Hereditary thrombotic thrombocytopenic purpura (hTTP)

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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 arteriolar platelet-rich thrombi that cause organ ischemia and produce neurologic abnormalities, kidney dysfunction, thrombocytopenia, and microangiopathic hemolytic anemia (MAHA).

- More than 90 percent of TTP cases are immune, caused by autoantibody-mediated inhibition of ADAMTS13 activity or clearance of ADAMTS13 protein.
- Hereditary TTP (hTTP; also called congenital TTP [cTTP]) is caused by pathogenic variants in the *ADAMTS13* gene; it is much less common but no less life-threatening. Individuals with hTTP require lifelong care and special attention during certain life stages, especially in the neonatal period and during pregnancy.
- The frequencies of immune TTP and hTTP are similar in children <9 years old [1].

This topic discusses diagnosis and management of hTTP.

Separate topic reviews also present the diagnosis and management of other TMAs including immune TTP and different forms of hemolytic uremic syndrome (HUS):

- **Overview of TMAs** – (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)
- **Immune TTP diagnosis** – (See "Diagnosis of immune TTP".)
- **Immune TTP management** – (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".)
- **HUS** – (See "Overview of hemolytic uremic syndrome in children" and "Complement-mediated hemolytic uremic syndrome in children" and "Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS".)

TERMINOLOGY

We use the following terms:

- **Hereditary TTP (hTTP)** – Refers to severe deficiency of the ADAMTS13 protease due to biallelic germline pathogenic variants in the *ADAMTS13* gene. ADAMTS13 activity is typically undetectable. This condition is also called congenital TTP (cTTP), inherited TTP, familial TTP, and Upshaw-Schulman syndrome [2].
- **ADAMTS13** – The protease that cleaves ultra-large von Willebrand factor multimers. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)", section on 'Deficient ADAMTS13 activity'.)
- **Symptoms** – Minor or transient abnormalities, such as headaches, lethargy, abdominal discomfort, transient loss of attention, and/or brief syncope, are described as symptoms. Often, they have no clearly defined times of onset or resolution. That they are caused by hTTP is supported by their resolution in response to plasma therapy [3].
- **Exacerbation** – More severe illness, often presenting suddenly and often related to a precipitating event, such as pregnancy and the turbulent circulation in newborn infants, is described as an exacerbation [4,5].
- **Episode** – While this term is used for immune TTP, it is generally avoided for hTTP because hTTP patients have a lifetime illness, often with ongoing symptoms without a defined onset or resolution.

GENETICS

Inheritance of hTTP (OMIM #274150) is autosomal recessive.

- Pathogenic variants affecting both alleles of the *ADAMTS13* gene are required to cause deficiency severe enough to lead to the clinical syndrome.
- Individuals who are heterozygous for an *ADAMTS13* pathogenic variant (only one allele affected) do not appear to be at risk for clinically apparent TTP during pregnancy or other settings that can precipitate TTP exacerbations in patients with biallelic *ADAMTS13* variants.

  However, heterozygous individuals have lower baseline ADAMTS13 activity and may have increased risk for certain disorders. This was illustrated in observations from the Rotterdam study, which evaluated cardiovascular outcomes in nearly 6000 healthy individuals 55 years of age or older. Those with ADAMTS13 activity in the lowest quartile of the normal range had a higher risk of stroke (7.3 percent, versus 3.8 percent in the highest quartile; adjusted hazard ratio [HR] 1.65, 95% CI 1.16-2.32) and increased all-cause and cardiovascular mortality [6-8].

More than 200 pathogenic variants in *ADAMTS13* have been described [2]. These include insertions, deletions, missense and nonsense point mutations, and splice site mutations [2,3,9,10]. These are cataloged by the Hereditary TTP Registry, which has enrolled over 140 patients and family members from 17 countries in America, Europe, Africa, the Middle East, and Asia [10,11]. Pathogenic mutations are spread throughout the *ADAMTS13* gene [2,3,10]. Most are private (confined to single families).

Siblings with the same genotype can have strikingly different clinical features. In one family enrolled in the Hereditary TTP Registry, a patient had recurrent strokes beginning at age 17 years, while her younger brother, who was healthy, was discovered to have absent ADAMTS13 activity and the same genotype at age 33 years.

Genotype-phenotype analyses have demonstrated inconsistent correlations between specific pathogenic variants and clinical features. However, genotypes associated with some residual ADAMTS13 activity, such as a common mutation in the United States and Europe, R1060W, may be associated with less severe disease and/or later age of presentation than genotypes associated with absent ADAMTS13 activity [3,9,12].

Residual ADAMTS13 activity is only weakly correlated with age at diagnosis and severity of symptoms, indicating that other factors modify disease phenotype [3,10]. Other modulators of

clinical phenotype may include physiologic stresses such as birth, pregnancy, or infections, as well as other unidentified genetic factors.

Additional discussion of ADAMTS13 function and its role in preventing microvascular thrombosis is presented separately. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)", section on 'TTP pathogenesis'.)

EPIDEMIOLOGY

hTTP is very rare in adults (<5 percent of all TTP; one per one million population) but is more common than immune TTP in infants and young children.

- **Overall** – In our overall experience, hTTP represents <5 percent of all TTP cases. The prevalence is often described as one patient per one million population. In the Oklahoma TTP Registry, representing a population of 2.4 million people, we have identified only one family in 26 years [13]. Three daughters in this family have hTTP, a prevalence of 1.25 patients per one million people. During this same period, 92 patients with immune TTP have been identified.

  A population-based cross-sectional study using medical records in one health district in Norway discovered a much higher prevalence, with 17 individuals affected per one million population [14]. The prevalence of the R1060W mutation in this Norway district was 0.3 to 1 percent, suggesting that the prevalence of hTTP may be higher than estimated, at least in this region. A founder effect in this community may also explain the findings. The increased availability of ADAMTS13 activity measurement is likely to increase the frequency with which the diagnosis of hTTP is made.

- **Neonates and young children** – The frequencies of immune TTP and hTTP are similar in children <9 years old [1,13]. hTTP commonly presents as severe hyperbilirubinemia in newborn infants [9]. The frequency of immune TTP begins to increase after age 8 [1]; immune TTP accounts for >90 percent of TTP in adults.

- **Pregnancy** – For TTP presenting during a first pregnancy, hTTP may account for up to one-fourth of cases [15].

Other than the founder population in Norway, there does not appear to be an increased rate of hTTP in specific populations [10]. Since hTTP is autosomal recessive with a rare gene frequency, some affected families may have a history of consanguinity, and the prevalence may be greater in populations in which consanguinity is common.

There is no sex disparity among patients diagnosed in infancy or early childhood; however, among patients diagnosed as adults, young females are more frequently recognized than males because of the high risk of exacerbation during pregnancy [9]. (See 'Pregnancy' below.)

CLINICAL FEATURES

Presenting symptoms — Unlike immune TTP, which can have a dramatic and discrete onset, hTTP often causes seemingly mild and nonspecific symptoms such as [3]:

- Lethargy
- Headache
- Loss of concentration
- Abdominal discomfort

We describe these as symptoms rather than episodes because in many patients, symptoms are ongoing without a clear time of onset or resolution. (See 'Terminology' above.)

Thrombocytopenia and microangiopathic hemolytic anemia can occur, but neurologic symptoms can occur without thrombocytopenia or anemia, and thrombocytopenia may occur without apparent hemolysis [2].

Acute, severe exacerbations are uncommon but may be life-threatening without appropriate treatment. Case reports have described otherwise healthy individuals with hTTP who died from acute exacerbations. In the early 1970s, before effective treatment was known, we cared for two teenage sisters who presented with acute exacerbations in the third trimester of their first pregnancies, two years apart; both died of hTTP [16].

Remarkably, individuals with hTTP and undetectable ADAMTS13 activity can also be asymptomatic with apparently excellent health into adulthood, and siblings with the same genotype can have remarkably different clinical courses. (See 'Genetics' above.)

Uncharacteristic of immune TTP, patients with hTTP may present with severe kidney failure [9,10]. This may occur because the lifelong ADAMTS13 deficiency causes gradual accumulation of thromboses in the vasculature of the kidney. (See "The endothelium: A primer".)

