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Review Article

# Diagnosis and Management of Thrombotic Thrombocytopenic Purpura

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## Abstract

TTP is a rare life-threatening disease resulting from absence of functional ADAMTS13. Aggregates of ultralarge vWF multimers–platelet will form microthrombi within the arterial and capillary microvessels of high shear inducing tissue ischemia, platelet consumption and MAHA. Only thrombocytopenia and MAHA without another clinically apparent etiology are required to suspect the diagnosis of TTP. TTP is mainly caused by an autoimmune mechanism. Although the survival rate in acquired TTP exceeds 80%, rapid-onset therapy to prevent further microthrombus formation by targeting the binding of platelets to ultralarge vWF multimers is a potential approach to the treatment. Immunosuppressive therapy (e.g., glucocorticoids and rituximab) inhibits autoantibody formation. Caplacizumab, an anti–vWF humanized single-variable-domain immunoglobulin targets the A1 domain of vWF, preventing interaction with the platelet glycoprotein Ib-IX-V receptor.

## Introduction

TTP is a rare life-threatening disease, characterized by MAHA, thrombocytopenia, fever, renal involvement and neurologic manifestations [1]. This pentad is not necessary for diagnosis. Only thrombocytopenia and MAHA without another clinically apparent etiology (e.g., disseminated intravascular coagulation, malignant hypertension, severe preeclampsia, sepsis, and systemic malignancy) are required to suspect the diagnosis of TTP and to initiate PEX [2].

**Epidemiology:** TTP has an average annual prevalence of ~10 cases/million people and an annual incidence of ~1 new case/million people in a cross-sectional analysis of the French national registry for thrombotic microangiopathy [3]. In probably more than 90% of cases, the onset of TTP occurs in adulthood, usually between 30 and 40 years of age, and preferentially in women (sex ratio of about 3F/1M) and in subjects from Afro-Caribbean origin. In about 10% of cases, TTP appears initially in infancy (sometimes as soon as the neonatal period) or in childhood. Rare familial forms of TTP (affecting mainly the siblings) are commonly observed in infancy or childhood but can also occur initially in adulthood [4].

The clinical course of TTP is characterized by a relapsing tendency [3]; there is no seasonal distribution, but viral infections, and drugs, such as clopidogrel, are risk factors [5]. Other well established predisposing factors for acquired TTP are female sex, black ethnicity, HLADRB1*11, and obesity whereas HLA-DRB1*04 is protective [3]. Pathophysiological conditions increasing plasma vWF levels such as inflammation, sepsis, or pregnancy act as potentially precipitating factors of acute acquired or inherited TTP episodes. Other still unknown players are suspected to be involved in TTP occurrence: these may be either proteins of the ADAMTS13/vWF system or cellular candidates such as platelets or endothelial cells. TTP has mortality rate of 10% to 20% in spite of appropriate therapeutic management [3].

**Etiology:** TTP is mainly caused by an autoimmune mechanism, but rare non immune inherited forms are described (USS) [3]. In adults, TTP is idiopathic in about one third of cases and occurs abruptly independent of any other associated condition. In contrast, in about two thirds of cases, TTP is encountered in a variety of clinical situations, potentially involved in triggering of the acute episode: bacterial or viral infections, HIV, pregnancy (especially during the last trimester and the postpartum period), oral contraceptives, drug ingestion (either an acute immune-mediated toxicity: quinine, ticlopidine, clopidogrel or an insidious dose-related toxicity: mitomycin C, alpha-

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interferon, cyclosporin, tacrolimus and other immunosuppressive and chemotherapeutic agents), autoimmune disorders mainly systemic lupus erythematosus, antiphospholipid syndrome, disseminated malignancy and bone marrow transplantation [4].

**Focus on some specific TTP cases:** Acute idiopathic TTP is the most common form of TTP [6].

Inherited TTP (USS) is due to frameshift and point mutations in the ADAMTS13 gene located on chromosome 9q34. Less than 1% of acute TTP cases [5] and less than 5 % of all TTP cases are due to USS. It may be seen in children and teens. Some congenital TTP patients present with overt TTP soon after birth, or remain asymptomatic into their fifth or sixth decades of life [7]. It typically has a mild phenotype, but can progress to acute TTP in situations when high levels of vWF are present, such as during infections or pregnancy [5]. Some patients show neurological symptoms, or kidney involvement up to renal failure. Both have an onset during pregnancy. Most of the patients with renal insufficiency do not carry genetic mutations in complement or complement regulatory genes known to predispose to renal insufficiency [7].

