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ISTH GUIDANCE & GUIDELINES

2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura

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Abstract

Background: Over the past few years, new information has emerged in the management of both immune thrombotic thrombocytopenic purpura (iTTP) and congenital (or hereditary) thrombotic thrombocytopenic purpura (cTTP).

Methods: In March 2024, the International Society on Thrombosis and Haemostasis (ISTH) formed a multidisciplinary panel comprising hematologists, intensivists, nephrologists, pathologists, patient representatives, and a methodology team. The panel discussed all treatment questions related to thrombotic thrombocytopenic purpura (TTP) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method to appraise evidence and formulate recommendations.

Results: For patients with cTTP in remission, a new strong recommendation was issued for the use of recombinant ADAMTS-13 over fresh frozen plasma in the context of moderate certainty evidence. The panel also revised a previous recommendation and suggested using fresh frozen plasma over a watch-and-wait approach for patients with cTTP in remission based on very low certainty evidence should recombinant. The panel reviewed and referenced new publications supporting therapeutic efficacy, potential survival benefit, and cost considerations of adding caplacizumab to therapeutic plasma exchange, corticosteroids, and rituximab, but concluded that no change was warranted to the previous recommendations in the management of iTTP. Good practice statements on the concomitant use of antithrombotic agents were marginally modified.

Conclusions: For patients with iTTP, no change to 2020's recommendations. For patients with cTTP, the panel supports ADAMTS-13 replacement. Where accessible, recombinant ADAMTS-13 provides the most favorable balance of benefits and risks. Otherwise, fresh frozen plasma may still be effective. Shared decision-making should include the benefits, the potential harms, and the burden of care.

KEYWORDS
ADAMTS-13, caplacizumab, congenital, immune, thrombotic thrombocytopenic purpura

1 | INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially fatal blood disorder [1]. It is primarily caused by autoantibodies against ADAMTS-13 [2] or, in rare cases, mutations of *ADAMTS13* [3], resulting in severe deficiency of plasma ADAMTS-13 activity [4]. ADAMTS-13 is produced primarily in hepatic stellate cells [5–7] and likely endothelial cells [7–9], and is released into the bloodstream where it cleaves ultra-large von Willebrand factor (UL-VWF) [10]. This proteolytic cleavage is crucial for normal hemostasis and regulation of inflammatory responses [11,12]. An inability to cleave UL-VWF owing to severe deficiency of plasma ADAMTS-13 activity leads to an accumulation of UL-VWF on endothelial surface, at sites of vascular injury, and in circulating blood [13]. This triggers excessive platelet adhesion and aggregation, and microvascular thrombus formation throughout the body, leading to ischemic organ damage and mortality, the pathognomonic feature of TTP [14,15].

Patients with TTP may present with severe thrombocytopenia (usually $<30 \times 10^9$/L), microangiopathic hemolytic anemia (eg, low hemoglobin, low hematocrit, increased lactate dehydrogenase, presence of fragmented red blood cells, etc), as well as various degrees of end-organ damage [16,17]. The diagnosis of TTP relies on a high index of clinical suspicion, careful assessment of patients' manifestations, and several key laboratory findings. Before the ADAMTS-13 test results are available from the laboratory, a clinical scoring system such as the French score [18] or Plasmic score [19] may be used to assess the likelihood of severe ADAMTS-13 deficiency, one of the key laboratory parameters for diagnosis and management of

suspected TTP. When plasma ADAMTS-13 activity is <10 IU/dL (or 10% of normal) with or without detectable anti-ADAMTS-13 IgGs (or inhibitors) in the proper clinical context, the diagnosis of TTP should be considered [20]. Positive test for anti-ADAMTS-13 IgGs (or inhibitors) may aid the differentiation of immune TTP (iTTP) from congenital (or hereditary) TTP (cTTP) [21–23]. However, the absence of detectable anti-ADAMTS-13 IgGs during initial acute episodes does not rule out the possibility of iTTP [24] because of possible lack of free antibodies for detection by enzyme-linked immunosorbent assay (ELISA) [24,25] and/or accelerated clearance of antibody-ADAMTS-13 complexes from circulation [24]. To confirm the diagnosis of cTTP, repeated negative testing of antibodies (or inhibitors) following therapy, alongside positive genetic testing for *ADAMTS13* mutations, should be obtained. To date, approximately 250 mutations on *ADAMTS13* have been reported to be causative for cTTP [26,27]. Most patients with cTTP carry compound heterozygous mutations, but homozygous mutations of *ADAMTS13* have also been reported [28]. These mutations may result in impaired secretion of ADAMTS-13 protein into bloodstream or render ADAMTS-13 protease nonfunctional [3,26,29–39].

