elusive. Infection, pregnancy, certain medications [54], complement activation [98, 99], and neutrophil activation and the release of human neutrophil peptides [100], extracellular DNA and histones [82, 83], etc. may all trigger the acute episode of TTP. While plasma infusion or exchange appears to be effective in most patients with hereditary or acquired TTP, respectively, in-hospital mortality and exacerbation or relapse remains a great concern. Therefore, further understanding of the potential triggers, identification of a biomarker for predicting long-term outcome or relapse, and development of additional novel and more effective therapies are urgently needed.

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References

1. Moake JL. Thrombotic microangiopathies. N Engl J Med. 2002; 347:589–600. [PubMed: 12192020]
2. Zheng XL, Sadler JE. Pathogenesis of thrombotic microangiopathies. Annu Rev Pathol. 2008; 3:249–77. [PubMed: 18215115]
3. Terrell DR, Williams LA, Vesely SK, Lammle B, Hovinga JA, George JN. The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS-13 deficiency. J Thromb Haemost. 2005; 3:1432–6. [PubMed: 15978100]
4. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009; 361:1676–87. [PubMed: 19846853]
5. Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, Daina E, Fenili C, Castelletti F, Sorosina A, Piras R, Donadelli R, Maranta R, van der Meer I, Conway EM, Zipfel PF, Goodship TH, Remuzzi G. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010; 5:1844–59. [PubMed: 20595690]
6. Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, Bettinaglio P, Mele C, Bresin E, Cassis L, Gamba S, Porrati F, Bucchioni S, Monteferrante G, Fang CJ, Liszewski MK, Kavanagh D, Atkinson JP, Remuzzi G, Familial HT. International Registry of R. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood. 2006; 108:1267–79. [PubMed: 16621965]
7. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nurnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, Sheerin NS, Trivelli A, Zimmerhackl LB,

Goodship T, Loirat C. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013; 368:2169–81. [PubMed: 23738544]

8. Moschcowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. Proc N Y Pathol Soc. 1924; 24:21–4.
9. Amorosi E, Ultmann J. Thrombotic thrombocytopenic purpura: report of 16 cases and reveiw of the literature. Medicine (Baltimore). 1966; 45:139–59.
10. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. Blood. 2004; 103:4043–9. [PubMed: 14982878]
11. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. N Engl J Med. 1991; 325:398–403. [PubMed: 2062331]
12. Moake JL, Rudy CK, Troll JH, Weinstein MJ, Colannino NM, Azocar J, Seder RH, Hong SL, Deykin D. Unusually large plasma factor VIII:von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med. 1982; 307:1432–5. [PubMed: 6813740]
13. Furlan M, Robles R, Solenthaler M, Wassmer M, Sandoz P, Lammle B. Deficient activity of von Willebrand factor-cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. Blood. 1997; 89:3097–103. [PubMed: 9129011]
14. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Eng J Med. 1998; 339:1585–94.
15. Zheng X, Chung D, Takayama TK, Majerus EM, Sadler JE, Fujikawa K. Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. J Biol Chem. 2001; 276:41059–63. [PubMed: 11557746]
16. Gerritsen HE, Robles R, Lammle B, Furlan M. Partial amino acid sequence of purified von Willebrand factor-cleaving protease. Blood. 2001; 98:1654–61. [PubMed: 11535494]
17. Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. Blood. 2001; 98:1662–6. [PubMed: 11535495]
18. Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN, McGee BM, Yang AY, Siemieniak DR, Stark KR, Gruppo R, Sarode R, Shurin SB, Chandrasekaran V, Stabler SP, Sabio H, Bouhassira EE, Upshaw JD Jr, Ginsburg D, Tsai HM. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 2001; 413:488–94. [PubMed: 11586351]
19. Zheng XL. Structure-function and regulation of ADAMTS-13 protease. J Thromb Haemost. 2013; 11(Suppl 1):11–23. [PubMed: 23809107]
20. Zheng XL. ADAMTS13 and von Willebrand Factor in Thrombotic Thrombocytopenic Purpura. Annu Rev Med. 2015; 66:211–25. [PubMed: 25587650]
21. Kokame K, Nobe Y, Kokubo Y, Okayama A, Miyata T. FRETS-VWF73, a first fluorogenic substrate for ADAMTS13 assay. Br J Haematol. 2005; 129:93–100. [PubMed: 15801961]
22. Gerritsen HE, Turecek PL, Schwarz HP, Lammle B, Furlan M. Assay of von Willebrand factor (vWF)-cleaving protease based on decreased collagen binding affinity of degraded vWF: a tool for the diagnosis of thrombotic thrombocytopenic purpura (TTP). Thrombosis and haemostasis. 1999; 82:1386–9. [PubMed: 10595623]
23. Jin SY, Xiao J, Bao J, Zhou S, Wright JF, Zheng XL. AAV-mediated expression of an ADAMTS13 variant prevents shigatoxin-induced thrombotic thrombocytopenic purpura. Blood. 2013; 121:3825–9. S1–3. [PubMed: 23515928]
24. Pickens B, Mao Y, Li D, Siegel DL, Poncz M, Cines DB, Zheng XL. Platelet-delivered ADAMTS13 inhibits arterial thrombosis and prevents thrombotic thrombocytopenic purpura in murine models. Blood. 2015; 125:3326–34. [PubMed: 25800050]
25. Jian C, Xiao J, Gong L, Skipwith CG, Jin SY, Kwaan HC, Zheng XL. Gain-of-function ADAMTS13 variants that are resistant to autoantibodies against ADAMTS13 in patients with acquired thrombotic thrombocytopenic purpura. Blood. 2012; 119:3836–43. [PubMed: 22289888]

