

Review article

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**CURRENT DIAGNOSTIC AND TREATMENT APPROACHES IN THROMBOTIC
THROMBOCYTOPENIC PURPURA**

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a subtype of thrombotic microangiopathies which is characterized by a clinical pentad: thrombocytopenia, hemolytic anemia, renal failure, neurologic symptoms, and fever. TTP can be an acquired or congenital disorder. The aim of this paper was to summarize the available literature on contemporary diagnostic and treatment strategies in patients with TTP.

Definitive diagnosis of TTP relies on ADAMTS13 activity testing, while the PLASMIC score may guide early treatment initiation. Standard first-line therapy remains plasma exchange with corticosteroids. The addition of rituximab to the standard treatment reduces relapse and mortality rates. Caplacizumab enables rapid symptom resolution and prolonged remission. Recent studies

suggest that new emerging modalities such as gene therapy, novel monoclonal antibodies, and immunomodulators can be used successfully for the treatment of TTP.

TTP is an acute hematological emergency requiring early recognition and prompt plasma exchange with corticosteroids. Emerging targeted therapies, including rituximab, caplacizumab, and recombinant ADAMTS13, demonstrate considerable therapeutic potential, and further studies are necessary to optimize management of different TTP subtypes.

Keywords: TTP, ADAMTS13, PLASMIC score, TTP treatment

Pregledni rad

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Savremeni dijagnostički i terapijski pristupi u trombotičkoj trombocitopenijskoj purpuri

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SAŽETAK

Trombotska trombocitopenična purpura (TTP) je podtip trombotičnih mikroangiopatija, koji se karakteriše kliničkom pentadom: trombocitopenijom, hemolitičkom anemijom, bubrežnom insuficijencijom, neurološkim simptomima i povišenom temperaturom. TTP može biti stečena ili kongenitalna bolest. Cilj ovog rada bio je pregled savremenih dijagnostičkih i terapijskih strategija kod pacijenata sa TTP-om.

Definitivna dijagnoza TTP-a zasniva se na određivanju aktivnosti ADAMTS13, dok se PLASMIC skor može koristiti kao orijentir za rano započinjanje terapije. Standard prve linije lečenja i dalje predstavlja plazmafereza u kombinaciji sa kortikosteroidima, pri čemu dodatak rituksimaba smanjuje učestalost relapsa i mortalitet. Primena kaplacizumaba tokom akutne epizode omogućava brzo povlačenje simptoma i produženje remisije bolesti. Najnovija istraživanja ukazuju i na potencijalnu uspešnost novih terapijskih modaliteta, uključujući terapiju rekombinantnim ADAMTS13, savremena monoklonalna antitela i različite imunomodulatorne pristupe. TTP je akutno

hematološko stanje u kojem su rana dijagnoza i započinjanje plazmafereze u kombinaciji sa kortikosteroidima od presudnog značaja. Novi lekovi, uključujući rituksimab, kaplacizumab i rekombinantni ADAMTS13, pokazuju značajan terapijski potencijal, te su potrebna dalja istraživanja u cilju otpimizacije lečenja različitih podtipova TTP-a.

Ključne reči: TTP, ADAMTS13, PLASMIC skor, terapija TTP-a

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a subtype of thrombotic microangiopathies (TMA), a diverse category of hematological disorders. Thrombotic microangiopathies include thrombocytopenia and microangiopathic hemolytic anemia (MAHA) with the fragmentation of erythrocytes, which leads to formation of thrombi that disrupt microcirculation and cause organ dysfunction (1). Thrombocytopenia, hemolytic anemia, renal failure, neurologic symptoms, and fever are the five symptoms that most frequently define TTP. Only 10% of TTP patients, however, exhibit all five pentad symptoms. Fever occurs in fewer than 10% of patients presenting with the classic pentad, whereas thrombocytopenia and microangiopathic hemolytic anemia represent the most common clinical features (2,3).

TTP was first described in 1924 by Eli Moschowitz after a 16-year-old female patient presented with the classic clinical pentad. Originally called "Moschowitz", the term is now outdated and replaced by thrombotic thrombocytopenic purpura (4).

There are two types of TTP: immune-mediated TTP (also known as acquired TTP) and congenital TTP (2). The immune-mediated form of TTP is caused by autoantibodies (most commonly IgG type), against an enzyme called ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), whose role is to break down von Willebrand factor (vWF) multimers (5). Congenital form of TTP, also known as Upshaw-Schulman syndrome, is a rare type of TTP characterized by an inherited deficiency of ADAMTS13 (6). This type of TTP occurs significantly less often than the immune-mediated one (up to 5% patients have the congenital type), and is more common in pediatric population (2). Some medications can trigger an acute TTP episode but are rarely linked with low ADAMTS13 activity; however, ticlopidine (a platelet aggregation inhibitor), has been linked to severe ADAMTS 13 inactivity and is, therefore, considered a secondary form of immune-mediated TTP (7).