Times of greatest risk — Two times of greatest risk are the neonatal period and pregnancy. However, individuals with hTTP can present at any age; diagnosis in the seventh decade has been described [9].

Other events that may trigger an exacerbation include infections, surgeries, and administration of DDAVP (desmopressin) [10,17]. DDAVP increases levels of circulating von Willebrand factor (VWF).

Neonatal period (first few days of life) — The first days of life are a critical period for hTTP. Case series have described severe hemolysis with neonatal hyperbilirubinemia requiring exchange blood transfusion [9,14]. None of these infants was recognized to have hTTP at birth; they were subsequently diagnosed at ages 1 month up to 25 years. Subsequent case reports in which the diagnosis was recognized have reported similar findings [18].

Typically, the most frequent cause of hyperbilirubinemia in neonates is blood group ABO incompatibility with alloimmune hemolytic anemia. The hyperbilirubinemia due to alloimmune hemolysis usually responds promptly to treatment with phototherapy (and intravenous immune globulin [IVIG] in severe cases). When hyperbilirubinemia does not respond to this treatment, whole blood exchange transfusion is often performed. This was routine treatment for severe hemolysis and hyperbilirubinemia caused by RhD alloimmunization, which was common in the era before RhD immune globulin. In infants with hTTP, hyperbilirubinemia will respond to whole blood exchange transfusion but not to phototherapy. Nevertheless, a diagnosis is rarely established; this is because hTTP is typically not considered [9,19].

A 2022 study of distinguishing features between hTTP and ABO incompatibility compared clinical features in 20 infants with ABO incompatibility versus four infants who were subsequently diagnosed with hTTP and found striking differences between the two conditions [20].

These are summarized in the table (table 1) and include the following:

- Most importantly, neonates with hTTP had severe thrombocytopenia. In infants with hTTP, jaundice began sooner and was more severe. **Severe neonatal thrombocytopenia accompanied by hyperbilirubinemia is unusual and is an indication to suspect hTTP and to measure ADAMTS13 activity**.
- In infants with ABO incompatibility, as with most other causes of neonatal hyperbilirubinemia, platelet counts were normal.

Neonatologists should be aware that hTTP is a cause of severe hyperbilirubinemia, particularly if accompanied by thrombocytopenia. (See 'When to suspect the diagnosis' below.)

Following recovery, these infants may have recurrent episodes of thrombocytopenia or, occasionally, no symptoms of hTTP until they are adults.

The reason that neonates with hTTP are at high risk is thought to involve the increased turbulence caused by the reversal of blood flow in the patent ductus arteriosus. Turbulence uncoils VWF and allows platelet adhesion and subsequent aggregation, promoting thrombosis [5,21-24]. Neonates also have a high hematocrit and increased concentration of VWF (especially ultra-large VWF multimers).

Untreated newborns with hTTP may die [25]. In the neonates described above, exchange transfusion was life-saving [9,14]. A 2022 report of an infant with suspected hTTP treated with recombinant ADAMTS13 anticipates future effective and simple management when recombinant ADAMTS13 becomes available [18]. (See 'Management' below.)

Pregnancy — Presentation in pregnancy is common. In some of the larger series, more than one-half of the affected females had their initial presentation or a severe exacerbation during their first pregnancy [3,9,10,16,26,27].

Pregnancy in an individual with undiagnosed hTTP almost always causes severe complications. Analysis of 61 pregnancies in 35 females with previously undiagnosed hTTP documented severe complications in 34 (97 percent) [4]. A history of a normal uncomplicated pregnancy is evidence against the diagnosis of hTTP.

Presenting findings during pregnancy include:

- Signs of severe preeclampsia and/or hypertension before 20 weeks gestation [28,29]
- Severe thrombocytopenia (platelet count <50,000/microL) at any time during pregnancy
- Evidence of hemolysis with fragmented red blood cells on the blood smear (picture 1)
- Transient neurologic symptoms
- Signs of acute kidney injury
- Intrauterine fetal death [28,30]

In our experience, individuals who are not treated during pregnancy have a very high likelihood of spontaneous pregnancy loss or death. Individuals who have suggestive signs or symptoms, such as severe preeclampsia with atypical features before 20 weeks gestation, should be evaluated with measurement of ADAMTS13 activity. (See 'Laboratory testing' below.)

DIAGNOSTIC EVALUATION

When to suspect the diagnosis — The newborn period and pregnancy are common times for hTTP to come to medical attention. Other common presentations are during early childhood or in young adults (eg, with unexplained neurologic symptoms or ischemic stroke).

We consider hTTP in individuals with any of the following presentations:

- **Severe neonatal hyperbilirubinemia** – Every newborn with severe hyperbilirubinemia due to hemolysis, particularly if accompanied by thrombocytopenia, should have ADAMTS13 activity measured to diagnose or exclude hTTP [9,14,25]. (See "Unconjugated hyperbilirubinemia in term and late preterm newborns: Escalation of care".)

- **Recurrent thrombocytopenia in a child or young adult** – These individuals should be evaluated for hTTP, especially if there is also microangiopathic hemolytic anemia (MAHA). Thrombocytopenia may spontaneously resolve, similar to childhood immune thrombocytopenia (ITP) [2]. In a series of 43 patients with hTTP, seven (16 percent) were diagnosed as children (ages 1 month to 14 years) [9]. Some had recurrent episodes of thrombocytopenia and were mistakenly thought to have ITP. Other series have reported similar findings, with childhood presentations at a median age of three years (range, 0 to 12 years) [3]. Acute symptomatic exacerbations are commonly precipitated by infections [3].

- **Transient neurologic symptoms or stroke in a child or young adult** – The incidence of stroke in patients with hTTP is 25 to 31 percent [3,10,31]. The median age for stroke is 19 years [31].

- **ESUS** – Embolic stroke of undetermined source (ESUS) should prompt consideration of hTTP in a patient of any age [32]. (See "Cryptogenic stroke and embolic stroke of undetermined source (ESUS)".)

- **Relatives** – All siblings of an affected individual should be evaluated, regardless of whether symptoms have occurred. This is especially important for sisters of a patient with hTTP, to know if prophylactic treatment will be required during pregnancy. (See 'Genetic counseling and testing of siblings' below.)

- **TTP without an inhibitor** – hTTP should be considered in any individual (child or adult) with new onset TTP and absence of an inhibitor, with caveats as discussed separately (see "Diagnosis of immune TTP", section on 'ADAMTS13 inhibitor'). Lack of a detectable inhibitor does not exclude the diagnosis of immune TTP; in one report, 15 of 86 individuals with immune TTP in the Oklahoma TTP Registry (17 percent) lacked an inhibitor on initial testing but subsequently had a demonstrable inhibitor [33].

Laboratory testing — Laboratory testing includes:

- **CBC** – Complete blood count (CBC) with platelet count. Each individual has a normal range for their own platelet count [34]. An individual with a normal platelet count in the higher range can have a significant decrease while still in the normal range (>150,000/microL). In hTTP, a platelet count below that individual's baseline suggests increased platelet consumption in microthrombi and should be an indication for treatment. (See 'Treatment of an acute episode (newborns and symptomatic individuals)' below.)

- **Hemolysis labs** – Laboratory evidence of nonimmune hemolysis includes increased indirect bilirubin, increased lactate dehydrogenase (LDH), decreased haptoglobin, and negative direct antiglobulin (Coombs) test (table 2). The laboratory criteria used within the PLASMIC algorithm, developed from patients with immune TTP, may not be appropriate for the diagnosis of hTTP [35].

- **Creatinine** – Unlike immune TTP, in hTTP there can be severe acute kidney injury. The creatinine may be normal or mildly increased. However, some patients present with acute kidney injury that may progress to end-stage kidney disease requiring dialysis or kidney transplantation [3,10,36].

- **Blood smear** – Evaluation of the peripheral blood smear for schistocytes (picture 1), indicative of MAHA, is critical. Rarely, some patients may lack schistocytes on the blood smear. Conversely, abnormal red blood cell (RBC) morphology may be more common in neonates without TTP due to physiologic hyposplenism.