Acute idiopathic TTP is an autoimmune disease associated with IgG antibodies to ADAMTS 13. IgM and IgA antibodies have been described [8]. The mechanisms involved in the loss of tolerance of the immune system against ADAMTS13 remain unknown [9]. HLA-DRB1*11 was reported as a susceptibility factor in Caucasians; while HLA-DRB1*04 has a possible protective effect in disease development [9].

**Drug-associated TTP:** Quinine and estrogen-containing medications should be avoided to prevent relapse in patients with a previous episode of TTP (2C). Women with previous TTP should be offered non-oestrogen containing contraception (1C) [6].

Transplant-associated microangiopathy may reflect endothelial toxicity associated with chemotherapy, infections, immunosuppressives such as cyclosporine A, and graft-versus-host disease. Transplant-associated microangiopathy TAM differ from de novo TTP, by absence of ADAMTS13 deficiency; rare neurological symptoms; a poor response to PEX and lack of evidence of systemic microthrombi formation [6].

Malignancy-associated thrombotic microangiopathy occurs in a variety of neoplasms, especially adenocarcinomas. Presentation may be either at an early stage of cancer or associated with disseminated disease. ADAMTS13 activity is not significantly reduced in these patients [6].

Pregnancy-associated TTP may represent either acquired TTP due to the changes in immune regulation that occur during pregnancy, or precipitation of an episode of symptomatic TTP in a patient with congenital TTP (which may or may not have been previously recognized). Acute TTP in pregnancy has a significant maternal/fetal morbidity and mortality and requires aggressive treatment [10].

**HIV-associated TTP:** TTP should be considered in an HIV-positive individual with a MAHA and thrombocytopenia (1A) [6].

**Pancreatitis-associated TTP** [6].

**Pathophysiology of TTP:** In physiologic conditions, ultralarge vWF multimers released from endothelial cells are cleaved by ADAMTS13 into smaller vWF multimers, less adhesive to platelets. In TTP, because of the absence of functional ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13-vWF cleaving protein), ultralarge vWF multimers are released into the blood and bind spontaneously to platelets to form aggregates [3] within the arterial and capillary microvessels of high shear, such as the microvasculature of the brain, heart and kidneys [6].The hyperadhesive ultralarge vWF–platelet aggregates form microthrombi within small arterioles inducing tissue ischemia, platelet consumption and MAHA [3].

In approximately 95% of cases, severe ADAMTS13 deficiency is acquired via inhibitory ADAMTS13 autoantibodies that are produced in primary or secondary acquired TTP [3]. Two types of anti-ADAMTS-13 antibodies have been described, one inhibiting (neutralizing) ADAMTS-13 proteolytic activity and the other binding to the protease and accelerating its clearance from plasma through opsonization and/or other yet unresolved mechanisms (non-neutralizing); both may be simultaneously present in many TTP patients [11].

Antibodies against multiple sites on the ADAMTS13 protein occur in most patients. Almost all patients have an antibody directed somewhere between the metalloprotease and spacer domains (in particular Y658-Y665 [R660, Y661, Y665] of the spacer domain). This region is crucial for the ADAMTS13 protease function. The antibodies are usually of immunoglobulin (Ig)G (and most frequently of the IgG4 subclass) [10]. Anti-ADAMTS13 IgGs usually inhibits the proteolytic activity of ADAMTS13 toward vWF [3]. Anti-ADAMTS13 IgG may not be detectable in ~20% to 25% of acute TTP, raising the hypothesis that severe ADAMTS13 deficiency in these patients may result from: involvement of other Ig isotypes; decreased synthesis/secretion of ADAMTS13 (ie, in acute liver insufficiency); degradation of ADAMTS13 by sepsis enzymes such as calpains, elastases, thrombin, or plasmin; and catalytic inhibition of ADAMTS13 by free hemoglobin or interleukins or as-yet-unclear mechanisms [3]. Anti-ADAMTS13 IgM and IgA associated with anti-ADAMTS13 IgG were rarely reported in acute TTP [6].