26. Tersteeg C, Schiviz A, De Meyer SF, Plaimauer B, Scheiflinger F, Rottensteiner H, Vanhoorelbeke K. Potential for Recombinant ADAMTS13 as an Effective Therapy for Acquired Thrombotic Thrombocytopenic Purpura. Arterioscler Thromb Vasc Biol. 2015; 35:2336–42. [PubMed: 26338302]
27. Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knobl P, Wu H, Artoni A, Westwood JP, Mansouri Taleghani M, Jilma B, Callewaert F, Ulrichts H, Duby C, Tersago D, Investigators T. Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2016; 374:511–22. [PubMed: 26863353]
28. Zheng XL. ADAMTS13, TTP and Beyond. Hereditary Genet. 2013; 2:e104. [PubMed: 24790789]
29. Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, Kremer Hovinga J, Lammle B, Matsumoto M, Pavenski K, Sadler E, Sarode R, Wu H. International Working Group for Thrombotic Thrombocytopenic P. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2016; 15:312–22.
30. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ. British Committee for Standards in H. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012; 158:323–35. [PubMed: 22624596]
31. Coppo P, Wolf M, Veyradier A, Bussel A, Malot S, Millot GA, Daubin C, Bordessoule D, Pene F, Mira JP, Heshmati F, Maury E, Guidet B, Boulanger E, Galicier L, Parquet N, Vernant JP, Rondeau E, Azoulay E, Schlemmer B. Reseau d'Etude des Microangiopathies Thrombotiques de lA. Prognostic value of inhibitory anti-ADAMTS13 antibodies in adult-acquired thrombotic thrombocytopenic purpura. Br J Haematol. 2006; 132:66–74. [PubMed: 16371021]
32. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, Krause M, Scharrer I, Aumann V, Mittler U, Solenthaler M, Lammle B. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med. 1998; 339:1578–84. [PubMed: 9828245]
33. Khan WA, Griffiths JK, Bennish ML. Gastrointestinal and extra-intestinal manifestations of childhood shigellosis in a region where all four species of Shigella are endemic. PLoS One. 2013; 8:e64097. [PubMed: 23691156]
34. Bell BP, Goldoft M, Griffin PM, Davis MA, Gordon DC, Tarr PI, Bartleson CA, Lewis JH, Barrett TJ, Wells JG. A multistate outbreak of Escherichia coli O157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers. The Washington experience. JAMA. 1994; 272:1349–53. [PubMed: 7933395]
35. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaime F, Dragon-Durey MA, Ngo S, Moulin B, Servais A, Provot F, Rostaing L, Burtey S, Niaudet P, Deschenes G, Lebranchu Y, Zuber J, Loirat C. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol. 2013; 8:554–62. [PubMed: 23307876]
36. Lemaire M, Fremeaux-Bacchi V, Schaefer F, Choi M, Tang WH, Le Quintrec M, Fakhouri F, Taque S, Nobili F, Martinez F, Ji W, Overton JD, Mane SM, Nurnberg G, Altmuller J, Thiele H, Morin D, Deschenes G, Baudouin V, Llanas B, Collard L, Majid MA, Simkova E, Nurnberg P, Rioux-Leclerc N, Moeckel GW, Gubler MC, Hwa J, Loirat C, Lifton RP. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat Genet. 2013; 45:531–6. [PubMed: 23542698]
37. Brazelton J, Oster RA, McCleskey B, Fuller J, Adamski J, Marques MB. Increased troponin I is associated with fatal outcome in acquired thrombotic thrombocytopenic purpura. J Clin Apher. 2016; doi: 10.1002/jca.21510
38. Zafrani L, Mariotte E, Darmon M, Canet E, Merceron S, Boutboul D, Veyradier A, Galicier L, Azoulay E. Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity. J Thromb Haemost. 2015; 13:380–9. [PubMed: 25523333]
39. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med. 1991; 325:393–7. [PubMed: 2062330]

