Diagnosis of immune TTP

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Literature review current through: **Jan 2024.**
This topic last updated: **Jul 13, 2023.**

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13. It is characterized by small-vessel platelet-rich thrombi that cause thrombocytopenia, microangiopathic hemolytic anemia, and sometimes organ damage. TTP is a medical emergency that is almost always fatal if appropriate treatment is not initiated promptly. With appropriate treatment, survival rates of over 90 percent are expected.

TTP can be immune-mediated, due to autoantibodies against ADAMTS13, or hereditary, due to pathogenic variants in the *ADAMTS13* gene. This topic reviews the clinical manifestations and our approach to the diagnosis of immune TTP. The management of immune TTP is presented separately. (See "Immune TTP: Initial treatment" and "Immune TTP: Treatment of clinical relapse".)

Our approach to evaluating patients with other suspected TMAs is presented in separate topic reviews:

- General diagnostic approach – (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)
- Hereditary TTP – (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)".)
- Drug-induced TMA (DITMA) – (See "Drug-induced thrombotic microangiopathy (DITMA)".)

- HUS, child – (See "Complement-mediated hemolytic uremic syndrome in children" and "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome in children".)
- HUS, adult – (See "Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS".)

TERMINOLOGY AND DISEASE DEFINITIONS

The terminology for TTP and related primary thrombotic microangiopathy (TMA) syndromes is evolving as advances are made in understanding disease pathophysiology [1]. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)".)

- **TMA** – Refers to a pathologic lesion seen on tissue biopsy; however, the presence of a TMA is often inferred from clinical features such as microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, along with signs of organ injury.

- **Primary TMA** – Refers to a TMA for which a specific cause requires specific management. Examples include:

  - Immune TTP
  - Hereditary TTP
  - Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)
  - Complement-mediated HUS (CM-HUS)
  - Drug-induced TMA (DITMA)
  - Other rare inherited TMA syndromes.

  Distinction among these primary TMA syndromes, and other possible causes of MAHA and thrombocytopenia, are discussed in more detail separately. (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

- **Immune TTP** – We use the term immune TTP to refer to the primary TMA characterized by severe ADAMTS13 deficiency (typically, activity <10 percent) due to an inhibitor (autoantibody) directed against ADAMTS13.

- **Medications** – It has been reported that immune TTP may occur in an individual who was recently started on a drug. We distinguish drug-associated TTP (DA-TTP) from drug-induced TMA (DITMA) as follows:

  - **DA-TTP** – We consider that severe ADAMTS13 deficiency in the setting of certain drugs may be drug-associated TTP (DA-TTP), which has implications for future drug avoidance

but is otherwise treated identically to other forms of immune TTP. (See 'Other evaluations' below.)

- **DITMA** – We consider TMA induced by a drug without severe ADAMTS13 deficiency to be DITMA; management is distinct from TTP in that the main interventions are supportive care and drug avoidance; therapeutic plasma exchange is not a standard treatment for DITMA. (See "Drug-induced thrombotic microangiopathy (DITMA)".)

ADAMTS13 activity is the principle way to distinguish DA-TTP from DITMA. It may be necessary to treat as TTP while awaiting results of ADAMTS13 testing. (See "Immune TTP: Initial treatment", section on 'Overview of treatment approach'.)

- **Hereditary TTP** – Patients with hereditary TTP have biallelic pathogenic variants in *ADAMTS13*.

EPIDEMIOLOGY

The incidence of immune TTP is approximately 3 per 1 million adults per year, based on data from the Oklahoma TTP-HUS Registry [2]. The median age for the diagnosis of immune TTP diagnosis is 40 years, with a wide range (9 to 78 years).

Immune TTP is very rare in children <9 years old. At ages ≥9 years, the frequency increases, predominantly among females [3]. In children, the possibility of hereditary TTP, in addition to immune TTP, must also be considered. In adults, immune TTP is approximately 30-fold more common than hereditary TTP. However, when TTP occurs during a first pregnancy, hereditary TTP must be considered [4]. (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)".)

Immune TTP is more common in females, Black people, individuals with a high body mass index (BMI), and during pregnancy, as discussed below. (See 'Overview of presentation' below.)

CLINICAL AND LABORATORY FINDINGS

Overview of presentation

Typical presentation — Immune TTP usually presents as severe microangiopathic hemolytic anemia (MAHA) and thrombocytopenia in a previously healthy individual. Some individuals may have another autoimmune disorder such as systemic lupus erythematosus (SLE); 10 percent of patients with immune TTP also have SLE [5,6]. A combination of autoimmune disorders may reflect a combination of shared demographic features and/or similar pathophysiology [7]:

- **Age** – The typical patient is a young adult. The median age is 40 years. Immune TTP is less common in children [3].
- **Sex** – Females are more commonly affected, accounting for 76 percent in the Oklahoma TTP-HUS Registry and 75 percent in the UK TTP Registry [2,8].
- **BMI** – Individuals with a body mass index (BMI) >40 kg/m^2 account for 24 percent; by contrast, age, sex, and race-adjusted BMI in the United States is 9 percent [9].
- **Pregnancy** – The frequency of immune TTP may be increased in pregnancy, where it may be misdiagnosed as preeclampsia with severe features or HELLP syndrome [10].

Black individuals account for 36 percent in the Oklahoma TTP-HUS Registry; Black people were overrepresented among individuals with TTP compared with the reference population by sevenfold [2].

The presenting clinical features are similar in adults and children, and during pregnancy, with the exception of older adults. Initial symptoms may include fatigue, dyspnea, petechiae, or other bleeding [11]. Not all patients with TTP are critically ill. They may walk into the clinician's office with what appear to be minor complaints of weakness and dizziness, abdominal pain, easy bruising, or nausea and vomiting. In some patients, the diagnosis of TTP may not be considered until the complete blood count (CBC) reveals severe thrombocytopenia and MAHA [12].

The presentation and clinical features may be different in older adults, and this can delay the diagnosis [13,14]. Patients ≥60 years old have more comorbidities (cancer, coronary heart disease, chronic kidney disease, and others). They may present earlier in the course of immune TTP with more organ involvement and less-severe thrombocytopenia. Diagnostic algorithms, the PLASMIC score (see 'PLASMIC score' below), and French immune TTP score have less sensitivity [15,16]. These different clinical features cause significantly increasing mortality with increasing age [14].

Organ involvement in TTP often affects the central nervous system and/or gastrointestinal system. Kidney involvement is seen on biopsy, but acute kidney injury is uncommon. Other organs such as the heart may also be affected. Pulmonary involvement is rare [17]. Elevation of serum troponin may occur and may be a harbinger of early death [18,19].

A review of 78 patients with immune TTP from the Oklahoma TTP-HUS Registry revealed the following findings (table 1) [20]:

- Median platelet count – 10,000/microL (only three patients [4 percent] had platelet counts ≥30,000/microL)
- Median hematocrit – 21 percent (equivalent to hemoglobin of approximately 7 g/dL; only two patients [3 percent] had hematocrits ≥30 percent)
- Gastrointestinal symptoms – 45 patients (69 percent)
- Weakness – 41 patients (63 percent)
- Bleeding or purpura – 35 patients (54 percent)
- Major neurologic findings (eg, coma, stroke, seizure, transient focal abnormalities) – 32 patients (41 percent)
- Minor neurologic findings (eg, headache, confusion) – 20 patients (26 percent)

One-third had no neurologic symptoms; only 10 percent had fever with chills [20].

The complete "pentad" of MAHA, thrombocytopenia, fever, acute kidney injury, and severe neurologic findings was also rare (<5 percent) [20]. The pentad was common before the routine use of therapeutic plasma exchange (TPE) because the majority of patients developed progressive thrombotic microangiopathy (TMA) and died from untreated disease [21]. Use of the pentad for diagnostic purposes has become obsolete.

