Immune TTP: Initial treatment

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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 (usually <10 percent). (See 'Terminology' below.)

TTP can be due to an autoantibody against ADAMTS13 (immune) or to biallelic *ADAMTS13* gene variants (hereditary). Immune TTP is much more common, and many patients with hereditary TTP are initially erroneously diagnosed with immune TTP.

This topic reviews initial therapy of immune TTP, a medical emergency that is almost always fatal without prompt appropriate treatment. With appropriate treatment, survival rates of >95 percent are expected.

The following aspects of immune TTP are discussed separately:

- **General evaluation** – (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)
- **Diagnosis** – (See "Diagnosis of immune TTP".)
- **Management after recovery** – (See "Immune TTP: Management following recovery from an acute episode and during remission".)

- **Refractory/relapsed disease** – (See "Immune TTP: Treatment of clinical relapse".)

Management of other primary TMAs is presented separately:

- **Hereditary TTP** – (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)".)
- **Drug-induced TMA** – (See "Drug-induced thrombotic microangiopathy (DITMA)".)
- **TMAs with acute kidney injury (AKI)**:
  - **Adults** – (See "Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS".)
  - **Children** – (See "Complement-mediated hemolytic uremic syndrome in children" and "Overview of hemolytic uremic syndrome in children".)
- **Pregnancy syndromes** – (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)" and "Thrombocytopenia in pregnancy", section on 'Preeclampsia with severe features/HELLP (PE/HELLP)'.)

TERMINOLOGY

Terminology for TTP and related conditions has evolved as their etiologies have become clearer.

- **Thrombotic microangiopathy (TMA)** – TMA describes a pathologic lesion with abnormalities in the vessel wall of arterioles and capillaries leading to microvascular thrombosis, microangiopathic hemolytic anemia (MAHA), and thrombocytopenia. (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)", section on 'Overview of primary TMA syndromes'.)
- **Immune TTP versus hereditary TTP** – Immune TTP (iTTP; also called acquired or autoimmune TTP) is the TMA caused by autoantibodies to ADAMTS13, the protease that cleaves ultralarge von Willebrand factor (VWF) multimers. Hereditary TTP (hTTP) refers to the TMA caused by biallelic pathogenic variants in the *ADAMTS13* gene. (See "Diagnosis of immune TTP".)
- **Outcomes of immune TTP** – We use the definitions from the International Working Group for TTP published in 2021 [1]; these are summarized in the table (table 1).

OVERVIEW OF TREATMENT APPROACH

Virtually every decision point in the therapy of TTP is based on a combination of clinical and laboratory features, and the best choice involves a risk-benefit analysis for the individual patient, as illustrated in the figure (algorithm 1). Early involvement of the consulting clinician with expertise in TTP is advised.

Several therapies are available for immune TTP:

- Therapeutic plasma exchange (TPE)
- Glucocorticoids
- Rituximab
- Caplacizumab

They differ in their mechanisms of action, efficacy, risks, burdens, and costs. We risk-stratify patients based on clinical and laboratory findings at presentation. We generally start treatment for people with an intermediate to high PLASMIC score with TPE and a glucocorticoid. If ADAMTS13 activity is <10 percent, we add rituximab and possibly caplacizumab. (See 'Initial decisions based on PLASMIC score' below and 'Incorporating ADAMTS13 results' below.)

We do not use eculizumab or other complement inhibitors for TTP.

Initial decisions based on PLASMIC score — The PLASMIC score (calculator 1) estimates the likelihood of TTP in patients with suspected TMA who have schistocytes on the blood smear. Schistocytes are included in the score because they are a prerequisite for using the score. The PLASMIC score assigns points for positive and negative clinical features (thrombocytopenia; hemolytic anemia; lack of cancer, macrocytosis, coagulopathy, or kidney failure). (See "Diagnosis of immune TTP", section on 'PLASMIC score'.)

We make a presumptive diagnosis of TTP when the PLASMIC score is intermediate-risk (5 points) or high-risk (6 to 7 points) or if there are other reasons to have a high suspicion for immune TTP (schistocytes and thrombocytopenia without another explanation).

An intermediate or high score generally supports initiation of presumptive treatment (TPE and a glucocorticoid) before results of ADAMTS13 activity testing are available, as this testing can take several days, and TTP is life-threatening if not treated urgently. (See 'Therapeutic plasma exchange (TPE)' below and 'Glucocorticoids' below.)

In centers with rapid access to ADAMTS13 results (hours), it may be reasonable to wait to start treatment until severe ADAMTS13 deficiency (typically <10 percent) is documented.

Incorporating ADAMTS13 results — TTP is initially a clinical diagnosis that is confirmed by a subsequent finding of severely reduced ADAMTS13 activity (typically <10 percent). In many

institutions, this is a send-out test with a turnaround time of up to a week. If the PLASMIC score is intermediate or high, TPE and a glucocorticoid will have been started while awaiting ADAMTS13 results.

- For individuals with ADAMTS13 activity <10, we typically start rituximab. (See 'Rituximab' below.)

- We generally reserve initial treatment with caplacizumab for those with ADAMTS13 activity <10 percent plus clinical features that warrant more aggressive initial therapy. (See 'Anti-VWF (caplacizumab)' below.)

  Examples include one or more of the following:

  - Neurologic abnormalities (seizures, transient focal weakness, aphasia, dysarthria, confusion, coma)
  - Symptoms suggesting encephalopathy (eg, "It seemed like I could not wake her up this morning")
  - High serum troponin levels
  - Thrombocytopenia due to TTP that does not improve after two to three days of TPE, a glucocorticoid, and rituximab

Test considerations, interpretation of ADAMTS13 results, and sources of error are discussed separately. (See "Diagnosis of immune TTP", section on 'ADAMTS13 testing'.)

Other aspects of evaluation and supportive care — Most patients will improve with treatment. However, vigilance is needed for other causes of thrombocytopenia and potential complications of TTP or of therapy.

- **Other causes of thrombocytopenia** – Individuals with suspected or confirmed immune TTP may have another cause of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia such as systemic metastatic cancer or disseminated intravascular coagulation (DIC). All patients should have ongoing assessment for other diagnoses that may account for clinical worsening, exacerbation of clinical findings, development of new symptoms, or lack of response to TPE. Other possible diagnoses are summarized separately. (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)", section on 'Evaluation for primary TMA syndromes'.)

  Ongoing evaluation is especially important if the platelet count does not increase with treatment, if ADAMTS13 activity is >20 percent, if there is transient improvement followed

by worsening, or a new neurologic or kidney abnormality develops. A patient with TTP may develop a complication such as catheter-associated sepsis. (See 'TPE complications' below.)

- **Platelet transfusion** – May be required in patients with severe thrombocytopenia who have clinically important bleeding or who require an invasive procedure. (See 'Bleeding/platelet transfusion' below.)

- **VTE prophylaxis** – Thrombocytopenia is not protective against venous thromboembolism (VTE). Prophylaxis should be administered, though mechanical prophylaxis may be preferred over pharmacologic prophylaxis in patients with platelet count <30,000/microL or active bleeding. (See "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults".)

  Treatment of thrombosis (venous or arterial) should not be withheld if indicated. (See "Anticoagulation in individuals with thrombocytopenia".)

THERAPEUTIC PLASMA EXCHANGE (TPE)

Decision to use TPE — Therapeutic plasma exchange (TPE) remains the mainstay of treatment for TTP [2]. It provides ADAMTS13 from donor plasma and removes the autoantibody against ADAMTS13.

All patients with a presumptive clinical diagnosis of TTP and/or a confirmed diagnosis based on severely deficient ADAMTS13 activity are treated with TPE until their platelet count recovers or until an alternate diagnosis is established (algorithm 1). (See 'Initial decisions based on PLASMIC score' above and 'Incorporating ADAMTS13 results' above.)

TPE is used for all patients because untreated TTP typically follows a progressive course in which neurologic deterioration, cardiac ischemia, irreversible kidney failure, and death are common [3]. Supporting evidence for TPE is discussed below. (See 'Evidence for efficacy of TPE' below.)

Although TPE can be lifesaving, the decision to start can be challenging because it requires synthesis of clinical and laboratory features, often before results of ADAMTS13 activity and inhibitor testing are available.

TPE carries substantial risks and burdens; its use requires the mobilization of individuals with expertise in managing the procedure and operating apheresis equipment. Transfer of the patient to another facility may be required. (See 'TPE complications' below.)

TPE is assumed to work by both replacing ADAMTS13 and removing the autoantibodies that are inhibiting ADAMTS13 activity as well as removing residual ultralarge von Willebrand factor (VWF) multimers. Correcting ADAMTS13 deficiency in turn restores proper cleavage of ultralarge VWF multimers, prevents microvascular thrombosis, and reverses symptoms of organ damage [4-7].

Venous access — TPE almost always requires a central venous catheter with a large bore and two lumens (eg, dialysis catheter) to facilitate the high volume of plasma exchanged at a rapid rate. Rarely, a patient will be able to undergo TPE via peripheral venous access.

Strategies to minimize catheter complications such as the use of ultrasound guidance are presented separately. (See "Central venous catheters: Overview of complications and prevention in adults".)

Plasma as the replacement fluid — Plasma is used as the replacement fluid because it provides ADAMTS13. Plasmapheresis with other replacement fluid(s) is not adequate therapy.

We believe all plasma products are equally effective for TTP:

- Fresh Frozen Plasma (FFP)
- Thawed Plasma (FFP that has been thawed and stored for up to five days at 1 to 6°C)
- Cryoprecipitate Reduced Plasma (plasma from which Cryoprecipitate has been removed, also called Cryo-Poor Plasma)
- Pathogen-inactivated products such as Solvent/Detergent (S/D)-treated or amotosalen-UVA-treated plasma

The choice of product is determined by the clinicians overseeing the procedure and product availability. Some clinicians prefer to use specific products; as an example, in the United Kingdom and Canada, S/D Plasma may be preferred due to the potential for reduced viral transmission [8]. (See "Clinical use of plasma components", section on 'Plasma products' and "Pathogen inactivation of blood products", section on 'Plasma/FFP'.)