40. Zini G, d'Onofrio G, Briggs C, Erber W, Jou JM, Lee SH, McFadden S, Vives-Corrons JL, Yutaka N, Lesesve JF. ICSH recommendations for identification, diagnostic value, and quantitation of schistocytes. Int J Lab Hematol. 2012; 34:107–16. [PubMed: 22081912]

41. Ruutu T, Barosi G, Benjamin RJ, Clark RE, George JN, Gratwohl A, Holler E, Iacobelli M, Kentouche K, Lammle B, Moake JL, Richardson P, Socie G, Zeigler Z, Niederwieser D, Barbui T. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. Haematologica. 2007; 92:95–100. [PubMed: 17229640]

42. Egan JA, Hay SN, Brecher ME. Frequency and significance of schistocytes in TTP/HUS patients at the discontinuation of plasma exchange therapy. J Clin Apher. 2004; 19:165–7. [PubMed: 15597353]

43. Laurence J. Atypical hemolytic uremic syndrome (aHUS): making the diagnosis. Clin Adv Hematol Oncol. 2012; 10:1–12.

44. Barrows BD, Teruya J. Use of the ADAMTS13 Activity Assay Improved the Accuracy and Efficiency of the Diagnosis and Treatment of Suspected Acquired Thrombotic Thrombocytopenic Purpura. Arch Pathol Lab Med. 2014; 138:546–9. [PubMed: 24678685]

45. Mackie I, Langley K, Chitolie A, Liesner R, Scully M, Machin S, Peyvandi F. Discrepancies between ADAMTS13 activity assays in patients with thrombotic microangiopathies. Thromb Haemost. 2013; 109:488–96. [PubMed: 23306535]

46. Kato S, Matsumoto M, Matsuyama T, Isonishi A, Hiura H, Fujimura Y. Novel monoclonal antibody-based enzyme immunoassay for determining plasma levels of ADAMTS13 activity. Transfusion. 2006; 46:1444–52. [PubMed: 16934083]

47. Jin M, Cataland S, Bissell M, Wu HM. A rapid test for the diagnosis of thrombotic thrombocytopenic purpura using surface enhanced laser desorption/ionization time-of-flight (SELDI-TOF)-mass spectrometry. J Thromb Haemost. 2006; 4:333–8. [PubMed: 16420561]

48. Knovich MA, Craver K, Matulis MD, Lawson H, Owen J. Simplified assay for VWF cleaving protease (ADAMTS13) activity and inhibitor in plasma. Am J Hematol. 2004; 76:286–90. [PubMed: 15224369]

49. Meyer SC, Sulzer I, Lammle B, Kremer Hovinga JA. Hyperbilirubinemia interferes with ADAMTS-13 activity measurement by FRETS-VWF73 assay: diagnostic relevance in patients suffering from acute thrombotic microangiopathies. J Thromb Haemost. 2007; 5:866–7. [PubMed: 17408415]

50. Muia J, Gao W, Haberichter SL, Dolatshahi L, Zhu J, Westfield LA, Covill SC, Friedman KD, Sadler JE. An optimized fluorogenic ADAMTS13 assay with increased sensitivity for the investigation of patients with thrombotic thrombocytopenic purpura. J Thromb Haemost. 2013; 11:1511–8. [PubMed: 23773695]