- **ADAMTS13 activity** – If there is severe deficiency (activity <10 percent), inhibitor testing should also be performed; often, a laboratory will perform reflex testing for an inhibitor if activity is severely deficient. Severe ADAMTS13 deficiency without an inhibitor is characteristic of hTTP but can also be seen in some individuals with immune TTP; reasons for lack of detection are discussed separately. (See "Diagnosis of immune TTP", section on 'ADAMTS13 testing'.)

  In some cases, severe ADAMTS13 deficiency may be obscured by transfusion of any plasma-containing product (plasma, RBCs, or platelets) or by plasma exchange. Retesting ADAMTS13 activity after recovery can be especially helpful in individuals suspected of having hTTP. In hTTP, ADAMTS13 activity remains low in recovery. In immune TTP, ADAMTS13 activity may normalize or remain low.

- **PT/aPTT/fibrinogen** – Coagulation testing is typically indicated in individuals with unexplained anemia and/or thrombocytopenia. In hTTP (and other primary thrombotic microangiopathies [TMAs]), baseline coagulation studies typically are normal, including the prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-

dimer, although D-dimer is likely to be increased during acute presentations. An exception may be a patient who develops disseminated intravascular coagulation (DIC) as a result of severe organ ischemia associated with TTP. In acute DIC, the PT and aPTT are typically prolonged and the fibrinogen is typically low.

- **Genetic testing** – Genetic testing is necessary to confirm the diagnosis in all individuals with a presumptive diagnosis of hTTP. (See 'Diagnosis' below and 'Genetic testing' below.)

Diagnosis

- **New presentation** – A presumptive diagnosis of hTTP is made in an individual who has severe ADAMTS13 deficiency without an inhibitor in the appropriate clinical setting. Genetic testing showing biallelic pathogenic variants in *ADAMTS13* is confirmatory.

- **Exacerbation in an individual with known hTTP** – Once the diagnosis is known, diagnosis of an exacerbation requiring treatment is made clinically, based on symptoms and laboratory findings. (See 'Presenting symptoms' above and 'Laboratory testing' above.)

- **Relatives** – In a relative (typically a sibling) of a patient with hTTP, diagnosis is made based on severely deficient ADAMTS13 activity and biallelic *ADAMTS13* pathogenic variants.

  A relative with a heterozygous *ADAMTS13* pathogenic variant may have an increased risk for stroke or cardiovascular disease [7]. Heterozygous individuals are not considered to have hTTP. (See 'Genetic counseling and testing of siblings' below and 'Heterozygous individuals' below.)

Genetic testing — Genetic testing of the *ADAMTS13* gene is the definitive means of documenting the diagnosis of hTTP and is appropriate in any individual with suspected hTTP based on undetectable or severely deficient ADAMTS13 activity without an inhibitor. Identification of biallelic pathogenic variants in *ADAMTS13* confirms the diagnosis of hTTP. Individuals who are heterozygous for a pathogenic variant in *ADAMTS13* are considered unaffected, but they may have an increased risk of stroke or cardiovascular disease. (See 'Genetics' above.)

Siblings of patients with documented hTTP should have measurement of ADAMTS13 activity, and if severe deficiency is found, hTTP should be confirmed by genetic testing. (See 'Genetic counseling and testing of siblings' below.)

Genetic analysis is available for patients in whom hTTP is strongly suspected by these criteria at no cost through the hTTP Registry (ttpregistry.net). In appropriately selected patients, the

likelihood of identifying biallelic pathogenic variants in *ADAMTS13* is very high.

Differential diagnosis — Of conditions in the differential diagnosis, only immune TTP is associated with severe ADAMTS13 deficiency (activity <10 percent). The remainder have normal or mildly decreased activity, as can be seen with any acute illness. (See "Diagnosis of immune TTP", section on 'ADAMTS13 activity'.)

- **Immune TTP** – Like hTTP, immune TTP is characterized by severe ADAMTS13 deficiency (activity <10 percent). Unlike hTTP, immune TTP is caused by an autoantibody that inhibits ADAMTS13 activity or increases its clearance. An inhibitor of ADAMTS13 is usually (but not always) detected at the time of ADAMTS13 measurement. (See "Diagnosis of immune TTP".)

- **Other primary TMAs** – Like hTTP, other primary thrombotic microangiopathies (TMAs) can present with thrombocytopenia and MAHA and may include neurologic symptoms and/or various degrees of kidney dysfunction. Unlike TTP, other TMAs do not have severe ADAMTS13 deficiency. (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

- **Disseminated intravascular coagulation (DIC)** – DIC typically occurs in critically ill patients with an apparent cause, such as sepsis or malignancy, and DIC can cause severe anemia with fragmented red cells and thrombocytopenia. Unlike TTP, in DIC, coagulation parameters (PT, aPTT, fibrinogen, D-dimer) are abnormal. (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults".)

- **Pregnancy-associated syndromes** – Preeclampsia with severe features and HELLP syndrome (hemolysis, elevated liver function tests, low platelets) may mimic all of the features of TTP. Like hTTP, preeclampsia and HELLP are associated with thrombocytopenia and MAHA. Unlike hTTP, patients with these syndromes do not have severe ADAMTS13 deficiency, and they require treatment of the underlying syndrome (which may include delivery) rather than a source of ADAMTS13. Unlike preeclampsia and HELLP, delivery of the infant does not affect the clinical course of hTTP. (See "Thrombocytopenia in pregnancy" and "Preeclampsia: Antepartum management and timing of delivery".)

- **Hemolytic disease of the fetus and newborn (HDFN)** – HDFN results from maternal alloantibodies to fetal RBC antigens, leading to fetal/neonatal hemolytic anemia. HDFN due to RhD incompatibility is rare in developed countries due to near-universal use of anti-D immune globulin when indicated, but HDFN can also be caused by maternal alloantibodies against other RBC antigens. Like hTTP, HDFN causes hemolytic anemia and hyperbilirubinemia, and there may be a history of hemolysis in a sibling. Unlike hTTP, in

HDFN the hemolysis is immune mediated and there is no thrombocytopenia. (See "Alloimmune hemolytic disease of the newborn: Postnatal diagnosis and management".)

- **Immune thrombocytopenia (ITP)** – Misdiagnosis of hTTP as ITP is common in children. Like hTTP, ITP can manifest as severe thrombocytopenia and/or recurrent episodes of spontaneously resolving thrombocytopenia, especially in children. Unlike hTTP, ITP is not typically associated with hemolytic anemia, and ITP does not cause kidney disease or neurologic abnormalities (unless caused by bleeding, which is rare). ITP is not associated with MAHA or severe ADAMTS13 deficiency. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis".)

- **Evans syndrome** – Evans syndrome involves two autoimmune cytopenias. Like hTTP, patients with Evans syndrome often present in childhood with hemolytic anemia and thrombocytopenia. Unlike hTTP, Evans syndrome is not associated with MAHA, and the anemia in Evans syndrome is immune mediated (Coombs positive). (See "Warm autoimmune hemolytic anemia (AIHA) in adults", section on 'Evans syndrome'.)

- **Hereditary thrombocytopenias** – Like hTTP, hereditary thrombocytopenias may present at any age, and siblings may be affected. Unlike hTTP, patients with hereditary thrombocytopenia do not have hemolytic anemia or ADAMTS13 deficiency. (See "Neonatal thrombocytopenia: Etiology", section on 'Genetic disorders' and "Causes of thrombocytopenia in children", section on 'Inherited platelet disorders' and "Inherited platelet function disorders (IPFDs)", section on 'Specific disorders'.)

MANAGEMENT

Overview of approach — The major components of management are summarized in the algorithm (algorithm 1) and include:

- **Treatment** – Rapid treatment by supplying a source of ADAMTS13 (by recombinant ADAMTS13, if available, or plasma infusion). (See 'Treatment of an acute episode (newborns and symptomatic individuals)' below.)

- **Prophylaxis**

  - Decision-making regarding regular (prophylactic) treatment with a source of ADAMTS13. (See 'Prophylaxis/prevention of future exacerbations' below.)

  - Planning for prophylactic treatment during pregnancy. (See 'Management of pregnancy' below.)

- **Siblings** – Counseling and testing of siblings. (See 'Genetic counseling and testing of siblings' below.)