Evidence to support the equivalent efficacy of the plasma products comes from extensive personal experience and small trials and case series:

- **Cryo-Poor Plasma versus FFP** – Two small trials (52 and 27 participants) that randomly assigned patients with TTP to receive TPE using Cryo-Poor Plasma versus FFP found no difference in outcomes [9,10]. These trials were conducted after retrospective studies suggested that Cryo-Poor Plasma might be superior to FFP, with the rationale that the lower content of VWF multimers in Cryo-Poor Plasma might reduce the formation of platelet-rich thrombi [6,11-13]. Cryo-Poor Plasma also has a lower content of factor VIII

and fibrinogen; thus, if it is used, coagulation assays and fibrinogen levels should be monitored closely, and it should be alternated with another plasma product.

- **Pathogen-inactivated plasma versus FFP**

  - A retrospective series of 108 patients with TTP in a French registry who underwent TPE using either S/D plasma or FFP found no difference in disease response between the two products [14].

  - A trial that randomly assigned 35 patients with TTP to receive TPE with amotosalen-UVA-treated plasma or control FFP found comparable outcomes and safety [15].

  - Several small observational studies and reports comparing TPE for TTP using S/D Plasma versus FFP have found similar efficacy [16-20]. Concerns have been raised about a reduced concentration of the anticoagulant protein S in S/D Plasma, and it has been suggested that appropriate measures to prevent venous thromboembolism (VTE) be used in patients who receive S/D Plasma (eg, mechanical methods in those with severe thrombocytopenia; pharmacologic methods in those with platelets >30,000/microL) [21,22]. These practices are similar to our approach to VTE prevention in all acutely ill medical patients. (See "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults".)

Two in vitro studies found that the concentration of ADAMTS13 was similar in samples of freshly obtained plasma, FFP, Thawed Plasma, Cryo-Poor Plasma, and S/D Plasma from two different suppliers [23,24].

Volume and schedule — One estimated plasma volume (approximately 40 mL/kg body weight) is exchanged per procedure. This is continued once daily until recovery or until TTP has been excluded and an alternative diagnosis has been established. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology", section on 'Exchange volumes'.)

Several days of TPE typically are required to increase the platelet count, and a week or longer is often required to normalize the count. On average, 7 to 10 daily exchanges may be required, with shorter or longer durations for some patients [4,5,25]. Incorporation of caplacizumab into initial therapy may shorten the duration of TPE. (See 'Anti-VWF (caplacizumab)' below.)

Discontinuation is discussed below. (See 'Platelet count increasing - continuation and completion of therapy' below.)

Timing relative to monoclonal antibodies — TPE removes certain biologic therapies including monoclonal antibodies.

- **Rituximab** – Rituximab is given soon **after** TPE, rather than before, to minimize removal of rituximab by TPE. However, if rituximab is inadvertently given immediately before the TPE procedure is due, we do not delay TPE; TPE is the primary therapy for halting disease activity. Rituximab may be effective even if given on the same day prior to TPE; this may be because the standard dose of 375 mg/m^2 is in excess of the dose required to deplete autoantibody-producing B cells [26]. (See 'Rituximab' below.)

- **Caplacizumab** – Caplacizumab is given as an initial intravenous dose followed by subcutaneous administration. The product information specifies that the first dose be given at least 15 minutes prior to initiation of TPE, and that the first subcutaneous dose be given after completion of plasma exchange on day 1 (two doses are given on the same day; one intravenously before TPE and the other subcutaneously after TPE). (See 'Anti-VWF (caplacizumab)' below.)

Evidence for efficacy of TPE — The efficacy of TPE was established in a landmark randomized clinical trial published in 1991 [4]. A separate review of the experience of a single institution supported the efficacy of TPE and of a glucocorticoid (which were not used in the randomized trial) [5]. Prior to these trials, TTP was almost uniformly fatal.

- The seminal trial randomly assigned 102 patients with TTP (defined as MAHA and thrombocytopenia without another identifiable cause) to TPE or plasma infusion for seven days, along with aspirin and dipyridamole [4]. Survival was greater with TPE than plasma infusion at day 9 (96 versus 84 percent) and at six months (78 versus 63 percent). The benefit of TPE may be greater, as patients whose disease did not respond to plasma infusion were able to cross over and receive TPE.

- A second study treated 108 patients with TTP who had rapid clinical deterioration with urgent TPE plus a glucocorticoid and those who were clinically stable with a glucocorticoid alone, followed by TPE if their disease did not respond [5]. Of the 78 patients who ultimately received TPE, most had a response. There were 10 deaths, nine of which occurred within four days of diagnosis (overall survival, 91 percent).

Multiple subsequent studies have confirmed the efficacy of TPE in TTP, as defined by various criteria [27-30]. Our interpretation of the accumulated evidence is that TPE is highly effective in individuals with immune TTP [4,7,25,31].

Some individuals with features of TTP who do not have documented ADAMTS13 deficiency also have a response to TPE; some of these patients may have conditions other than TTP that respond to a simultaneous intervention rather than TPE (eg, resolution of drug-induced thrombotic microangiopathy [DITMA] upon drug discontinuation) [32]. In addition, some patients with complement-mediated TMA may have a response to TPE [32]. (See "Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS", section on 'Overview of management and supportive measures' and "Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS", section on 'Management'.)

TPE complications — Complications may be related to the central venous catheter or exposure to donor plasma (eg, allergic reactions, transfusion-related acute lung injury [TRALI]). (See "Therapeutic apheresis (plasma exchange or cytapheresis): Complications".)

We do not routinely premedicate patients before TPE; however, patients with plasma-induced urticaria or hives may be pretreated with diphenhydramine 50 mg intravenously and hydrocortisone 100 mg intravenously [33]. Hydrocortisone may be omitted for individuals receiving a high-dose glucocorticoid for TTP therapy.

For individuals with anaphylaxis to donor plasma, factor VIII concentrate containing sufficient ADAMTS13 (Koate-DVI) may be effective [34-36]. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Complications", section on 'Anaphylactic reactions' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Factor VIII products for hemophilia A'.)

Major complications of TPE occur in approximately 25 percent of patients with TTP. Catheter-related complications, especially sepsis from the central venous catheter, tend to be more life-threatening. In a series of 68 patients in the Oklahoma TTP registry who had an initial episode of TTP between 1996 and 2014, three individuals (4.4 percent) died from complications of TPE (one from pulmonary hemorrhage caused by central venous catheter insertion and two from sepsis) [37]. Among the 65 survivors, 36 (55 percent) had nonfatal major complications of TPE:

- Bacteremia – 12 patients (18 percent)
- Catheter-related thrombosis requiring systemic anticoagulation – 3 patients (5 percent)
- Adverse effects of plasma such as anaphylaxis or cardiac arrest – 1 patient

A decline in complications has been observed over a 15-year period of observation [38]. This likely reflects shorter duration of TPE due to more aggressive immunosuppression (glucocorticoids, rituximab), use of caplacizumab, stopping TPE abruptly rather than tapering, and better central venous catheter care. (See "Central venous catheters for acute and chronic hemodialysis access and their management" and "Routine care and maintenance of intravenous devices".)

Plasma infusion as a temporizing measure — Plasma infusion is not an adequate substitute for TPE in the treatment of immune TTP, and TPE should not be delayed to allow for plasma infusion or because plasma infusion has been administered.

Plasma infusion does not remove the inhibitor (autoantibody) to ADAMTS13, and the volume of plasma (and amount of ADAMTS13) that can be delivered is significantly less than in TPE. In the landmark trial that compared plasma infusion with TPE, those undergoing infusion received an average of approximately 7 liters of plasma compared with approximately 22 liters in those undergoing TPE [4]. (See 'Evidence for efficacy of TPE' above.)

TPE may not be immediately available to all patients, and plasma infusion may provide temporary benefit, particularly in patients who require transport to a facility that can provide TPE. In a retrospective analysis of 57 patients who received plasma infusion (25 to 30 mL/kg per day) versus TPE, infusion was inferior to TPE but was effective in some patients [39]. Adverse events were greater in the infusion group; six were unable to tolerate the volume of plasma infused and were switched to TPE. Another retrospective review of 20 patients found that plasma infusion had similar efficacy to TPE if equivalent volumes of plasma were administered [40].

Like plasma infusion, caplacizumab may serve as a temporizing measure if TPE is not immediately available. (See 'Anti-VWF (caplacizumab)' below.)

For patients with an expected delay of more than six hours to starting TPE and if caplacizumab is unavailable, we transfuse plasma if it does not interfere with or delay the appropriate institution of TPE. A reasonable practice is to give two units of plasma (approximately 10 to 15 mL/kg); more may be used if tolerated.

IMMUNOSUPPRESSION

Adding a glucocorticoid and rituximab improves outcomes and decreases the duration of therapeutic plasma exchange (TPE) [38].

- We give a glucocorticoid to all patients with an intermediate to high PLASMIC score (5 to 7 points) (algorithm 1). (See 'Glucocorticoids' below.)
- We add rituximab for all patients once ADAMTS13 activity <10 percent is confirmed. (See 'Rituximab' below.)

Glucocorticoids — Glucocorticoids are thought to hasten recovery because they reduce production of the ADAMTS13 inhibitor (autoantibody). Reduced cytokine production or

decreased autoantibody-mediated clearance of ADAMTS13 may also occur.

- **Indications** – We routinely add a glucocorticoid to TPE for patients with a presumptive diagnosis of immune TTP. This was a strong recommendation in a 2020 Guideline from the International Society on Thrombosis and Haemostasis (ISTH) and earlier guidance from several sources [2,5,8,25,41].

  The rationale is that the potential benefits in reducing inhibitor production and number of required TPE treatments outweigh the risks, which are relatively minor for the limited duration of administration [2].

- **Choice of glucocorticoid** – We generally use oral prednisone for routine presentations and high-dose methylprednisolone for presentations with high-risk features as defined below under dosing.

- **Dosing** – We generally adjust the dose and administration route according to the severity of presentation; evidence to guide dosing is limited [25]:

  - **Standard risk** – For a patient who is alert and awake without neurologic abnormalities or elevated troponin, a typical dose is prednisone 1 mg/kg per day orally. If the platelet count does not increase within three to four days, we switch to methylprednisolone 1000 mg per day intravenously until a response is seen. Caplacizumab may also be added if available. (See 'Anti-VWF (caplacizumab)' below.)

