

# Update on Thrombotic Thrombocytopenic Purpura

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**Abstract:** Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy, which is classically associated with signs and symptoms of fever, thrombocytopenia, neurologic deficits, hemolytic anemia, and renal failure. It is caused by a deficiency of A Disintegrin-like And Metalloprotease with a Thrombospondin type1 motif 13 (ADAMTS13), which may be an inherited disorder, but more commonly is an acquired disease due to autoantibodies directed against ADAMTS13. Low ADAMTS13 levels result in increased ultra-large von Willebrand factor multimers, which induce platelet adhesion and thrombosis. Plasma exchange therapy is the standard of care, and has greatly reduced morbidity and mortality. A recent TTP case is reviewed, and treatments for recurrent or refractory TTP are summarized. A scoring system using clinical and laboratory parameters to evaluate which suspected TTP patients will benefit from plasma exchange therapy is also discussed.

## Introduction

Thrombotic thrombocytopenic purpura (TTP) is a microangiopathic disorder, which has become remarkably better understood over the last 3 decades. This disease, with a nearly 90% mortality rate when left untreated, is now managed with great success and typically without long-term sequela.<sup>1</sup> There are approximately 2–7 cases per million person years, with cases occurring more frequently in females, with nearly a 2:1 female:male ratio.<sup>2,3</sup> Most patients are 20–60 years of age. There is no seasonal distribution, but viral infections, pregnancy, obesity, African-American race, and drugs, such as clopidogrel, are risk factors.<sup>2,3</sup>

## Cases

The first case of TTP was described in 1925 by Eli Moschcowitz at Beth Israel Hospital in New York City.<sup>4</sup> A 16-year-old female presented with fever, pallor, and upper extremity weakness. She was found to have anemia and proteinuria, but her blood urea nitrogen (BUN) and creatinine levels were normal. A platelet count was not

### Keywords

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performed. On hospital day 5, she developed left-sided paresis, and her mental status deteriorated. The next day, she became comatose and died. Autopsy revealed hyaline casts in the terminal arterioles, and capillaries of the heart and kidneys. Moschowitz concluded that death “resulted from some powerful poison which had both agglutinative and hemolytic properties.”

### A Recent Case

A 28-year-old, gravida 2, para 1 female with a 36.5-week gestational pregnancy was transferred from an outside facility for suspected recurrent TTP, with a platelet count of 14,000/ $\mu$ L on admission. She reported a history of TTP with her previous pregnancy, which required several weeks of plasma exchange prior to a Cesarean section delivery in 2008. She had taken 30-mg prednisone orally, once daily for several months. On admission, she had no neurologic complaints, was afebrile, and had a petechial rash on the medial malleoli bilaterally with no other signs of gross hemorrhage. She presented with a lactate dehydrogenase (LDH) of 2,186 U/L, hematocrit of 25.8%, reticulocyte count of 3.9%, BUN of 16 mg/dL, creatinine of 0.74 mg/dL, urine protein of 100 mg/day, D-dimer of 1.7  $\mu$ g/mL, and indirect bilirubin of 1.7 mg/dL. Schistocytes were present on the peripheral blood smear, and a direct Coombs test was negative. Plasma exchange (PE) therapy with fresh frozen plasma (FFP) was started while an ADAMTS13 level was pending, which returned later as less than 5% of normal activity. Prednisone dosing was increased to 80 mg orally, twice daily, and the patient received packed red blood cell transfusions to maintain her hematocrit above 25% due to oxygen requirements of the fetus. On day 5, the platelet count increased to 35,000/ $\mu$ L, and a Cesarean section delivery was performed without complications to the mother or child. By day 10, despite daily plasma exchange, the platelet count and LDH had not normalized, and a laparoscopic splenectomy was performed. On day 13, a 4-cycle course of weekly intravenous rituximab (Rituxan, Genentech) 375 mg/m<sup>2</sup> infusions was started. On day 25, platelet count and LDH normalized, and she received 2 more days of plasma exchange and was discharged home. Her creatinine remained below 1.25 mg/dL throughout the hospitalization. She received 4 cycles of rituximab, and a prednisone taper was completed over a 9-week period.