MAHA and thrombocytopenia — Microangiopathic hemolytic anemia (MAHA) and thrombocytopenia are hallmarks of TTP, and the possibility of TTP should be evaluated in any patient who presents with these findings without an alternative explanation.

Confirmation of both of these findings requires review of the peripheral blood smear by an experienced clinician. Automated instruments and less experienced individuals may mistake other red blood cell (RBC) abnormalities for microangiopathic changes (eg, anisopoikilocytosis, megaloblastic changes, teardrop cells) [22,23].

- **MAHA** – MAHA is a hemolytic anemia that results from mechanical shearing (fragmentation) of RBCs as they pass through platelet-rich microthrombi in the microvasculature; it is documented by the finding of prominent schistocytes, including helmet cells and triangular cells, on the peripheral blood smear (picture 1) [24]. Polychromasia (consistent with reticulocytosis) is common. Microspherocytes and nucleated RBCs may also be seen, but microspherocytes are more prominent in patients with warm autoimmune hemolytic anemia, and many nucleated RBCs may suggest a myelophthisic process such as metastatic malignancy, which may mimic the clinical features of TTP.

  Patients with MAHA typically have other features of hemolytic anemia including elevation of the serum indirect bilirubin and reduction in the serum haptoglobin concentration. The

reticulocyte count is generally increased to compensate for accelerated RBC destruction. The serum lactate dehydrogenase (LDH) is typically extremely high, reflecting both hemolysis and tissue damage due to ischemia [25]. Tests for immune hemolysis such as anti-RBC antibodies, including direct and indirect antiglobulin testing (Coombs testing), are negative. Patients may have dark urine from hemoglobinuria because hemolysis is intravascular.

Rarely, a patient with early TTP may not have schistocytes appreciated on the blood smear; this may occur in a patient in the early stages of relapse who is being followed closely.

- **Thrombocytopenia** – Thrombocytopenia is thought to result from deposition of platelets in microthrombi; severe thrombocytopenia is common. In the Oklahoma series of 78 patients with TTP, the mean platelet count on presentation was 10,000/microL [20].

  Bleeding is sometimes seen; it may result from a combination of thrombocytopenia, vascular injury, and/or tissue infarction. In the same series, bleeding was reported in 35 of 65 patients (54 percent), typically as petechiae and purpura [26]. Major, overt bleeding at presentation is rare.

  Confirming thrombocytopenia on the peripheral blood smear (excluding pseudothrombocytopenia) is discussed separately. (See "Diagnostic approach to thrombocytopenia in adults", section on 'Peripheral blood smear'.)

Neurologic and other organ involvement — When present, signs of organ involvement typically accompany hematologic changes. Rarely, neurologic findings or gastrointestinal symptoms can precede hematologic changes. (See 'Atypical presentations' below.)

- **Neurologic findings** – Neurologic findings are common, especially subtle changes such as confusion and headache [20,26-29]. Transient focal neurologic findings such as difficulty speaking or transient numbness and weakness, seizures, and coma also occur [8,30]. In a series of 78 patients with TTP, minor abnormalities such as confusion or headache were seen in 21 (27 percent); focal abnormalities were seen in 31 (40 percent); and seizure, stroke, and coma were seen in 15, 12, and 8 percent, respectively [20].

  If performed, imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) are often normal, but they may show changes consistent with small silent infarction or with reversible posterior leukoencephalopathy syndrome (RPLS, also called posterior reversible encephalopathy syndrome [PRES]) [31-33]. Some patients may have large territorial infarcts and permanent deficits [34]. (See "Reversible posterior leukoencephalopathy syndrome".)

- **Gastrointestinal symptoms** – Gastrointestinal symptoms are common and may include pain, nausea, vomiting, or diarrhea. In our series of 65 patients with TTP, these gastrointestinal symptoms were the most common finding, seen in 45 individuals (69 percent) [26]. It is important to establish the temporal relationship between diarrhea and other TMA symptoms if possible. In Shiga toxin-induced TMA, a prodromal gastrointestinal illness with abdominal pain, vomiting, and diarrhea generally precedes the development of MAHA and thrombocytopenia by several days. (See "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome in children", section on 'Typical course'.)

- **Kidney involvement** – Decreased kidney function can be seen in TTP, but anuria and acute kidney injury are rare [1,20]. In the Oklahoma series of patients with TTP, the median serum creatinine was 1.3 mg/dL (115 micromol/L) [20]. Of 78 patients, 37 had normal kidney function (47.5 percent), 37 had increased serum creatinine (47.5 percent), and four had acute kidney injury (5 percent), defined as an increasing serum creatinine (≥0.5 mg/dL per day for two consecutive days) or a serum creatinine ≥4 mg/dL and hemodialysis [35]. A separate study suggested that acute kidney injury may be common in patients with TTP who are hospitalized in a referral center intensive care unit [36].

  The urinalysis is normal or may show mild proteinuria (1 to 2 g per day) and few cells or casts [37,38]. These findings of mildly reduced or normal kidney function contrast with other primary TMA syndromes such as Shiga toxin-induced TMA, complement-mediated TMA, or immune mediated drug-induced TMA (DITMA; eg, due to quinine), in which acute kidney injury is common. (See "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome in children" and "Drug-induced thrombotic microangiopathy (DITMA)".)

- **Cardiac symptoms** – Cardiac involvement may occur in TTP, although the exact incidence may be difficult to determine. In the Oklahoma series of patients with TTP, 14 had chest pain (22 percent) [20]. Other series have reported arrhythmia, sudden cardiac death, myocardial infarction, cardiogenic shock, and/or heart failure [18,19,39-44]. Elevated troponin was independently associated with mortality [19].

Involvement of other organs, including pancreas, thyroid, adrenal glands, and other organs, may also be seen. Pulmonary involvement is rare [17].

Tissue biopsy is not required for diagnosis, but if performed, it may show classic changes of a TMA including platelet microthrombi in small arterioles or capillaries, or hyaline changes in and around vessel walls. There are no specific findings on tissue biopsy that distinguish TTP from

other primary TMAs. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)", section on 'Histopathology of TMA'.)

In contrast to these findings related to microvascular thrombosis, large-vessel thrombosis such as arterial thromboembolism or venous thromboembolism (VTE) is less common among patients with TTP. Risk factors such as hospitalization and the presence of a central venous catheter are common and may contribute to the risk of VTE among patients with TTP. (See "Overview of the causes of venous thrombosis".)

Reduced ADAMTS13 activity — Severely reduced ADAMTS13 activity (generally <10 percent) during an acute episode is a hallmark of immune TTP. However, these results are not always immediately available. Regardless of availability, ADAMTS13 activity should not be used in isolation to diagnose TTP or to guide initiation or discontinuation of therapy. The use of ADAMTS13 activity and inhibitor testing in the diagnostic evaluation are discussed below. (See 'ADAMTS13 testing' below.)

Atypical presentations — Presentations in older adults may include less-severe thrombocytopenia and more severe organ involvement, as discussed above. (See 'Typical presentation' above.)

Other atypical presentations of TTP are rare but possible. There have been several reports of patients presenting with neurologic symptoms without MAHA and thrombocytopenia who subsequently (within days to weeks) developed typical TTP findings [45-49].

EVALUATION AND DIAGNOSIS

Overview of our approach — TTP should be suspected when a patient presents with microangiopathic hemolytic anemia (MAHA; hemoglobin almost always <10 gm/dL) and severe thrombocytopenia (platelet count almost always <30,000/microL), with or without symptoms of organ involvement and without another clinically apparent etiology (table 2).

Considering TTP and initiating therapeutic plasma exchange (TPE), if appropriate, is urgent and should not await diagnostic testing. The finding of MAHA with thrombocytopenia in the appropriate clinical setting is sufficient for a presumptive diagnosis of immune TTP and for initiation of TPE and other therapies. (See 'Presumptive diagnosis' below.)