  - **High risk** – For a patient with neurologic or cardiac abnormalities or platelet count not improving, intravenous methylprednisolone 1000 mg as a single daily dose for three days or 125 mg two to four times daily can be used. This is continued if the patient remains at high risk. These doses are based on extrapolating from doses in other severe autoimmune disorders such as systemic lupus erythematosus; even in those conditions, evidence to guide dosing is limited [42]. Intravenous dosing is also appropriate for individuals with gastrointestinal symptoms who may not be able to take or absorb oral medications.

    We usually taper this dose to avoid potentially severe side effects. The taper is individualized based on clinical status. If the patient is clinically improving, we switch to prednisone 1 mg/kg per day orally [25].

- **Duration** – Prednisone 1 mg/kg daily is continued after TPE is stopped. (See 'Platelet count increasing - continuation and completion of therapy' below.)

- **Adverse effects** – (See "Major adverse effects of systemic glucocorticoids".)

- **Supporting evidence** – Evidence comes from extensive clinical experience and observational studies such as the following:

  - Prednisone given alone to patients with suspected immune TTP who were in stable condition (200 mg daily, without TPE) resulted in some responses (30 of 54 patients; 56 percent), although this was before routine ADAMTS13 testing, and some patients may not have had TTP [5].

  - A randomized trial in 26 patients compared prednisone 1 mg/kg daily versus cyclosporine 2 to 3 mg/kg daily and found prednisone was superior for increasing ADAMTS13 activity and suppressing ADAMTS13 autoantibodies [43].

Rituximab — Rituximab is a monoclonal antibody against CD20 that has immunosuppressive activity in many autoimmune disorders. CD20 is a cell surface protein on mature B cells but not plasma cells. Mechanisms by which rituximab suppresses autoantibody production are presented separately. (See "Secondary immunodeficiency induced by biologic therapies", section on 'Rituximab'.)

- **Indication** – We suggest rituximab as a component of initial therapy (along with TPE and glucocorticoids) in all patients with a confirmed diagnosis of TTP unless there is a contraindication (algorithm 1). Inclusion of rituximab as routine initial treatment together with TPE and glucocorticoids is likely to reduce the likelihood of early recurrence. (See 'Incorporating ADAMTS13 results' above.)

  If confidence in the diagnosis is high, it may be reasonable to start rituximab before the ADAMTS13 activity result, especially if prolonged turnaround time is anticipated.

- **Dose** – The optimal dose of rituximab in immune TTP is unknown.

  - We and some others use 375 mg/m^2 intravenously once a week for four consecutive weeks, based on experience with this dose in other conditions [44-46].

  - Lower doses or other schedules may be effective.

    - Some experts have given the first three doses of rituximab within a week and the fourth dose one week after the third dose [47].

    - A prospective study that used a rituximab at 100 mg approximately once per week for four weeks reported similar response rates and reductions in relapse, suggesting this may provide similar efficacy [48]. The rationale is that autoimmune

disorders may require lower doses than lymphoproliferative disorders. Additional study is needed.

- **Timing** – Rituximab should be timed immediately **after** the day's TPE, if possible, because TPE will remove rituximab from the circulation. (See 'Volume and schedule' above.)

- **Adverse effects** – Rituximab with TPE is generally well tolerated, with major complications not reported in larger case series [45-47].

  Risks associated with rituximab including infusion reactions, mucocutaneous reactions, prolonged immunosuppression, hepatitis B reactivation, and progressive multifocal leukoencephalopathy (PML), which is very rare. We do not place patients on antimicrobial prophylaxis, except for patients with a history of hepatitis B virus infection, in whom antiviral therapy may be indicated. Antiviral prophylaxis for hepatitis B is made in consultation with a hepatologist or infectious disease specialist. Prescribing information contains Boxed Warnings about infusion reactions, hepatitis B reactivation, and PML. (See "Overview of therapeutic monoclonal antibodies", section on 'Adverse events' and "Rituximab: Principles of use and adverse effects in rheumatoid arthritis", section on 'Adverse effects' and "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

- **Supporting evidence** – Based on our experience, approximately one-half of individuals who did not receive rituximab during initial therapy may have a recurrence (exacerbation or clinical relapse) [37].

  Observational studies have demonstrated reduced exacerbation and relapse rates and possibly faster response to therapy. A 2019 meta-analysis reported [49]:

  - Lower relapse rate with rituximab during the acute TTP episode (odds ratio [OR] 0.40, 95% CI 0.19-0.85)
  - Lower relapse rate with preemptive rituximab during recovery (OR 0.09, 95% CI 0.04-0.24)
  - Lower mortality rate after rituximab (OR 0.41, 95% CI 0.18-0.91)

  Randomized trials are lacking [50,51]. A randomized trial evaluating rituximab added to TPE and glucocorticoids was terminated due to poor accrual (The STAR trial, NCT00799773) [51].

ANTI-VWF (CAPLACIZUMAB)

Caplacizumab is a humanized bivalent variable-domain-only monoclonal antibody fragment that binds von Willebrand factor (VWF) and blocks its interactions with platelet glycoprotein Ib-IX-V (GPIb-IX-V). It was approved by the US Food and Drug Administration in February 2019 for initial treatment of TTP together with therapeutic plasma exchange (TPE) and immunosuppression.

- **Indications** – Caplacizumab may not be needed in all patients. Its optimal incorporation into clinical practice remains to be determined.

  - Many hematologists are using caplacizumab as routine initial treatment, together with TPE, glucocorticoids, and rituximab. Caplacizumab is routinely used in many European countries.

  - Our use of caplacizumab is increasing, but we do not use it for all patients. Reasons for avoiding caplacizumab include equipoise regarding clinical benefit and increased risk of bleeding [52]. Cost is a factor in many jurisdictions.

    We are more likely to use caplacizumab in patients with severe features, where the benefit and cost-effectiveness is likely to be greatest (algorithm 1). The 2020 International Society on Thrombosis and Haemostasis Guideline makes a conditional recommendation in favor of caplacizumab [2].

    - For patients who present with severe features such as critical illness, neurologic findings, or high troponin, we suggest caplacizumab with initial therapy. The rationale is that these individuals are most likely to die during the acute episode and early death may be reduced by a more rapid halting of the underlying disease process.

    - For individuals without severe features on presentation, we do not use caplacizumab initially. The rationale is that disease in most of these individuals will improve with TPE and immunosuppression. However, some experts use caplacizumab as part of initial therapy in all patients without a contraindication.

  - There are rare situations in which caplacizumab and immunosuppression can replace TPE as an initial treatment:

    - Patients who decline blood products [53]. (See 'Patient who cannot accept plasma/Jehovah's Witness' below.)
    - Patients with a severe allergic reaction to plasma or other need to avoid TPE [54,55].

- Rapid platelet count response to caplacizumab resulting in TPE deferral [56].

Outside of these situations, we would avoid omitting TPE until further studies are available [55].

- **Dose** – Dosing should be guided by the package insert. The dose and schedule of caplacizumab from clinical trials was 10 mg intravenously on day 1 followed by 10 mg subcutaneously on day 1 after TPE (ie, two doses on the first day) and continued once daily subcutaneously for 30 days after TPE has been stopped. We discontinue when ADAMTS13 activity rises above 20 to 30 percent rather than after a fixed duration of treatment. (See 'Platelet count increasing - continuation and completion of therapy' below.)

  The United States package insert lists the product as 11 mg; it is the same dose referred to as 10 mg in clinical trials and labeled in Europe as 10 mg.

- **Adverse effects** – Among two randomized trials and three real-world studies, minor bleeding occurred in approximately one-third of patients and major bleeding in 13 of 343 patients (4 percent) [57]. Caplacizumab was discontinued due to bleeding in 17 patients (5 percent).

  If caplacizumab-associated clinically significant bleeding occurs, this may be treated with VWF concentrate, although clinical experience is extremely limited. There are anecdotal reports of severe skin reactions at the injection site.

- **Supporting evidence**

  - **Randomized trials** – The HERCULES trial randomly assigned 145 patients (mostly adults) with a clinical diagnosis of immune TTP to receive caplacizumab or placebo daily until 30 days beyond the last TPE procedure [58]. All patients received daily TPE and glucocorticoids, and slightly less than one-half received rituximab. Caplacizumab treatment resulted in:

    - Fewer deaths (1 with caplacizumab versus 3 with placebo [1 versus 4 percent]).
    - Faster normalization of the platelet count, which correlated with fewer days of TPE (mean, 5.8 versus 9.4).
    - Fewer exacerbations (12 versus 38 percent). Exacerbations occurred up to 25 days after stopping TPE.
    - Shorter hospitalization (mean, 9.9 versus 14.4 days) and fewer days in the intensive care unit (mean, 3.4 versus 9.7).

Caplacizumab was well tolerated but was associated with more bleeding (65 versus 48 percent). One caplacizumab-treated patient with severe epistaxis was treated with VWF concentrate.

The TITAN trial (75 patients randomly assigned to caplacizumab or placebo) reported faster responses, reduced use of TPE, and fewer exacerbations with caplacizumab [59].

- **Real world** – Additional studies have compared outcomes in caplacizumab-treated patients (312 patients total from among four studies, including children) with historical or untreated controls [60-63]. These all showed similar findings to those from the randomized trials, with more rapid improvement in the platelet count of caplacizumab-treated patients (typically within three to four days) than seen with controls.

  A 2022 study demonstrated reduced risk of relapse or refractory TTP with caplacizumab [63]. Bleeding occurred with caplacizumab, but it was mostly mild; rare, severe cases were treated with VWF concentrate as mentioned above. In some individuals, the platelet count increased to above the normal range (thrombocytosis).

  The effect of caplacizumab is usually prompt. Within one day the platelet count begins to increase and transient neurologic symptoms stop [53].

- **Mechanism of action** – Binding of ultralarge VWF multimers to platelets mediates formation of small vessel microthrombi in immune TTP. Because caplacizumab blocks this binding, it is expected to rapidly halt disease complications but not affect autoantibody production. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)", section on 'TTP pathogenesis'.)

SUBSEQUENT THERAPY BASED ON RESPONSE

Monitoring schedule (platelet count and ADAMTS13 activity) — Patients should have ongoing evaluation throughout their hospitalization. We usually monitor the platelet count as the primary measure of disease response; an increase in the platelet count is typically accompanied by other signs of improvement.