- **General preventive care** – We also reinforce general guidelines regarding appropriate immunizations, healthy diet, exercise, and avoidance of nicotine to reduce the risk of infectious and cardiovascular illnesses that could contribute to an exacerbation. (See "Standard immunizations for nonpregnant adults" and "Healthy diet in adults" and "Prevention of smoking and vaping initiation in children and adolescents" and "Overview of smoking cessation management in adults" and "Standard immunizations for children and adolescents: Overview", section on 'Routine schedule'.)

For those with severely impaired kidney function, kidney transplantation has been used successfully [36]. (See "Kidney transplantation in adults: Evaluation of the potential kidney transplant recipient".)

Treatment of an acute episode (newborns and symptomatic individuals) — Disease activity in newborns may be manifested by hyperbilirubinemia, which can be severe. Any individual (child or adult) can have thrombocytopenia; microangiopathic hemolytic anemia (MAHA); or subtle neurologic symptoms, abdominal pain, lethargy, or headaches. (See 'Presenting symptoms' above.)

The platelet count reflects disease activity in hTTP; if the platelet count is <150,000/microL or below the patient's baseline [34], it must be assumed that microvascular thrombosis is occurring and treatment is required. (See 'Plasma infusion' below.)

Treatment requires a source of ADAMTS13, which may be from recombinant ADAMTS13 (rADAMTS13) or plasma. If both are available, we suggest rADAMTS13 over plasma. However, plasma may be an appropriate choice for some patients depending on availability, patient preference, and cost. Shared-decision making is encouraged.

Rapid resolution of symptoms provides further confirmation of the diagnosis [3]. (See 'Expected recovery' below.)

Recombinant ADAMTS13 — rADAMTS13 was approved by the US Food and Drug Administration (FDA) in late 2023 [37]. It is a form of enzyme replacement therapy that supplies the ADAMTS13 protease enzyme without exposing the patient to donor plasma [38].

- **Indications** – rADAMTS13 is appropriate for infants, children, and adults with hTTP. It can be used for either prophylactic or on-demand treatment. Cost may be prohibitive.

Decision-making about prophylactic use is discussed below. (See 'Prophylaxis/prevention of future exacerbations' below.)

Safety in pregnancy has not been established, although it is likely to be safe. Shared decision-making is appropriate to review the relative risks and benefits of rADAMTS13 and plasma.

- **Dosing** – Administration is by slow intravenous push (2 to 4 mL per minute).
  - Prophylaxis: 40 IU/kg once every other week. The interval may be shortened if every other week is insufficient, and it may be possible to extend the interval after the first dose.
  - On-Demand: 40 IU/kg on day 1, followed by 20 IU/kg on day 2, followed by 15 IU/kg on day 3 and daily until two days after the acute event has resolved.
- **Supporting data**
  - In a prospective study in 15 individuals with hTTP, rADAMTS13 was well tolerated and did not cause serious adverse events or development of anti-ADAMTS13 antibodies [39]. Case reports in individuals who were unable to receive plasma or for whom other treatments were ineffective have demonstrated dramatic recovery in individuals treated with rADAMTS13 obtained by compassionate use [18,40].
  - The package insert describes results of an unpublished randomized trial in 46 individuals with hTTP (age range, 3 to 58 years), who were assigned to prophylactic rADAMTS13 or plasma and then crossed over to the other treatment [41,42]. There were five TTP-related events in patients receiving plasma (one acute exacerbation and four subacute) and none in patients receiving rADAMTS13. Both therapies were well tolerated. Treatment with rADAMTS13 was also effective in a small number of patients treated on-demand rather than prophylactically.
  - Preclinical studies (mouse model, patient plasma) demonstrated that rADAMTS13 could cleave von Willebrand factor (VWF) and reduce ultra-large VWF multimers; it also abrogated symptoms in the mouse model [43,44].

Plasma infusion — Plasma infusion provides ADAMTS13 for individuals with hTTP, either to treat symptoms or an exacerbation (treatment) or to prevent future exacerbations (prophylaxis).

Its efficacy is highly predictable, as evidenced by our own observations and other published reports such as those described below.

Any plasma product (Fresh Frozen Plasma, solvent/detergent plasma, thawed plasma, Plasma Frozen Within 24 Hours of Collection) can be used. Virally inactivated products are available in some institutions. (See "Clinical use of plasma components", section on 'Plasma products' and "Pathogen inactivation of blood products", section on 'Plasma/FFP'.)

The main difference between treatment and prophylactic dosing is the frequency (typically, daily for treatment versus every two weeks for prophylaxis) [45].

- **Treatment** (signs and symptoms of disease):
  - **Dose** – A typical initial plasma dose is 10 to 15 mL/kg.
  - **Frequency** – Given once daily.
  - **Duration** – Continue until the platelet count recovers to normal or baseline (may require only one to three days).
- **Prophylaxis** (when clinically well, to prevent recurrent symptoms or an exacerbation):
  - **Dose** – A typical initial plasma dose is 10 to 15 mL/kg.
  - **Frequency** – Given once every two weeks.
  - **Duration** – Can be indefinite for individuals with frequent symptoms or for the duration of a stressor such as pregnancy or an acute illness.

  In an average-sized adult, 10 to 15 mL/kg is equivalent to two to three units of plasma (approximately 500 to 750 mL). The dose for adults may be rounded to the nearest unit of plasma (do not discard unused plasma in order to administer an exact dose). Dosing frequencies are based on a half-life of ADAMTS13 in the circulation of 2.5 to 5.4 days [2]. The target ADAMTS13 activity is higher for treating an exacerbation than for prophylaxis. However, specific targets have not been defined, and we do not measure ADAMTS13 activity to guide therapy. (See 'Routine monitoring' below.)

- **Plasma transfusion versus plasma exchange** – For patients with high confidence for the diagnosis of hTTP rather than immune TTP, we recommend plasma transfusion rather than therapeutic plasma exchange (TPE). TPE is not required for hTTP because patients do not have an ADAMTS13 inhibitor that needs to be removed, and TPE carries additional risk for adverse effects, especially those related to the use of a central venous catheter, which is often required [33]. The ability to use plasma infusion rather than TPE eliminates the

need to mobilize the apheresis staff and/or transfer the patient to a facility capable of performing TPE.

However, if there is a suspicion for immune TTP, TPE rather than plasma transfusion should be used since TPE will effectively treat both immune TTP and hTTP.

Often (especially with the initial presentation), the diagnosis of hTTP is uncertain, due to the delay in ADAMTS13 activity results, lack of precision in inhibitor testing, and more extensive delay in genetic testing.

The following features increase the confidence that treatment with plasma transfusion for hTTP is sufficient and TPE for immune TTP is not required:

- Newborn infant with severe hemolytic anemia and thrombocytopenia
- Child <9 years old with repeated episodes of thrombocytopenia, sometimes associated with MAHA
- Sibling of a patient with hTTP
- Previous episode of TTP that responded rapidly (within one to two days) and completely to plasma infusion (without TPE)

For all other individuals with a clinical presentation consistent with TTP and for whom an alternative diagnosis has not been made, we presume the diagnosis is immune TTP and treat accordingly with urgent TPE and other therapies. This includes the majority of adults and pregnant individuals. The rationale is that hTTP is rare in adults (<5 percent of all TTP cases), plasma infusion is not sufficient therapy for immune TTP, and delays in instituting TPE for immune TTP may be life-threatening. Additional therapies and details of TPE are presented separately. (See "Immune TTP: Initial treatment".)

- **Individuals who cannot receive plasma** – Individuals who cannot accept plasma (eg, Jehovah's Witnesses) or do not tolerate plasma due to severe allergic reactions or other side effects may be treated with other therapies including rADAMTS13 (if available) or a plasma-derived factor VIII concentrate (Koate DVI) that contains ADAMTS13 [46]. (See 'Recombinant ADAMTS13' above and "Immune TTP: Initial treatment", section on 'Patient who cannot accept plasma/Jehovah's Witness'.)

  One of our patients who used plasma prophylaxis every two weeks for six years has switched to Koate because of severe allergic reactions to plasma. She receives 1500 units of factor VIII (30 units of factor VIII/kg, estimated 3 units/kg of ADAMTS13) once per week, which she can self-administer. This has resulted in fewer TTP symptoms, fewer adverse

effects, and much greater convenience. (See "Immune TTP: Initial treatment", section on 'Patient who cannot accept plasma/Jehovah's Witness'.)