A rare mechanism (~2% of all cases) for severe ADAMTS13 deficiency is genetic via recessively inherited biallelic mutations of the ADAMTS13 gene causing congenital TTP (Arg1060Trp [3].These mutations within the *ADAMTS13* gene result in loss of function of the protein product. The mutations seen in congenital TTP are heterogeneous and consist of a mixture of missense (approximately 60%) mutations, nonsense mutations, insertions, and deletions that are distributed throughout the coding region of the gene. In approximately 65% of cases, mutations are present in compound heterozygous state, with the remainder occurring as homozygous mutations. This genetic heterogeneity is reflected in varied age of onset and severity/frequency of TTP episodes [10]. The numerous mutations identified in childhood-onset USS are distinct from those found in adulthood-onset USS, characterized by the high frequency of 1 specific mutation, p.Arg1060Trp [3].

The acute episode of TTP is usually characterized by non-specific presenting complaints like weakness (often anemia-related), arthralgia, myalgia [4], nonspecific abdominal pain (possibly the result of microvascular ischemia of the gastrointestinal tract) [10], nausea, vomiting, diarrhea, fever and jaundice (related to hemolysis). Some skin and mucosal bleeding

secondary to the thrombocytopenia (purpura, ecchymosis, menorrhagia, epistaxis, hematuria, and gastrointestinal hemorrhage) are also common [4].

Symptoms linked to systemic platelet clumping-induced ischemia may be associated. The brain is the most common target for ischemia (75%) translating either in headache, confusion, severe mental status abnormalities, visual disturbance, focal abnormalities (i.e. aphasia, focal motor deficits) or seizures and coma [4].Neurologic signs are characteristically of transient and fluctuating nature. This is explained by brief episodes of focal ischemia caused by microthrombi that occludes terminal arterioles and capillaries resulting in diffuse small infarcts and petechial hemorrhages generally confined to the gray matter. Extensive infarct is unusual [1].

Ischemia of both the gastrointestinal tract and kidneys also occurs frequently [10]. Renal manifestations consist of an isolated proteinuria, renal insufficiency or more rarely an oliguric acute renal failure. Heart dysfunction (e.g., conduction defects, congestive cardiac failure, raised serum troponin) also occurs. The median duration of symptoms prior to diagnosis is about 1 week with extreme values ranging from 1 day to 3 weeks [4].

In the infancy-onset TTP, the first acute episode may occur spontaneously as soon as birth and usually consists of a major hemolysis requiring an exchange --transfusion. In other cases, the disease begins later and is often triggered by a viral or bacterial infection [4].

**Investigations:** Median hemoglobin levels on admission are typically 80–100 g/l, with schistocytes (usually > 1% of total erythrocytes) in the film. The direct Coombs test is negative [6]. The mechanism for the anemia is mechanical hemolysis (MAHA) where fragmented red cells are produced as blood flows through the microvessels partially occluded by platelet aggregates. Classical parameters for hemolysis show a high reticulocyte count, an undetectable serum haptoglobin concentration and elevated LDH values [4]; the combination of hemolysis and tissue ischemia produces elevated LDH often out of proportion to the degree of hemolysis [6].

The median platelet count is typically 10–30 X $10^9$/l at presentation as a result of consumption of platelets in platelet-rich thrombi in almost all cases. The clotting screen (prothrombin time, activated partial thromboplastin time and fibrinogen) is usually normal. Troponin T levels are raised in 50% of acute idiopathic TTP cases, highlighting that cardiac involvement is common [6].

Renal testing may show proteinuria, hematuria, increased plasma urea and creatinine in about half of the cases [4].A pre-treatment virology screen is necessary to exclude HIV and other viral-associated TTP [6]. Viral load should be measured in HIV-associated TTP [6]. Tomodensitometry may be helpful to localize the various visceral ischemic lesions [4].

The laboratory confirmation of TTP is made by demonstration of a profound decrease in plasma ADAMTS13 enzyme activity (usually <10%). ADAMTS13 activity can be measured by detecting the ADAMTS13-mediated cleavage products (10). Detection of anti-ADAMTS13 IgG is the second step, whereas ADAMTS13 gene sequencing is limited to selected indications [3].