We consider the entire clinical picture but regard the platelet count trend to be the most reliable measure of clinical response. We consider good evidence of a platelet count response to be a platelet count ≥150,000/microL for at least two days or a stable plateau in the normal or supranormal range for three days. (See 'Platelet count increasing - continuation and completion of therapy' below.)

ADAMTS13 activity is a useful adjunct but is not used in isolation to guide initial decision-making [64,65]. Preemptive rituximab for ADAMTS13 relapse is discussed separately. (See "Immune TTP: Management following recovery from an acute episode and during remission", section on 'Rituximab during remission to prevent relapse' and "Immune TTP: Treatment of clinical relapse".)

First week — Most exacerbations of TTP occur during the first week after stopping TPE or the week after stopping caplacizumab. We use the following monitoring during the end of the hospitalization and initial days at home (table 2):

- **Daily CBC** – We continue to obtain a complete blood count (CBC) and monitor the platelet count. Initially this is done daily and gradually extended to every two to three days. We also check the lactate dehydrogenase (LDH) at the time of CBC. The interval can be extended if the patient continues to recover.

  This can often be done as an outpatient, although this depends on the patient's access to outpatient testing with rapid communication of results, caregiver support, and ability to rapidly communicate any change in symptoms, as a clinical exacerbation could be life-threatening.

  In some patients, the platelet count may exceed the baseline and then decrease or fluctuate before stabilizing in the patient's normal range [53]. We do not check ADAMTS13 activity during the first week unless there are clinical or laboratory features suggesting clinical relapse.

  Typically, exacerbation is characterized by a sharp decrease in the platelet count within the first week, which often occurs without any associated symptoms of TTP. If the platelet count decreases to <150,000/microL but not less than 100,000/microL and the patient has no TTP symptoms, daily monitoring alone may be appropriate, as some patients will subsequently have a spontaneous recovery of the platelet count back to the normal range.

  Microangiopathic changes (schistocytes) may persist on the blood smear after thrombocytopenia has resolved.

- **Clinical status** – We monitor the clinical status daily. Some observations indicate that neurologic symptoms and the serum LDH improve first (often within one day), and the platelet count starts to rise after two to three days.

First month — Monitoring intervals are extended and therapies are gradually discontinued as follows (table 2):

- **Clinical status and CBC** – Clinical status is monitored on an ongoing basis.

  The interval of CBC and platelet count monitoring is increased to once weekly and then to every other week. Some individuals may have a platelet count that exceeds their baseline and then decreases or fluctuates before stabilizing in their baseline range.

  Once the platelet count has been maintained in the normal range for one month after discontinuing TPE or caplacizumab, we are confident that a durable remission has occurred. We provide our patients with a wallet card (form 1) that explains the condition, provides our contact information, and emphasizes that any symptoms consistent with TTP call for an immediate CBC with platelet count and triage to a physician who can assess the possibility of relapse. (See "Immune TTP: Management following recovery from an acute episode and during remission", section on 'Monitoring for clinical relapse'.)

  If the serum creatinine and/or LDH were abnormal at the time of hospital discharge, they are monitored until they become normal or another explanation for the abnormality is found. If the serum creatinine and LDH were normal at the time of hospital discharge, they do not require continued monitoring.

  The hemoglobin concentration generally will recover more slowly, and schistocytes may also persist for a few weeks and do not affect management.

  Individuals who have a clinical exacerbation, incomplete recovery, or develop new neurologic abnormalities during this period are considered to have refractory disease. (See "Immune TTP: Treatment of clinical relapse", section on 'Refractory disease'.)

- **ADAMTS13 activity** – We measure ADAMTS13 activity one week after TPE was stopped and weekly during the first month, with the understanding that results may not be immediately available. This continues after discharge from the hospital. The frequency is subsequently reduced based on the patient's clinical course.

  - If ADAMTS13 activity does not recover (remains <20 percent), we continue caplacizumab. An exception is an individual who lacks an ADAMTS13 inhibitor; such individuals may be evaluated for hereditary TTP. (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)", section on 'When to suspect the diagnosis'.)

  - If activity is >20 percent, we extend the monitoring interval to once per month, followed by once every two months, followed by once every three months. (See

"Immune TTP: Management following recovery from an acute episode and during remission", section on 'First year and beyond'.)

We believe that ADAMTS13 activity of 20 to 60 percent indicates protection from relapse but requires more frequent monitoring. When ADAMTS13 activity is normal (>60 percent or above the lower limit of normal for the assay), we begin to measure it less frequently.

Decisions about subsequent monitoring and therapy are generally based on the platelet count response and resolution of neurologic symptoms, with ADAMTS13 activity used as supportive evidence (algorithm 2).

Platelet count increasing - continuation and completion of therapy

- **TPE** – TPE can be stopped abruptly once clinical recovery has occurred. One author (JNG) continues TPE until the platelet count is ≥150,000/microL for at least two days. The other (AC) continues TPE until the platelet count reaches a stable plateau in the normal or supranormal range for three days, based on the premise that a platelet count of 150,000/microL may not be "normal" for all patients. Tapering has not been shown to increase the likelihood of a durable response, and eliminating a taper reduces the number of days the central venous catheter is in place, and the total donor plasma exposure.

- **Stop TPE** – When there is a clinical response, indicated by a normal platelet count for two days or a stable plateau platelet count in the normal or supranormal range for three days, TPE is stopped, and immunosuppressive therapy is continued. The patient usually can be discharged from the hospital.

- **Central venous catheter** – A central venous catheter increases risk for infection, including sepsis, and we anticipate exacerbations will be less of a concern in individuals treated with rituximab and in some cases caplacizumab.

  Timing of catheter removal depends on the risks and burdens of having to replace the catheter if the platelet count drops and TPE needs to be restarted.

  We generally keep the central venous catheter in place for several days (eg, for three to five days [JNG] or five to seven days [AC]) after stopping TPE and discharging the patient (if it is an internal jugular or subclavian catheter) to be sure that the platelet count remains normal. This avoids the risks associated with placement of a new catheter if an exacerbation occurs. Practice will vary between centers based on access to catheter insertion, care, and removal.

- **Glucocorticoids** – We continue glucocorticoid treatment (typically prednisone, 1 mg/kg daily) at full dose after stopping TPE.

  We initiate a glucocorticoid taper once the ADAMTS13 activity is above 20 to 30 percent, typically during the second week after stopping TPE. The taper is completed over the ensuing two to three weeks. Responses are durable for most patients, and this rapid taper minimizes glucocorticoid toxicities and does not increase relapses.

- **Rituximab** – We continue the full course of rituximab (eg, 375 mg/m^2 once per week for four weeks). Patients who do not have recovery of ADAMTS13 activity to >20 percent after a full course of rituximab may require additional rituximab or other immunosuppression. (See "Immune TTP: Treatment of clinical relapse", section on 'Refractory disease'.)

  The possibility of hereditary TTP should be considered in patients who have persistent severe ADAMTS13 deficiency (activity <5 percent) without an ADAMTS13 inhibitor. (See "Hereditary thrombotic thrombocytopenic purpura (hTTP)", section on 'When to suspect the diagnosis'.)

  The timing of TPE and rituximab should be adjusted to allow the maximum interval between rituximab administration and the next daily TPE procedure. (See 'Volume and schedule' above.)

- **Caplacizumab** – For patients treated with caplacizumab, we continue therapy after TPE is stopped until ADAMTS13 activity recovers, to avoid exacerbations. We discontinue caplacizumab when ADAMTS13 activity is above 20 to 30 percent, even if this is before the 30-day continuation period recommended in the US Food and Drug Administration package insert.

  If the ADAMTS13 activity has not recovered to over 20 to 30 percent by 30 days after TPE is completed, we continue the caplacizumab until the ADAMTS13 activity recovers (beyond the duration specified in the package insert). For individuals who have persistent severe ADAMTS13 deficiency despite rituximab, discontinuation of caplacizumab is individualized; one approach is to discontinue caplacizumab 30 days after completion of the course of rituximab.

Platelet count recovery followed by decline

- **Exacerbation** – Approximately 15 to 20 percent of patients have an exacerbation when TPE is discontinued. A clinical exacerbation is commonly manifested by a decreasing platelet count and rarely by development of new neurologic symptoms.

Use of caplacizumab until ADAMTS13 recovery reduces the occurrence of exacerbations.

Exacerbations are considered a form of refractory disease. (See "Immune TTP: Treatment of clinical relapse", section on 'Refractory disease'.)

- **Clinical relapse** – Approximately 40 percent of patients have a clinical relapse following remission when rituximab is not used; most of these relapses occur within the first several years. With rituximab, the frequency of relapse was decreased to 13 percent in a meta-analysis of published evidence [49]. As noted above, this supports the routine use of rituximab at the time of initial therapy. (See 'Immunosuppression' above.)

  Treatment of relapse is discussed separately. (See "Immune TTP: Treatment of clinical relapse", section on 'Clinical relapse'.)

Platelet count not increasing — Lack of a platelet count increase or incomplete platelet count recovery within the first several days of therapy, including caplacizumab, often indicates requirement for a change in management, either to intensify therapy or to treat another condition. Discussion with the consulting expert is advised.

Refractory disease — Patients for whom confidence is high in the initial diagnosis of TTP but for whom the disease does not respond to TPE are considered to have refractory disease.

Features that increase our confidence in the initial diagnosis include the following:

- Significant microangiopathic hemolytic anemia (MAHA) and thrombocytopenia
- Mild to no reduced kidney function
- Transient focal neurologic abnormalities or transient confusion
- Lack of an alternative diagnosis
- Severe ADAMTS13 deficiency (activity <10 percent) with an inhibitor

Management of refractory disease is presented separately. (See "Immune TTP: Treatment of clinical relapse", section on 'Refractory disease'.)

Alternative diagnosis — A condition other than immune TTP may be responsible for the entire clinical picture (eg, drug-induced TMA [DITMA], cancer), or may have arisen after treatment for TTP was initiated. Patients with an apparent initial response who do not have a complete recovery should be evaluated for these possibilities.

- A patient with normal or only mildly reduced ADAMTS13 activity should have a thorough evaluation for other potential causes of MAHA and thrombocytopenia. We have occasionally found a systemic malignancy or infection that only became apparent after

extensive investigations [66-69]. (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

If the other condition appears to be the primary cause of MAHA and thrombocytopenia, TPE can be discontinued. ADAMTS13 activity >10 percent cannot be used in isolation to conclude that another condition is the cause of the patient's clinical findings because prior therapy may falsely elevate ADAMTS13 activity and not all ADAMTS13 assays have the same performance characteristics [65,70]. (See "Diagnosis of immune TTP", section on 'Reduced ADAMTS13 activity'.)