The first International Society on Thrombosis and Haemostasis (ISTH) guidelines for diagnosis and management of TTP, along with good practice statements (GPS) for caring patients with TTP, were published in July 2020 [20,40,41]. There are also several similar guidelines or guidances for the diagnosis and management of TTP from China [42], England [43,44], and Japan [45] published subsequently. The 2020 ISTH guidelines for management of TTP have received the endorsement from European Renal Best Practice with some refinements for Europe [46] and have been widely cited [47], likely resulting in significant improvements in patient care, education, and payor reimbursement rate.

However, many new publications have emerged since the initial publication of the 2020 guidelines. These include our better understandings of pathophysiology, the development of new and improved tools for rapid and accurate diagnosis, and the advancements of new targeted therapies or better refined treatment protocols for TTP. A number of real-world observational studies, mostly based on routinely collected data, have reported that the use of caplacizumab in conjunction with therapeutic plasma exchange (TPE) and immunosuppression (eg, corticosteroids and rituximab), known as the triple therapy, has significantly accelerated the disease recovery, shortened the hospital stay, and reduced the number of TPE sessions, and reudced exacerbations and mortality rates [48–56]. A few other studies have also shown that addition of caplacizumab to TPE and immunosuppressives is more cost-effective for managing iTTP than the use of TPE alone [53,57]. Furthermore, the management of iTTP with caplacizumab and immunosuppressives without TPE, known as the double therapy, appears to show a similar efficacy and safety profile as the triple therapy, although the interpretations of the data are limited due to the potential selection bias for patients with less severe iTTP [58]. Further studies are needed to determine the safety and efficacy of this double therapy without TPE for patients with more severe disease before this therapeutic regimen can be widely adopted.

Breakthroughs came from the approval of recombinant ADAMTS-13 for prophylaxis of cTTP by the US Food and Drug Administration (FDA), European Commission, and Japanese Ministry of Health in 2024. Such a targeted therapy would not have been possible without the identification and molecular cloning of *ADAMTS-13* [3,59]. The development of rapid and reliable ADAMTS-13 activity tests [60–67] and the success in conducting preclinical [68–70] and clinical trials [71–75] that demonstrated the efficacy and safety of using recombinant ADAMTS-13 in cTTP have accelerated the advancement of this transformational therapy.

Moreover, information about potential disease complications, relapses, and long-term risks associated with TTP treatments is evolving [28,76–84]. Variations in availability of treatments and health care resources across different regions or countries may lead to inconsistencies in caring for patients with TTP. Thus, updated and internationally relevant guidelines may help bridge these gaps and improve global standards for caring patients with TTP, which may lead to better outcomes.

In the 2025 updated guidelines, we have discussed the guideline development process, guideline panel composition, updated literature analysis, prioritization of Population, Intervention, Comparison, Outcome (PICO) questions, and proper use of the guidelines. We focus on the discussion of the evidence for issuing new recommendations for the management of cTTP and provided a good practice statement (GPS) for using additional antiplatelet or anticoagulant therapy in TTP when platelet counts recover. We also provide tables showing a side-by-side comparison with the previous recommendations and any updates. Finally, we discuss and update new literature about the management of iTTP despite no change in direction and strength of recommendations currently.

2 | METHODS

2.1 | Guideline development process

The guideline panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach and the PICO framework to develop and grade the recommendations contained in these guidelines, and to assess the certainty of the evidence. These guidelines are developed according to the standards for trustworthy guidelines set by the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (formerly called the Institute of Medicine), and the procedures outlined in the Guidelines International Network-McMaster Guidelines Development Checklist [85,86]. The draft recommendations and related materials were posted publicly for external peer review and internally for ISTH members, Guidelines and Guidance Committee, and Council. Finally, the

guideline manuscript was approved by all panelists and peer-reviewed before its publication.

