JAMA | Review

Immune Thrombotic Thrombocytopenic Purpura
A Review

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IMPORTANCE Immune thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy that presents with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Worldwide annual incidence of iTTP is 2 cases per million to 6 cases per million.

OBSERVATIONS Immune TTP is caused by an autoantibody to a disintegrin and metallopeptidase with thrombospondin type 1 motif 13 (ADAMTS13), an enzyme that cleaves von Willebrand factor (vWF). With severely low ADAMTS13 activity (<10%), large multimers of vWF accumulate and bind platelets, forming microvasculature thromboses that cause ischemic organ injury (eg, myocardial infarction and stroke). The incidence of iTTP is higher in adults than children (incident rate ratio [IRR], 31.62 per million person-years [95% CI, 14.68-68.10]), females than males (IRR, 3.19 [95% CI, 2.65-3.85]), and Black compared with non-Black individuals (IRR, 7.09 [95% CI, 6.05-8.31]). Common presenting symptoms are neurologic (eg, headache, confusion, or seizures [39%-80%]) and abdominal pain (35%-39%). For patients presenting with MAHA and thrombocytopenia, clinical prediction scores for iTTP using laboratory data, such as platelet count less than 30×10^9/L and creatinine level less than 2.0 mg/dL (176.8 µmol/L), can help guide empirical treatment initiation for iTTP before ADAMTS13 results are available. Prompt initiation of therapy with therapeutic plasma exchange, corticosteroids, and rituximab improves survival with iTTP from almost zero to approximately 93%. Caplacizumab, a synthetic small antibody (nanobody) that blocks platelet binding to vWF, administered concurrently with immunosuppression and therapeutic plasma exchange and continued until ADAMTS13 recovery, reduces the time to normalization of platelet count and decreases the risk of early recurrence (defined as within 30 days of completing therapeutic plasma exchange) compared with placebo (risk difference [RD], −29% [95% CI, −42 to −14%]) but increases bleeding risk (RD, 17% [95% CI, 4%-30%]). After obtaining clinical remission (defined as at least 30 days of sustained normalization of platelet count, decreased serum lactate dehydrogenase level, and absence of new or progressive ischemic organ injury without therapeutic plasma exchange or caplacizumab), 16% of patients have at least 1 relapse of iTTP. Regular monitoring of ADAMTS13 activity in remission and administration of rituximab when ADAMTS13 activity is less than 20% reduces risk of relapse (odds ratio, 0.09 [95% CI, 0.04-0.24]).

CONCLUSIONS AND RELEVANCE Immune TTP is a rare immune-mediated disorder that presents with thrombocytopenia and MAHA and may cause life-threatening thrombosis. Treatment with therapeutic plasma exchange, corticosteroids, and rituximab is associated with 30-day survival rates of more than 90%. Addition of caplacizumab shortens time to normalization of platelet count and reduces recurrences while receiving the drug but increases bleeding risk. Monitoring ADAMTS13 activity in survivors and initiation of rituximab for those with low ADAMTS13 activity reduces the risk of clinical relapse.

JAMA. doi:10.1001/jama.2025.3807
Published online May 19, 2025.

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Immune thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy with hemolytic anemia and thrombocytopenia that is caused by an acquired severe deficiency of a disintegrin and metallopeptidase with thrombospondin type 1 motif 13 (ADAMTS13) (<10%), which normally cleaves ultralarge multimers of von Willebrand factor (vWF).[1,2] Microangiopathic thrombosis associated with iTTP may cause complications such as stroke, myocardial infarction, and kidney injury.[3] This review highlights the epidemiology of iTTP and clinical prediction scores for the diagnosis of TTP in adults; reviews evidence for treatment of acute iTTP and prevention of relapse; and discusses potential long-term complications of iTTP (**Box**).

Methods

We searched PubMed for English-language studies on the epidemiology, pathophysiology, diagnosis, treatment, and prognosis of iTTP from January 1, 2010, to April 2, 2025. We manually reviewed the reference lists of selected articles and reviews for other relevant sources such as earlier studies of therapeutic plasma exchange, corticosteroids, and splenectomy. Of the 1841 articles reviewed, we included 76 articles, composed of 4 randomized clinical trials; 2 single-group clinical trials; 53 retrospective or observational studies; 5 meta-analyses; 8 society guideline or recommendation, working group guidance, or expert consensus documents; 4 narrative reviews.

Box. Commonly Asked Questions About iTTP

How Is iTTP Distinguished From Other Thrombotic Microangiopathies?
A clinical prediction score, such as the PLASMIC or FRENCH score, can be used to predict the likelihood of iTTP. The pathognomonic finding of iTTP is thrombotic microangiopathy with ADAMTS13 activity less than 10%, although patients with ADAMTS13 activity of 10% to 20% may have iTTP.

What Are the Benefits and Risks of Caplacizumab for iTTP?
For patients with iTTP, the addition of caplacizumab to treatment with therapeutic plasma exchange, corticosteroids, and rituximab shortens time to normalization of platelet count and reduces risk of recurrence while receiving the drug but does not reduce relapse risk (beyond 30 days of caplacizumab discontinuation). The major adverse effect of caplacizumab is bleeding.

How Should Patients With iTTP Be Monitored Long Term?
After recovery from an initial episode of iTTP, patients are at risk for relapse of the disease. Monitoring ADAMTS13 activity at regular intervals and administering rituximab if ADAMTS13 activity falls below 20% decreases the risk of relapse.

Abbreviations: ADAMTS13, a disintegrin and metallopeptidase with thrombospondin type 1 motif 13; iTTP, immune thrombotic thrombocytopenic purpura.

Discussion

Pathophysiology

TTP results from severe deficiency of the enzyme ADAMTS13, which normally cleaves vWF. Without ADAMTS13, large multimers of vWF accumulate and bind platelets, leading to the formation of thrombi in the microvasculature.[4] These thrombi shear red blood cells and cause ischemic organ injury, such as stroke and myocardial infarction (**Figure 1**).In iTTP, autoantibodies (typically IgG) result in the inhibition or clearance of ADAMTS13.[2] Severe deficiency in ADAMTS13 activity (<10%) is necessary for development of TTP, but some patients with iTTP may have extended periods of severe deficiency of ADAMTS13 prior to presenting with clinical relapse.[5]

Epidemiology

TTP is a rare disease, with a worldwide annual incidence of 2 to 6 cases per million.[6-8] The incidence rate of iTTP is higher in adults than children (incident rate ratio [IRR] for adults vs children, 31.62 per 100 000 person-years [95% CI, 14.68-68.10]), females than males (IRR, 3.19 per 100 000 person-years [95% CI, 2.65-3.85]), and Black individuals compared with non-Black individuals (race assigned by investigators) (IRR, 7.09 per 100 000 person-years [95% CI, 6.05-8.31]).[7] Most cases of TTP in adults (>95%) are immune-mediated from autoantibodies to ADAMTS13 (iTTP), with the remaining 3% to 5% due to congenital deficiency of ADAMTS13.[6] A cross-sectional analysis of a FRENCH cohort of 939 adult patients with TTP reported associated conditions of autoimmune disease (eg, severe systemic lupus erythematosus or catastrophic antiphospholipid syndrome [14%]), infection (eg, HIV [13%]), pregnancy (7%), disseminated malignancy (4%), transplantation (1%), or drugs (eg, ticlopidine, quinine, gemcitabine, and calcineurin inhibitors [1%]).[6]