- If the other condition appears to have arisen during therapy, such as central venous catheter sepsis, treatment for TTP should continue while the other condition is treated. The initial central venous catheter may need to be removed and a new central venous catheter placed.

BLEEDING/PLATELET TRANSFUSION

Clinically important bleeding is rare in TTP despite severe thrombocytopenia. We do not use platelet transfusions to correct thrombocytopenia unless clinically important bleeding occurs or an invasive procedure associated with significant bleeding risk is required. However, we do not withhold platelet transfusions needed to manage bleeding for fear of "fueling the fire" [71]. (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'TTP or HIT'.)

In a large observational study of patients with TTP and other causes of platelet consumption, patients with TTP who had an arterial thrombosis were more likely than not to have received platelet transfusion [72]. However, these data cannot be interpreted as evidence for a causal association, as platelet transfusions were likely given to patients with more severe illness. A systematic literature review that included prospective review of 54 consecutive patients with TTP concluded that there was no evidence of harm from platelet transfusions in TTP [71].

Insertion of a central venous catheter by experienced personnel appears to be safe at any platelet count, even <10,000/microL. However, the ultimate decision regarding platelet transfusion prior to central venous catheter placement is made by the person performing the procedure. (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'Indications for platelet transfusion'.)

If platelet transfusion is planned, it should occur immediately prior to the procedure; the utility of a post-transfusion platelet count is disputed since it is unlikely to normalize, and the delay awaiting the results may allow destruction of transfused platelets.

SPECIAL SCENARIOS

Pregnancy — Therapeutic plasma exchange (TPE) is the treatment of choice for immune TTP occurring during pregnancy, despite the resulting removal of pregnancy-maintaining hormones [5,73]. Maternal and fetal mortality rates are approximately 90 percent without TPE. (See "Thrombocytopenia in pregnancy".)

- In a series of 108 pregnant patients, nine were in their third trimester at the time of initial presentation of immune TTP; all pregnancies resulted in delivery of healthy infants [5].
- The United Kingdom TTP Registry reported their experience with 12 episodes of immune TTP during pregnancy treated with TPE and glucocorticoids [73].
    - Two patients presented before 20 weeks gestation; one pregnancy resulted in intrauterine fetal demise; in the other, treatment of TTP was successful, but the pregnancy was terminated for unrelated fetal abnormalities.
    - Four patients presented between 21 to 29 weeks gestation; all were successfully treated, but there was only one live birth; three pregnancies resulted in intrauterine fetal demise.
    - Six patients presented after 30 weeks gestation; all were successfully treated, and all had live births.

Rituximab can be given safely during the first trimester of pregnancy because immunoglobulins do not cross the placenta during the first trimester [74]. (See "Placental development and physiology", section on 'Immunoglobulin G transfer'.)

There is little information about the safety of caplacizumab during pregnancy [75].

Delivery does not cause resolution of TTP; in fact, pregnancy-associated immune TTP may occur postpartum. Delivery should be guided by obstetric indications. (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)", section on 'Differential diagnosis'.)

There have been no reports of transmission of TTP from a pregnant woman to an infant [5,76,77]. However, intrauterine fetal death may occur due to placental infarction caused by thrombosis of the decidual arterioles [78].

Patient who cannot accept plasma/Jehovah's Witness — Very rarely, a patient may not be able to accept plasma as a replacement fluid during TPE, as is the case with some Jehovah's

Witnesses. (See "Approach to the patient who declines blood transfusion", section on 'Jehovah's Witnesses'.)

Options for such patients include the following:

- Discussion with their religious advisors, as practice with respect to use of plasma and other noncellular blood products varies widely even within a common belief system.
- Caplacizumab. (See 'Anti-VWF (caplacizumab)' above.)

  Caplacizumab without TPE has not been studied systematically. However, we successfully used caplacizumab to treat a Jehovah's Witness with immune TTP (ADAMTS13 activity <5 percent) who declined TPE and whose disease did not respond to immunosuppressive therapy with prednisone and rituximab [53]. She had a dramatic improvement in platelet count within one day of starting caplacizumab. Her daily minor neurologic symptoms also stopped after initiating caplacizumab. She has remained well with normal ADAMTS13 activity following a 30-day course.
- High-dose glucocorticoids (eg, methylprednisolone, 1000 mg intravenously per day for three days followed by doses described above) plus rituximab [79]. (See 'Immunosuppression' above.)
- Other forms of immunosuppression [80].
- If the patient will accept plasma derivatives, factor VIII concentrates containing sufficient amounts of ADAMTS13 (eg, Koate-DVI) may be used [34-36].
- Plasmapheresis with albumin as the replacement fluid (should only be used in this specialized setting).
- Recombinant ADAMTS13 would be effective in patients who could not receive plasma.

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

- **Initial treatment** – Thrombotic thrombocytopenic purpura (TTP) is a medical emergency that is almost always fatal if not treated promptly (algorithm 1). The following treatments are used (see 'Overview of treatment approach' above):

  - **TPE** – Therapeutic plasma exchange (TPE) is the mainstay of treatment for all individuals with a presumptive diagnosis of TTP based on a PLASMIC score (calculator 1) in the intermediate-risk to high-risk range (score of 5 to 7 points) and confirmed by a finding of severe ADAMTS13 deficiency (activity <10 percent).

    For **all patients** with a presumptive or confirmed diagnosis of immune TTP, we recommend prompt initiation of TPE rather than plasma infusion and/or immunosuppressive therapy alone (**Grade 1B**). (See 'Evidence for efficacy of TPE' above.)

    - TPE is performed daily with plasma as the replacement fluid. Complications include catheter-associated sepsis and transfusion reactions. (See 'Plasma as the replacement fluid' above and 'Volume and schedule' above and 'TPE complications' above.)

    - Plasma infusion does not substitute for TPE and should not delay TPE initiation but can be used as a temporizing measure. (See 'Plasma infusion as a temporizing measure' above.)

  - **Glucocorticoid** – In addition to TPE, for **all patients** with a presumptive or confirmed diagnosis of immune TTP, we suggest a glucocorticoid (**Grade 2C**). A typical regimen is prednisone, 1 mg/kg per day orally; individuals with high-risk features can be treated with methylprednisolone 1000 mg per day intravenously for the first three days followed by prednisone 1 mg/kg/day. (See 'Glucocorticoids' above.)

  - **Rituximab** – Once TTP is confirmed (ADAMTS13 activity <10 percent), we suggest adding rituximab (**Grade 2C**). Rituximab reduces risks of exacerbation and relapse and may hasten clinical response. We administer 375 mg/m^2 weekly for four weeks. Lower

doses may be equally effective. Some experts may reasonably omit rituximab due to concerns about toxicity. (See 'Rituximab' above.)

- **Caplacizumab** – For patients with severe features (critical illness, neurologic findings, high troponin), we suggest adding caplacizumab (**Grade 2B**). Some experts may reasonably use caplacizumab more broadly, and some may omit caplacizumab. (See 'Anti-VWF (caplacizumab)' above.)

- **Monitoring and stopping treatments** – Patients are monitored clinically and with daily complete blood counts (CBCs) and lactate dehydrogenase (LDH, if abnormal) (table 2). We discontinue TPE when the platelet count is ≥150,000/microL for at least two days or in the normal or supranormal range for three days (algorithm 2). We taper and discontinue the glucocorticoid rapidly (over two to three weeks) rather than a slower taper. Once-weekly rituximab is continued until the course is complete. (See 'Monitoring schedule (platelet count and ADAMTS13 activity)' above.)

  CBC and ADAMTS13 activity are monitored after TPE and the glucocorticoid are discontinued. Caplacizumab discontinuation is based on recovery of ADAMTS13 activity. Most exacerbations of immune TTP occur during the first week after stopping TPE or caplacizumab. (See 'Subsequent therapy based on response' above.)

  Terminology for remission is summarized in the table (table 1). Management following recovery (after the first month) is discussed separately. (See "Immune TTP: Management following recovery from an acute episode and during remission".)

- **Lack of response** – Possible explanations for lack of response or transient response followed by recurrent symptoms or thrombocytopenia include refractory disease, alternative diagnoses, or development of a complication such as catheter-associated sepsis. A change in management is often required. (See 'Platelet count not increasing' above.)

- **Pregnancy** – Immune TTP during pregnancy or postpartum is treated with TPE. Delivery does not treat TTP, and premature delivery should be considered only for obstetric indications. (See 'Special scenarios' above.)

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REFERENCES

1. Cuker A, Cataland SR, Coppo P, et al. Redefining outcomes in immune TTP: an international working group consensus report. Blood 2021; 137:1855.
2. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost 2020; 18:2496.
3. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine (Baltimore) 1966; 45:139.
4. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 1991; 325:393.
5. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. N Engl J Med 1991; 325:398.
6. Byrnes JJ, Moake JL, Klug P, Periman P. Effectiveness of the cryosupernatant fraction of plasma in the treatment of refractory thrombotic thrombocytopenic purpura. Am J Hematol 1990; 34:169.
7. Moake JL. Thrombotic microangiopathies. N Engl J Med 2002; 347:589.
8. Blombery P, Scully M. Management of thrombotic thrombocytopenic purpura: current perspectives. J Blood Med 2014; 5:15.
9. Zeigler ZR, Shadduck RK, Gryn JF, et al. Cryoprecipitate poor plasma does not improve early response in primary adult thrombotic thrombocytopenic purpura (TTP). J Clin Apher 2001; 16:19.
10. Rock G, Anderson D, Clark W, et al. Does cryosupernatant plasma improve outcome in thrombotic thrombocytopenic purpura? No answer yet. Br J Haematol 2005; 129:79.
11. Blackall DP, Uhl L, Spitalnik SL, Transfusion Practices Committee. Cryoprecipitate-reduced plasma:rationale for use and efficacy in the treatment of thrombotic thrombocytopenic purpura. Transfusion 2001; 41:840.
12. Rock G, Shumak KH, Sutton DM, et al. Cryosupernatant as replacement fluid for plasma exchange in thrombotic thrombocytopenic purpura. Members of the Canadian Apheresis Group. Br J Haematol 1996; 94:383.
13. Raife TJ, Friedman KD, Dwyre DM. The pathogenicity of von Willebrand factor in thrombotic thrombocytopenic purpura: reconsideration of treatment with cryopoor plasma.