Our general approach is to make a presumptive diagnosis of immune TTP based on clinical features and initial laboratory testing, which is incorporated into the PLASMIC score (see 'PLASMIC score' below), and for patients with a presumptive diagnosis of immune TTP, to

initiate TPE, glucocorticoids, and rituximab, which is potentially life-saving therapy. Some individuals may also be treated with caplacizumab. (See "Immune TTP: Initial treatment".)

Other findings consistent with immune TTP include markedly elevated lactate dehydrogenase (LDH) and other biochemical markers of non-immune hemolysis including elevated indirect bilirubin and negative Coombs testing. Creatinine may be normal or slightly increased; creatinine >2 mg/dL is rare. Coagulation testing is almost always normal, but severe organ ischemia may cause disseminated intravascular coagulation (DIC) with associated coagulation abnormalities. (See 'Other evaluations' below.)

Medication history is discussed below. (See 'Post-diagnostic evaluation' below.)

ADAMTS13 activity testing is important for the diagnosis, but this testing cannot be used in isolation, nor should therapy be delayed when appropriate while waiting for results. Severe ADAMTS13 deficiency with an inhibitor is typically seen, although this result usually is not immediately available and is not required for a presumptive diagnosis. (See 'ADAMTS13 testing' below.)

Concurrently with initiation of therapy, individuals with a presumptive diagnosis of TTP should have ongoing consideration of other possible causes of their symptoms, including other primary TMAs and other systemic conditions. (See 'Differential diagnosis' below and "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

The same diagnostic testing is done during pregnancy and in children as done in nonpregnant adults; however, hereditary TTP is more frequent in these patients [3,4]. Other diagnostic possibilities may be more likely and should be considered in these populations. (See 'Differential diagnosis' below.)

PLASMIC score — The PLASMIC score can be easily calculated using findings available on presentation and has been devised to predict the likelihood of ADAMTS13 activity ≤10 percent (to help estimate the pretest probability and support the diagnosis of TTP) in adults with features of thrombotic microangiopathy (TMA), which is commonly considered whenever schistocytes (fragmented red blood cells) and thrombocytopenia are present [15,50].

While this score cannot substitute for clinical judgment and cannot be used to definitively confirm or exclude the diagnosis of TTP, it may be helpful for guiding the decision of whether to initiate therapy while awaiting the results of ADAMTS13 testing.

The clinical parameters of the PLASMIC score were developed using a cohort of 214 adults with suspected TMA, and validation was performed in two additional cohorts [50].

The score gives one point each for the following features (calculator 1):

- Platelet count <30,000/microL
- Hemolysis (defined by reticulocyte count >2.5 percent, undetectable haptoglobin, or indirect bilirubin >2 mg/dL)
- No active cancer
- No solid organ or stem cell transplant
- MCV <90 fL
- INR <1.5
- Creatinine <2.0 mg/dL

Schistocytes are not included in the score because they are a predicate for using the PLASMIC score. The higher the score, the greater the likelihood of TTP:

- 6 to 7 points – high probability of TTP
- 5 points – intermediate probability of TTP
- 0 to 4 points – low probability of TTP

A 2020 systematic review and meta-analysis confirmed the diagnostic accuracy of the PLASMIC score in individuals with suspected TTP [51]. The review identified 13 studies (970 patients), with a median TTP prevalence of 35 percent. A PLASMIC score of 5 or higher provided a sensitivity of 99 percent (95% CI 0.91-1.00) and a specificity of 57 percent (95% CI 0.41-0.72). A score of 6 or higher lowered the sensitivity to 85 percent and raised the specificity to 89 percent. These results suggest that, for this potentially fatal disease where withholding therapy can be life-threatening, all patients with a PLASMIC score of 5 or higher should be empirically treated for TTP unless there is an obvious alternative explanation for the individual's clinical presentation. The PLASMIC and French scores have less sensitivity in older patients [13,15,16].

Other evaluations — The following diagnostic testing for TTP is appropriate if not done already:

- Complete blood count (CBC) with platelet count
- Review of the peripheral blood smear
- Serum chemistries including creatinine
- Serum lactate dehydrogenase (LDH)
- Serum bilirubin level
- Serum haptoglobin level
- Coagulation testing (PT, aPTT, fibrinogen, D-dimer)
- Direct antiglobulin (Coombs) test (DAT)
- ADAMTS13 activity and inhibitor testing (See 'ADAMTS13 testing' below.)

Additional review and/or diagnostic testing may be appropriate in selected patients. Examples include the following:

- **Review of medications and other medical conditions –** Medication review may reveal an association between immune TTP and a specific drug. Review of the medical history may reveal an autoimmune disorder such as systemic lupus erythematosus (SLE). These conditions may occur independently of TTP, or both SLE (or other autoimmune disorder) and TTP may occur together [5,6]. Identification of an associated drug or medical condition may affect management (eg, drug discontinuation, interventions for SLE) and may alter the classification of immune TTP as primary versus secondary to (or associated with) a drug or disorder.

- **Family history, personal history, and genetic testing** – Testing for pathogenic variants in the *ADAMTS13* gene is appropriate for patients with suspected hereditary TTP (positive family history, onset during childhood or pregnancy, multiple recurrent episodes, absence of a demonstrable inhibitor, persistence of severe deficiency during remission). This testing is available at no charge for patients with these criteria for suspected TTP through the Hereditary TTP (Upshaw-Schulman syndrome) Registry (www.ttpregistry.net). (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)".)

- **Imaging** – Magnetic resonance imaging (MRI) of the brain is appropriate for patients with TTP who have any neurologic abnormalities, as small silent cerebral infarctions may be common. In a series of 27 patients who had recovered from an episode of TTP, 17 (63 percent) had neurocognitive impairment and 9 of 23 (39 percent) had abnormalities on MRI [52]. Patients with transient focal neurologic abnormalities, seizure, encephalopathy, or coma should be evaluated with MRI. In patients with clinical features consistent with TTP without neurologic findings, imaging may not be necessary. (See 'Evaluation for organ injury' below.)

- **Blood cultures** – Blood cultures and other infectious disease evaluations are appropriate for those with fever or other evidence of systemic infection.

- **Stool testing** – Stool studies (cultures, toxin testing) for Shiga toxin or Shiga toxin-producing organisms are indicated in individuals (children or adults) with severe diarrhea as the predominant clinical feature, especially bloody diarrhea. (See "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome in children", section on 'Evaluation'.)

ADAMTS13 testing — TTP is caused by deficiency of the ADAMTS13 protease (**A** **D**isintegrin **A**nd **M**etalloprotease with a **T**hrombo**S**pondin type 1 motif, member **13**), which cleaves ultralarge

von Willebrand factor (VWF) multimers on the endothelial surface. The ultralarge VWF multimers that accumulate in the absence of ADAMTS13 activity are thought to be responsible for causing the TMA. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)".)

ADAMTS13 activity and inhibitor testing provide important information for the diagnosis of immune TTP. Although these results alone should never change the decision to initiate or withhold treatment, they can significantly contribute to the confidence in the clinical diagnosis. Importantly, these values should not be used in isolation, and definitive therapy with TPE should not be delayed while determining ADAMTS13 activity levels in patients with a reasonable clinical suspicion for TTP, because such delays may be fatal [53]. (See "Immune TTP: Initial treatment", section on 'Therapeutic plasma exchange (TPE)'.)

ADAMTS13 activity — ADAMTS13 assays report the activity of the protease as a percentage of normal, based on unaffected individuals. ADAMTS13 activity testing can be performed on plasma or serum [54]. Whenever possible, a sample for ADAMTS13 activity measurement should be collected prior to blood product transfusions and/or initiation of TPE. The following test interpretations are often used [53]:

- **Severe deficiency (activity <10 percent)** – This finding typically confirms the diagnosis of TTP in the appropriate clinical setting (MAHA and thrombocytopenia without another obvious cause) and the appropriateness of therapy with TPE and immunosuppressive therapy (eg, glucocorticoids and rituximab). However, as discussed below, activity <10 percent is not 100 percent sensitive or specific for TTP, and laboratory values alone cannot be used to make or exclude the TTP diagnosis. ADAMTS13 activity <10 percent has also been reported in patients with other causes of MAHA and thrombocytopenia including sepsis and systemic cancer [20,45,54,55].