TTP is a rare disorder, with the reported annual incidence of acute immune-mediated TTP ranging from 1.81 to 3.93 cases per million population, while congenital TTP is substantially less common, with an estimated incidence of 0.19 to 0.35 cases per million annually. Pregnancy and acute infection were the most common triggers of acute TTP attack. Both the congenital and the immune-mediated form of TTP are more common in women than men, both in the adult and pediatric populations. The median age of acute immune-mediated TTP episode was between 41 and

54 years, whereas the median age of congenital TTP episode was between birth and 35 years. There is still no sufficient evidence to confirm an ethnic predisposition to TTP (8).

TTP is a life-threatening condition and a hematologic emergency. Even with prompt onset of treatment the mortality is estimated to be between 10% and 20% (2). Early diagnosis of TTP is crucial, as timely recognition significantly improves survival. However, establishing the diagnosis can be challenging since patients often do not present with all five signs of the classical pentad. Therefore, the most important diagnostic tool remains laboratory testing which, almost invariably, demonstrates hemolytic anemia and thrombocytopenia. Signs of acute renal impairment may or may not be present, while neurological manifestations and fever occur less frequently (2,3). The first-line of treatment remains therapeutic plasma exchange with or without corticosteroids. However, about 50% of patients are refractory or unresponsive to the first-line therapy. In these patients, the most effective medication is Rituximab, anti-CD20 antibody. Recent studies have shown that some new agents, such as caplacizumab (anti-vWF antibody) can be highly effective as a frontline treatment of TTP (2,3).

The aim of this review paper was to summarize the diagnostic strategies for TTP and the most up-to-date therapeutic options and clinical guidelines.

CLINICAL PRESENTATION

Diagnosing TTP is very difficult, even for experienced clinicians, as the clinical manifestations are non-specific and can easily be mistaken for another medical condition. Acute TTP episode rarely presents with all classical signs of pentad (in less than 10% of patients), with thrombocytopenia and hemolytic anemia representing the two most consistent findings (2).

The most common clinical signs at presentation are weakness, nausea, vomiting, and diarrhea (2). Viral infections, HIV, influenza, cytomegalovirus (CMV) and hepatitis C can be a potential trigger for TTP (9,10).

About 60% of patients with TTP have neurological symptomatology (2). The most common pathological neurological findings in acute TTP episode are altered sensorium, headaches, vertigo, mental disorders, focal neurological deficit, movement disorders or even an acute epileptic episode (11). More severe vision loss can arise from optic disc edema, retinal/vitreous hemorrhage (12) or,

rarely, retinal detachment in acute TTP (13). Additionally, a first-time complex migraine was reported as the initial TTP symptom (14).

Kidney impairment is a part of classic TTP pentad, although it is far more common in patients with hemolytic uremic syndrome (HUS) (15). The most common signs of renal impairment in patients with immune-mediated TTP are proteinuria and hematuria due, to formation of microthrombi in renal blood vessels. However, these symptoms are usually mild or non-severe. Hypertension, azotemia and fluid overload are very rare. More serious renal complications in patients with acquired TTP occur mostly in those who already had some pre-existing renal condition (16).

Several studies have shown that patients with congenital form of TTP have more severe forms of kidney impairment, including acute and, in later course of disease, chronic renal failure. However, it is still not fully determined why patients with congenital form of TTP have more severe kidney damage compared to those with an immune-mediated one. Recent findings suggest local ADAMTS13, possibly expressed by podocytes, cleaves glomerular vWF. Consequently, congenital TTP patients lacking this protection are more prone to diffuse glomerular thrombosis and renal failure (16,17).

Fever is the least common among the classic pentad. It is estimated that it occurs in less than 10% of patients with TTP (3).

Although it is not commonly mentioned, patients with acute TTP can develop severe cardiac problems. Symptoms can range from mild chest pain and slightly elevated troponin I levels to arrhythmias, congestive heart failure and, in rare cases, acute myocardial infarction and sudden cardiac death (2, 18). Isolated elevation of troponin I, even in the absence of cardiac symptoms, is considered a poor prognostic indicator (3).

Due to low platelets levels, patients can often present with hemorrhagic syndrome, most commonly petechial bleeding and purpura. Jaundice can be present because of hemolytic anemia (2).

LABORATORY FINDINGS

Patients usually present with a severe form of thrombocytopenia with the median platelet count of $10\text{--}17 \times 10^9/\text{L}$ at presentation. However, higher values of platelets should not immediately exclude TTP and additional blood tests should be performed (19).

Microangiopathic hemolytic anemia is, along with thrombocytopenia, the most common feature of TTP (2). Laboratory findings of these patients show typical signs of hemolytic anemia: low haptoglobin levels, elevated reticulocyte count, hyperbilirubinemia (elevation of unconjugated bilirubin), and elevation of LDH. In most cases Coombs test is negative (20). Schistocytes can be seen on blood smear as a result of erythrocyte fragmentation. Compared to other TMAs, schistocytes are more frequently observed in patients with TTP (2). Coagulation tests are usually normal or, in some patients, slightly altered, which helps distinguish TTP from other conditions, especially disseminated intravascular coagulation (DIC) (2, 20).