Transfusion 2006; 46:74.

14. Toussaint-Hacquard M, Coppo P, Soudant M, et al. Type of plasma preparation used for plasma exchange and clinical outcome of adult patients with acquired idiopathic thrombotic thrombocytopenic purpura: a French retrospective multicenter cohort study. Transfusion 2015; 55:2445.
15. Mintz PD, Neff A, MacKenzie M, et al. A randomized, controlled Phase III trial of therapeutic plasma exchange with fresh-frozen plasma (FFP) prepared with amotosalen and ultraviolet A light compared to untreated FFP in thrombotic thrombocytopenic purpura. Transfusion 2006; 46:1693.
16. Moake J, Chintagumpala M, Turner N, et al. Solvent/detergent-treated plasma suppresses shear-induced platelet aggregation and prevents episodes of thrombotic thrombocytopenic purpura. Blood 1994; 84:490.
17. Horowitz MS, Pehta JC. SD Plasma in TTP and coagulation factor deficiencies for which no concentrates are available. Vox Sang 1998; 74 Suppl 1:231.
18. Evans G, Llewelyn C, Luddington R, et al. Solvent/detergent fresh frozen plasma as primary treatment of acute thrombotic thrombocytopenic purpura. Clin Lab Haematol 1999; 21:119.
19. Harrison CN, Lawrie AS, Iqbal A, et al. Plasma exchange with solvent/detergent-treated plasma of resistant thrombotic thrombocytopenic purpura. Br J Haematol 1996; 94:756.
20. Pehta JC. Clinical studies with solvent detergent-treated products. Transfus Med Rev 1996; 10:303.
21. Flamholz R, Jeon HR, Baron JM, Baron BW. Study of three patients with thrombotic thrombocytopenic purpura exchanged with solvent/detergent-treated plasma: is its decreased protein S activity clinically related to their development of deep venous thromboses? J Clin Apher 2000; 15:169.
22. Yarranton H, Cohen H, Pavord SR, et al. Venous thromboembolism associated with the management of acute thrombotic thrombocytopenic purpura. Br J Haematol 2003; 121:778.
23. Rock G, Yousef H, Neurath D, Lu M. ADAMTS-13 in fresh, stored, and solvent/detergent-treated plasma. Transfusion 2006; 46:1261.
24. Scott EA, Puca KE, Pietz BC, et al. Comparison and stability of ADAMTS13 activity in therapeutic plasma products. Transfusion 2007; 47:120.
25. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood 2010; 116:4060.
26. McDonald V, Manns K, Mackie IJ, et al. Rituximab pharmacokinetics during the management of acute idiopathic thrombotic thrombocytopenic purpura. J Thromb

Haemost 2010; 8:1201.

27. Kremer Hovinga JA, Vesely SK, Terrell DR, et al. Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood 2010; 115:1500.
28. Vesely SK, George JN, Lämmle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood 2003; 102:60.
29. Pene F, Vigneau C, Auburtin M, et al. Outcome of severe adult thrombotic microangiopathies in the intensive care unit. Intensive Care Med 2005; 31:71.
30. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. Blood 2004; 103:4043.
31. von Baeyer H. Plasmapheresis in thrombotic microangiopathy-associated syndromes: review of outcome data derived from clinical trials and open studies. Ther Apher 2002; 6:320.
32. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med 2014; 371:654.
33. Apter AJ, Kaplan AA. An approach to immunologic reactions associated with plasma exchange. J Allergy Clin Immunol 1992; 90:119.
34. Scully M, Gattens M, Khair K, Liesner R. The use of intermediate purity factor VIII concentrate BPL 8Y as prophylaxis and treatment in congenital thrombotic thrombocytopenic purpura. Br J Haematol 2006; 135:101.
35. Peyvandi F, Mannucci PM, Valsecchi C, et al. ADAMTS13 content in plasma-derived factor VIII/von Willebrand factor concentrates. Am J Hematol 2013; 88:895.
36. Naik S, Mahoney DH. Successful treatment of congenital TTP with a novel approach using plasma-derived factor VIII. J Pediatr Hematol Oncol 2013; 35:551.
37. Page EE, Kremer Hovinga JA, Terrell DR, et al. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Adv 2017; 1:590.
38. Som S, Deford CC, Kaiser ML, et al. Decreasing frequency of plasma exchange complications in patients treated for thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, 1996 to 2011. Transfusion 2012; 52:2525.
39. Coppo P, Bussel A, Charrier S, et al. High-dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. Medicine (Baltimore) 2003; 82:27.

40. Novitzky N, Jacobs P, Rosenstrauch W. The treatment of thrombotic thrombocytopenic purpura: plasma infusion or exchange? Br J Haematol 1994; 87:317.
41. Allford SL, Hunt BJ, Rose P, et al. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. Br J Haematol 2003; 120:556.
42. Franchin G, Diamond B. Pulse steroids: how much is enough? Autoimmun Rev 2006; 5:111.
43. Cataland SR, Kourlas PJ, Yang S, et al. Cyclosporine or steroids as an adjunct to plasma exchange in the treatment of immune-mediated thrombotic thrombocytopenic purpura. Blood Adv 2017; 1:2075.
44. Sayani FA, Abrams CS. How I treat refractory thrombotic thrombocytopenic purpura. Blood 2015; 125:3860.
45. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood 2011; 118:1746.
46. Scully M, Cohen H, Cavenagh J, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. Br J Haematol 2007; 136:451.
47. Froissart A, Buffet M, Veyradier A, et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. Crit Care Med 2012; 40:104.
48. Zwicker JI, Muia J, Dolatshahi L, et al. Adjuvant low-dose rituximab and plasma exchange for acquired TTP. Blood 2019; 134:1106.
49. Owattanapanich W, Wongprasert C, Rotchanapanya W, et al. Comparison of the Long-Term Remission of Rituximab and Conventional Treatment for Acquired Thrombotic Thrombocytopenic Purpura: A Systematic Review and Meta-Analysis. Clin Appl Thromb Hemost 2019; 25:1076029618825309.
50. Lim W, Vesely SK, George JN. The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura. Blood 2015; 125:1526.
51. Uhl L, Kiss JE, Malynn E, et al. Rituximab for thrombotic thrombocytopenic purpura: lessons from the STAR trial. Transfusion 2017; 57:2532.
52. Goshua G, Sinha P, Hendrickson JE, et al. Cost effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood 2021; 137:969.
53. Chander DP, Loch MM, Cataland SR, George JN. Caplacizumab Therapy without Plasma Exchange for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med 2019; 381:92.

54. Irani MS, Sanchez F, Friedman K. Caplacizumab for treatment of thrombotic thrombocytopenic purpura in a patient with anaphylaxis to fresh-frozen plasma. Transfusion 2020; 60:1666.
55. Sukumar S, George JN, Cataland SR. Shared decision making, thrombotic thrombocytopenic purpura, and caplacizumab. Am J Hematol 2020; 95:E76.
56. Völker LA, Brinkkoetter PT, Knöbl PN, et al. Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab. J Thromb Haemost 2020; 18:3061.
57. Siddiqui A, Journeycake JM, Borogovac A, George JN. Recognizing and managing hereditary and acquired thrombotic thrombocytopenic purpura in infants and children. Pediatr Blood Cancer 2021; 68:e28949.
58. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med 2019; 380:335.
59. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med 2016; 374:511.
60. Völker LA, Kaufeld J, Miesbach W, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv 2020; 4:3085.
61. Coppo P, Bubenheim M, Azoulay E, et al. A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood 2021; 137:733.
62. Dutt T, Shaw RJ, Stubbs M, et al. Real-world experience with caplacizumab in the management of acute TTP. Blood 2021; 137:1731.
63. Izquierdo CP, Mingot-Castellano ME, Fuentes AEK, et al. Real-world effectiveness of caplacizumab vs the standard of care in immune thrombotic thrombocytopenic purpura. Blood Adv 2022; 6:6219.
64. Shah N, Rutherford C, Matevosyan K, et al. Role of ADAMTS13 in the management of thrombotic microangiopathies including thrombotic thrombocytopenic purpura (TTP). Br J Haematol 2013; 163:514.
65. George JN. ADAMTS13: what it does, how it works, and why it's important. Transfusion 2009; 49:196.
66. Parekh HD, Reese JA, Cobb PW, George JN. Bone marrow necrosis discovered in a patient with suspected thrombotic thrombocytopenic purpura. Am J Hematol 2015; 90:264.
67. Booth KK, Terrell DR, Vesely SK, George JN. Systemic infections mimicking thrombotic thrombocytopenic purpura. Am J Hematol 2011; 86:743.

68. George JN. Systemic malignancies as a cause of unexpected microangiopathic hemolytic anemia and thrombocytopenia. Oncology (Williston Park) 2011; 25:908.
69. Wills-Sanin B, George JN, Boiocchi L, et al. Occult recurrent breast cancer masquerading as thrombotic thrombocytopenic purpura. Am J Hematol 2023; 98:830.
70. George JN. Measuring ADAMTS13 activity in patients with suspected thrombotic thrombocytopenic purpura: when, how, and why? Transfusion 2015; 55:11.
71. Swisher KK, Terrell DR, Vesely SK, et al. Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. Transfusion 2009; 49:873.
72. Goel R, Ness PM, Takemoto CM, et al. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. Blood 2015; 125:1470.
73. Scully M, Thomas M, Underwood M, et al. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. Blood 2014; 124:211.
74. Pentsuk N, van der Laan JW. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. Birth Defects Res B Dev Reprod Toxicol 2009; 86:328.
75. Odetola O, Martin KA, Dreyer M, et al. A safe and effective use of caplacizumab in pregnancy-related acquired thrombotic thrombocytopenic purpura. Br J Haematol 2023; 202:879.
76. Egerman RS, Witlin AG, Friedman SA, Sibai BM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in pregnancy: review of 11 cases. Am J Obstet Gynecol 1996; 175:950.
77. Ezra Y, Rose M, Eldor A. Therapy and prevention of thrombotic thrombocytopenic purpura during pregnancy: a clinical study of 16 pregnancies. Am J Hematol 1996; 51:1.
78. Wurzei JM. TTP lesions in placenta but not fetus. N Engl J Med 1979; 301:503.
79. George JN, Sandler SA, Stankiewicz J. Management of thrombotic thrombocytopenic purpura without plasma exchange: the Jehovah's Witness experience. Blood Adv 2017; 1:2161.
80. Dabak V, Kuriakose P, Raman S. Successful management of a Jehovah's Witness with thrombotic thrombocytopenic purpura unwilling to be treated with therapeutic plasma exchange. J Clin Apher 2007; 22:330.