- **Very low activity (11 to 20 percent)** – Levels of 11 to 20 percent may occur in patients with TTP who have received transfusions or after TPE. Some individuals with TTP may have ADAMTS13 activity in this range [56].

- **Low activity (21 to 60 percent)** – This finding is seen in many hospitalized patients with inflammatory disorders (sepsis, malignancy). As illustrated in the studies below, some individuals with TTP may have ADAMTS13 activity >20 percent.

- **Normal (>60 percent)** – This finding suggests an etiology for the clinical findings other than TTP, with very rare exceptions [57].

In summary, severe ADAMTS13 deficiency (activity <10 percent) supports the clinical diagnosis of TTP and confirms the diagnosis in a patient with MAHA and thrombocytopenia without another obvious cause. However, the converse is not always true; ADAMTS13 activity ≥10 percent does not eliminate the possibility of TTP in individuals with a high confidence in the TTP diagnosis based on clinical features. (See 'Confirmed diagnosis' below and 'Differential diagnosis' below.)

Our approach to interpretation of ADAMTS13 activity is consistent with 2020 guidelines from the International Society on Thrombosis and Haemostasis (ISTH) [58]; one exception is that we designate activity of 11 to 20 percent as very low and possibly consistent with the diagnosis of TTP [56].

The range of ADAMTS13 activity has been illustrated by several case reports and patient series, which typically show a good correlation between severe ADAMTS13 deficiency and an established diagnosis of TTP, with occasional exceptions. The prevalence of confirmed TTP in cohorts with TMA varies depending on the criteria used for entry into a disease registry. As examples:

- Of 810 patients in a 2015 series from the United Kingdom TTP Registry, 350 (43 percent) had ADAMTS13 activity <10 percent and/or the presence of anti-ADAMTS13 antibodies [59]. The median ADAMTS13 activity in patients with TTP was 5 percent (range, 0 to 11 percent). For other TMAs, the median ADAMTS13 activities were 56 to 66 percent. An earlier study from this registry reported similar findings [8].

- The Harvard TMA research collaborative found that, of 254 patients with suspected TTP, there was a bimodal distribution of ADAMTS13 activity, with severe deficiency (activity <10 percent) in 68 (27 percent) [60]. The remaining 186 had a median ADAMTS13 activity of 56 percent (range, 42 to 68 percent). Patients in the cohort with severe ADAMTS13 deficiency were less likely to have an alternative cause of MAHA and thrombocytopenia such as disseminated intravascular coagulation (DIC), drug-induced TMA, or transplantation, and their disease was more likely to respond to TPE, further supporting the correlation between severe ADAMTS13 deficiency and the clinical diagnosis of immune TTP.

- A 2014 study that compared ADAMTS13 activity in 57 patients with TTP versus 57 patients with other TMAs found that a threshold of <10 percent yielded 100 percent sensitivity and 100 percent specificity [61]. A lower threshold (ie, <5 percent) retained 100 percent specificity, but sensitivity was reduced to approximately 95 percent.

- In our experience, patients with TTP occasionally have ADAMTS13 activity ≥10 percent [56].

- An analysis of 22 patients in the Oklahoma Registry with ADAMTS13 activity 10 to 20 percent determined that four patients were appropriately diagnosed as having TTP [56]. The ADAMTS13 activities of these four patients were 10 to 16 percent; three had not been previously transfused. The clinical features that distinguished these four patients from the other 18 were younger age, transient focal neurologic symptoms, platelet count <30,000/microL, serum creatinine <3.0 mg/dL, suspected diagnosis ≤2 days following hospital admission, and response to TPE.

- A 2017 series from the Oklahoma Registry that included 80 patients with a first episode of TTP in which severe ADAMTS13 activity was assayed using both a fluorescence resonance energy transfer (FRET) assay and immunoblotting found severe deficiency (activity <10 percent) in 78 (97.5 percent) using one or both assays [20]. Eighteen (23 percent) of these 78 patients had ADAMTS13 activity <10 percent by one method and not the other. Five additional patients who had ADAMTS13 activity <10 percent by one of the two methods were determined by clinical features or autopsy to have an alternative (non-TTP) diagnosis. Two patients who had ADAMTS13 activity >10 by both methods had clinically typical TTP with multiple relapses.

- In another example, a patient with relapsing TTP had ADAMTS13 activity >50 percent with the first episode and <10 percent with subsequent relapses [57].

Possible explanations for ADAMTS13 activity ≥10 percent in patients with TTP include assay variability and interfering substances. (See 'Assay considerations' below.)

Assay considerations — Assays for ADAMTS13 activity are based on the cleavage of VWF. However, most commercially available assays use an artificial substrate (a VWF peptide) and hence do not actually measure the proteolysis of VWF multimers. Inter-assay agreement continues to improve, but discrepancies among assays persist [20,53]. Additionally, ADAMTS13 activity can be falsely increased by transfusions, which may be given before the possibility of TTP is evaluated. These concerns provide the rationale for not basing a TTP diagnosis on ADAMTS13 activity measurements alone. (See 'Presumptive diagnosis' below.)

In patients with clinically typical TTP and no alternative diagnosis who have ADAMTS13 activity ≥10 percent, the higher values may be related to measurement methodology [29,57]. Examples include:

- **Assay method** – Almost all commercial assays use fluorescence-based detection such as fluorescence resonance energy transfer (FRET) to detect proteolysis of a 73 amino acid peptide from VWF that contains the ADAMTS13 cleavage site. Unlike intact VWF, this peptide does not require extensive denaturation to expose the cleavage site. Exposure of

VWF to shear force is thought to expose the cleavage site in vivo; however, the contribution of shear force is especially challenging to measure in a laboratory assay and is not incorporated into standard laboratory testing. The original assays that used gel electrophoresis of VWF multimers to observe their degradation by ADAMTS13 are generally not commercially available [62,63].

- **Reference ranges** – There is no ideal cutoff value above which TTP is eliminated or below which TTP is assured. We have chosen a value of <10 percent as this identifies almost all patients with immune TTP. However, other experts may use other cutoff values to increase sensitivity or specificity. Identification of patients with TTP for development of the PLASMIC score used a value of ≤10 percent [15].

- **Interference** – Some conditions may affect the results in some assays more than others. As examples, high bilirubin levels (eg, >20 mg/dL) may interfere with fluorescence in FRET-based assays [54,64,65]. High levels of free hemoglobin caused by intravascular hemolysis can also interfere with FRET-based assays [66]. Reported ADAMTS13 activity can be artificially high if the anti-ADAMTS13 autoantibodies dissociate from ADAMTS13 during the in vitro incubation required for the assay [57].

- **Presence of ADAMTS13 in plasma used for TPE or transfusions** – Ideally, the sample for measuring ADAMTS13 activity is obtained before transfusions are administered or TPE is initiated, so that activity is not increased by these interventions. However, there is value in obtaining a measurement as early as possible after initiation of TPE, if ADAMTS13 activity was not measured prior to the first TPE procedure. The ability to detect severe ADAMTS13 deficiency after initiation of TPE was demonstrated in a study that tested the ADAMTS13 activity in the plasma of 18 patients before and after TPE treatments [67]. This showed persistent ADAMTS13 activity <10 percent after the first one or two exchanges in most patients (in 16 of 18 patients [89 percent] after the first exchange and in 15 of 18 patients [83 percent] after the second exchange).