51. Coppo P, Schwarzinger M, Buffet M, Wynckel A, Clabault K, Presne C, Poullin P, Malot S, Vanhille P, Azoulay E, Galicier L, Lemiale V, Mira JP, Ridel C, Rondeau E, Pourrat J, Girault S, Bordessoule D, Saheb S, Ramakers M, Hamidou M, Vernant JP, Guidet B, Wolf M, Veyradier A. French Reference Center for Thrombotic M. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. PLoS One. 2010; 5:e10208. [PubMed: 20436664]

52. Bendapudi PK, Hurwitz S, Fry A, Marques MB, Waldo SW, Li A, Sun L, Upadhyay V, Hamdan A, Brunner AM, Gansner JM, Viswanathan S, Kaufman RM, Uhl L, Stowell CP, Dzik WH, Makar RS. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol. 2017

53. Bennett CL, Jacob S, Dunn BL, Georgantopoulos P, Zheng XL, Kwaan HC, McKoy JM, Magwood JS, Qureshi ZP, Bandarenko N, Winters JL, Raife TJ, Carey PM, Sarode R, Kiss JE, Danielson C, Ortel TL, Clark WF, Ablin RJ, Rock G, Matsumoto M, Fujimura Y. Ticlopidine-associated ADAMTS13 activity deficient thrombotic thrombocytopenic purpura in 22 persons in Japan: a report from the Southern Network on Adverse Reactions (SONAR). Br J Haematol. 2013; 161:896–8. [PubMed: 23530950]

54. Jacob S, Dunn BL, Qureshi ZP, Bandarenko N, Kwaan HC, Pandey DK, McKoy JM, Barnato SE, Winters JL, Cursio JF, Weiss I, Raife TJ, Carey PM, Sarode R, Kiss JE, Danielson C, Ortel TL, Clark WF, Rock G, Matsumoto M, Fujimura Y, Zheng XL, Chen H, Chen F, Armstrong JM,

Raisch DW, Bennett CL. Ticlopidine-, clopidogrel-, and prasugrel-associated thrombotic thrombocytopenic purpura: a 20-year review from the Southern Network on Adverse Reactions (SONAR). Semin Thromb Hemost. 2012; 38:845–53. [PubMed: 23111862]

55. Park YA, Hay SN, King KE, Matevosyan K, Poisson J, Powers A, Sarode R, Shaz B, Brecher ME. Is it quinine TTP/HUS or quinine TMA? ADAMTS13 levels and implications for therapy. J Clin Apher. 2009; 24:115–9. [PubMed: 19260037]
56. Gottschall JL, Elliot W, Lianos E, McFarland JG, Wolfmeyer K, Aster RH. Quinine-induced immune thrombocytopenia associated with hemolytic uremic syndrome: a new clinical entity. Blood. 1991; 77:306–10. [PubMed: 1898704]
57. Said T, Al-Otaibi T, Al-Wahaib S, Francis I, Nair MP, Halim MA, El-Sayed A, Nampoory MR. Posttransplantation calcineurin inhibitor-induced hemolytic uremic syndrome: single-center experience. Transplant Proc. 2010; 42:814–6. [PubMed: 20430179]
58. Mor E, Lustig S, Tovar A, Bar-Nathan N, Shharabani E, Shapira Z, Yusim A. Thrombotic microangiopathy early after kidney transplantation: hemolytic uremic syndrome or vascular rejection? Transplant Proc. 2000; 32:686–7. [PubMed: 10856542]
59. Karthikeyan V, Parasuraman R, Shah V, Vera E, Venkat KK. Outcome of plasma exchange therapy in thrombotic microangiopathy after renal transplantation. Am J Transplant. 2003; 3:1289–94. [PubMed: 14510703]
60. Hochstetler LA, Flanigan MJ, Lager DJ. Transplant-associated thrombotic microangiopathy: the role of IgG administration as initial therapy. Am J Kidney Dis. 1994; 23:444–50. [PubMed: 8128949]
61. Van Buren D, Van Buren CT, Flechner SM, Maddox AM, Verani R, Kahan BD. De novo hemolytic uremic syndrome in renal transplant recipients immunosuppressed with cyclosporine. Surgery. 1985; 98:54–62. [PubMed: 3892747]
62. Medina PJ, Sipols JM, George JN. Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol. 2001; 8:286–93. [PubMed: 11604563]
63. Groff JA, Kozak M, Boehmer JP, Demko TM, Diamond JR. Endotheliopathy: a continuum of hemolytic uremic syndrome due to mitomycin therapy. Am J Kidney Dis. 1997; 29:280–4. [PubMed: 9016902]
64. Izzedine H, Escudier B, Lhomme C, Pautier P, Rouvier P, Gueutin V, Baumelou A, Derosa L, Bahleda R, Hollebecque A, Sahali D, Soria JC. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center. Medicine (Baltimore). 2014; 93:333–9. [PubMed: 25500702]
65. Izzedine H, Isnard-Bagnis C, Launay-Vacher V, Mercadal L, Tostivint I, Rixe O, Brocheriou I, Bourry E, Karie S, Saeb S, Casimir N, Billemont B, Deray G. Gemcitabine-induced thrombotic microangiopathy: a systematic review. Nephrol Dial Transplant. 2006; 21:3038–45. [PubMed: 16968717]
66. Mal H, Veyradier A, Brugiere O, Da Silva D, Colombat M, Azoulay E, Benayoun L, Rondeau E, Dauriat G, Taille C, Leseche G, Castier Y, Fournier M. Thrombotic microangiopathy with acquired deficiency in ADAMTS 13 activity in lung transplant recipients. Transplantation. 2006; 81:1628–32. [PubMed: 16794526]
67. Koskinen AR, Tukiainen E, Arola J, Nordin A, Hockerstedt HK, Nilsson B, Isoniemi H, Jokiranta TS. Complement activation during liver transplantation-special emphasis on patients with atypical hemolytic uremic syndrome. Am J Transplant. 2011; 11:1885–95. [PubMed: 21812916]
68. George JN, Terrell DR, Vesely SK, Kremer Hovinga JA, Lammle B. Thrombotic microangiopathic syndromes associated with drugs, HIV infection, hematopoietic stem cell transplantation and cancer. Presse Med. 2012; 41:e177–88. [PubMed: 22244728]
69. Noris M, Remuzzi G. Thrombotic microangiopathy after kidney transplantation. Am J Transplant. 2010; 10:1517–23. [PubMed: 20642678]
70. Lechner K, Obermeier HL. Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine (Baltimore). 2012; 91:195–205. [PubMed: 22732949]