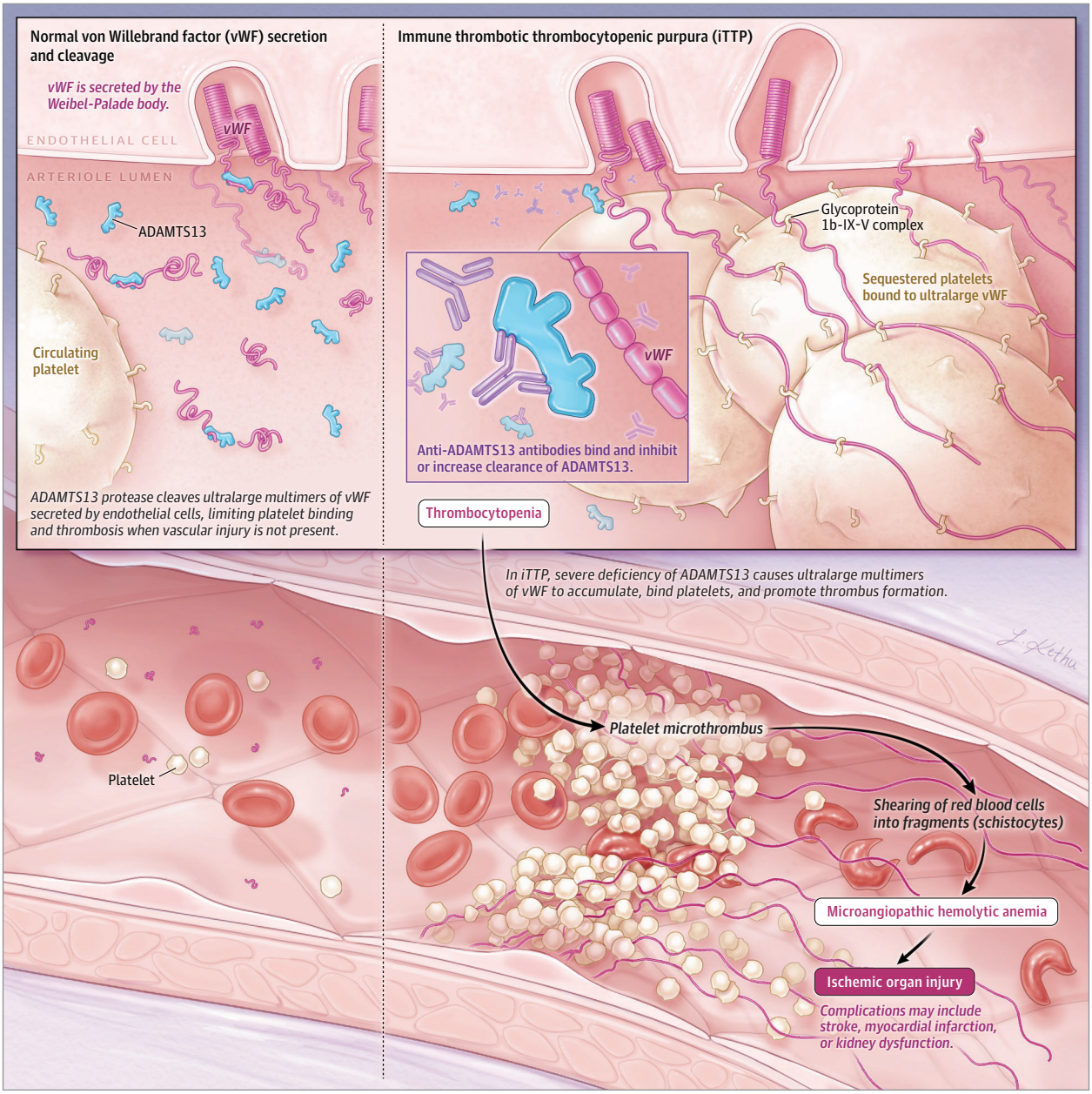
Diagnosis of iTTP

Clinical Presentation and Initial Laboratory Findings

Common presenting features of iTTP include neurologic symptoms (eg, headache, confusion, vision changes or seizures [39%-80%]), abdominal pain or nausea (35%-39%), and fever (10%-35%).[9-11] Less than 10% of patients exhibit the full "pentad" of TTP manifestations (hemolytic anemia, thrombocytopenia, fever, kidney and neurologic dysfunction) at presentation.[6,12]

Key laboratory findings in iTTP are thrombocytopenia (typical platelet count <30 × 10^9/L) and microangiopathic hemolytic anemia (MAHA). MAHA is hemolytic anemia, diagnosed by elevated serum lactate dehydrogenase (LDH) and indirect bilirubin levels; reticulocyte count above the upper limits of normal; serum haptoglobin level below the lower limits of normal; and a negative result from Coombs testing for anti-red cell antibody or complement. With MAHA, schistocytes are the prominent red blood cell morphologic abnormality on a peripheral blood smear, at a frequency of 1% of red blood cells or greater.[13] Daily blood smear examination should be performed in patients with high clinical suspicion for iTTP because schistocytes may not be present initially.[13] Coagulation tests (prothrombin time, activated partial thromboplastin time) are typically normal or only mildly prolonged with iTTP. In a study of 363 patients with iTTP, acute kidney injury occurred in up to 48% of patients (creatinine level ≥1.5 mg/dL [to convert creatinine values to μmol/L, multiply by 88.4]), but only 14% have a serum creatinine level 2.5 mg/dL or greater.[10] Only 5% had kidney failure, defined as either a serum creatinine level increasing by 0.5 mg/dL or more per day for 2 days or a serum creatinine level 4.0 mg/dL or greater plus dialysis within 7 days of the diagnosis.[10] A diagnostic and initial treatment workflow is summarized in **Figure 2**.