ADAMTS13 activity measurements must be interpreted in the clinical context [29]. As an example, decrease of the ADAMTS13 activity to <20 percent without thrombocytopenia or other findings of acute TTP following recovery from an episode of TTP is termed an ADAMTS13 relapse [68]. ADAMTS13 relapse increases the risk of clinical relapse. (See "Immune TTP: Management following recovery from an acute episode and during remission", section on 'Terminology for response criteria'.)

Conversely, ADAMTS13 activity ≥10 percent in a patient who does have MAHA and thrombocytopenia without another apparent cause should not be used to justify withholding

TPE or as a sole rationale for stopping TPE if it has been started based on clinical features [69]. We believe some individuals without TTP may have activity <10 percent in some assays, and some individuals with TTP will have activity ≥10 percent [20]. Additionally, in our experience, some individuals who have recovered from an episode of immune TTP will have persistently low ADAMTS13 activity, often (but not always) with a demonstrable ADAMTS13 inhibitor, for many years despite being clinically well [70]. These observations were made before the importance of prophylactic rituximab was documented for patients with an ADAMTS13 relapse with activity <20 percent [71]. (See "Immune TTP: Management following recovery from an acute episode and during remission".)

Greater accessibility of ADAMTS13 activity measurements (and inhibitor testing (see 'ADAMTS13 inhibitor' below)), along with more rapid return of the results, will help clinicians substantially in making the diagnosis of immune TTP [29].

Individuals with immune TTP generally have recovery of ADAMTS13 activity during remission. Our approach to monitoring during recovery and to incorporating the individual's symptoms, platelet count, and ADAMTS13 activity into the patient assessment are discussed separately. (See "Immune TTP: Management following recovery from an acute episode and during remission", section on 'Monitoring and therapy after response to treatment'.)

ADAMTS13 inhibitor — In patients with immune TTP, severely deficient ADAMTS13 activity is caused by an inhibitor (autoantibodies against ADAMTS13). Most laboratories reflexively test for an inhibitor in patients with severe deficiency; if this does not occur, testing for an inhibitor should be obtained for patients with severe deficiency.

Most inhibitor assays use a mixing study, similar in principle to the tests for inhibitors of factor VIII in patients with hemophilia A (see "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication"). In these assays, patient plasma is mixed with normal plasma, and when inhibitory autoantibodies are present, they inhibit the normal ADAMTS13 activity in the normal plasma.

The titer of the inhibitor is determined from the number of serial dilutions of patient plasma after which the inhibitor continues to inhibit ADAMTS13 activity. Inhibitor titers are often presented in Bethesda units (the reciprocal of the dilution required to neutralize 50 percent of the inhibitor).

It is often assumed that the titer of the inhibitor correlates with clinical outcomes, and that disease in patients with high-titer inhibitors may be more refractory to standard treatment. However, our experience is that the strength of the ADAMTS13 inhibitor is not related to the severity of the clinical presentation and is not predictive of survival [20].

In the United Kingdom TTP Registry, mixing studies showed the presence of an inhibitor in 78 percent of TTP cases [8]. An enzyme-linked immunosorbent assay (ELISA) for IgG antibodies to ADAMTS13 identified inhibitors in 95 percent. However, an inhibitor is not always detected. Potential explanations may include:

- The inhibitor titer is too low to measure in vitro
- The inhibitor reduces ADAMTS13 protein stability or increases clearance rather than blocking enzymatic activity (a "non-neutralizing" inhibitor) [64]
- The inhibitor may have been neutralized by ADAMTS13 or anti-idiotype antibodies present in blood product transfusions
- The patient has hereditary TTP

In hereditary TTP, severely deficient ADAMTS13 activity is caused by biallelic disease variants in the *ADAMTS13* gene rather than an inhibitor. The diagnosis of hereditary TTP should be considered in a patient with severe ADAMTS13 deficiency in whom an inhibitor is not demonstrated, especially if the patient has other clinical features suggestive of inherited disease (suggestive family history, onset in childhood or during first pregnancy). (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)".)

Antibodies to ADAMTS13 detected by ELISA assays have been reported in healthy individuals who have never had an episode of TTP and who do not have ADAMTS13 deficiency [55,72]. The clinical interpretation and importance of anti-ADAMTS13 antibodies measured by ELISA are not known, and the level of anti-ADAMTS13 antibodies that should be considered abnormal is not consistently defined.

Presumptive diagnosis — The presumptive diagnosis of TTP is made by the findings of MAHA and thrombocytopenia without another obvious cause in the appropriate clinical setting. Fever, neurologic findings, and/or reduced kidney function may be present but are not required. (See 'MAHA and thrombocytopenia' above.)

All patients with a presumptive diagnosis of TTP should be treated urgently with TPE and glucocorticoids while awaiting results of ADAMTS13 activity testing. (See "Immune TTP: Initial treatment", section on 'Therapeutic plasma exchange (TPE)'.)

Confirmed diagnosis — The diagnosis of immune TTP is confirmed by the finding of severe ADAMTS13 deficiency (activity <10 percent, sometimes higher) and an ADAMTS13 inhibitor in the appropriate clinical setting (a patient with MAHA and thrombocytopenia that responds to TPE). Some individuals with immune TTP may have higher levels of ADAMTS13 activity, and in some an inhibitor may not be detectable. Diagnosis should not be considered confirmed (or

excluded) based on ADAMTS13 testing alone. (See 'Reduced ADAMTS13 activity' above and 'ADAMTS13 testing' above.)

All patients with a confirmed diagnosis of TTP should be treated without delay. (See "Immune TTP: Initial treatment", section on 'Summary and recommendations'.)

Evaluation for organ injury — TTP has the potential to affect any organ, including the central nervous system, gastrointestinal tract, heart, and/or kidneys. (See 'Neurologic and other organ involvement' above.)

Our practice is shifting towards greater use of testing to document organ involvement as we continue to see long-term complications of disease. We generally do the following testing if not done during the initial evaluation:

- Serum troponin level and electrocardiogram
- Brain imaging with MRI in patients with neurologic symptoms

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of immune TTP is broad and includes all conditions that may present with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, including other primary thrombotic microangiopathies (TMAs) as well as a variety of systemic conditions (table 2).

Other conditions in the differential diagnosis include causes of anemia and thrombocytopenia associated with red blood cell (RBC) abnormalities on the peripheral blood smear that may appear to be schistocytes to some observers (or to automated counters) but actually are not.

- **Other primary TMAs**:
  - Hereditary TTP (see "Hereditary thrombotic thrombocytopenic purpura (hTTP)")
  - Drug-induced TMA (DITMA) (see "Drug-induced thrombotic microangiopathy (DITMA)")
  - Shiga toxin-associated hemolytic uremic syndrome (ST-HUS) (see "Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS" and "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome in children")
  - Complement-mediated TMA (see "Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS" and "Complement-mediated hemolytic uremic syndrome in children")

- Metabolism-mediated TMA, coagulation-mediated TMA, and others (see "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)")

Like immune TTP, many of these conditions present with MAHA and thrombocytopenia, and the spectrum of clinical presentations is broad. Unlike immune TTP, the other primary TMAs often have significant kidney impairment as a more prominent finding. Unlike immune TTP, the other primary TMAs (with the exception of hereditary TTP) are not characterized by severe ADAMTS13 deficiency (activity <10 percent).