71. Fontana S, Gerritsen HE, Kremer Hovinga J, Furlan M, Lammle B. Microangiopathic haemolytic anaemia in metastasizing malignant tumours is not associated with a severe deficiency of the von Willebrand factor-cleaving protease. Br J Haematol. 2001; 113:100–2. [PubMed: 11328288]

72. George JN. Systemic malignancies as a cause of unexpected microangiopathic hemolytic anemia and thrombocytopenia. Oncology (Williston Park). 2011; 25:908–14. [PubMed: 22010388]

73. van den Born BJ, Koopmans RP, van Montfrans GA. The renin-angiotensin system in malignant hypertension revisited: plasma renin activity, microangiopathic hemolysis, and renal failure in malignant hypertension. Am J Hypertens. 2007; 20:900–6. [PubMed: 17679041]

74. Linton AL, Gavras H, Gleadle RI, Hutchison HE, Lawson DH, Lever AF, Macadam RF, McNicol GP, Robertson JI. Microangiopathic haemolytic anaemia and the pathogenesis of malignant hypertension. Lancet. 1969; 1:1277–82. [PubMed: 4182177]

75. Khanal N, Dahal S, Upadhyay S, Bhatt VR, Bierman PJ. Differentiating malignant hypertension-induced thrombotic microangiopathy from thrombotic thrombocytopenic purpura. Ther Adv Hematol. 2015; 6:97–102. [PubMed: 26137201]

76. van den Born BJ, van der Hoeven NV, Groot E, Lenting PJ, Meijers JC, Levi M, van Montfrans GA. Association between thrombotic microangiopathy and reduced ADAMTS13 activity in malignant hypertension. Hypertension. 2008; 51:862–6. [PubMed: 18332284]

77. Moatti-Cohen M, Garrec C, Wolf M, Boisseau P, Galicier L, Azoulay E, Stepanian A, Delmas Y, Rondeau E, Bezieau S, Coppo P, Veyradier A. French Reference Center for Thrombotic M. Unexpected frequency of Upshaw-Schulman syndrome in pregnancy-onset thrombotic thrombocytopenic purpura. Blood. 2012; 119:5888–97. [PubMed: 22547583]

78. Fakhouri F. Pregnancy-related thrombotic microangiopathies: Clues from complement biology. Transfus Apher Sci. 2016; 54:199–202. [PubMed: 27158062]

79. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol. 2009; 145:24–33. [PubMed: 19222477]

80. Schwameis M, Schorgenhofer C, Assinger A, Steiner MM, Jilma B. VWF excess and ADAMTS13 deficiency: a unifying pathomechanism linking inflammation to thrombosis in DIC, malaria, and TTP. Thromb Haemost. 2015; 113:708–18. [PubMed: 25503977]

81. Ono T, Mimuro J, Madoiwa S, Soejima K, Kashiwakura Y, Ishiwata A, Takano K, Ohmori T, Sakata Y. Severe secondary deficiency of von Willebrand factor-cleaving protease (ADAMTS13) in patients with sepsis-induced disseminated intravascular coagulation: its correlation with development of renal failure. Blood. 2006; 107:528–34. [PubMed: 16189276]

82. Fuchs TA, Kremer Hovinga JA, Schatzberg D, Wagner DD, Lammle B. Circulating DNA and myeloperoxidase indicate disease activity in patients with thrombotic microangiopathies. Blood. 2012; 120:1157–64. [PubMed: 22611154]

83. Jimenez-Alcazar M, Napirei M, Panda R, Kohler EC, Kremer Hovinga JA, Mannherz HG, Peine S, Renne T, Lammle B, Fuchs TA. Impaired DNase1-mediated degradation of neutrophil extracellular traps is associated with acute thrombotic microangiopathies. J Thromb Haemost. 2015; 13:732–42. [PubMed: 25418346]

84. Malak S, Wolf M, Millot GA, Mariotte E, Veyradier A, Meynard JL, Korach JM, Malot S, Bussel A, Azoulay E, Boulanger E, Galicier L, Devaux E, Eschwege V, Gallien S, Adrie C, Schlemmer B, Rondeau E, Coppo P. Reseau d'Etude des Microangiopathies T. Human immunodeficiency virus-associated thrombotic microangiopathies: clinical characteristics and outcome according to ADAMTS13 activity. Scand J Immunol. 2008; 68:337–44. [PubMed: 18782260]

85. Takatsuka H, Wakae T, Mori A, Okada M, Fujimori Y, Takemoto Y, Okamoto T, Kanamaru A, Kakishita E. Endothelial damage caused by cytomegalovirus and human herpesvirus-6. Bone Marrow Transplant. 2003; 31:475–9. [PubMed: 12665843]

86. Furlan M, Robles R, Morselli B, Sandoz P, Lammle B. Recovery and half-life of von Willebrand factor-cleaving protease after plasma therapy in patients with thrombotic thrombocytopenic purpura. Thrombosis and haemostasis. 1999; 81:8–13. [PubMed: 10348715]

87. Fujimura, Y., Kokame, K., Yagi, H., Isonishi, A., Matsumoto, C., Miyata, T. Hereditary deficiency of ADAMTS13 activity: Upshaw-Schulman syndrome. In: Rodgers, GM., editor. ADAMTS13 Biology and Disease. Cham, Heidlberg, New York, Dordrecht, London: Springer; 2015. p. 73-90.

88. Schiviz A, Wuersch K, Piskernik C, Dietrich B, Hoellriegl W, Rottensteiner H, Scheiflinger F, Schwarz HP, Muchitsch EM. A new mouse model mimicking thrombotic thrombocytopenic purpura: correction of symptoms by recombinant human ADAMTS13. Blood. 2012; 119:6128–35. [PubMed: 22529289]

89. Byrnes JJ, Khurana M. Treatment of thrombotic thrombocytopenic purpura with plasma. N Engl J Med. 1977; 297:1386–9. [PubMed: 562982]

90. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010; 116:4060–9. [PubMed: 20686117]

91. Zheng X, Pallera AM, Goodnough LT, Sadler JE, Blinder MA. Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and rituximab. Ann Intern Med. 2003; 138:105–8. [PubMed: 12529092]

92. Swisher KK, Terrell DR, Vesely SK, Kremer Hovinga JA, Lammle B, George JN. Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. Transfusion. 2009; 49:873–87. [PubMed: 19210323]

93. Laje P, Shang D, Cao W, Niiya M, Endo M, Radu A, DeRogatis N, Scheiflinger F, Zoltick PW, Flake AW, Zheng XL. Correction of murine ADAMTS13 deficiency by hematopoietic progenitor cell-mediated gene therapy. Blood. 2009; 113:2172–80. [PubMed: 19141866]