Figure 1. Pathophysiology of Immune Thrombotic Thrombocytopenic Purpura



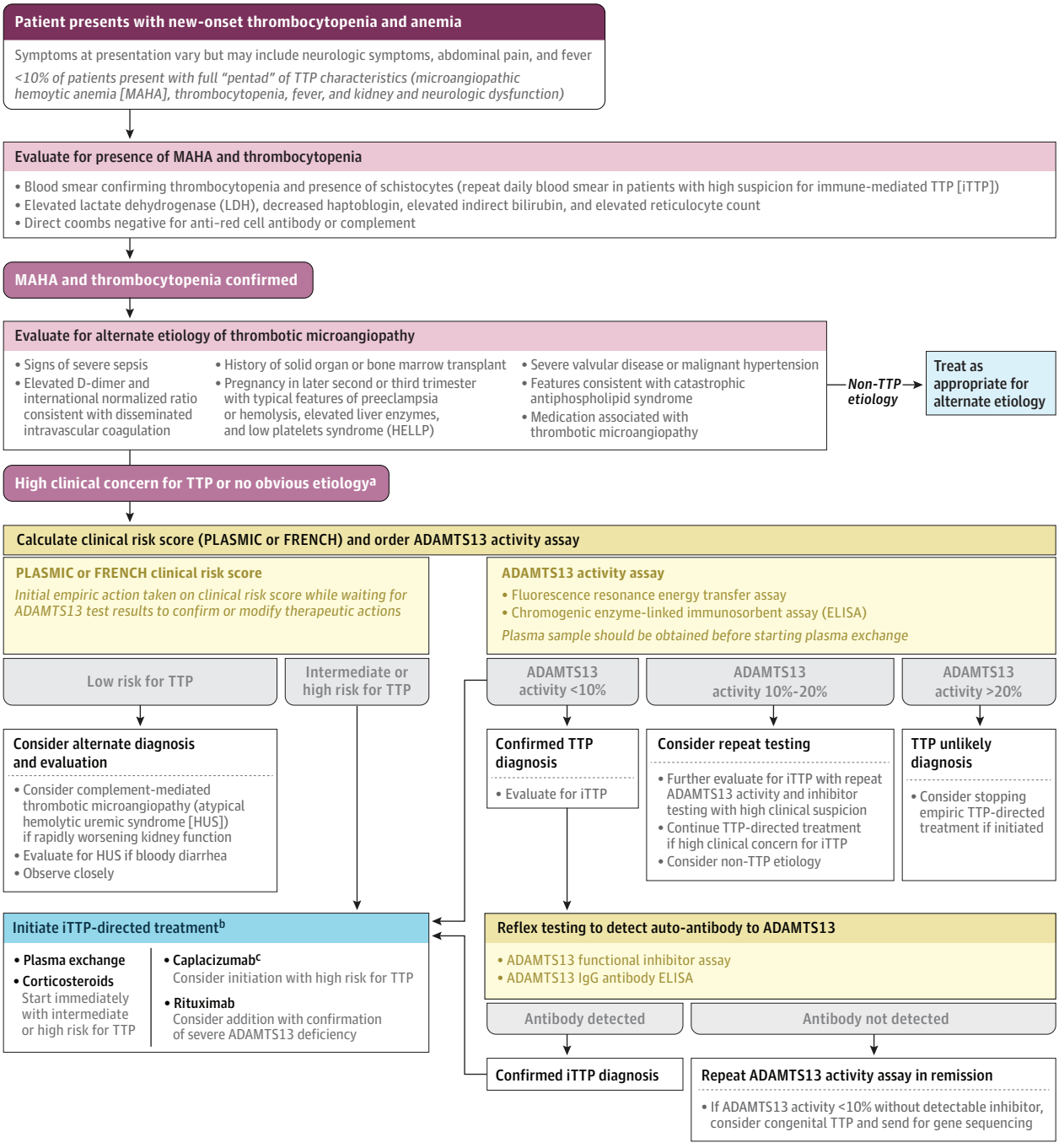
ADAMTS13 indicates a disintegrin and metallopeptidase with thrombospondin type 1 motif 13.

ADAMTS13 Activity Testing and Interpretation

Patients with MAHA and thrombocytopenia without another clear etiology for thrombotic microangiopathy, such as active malignancy, transplantation, severe sepsis, or disseminated intravascular coagulation,[14] should undergo testing of ADAMTS13 activity. The diagnosis of TTP is made in patients with MAHA, thrombocytopenia, and ADAMTS13 activity less than 10% (lower limit of normal for ADAMTS13 activity varies by method and assay, generally 40%-60%).[15-17] Patients with ADAMTS13 activity of 10% to 20% and high suspicion for iTTP should undergo repeat ADAMTS13 activity testing to avoid missing iTTP, and treatment should be initiated for those deemed likely to have iTTP.[14]

ADAMTS13 activity is most commonly measured by a fluorescence resonance energy transfer assay or a chromogenic enzyme-linked immunosorbent assay.[16] Plasma samples for ADAMTS13 activity should ideally be obtained prior to therapeutic plasma exchange, because the levels may be falsely elevated by ADAMTS13 in the donor plasma. A study of 19 patients with iTTP reported the sensitivity of detecting severe deficiency (ADAMTS13 activity <10%) at 89% within 1 day of therapeutic plasma exchange initiation, 83% within 2 days, and 78% within 3 days of therapeutic plasma exchange initiation.[18] Due to the need for technical expertise to perform these assays, ADAMTS13 testing is often sent to reference laboratories, and reporting of results typically takes more than 72 hours.

Figure 2. Initial Diagnostic Workflow for Patients With Suspected Thrombotic Thrombocytopenic Purpura



ADAMTS13 indicates a disintegrin and metallopeptidase with thrombospondin type 1 motif 13; TTP, thrombotic thrombocytopenic purpura.

[a]If atypical or severe features of another etiology are present (eg, severe neurologic symptoms with preeclampsia), consider proceeding with risk score calculation and ADAMTS13 testing.

[b]Prompt hematological consultation to evaluate for initiation of empirical treatment for TTP for PLASMIC score 5 or higher or FRENCH score 1 or higher.

[c]International Society on Thrombosis and Haemostasis guidelines suggest using caplacizumab in all patients with immune TTP (confirmed by ADAMTS13 activity <10% or high pretest suspicion with ADAMTS13 results available within 72 hours). Some experts reserve it for cases of severe illness and/or refractory disease.

Hospitals with on-site testing can provide results within 6 to 24 hours, but testing is often batched and only offered during business hours.[9] To address diagnostic delays, rapid ADAMTS13 assays have been developed that can be performed in less than 60 minutes, although these rapid assays have not been widely validated.[16,19-22]

Anti-ADAMTS13 Antibody Testing

To confirm the diagnosis of iTTP, patients with low ADAMTS13 activity (predefined by the laboratory performing ADAMTS13 testing, generally 10%-30%) should undergo anti-ADAMTS13 antibody testing using a functional inhibitor assay (mixing study) and/or

Table 1. Differential Diagnosis and Features of Thrombotic Microangiopathies

Diagnosis[a]	Hemolysis[b]	Platelet count, $\times 10^9$/L[c]	Creatinine level, mg/dL[c]	Key Features[d]	Therapies
Thrombotic thrombocytopenic purpura	Yes	<30	<2	ADAMTS13 deficiency (<10%-20%)	Immune: therapeutic plasma exchange, immune suppression, caplacizumab Congenital: donor plasma or recombinant ADAMTS13
Complement-mediated thrombotic microangiopathy	Yes	>30 <100	>2	Complement dysregulation	Complement inhibitors
Infection					
Shiga toxin producing *Escherichia coli* (O157:H7)	Yes	Variable	Variable	Variable	Supportive care Disease-specific antivirals/ antimicrobials
Advanced HIV infection					
Sepsis					
Autoimmune					
Systemic lupus erythematosus	Yes	Variable	Variable	Variable	Corticosteroid with-without other immunosuppressant Anticoagulation with/without therapeutic plasma exchange
Catastrophic antiphospholipid syndrome					
Pregnancy					
Preeclampsia	Yes	Variable	Variable	Variable	Delivery of fetus
HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count)					
Cardiac					
Malignant hypertension	Yes	Variable	Variable	Variable	Treatment of hypertension or valvular disease
Malfunctioning mechanical valve					
Cancer					
Disseminated cancer	Yes	Variable	Variable	Variable	Treatment of cancer
Transplant					
Hematopoietic cell	Yes	Variable	Variable	Variable	Treatment of rejection or graft-vs-host disease, supportive care, stop offending drugs
Solid organ					
Drugs					
Quinine	Yes	Variable	Variable	Variable	Stop offending drug
Ticlopidine					
Tacrolimus					
Gemcitabine					
Mitomycin					

Abbreviation: ADAMTS13, a disintegrin and metallopeptidase with thrombospondin type 1 motif 13.

SI conversion factor: To convert creatinine values to µmol/L, multiply by 88.4.

[a] Common etiologies are listed, although the list is not meant to be exhaustive.