- **Complications of plasma** – The main complications of plasma infusion are allergic reactions. These may be treated or prevented (if they occur repeatedly) using antihistamines. If allergic reactions are severe, other therapies may be used instead of plasma. (See "Clinical use of plasma components", section on 'Risks' and "Immunologic transfusion reactions", section on 'Allergic reactions'.)

  Other transfusion reactions are also possible. (See "Approach to the patient with a suspected acute transfusion reaction", section on 'Types of acute transfusion reactions'.)

  An apparently rare complication of treatment with a product containing ADAMTS13 is the development of an alloantibody (inhibitor) to ADAMTS13. In principle, this may occur in an individual with no endogenous ADAMTS13 expression, for whom ADAMTS13 in donor plasma is recognized as a foreign protein. Only two cases have been reported in patients with hTTP [9,47]. Appropriate management of an inhibitor is unknown and would be managed on a case-by-case basis.

Expected recovery — Individuals with hTTP experience prompt, complete recovery following treatment. Typically, the platelet count increases within one to two days.

- For individuals whose disease responds completely and rapidly, we continue to monitor the platelet count and pursue genetic testing to confirm the diagnosis. (See 'Genetic testing' above.)

- For individuals with a presentation consistent with TTP whose disease does not respond rapidly to plasma infusion, confidence in the diagnosis of hTTP is decreased, and we treat presumptively for immune TTP while continuing to evaluate for other possible diagnoses. (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

Some individuals with hTTP may have only subtle symptoms suggesting that their disease continues to be active. These individuals may benefit from prophylactic treatment, although the decision requires considerable thought and discussion with the patient [3]. (See 'Prophylaxis/prevention of future exacerbations' below.)

Prophylaxis/prevention of future exacerbations — Our approach to prophylactic therapy is summarized in the algorithm (algorithm 1). Key points include:

- **Shared decision-making** – The decision to initiate prophylactic therapy is complex and requires thorough discussions with the individual (and/or family members or caregivers) to ensure that risks and benefits as well as patient values and preferences have been adequately weighed [38]. Larger case series have reported the use of routine prophylaxis in approximately 70 percent of affected individuals, the majority for recurrent symptoms or thrombocytopenia [3,10]. Some patients may require weekly plasma prophylaxis [3].

  - **Benefits of prophylaxis** – Supporting evidence for routine prophylaxis is based on observational data; there are no randomized trials comparing prophylactic versus on-demand therapy at the time of an exacerbation. The International hTTP Registry found that the frequency of episodes was no different between patients managed with plasma prophylaxis and patients managed without prophylaxis [48].

    However, we believe it is likely that all patients would benefit from lifelong prophylactic treatment. Our experience and published reports demonstrate that individuals with frequent or persistent symptoms or recurrent exacerbations who do not receive regular prophylaxis are at risk of permanent morbidities (stroke, kidney failure) [14].

    Once prophylactic ADAMTS13 replacement has begun, the patient may notice changes that validate the decision. Energy and attentiveness may improve, or headaches may become less frequent or disappear. In one series, 88 percent of individuals with headaches, lethargy, and/or abdominal pain had symptom resolution once they started prophylactic plasma infusions [3]. The resulting improvement in quality of life provides the incentive to continue regular plasma infusions.

  - **Choice of prophylaxis (source of ADAMTS13)** – If both rADAMTS13 and plasma are available, we suggest rADAMTS13 over plasma, due to much greater ease of administration (can be done over a few minutes at home versus a few hours in an infusion center) and the lower risk of adverse effects (transfusion reactions, infection risk). Also higher levels of ADAMTS13 activity are reached using rADAMTS13 [39].

    These considerations become much more relevant for patients on long-term prophylaxis than for those being treated in the hospital for an acute episode. (See 'Treatment of an acute episode (newborns and symptomatic individuals)' above.)

    However, plasma may be an appropriate choice for some patients depending on availability, patient preference, and cost. Shared-decision making is encouraged.

  - **Risks of prophylaxis** – Risks are lower with rADAMTS13 than with plasma. (See 'Recombinant ADAMTS13' above.)

Burdens and risks of plasma infusions include transfusion reactions (transfusion-related acute lung injury [TRALI], transfusion-associated circulatory overload [TACO], allergic reactions) and risks of transfusion-transmitted infection, which is unlikely in resource-abundant countries but theoretically possible); risks vary depending on the local blood donor testing practices. Use of pathogen-inactivated plasma products may further decrease the risk of transfusion-transmitted infections. (See "Pathogen inactivation of blood products", section on 'Plasma/FFP'.)

Prophylactic plasma infusion also requires intravenous access and travel to a facility every other week, which may present a significant inconvenience, burden, and/or cost for some patients.

These risks may be acceptable for patients with recurrent thrombocytopenia or persistent symptoms, even minor nonspecific symptoms [3]. (See "Clinical use of plasma components", section on 'Risks'.)

- **Central venous catheter** – Plasma infusion and administration of recombinant rADAMTS13 do not require a central venous catheter. However, most individuals who receive regular plasma prophylaxis will eventually require an indwelling central venous catheter. In our experience, for patients receiving prophylaxis with plasma, it is better to consider this soon after prophylaxis has begun to avoid the issues of difficult venipunctures for infusion. Once the decision to use prophylaxis has been made in a nonpregnant individual, it is assumed that this therapy will continue indefinitely. (See "Central venous access: Device and site selection in adults", section on 'Long-term'.)

- **Indications and indication-specific dosing**

  - **Recurrent exacerbations/symptoms** – For patients with recurrent exacerbations, especially with neurologic symptoms, or those who have significant morbidity from ongoing TTP activity (eg, headaches, lethargy, or other symptoms), we suggest prophylactic administration of a source of ADAMTS13.

    - rADAMTS13 – Initial dosing is 40 IU/kg once every other week. The interval may be shortened if every other week is insufficient, and it may be possible to extend the interval after the first dose. (See 'Recombinant ADAMTS13' above.)

      or-

    - **Plasma** – Initial dosing is 10 to 15 mL/kg once every two weeks [45]. (See 'Plasma infusion' above.)

Symptoms and platelet count are the most reliable and direct measures of disease activity. If symptoms or thrombocytopenia resolve with prophylactic therapy, this provides additional evidence that the therapy is appropriate. If symptoms and/or thrombocytopenia do not improve, potential reasons should be evaluated, including an alternative or additional diagnosis or insufficient plasma dose.

For those who do not completely recover, the dose may be increased or the interval may be shortened. The decision of which to change is individualized based on the clinical picture and burdens of additional infusions; reducing the interval is most common. In one series, administration of plasma every three weeks was insufficient in the majority of individuals; every two weeks was the most common frequency, and shorter intervals were required in a subset [3]. Children were more likely to increase the frequency of plasma infusion due to thrombocytopenia, adults due to persistent lethargy or neurologic symptoms [3].

A reasonable alternative for selected individuals is close observation with a plan for ADAMTS13 administration at the first signs or symptoms attributable to hTTP. Those who use routine prophylaxis may elect to stop if the frequency of triggering events diminishes.

- **Pregnancy** – Even in patients who are not on prophylaxis outside of pregnancy, we give prophylactic ADAMTS13 throughout pregnancy, beginning as soon as the pregnancy is documented and for six weeks postpartum, without waiting for an acute episode to develop. (See 'Management of pregnancy' below.)

- **Surgery/acute illness** – A single prophylactic dose of a source of ADAMTS13 may also be appropriate for individuals with the following:

  - Undergoing surgical procedures
  - Trauma
  - Acute illness, especially if requiring hospitalization or treatment

For individuals who have never had symptoms of hTTP (eg, individuals diagnosed by genetic testing of a family member), we suggest not using prophylactic ADAMTS13. Prophylaxis may be reasonably omitted for those who have only brief or minor symptoms, those who had only one hTTP exacerbation with a clear and obvious trigger (eg, pregnancy), and those who prefer to avoid the burdens associated with plasma infusion. Close monitoring for symptoms of disease activity continues to be important for these individuals.