As mentioned above, azotemia is not a common finding in TTP (16). Mean levels of creatinine in immune-mediated TTP are 1.09- 1.3 mg/dL (21). Troponin I can be elevated in some patients with TTP and, in the absence of other cardiac symptoms, is considered a bad prognostic sign (3).

TTP DIAGNOSIS

Correct identification of clinical signs and laboratory abnormalities offers strong evidence supporting the diagnosis of TTP, but confirmation of decreased ADAMTS13 activity is essential for confirming the diagnosis. However, many healthcare facilities do not have an easy access to ADAMTS13 assays and even when these tests are available, it takes several days to receive results, which impedes prompt and appropriate treatment (22). Therefore, several scoring systems that are based on clinical and laboratory findings have been developed in order to predict low ADAMTS13 activity and initiate proper treatment. Even in those centers where ADAMTS13 testing is easily and promptly accessible, it is advisable to use these scoring systems to predict the probability of positive TTP diagnosis and initiate plasma exchange therapy while awaiting the test results (21).

The most commonly used scoring tool for predicting the possibility of TTP is the PLASMIC score. It was developed by Bendapudi and colleagues in 2017 (23,24). Platelet count, hemolysis, history of solid organ malignancy or stem cell transplant, mean corpuscular volume (MCV), international normalized ratio (INR), and creatinine values are all part of the PLASMIC score (Table

1) for TTP prediction (22,24). Patients can score 0 to 7 points on the PLAMISC score. Any patient with a PLASMIC score of 5 or above should receive empirical treatment for TTP, unless an alternative diagnosis better explains the clinical presentation (22). A systematic review and meta-analysis done by Paydary and colleagues showed that PLASMIC score ≥ 5 has a sensitivity of 99% and specificity of 57%, whereas PLASMIC score ≥ 6 has a sensitivity of 85% and specificity of 89% (25).

Table 1 PLASMIC score (22,24)

Parameter	Points
Platelet count $<30 \times 10^9/L$	1
Signs of hemolysis (haptoglobin low or undetectable, reticulocyte count $>2.5\%$, or indirect bilirubin >2.0 mg/dL)	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1.5	1
Creatinine <2.0 mg/dL	1
Interpretation of the results: 0-4: Low risk for severe ADAMTS-13 deficiency. 5: Intermediate risk for severe ADAMTS-13 deficiency. 6-7: High risk for severe ADAMTS-13 deficiency.	

INR: international normalized ratio; MCV: mean corpuscular volume

Another score which can be used to predict the probability of TTP is the French score (21). Classic French score has three parameters: platelet count $<30 \times 10^9/L$, serum creatinine <2.26 mg/dL and positive antinuclear antibodies (ANA) but the modified score, which comprises two components that include only the platelet count and serum creatinine, is used more frequently

(21). A cross-sectional analysis done by Coppo and colleagues showed that French score ≥ 1 has a sensitivity of 98.8% and specificity of 48.1% (26). Numerous studies have demonstrated a clear advantage of the PLASMIC scoring system over the French scoring system (21).

A definitive diagnosis of TTP is made by confirming decreased ADAMTS13 activity by using ADAMTS13 activity assays. Based on the method of detection, assays can be direct or indirect. Direct assays measure the cleavage product, whereas indirect assays measure the residual VWF (19). The activity of ADAMTS13 which is less than 10%, in the presence of thrombocytopenia and hemolytic anemia, confirms the diagnosis of TTP. However, it is important to note that low ADAMTS13 activity can also be found in patients with other pathological conditions, such as sepsis. After the initial recovery, if the activity of ADAMTS13 is less than 20%, even in the absence of thrombocytopenia and hemolytic anemia, it is considered that the patient has a relapse of the disease (3). A practical diagnostic approach for patients with suspected TTP is summarized in Figure 1.