[b] Hemolysis: low hemoglobin level, high reticulocyte counbt/serum lactate dehydrogenase level/indirect bilirubin, low haptoglobin levels.

[c] Common laboratory values at presentation, although patients may differ.

[d] All thrombotic microangiopathies can have neurologic, cardiac, and abdominal features due to involvement of microvasculature.

an enzyme-linked immunosorbent assay for ADAMTS13 IgG antibody, preferably on a sample drawn before therapeutic plasma exchange.[18] While 67% to 97.8% of patients with iTTP have a detectable ADAMTS13 antibody, absence of an antibody does not exclude the diagnosis of iTTP.[9] When using a functional inhibitor assay, weak inhibitors or antibodies that cause increased clearance of ADAMTS13 may not be detected.[16] Furthermore, in 1 cohort of 191 patients with TTP without detectable anti-ADAMTS13 antibody on presentation, 21% had detectable antibody at subsequent follow-up.[23] If ADAMTS13 activity remains less than 10% during clinical remission with no detectable anti-ADAMTS13 antibody, congenital rather than immune-mediated deficiency of ADAMTS13 may be present.[9] The diagnosis of congenital TTP can be confirmed by genetic sequencing of the ADAMTS13 gene.[24]

Differential Diagnoses

The differential diagnosis of iTTP (**Table 1**) includes complement-mediated thrombotic microangiopathy (also known as atypical hemolytic uremic syndrome), although iTTP typically presents with more severe thrombocytopenia (platelet count <30 × 10^9/L) and relatively mild kidney dysfunction (creatinine level <2 mg/dL) (Table 1).[25] During pregnancy, the most common etiologies of thrombotic microangiopathy presenting in the second or third trimester is HELLP syndrome (preeclampsia hemolysis, elevated liver enzyme levels, and low platelet count). However, in patients with thrombotic microangiopathy presenting earlier in pregnancy or with other atypical features (eg, neurologic features or cardiac ischemia), a severely low ADAMTS13 activity level (<10%-20%) distinguishes TTP from these other pregnancy-specific conditions.[26]

Table 2. Components and Operating Characteristics of Clinical Prediction Scores for Severe ADAMTS13 Deficiency in Patients With Microangiopathic Hemolytic Anemia and Thrombocytopenia

	PLASMIC[a]	FRENCH score (modified)[b]
Components (points)	Platelet count <30 × 10^9/L (+1) Creatinine <2 mg/dL (+1) Hemolysis (indirect bilirubin >2 mg/dL or reticulocytes >2.5% or undetectable haptoglobin) (+1) INR <1.5 (+1) MCV <90 fL (+1) No active cancer (+1) No history of solid-organ or stem-cell transplant (+1)	Platelet count <30 × 10^9/L (+1) Creatinine <2.26 mg/dL (+1)
Probability of severe ADAMTS13 deficiency	Score ≥5: sensitivity, 99% (95% CI, 91%-100%); specificity, 57% (95% CI, 41%-72%)[29]	Score ≥1: sensitivity, 98.8%; specificity, 48.1%[30]

Abbreviations: ADAMTS13, a disintegrin and metallopeptidase with thrombospondin type 1 motif 13; INR, International Normalized Ratio; MCV, mean corpuscular volume.

[a] The PLASMIC score was derived in patients with microangiopathic hemolytic anemia (+schistocytes, +thrombocytopenia) for whom ADAMTS13 activity testing was sent by the treating physician. It should only be used in patients with schistocytes and clinical suspicion for thrombotic thrombocytopenic purpura.

[b] The FRENCH score was derived in patients with microangiopathic hemolytic anemia (+schistocytes, +thrombocytopenia) for whom ADAMTS13 activity testing was sent and after exclusion for known associated condition (including active cancer, transplantation, severe sepsis, and disseminated intravascular coagulation). The performance metric was estimated after exclusion of antinuclear antibody testing. The performance reported was estimated from initial derivation cohort without validation (N = 160/214 with ADAMTS13 deficiency).

Additionally, anemia from severe vitamin B_{12} deficiency (average hemoglobin level <5.5-6.1 g/L), with thrombocytopenia and hemolysis from ineffective erythropoiesis, can present similarly to MAHA but typically is associated with elevated mean corpuscular volume (mean, 109 fL), very high serum LDH level (mean, 3539 U/L [59.1 µkat/L]), low reticulocyte count (mean, 0%-4%), and near-normal bilirubin level (mean, 1.6 mg/dL [27.37 µmol/L]).[27,28]

Clinical Prediction Scores

Clinical prediction scores are useful to estimate the likelihood of severe ADAMTS13 deficiency because treatment should begin urgently in patients with iTTP, often before the results of ADAMTS13 activity are available (**Table 2**; Figure 2).[9]

The most commonly used prediction score is the PLASMIC score (Table 2).[25] A systematic review that included 13 validation cohort studies with 970 patients with thrombotic microangiopathy (defined as platelet count <150 × 10^9/L and presence of schistocytes on peripheral smear) found that a PLASMIC score of 5 or higher had a sensitivity of 99% (95% CI, 91%-100%) and specificity of 57% (95% CI, 41%-72%) for the diagnosis of iTTP.[29] Prompt hematologic consultation to evaluate for initiation of empirical treatment for TTP prior to return of an ADAMTS13 activity result should be obtained for patients with a PLASMIC score of 5 or higher.

The French Thrombotic Microangiopathy Reference Center score, derived from patients with MAHA and ADAMTS13 levels, includes only the platelet count, serum creatinine level, and antinuclear antibody test result, after excluding persons with known associated secondary causes of microangiopathy such as active malignancy, transplantation, severe sepsis, and disseminated intravascular coagulation.[30] A score of 1 or higher has a sensitivity of 98.8% (95% CI, 96.9%-100%) and specificity of 48.1% (95% CI, 38.9%-59.3%) for the diagnosis of iTTP.[30] A modified FRENCH score excluding antinuclear antibody (which is not readily available at presentation in most patients) performed similarly in the derivation study and is more commonly used.[30] No meta-analysis of validation studies is available for the FRENCH score. Prompt hematologic consultation to evaluate for initiation of empirical treatment should occur for patients with a thrombotic microangiopathy with no obvious secondary cause and a FRENCH score of 1 or higher.

In a study of 75 patients with iTTP and 57 with other causes of thrombotic microangiopathy, the sensitivity of a PLASMIC score of 5 or higher for diagnosis of iTTP was 91.4% for patients aged 18 to 39 years, 78.3% for those aged 40 to 59 years, and 76.9% for those 60 years or older.[31] The sensitivity of a FRENCH score of 1 or higher for diagnosis of iTTP was 100% for patients aged 18 to 39 years, 96.2% for those aged 40 to 59 years, and 76.9% for those 60 years or older. No clinical risk score has been derived or validated for thrombotic microangiopathy diagnosis during pregnancy.[26]