- **Other systemic conditions that produce MAHA and thrombocytopenia**

  - Pregnancy-associated disorders such as preeclampsia and HELLP (hemolysis, elevated liver function tests, and low platelets) (see "Thrombocytopenia in pregnancy")
  - Disseminated intravascular coagulation (DIC) (see "Evaluation and management of disseminated intravascular coagulation (DIC) in adults")
  - Infection (see "Malaria: Clinical manifestations and diagnosis in nonpregnant adults and children" and "Babesiosis: Clinical manifestations and diagnosis")
  - Cancer (see "Causes of anemia in patients with cancer")
  - Severe hypertension (see "Approach to hypertensive emergencies and urgencies in children")
  - Rheumatologic conditions such as catastrophic antiphospholipid syndrome (CAPS) (see "Catastrophic antiphospholipid syndrome (CAPS)")
  - Systemic lupus erythematosus (SLE) (see "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults")

  Like immune TTP, these conditions are associated with MAHA and thrombocytopenia, with or without organ involvement. Like TTP, the pregnancy-associated syndromes are more likely to occur near term, at delivery, or immediately postpartum. Unlike TTP, these conditions do not cause severe ADAMTS13 deficiency, although they may be associated with low activity (between 10 and 60 percent). Unlike TTP, DIC is associated with alterations in coagulation testing. Unlike TTP, these conditions respond to treatment focused on the underlying condition rather than to TPE. Unlike TTP, the pregnancy-associated syndromes typically resolve following delivery (often within 36 hours).

- **CAPS and SLE** – Unlike TTP, catastrophic APS (CAPS) is associated with antiphospholipid antibodies. (See "Catastrophic antiphospholipid syndrome (CAPS)".)

  SLE may mimic the clinical features of TTP, and kidney biopsy in SLE may show pathologic features of a TMA. Further complicating the differentiation of SLE from TTP is our

observation that SLE was more prevalent in individuals with immune TTP than in the general population [73].

- **Vascular lesions that cause MAHA** – A variety of vascular lesions may cause MAHA by mechanical fragmentation of RBCs. Examples include kaposiform capillary hemangioendotheliomas (Kasabach-Merritt syndrome), transjugular intrahepatic portosystemic shunts (TIPS), and malfunctioning cardiac valves or cardiac assist devices. Unlike TTP, patients with these lesions typically have an obvious source for RBC fragmentation, and they lack severe thrombocytopenia. (See "Non-immune (Coombs-negative) hemolytic anemias in adults", section on 'Fragmentation'.)

- **Heparin-induced thrombocytopenia (HIT) and HIT variants** – HIT is a potentially life-threatening condition caused by antibodies to complexes of platelet factor 4 and heparin. (See "Clinical presentation and diagnosis of heparin-induced thrombocytopenia".)

  Like immune TTP, patients may be acutely ill and have signs of organ infarction and thrombocytopenia. Unlike immune TTP, patients with HIT have a temporal relationship between the clinical syndrome and heparin exposure; patients with HIT more commonly have venous or arterial thrombosis, whereas TTP causes microvascular thrombosis; HIT is associated with antibodies to platelet factor 4 (PF4), and HIT does not cause MAHA or severe ADAMTS13 deficiency.

  Autoimmune HIT refers to a HIT-like syndrome that occurs in the absence of heparin. VITT refers to a HIT-like autoimmune disorder that occurs following certain adenoviral vectored coronavirus disease 2019 (COVID-19) vaccines. (See "Clinical presentation and diagnosis of heparin-induced thrombocytopenia", section on 'Terminology and HIT variants' and "COVID-19: Vaccine-induced immune thrombotic thrombocytopenia (VITT)".)

- **Hemophagocytic lymphohistiocytosis** – Hemophagocytic lymphohistiocytosis (HLH) is a disorder of immune dysregulation that leads to excessive macrophage activity, often with life-threatening consequences. Causes include infections, malignancies (especially hematologic), rheumatologic conditions, and genetic defects in macrophage activation. Children are more frequently affected, but HLH can occur in all age groups. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis".)

  Like TTP, HLH can present as a life-threatening illness with severe anemia, thrombocytopenia, and neurologic findings. Unlike TTP, patients with HLH often have abnormalities in the bone marrow and very high serum ferritin. Unlike TTP, patients with HLH do not have true MAHA, and severe thrombocytopenia is uncommon.

- **Paroxysmal nocturnal hemoglobinuria** – Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem cell disorder in which lack of complement regulatory proteins (decay accelerating factor [DAF, CD55] and CD59) leads to hemolytic anemia. Venous thrombosis, including thrombosis in unusual sites such as the portal vein, may ultimately occur in up to 40 percent of individuals. (See "Clinical manifestations and diagnosis of paroxysmal nocturnal hemoglobinuria".)

  Like TTP, patients have direct antiglobulin test (DAT, Coombs test)-negative hemolytic anemia; there may be other cytopenias including thrombocytopenia; patients may have a variety of nonspecific symptoms; and some may have renal insufficiency. Unlike TTP, when thrombosis occurs in PNH it is seen in large vessels rather than small vessels, and microangiopathic changes are not characteristic of PNH.

- **Megaloblastic anemia (vitamin B12, folate, or copper deficiency)** – Megaloblastic anemia occurs when maturation of precursor cells in the bone marrow is disrupted. Interference with DNA synthesis is usually the mechanism, and common causes include medications used for cancer or autoimmune disorders or deficiencies of vitamin B12, folate, or copper. (See "Macrocytosis/Macrocytic anemia", section on 'Megaloblastic anemia' and "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)", section on 'Exclude systemic disorders associated with MAHA and thrombocytopenia'.)

  Like TTP, patients may have Coombs-negative hemolytic anemia, markedly increased lactate dehydrogenase (LDH), and thrombocytopenia, and abnormally shaped RBCs flagged by automated counters as schistocytes. Like TTP, megaloblastic anemia may be associated with a variety of neurologic findings, especially vitamin B12 deficiency. Unlike TTP, megaloblastic anemia may also cause leukopenia. The peripheral blood smear in megaloblastic anemia often shows macro-ovalocytes rather than schistocytes, although schistocytes may be seen [74]. In most cases of megaloblastic anemia, a review of medications or diagnostic testing will reveal the cause.

- **Myelodysplastic syndrome** – Myelodysplastic syndromes (MDS) are hematopoietic stem cell neoplasms, although in many cases the primary findings are of dysplasia or cytopenias rather than malignant cells. (See "Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS)".)

  Like TTP, MDS may present with anemia and thrombocytopenia, and the RBC morphology may be abnormal. Unlike TTP, MDS may be associated with leukopenia and/or immature white blood cells in the peripheral blood, and MDS is not associated with true MAHA.

- **Evans syndrome** – Evans syndrome is the combination of two or more autoimmune cytopenias, most commonly warm autoimmune hemolytic anemia and immune thrombocytopenia (ITP). It is often seen in the setting of an underlying autoimmune, infectious, lymphoproliferative, or immunodeficiency syndrome. (See "Warm autoimmune hemolytic anemia (AIHA) in adults", section on 'Evans syndrome'.)

  Like TTP, the patient may present with anemia and thrombocytopenia. Unlike TTP, in Evans syndrome, the direct antiglobulin test (DAT, Coombs test) is positive and there is not true MAHA.

- **Complications of sickle cell disease** – Some complications of sickle cell disease (SCD) may raise the suspicion of TTP, and the evaluation of MAHA may be more challenging when the peripheral blood smear shows numerous sickled cells. Examples include hyperhemolytic crisis, multiorgan failure, or stroke. (See "Overview of the clinical manifestations of sickle cell disease".)

  Like TTP, patients with SCD and these complications may have severe anemia, an abnormal blood smear, increased LDH, neurologic findings, and/or abnormal kidney function. Unlike TTP, patients with these complications of SCD generally do not have severe thrombocytopenia or true MAHA [75].

POST-DIAGNOSTIC EVALUATION

Additional evaluations may be appropriate following diagnosis, but these generally do not affect acute management.

Review of possible contributing conditions (medications, autoimmune disorders) — Review of medication exposures and the medical history may reveal a drug or condition associated with immune TTP. (See 'Terminology and disease definitions' above.)