Patients with severe deficiency (< 5%) of ADAMTS 13 activity are considered to have idiopathic autoimmune TTP or a congenital absence of ADAMTS 13 [8]. The congenital form of the disease is confirmed by absence of antibody and confirmation of homozygous or compound heterozygous defects of the ADAMTS13 gene (1A) [6].

Point-based TTP prediction scores have been validated to predict an acquired ADAMTS13 deficiency. These scores include platelet count, serum creatinine level, and either detectable antinuclear antibodies or D-dimer, reticulocytes, and indirect bilirubin [3].

In mothers with acquired TTP, ADAMTS13 activity should be monitored throughout pregnancy to predict the need for adjuvant therapy and outcome (1B) [6].

## Fallacies

- Anti-ADAMTS13 autoantibodies, predominantly of the IgG class, are found in approximately 5% of plasma of healthy individuals. ADAMTS13-specific autoantibodies from healthy individuals remain ill-defined and their binding specificities are unknown (12).
- Most TTP patients secondary to hematopoietic stem cell transplantation, pregnancy, bloody diarrhea, HIV infection, autoimmune diseases and malignancies have detectable or even normal ADAMTS-13 levels at presentation [11].
- A subset of TTP patients may not show ADAMTS13 deficiency during an acute episode, but may still benefit from PEX (13).
- Lower ADAMTS13 activity levels (approximately 50% of normal) may be seen in pregnant women, in newborns and in patients with liver disease, disseminated malignancy, chronic metabolic, inflammatory disorders, and malignant hypertension [5]. ADAMTS13 may be decreased in HELLP syndrome (13).
- Decreased ADAMTS13 activity (<40% but >5%) has been reported in uremia, inflammatory states, post-operatively and during pregnancy [6]. Levels less than 5% of normal have been reported in sepsis [11].
- Severe deficiency of ADAMTS-13 has been observed in 13% of typical HUS and 16% of DIC cases [11].The specificity of severe ADAMTS13 deficiency (<5%) in distinguishing acute TTP from HUS is 90% [6].

## Diagnosing TTP usually proceeds with these steps:

(i) Identifying the first acute episode of the disease by clinical criteria [4]. (multivisceral ischemic symptoms mainly of the brain) and standard biology criteria (MAHA and severe thrombocytopenia) occurring in the absence of other apparent causes. This definition was completed by presence of severe deficiency of ADAMTS13 activity (<10%) (3).

(ii) Predicting the evolutionary form of the disease [4].

(iii) Congenital TTP should be considered in neonates presenting with severe jaundice and in children and

adults presenting with unexplained thrombocytopenia (1B) [6].

## TTP has to be differentiated from:

- Other TMAs which include the HUS and TMA associated with cancer, allogeneic hematopoietic stem cell transplantation, chemotherapy, HIV and infection, etc [14]. They can clinically and pathologically mimic TTP, however, they are occasionally associated with decreased ADAMTS13 activity, but not associated with severe ADAMTS13 deficiency (<10%) [10].
- Pregnancy-related complications like pre-eclampsia/eclampsia/HELLP syndrome [4].
- An immune thrombocytopenic purpura, if isolated, or Evan's syndrome, if associated with a hemolytic anemia at the very initial phase of the disease [4].
- Conditions associated with multiorgan failure like disseminated malignancies and bone marrow transplantation (which also share the use of multiple high toxicity-drugs and a high risk for opportunistic infections). In addition, disseminated malignancy and bone marrow transplantation have been frequently associated with TTP [4].

## Prognosis

With prompt initiation of TPE, the average survival rate from a first episode of TTP is 80% to 90% [3]. Platelet count, older age; a very high LDH level (10 times the upper normal value), reflecting mostly organ damage; and an increased cardiac troponin level on diagnosis (troponin level > 0.25 ng/mL) are associated with death and treatment refractoriness [3]. An index was based upon age, hemoglobin and the presence of fever at presentation [11].

Measuring the activity of ADAMTS-13 is critical to define the long-term prognosis and follow-up of patients with acquired TTP. Patients with severe ADAMTS-13 deficiency at presentation often develop relapsing disease, whereas patients without severe deficiency rarely relapse [11]. Patients, who have no deficiency during the acute phase, are unlikely to develop a severe deficiency of ADAMTS-13 during remission nor to relapse [11].