2.2 | Guideline panel

In March 2024, the ISTH formed a multidisciplinary guideline panel consisting of the majority of the original guideline panel members, with the addition of several new members. The guideline panel comprises a diverse team of experts including hematologists, pathologists, intensive care physicians, nephrologists, methodologists, and patient representatives. X.L.Z., the Russel J Eliers Endowed Professor and Department Chair of Pathology and Laboratory Medicine at the University of Kansas Medical Center, Kansas City, Kansas, USA served as the Clinical Co-Chair of the guideline panel. Zheng is globally recognized for his groundbreaking research on biology of ADAMTS-13 and pathogenesis of TTP. He is the leading authority on the diagnosis and management of TTP and other thrombotic microangiopathies. S.K.V., a Professor of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA, served as the Methodology Co-Chair of the guideline panel. She brings extensive experience in developing GRADE guidelines and conducts clinical research on TTP. A.I., a professor and the Mike Gent Chair in HealthCare Research. A.K., F.G., and Z.S.A.A.-H. at the McMaster University provided the methodological support for the guideline development process, conducting updated systematic literature reviews to inform the guidelines-based PICO questions, providing training to the guideline panel members, guiding the discussion at guideline panel meetings, and preparing the summary of evidence report. Other panelists include S.R.C. (USA), P.C. (France), B.G. (USA), C.M. (USA), M.M. (Japan), K.R.M. (USA), J.M. (UK), R.A.M. (USA), F.P. (Italy), L.R. (Denmark), and R.T. (USA), as well as the ISTH leadership (Cary Clark and Andrea Hickman). This multidisciplinary team ensured a comprehensive and evidence-based approach for the development of the updated guidelines for the management of TTP, incorporating both clinical expertise and patient perspectives.

2.3 | Conflict of interest management

In alignment with the ISTH Guidelines and Guidance Conflict of Interest Policy, the members of the guideline panel disclosed all their relevant financial and nonfinancial relationships from 12 months before guideline development to the date of submitting the manuscript for publication. Financial conflicts included commercial entities with interests related to guideline recommendations, and nonfinancial conflicts such as the involvement in TTP or thrombotic microangiopathy research supported by the commercial entities. Individuals with major declaration of competing interest with respect to an individual PICO were required to abstain from formulating and voting on the recommendations. They were, however, allowed to participate in the discussion leading up to the final vote. The detailed conflict of interest for each panelist is reported in the declaration of competing interest section.

2.4 | Public comments

The updated recommendations approved by all panelists were made available on the ISTH website for public comments for 2 weeks. All ISTH members and the hematology community were invited to provide their inputs. Comments received were discussed in guideline panel meetings and incorporated in the final updated guidelines when appropriate.

2.5 | Updated literature review and prioritization of PICO questions

The ISTH published the first clinical practice guidelines for diagnosis and treatment of TTP in July 2020 [20,40,41]. Tremendous progress has been made in the field, requiring an update of these guidelines. In January 2024, the methodology team was tasked to perform an updated literature review including articles published from 2019. In September 2024, data were extracted, and evidence profiles (EPs) were prepared for distribution to the guideline panelists. The guideline panel met, systematically reviewed the new evidence, and carefully categorized previously issued recommendations into the following 3 groups: (1) Group A: recommendations not requiring an update; (2) Group B: recommendations requiring incorporation of new evidence, but with no anticipated change in directionality and strength of previously issued recommendations; and (3) Group C: new recommendations to be issued or previous recommendations requiring assessment, vote, and update considering the new evidence.