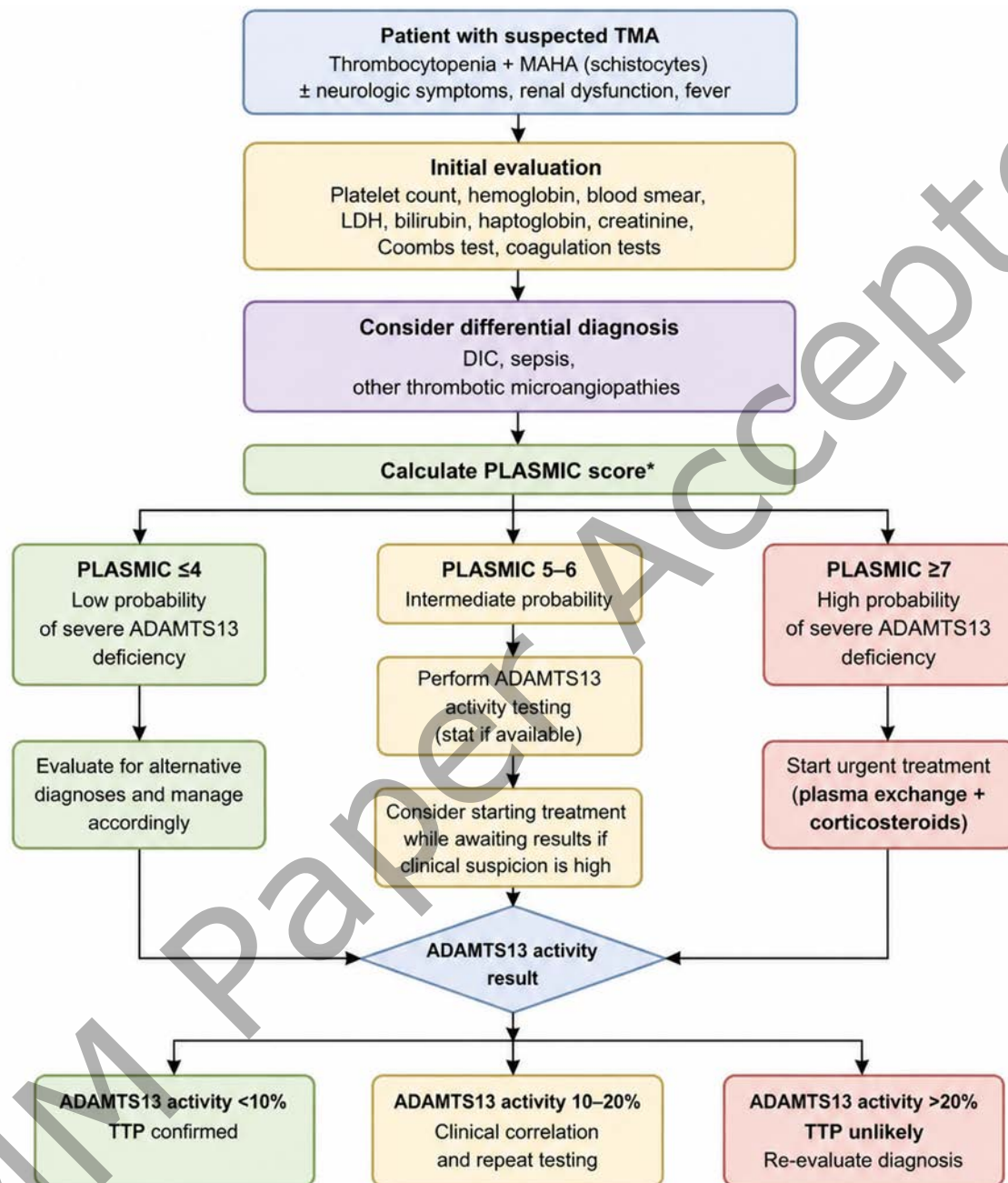


Figure 1 Proposed diagnostic algorithm for evaluation and early management of suspected thrombotic thrombocytopenic purpura (1,2,3,19,20,21,22,23,24)

Bone marrow biopsy is rarely done in patients with suspected TTP. If done, it usually shows standard trilineage maturation (3).

DIFFERENTIAL DIAGNOSIS

The key element in the differential diagnosis of TTP is distinguishing it from HUS. Both TTP and HUS are thrombotic microangiopathies and were once considered to be two entities of the same disorder. One of the main differences between HUS and TTP is their etiology (3). TTP is caused by low activity of ADAMTS13, whereas HUS is most commonly caused by an infection in which Shiga toxin is produced (so called STEC HUS). The most common infectious agents which can cause HUS are the enterohemorrhagic *Escherichia coli* serotypes. Less frequently, HUS may result from *Shigella* infection, while *Streptococcus pneumoniae* infection represents the least common cause. However, HUS caused by *Streptococcus pneumoniae* infection has the most aggressive clinical presentation. Approximately 5-10% cases of HUS are not caused by Shiga toxin. This type of HUS is called atypical HUS (aHUS) and has a less favorable clinical outcome. The main pathophysiological mechanism of aHUS is thought to be uncontrolled activation of the alternative complement pathway (27). Unlike TTP, which is defined as a pentad of symptoms, HUS is characterized by a triad consisting of thrombocytopenia, hemolytic anemia and acute kidney injury (28).

Typically, HUS is a pediatric condition and it mostly occurs in children younger than 5 years. In contrast, TTP is extremely rare in children. Atypical HUS is, however, more common in adults, whereas only 5–10% of cases have been reported in children (27). In these cases, it can be difficult to differentiate HUS from TTP. Laboratory findings are mostly the same in HUS and TTP due to the fact that both conditions are characterized by thrombocytopenia and hemolytic anemia. However, acute kidney injury is much more severe in HUS compared to TTP with higher levels of azote products and severe kidney injury symptoms. Neurological symptomatology is, on the other hand, rarely present in HUS (3, 28). In cases of STEC HUS, hemorrhagic enterocolitis commonly precedes the development of the acute HUS episode within a 2–12 day period. In approximately 44-61% of patients with aHUS, there is an underlying genetic mutation of one or more complement regulatory proteins. The mutations most commonly associated with aHUS are those affecting the genes encoding membrane cofactor protein, factor I, factor H, and diacylglycerol kinase ϵ . (28). Regardless of the HUS variant, ADAMTS13 activity testing remains essential for a

definitive differential diagnosis from TTP. When a clear distinction cannot be made, therapeutic plasma exchange should be initiated in patients with a high clinical suspicion of TTP after blood sampling for ADAMTS13 testing, without waiting for test results (2,3).