Topic 1344 Version 75.0

GRAPHICS

Terminology and outcomes definitions for thrombotic thrombocytopenic purpura (TTP)

Syndromes	
Thrombotic microangiopathy (TMA)	Condition in which small vessel microthrombi form and cause thrombocytopenia (platelet count <150,000/microL) and microangiopathi hemolytic anemia (MAHA; schistocytes and evidence of hemolysis)
Thrombotic thrombocytopenic purpura (TTP)	TMA caused by severe deficiency of the ADAMTS13 protease, which cleaves large VWF multimers
▪ Immune TTP	Acquired TTP caused by an autoantibody against ADAMTS13
▪ Hereditary TTP	Genetic condition caused by biallelic variants in the *ADAMTS13* gene
Outcomes of therapy for immune TTP	
Clinical response	Resolution of thrombocytopenia and hemolysis -and- Cessation of clinical deterioration
Remission	Sustained response after stopping TPE and/or anti-VWF therapy
▪ Clinical remission	Sustained clinical response for ≥30 days -or- ADAMTS13 remission (partial or complete)
▪ ADAMTS13 remission (partial)	ADAMTS13 activity ≥20% but below the assay's lower limit of normal
▪ ADAMTS13 remission (complete)	ADAMTS13 activity above the assay's lower limit of normal
Relapse	Clinical and/or laboratory deterioration following remission
▪ Clinical relapse	Recurrence of thrombocytopenia following a remission, without another cause (subsequently must be confirmed by documenting ADAMTS13 activity <10%)
▪ ADAMTS13 relapse	ADAMTS13 activity <20% following an ADAMTS13 remission
Exacerbation	Recurrence of thrombocytopenia without another cause following a response but ≤30 days after stopping TPE or anti-VWF therapy

Refractory disease	Lack of a clinical response to initial treatment*

Refer to separate discussions in UpToDate for the approach to managing immune TTP, hereditary TTP, and other TMAs.

- Clinical remission can occur without ADAMTS13 remission, but ADAMTS13 remission is always accompanied by clinical remission.
- Clinical relapse is always accompanied by ADAMTS13 relapse, but ADAMTS13 relapse can occur without clinical relapse.
- Preemptive treatment of ADAMTS13 relapse can induce ADAMTS13 remission and reduce the risk of clinical relapse.

Anti-VWF therapy includes caplacizumab and other therapies under development.

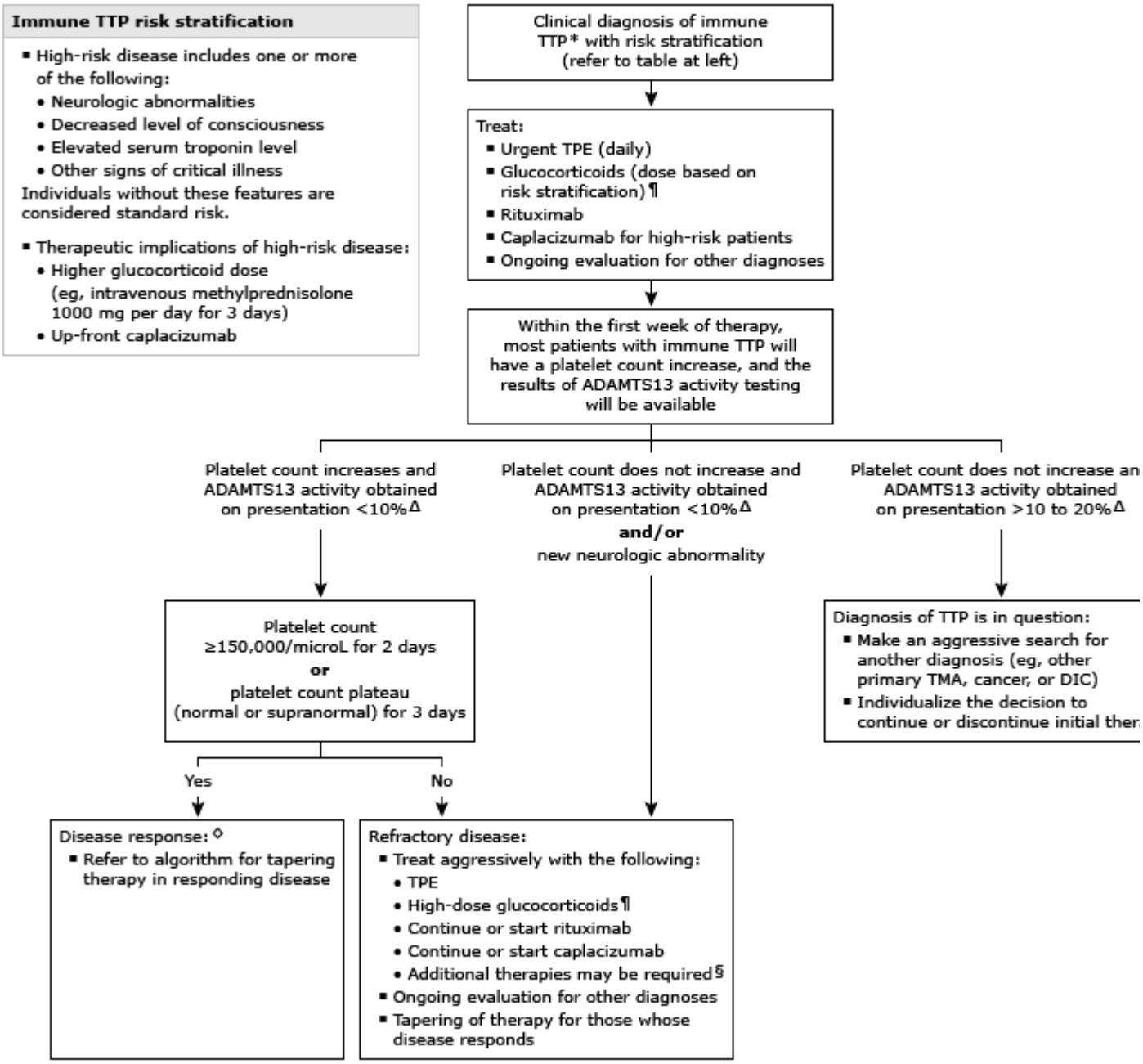
VWF: von Willebrand factor; TPE: therapeutic plasma exchange; LLN: lower limit of normal; DIC: disseminated intravascular coagulation.

* Refractory disease is rare in the era of rituximab and anti-VWF therapy. If thrombocytopenia persists despite TPE, rituximab, and anti-VWF therapy, other potential causes such as sepsis, DIC, and drug-induced thrombocytopenia should be investigated.

Adapted from: Cuker A, Cataland SR, Coppo P, et al. Redefining outcomes in immune TTP: An international working group consensus report. Blood 2021; 137:1855.

Graphic 132744 Version 1.0

Algorithm for the initial treatment of immune thrombotic thrombocytopenic purpura (TTP)



This algorithm applies to individuals with a presumptive diagnosis of immune TTP that is caused by autoantibody-induced ADAMTS13 deficiency. It should not be used for individuals with drug-induced TMA, hereditary TTP, or other causes of MAHA and thrombocytopenia such as malignancy or DIC. Refer to UpToDate for additional details.

TTP: thrombotic thrombocytopenic purpura; TPE: therapeutic plasma exchange; TMA: thrombotic microangiopathy; DIC: disseminated intravascular coagulation; MAHA: microangiopathic hemolytic anemia.

* Diagnosis is based on the finding of MAHA and thrombocytopenia without another explanation. Neurologic findings may be present but are not seen in all patients; kidney impairment is rare. We risk-stratify patients based on clinical criteria. ADAMTS13 activity testing should be performed as soon as possible, ideally before TPE is initiated; however, results may not be available for several days. Refer to UpToDate for details of the diagnostic evaluation, including the use of the PLASMIC score and other criteria that give high confidence in the diagnosis of TTP, which is based on clinical criteria rather than solely on ADAMTS13 activity.

¶ The following therapies are used in addition to TPE:

- Glucocorticoids are given to all patients based on their potential to improve ADAMTS13 levels. Dosing is based on risk stratification (refer to inset box):
  - High-risk disease – Methylprednisolone 1000 mg intravenously per day for 3 days followed by prednisone 1 mg/kg daily orally.
  - Standard-risk disease – Prednisone 1 mg/kg per day orally.
- Rituximab is used as part of initial therapy unless there is a contraindication. This is based on emerging evidence that rituximab may reduce the risks of exacerbation and relapse and may hasten the response to therapy.
- Caplacizumab is given to those with high-risk disease to avoid potentially life-threatening complications.

Δ Response criteria are based on platelet count, with the exact details individualized according to the judgment of the treating clinician; refer to UpToDate for further discussion of these criteria.

◇ ADAMTS13 activity <10% is consistent with a diagnosis of TTP. Rarely, patients may have a slightly higher value; examples include an individual who has already undergone TPE before the blood sample was obtained. ADAMTS13 activity >20% is generally consistent with response to treatment or a condition other than TTP; in some cases, individuals with slightly lower values (10 to 20%) may have a condition other than TTP. If an individual has an increase in platelet count and ADAMTS13 activity >10 to 20%, therapy is individualized based on the clinical distinction between resolving TTP and another resolving cause of thrombocytopenia. Refer to UpToDate for further discussion of ADAMTS13 testing, test interference, and interpretation.

§ Refer to UpToDate for options if TTP does not respond to TPE, high-dose glucocorticoids, rituximab, and caplacizumab.