The guideline panel focused on the discussions on new evidence published in 2024 in the New England Journal of Medicine [74], which provides direct evidence on the efficacy and safety of recombinant ADAMTS-13 compared with infusion of fresh frozen plasma (FFP) for the treatment of cTTP, and also provides noncomparative evidence on the efficacy and safety of using FFP in the standard care arm. The guideline panel also reviewed the registry data generated between 2019 and 2024, providing new insight into the severity and impact on the lives of patients with cTTP. The registries and literature demonstrated a high incidence of major long-term morbidities resulting from cTTP, including ischemic stroke, end-stage renal disease, and cardiovascular injury [28,87]. Additionally, organ damage occurred in 22 of 78 (28.2%) patients during acute episodes in the study period or during isolated TTP manifestations at index, which included neurological (n = 15), renal (n = 11), and cardiac (n = 8) damage [88]. A systematic review of 226 patients across 96 reports found that 14% of patients experienced premature death, including 9 neonatal deaths due to severe hemolysis [89]. Among survivors >40 years, 51% experienced at least 1 major morbidity, such as stroke, end-stage renal disease, or severe cardiac dysfunction. Women with undiagnosed or

poorly managed cTTP frequently experience miscarriages, fetal growth restriction, and preeclampsia-like complications with fetal mortality rates up to 50% [45]. The guideline panel ultimately decided to add a new PICO to the guidelines, and to revise the old PICO about FFP vs watch-and-wait strategy for management of cTTP.

Many new reports became available with relevance to recommendations 1, 2, 3, and 5 for the management of patients with acute and relapsed iTTP. They are mostly observational data, case series, registry data, and routinely collected data [52–54,90–100]. More recently, Coppo et al. [101] reported the favorable outcomes (eg, mortality, exacerbation, and burden of health care utilization) of The Capla 1000+ project, an international multicenter retrospective cohort study. These new data for the use of caplacizumab in conjunction with TPE and immunosuppression do not necessarily have the same rigor in the trial design and data collection as do the phase 3 randomized and controlled clinical trials. The data and conclusions may have limitations of retrospective design, with more variability in the treatment protocol and outcomes. A new forest plot is available in the meta-analysis, but this does not result in a change in directionality or strength of the recommendations for the management of iTTP published in2020.

2.6 | How to use the guidelines?

The ISTH focused update of the guidelines applies primarily to the management of patients with cTTP and reaffirms the previously issued recommendation for iTTP. The target audiences of these guidelines are health care providers involved in the diagnosis and management of patients with a suspected TTP, including primary care physicians, emergency or critical care physicians, hematologists, nephrologists, neurologists, pathologists or transfusion medicine specialists, surgeons, obstetricians, gynecologists, hospitalists, and nurse practitioners. The guidelines do not explicitly cover the management of pediatric patients with TTP, which is informed primarily from studies in adult populations for the most part. Application of these recommendations to pediatric populations should be done with caution. No guideline can account for the unique features of a specific patient and clinical circumstance. Thus, the guidelines are not meant to replace clinical judgment.

In accordance with the GRADE guideline development methodology process, each recommendation is graded for strength and certainty of the evidence. Interpretations of the strength of the recommendations in clinical circumstances are described in Table 1 [102].

Clinicians should note that different choices may be appropriate for different patients. Policymaking and standard setting around conditional recommendations should be undertaken with caution; it requires substantial debate and engagement of a wide range of stakeholders (eg, patients, treating physicians, and insurance companies or payors). For each recommendation, an EP summarizes the evidence appraisal, and a comprehensive evidence-to-decision table is available in the Supplementary Material.

3 | UPDATED RECOMMENDATIONS

3.1 | Recommendation 8B (new)

For patients with cTTP who are in remission, the guideline panel recommends recombinantADAMTS-13over plasma infusion to prevent acute episodes. (A strong recommendation in the context of moderate certainty evidence).

3.1.1 | Remark

The guideline panel acknowledged the methodological limitations of the study by Scully et al. [74], but also the extremely rare nature of the condition, and the current and future barriers to generating new evidence in the field. A strong recommendation based on moderate certainty evidence is issued for high likelihood of critically important benefits in a potentially life-threatening condition against low likelihood of side effects.