The differential diagnosis of TTP also includes idiopathic thrombocytopenic purpura (ITP) and disseminated intravascular coagulation (DIC). Whereas symptoms between these conditions can overlap, laboratory findings are essential for distinguishing TTP from ITP and DIC. In DIC schistocytes are rarely present whereas; however, unlike in TTP, coagulation tests are impaired. Although in both ITP and TTP coagulation tests are relatively normal, ITP rarely presents with hemolytic anemia and acute kidney injury (2,3).

TREATMENT OF TTP

As aforementioned, TTP is an acute and life-threatening condition which requires immediate treatment. When a patient has both clinical and laboratory signs of TTP and the PLASMIC score is 5 or higher, prompt initiation of appropriate therapy is mandatory, with a blood sample for ADAMTS13 activity obtained beforehand. Although there are differences in how TTP is treated in the later course of the disorder depending on whether it is an immune-mediated or congenital type, the initial management is the same for both types and it includes plasma exchange therapy (2,3,7,22).

IMMUNE-MEDIATED TTP

The first-line treatment for immune-mediated TTP is therapeutic plasma exchange (TPE) with fresh frozen plasma (7). The mechanism of TPE is based on the removal of vWF multimers and inhibitors/proteolytic inactivators of ADAMTS13 (autoantibodies, IL-6, granulocyte elastase), as well as replenishment of ADAMTS13 (29). Delayed initiation of TPE significantly increases the risk of fatal outcome. Standard practice involves exchanging 1–1.5 plasma volumes per day for the first three days, then subsequently continuing with daily exchanges of one plasma volume. TPE should be continued everyday until clinical response has been attained and sustained for two consecutive days (clinical response has been defined as normalization of the platelets above $150 \times 10^9/L$ as well as normalization of the LDH levels to less than $1.5 \times$ the upper limit of normal values). In cases of refractory form of TTP, doing TPE twice a day can be considered (refractory form of TTP is considered when platelets are constantly less than $50 \times 10^9/L$, with LDH persistently $1.5 \times$ the upper limit of normal, in spite of five plasma exchange treatments along with corticosteroids) (7).

Current recommendations suggest that corticosteroids should always be given in acute TTP episode alongside TPE. The recommended corticosteroid regimen typically involves prednisone at 1 mg/kg/day or an equivalent corticosteroid dose. In severe forms of TTP, higher doses of corticosteroids can be used, usually methylprednisolone, 1 g/day for 3 days (30). Several studies have shown that corticosteroids reduce the number of TPE, enhance the probability of achieving complete remission, and reduce the risk of TPE-related adverse events. The overall beneficial therapeutic effect of corticosteroids in TTP is based on their immunosuppressive properties (2,3,30).

Rituximab, an anti-CD20 antibody, has proven to be highly effective in the management of acute TTP episode which is unresponsive to the first-line treatment (2). A phase 2 study of the safety and efficacy of rituximab conducted by Scully and colleagues (31) showed that addition of rituximab to corticosteroids and TPE significantly reduces the number of inpatient days, as well as the chances of the future relapse. There was also a not so significant difference in the number of TPE needed to achieve a complete response in favor of those receiving rituximab. This study also showed that the use of rituximab in acute TTP episode is rather safe and well-tolerated. These beneficial effects of rituximab are based on its ability to reduce the production of anti-ADAMTS13 IgG antibodies and increase the activity of ADAMTS13 (31). A systematic review and meta-analysis done by Owattanapanich and colleagues (32) confirmed the previous data of rituximab efficacy in the treatment of acute TTP episode and showed that, in addition to reducing the relapse rate, rituximab also significantly reduces the mortality rate (32). Rituximab is usually given during the first few days of hospitalization. The recommended dose of Rituximab is 375 mg/m² for four weeks in both initial immune-mediated TTP episodes and the acute phase of relapsed episodes (7).