## Diagnosis

When evaluating patients for possible TTP, the differential diagnosis should include all causes of thrombotic microangiopathies (TMAs). These disorders all have features of consumptive thrombocytopenia, along with microangiopathic hemolytic anemia and thrombosis.

**Table 1.** Classification of Thrombotic Microangiopathies

Renal Failure Uncommon	Renal Failure Common
<ul style="list-style-type: none"> <li>• TTP</li> <li>• Upshaw-Shulman syndrome</li> <li>• Disseminated cancer</li> <li>• HELLP syndrome</li> <li>• Prosthetic heart valve</li> </ul>	<ul style="list-style-type: none"> <li>• Typical HUS               <ul style="list-style-type: none"> <li>– Enterotoxin or Shiga-like toxin-related</li> </ul> </li> <li>• Atypical HUS               <ul style="list-style-type: none"> <li>– Deficiencies of complement factor H, factor I, factor B, or membrane cofactor protein</li> </ul> </li> <li>• DIC               <ul style="list-style-type: none"> <li>– Bone marrow transplant/solid organ transplant</li> </ul> </li> <li>• Drugs               <ul style="list-style-type: none"> <li>– Chemotherapy, quinine, calcineurin inhibitors</li> </ul> </li> <li>• Malignant hypertension</li> </ul>

DIC=disseminated intravascular coagulopathy; HELLP=hemolytic anemia, elevated liver enzymes, and low platelet count; HUS=hemolytic uremic syndrome; TTP=thrombotic thrombocytopenic purpura.

Adapted from Tsai HM. Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and related disorders. In: Greer JP, Foerster J, Rodgers GM, et al, eds. *Wintroub's Clinical Hematology*. 12th ed. Philadelphia, PA: Lippincott, Williams, and Wilkins; 2009;1314-1325.

Table 1 summarizes TMAs classified by the presence or absence of renal failure.

The classical presentation of TTP is a pentad of fever, hemolytic anemia, thrombocytopenia, renal failure, and neurologic symptoms.<sup>5,6</sup> Fever and hemolytic anemia are the most common symptoms, seen in nearly 98% of cases. Coagulation studies and bone marrow biopsy are typically normal; urine sediment changes are present, but renal function is typically normal or only mildly abnormal. The microangiopathic hemolytic anemia will result in elevated LDH and indirect bilirubin values, and schistocytes will be present on peripheral blood smear. On histopathology, hyaline thrombi are present in the terminal arterioles and capillaries, most commonly in the brain, heart, spleen, kidneys, pancreas, and adrenals. Despite these findings, there are no set criteria for the diagnosis of TTP; it remains a clinical diagnosis. Case report studies in the 1960s to early 1980s found that although only 51% of patients present with the classic pentad of symptoms, 68% will have hemolytic anemia, thrombocytopenia, and neurologic deficits.<sup>6</sup> Therefore, TTP must be included in the differential diagnosis of patients with these 3 signs and symptoms, which are not clearly explained by another etiology.

## Pathophysiology

In just the last 10 years, we have gained a remarkably better understanding of the pathophysiology of TTP, regarding a metalloprotease's role in normal hemostasis. TTP is a state of dysfunction or deficiency in von Willebrand factor (vWF)-cleaving protease, identified as A Disintegrin-like And Metalloprotease with a ThromboSpondin type1 motif 13 (ADAMTS13). Plasma vWF is secreted by endothelial cells (EC), as well as stored in ECs in Weibel-Palade bodies and in platelet granules. Its role is to mediate platelet adhesion and initiate thrombosis at sites of vascular injury. vWF is secreted as a polymeric protein consisting of multimers, with some measuring up to  $20 \times 10^6$  Da, and the largest multimers are most effective in promoting platelet adhesion by binding to the platelet glycoprotein Ib $\alpha$ -IX-V surface receptors.<sup>7</sup> ADAMTS13 cleaves the ultra-large multimers, preventing inappropriate platelet adhesion and thrombosis.<sup>8,9</sup> UL-vWF secretion from ECs is stimulated by inflammatory cytokines (tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], interleukin [IL]-8 and IL-6), Shiga toxin, estrogen, and other agonists.<sup>10</sup>