Routine monitoring — If the patient has no symptoms and is not receiving prophylaxis, we see them at four- to six-month intervals. These evaluations are to confirm the absence of minor symptoms and to confirm that the platelet count remains within the patient's normal range. The main component of monitoring is attention to clinical symptoms.

- Symptoms that may suggest ongoing microvascular thrombosis include headache (especially if preceded by migraine aura), transient moments of loss of attention, or syncopal episodes.
- Nonspecific symptoms such as fatigue or abdominal discomfort may also be due to hTTP [3].

Measurement of the platelet count in a patient who experiences these symptoms may be helpful, especially if it is low. However, even if the platelet count remains >150,000/microL, symptoms attributable to hTTP may occur and may resolve with treatment; the platelet count will also increase to the patient's unique baseline level [3]. Documentation of an individual's platelet count when well is critical for determining whether a decrease in platelet count has occurred.

There is no role for additional testing of ADAMTS13 activity once the diagnosis of hTTP has been made.

Management of pregnancy — Pregnancy should not be discouraged in individuals with hTTP, but it should be treated as extremely high risk (see 'Times of greatest risk' above). Management requires close collaboration between the hematologist and obstetrician specializing in maternal-fetal medicine. Without plasma prophylaxis to maintain the normal platelet count, complications may be inevitable.

We recommend prophylaxis, to be started as soon as the pregnancy is established, as a means of preventing potentially life-threatening complications (algorithm 1). This is consistent with 2020 Guidelines from the International Society on Thrombosis and Haemostasis (ISTH), which makes a strong recommendation for prophylactic treatment of hTTP during pregnancy [49].

- **Source of ADAMTS13** – The choice between rADAMTS13 and plasma is individualized, as safety data during pregnancy are not available. It is likely that rADAMTS13 is safe, but shared decision-making and informing patients regarding the lack of data is essential.
- **Dose** – Regular prophylaxis is started as soon as pregnancy is known. The initial plasma dose is 10 to 15 mL/kg. The initial rADAMTS13 dose is 40 IU/kg body weight.

- **Frequency/monitoring/dose adjustments** – The initial frequency is once every two weeks. We monitor the patient clinically with a focus on hTTP-related symptoms and blood pressure, and we measure the platelet count at every prenatal visit. If symptoms related to hTTP develop or if the platelet count decreases to <150,000/microL or below the patient's baseline, as it typically does in the second or third trimester, then the dose of plasma is increased to 15 mL/kg; the frequency often needs to be increased to once weekly during the third trimester. This means that virtually all pregnant individuals will be receiving once weekly plasma when they are nearing delivery.

- **Duration** – We continue prophylaxis after delivery for a total of six weeks postpartum. The dose of plasma is 10 mL/kg every two weeks; the dose of rADAMTS13 is 40 IU/kg every two weeks. At six weeks postpartum, we are more confident that the risk of an exacerbation has returned to baseline. Plasma infusions are not a contraindication to breastfeeding. It is likely that rADAMTS13 is safe during breastfeeding, but shared decision-making and informing patients regarding the lack of data is essential.

Severe complications of pregnancy may be inevitable in hTTP and can cause fetal and/or maternal death if prompt recognition and treatment are not instituted [4]. Pregnancy-related deaths occurred in the era before hTTP was recognized and plasma was known to be effective [16]. However, in our experience and the experience of others, many individuals have had successful pregnancies when treated as soon as possible with regular plasma infusions [50,51]. In one series that included 38 pregnancies in individuals with hTTP for whom the diagnosis had not been made, 16 (42 percent) were associated with fetal loss; in 15 pregnancies in which the diagnosis of hTTP was known and a source of ADAMTS13 provided, there were no fetal losses [50].

Although data are lacking, we presume hTTP increases the risk of preeclampsia, similar to immune TTP [52].

There is no role for premature delivery outside of standard indications as prophylactic plasma infusions can prevent symptoms related to TTP and delivery does not treat TTP. If prophylactic plasma infusion does not result in normalization of the platelet count within one to two days, there is likely to be another reason for the patient's thrombocytopenia (or symptoms). Possible alternative or additional diagnoses are discussed separately. (See "Thrombocytopenia in pregnancy".)

Genetic counseling and testing of siblings — Some asymptomatic patients are only identified when genetic testing is performed after diagnosis is made in a relative (typically a sibling).

Full siblings of an individual with hTTP have a 25 percent chance of being affected (inheriting both pathogenic variants in the *ADAMTS13* gene), a 50 percent chance of being heterozygous, and a 25 percent chance of carrying no pathogenic variants in *ADAMTS13*. (See 'Heterozygous individuals' below.)

We measure ADAMTS13 activity in all siblings as soon as the index case is identified. If ADAMTS13 activity is severely deficient, we confirm the diagnosis of hTTP with genetic testing. This is critical because symptoms (including life-threatening thrombocytopenia or neurologic abnormalities) commonly occur in childhood. This is especially important for sisters, to prevent severe pregnancy-related complications. (See 'Times of greatest risk' above.)

Individuals with hTTP are counseled that the likelihood of their own children being affected is exceedingly low, due to the extreme rarity of *ADAMTS13* pathogenic variants in the general population. In contrast to some of the more common autosomal recessive disorders, we do not test the partner for an *ADAMTS13* gene mutation. (See 'Epidemiology' above.)

We also do not perform *ADAMTS13* genetic testing in parents or children of an individual with hTTP outside of a research study. An exception may be when the likelihood of consanguinity (and hence the possibility of having an affected child) is greater. (See 'Epidemiology' above.)

Prognosis — Prior to the era of plasma infusion, hTTP was a fatal disorder [16]. The long-term prognosis in the era of plasma infusion and rADAMTS13 is uncertain, although prophylactic treatment is potentially life-saving in pregnancy, preventing the almost inevitable severe complications [4]. We expect that regular prophylaxis should prevent serious thrombotic events such as stroke, as well as more indolent morbidities including diminished kidney function.

Very long-term follow-up of patients with hTTP has not been published, in part because the etiology and genetic documentation of hTTP has only been available since 2001 [53]. Some individuals in the pre-plasma era had major morbidities, especially stroke and complications of end-stage kidney disease (ESKD) [3,10].

- **ESKD** – The original patient described by Schulman in 1960 was diagnosed at the age of eight years and developed ESKD requiring dialysis 45 years later [54,55]. Another case report described a patient who developed ESKD at age 22 and had been on dialysis for 19 years [56]. In a 2019 series from the hTTP Registry, one-fourth had chronic kidney disease, including 10 percent requiring dialysis and 2.5 percent undergoing kidney transplantation [10].

- **Stroke/TIA/cardiovascular complications** – In a 2019 series involving individuals with hTTP, one-fourth of those diagnosed in adulthood had a stroke or transient ischemic

attack (TIA) prior to diagnosis [3]. Experimental studies have suggested that the absence of ADAMTS13 can contribute to cardiovascular complications [57,58]. These observations suggest the possibility of major risk for cardiac morbidity with advancing age.

- **VTE** – Another report described the clinical course of a family with two affected brothers followed for 44 years [59]. One brother had a splenectomy for thrombocytopenia before hTTP was diagnosed, followed by recurrent pulmonary emboli requiring lifelong anticoagulation. The other brother had chronic kidney disease, atrial fibrillation, and stroke. Splenectomy is not a component of management of hTTP and may have exacerbated thrombotic risk. (See "Elective (diagnostic or therapeutic) splenectomy", section on 'Postoperative risks'.)

- **Neuropsychiatric symptoms** – Patients with hTTP can have long-term neuropsychiatric symptoms [60]; this is similar to patients with immune TTP [61,62]. Analysis of 26 patients with hTTP (ages 12 to 63 years) documented that 25 (97 percent) had one or more of 14 neuropsychiatric symptoms [60].

HETEROZYGOUS INDIVIDUALS

An individual may become aware that they are heterozygous for a pathogenic variant in *ADAMTS13* because they undergo genetic testing.

This might occur:

- After hTTP is diagnosed in a relative
- As a secondary finding from genetic testing for another reason

Heterozygous individuals may have excellent health. However, their risk for stroke or cardiovascular disease may be greater than in people without heterozygosity for a pathogenic variant in *ADAMTS13* [6-8]. (See 'Genetics' above.)