94. Verhenne S, Vandeputte N, Pareyn I, Izsvak Z, Rottensteiner H, Deckmyn H, De Meyer SF, Vanhoorelbeke K. Long-Term Prevention of Congenital Thrombotic Thrombocytopenic Purpura in ADAMTS13 Knockout Mice by Sleeping Beauty Transposon-Mediated Gene Therapy. Arterioscler Thromb Vasc Biol. 2017

95. Tersteeg C, Roodt J, Van Rensburg WJ, Dekimpe C, Vandeputte N, Pareyn I, Vandenbulcke A, Plaimauer B, Lamprecht S, Deckmyn H, Lopez JA, De Meyer SF, Vanhoorelbeke K. N-acetylcysteine in preclinical mouse and baboon models of thrombotic thrombocytopenic purpura. Blood. 2017; 129:1030–8. [PubMed: 28011677]

96. Zheng L, Mao Y, Abdelgawwad MS, Li M, Dai X, Li B, Zheng XL. Therapeutic Efficacy of Anfibatide in a Murine Model of Thrombotic Thrombocytopenic Purpura (TTP). Blood Adv. 2016; 1:75–83. [PubMed: 28480350]

97. Callewaert F, Roodt J, Ulrichts H, Stohr T, van Rensburg WJ, Lamprecht S, Rossenu S, Priem S, Willems W, Holz JB. Evaluation of efficacy and safety of the anti-VWF Nanobody ALX-0681 in a preclinical baboon model of acquired thrombotic thrombocytopenic purpura. Blood. 2012; 120:3603–10. [PubMed: 22948047]

98. Cao WJ, Pham HP, Williams LA, Siniard RC, Lorenz RG, Marques MB, Zheng XL. Increased Plasma Levels of Human Neutrophil Peptides (HNPs) and Complement Activation Markers in Patients with Acquired Thrombotic Thrombocytopenic Purpura (TTP). Blood. 2015; 126:1147.

99. Tati R, Kristoffersson AC, Stahl AL, Rebetz J, Wang L, Licht C, Motto D, Karpman D. Complement activation associated with ADAMTS13 deficiency in human and murine thrombotic microangiopathy. J Immunol. 2013; 191:2184–93. [PubMed: 23878316]

100. Cao W, Pham HP, Williams LA, McDaniel J, Siniard RC, Lorenz RG, Marques MB, Zheng XL. Human neutrophil peptides and complement factor Bb in pathogenesis of acquired thrombotic thrombocytopenic purpura. Haematologica. 2016; 101:1319–26. [PubMed: 27662014]

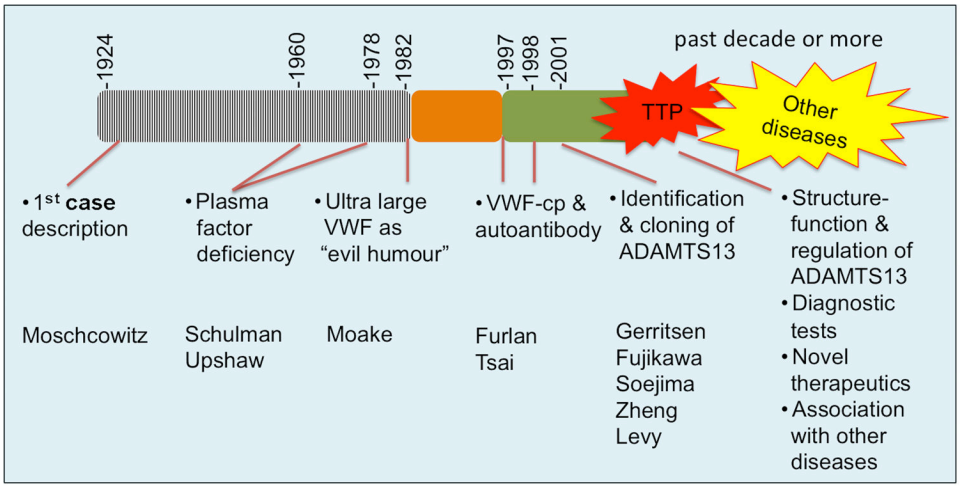

Fig. 1. Historic prospective of TTP research

Several landmark discoveries have been made since the initial case report in 1924, leading to understanding pathogenesis of TTP, basic biology of ADAMTS13 metalloprotease, and the association of ADAMTS13 abnormality with other arterial and inflammatory diseases. Here, VWF-cp denotes VWF-cleaving protease.