In 1998, 2 investigator groups identified this vWF-cleaving protease as having low activity during acute TTP, but noted that activity levels normalized after resolution of disease.<sup>11-13</sup> They hypothesized that an immunoglobulin G autoantibody against the metalloprotease was the etiology of TTP. More recent studies have found that absence of ADAMTS13 activity is 89% sensitive and 100% specific for a diagnosis of acute TTP.<sup>14</sup> Lower ADAMTS13 activity levels (approximately 50% of normal) may be seen in pregnant women and in newborns and in patients with disorders such as liver disease, disseminated malignancy, chronic metabolic and inflammatory disorders, and malignant hypertension.<sup>15,16</sup> TTP is typically associated with levels of less than 5% of normal, but levels this low have been reported in cases of sepsis.<sup>17</sup> Thus, ADAMTS13 activity levels in the appropriate clinical circumstances can be diagnostic of TTP. Demonstration of the presence of an ADAMTS13 inhibitor is a confirmatory test for acquired TTP.

Although most cases of adult TTP are acquired and due to antibodies to ADAMTS13, inherited TTP (Upshaw-Schülman syndrome) is an inherited ADAMTS13 deficiency due to frameshift and point mutations in the ADAMTS13 gene located on chromosome 9q34.<sup>18-22</sup> It may be seen in children and teens. Inherited TTP typically has a mild phenotype, but can progress to acute TTP in situations when high levels of vWF are present, such as during infections or pregnancy. It is suspected that less than 1% of acute TTP cases are due to Upshaw-Schülman syndrome.<sup>23</sup> Inherited TTP patients are typically treated with FFP infusions every 2–3 weeks to maintain ADAMTS13 levels.<sup>10</sup>

## Treatment of Adult TTP

Although acquired TTP is usually fatal when untreated, there are now good survival rates of 80–90%, and patients often have complete recovery with current treatments.<sup>10,24</sup> Plasma exchange with large volume infusion of FFP has been the standard of care since the early 1990s.<sup>25</sup> PE is effective because it removes the anti-ADAMTS13 antibodies and inflammatory cytokines through plasmapheresis, while FFP infusions replete the levels of ADAMTS13. FFP should be administered as soon as TTP is suspected as the most likely disorder, even before PE is arranged. PE of approximately 3 liters (or one plasma volume) should occur daily until 2 days after platelet counts, LDH, and bilirubin values have normalized. High-dose steroids are also frequently used as an adjunct therapy.<sup>26</sup> Steroids should be tapered slowly, as recurrence may occur with rapid taper. In recurrent or refractory TTP, which occurs in 20–30% of cases,<sup>25,27</sup> treatment options include plasma exchange with splenectomy, rituximab, and other immunosuppressive therapies.<sup>10,13,26</sup> Novel approaches to treatment of TTP include infusions of recombinant ADAMTS13 (a possible future therapy), and new drugs that bind to vWF.<sup>28</sup> ARC 1779 is an aptamer that binds to vWF and inhibits vWF-dependent platelet function; it has been approved for recurrent or refractory TTP.<sup>29,30</sup> It is being tested as an adjunctive therapy with PE.<sup>31</sup>

The major dilemma that occurs with TMA patients is identifying which patients should receive PE therapy, since this treatment is only effective in TTP and atypical-hemolytic uremic syndrome (a-HUS), and not in other microangiopathies. One retrospective study performed by our group evaluated clinical and laboratory features of suspected TMA patients at presentation by using a modified scoring system to determine which patients were most likely to benefit from PE.<sup>32</sup> This study involved a chart review of 110 cases of clinically-suspected TTP patients in whom an ADAMTS13 level was ordered, at 2 medical centers from 2005–2009. Multivariate logistic regression was used to identify variables predictive of low ADAMTS13 activity, and receiver operator characteristic curves were generated using both individual predictors and combinations of predictors. Analysis of 11 categorical and 16 continuous variables identified 4 statistically significant laboratory variables, including elevated indirect bilirubin values and reticulocyte percentage, thrombocytopenia, and normal creatinine levels. D-dimer was just outside of significance, but was included in a scoring algorithm (Table 2). It was concluded that PE could safely be deferred in patients with ADAMTS13 levels higher than 15% and a TTP prediction score of less than 20 points.