The evidence to address this question comes from the interim analysis of a single prospective phase 3, multicenter, open-labeled, randomized, controlled, crossover trial assessing the efficacy and safety of prophylaxis with recombinant ADAMTS-13 among children and adults with cTTP compared with plasma infusion [74] (Supplementary Material S1). The guideline panel felt confident in the balance of benefits and harms given the available evidence. While there was no significant difference in primary outcomes such as mortality and acute TTP events, differences were observed in prespecified TTP manifestations (eg, thrombocytopenia, elevated lactate dehydrogenase, increased creatinine, neurological symptoms, and abdominal pain) and exploratory outcomes (eg, composite TTP manifestations and other TTP manifestations) that favored recombinant ADAMTS-13 [74]. In addition, the levels of plasma ADAMTS-13 activity (surrogate outcome) were higher and more sustained at levels >10% in patients who received recombinant ADAMTS-13 than in those who were treated with plasma. Patients with cTTP may present their first acute episode at an early age [27] and subsequently develop long-term organ damage [103–106], suggesting that an early prophylactic treatment may be necessary. However, which product to choose depends on the availability, safety, and patient preference. Sakai et al. [107] report that patients prefer recombinant ADAMTS-13 to FFP when efficacy, safety, and portability are considered [107]. Many patients with cTTP in Japan have switched from plasma to recombinant ADAMTS-13 replacement. Such a real-world experience suggests that recombinant ADAMTS-13 may be a safe and effective alternative to plasma for cTTP prophylaxis [107]. The guideline panel acknowledges the lack of pricing and cost-effectiveness data for the use of recombinant ADAMTS-13 and recognizes that these may be a barrier to its full adoption. In summary, the guideline panel believes, after weighing the evidence and practical considerations that a strong recommendation for the use of recombinant ADAMTS-13 over plasma

TABLE 1 Interpretation of strong and conditional recommendations in clinical circumstances.

Users	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation, according to the guideline, could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low certainty or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Adapted from Bucher et al. [102].

should be issued in the context of moderate certainty evidence (Figure 1 and Table 2).

3.2 | Recommendation 7 (revised, change in direction)

For patients with cTTP who are in remission, the guideline panel suggests the use of plasma infusion over awatch-and-waitstrategy. (A conditional recommendation in the context of very low certainty evidence).

3.2.1 | Remark

Factors to be considered in the shared-decision-making (SDM) process include patient characteristics (eg, age, which increases the risk of exacerbations; trauma, pregnancy, infections, or other factors that may trigger the acute episode), safety and availability of plasma, feasibility of adopting the treatment, acceptability of the associated burden, patient preferences, and values for the balance of risks and benefits. This is a change in directionality from neutral to favoring FFP over watch-and-wait strategy (PICO Q 7; 2.5.1 in the original publication)[40].

While available evidence to address this question was limited in 2019, the standard-of-care arm in the study by Scully et al. [74] provides sufficient noncomparative evidence supporting that regular prophylactic administration of FFP does prevent mortality and acute events in patients with cTTP. The evidence was judged as noncomparative because a watch-and-wait arm was not included in this trial, leaving the possibility that such an arm would have shown no events, as with FFP or recombinant ADAMTS-13. For the same reasons, the trial by Scully et al. [74] provides only indirect evidence to support such a recommendation. However, the guideline panel feels a conditional recommendation for FFP over watch-and-wait is warranted despite the understanding that regular plasma infusion requires significant resources, and the treatment can be burdensome to patients (Supplementary Material S2). The guideline panel believes that an SDM conversation should occur to inform patients that FFP remains effective in preventing acute events of TTP and disease-associated manifestations, should recombinant ADAMTS-13 not be available or accessible. Individual patient preferences and clinical circumstances should also be taken into consideration to guide the SDM process (Figure and Table 2). The guideline panel noted the need for new evidence comparing the efficacy and safety of recombinant ADAMTS-13, FFP, and a watch-and-wait strategy.

4 | UPDATED GPS AND REMARKS

The guideline panel initially asked an additional question about the concomitant use of caplacizumab and antithrombotic therapy (eg, antiplatelets and anticoagulants) in patients at risk for thrombotic events.