Periodic measurement of ADAMTS-13 activity may be useful particularly in patients who had ADAMTS-13 deficiency and anti-ADAMTS-13 antibodies during the acute episode [11]. Patients with ADAMTS13 activity <10% or an anti-ADAMTS13 antibody in remission had a 3-fold increase in relapse over 1 year (6). The titer of ADAMTS-13 inhibitor during acute disease and the presence of anti-ADAMTS-13 antibodies during recurrence are predictive of recurrent disease. An association between anti-ADAMTS-13 IgG subclass 4 and recurrent disease has been reported [11].

**Treatment:** The majority of patients with TTP achieve remission with PEX + steroid therapy; more than one-third of patients survive the acute phase relapse within 10 years [2].

**Response criteria:** A complete response to treatment is defined by a platelet count above 150 x $10^9$/L for 2 consecutive days, together with normal or normalizing LDH and clinical recovery. A durable treatment response is lasting at least 30 days after discontinuation of TPE. Recurrent disease within 30 days after reaching treatment response defines an exacerbation A refractory disease is defined by no treatment response by day 30 and/or no durable treatment response by day 60 [3]. Relapse is defined as an episode of acute TTP more than 30 days after remission. It occurs in 20-50% of cases [6].

**Treatment of congenital TTP:** Solvent/detergent-treated plasma infusion or intermediate purity Factor VIII should be used (1C). Treatment regimens should be individualized according to the patient's phenotype (1A) [6].

**Treatment of acquired TTP:** Rapid initiation of PEX is used to remove autoantibodies and ultralarge vWF multimers and to replenish ADAMTS13. Although the survival rate in acquired TTP exceeds 80%, rapid-onset therapy to prevent further microthrombus formation by targeting the binding of platelets to ultralarge vWF multimers is a potential approach to the treatment [15]. Immunosuppressive therapy (e.g., glucocorticoids and rituximab) inhibits autoantibody formation [15]. Caplacizumab, an anti–vWF humanized single-variable-domain immunoglobulin (Nanobody, Ablynx) targets the A1 domain of vWF, preventing interaction with the platelet glycoprotein Ib-IX-V receptor [15].

**Treatment of acute TTP:** PEX should be started with 1·5 PV exchanges, using S/D plasma in all age groups and daily reassessment (1B). The volume of exchange can be reduced to 1·0 PV when the clinical condition and laboratory test results are stabilizing (2C). Intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases (2B). Daily PEX should continue for a minimum of 2 days after platelet count has been >150 x $10^9$/l and then stopped (2B) [6].In acute idiopathic TTP with neurological/cardiac pathology, which are associated with a high mortality, rituximab should be considered on admission, in conjunction with PEX and steroids (1B) [6].

## Patients with refractory or relapsing immune-mediated TTP

**Refractory TTP:** Increased frequency of PEX and addition of rituximab can be considered (1B) [6]. Second-line immunosuppression agents including mycophenolate mofetil, cyclosporine, and vincristine may be used in acquired refractory TTP despite adequate rituximab therapy (or true rituximab intolerance) [10]. New drugs including N-acetylcysteine, bortezomib, recombinant ADAMTS13, and caplacizumab show promise. Long-term follow-up is crucial to identify the occurrence of other autoimmune diseases, to control relapses, and to evaluate psychophysical sequelae [3].

**Relapsed TTP:** Increased PEX and/or rituximab therapy are the agents of choice (1B) [6]. Rituximab may be used pre-emptively to prevent relapse of TTP (10). The use of rituximab in an acute episode reduces and delays the incidence of relapse. Cyclosporin may be considered as second line therapy in patients with acute or chronic relapsing acquired TTP (1C) [6]. Splenectomy has limited proven benefit (2C). Antiplatelet agents are relatively safe (1B) [2]. Low dose aspirin (75 mg OD) may be given during platelet recovery (platelet count >50 x $10^9$/l) (2B) [6].

## Treatment of TTP in pregnancy

**Treatment of an acute TTP in pregnancy:** Regular fetal growth scan and uterine artery Doppler monitoring are required.