Unexpected findings in this study included the degree of thrombocytopenia with platelet counts less than 35,000/ $\mu$ L, and that normal to just mildly elevated renal

**Table 2.** Clinical Prediction Score to Identify TMA Patients Likely to Respond to Plasma Exchange

Variable	Assigned Points
Creatinine >2.0 mg/dL	-11.5
Platelet count >35,000/dL	-30
D-dimer >4.0 mcg/mL	-10
Reticulocytes >3%	21
Indirect bilirubin >1.5mg/dL	20.5

Total Score by Model (Points)	Probability of TTP (%)
<20	0
20–30	40
>30	100

TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura

Note: Laboratory results are assessed on patient admission. Points are assigned as indicated and a total point score is obtained. Patients with scores of <20 are at extremely low likelihood of having TTP, and consequently do not need plasma exchange urgently. Patients with point scores >30 are highly likely to have TTP and should receive urgent plasma exchange. Patients with point scores of 20–30 points have an intermediate likelihood of having TTP, and starting plasma exchange prior to receiving results of the ADAMTS13 level is left to physician judgment.

Data taken from Bentley MJ, Lehman CM, Blaylock RC, et al. The utility of patient characteristics in predicting severe ADAMTS13 deficiency and response to plasma exchange. *Transfusion*. 2010;50:1640-1642.

function positively predicted TTP, making “renal failure” a factor that should not be considered part of the classic pentad. Of the 11 patients identified with ADAMTS13 activity levels of less than 15%, none had a creatinine higher than 1.4 mg/dL on admission. Similarly, in a series of 142 patients with clinically suspected TTP-HUS in an Oklahoma registry, only 1 of the 18 patients with idiopathic severe ADAMTS13 deficiency had renal failure.<sup>33</sup> This variation from the earlier case reports of the 1960s–1980s, where 76% of cases had reported renal disease, is likely due to the advancements in differentiating TTP from HUS.<sup>6,32</sup>

Since we believe that not all TMA patients will benefit from PE, we present the above algorithm to let clinicians be aware of a method to rapidly identify which patients should empirically receive PE while the ADAMTS13 level is pending. Clinical treatment decisions should not be based solely on this model, but for cases in which a TTP diagnosis is suspected, but not “classic,” the model may be helpful in guiding clinical decisions about early

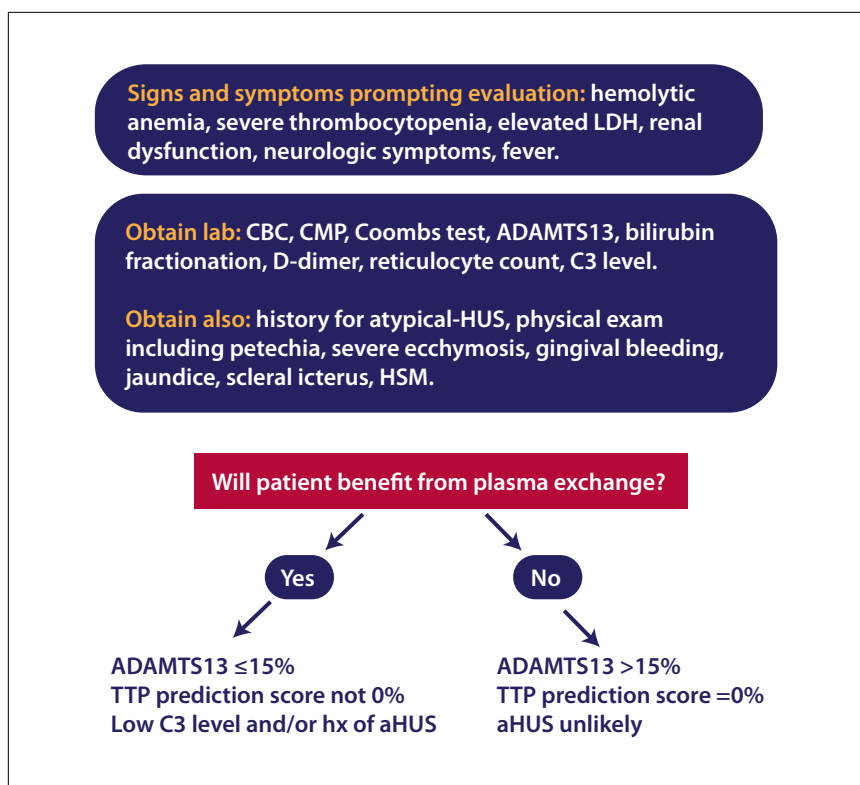
use of PE. Our model is limited by being a retrospective study, as well as having a relatively small number of severely deficient ADAMTS13 patients, and it has not yet been validated by others.