Caplacizumab, an anti-von Willebrand factor humanized, bivalent variable-domain-only immunoglobulin fragment, which inhibits the interaction between platelets and von Willebrand factor multimers, was approved for the treatment of acute TTP, alongside TPE and corticosteroids, in 2019 by FDA (Food and Drug Administration) (3,7). The drug was approved for TTP as a result of phase 3 HERCULES trial (33) and phase 2 TITAN trial (34). The phase 3 of HERCULES trial showed that the addition of caplacizumab to the standard first-line treatment reduces relapse rate, as well as the rate of TTP-related mortality, promotes rapid normalization of platelets, and lowers a chance of thromboembolic events during the treatment period (33). The results of phase 2 of TITAN trial

showed similar results; caplacizumab was associated with faster resolution of the acute TTP episode compared to placebo (34). Both studies showed that the medication is relatively safe and well-tolerated and that the most common adverse effect was bleeding, ranging from mild to moderate in severity (33,34). It should be noted that caplacizumab acts by preventing the formation of microthrombi; however, it lacks immunosuppressive properties and, consequently, does not prevent the production of autoantibodies against ADAMTS13. The drug should, therefore, not be discontinued until ADAMTS13 activity rises above 20% (3,7). The usual dosage of caplacizumab in TTP is 10 mg given intravenously before the first TPE, followed by 10 mg given subcutaneously daily, typically for 30 days after the discontinuation of TPE (3,7).

Although therapeutic plasma exchange remains the cornerstone of acute immune-mediated TTP management, outcomes have significantly improved with adjunctive immunosuppressive and targeted therapies (2,3,7). Rituximab is primarily used for immunosuppression and relapse prevention, whereas caplacizumab provides rapid protection against ongoing microvascular thrombosis and improves short-term outcomes. Therefore, these agents provide complementary therapeutic benefits and are increasingly used in combination with TPE as part of the standard management of acute immune-mediated TTP. However, important differences exist in the strength of supporting evidence and clinical limitations. Caplacizumab is supported by randomized clinical trials demonstrating faster platelet recovery and reduced TTP-related events; however, its use is associated with an increased risk of mostly mild bleeding, which may limit its broader clinical application. In contrast, evidence supporting rituximab is largely derived from observational and cohort studies, with its main benefit appearing to be relapse prevention rather than rapid resolution of acute episodes (2,3,7,31,33,34).

Multiple studies have mentioned other medications that may demonstrate effectiveness in the management of TTP. N-Acetylcysteine, an antioxidant, lowers mucus viscosity by disrupting the disulfide linkages between mucin multimers. N-Acetylcysteine has been shown to possess the ability to promptly break down large vWF multimers, as they share a striking structural similarity with mucin (35). A study conducted by Español and colleagues (35) showed that the addition of N-acetylcysteine to TPE and corticosteroids at a dose of 150 mg/kg/day led to a faster clinical response, as well as that the medication was well tolerated. The limitations of this study were, however, a small number of participants as well as the fact that eight of those patients were also

receiving rituximab (35). Another study, conducted by Beyler and Demir, which included four patients with refractory form of TTP, showed that addition of N-acetylcysteine to TPE and corticosteroids can lead to a positive treatment outcome (36). However, all these studies were based on a relatively small number of participants and there still hasn't been enough information about the safety profile of the drug (7).

Recent studies have been focused on the potential use of a novel DNA anti-VWF A1 aptamer, TAGX-0004. This drug has been shown to have a much stronger ability to inhibit botrocetin or ristocetin-induced platelet agglutination/aggregation compared to its predecessor ARC1779 (7). A study conducted by Sakai and colleagues (37) compared the efficacy of TAGX-0004 and caplacizumab and showed that TAGX-0004 holds greater pharmacological characteristics and that it could be a more potent drug than caplacizumab in the treatment of immune-mediated TTP. However, these are only preliminary findings and there is a need for more research concerning this topic (37).

Other medications which could be given to patients with TTP are certain antineoplastic drugs such as cyclophosphamide, cyclosporine and vincristine (38,39). Several studies have shown that bortezomib, a proteasome inhibitor, can induce remission in relapse/refractory TTP patients, potentially by diminishing ADAMTS13 autoantibodies. The dosage is usually the same as the one in multiple myeloma: 1.3 mg/m² on days 1, 4, 8, 11 repeated every 21 days (38). More recently, daratumumab has demonstrated encouraging outcomes in refractory TTP, most likely by reducing ADAMTS13 inhibitors and suppressing autoantibody-producing plasma cells (40,41). Few studies indicated a potential use of mycophenolate mofetil in relapse/refractory TTP (7).

Splenectomy remains an option of last resort, restricted to severe relapsed/refractory TTP that does not respond to any previously applied treatment. This intervention is associated with an increased risk of adverse events, occurring both intra- and postoperatively (38).

Although fresh frozen plasma transfusions are not contraindicated in TTP, their use as a sole therapy in the absence of prompt TPE is not recommended. Adverse effects of platelet transfusion in TTP patients have been documented in several studies; therefore these transfusions should be limited to situations where there is a substantial risk of bleeding (2). A practical treatment algorithm for acute immune-mediated TTP is summarized in Figure 2.