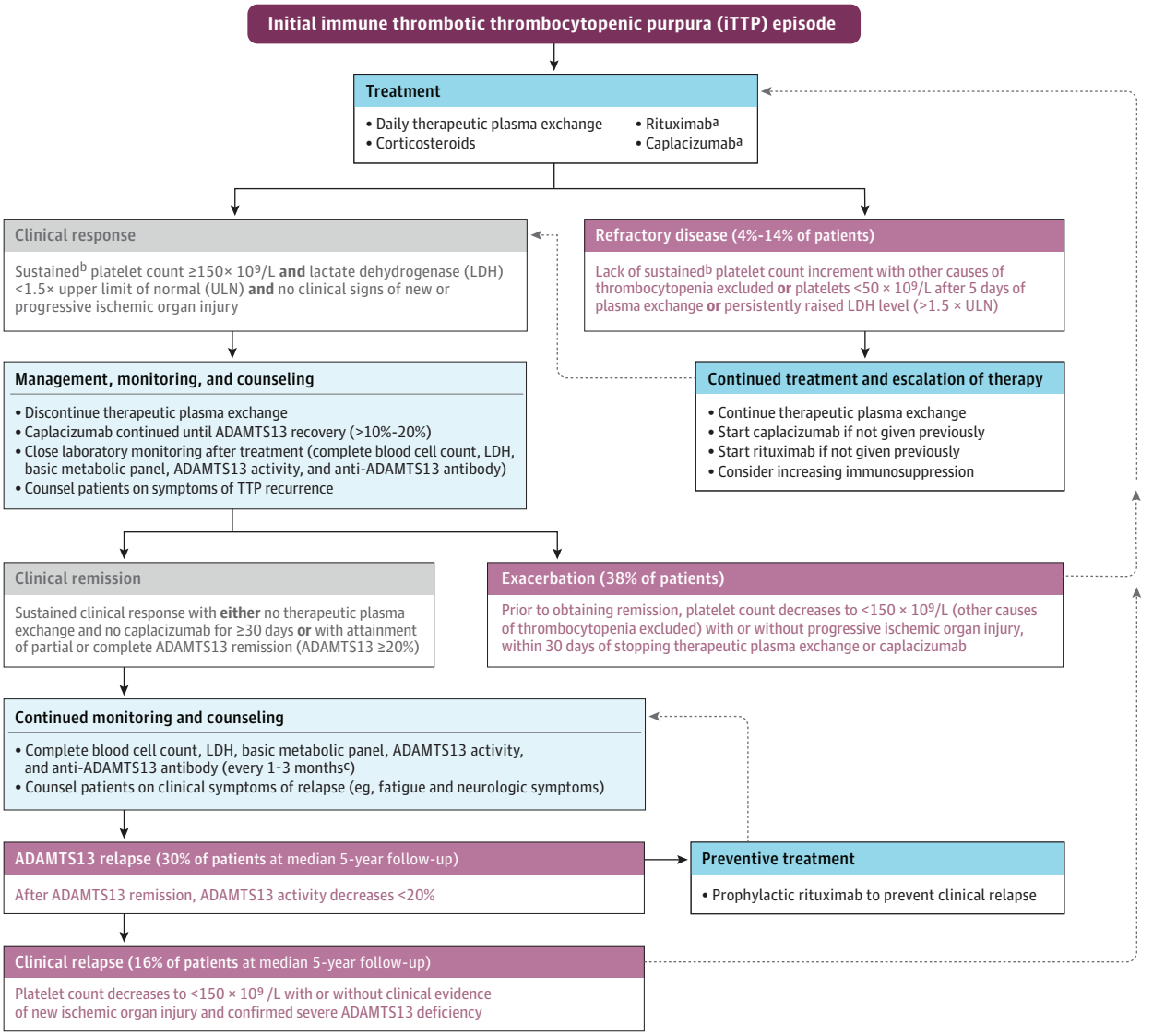
Natural History of iTTP and Outcome Definitions

Figure 3 outlines the 2021 International Working Group outcome definitions for iTTP and implications for management.[12] Most early morbidity and mortality associated with acute iTTP is due to microvascular thrombosis leading to ischemic organ injury, such as myocardial infarction and stroke. A clinical response to acute iTTP treatment is characterized by normalization of platelet count, a decrease in serum LDH level, and absence of new or progressive ischemic organ injury.[12] Patients who achieve clinical response may still have persistent deficiency of ADAMTS13 activity less than 10% caused by anti-ADAMTS13 autoantibodies, and up to 38% have an iTTP exacerbation (a recurrence within 30 days of stopping therapeutic plasma exchange and caplacizumab).[32,33] Patients who are 30 days post therapeutic plasma exchange and caplacizumab therapy with sustained clinical response have obtained clinical remission; if ADAMTS13 increases to at least 20%, they have achieved an ADAMTS13 remission.[12] Similar to other autoimmune diseases, the ADAMTS13 autoantibody may recur, and patients can have clinical or ADAMTS13 relapse years after recovery, with relapse occurring in approximately 30% of patients (16% clinical relapse, 13% ADAMTS13 relapse only) at 5-year follow-up.[5]

Treatment of an Initial iTTP Episode

For a first acute episode, the 2020 International Society on Thrombosis and Hemostasis (ISTH) guidelines recommend first-line

Figure 3. Immune Thrombotic Thrombocytopenic Purpura Outcome Definitions and Implications for Management



Boxes with headings in gray or purple are the 2021 International Working Group for Thrombotic Thrombocytopenic Purpura outcome definitions.[12] Other boxes outline steps in management. ADAMTS13 indicates a disintegrin and metallopeptidase with thrombospondin type 1 motif 13.

[a]Rituximab and caplacizumab are suggested by International Society on Thrombosis and Haemostasis guidelines (conditional recommendation). Some experts advocate for caplacizumab use in all patients with iTTP (confirmed by ADAMTS13 activity <10% or high pretest suspicion). Others reserve if for severe illness and/or refractory diseases.

[b]Sustained platelet count was not defined by working group. In our practice, we consider the patient to have achieved a clinical response when they have met the International Working Group criteria for clinical response for at least 3 days.

[c]Interval for monitoring has not been studied.

treatment of iTTP as the combination of therapeutic plasma exchange and corticosteroids (strong recommendation) along with rituximab and caplacizumab (conditional recommendation) (**Table 3**).[35]

Therapeutic Plasma Exchange

Therapeutic plasma exchange removes the antibody to ADAMTS13 and provides ADAMTS13 via donor plasma.[40,41] Therapeutic plasma exchange decreases mortality during an acute episode of iTTP from more than 90% to 9% to 20% and should be started promptly, prior to the reporting of ADAMTS13 results, in patients with intermediate or high clinical suspicion for TTP (Figure 2).[9,35] Therapeutic plasma exchange is initiated with 1 to 1.5 plasma volumes (the total estimated amount of plasma in a person's body) removed and replaced with donor plasma per procedure and continued daily until clinical response (sustained platelet count ≥150 × 10^9/L) or an alternate diagnosis has been established (ie, iTTP ruled out by ADAMTS13 activity >20%). Therapeutic plasma exchange requires apheresis catheter insertion, which is associated with procedural risks of bleeding, arterial injury, and pneumothorax[42] as well as central line infection and thrombosis.[43] There is also a risk of plasma-related transfusion reactions, occurring in 12% of patients with TTP in 1 cohort, including life-threatening anaphylaxis.[10] For patients awaiting emergent transfer to a center capable of performing therapeutic plasma exchange, plasma infusion (with infusion volume

Table 3. First-Line Therapies in Addition to Therapeutic Plasma Exchange for an Initial Episode of TTP