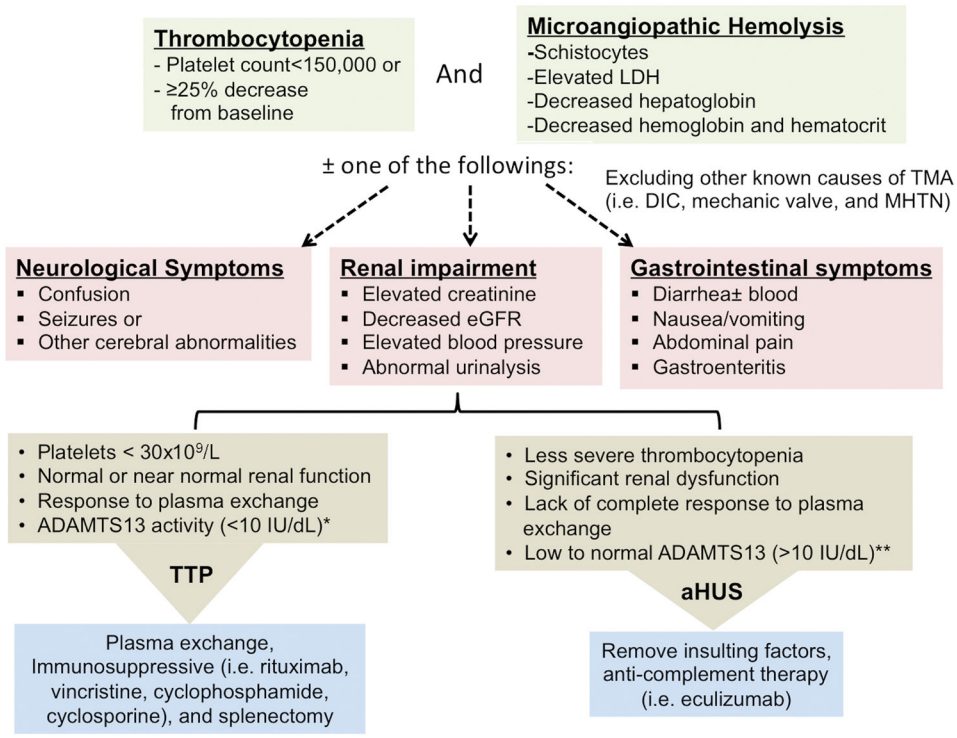

Fig. 2. Algorithm for differentiating TTP from aHUS and their therapeutic modalities

Plasma ADAMTS13 activity <10 IU/dL is the single most important test for differentiating TTP from aHUS after excluding other known causes of TMA, including disseminated intravascular coagulation (DIC), mechanic valves, and malignant hypertension (MHTN). Other clinical features including the platelet counts ($<30\times10^9$/L), degree of renal injury (creatine<2.2 mg/dL), and swift response to plasma exchange therapy are also crucial for the initial diagnosis before ADAMTS13 activity becomes available. The asterisk (*) indicates that the cut-off value may vary from laboratory to laboratory depending on the assay used. The double asterisks (**) indicate that ADAMTS13 activity in non-TTP patients is usually much higher than 10 IU/dL.

Table 1

Differential diagnosis of TTP* from other TMAs

TTP

- Hereditary TTP: Mutations in *ADAMTS13*
- Acquired TTP: Autoantibodies against ADAMTS13

HUS

- Infection-associated HUS: Shigatoxin-producing *E. Coli*, shigella, and pneumococci, etc.
- Atypical HUS: Complement activation, platelet activation, and unknown etiology

Other TMAs

- Medications-induced: Calcineurin Inhibitors
- Chemotherapy-associated: Gemcitabine, mitomycin, and anti-VEGF therapy
- Transplantation-associated: Solid organ and hematopoietic stem cell transplantation
- Malignancy-related: Disseminated breast, lung, and gastric cancers
- Infections: HIV
- Disseminated intravascular coagulation (DIC)
- Pregnancy-associated: HELLP syndrome and preeclampsia
- Malignant hypertension

* TTP, thrombotic thrombocytopenic purpura; HUS, atypical hemolytic uremic syndrome; TMAs, thrombotic microangiopathies; HIV, human immune deficiency virus; HELLP, Hemolysis, Elevated liver enzymes, and Low platelet count