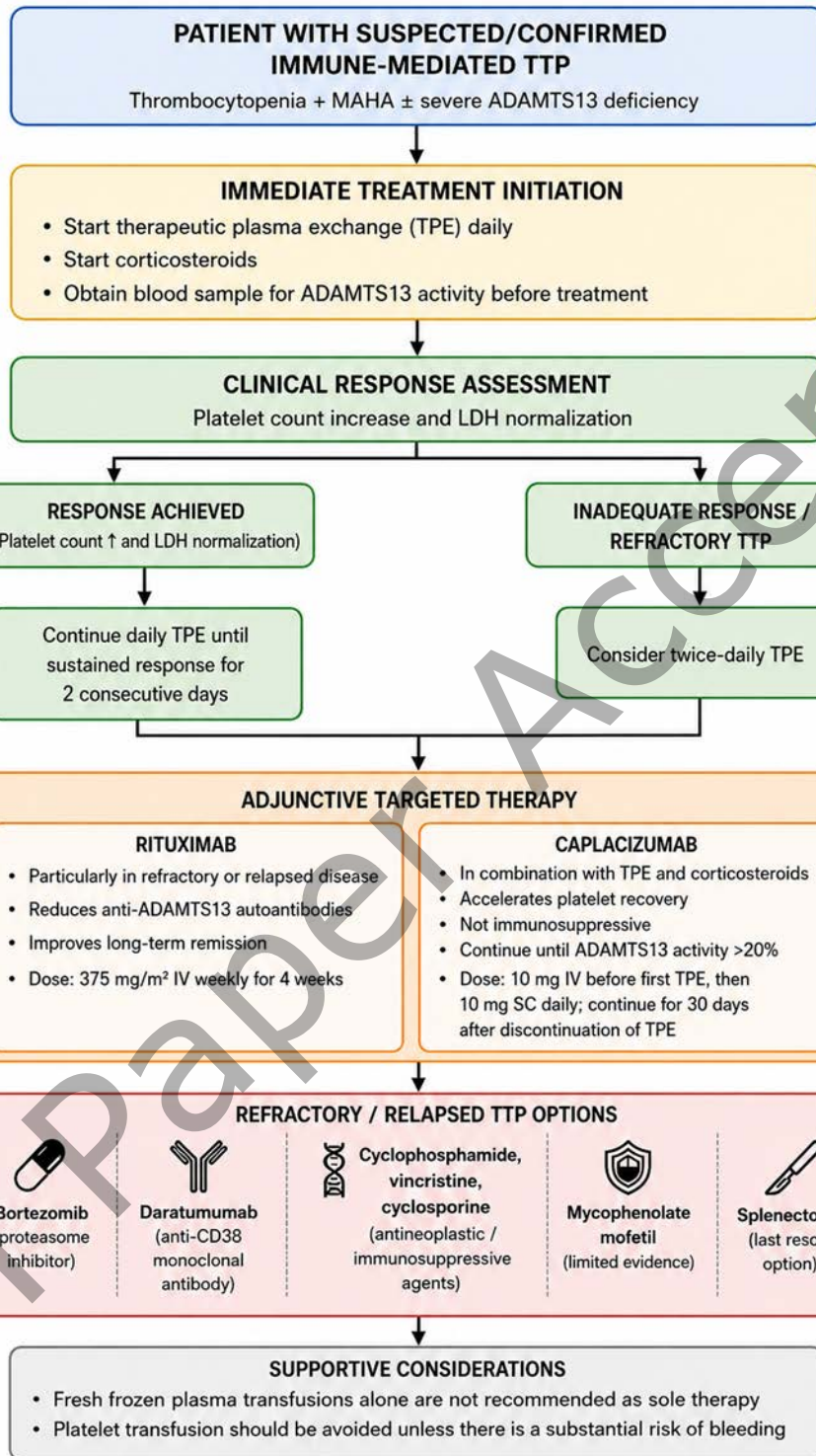


Figure 2 Treatment algorithm for acute immune-mediated TTP
(2,3,7,22,30,31,32,33,34,38,39,40)

CONGENITAL TTP

As aforementioned, treatment of an acute episode of both immune-mediated and congenital form of TTP is based on TPE. However, patients with congenital form of TTP can also be treated with fresh frozen plasma transfusions, usually 10–15 mL/kg/day until achieving complete response. Patients with congenital TTP who have experienced more than one attack are also advised to receive prophylactic fresh frozen plasma transfusions, typically 10–15 mL/kg every 2–3 weeks (7).