The contributions of these medications and conditions is unclear; it is unknown whether they are causative, trigger TTP in an otherwise predisposed individual, or serve as a marker for immune dysregulation [76]. Thus, we prefer the term drug-associated TTP (DA-TTP) rather than drug-induced TTP to reflect the uncertainty about pathogenesis. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)", section on 'TTP pathogenesis'.)

This information may not affect the acute management of immune TTP, but it may be important for disease classification and/or to alert the medical team to the other diagnosis.

- **Medications** – Several medications have been associated with immune TTP [77].

- Immune checkpoint inhibitors (ICIs; ipilimumab, pembrolizumab, atezolizumab)
- Other biologic agents or small molecules (dasatinib, lenalidomide, pazopanib)
- Coronavirus disease 2019 (COVID-19) vaccines
- Other vaccines (influenza, pneumococcal, rabies)
- Interferon
- Immunosuppressive therapies (infliximab, methotrexate, ustekinumab)
- Antibiotics (rifampin, cephalexin, ciprofloxacin, sulfamethoxazole-trimethoprim, leflunomide, terbinafine, ribavirin)
- Anti-platelet agents (ticlopidine, clopidogrel, ticagrelor)
- Others (analgesics, statins, lacosamide, methimazole)

- **Medical conditions:**
  - Systemic lupus erythematosus
  - COVID-19

Genetic testing — Selected individuals may undergo genetic testing of the *ADAMTS13* gene to evaluate for biallelic pathogenic variants, which would indicate hereditary TTP.

Clues to possible hereditary TTP include:

- Positive family history for TTP (typically affecting siblings but not parents)
- Onset of acute TTP during childhood or pregnancy
- Multiple recurrent episodes of TTP
- Absence of a demonstrable ADAMTS13 inhibitor
- Persistence of severe ADAMTS13 deficiency during clinical remission

Genetic testing for *ADAMTS13* variants is available at no charge for patients with these criteria for suspected TTP through the Hereditary TTP (Upshaw-Schulman syndrome) Registry (www.ttpregistry.net). (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)".)

Initial treatment of hereditary TTP with therapeutic plasma exchange and other treatments for immune TTP will be effective, but once the diagnosis of hereditary TTP becomes established, treatment can be restricted to plasma infusion without immunosuppressive therapy. (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)", section on 'Management'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Thrombotic microangiopathies (TTP, HUS, and related disorders)".)

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: Thrombotic thrombocytopenic purpura (TTP)".)

SUMMARY AND RECOMMENDATIONS

- **Definition and prevalence** – Immune thrombotic thrombocytopenic purpura (TTP) is a primary thrombotic microangiopathy (TMA) caused by severe ADAMTS13 deficiency (typically, activity <10 percent) due to inhibitory autoantibodies against ADAMTS13. It occurs in approximately 3 in 1 million adults and 0.1 in 1 million children annually. Female sex is a risk factor, and the incidence is increased in Black individuals. (See 'Terminology and disease definitions' above and 'Epidemiology' above.)

- **Clinical** – Immune TTP usually presents as severe microangiopathic hemolytic anemia (MAHA) and thrombocytopenia in a previously healthy individual (table 1). The typical patient is a young adult, but children and older adults can be affected. Pregnancy is not uncommon. Not all patients are critically ill; some may have minor weakness, dizziness, gastrointestinal symptoms, cardiac impairment, or reduced kidney function. The complete blood count (CBC) shows severe thrombocytopenia and MAHA (picture 1). (See 'Overview of presentation' above.)

- **Presumptive diagnosis** – Diagnosing TTP and initiating therapeutic plasma exchange (TPE) are urgent. We make a presumptive diagnosis of immune TTP based on clinical features and initial laboratory testing with platelet count and review of the peripheral blood smear, serum chemistries and creatinine, testing to demonstrate hemolysis, and direct Coombs test. This evaluation is quantified using the PLASMIC score (calculator 1). A presumptive diagnosis is an indication to initiate TPE, glucocorticoids, rituximab, and in selected patients, caplacizumab. These potentially life-saving therapies should not be

delayed while awaiting confirmatory testing. (See 'PLASMIC score' above and 'Presumptive diagnosis' above and "Immune TTP: Initial treatment", section on 'Therapeutic plasma exchange (TPE)'.)

- **Confirmed diagnosis** – Immune TTP is characterized by severe ADAMTS13 deficiency (activity <10 percent) and an inhibitor (autoantibodies directed against ADAMTS13). ADAMTS13 activity and inhibitor testing is important for diagnosis, but results cannot be used in isolation. Results often are not immediately available, may differ by assay method, and may be altered by transfusions, TPE, or bilirubin >20 mg/dL. ADAMTS13 deficiency after recovery (biochemical relapse) has different implications than clinical relapse. In a patient with MAHA and thrombocytopenia that responds to TPE, severe ADAMTS13 deficiency with an inhibitor confirms the diagnosis of immune TTP. (See 'ADAMTS13 testing' above and 'Confirmed diagnosis' above and "Immune TTP: Management following recovery from an acute episode and during remission", section on 'Detecting and preventing relapse'.)

- **Differential** – The differential diagnosis includes other primary TMAs such as hereditary TTP, drug-induced TMA, and complement-mediated TMA; other systemic conditions associated with MAHA and thrombocytopenia; disorders with mechanical red blood cell fragmentation; and conditions with cytopenias and abnormalities of the peripheral blood smear that could be confused with MAHA (table 2). (See 'Differential diagnosis' above and "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

- **Post-diagnostic testing** – Once immune TTP is diagnosed, it may be helpful to identify associated medications such as immune checkpoint inhibitors and others listed above, as these may be candidates for future avoidance, as well as associated medical conditions for which treatments are available. Genetic testing may be helpful in individuals with suspicion for hereditary TTP. (See 'Post-diagnostic evaluation' above.)

- **Management** – Management is discussed separately. (See "Immune TTP: Initial treatment" and "Immune TTP: Management following recovery from an acute episode and during remission" and "Immune TTP: Treatment of clinical relapse".)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Lawrence LK Leung, MD, who contributed to earlier versions of this topic review.

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Topic 1338 Version 56.0

GRAPHICS

Presenting features of 78 consecutive patients with immune TTP

Signs and symptoms	Number affected*
Microangiopathic hemolytic anemia (MAHA)	78 (100%)
Thrombocytopenia	78 (100%)
Neurologic abnormalities	
▪ Severe (coma, stroke, seizure, focal signs)	41 (53%)
▪ Minor (confusion, headache)	21 (27%)
▪ No neurologic abnormalities	16 (20%)
Kidney function abnormalities	
▪ Acute kidney failure¶	4 (5%)
▪ Reduced kidney function	37 (47%)
▪ Normal kidney function	37 (47%)
Fever	8 (10%)

Refer to UpToDate for additional details.

TTP: thrombotic thrombocytopenic purpura; MAHA: microangiopathic hemolytic anemia.

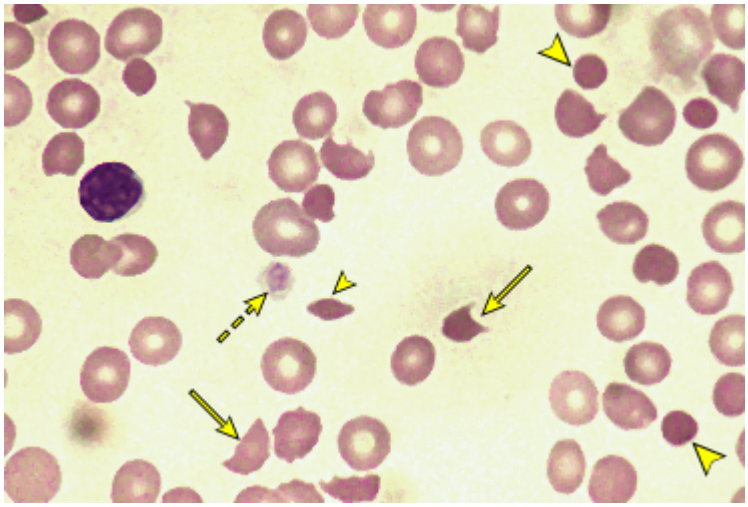
* Data are from the day of diagnosis, defined as the day of the first therapeutic plasma exchange. ADAMTS13 activity was <10% of normal in all cases.