Therapy type	Medication and dosing	Mechanism	Time to normalization of platelet count, d	Incidence of refractory TTP	Incidence of TTP exacerbation	Incidence of TTP relapse	Overall mortality	Adverse events[a]
Immunosuppression	Prednisone (1 mg/kg/d orally) or methylprednisolone (1000 mg intravenously daily ×3 d) for severe features such as neurologic symptoms	Decrease auto-antibody production	NR	NR	NR	NR[b]	Corticosteroids: 7.9% (5/63)[35] Control: 20% (8/40)[35] Absolute risk effect: 176 fewer per 1000 (from 195 fewer to 111 fewer)[35]	Infection: NR Hyperglycemia: 9%[36] Fluid retention: 9%[36] Mood disorders: NR Hypertension: NR Gastric irritation: NR Weight gain: NR Insomnia: 9%[36] Myopathy: NR Decreased bone density (>6 wk of use) Glaucoma (>6 wk of use)
	Rituximab (375 mg/m^2 weekly ×4 doses)[c]	Deplete CD20$^+$ B cells to decrease auto-antibody production	NR	NR	NR	Rituximab: 22/139[37] Control: 74/226[37] OR, 0.4 (95% CI, 0.19-0.85)[37]	Rituximab: 8/263[37] Control: 28/262[37] OR, 0.41 (95% CI, 0.18-0.91)[37]	Infections: 19%-63%[34] Infusion reactions: 12%-77%[34] Hypogammagloublinemia: 51%-72%[34] Lymphocytopenia: 48%[34] Hepatitis B reactivation (screen and give antiviral prophylaxis) Serum sickness: <1%[34] Progressive multifocal leukoencephalopathy: <1%[34]
Anti-vWF	Caplacizumab (11 mg intravenously prior to therapeutic plasma exchange, then 11 mg subcutaneously for 30 d following therapeutic plasma exchange administration or until ADAMTS13 recovery)[d]	Nanobody blocks binding of platelets to A1 domain of von willebrand factor	Caplacizumab (median days): 2.75 (95% CI, 2.53-2.87)[38e] Placebo (median days): 3.51 (95% CI, 2.88-3.86)[38e] Pooled mean difference (days): −0.66 (95% CI, −0.90 to −0.43)[39e]	Caplacizumab: 0% (0/108)[39e] Placebo: 8.0% (89/112)[39e] Pooled risk difference: −8% (95% CI, −13% to −2%)[39e]	Caplacizumab: 5.6% (6/108)[39e] Placebo: 34.8% (39/112)[39e] Pooled risk difference: −29% (95% CI, −42% to −14%)[39e]	Caplacizumab: 15.7% (17/108)[39e] Control: 2.7% (3/112)[39e] Pooled risk difference: 14% (95% CI, 0%-27%)[39e]	Caplacizumab: 0.93% (1/108)[39e] Control: 4.5% (5/112)[39e] Pooled risk difference: −4% (95% CI, −8% to 1%)[39e]	Any bleeding: 58.5%[38] Serious bleeding: 11.3%[38] Fatigue: 15.1%[38] Headache: 20.8%[38] Nausea: 15.1%[38] Urticaria: 14.2%[38] Pyrexia: 13.2%[38] Parasthesias: 12.3%[38] Constipation: 11.3%[38] Insomnia: 10.3%[38] Injection site reactions: 3%-6%[38]

Abbreviations: ADAMTS13, a disintegrin and metallopeptidase with thrombospondin type 1 motif 13; NR, not reported; OR, odds ratio; TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor.

[a] Adverse events from studies specifically of patients with thrombotic thrombocytopenic purpura. When unavailable, incidence of adverse events of medication reported from product labeling.

[b] While some observational studies have reported relapse risk with corticosteroid use as per International Society on Thrombosis and Haemostasis treatment guideline panel, overall quality of evidence is very low, supported by only small studies with a heterogenous population and varied interventions. Thus, relapse risk with corticosteroids is not reported.

[c] Off-label use, indication not approved by the US Food and Drug Administration.

[d] The clinical trial reported using caplacizumab (10 mg), but a posttrial dose-recovery study showed that the mean dose that can be withdrawn from the vial and reconstituted is 11 mg. Thus, labeling of the commercial product labeling is 11 mg, which is equivalent to the dose used in the study.

[e] Only data from randomized trials included.

dependent on cardiac and volume status) can be considered as a temporizing measure to replace ADAMTS13.[40,44] Table 3 reviews adjunctive therapies that current ISTH guidelines recommend or suggest in the first-line setting with therapeutic plasma exchange.[35]

Corticosteroids

For patients with iTTP, corticosteroids help suppress production of autoantibodies to ADAMTS13.[35,36] The ISTH guideline panel combined data from 2 comparative observational studies (103 patients) and estimated an absolute risk reduction of 176 fewer deaths per 1000 patients (95% CI, 111-195) with corticosteroids plus therapeutic plasma exchange vs therapeutic plasma exchange alone, although the quality of evidence was considered very low due to the small sample size with heterogenous populations in the 2 studies.[35] The ISTH guidelines do not recommend a specific corticosteroid, dose, or duration, although oral prednisone (1 mg/kg daily) is commonly used. Some experts suggest treating high-risk iTTP (severe neurologic features or elevated troponin level) with intravenous methylprednisolone (1000 mg/d for 3 days).[35] Adverse effects of corticosteroids may include hyperglycemia, mood disorders (eg, depression, mania, insomnia), and increased risk of infection. Corticosteroids are generally continued during therapeutic plasma exchange and until ADAMTS13 activity increases to more than 10% to 20%, then doses are rapidly tapered to limit toxicity (duration of taper has not been studied).[44,45]

Rituximab

Rituximab, an anti-CD20 monoclonal antibody that depletes B lymphocytes, reduces autoantibody production to ADAMTS13 and helps restore ADAMTS13 activity.[37] ISTH guidelines do not specify dosing, but most studies of rituximab used 4 weekly infusions of 375 mg/m^2,[46,47] although lower doses and different schedules have been described.[48] There are currently no randomized trials of rituximab in combination with corticosteroids and therapeutic plasma exchange as first-line therapy for iTTP. A 2019 meta-analysis (6 cohort studies, 365 patients) reported a lower rate of clinical relapse with rituximab administration during an acute iTTP episode (22 relapses among 139 patients) compared with no rituximab (74 relapses among 226 patients; odds ratio, 0.40 [95% CI, 0.19-0.85])[37].

Rituximab is associated with increased risk of viral infections, including hepatitis B reactivation. Prior to initiation of rituximab, patients should be tested for total hepatitis B core antibody and hepatitis B surface antigen and, if positive, should receive antiviral prophylaxis (eg, entecavir or tenofovir).[49] Other anti-CD20 therapies, such as ofatumumab and obinutuzumab, have been used as an alternative treatment in patients with rituximab infusion–related reactions or serum sickness.[50]