If the above-described TTP prediction score is applied to the previously discussed case of the 28-year-old, pregnant female with suspected TTP, she is identified as a good candidate for PE therapy. Her creatinine and D-dimer results were within normal limits. The platelet count was below the 35,000/ $\mu$ L parameter, and the reticulocyte count and indirect bilirubin were above the set parameters. The TTP prediction score is 41.5, making PE the recommended treatment prior to receiving results of the ADAMTS13 assay.

The only other TMA disorder likely to respond to plasma therapy is a-HUS. A-HUS is a syndrome of renal failure and TMA, which lacks the prodrome of bloody diarrhea seen in typical-HUS. It occurs in children and young adults, and genetic deficiency of complement regulatory proteins has been identified in 40–80% of cases. The most common deficiencies involve factor H (21–41%), membrane cofactor protein (10–15%), factor I (5–10%), C3 mutations (5–10%), and factor B (1–2%).<sup>34-37</sup> Family histories of renal failure may be noted, and a history of recurrent infections may occur. Serum C3 levels are usually low.

The Oklahoma registry suggested that TTP could not be distinguished from HUS;<sup>33</sup> however, we believe that these can be clinically identified, and we do not believe that all HUS patients should receive PE. A 2009 Cochrane review of randomized treatment trials in TTP and HUS confirms previous findings that PE is not effective therapy in typical HUS.<sup>38</sup> Our above-mentioned algorithm may be useful in identifying patients unlikely to respond to PE. Atypical HUS patients may respond to PE as discussed in the preceding paragraph.

We propose the following approach when evaluating a potential TMA patient, who may include any patient with thrombocytopenia, a suspicion for hemolytic anemia, or neurologic symptoms not well explained by another etiology (Figure 1). First, evaluate the patient for signs and symptoms, such as fever, petechiae, ecchymosis, jaundice, or focal neurologic deficits. Ask about personal and family history of excessive bleeding, thrombosis, autoimmune disease, renal disease, and recurrent infections. Obtain readily available laboratory tests including a complete blood count, chemistry panel, liver function tests, LDH, bilirubin fractionation, D-dimer, and reticulocyte count. Draw a direct Coombs test to rule out immune-mediated hemolytic anemia (Evans syndrome). Check C3 level to assess a-HUS. Finally, draw an ADAMTS13 level. If laboratory results and physical examination further warrant suspicion of hemolytic anemia or thrombocytopenia, start infusions of FFP and arrange for plasma exchange. If



**Figure 1.** Evaluation of patients presenting with possible TMA.

CBC=complete blood count; CMP=complete metabolic panel; C3=complement protein 3; HSM=hepatosplenomegaly; HUS=hemolytic-uremic syndrome; hx=history; LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

clinical suspicion for TTP is high (as discussed by Bentley and colleagues<sup>32</sup>), or if patient history or a low C3 level supports a diagnosis of a-HUS, start FFP infusions immediately and arrange PE therapy before the ADAMTS13 level is reported. If suspicion is initially low for TTP or a-HUS, but the ADAMTS13 level is less than 15% of normal, plasma exchange therapy should be started.

## Conclusion

The “powerful poison which had both agglutinative and hemolytic properties” described by Moschowitz in the initial TTP case report is now recognized to be high molecular weight multimers of vWF that result from ADAMTS13 deficiency. A clinical scoring system may be helpful in diagnosing TTP, and patients with the presumptive diagnosis should be empirically treated with FFP and plasma exchange as well as steroids. The diagnosis of TTP is confirmed by ADAMTS13 levels less than 10–15% of normal, with tests confirming the presence of an inhibitor. Although many patients will respond to plasma exchange with FFP, some patients will experience recurrent disease, whereas others will not respond to plasma exchange. Numerous options exist for these patients, including splenectomy, immunosuppression with rituximab (or other drugs), and future novel therapies.

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