¶ Acute kidney failure was defined as an increased serum creatinine of ≥0.5 mg/dL/day for two consecutive days or a serum creatinine of ≥4.0 mg/dL with hemodialysis.

Data from: Page EE, Kremer Hovinga JA, Terrell DR, et al. Thrombotic thrombocytopenic purpura: Diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Advances 2017; 1:590.

Graphic 57941 Version 10.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

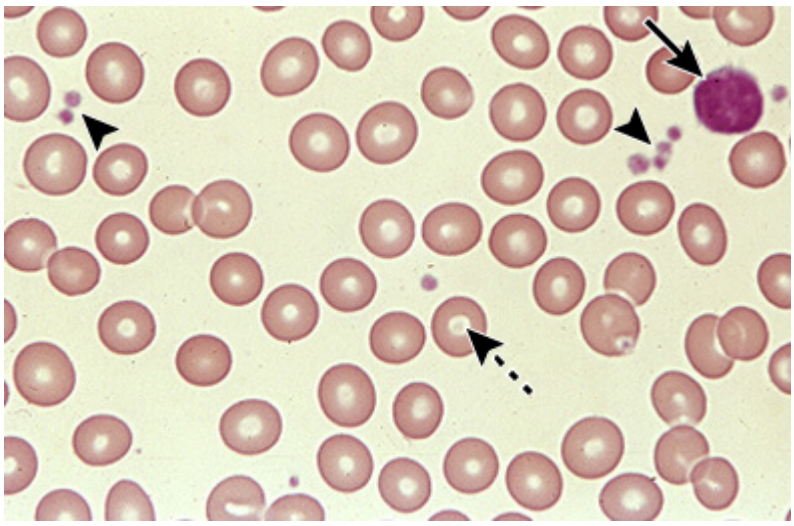


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows) and other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large platelet in the center (dashed arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70851 Version 8.0

Normal peripheral blood smear



High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter

of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

TMA syndromes and other systemic disorders associated with microangiopathi hemolytic anemia (MAHA) and thrombocytopenia

Syndrome	Clinical features	Laboratory findings
Primary thrombotic microangiopathy (TMA) syndromes		
Thrombotic thrombocytopenic purpura (TTP)	May have severe neurologic abnormalities. Immune TTP is uncommon in children. Hereditary TTP may present in a newborn infant, a child with thrombocytopenia, or, less commonly, an adult. Among adults, a common presentation is during a first pregnancy.	Severe MAHA and thrombocytopenia; acute kidney injury is rare. Severe deficiency of ADAMTS13 (activity <10%). ▪ Immune TTP often has a detectable ADAMTS13 inhibitor (autoantibody). ▪ Hereditary TTP has biallelic pathogenic variants in the *ADAMTS1* gene.
Complement-mediated TMA	Hereditary and acquired disorders may present in children or adults.	Kidney failure is prominent. Hereditary disorders usually are heterozygous for a pathogenic variant in a gene encoding a regulatory protein in the alternate complement pathway (eg, *CFH*, *CFI*, *CD46/MCP*, *C3*, *CFB*, *CFHRs*) Acquired disorders typically have antibodies to complement factor H.
Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)	Abdominal pain; diarrhea (often bloody); possible history of outbreak or exposure to livestock or contaminated food, although most cases are sporadic.	Kidney failure is prominent. Stool may be positive for the organism (*Escherichia coli* or *Shigella dysenteriae*) or Shiga toxin.
Drug-induced TMA	History of exposure to an implicated medication. Immune-mediated forms have an abrupt onset with fever, chills, abdominal pain, nausea, anuric acute kidney injury. Non-immune forms may arise gradually, or onset may be sudden with an intravenous toxic agent (eg, Opana-ER).	Immune-mediated: Severe acute kidney injury; drug-dependent antibodies to platelets and/or neutrophils can be demonstrated. Non-immune: May have gradual or sudden onset of kidney failure and hypertension.
Coagulation-mediated TMA	Heritable, typically presents in children <1 year old.	Pathogenic variants in the genes for diacylglycerol kinase epsilon (*DGKE*), thrombomodulin, or plasminogen.

Metabolism-mediated TMA	Heritable, typically presents in children <1 year old. Rarely, may be recognized for the first time in adults.	Elevated serum homocysteine and methylmalonic acid, and low methionine levels; increased urinary methyl-malonic acid. Pathogenic variants in the *MMACHC* gene.
Systemic disorders that may present with MAHA and thrombocytopenia		
Disseminated intravascular coagulation (DIC)	May be caused by infection, malignancy, postpartum hemorrhage with hypotension, or a vascular abnormality such as a giant hemangioma (eg, Kasabach-Merritt syndrome).	Thrombocytopenia, decreased fibrinogen, and elevated D-dimer are typical with acute or chronic DIC. MAHA may occur. Prolongation of the PT and aPTT are seen in acute DIC.
Systemic infection	May include bacterial, viral, rickettsial, or fungal organisms. High fever and shaking chills are common.	
Systemic malignancy	May occur with occult systemic malignancy. Breast, prostate, lung, pancreatic, or gastrointestinal tumors are often responsible.	Depends on specific tumor.
Pregnancy-related syndromes (eg, severe preeclampsia, HELLP)	Typically present in third trimester or postpartum. Severe hypertension and liver involvement are often present. Abnormalities resolve with delivery.	Elevated hepatic transaminases. Acute kidney injury is uncommon.
Severe hypertension	Typically, systolic BP >200 mmHg and diastolic BP >100 mmHg. Neurologic features including PRES may be present. Hypertension may also occur in primary TMAs with severe kidney involvement, so the temporal relationship is important. Abnormalities resolve with control of the BP.	Often associated with severe kidney failure. Kidney biopsy demonstrates TMA identical to the primary TMA syndromes.
Systemic rheumatic diseases (eg, SLE, SSc, APS)	SLE may be associated with hypertension, chronic kidney disease, and autoimmune cytopenias. APS typically presents with arterial and/or venous thromboembolism but can also produce a TMA.	Serologic testing may show autoantibodies characteristic of the underlying condition; APS may have prolonged aPTT. Kidney biopsy may demonstrate TMA identical to the primary TMA syndromes.
Hematopoietic stem cell transplantation	May occur with autologous or allogeneic hematopoietic stem cell transplantation. May be associated with exposure to cytotoxic chemotherapy,	No specific findings.

	radiation, systemic infection, or a calcineurin inhibitor.	
Solid organ transplant	May be associated with calcineurin inhibitor administration. May be associated with infection such as CMV in the setting of immunosuppression. In patients receiving a kidney transplant for a primary TMA syndrome, the syndrome may recur in the transplanted kidney.	Kidney biopsy may have features of rejection.

Therapy for primary TMAs is directed at the underlying pathophysiology; therapy for other systemic disorders associated with MAHA and thrombocytopenia is focused on the underlying disorder. Refer to UpToDate topics on evaluating patients with suspected TMA and on specific syndromes for additional information on presentation/diagnosis and management.

TMA: thrombotic microangiopathy; ADAMTS13: A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13; DGKE: diacylglycerol kinase epsilon; HELLP: hemolysis, elevated liver function tests, and low platelets; BP: blood pressure; PRES: posterior reversible encephalopathy; SLE: systemic lupus erythematosus; SSc: systemic sclerosis (scleroderma); APS: antiphospholipid syndrome; CMV: cytomegalovirus; PT: prothrombin time; aPTT: activated partial thromboplastin time.

Modified from: George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Eng J Med 2014; 371:654.

Graphic 100722 Version 7.0