Caplacizumab

Caplacizumab is a nanobody (synthetic small antibody) that binds to the A1 domain of vWF with high affinity and blocks binding of the platelet glycoprotein 1b-IX-V complex. By inhibiting platelet binding, caplacizumab prevents formation of microvascular thrombosis in patients with an acute episode of iTTP.[32,33] Caplacizumab was approved by the US Food and Drug Administration in 2019 for adult patients with iTTP in combination with therapeutic plasma exchange and immunosuppression, such as corticosteroids and rituximab.[51] A meta-analysis of 2 clinical trials (220 patients)[32,33] in which caplacizumab (10 mg) was administered intravenously once prior to therapeutic plasma exchange and continued subcutaneously following daily therapeutic plasma exchange for at least 30 days, found that patients treated with caplacizumab had a shorter time to platelet count recovery (mean difference, 0.7 days [95% CI, 0.4-0.9]) and decreased mortality (1/108 [0.9%] vs 5/112 [4.5%] in the standard-care group; risk difference [RD] of death from any cause, −4% [95% CI, −8% to 1%]; relative risk, 0.21 [95% CI, 0.05-1.74]).[39] Individuals who received caplacizumab during the first 30 days after therapeutic plasma exchange cessation had a significant decrease in iTTP exacerbations (RD, −29% [95% CI, −42% to −14%]) and refractory iTTP (RD, −8% [95% CI, −13% to −2%]) compared with standard care.[39] However, caplacizumab treatment was associated with an increase in relapse risk beyond 30 days after therapeutic plasma exchange (RD, 14% [95% CI, 0%-27%]).[39] This increased risk of relapse may occur because caplacizumab does not affect anti-ADAMTS13 antibody production, so iTTP may recur if severe ADAMTS13 deficiency persists after drug cessation. In a retrospective multicenter cohort study, 1015 patients who received caplacizumab along with therapeutic plasma exchange and immunosuppression (corticosteroids with or without rituximab) showed improved outcomes compared with 510 historic controls who received only therapeutic plasma exchange and immunosuppression (corticosteroids with or without rituximab).[52] Caplacizumab was associated with higher 3-month survival (98.5% vs 94%, $P < .001$), lower rates of refractory iTTP (1% vs 10%, $P < .001$), and fewer exacerbations (4% vs 32%, $P < .001$).[52] In the phase 3 clinical trial, caplacizumab was continued for 30 days following cessation of therapeutic plasma exchange and could be extended up to an additional 28 days if severe ADAMTS13 deficiency persisted, with immunosuppression adjusted accordingly to increase ADAMTS13 levels.[33] Subsequent observational studies used ADAMTS13 recovery (>10%) to guide discontinuation (prior to 30 days) or extension of caplacizumab (beyond 30 days).[53] Current recommendations are for use of caplacizumab with immunosuppression (corticosteroid and rituximab)[35] and therapeutic plasma exchange, but use of caplacizumab and immunosuppression (corticosteroid with or without rituximab) without therapeutic plasma exchange is under investigation (NCT05468320). A retrospective analysis of 41 patients treated initially with caplacizumab without therapeutic plasma exchange showed clinical response in all but 4 patients (9.5%) who then initiated therapeutic plasma exchange.[54]

Bleeding is the major adverse effect of caplacizumab due to impaired platelet adhesion to vWF.[38] In the 2 clinical trials, treatment-emergent bleeding occurred in 65 of 106 patients (61%) in the caplacizumab groups vs 49 of 110 patients (45%) in the standard-care groups (RD, 17% [95% CI, 4%-30%]), although major bleeding events were not significantly increased (RD, 2% [95% CI, −2% to 7%]).[39] With clinically significant bleeding, caplacizumab was held until resolution or permanently discontinued, and 1 patient was treated with vWF concentrate.[32] Patients with clinically active bleeding or high risk of bleeding (other than thrombocytopenia) were excluded from clinical trials of caplacizumab.[32,33] A retrospective cohort study of 85 patients treated with caplacizumab suggested that patients with iTTP complicated by stroke may be a group at high risk for intracranial bleeding with caplacizumab treatment (occurring in 2% in this cohort).[55] In a cohort of 1015 patients treated with caplacizumab, major bleeding occurred in 2% (0.3% intracranial

Table 4. Preemptive Therapies Used During Clinical Remission to Prevent iTTP Relapse

Preemptive therapy	Source (No.)	No. of patients	Clinical relapse rate (relapses per patient-year)	
			No preemptive therapy[a]	With preemptive therapy[a]
Rituximab	Hie et al,[63] 2014	30	Median, 0.57 (IQR, 0.46-0.7)	Median, 0 (IQR, 0-0.81)
	Jestin et al,[61] 2018	92	Median, 0.33 (IQR, 0.23-0.66)	Median, 0 (IQR, 0-1.32)
Splenectomy	Crowther et al,[64] 1996	6	Mean, 2.3 (SD, 2.0)	Mean, 0.1 (SD, 0.1)
	Kappers-Klunne et al,[65] 2005	33	Mean, 0.74	Mean, 0.10
	Aqui et al,[66] 2003	14	Mean, 1.0	Mean, 0.3
	Outschoorn and Ferber,[67] 2006	10	Mean, 0.60	Mean, 0.27
	Veltman et al,[68] 1995	5	Mean, 1.5	Mean, 0
Cyclosporin A	Comparon et al,[69] 2023	14	Median, 1 (IQR, 0.5-1)	Median, 0 (IQR, 0-0.2)

[a] Data from observational studies reporting relapse rate prior to initiation of preemptive therapy to prevent relapse.

hemorrhage).[52] Patients with bleeding events were older than patients without bleeding events (median age, 57 years vs 45 years; $P < .001$).[52]

Refractory iTTP

Refractory iTTP is defined by lack of sustained platelet count increment or platelet count less than 50×10^9/L with persistently increased serum LDH level (>1.5 times the upper limit of normal) after 5 or more therapeutic plasma exchange sessions (Figure 3).[12] A retrospective study of 122 patients with iTTP reported refractory iTTP in 14.1% of patients receiving therapeutic plasma exchange plus immunosuppression (100% corticosteroids and 84% rituximab) and in 4.5% of patients receiving caplacizumab in addition to therapeutic plasma exchange and immunosuppression (100% corticosteroids and 68% rituximab).[56] Because refractory iTTP is relatively uncommon, other etiologies of persistent thrombocytopenia, such as infection (typically related to the apheresis catheter) or drug-induced thrombocytopenia, should be considered.[57]

In a cohort study of 22 patients with refractory TTP or exacerbation (6 with refractory TTP, 16 with exacerbations) who were not treated with rituximab at initial presentation, addition of rituximab after lack of response to therapeutic plasma exchange or after an exacerbation shortened time to platelet count recovery compared with historical controls, with remission achieved by day 35 in all rituximab-treated survivors compared with 78% of controls.[58] If caplacizumab was not initially used, retrospective data suggest that starting caplacizumab in patients with refractory iTTP has a high response rate (18/19 patients [95%]).[56] For patients unresponsive to therapeutic plasma exchange, corticosteroids, and rituximab, increased doses of corticosteroids, cyclosporine, cyclophosphamide, vincristine, daratumumab, bortezomib, and splenectomy have been used, but data are limited to case studies and small case series.[57,59,60]

Exacerbation

In up to 38% of patients, iTTP recurs in the days to weeks after discontinuation of therapeutic plasma exchange or after discontinuation of therapeutic plasma exchange and caplacizumab.[32,33] Termed exacerbations, these early recurrences (within 30 days of discontinuing therapeutic plasma exchange or caplacizumab) occur because therapeutic plasma exchange and caplacizumab are temporizing measures that do not treat the underlying autoimmunity causing ADAMTS13 deficiency.[12] Thus, patients with persistent ADAMTS13 deficiency (<10%) remain at risk of recurrence on cessation of these therapies.[12] With an exacerbation of iTTP, therapeutic plasma exchange should be reinitiated.[57] Similar to use in the refractory iTTP setting, caplacizumab initiated at time of iTTP exacerbation (if not used on initial presentation) had a high response rate (13/14 patients [93%]) in a retrospective cohort study.[56]

Clinical Remission

A clinical remission is defined by a sustained clinical response (platelet count ≥150×10^9/L) without therapeutic plasma exchange or caplacizumab for 30 days and ADAMTS13 activity of 20% or greater.[12]

For patients with iTTP who are in clinical remission, expert opinion suggests that regular laboratory monitoring (including complete blood cell count, LDH level, and basic metabolic panel) at least every 1 to 3 months.[45] An optimal schedule for ADAMTS13 monitoring during clinical remission has not been established, but expert opinion is to monitor once monthly in the first year after an initial episode and then every 3 to 6 months thereafter.[45] Patients in clinical remission from iTTP should be also informed about potential signs and symptoms of relapse such as petechiae, headaches, and fatigue and instructed to seek medical attention immediately if these symptoms arise.