Patients with congenital form of TTP who are, for some reason, unable to receive fresh frozen plasma should be treated with some alternative treatment, such as caplacizumab or recombinant ADAMTS13 (42). Although a US cohort study (43) and a UK study (44) have reported on the potential success of using FVIII in the treatment of congenital TTP, the current ISTH TTP guidelines (45) advise against its use in congenital TTP because of its low ADAMTS13 levels and insufficient evidence regarding the safety and efficacy of this treatment (42). Caplacizumab is thought to be effective in the treatment of congenital TTP, although more research is needed about its use for this purpose (42). In 2023, FDA approved the use of recombinant form of ADAMTS13 for the treatment of pediatric and adult patients with congenital TTP as a result of phase 3, open-label, crossover trial (46). In this study, patients with congenital TTP received alternating 6-month periods of prophylaxis with recombinant ADAMTS13 or standard therapy, followed by an additional 6 months of recombinant ADAMTS13. The results showed that patients who received prophylaxis with recombinant ADAMTS13 achieved almost normal levels of ADAMTS13 activity. Adverse reactions were mostly mild (headache, dizziness, nausea) and did not require premature discontinuation of therapy. For prophylaxis, recombinant ADAMTS13 is typically administered at 40 IU/kg intravenously every two weeks. In acute episodes, the regimen consists of 40 IU/kg on day 1, 20 IU/kg on day 2, and 15 IU/kg every other day from day 3 until resolution of symptoms, continued for two additional days (46). A study done by Bendapudi and colleagues (47) suggested that recombinant human ADAMTS13 could also be used in the treatment of acute episode of immune-mediated TTP. In this study, critically ill patients with refractory form of immune-mediated TTP received recombinant human ADAMTS13 and achieved a complete recovery (47). Nevertheless, additional studies are needed in this area.

TTP IN PREGNANCY

TTP in pregnant women is a rare condition with a very high mortality rate. Pregnancy can be a trigger for an acute TTP episode in women with congenital TTP (7). Diagnosis of TTP in pregnancy is difficult since its presentation can mimic other pathological conditions which occur in pregnancy, such as HELLP syndrome and preeclampsia. As in the non-pregnant population, prompt diagnosis and treatment are essential to improve survival chances (2,3,48). The effectiveness of the PLAMIS score in prediction of TTP in pregnant women has still not been confirmed. The final diagnosis, again, relies on the confirmation of the low ADAMTS13 activity. It should be noted, however, that even in healthy pregnant women levels of ADAMTS13 can decrease, due to the fact that pregnancy itself is a procoagulant condition, with activity sometimes dropping to as low as 25–30% (48).

It's critical to distinguish TTP from HELLP syndrome and preeclampsia in differential diagnosis. During pregnancy, TTP typically arises in the third trimester or more than 72 hours after giving birth, but it is also notably the sole thrombotic microangiopathy that can develop in the first trimester. The primary symptoms are mainly neurological, and platelet count is usually below $30 \times 10^9/L$, accompanied by increased LDH levels and comparatively normal creatinine levels (<1.1 mg/dL) (49). HELLP syndrome rarely occurs before the 20th gestational week or more than 72 hours after the delivery. The primary symptoms are disturbances in the vision and jaundice, and there is an evident increase in the level of transaminases. Preeclampsia also rarely occurs before the 20th gestational week or more than 72 hours after giving birth, and the dominant signs are new-onset hypertension and the occurrence of peripheral edema (49).

The treatment of an acute TTP episode in pregnancy again involves TPE in combination with corticosteroids (7,48). Although corticosteroids may be potentially harmful if given in the first trimester, benefits of this treatment outweigh the risk (7). The use of rituximab in pregnant women is still not recommended due to the lack of data on its safety profile (49). Caplacizumab is contraindicated in the treatment of TTP in pregnancy due to a high risk of fetal hemorrhage (7).

In women who are diagnosed with congenital TTP prior to pregnancy, ISTH guidelines advice prophylactic treatment with plasma infusion during pregnancy to prevent an acute TTP episode (45). Women who had a previous episode of immune-mediated TTP and want to get pregnant in the future should have their level of ADAMTS13 monitored regularly (7). The ISTH

guidelines recommend prophylaxis in pregnant women with a history of immune-mediated TTP; however, they do not specify the type of treatment (e.g., immunosuppression or plasma transfusion) (45).

LIMITATIONS OF THE STUDY

This review paper has several limitations. First, the field of thrombotic thrombocytopenic purpura is changing rapidly, especially with new diagnostic algorithms and emerging treatments, such as monoclonal antibodies, which may result in certain information becoming outdated over time. Second, the studies included in this review vary widely in their design and quality, which affects the applicability of the conclusions. Last, as a narrative review, this paper does not present a meta-analytic synthesis, and its conclusions rely upon the accuracy and methodological rigor of previously published research.

CONCLUSION

TTP is an acute hematological emergency in which early recognition, supported by the PLASMIC score and ADAMTS13 testing, is crucial to ensure prompt initiation of therapy. The current standard of care involves urgent plasma exchange combined with corticosteroid therapy, which remains the cornerstone for inducing remission. Targeted agents, including rituximab and caplacizumab, have further improved outcomes, particularly in relapsed/refractory cases. Future studies should focus on evaluating the clinical efficacy and safety of novel targeted therapies in TTP. This includes the use of novel agents such as anti-vWF A1 aptamers and further exploration of emerging monoclonal antibodies such as daratumumab. Further studies are needed to explore the pharmacological properties of recombinant ADAMTS13 in congenital TTP and assess its potential role in the immune-mediated TTP. Additionally, investigations into adjunctive therapies, including N-acetylcysteine, may provide new insights into improving outcomes. Larger, well-designed clinical trials are needed to validate these approaches and to optimize treatment strategies for different TTP subtypes.

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