The mainstay of treatment is PEX. Once platelet counts have normalized, weekly plasma infusion for congenital TTP and PEX at regular intervals for immune mediated TTP will be required during the remainder of pregnancy and the postpartum period. The frequency of plasma therapy will be guided by the platelet count for congenital TTP cases and subsequent platelet counts and ADAMTS13 activity levels in acquired disease. Rituximab is reserved only for the emergency situation such as severe or refractory immune-mediated disease, and if the mother's life is in danger. Caesarean section is undertaken if there are progressive clinical symptoms or fetal distress. Intensive PEX should be considered pre-caesarean. Pulsed methylprednisolone should be given post-PEX in immune-mediated TTP [16]. Platelet transfusions may be considered in severe thrombocytopenia, ensuring PEX following delivery. On achieving a platelet count of 50 X $10^9$/l, low-dose aspirin should be started. Following an acute presentation, LMWH thromboprophylaxis should be given [16].

Mothers with congenital TTP should receive regular ADAMTS13 supplementation throughout pregnancy and the post-partum period (1A) [6].

Women with normal ADAMTS13 activity at the onset of pregnancy, and maintain normal routine laboratory parameters, ADAMTS13 activity and anti-ADAMTS13 antibody levels throughout pregnancy, do not usually require intervention for TTP. Full blood counts should be monitored at least monthly. ADAMTS13 activity should be monitored at least in each trimester throughout pregnancy. A fall in ADAMTS13 activity to <10% prompts elective PEX therapy to prevent relapse [16].

Women with a previous pregnancy loss due to TTP or low ADAMTS13 activity at the onset of pregnancy are at increased risk of further placental disorder in subsequent pregnancies. Low dose aspirin and prophylactic LMWH should be considered to optimize implantation and preserve placental function given that insufficient utero-placental circulation is established in the first trimester [16].

**Low ADAMTS13 activity precedes pregnancy**: rituximab may be used electively to normalize ADAMTS13 activity before conception. Patients are advised to wait 12 months following rituximab before conceiving. Waiting until normalization of CD19 lymphocyte levels, at approximately 6 months, with no detectable serum rituximab may be satisfactory [16].

**HIV-associated TTP:** PEX in conjunction with HAART (triple or quadruple therapy) should be started as soon as the diagnosis is made (1B) [6]. Patients with higher viral loads at presentation (e.g., 500.000 copies/mL) require more PEX to achieve remission [10]. HAART should be given immediately after PEX therapy to maximize absorption (1A) [6]. HAART combined with PEX and corticosteroid alone (without rituximab) is usually sufficient to achieve a remission from the acute episode of TTP 10]. HAART should be continued after remission to prevent further relapse (1B). In resistant HIV-related TTP, rituximab could be considered (2B) [6].

**Malignancy-associated thrombotic microangiopathy:** Treatment of the underlying cancer should be considered (1A) [6].

## Supportive therapy

1. Red cell transfusion should be administered according to clinical need especially if there is cardiac involvement (1A).
2. Folate supplementation is required during active hemolysis (1A).
3. Platelet transfusions are contraindicated in TTP unless there is life-threatening hemorrhage (1A [6].
4. Rituximab is not advocated during pregnancy due to unknown risks to the developing fetus [16].
5. Thromboprophylaxis with LMWH is recommended once platelet count has reached >50 x $10^9$/l (1B).
6. Plasma exchange is not indicated in the management of malignancy and bone marrow transplant-associated TMA (1A) [6].

## Abbreviations

FFP: Fresh frozen plasma; vWF: Von Willebrand factor; TTP: Thrombotic thrombocytopenic purpura; MAHA: Microangiopathic hemolytic anemia; PEX: Plasma exchange; LDH: Lactate dehydrogenase; TMA: Thrombotic microangiopathy; S/D FFP: solvent/detergent-treated fresh frozen plasma; HIV: human immunodeficiency virus; HAART: highly active anti-retroviral therapy; TAM: Transplant-associated microangiopathy; LMWH: low molecular weight heparin; OD: once daily; USS: Upshaw-Schulman syndrome; TPE: Therapeutic plasma exchange.

## Conclusion

The development of new therapies that are rationally targeted at the disease biology could lead to prevention of unnecessary early mortality of acute TTP and better treatment in the future.

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