During clinical remission, a decrease in ADAMTS13 activity below 20% (ADAMTS13 relapse) may be an early sign of impending clinical relapse. In a French cohort of 23 patients with iTTP in clinical remission whose ADAMTS13 activity was persistently less than 10%, the incidence of clinical relapse was 74% at 7 years after the initial TTP episode.[61] The time from ADAMTS13 relapse to clinical relapse is highly variable. Data from the Oklahoma TTP registry reported a median time to clinical relapse of 5.4 (range, 0.3-9.5) years after a first ADAMTS13 activity less than 10% during remission.[62]

Prevention of Relapse During Clinical Remission

For patients in clinical remission who have low ADAMTS13 activity, ISTH guidelines suggest preemptive therapy with rituximab to increase the ADAMTS13 activity and reduce the risk of clinical relapse.[35] A threshold of ADAMTS13 activity below 20% is used by many experts for preemptive rituximab.[45] In a UK study, 96% of patients with ADAMTS13 relapse in clinical remission experienced an increase in ADAMTS13 activity to 20% or greater after treatment with rituximab at a median of 21 days (IQR, 14-21 days).[5] A meta-analysis of 2

cohort studies (163 patients) demonstrated a reduction in clinical relapse when rituximab was prescribed to patients in clinical remission with ADAMTS13 activity less than 10% compared with no rituximab (17 relapses among 122 patients vs 24 relapses among 41 patients; odds ratio, 0.09 [95% CI, 0.04-0.24])[37] (**Table 4**).

For patients with an ADAMTS13 relapse only (no symptoms attributable to ongoing thrombotic microangiopathy) who do not have an ADAMTS13 response (ADAMTS13 activity ≥20%) with rituximab or who do not tolerate rituximab, observation or other preemptive therapies may be considered, although evidence for these treatments is limited to case series (Table 4).[64-69] Splenectomy removes splenic ADAMTS13-specific memory B cells but is currently infrequently performed for relapse prevention of iTTP.[66-68,70]

Clinical Relapse

A clinical relapse is defined by thrombocytopenia (platelet count <150 × 10^9/L) with or without clinical evidence of new ischemic organ injury after clinical remission of iTTP.[12] In the UK TTP registry of 443 patients with iTTP (54% of whom received rituximab at initial presentation) with a median follow-up of 8 years, 16% of patients had 1 or more clinical relapses at least 6 months after the initial TTP episode.[5] While most relapses occur in the first few years, relapses have been described more than 10 years after the initial episode, and some patients have frequent relapses (≥0.5 episodes per year).[5]

Treatment of an iTTP Clinical Relapse

Clinical relapse (ADAMTS13 activity <10%-20% with thrombocytopenia with and without signs of organ injury) is treated similarly to an initial iTTP episode, with ISTH guidelines strongly recommending therapeutic plasma exchange and corticosteroids and conditionally recommending use of rituximab and caplacizumab.[35] A retrospective single-center analysis of 35 initial TTP episodes vs 76 relapsed TTP episodes found no significant differences in clinical response, exacerbation, refractory TTP, or death.[71]

Prognosis and Long-Term Complications

An analysis from the multicenter US TMA registry of 770 patients with an acute TTP episode reported overall iTTP mortality within 30 days of 6.6%, a rate which has declined from 14% over the past 3 decades.[3] In a French cohort study (281 patients in the derivation cohort and 66 in the validation cohort, all enrolled prior to 2011), independent predictors of 30-day mortality during iTTP episodes were neurologic features on presentation (headache, stupor, seizure, or focal deficit), age (especially 60 years or older), and serum LDH lavel more than 10 times the upper limit of normal.[72] Another, more recent, retrospective study of 292 patients in the UK TTP registry reported higher mortality in patients presenting with troponin levels elevated above the upper limit of normal (12.1% vs 2.0%, $P = .04$) or with Glasgow coma scale of 14 or less (20% vs 2.0%, $P < .001$) on presentation.[73]

Survivors of an initial iTTP episode have higher mortality rates than an age-, sex-, and race-standardized reference US population (2228.3 deaths per 100 000 person years vs 1273.8 per 100 000 person years).[74] In a US cohort study of 222 patients with iTTP followed up for a median of 4.5 years (IQR, 0.4-11.5 years), cardiovascular diseases including sudden cardiac death, ischemic heart disease, and stroke were the leading non-TTP cause of death in survivors of an initial TTP episode (29 died after surviving an initial episode of TTP).[74] Another cohort study of 137 survivors of an acute iTTP episode reported that ischemic stroke occurred in 13% during clinical remission, a 5-fold higher rate than expected based on an age- and sex-matched general population.[75]

Immune TTP and Pregnancy

In a cohort of 280 female patients with TTP younger than 45 years, 42 (15%) had their first TTP episode during pregnancy or postpartum (76% iTTP and 24% congenital TTP).[76] Treatment of an iTTP episode during pregnancy includes corticosteroids and therapeutic plasma exchange, and treatment response rates are similar to those for nonpregnant individuals.[26,77] Rituximab is generally reserved for refractory cases after risk-benefit discussion due to its ability to cross the placenta and potentially cause neonatal adverse events such as lymphopenia and infection.[26,78]Caplacizumab is not recommended during pregnancy due to potential risks of maternal and fetal hemorrhage.[26]

Limitations

This review has several limitations. First, the literature search was limited to articles in English. Second, there are few randomized clinical trials of patients with iTTP, and the reported benefit of some therapies may be confounded by use of historical controls or incomplete data from registry studies. Third, this review does not address management of congenital TTP.

Conclusions

Immune TTP is a rare immune-mediated disorder that presents with thrombocytopenia and MAHA and may cause life-threatening thrombosis. Treatment with therapeutic plasma exchange, corticosteroids, and rituximab is associated with 30-day survival rates of more than 90%. Addition of caplacizumab shortens time to normalization of platelet count and reduces recurrences while receiving the drug but increases bleeding risk. Monitoring ADAMTS13 activity in survivors and initiation of rituximab for those with low ADAMTS13 activity reduces the risk of clinical relapse.

ARTICLE INFORMATION

Accepted for Publication: March 10, 2025.

Published Online: May 19, 2025. doi:10.1001/jama.2025.3807

Conflict of Interest Disclosures: Dr Pishko reported receiving grants (to her institution) from the Hemostasis and Research Thrombosis Society and Sanofi Genzyme; receiving speaking honoraria from the American Society of Hematology; receiving royalties from UpToDate for an article on heparin-induced thrombocytopenia; and serving on an advisory board on gene therapy for Biomarin LLC outside the submitted work. Dr Cuker reported receiving consulting fees from MingSight, Pfizer, Sanofi, and Synergy and receiving royalties from UpToDate outside the submitted work. No other disclosures were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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