Graphic 120708 Version 3.0

Monitoring protocol after recovery from an episode of immune TTP

	Therapy	Monitoring	Routine care	Comments
First week	▪ Continue glucocorticoids, rituximab, and caplacizumab (if used)	▪ Symptom assessment daily ▪ CBC daily ▪ LDH at time of CBC	▪ Removal of central venous catheter	▪ The highest risk of exacerbation is during the first week. ▪ Exacerbations are treated with TPE, glucocorticoids, rituximab, and sometimes caplacizumab.
First month (assuming ADAMTS13 activity has increased to >20 to 30%)	▪ Taper and discontinue glucocorticoids ▪ Complete rituximab ▪ Discontinue caplacizumab	▪ Symptom assessment (ongoing) ▪ CBC weekly, then every other week ▪ ADAMTS13 activity weekly ▪ LDH and creatinine with CBC until they become normal	▪ Provision of wallet card/letter ▪ Resumption of normal activities	
First and second year (assuming clinically stable with ADAMTS13 activity >20 to 30%)		▪ ADAMTS13 activity every three months	▪ Return to primary care clinician ▪ Updating of vaccinations ▪ Seek medical attention (and immediate CBC) for any return of symptoms	▪ The risk of relapse is greater during the first two years and greater for those with ADAMTS13 <10% (risk of 20 to 30%), but relapse may no occur imminently (median time to relapse: 5 to 9 years). ▪ For ADAMTS13 <20%, prophylactic rituximab as a single dose followed by retesting of ADAMTS13 is reasonable.
Subsequent years		▪ ADAMTS13 activity annually	▪ Routine primary care ▪ Annual hematologist visit ▪ Monitoring for and treatment	

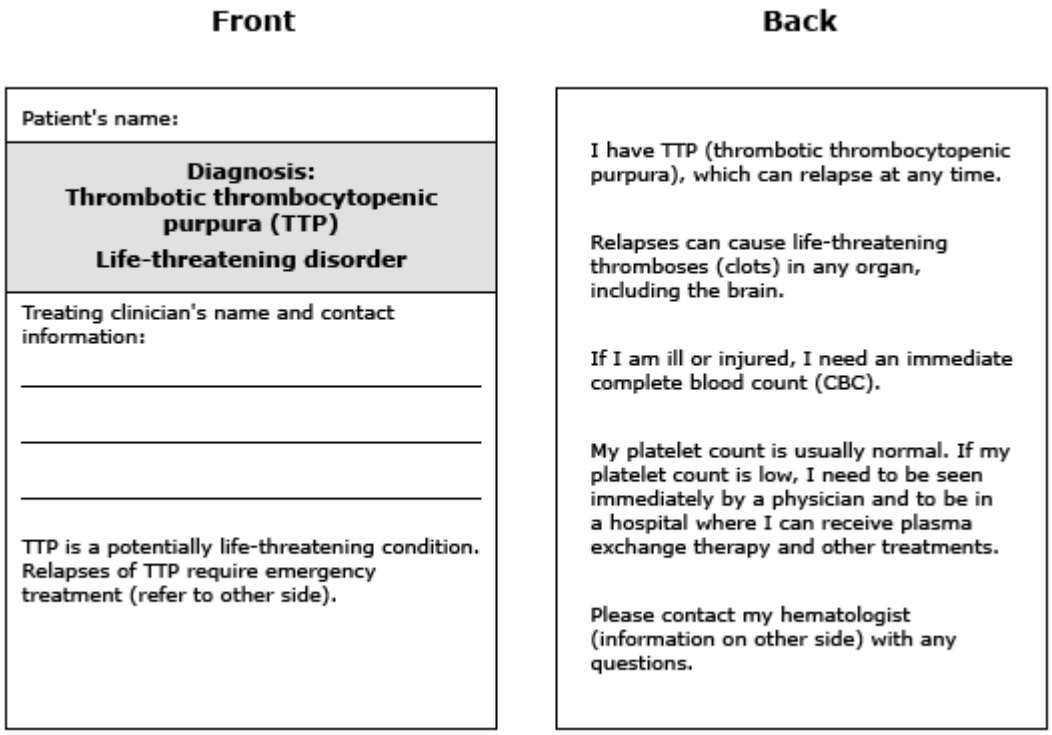
			▪ of long-term complications of TTP ▪ Seek medical attention (and immediate CBC) for any return of symptoms	▪ For frequent relapses with persistent severe ADAMTS13 activity <20%, splenectomy maintenance rituximab once every 3 months for 2 to 3 years, or other immunosuppressiv agents are reasonable options

The optimal approach to monitoring patients after recovery from an episode of acute TTP is evolving, and the interventions to reduce the risk of relapse are an area of active investigation. Judgment of a clinician with experience in managing TTP is required. Refer to UpToDate for details.

TTP: thrombotic thrombocytopenia purpura; CBC: complete blood count; LDH: lactate dehydrogenase; TPE: therapeutic plasma exchange.

Graphic 116648 Version 3.0

Wallet card that can be carried by patients with TTP

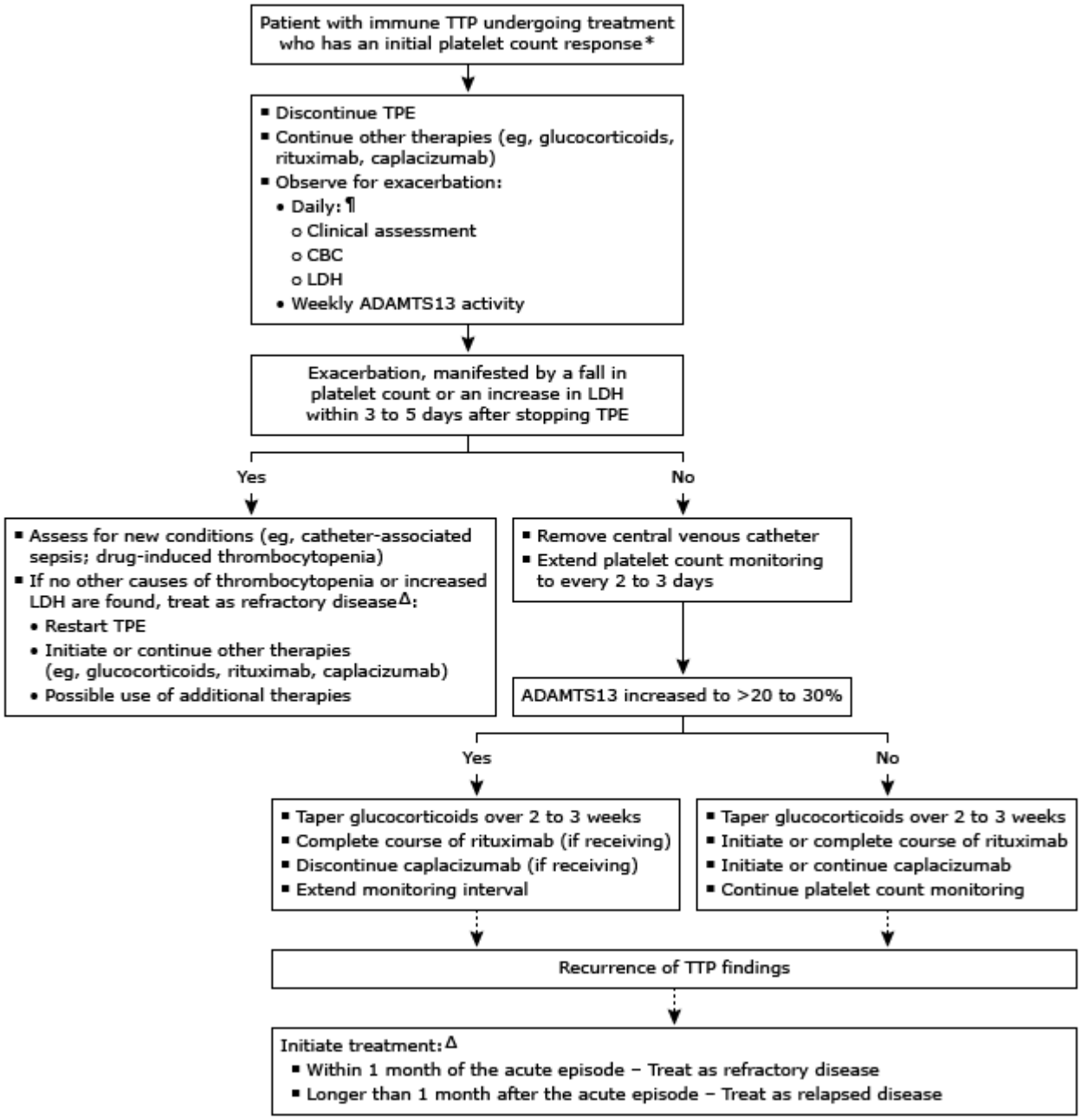


Patients with TTP can carry this wallet card and show it to emergency department personnel or clinicians who are not familiar with their diagnosis as a way to ensure that they convey the potential life-threatening severity of their disease and the importance of obtaining a CBC with platelet count, even for nonspecific symptoms that might herald a relapse. This may be especially important if they become confused and cannot adequately convey this information.

TTP: thrombotic thrombocytopenic purpura; CBC: complete blood count.

Graphic 116336 Version 2.0

Algorithm for tapering therapy after an initial response in a patient with immune thrombotic thrombocytopenic purpura (TTP)



This algorithm outlines our approach to tapering therapy in an individual with immune TTP who is receiving therapy and has a documented platelet count response, defined as a platelet count ≥150,000/microL for 2 days or a platelet count plateau (normal or supranormal) for 3 days. Refer to UpToDate topics on treatment of acquired autoimmune TTP and management following recovery from an acute episode of TTP for additional details about monitoring and interventions.

TTP: thrombotic thrombocytopenic purpura; TPE: therapeutic plasma exchange; CBC: complete blood count; LDH: lactate dehydrogenase.

* Defined as a platelet count ≥150,000/microL for at least 2 days or a stable platelet count plateau in the normal or supranormal range for 3 days. Refer to UpToDate for details.

¶ Daily assessment of clinical status, CBC, and LDH is done for approximately 2 to 3 days after stopping TPE; monitoring is then extended slowly, with the exact timing dependent on clinical status.

Δ Individuals who have a recurrence within a month of the acute episode are considered to have refractory disease and are treated more aggressively. Those who have a recurrence >1 month after the acute episode are considered to have a relapse and are treated for a new episode, similarly to the previous episode. Refer to the UpToDate algorithm on initial treatment of TTP and the UpToDate topic on treatment of refractory or relapsed TTP for details of management.

Graphic 120707 Version 2.0