Aside from general health maintenance (smoking cessation, management of hypertension and lipids), we do not alter their medical care based on heterozygosity for an *ADAMTS13* variant.

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

- **Pathophysiology** – Hereditary thrombotic thrombocytopenic purpura (hTTP) is an autosomal recessive thrombotic microangiopathy (TMA) caused by biallelic pathogenic variants in the *ADAMTS13* gene. hTTP is very rare in adults (<5 percent of all TTP; one per one million population) but is more common than immune TTP in infants and young children. (See 'Terminology' above and 'Genetics' above and 'Epidemiology' above.)

- **Presentation** – Common presentations include (see 'Clinical features' above):

  - **Neonates** – Severe hemolysis with hyperbilirubinemia at birth (table 1), frequently accompanied by thrombocytopenia.

  - **Pregnancy** – Signs of preeclampsia before 20 weeks, neurologic symptoms, hemolysis, and thrombocytopenia.

  - **Children and adults** – Thrombocytopenia, microangiopathic hemolytic anemia (MAHA) (picture 1), and/or nonspecific findings (neurologic symptoms, lethargy, headache, loss of concentration, abdominal discomfort).

- **Evaluation** – hTTP should be considered in any individual with unexplained thrombocytopenia and/or MAHA, especially a newborn with the presentations described above. (See 'When to suspect the diagnosis' above.)

  - **Initial testing** – Review the complete blood count (CBC), hemolysis testing (table 2), creatinine, and blood smear. (See 'Laboratory testing' above.)

  - **ADAMTS13 activity** – Measure ADAMTS13 activity. If there is severe deficiency (activity <10 percent), obtain inhibitor testing. Severe deficiency without an inhibitor that persists during remission is consistent with hTTP. (See 'Diagnosis' above.)

- ***ADAMTS13* genetic testing** – Obtain genetic testing in individuals with severe ADAMTS13 deficiency without an inhibitor. This is available without cost via the hTTP Registry (ttpregistry.net). A finding of biallelic pathogenic variants in *ADAMTS13* is confirmatory. (See 'Genetic testing' above.)

- **Differential** – Other causes of neonatal hemolysis and other TMAs should be considered. (See 'Differential diagnosis' above.)

- **Treatment** – Neonatal hyperbilirubinemia and any exacerbations require treatment with a source of ADAMTS13 (algorithm 1). If both recombinant ADAMTS13 (rADAMTS13) and plasma are available, we suggest rADAMTS13 (**Grade 2C**). Risks are lower with rADAMTS13; however, plasma may be an appropriate choice for some patients depending on availability, patient preference, and cost. Shared-decision making is encouraged. (See 'Treatment of an acute episode (newborns and symptomatic individuals)' above.)

  - rADAMTS13 – Initial dosing for treatment is 40 IU/kg on day 1, followed by 20 IU/kg on day 2, followed by 15 IU/kg on day 3 and daily until two days after the acute event has resolved.

  - **Plasma** – We typically give 10 to 15 mL/kg daily until resolution; often one to three days of treatment are sufficient.

- **Prophylaxis** – Our approach is illustrated in the algorithm (algorithm 1). (See 'Prophylaxis/prevention of future exacerbations' above.)

  - **Shared decision-making** – Involves discussion of the uncertain benefit and possible risks and the choice of a source of ADAMTS13. Pregnancy is high risk as nearly all patients develop complications if not given prophylaxis.

  - **Indications**

    - **Frequent exacerbations** – For recurrent exacerbations, especially with neurologic symptoms, headaches, lethargy, or other frequent symptoms or thrombocytopenia, we suggest regular prophylaxis (**Grade 2C**). We suggest rADAMTS13 over plasma (**Grade 2C**); however, as for treatment, plasma may be an appropriate choice for some patients. An alternative is prophylaxis for surgery, trauma, or hospitalization, with on-demand therapy for symptoms.

    - **Pregnancy** – Collaboration between the hematologist and maternal-fetal medicine specialist is essential. For individuals with hTTP who become pregnant, we recommend ADAMTS13 prophylaxis as soon as the pregnancy is documented

(**Grade 1B**). The choice between rADAMTS13 and plasma is individualized, as safety data during pregnancy are lacking. Prophylaxis is continued until six weeks postpartum. There is no role for premature delivery outside of standard indications. (See 'Management of pregnancy' above.)

- **Dosing**
  - rADAMTS13 – The prophylaxis dose is 40 IU/kg every two weeks, adjusted for symptoms and platelet count. (See 'Recombinant ADAMTS13' above.)
  - **Plasma** – The prophylaxis dose is 10 to 15 mL/kg every two weeks, adjusted for symptoms and platelet count. (See 'Plasma infusion' above.)

- **Siblings** – Siblings of an individual with hTTP have a 25 percent chance of being affected; we test their ADAMTS13 activity as soon as possible, as major morbidities can occur in childhood. Severe ADAMTS13 deficiency warrants genetic testing. Individuals who are heterozygous for a pathogenic variant in *ADAMTS13* do not have hTTP but may have an increased risk of cardiovascular disease. (See 'Genetic counseling and testing of siblings' above and 'Heterozygous individuals' above.)

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Topic 101504 Version 28.0

GRAPHICS

Comparison of laboratory findings in hereditary TTP versus ABO incompatibilit in neonates

Characteristic	hTTP (n = 4)	ABO incompatibility (n = 20)
Platelet count minimum	17,000±12,000/microL	291,000±76,000/microL
Anemia (percentage of patients)	100%	25%
Minimum hemoglobin (g/dL)	10.6±2.4	16.3±2.3
Maximum total bilirubin (mg/dL)	24±6	16±3
Time to jaundice onset (hours)	10 (5 to 13)	69 (18 to 82)
Time to maximum bilirubin (hours)	39±16	74±27
Bilirubin response to phototherapy and IVIG (change, in mg/dL)	3±4	–4±3
BUN (mmol/L)	8 (5 to 42)	41 (28 to 75)
Creatinine (micromol/L)	93 (58 to 149)	41 (28 to 75)
Positive direct Coombs test, percentage	0%	65%

All patients with hTTP had ADAMTS13 activity <5% without an inhibitor and biallelic pathogenic variants in the ADAMTS13 gene. A major difference between groups was severe thrombocytopenia in the TTP group and positive direct Coombs test in the ABO incompatibility group. Other differences included earlier and more severe jaundice, with greater likelihood of anemia, in neonates with hTTP. Most of the above differences were statistically significant with p values <0.001 (exceptions: time to maximum bilirubin, p = 0.02; presence of anemia, p = 0.01; creatinine, p = 0.02; positive direct Coombs test, p = 0.07). Parameters that were not statistically different between groups included WBC count, C-reactive protein, albumin, and hepatic alanine aminotransferase. Refer to the original paper for details and to UpToDate for additional discussions of hTTP.

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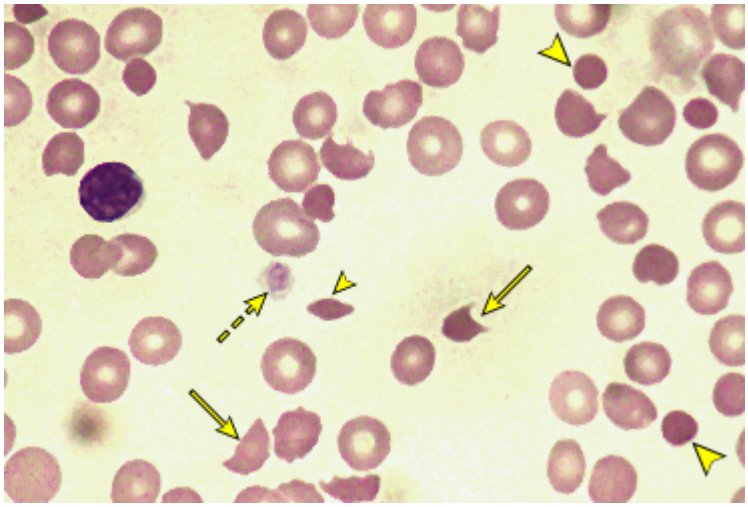
hTTP: hereditary thrombotic thrombocytopenic purpura; BUN: Blood urea nitrogen; WBC: white blood cell.

Graphic 141631 Version 1.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

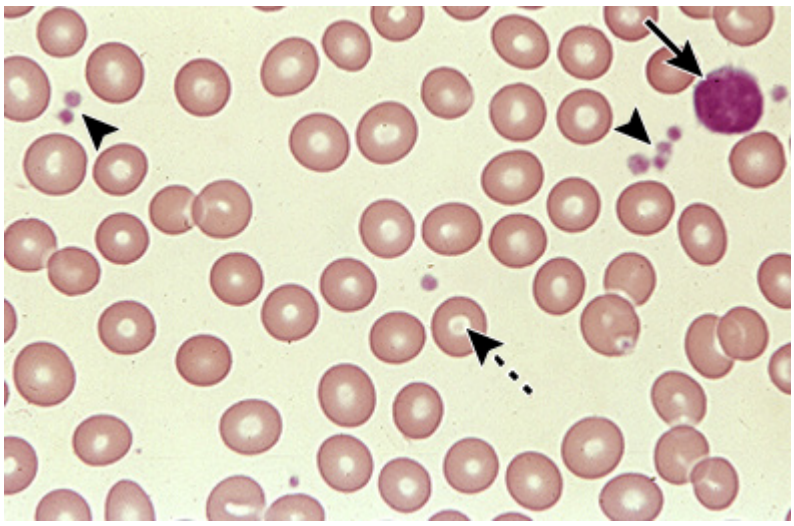


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows) and other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large 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

Laboratory findings in hemolysis and hemolytic anemia

Finding	Change in hemolytic anemia
Anemia*	Decreased hemoglobin Decreased hematocrit
Bone marrow response/recovery	Increased reticulocyte count Underestimation of HbA1C
Release of RBC contents	Increased LDH Increased indirect bilirubin Decreased haptoglobin Hemoglobinemia in intravascular hemolysis¶ Hemoglobinuria in intravascular hemolysis¶
RBC morphology changesΔ	Spherocytes or microspherocytes in immune hemolysis Schistocytes in microangiopathic hemolysis Blister or bite cells in oxidant injury Sickle cells in sickle cell disease Target cells and teardrop cells in thalassemia

Intravascular hemolysis often starts acutely and can be a medical emergency associated with DIC, AKI, and hypotension. Extravascular hemolysis can be chronic. Severe hemolysis can have intravascular and extravascular features. Values for HbA1C may be lower due to increased RBC turnover. Refer to UpToDate for details of the evaluation, interpretation of laboratory findings, use of the Coombs (antiglobulin) test, and management.

HbA1C: glycosylated (glycated) hemoglobin; RBC: red blood cell; LDH: lactate dehydrogenase; DIC: disseminated intravascular coagulation; AKI: acute kidney injury.

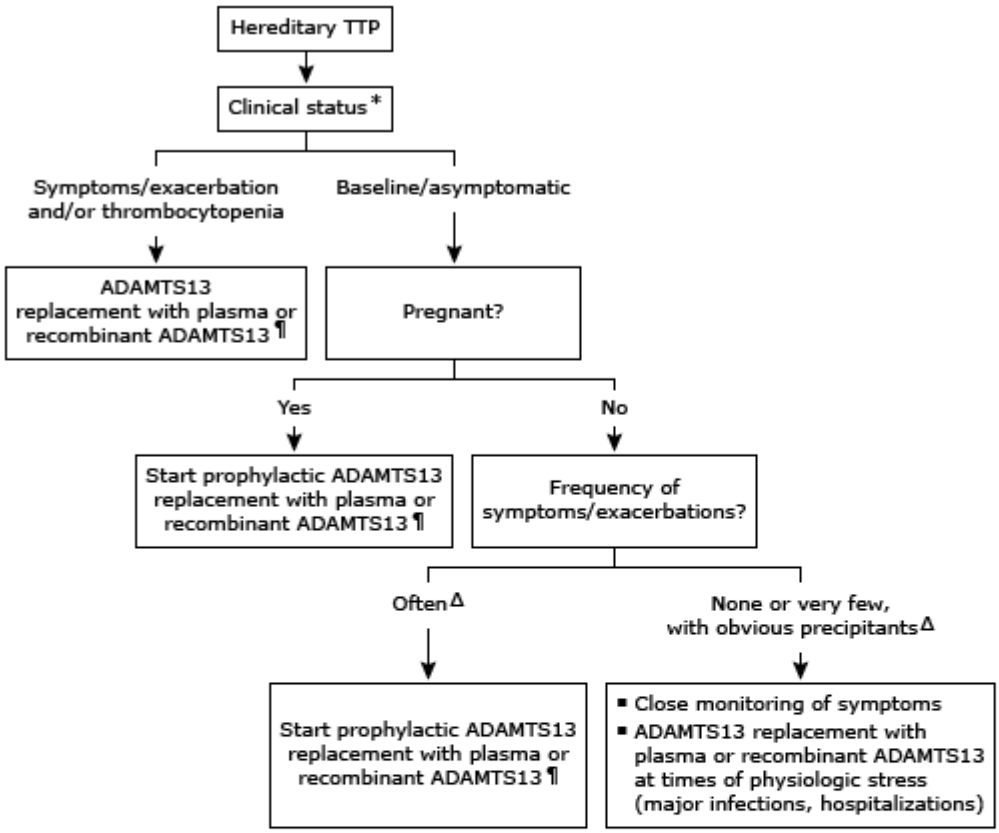
* The presence and severity of anemia depends on the degree of hemolysis and capacity of the bone marrow to compensate by increasing erythropoiesis.

¶ Intravascular hemolysis can be a medical emergency with free hemoglobin in the blood and associated with complications including DIC and acute renal failure. Findings associated with intravascular hemolysis may include schistocytes on the blood smear, hemoglobinemia (with red serum), hemoglobinuria (with dark or red urine), and hemosiderinuria in the urine sediment.

Δ Refer to UpToDate for additional details of these and other RBC morphologies and their implications.

Graphic 126234 Version 3.0

Algorithm for management of hereditary TTP



	Plasma	Recombinant ADAMTS13	Notes
Acute exacerbation	10 to 15 mL/kg daily, continued until recovery	40 international units/kg on day 1, followed by 20 international units/kg on day 2, followed by 15 international units/kg on day 3 and daily until 2 days after recovery	If recovery does not occur within 2 to 3 days, evaluate for other causes of symptoms and thrombocytopenia.
Prophylaxis (non-pregnant)	10 to 15 mL/kg once every 2 weeks	40 international units/kg once every 2 weeks	Adjust the interval if needed to maintain the patient's normal platelet count. *
Prophylaxis (pregnancy)	10 to 15 mL/kg once every 2 weeks	40 international units/kg once every 2 weeks	Begin when pregnancy is confirmed; continue throughout pregnancy and for 6 weeks postpartum. Dose and frequency may need to be increased in the third trimester.

This algorithm addresses the use of ADAMTS13 replacement with plasma or recombinant ADAMTS13 for individuals with hereditary TTP. It is not appropriate for those with immune TTP. If both forms of replacement are available, we suggest recombinant ADAMTS13 over plasma. However, plasma may be an appropriate choice for some patients depending on availability, patient preference, and cost. Shared decision-making is encouraged.

TTP: thrombotic thrombocytopenic purpura.

* Each person has an individual normal platelet count that may be >300,000/microL or <150,000/microL. Thrombocytopenia should be assessed relative to the individual's baseline rather than a laboratory reference range. Every individual with hereditary TTP should have their baseline platelet count determined when they are asymptomatic. Refer to UpToDate for details.

¶ Refer to inset for dosing. The volume, frequency, and duration may require modification based on the patient's prior experience, clinical status, and other factors. Specialist input (hematology, transfusion medicine) is advised. Pregnant individuals who are receiving prophylaxis are not expected to have symptoms of hereditary TTP; however, if an exacerbation does occur during pregnancy, it is treated the same as in non-pregnant individuals.

Δ The severity of persistent symptoms or the frequency of exacerbations that warrant initiation of prophylaxis is individualized. Refer to UpToDate for details.

Graphic 130009 Version 4.0