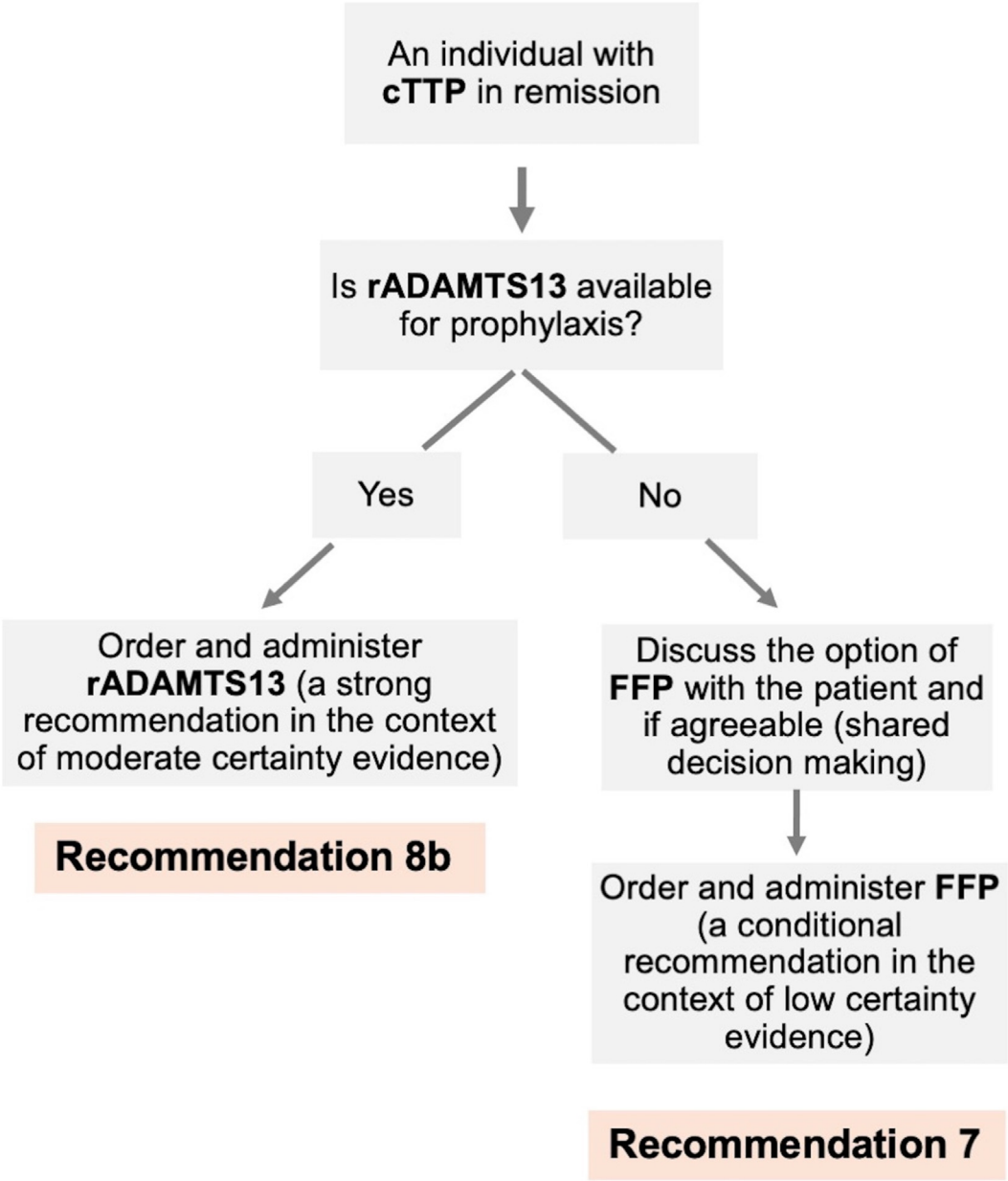

FIGURE Recommended decision tree for management of congenital thrombotic thrombocytopenic purpura (cTTP) during remission. For an individual with cTTP in remission, a prophylactic treatment with ADAMTS-13 replacement should be considered. If available, recombinant ADAMTS-13 should be ordered and administered, a strong recommendation based on moderate certainty evidence (Recommendation 8b); however, if recombinant ADAMTS-13 is not available or accessible, the option for administration of fresh frozen plasma should be discussed with the individual for the benefits and potential harms. A shared decision-making is recommended. This is a conditional recommendation in the context of low certainty evidence (Recommendation 7).

A systematic review of the literature was performed, and results were presented to the panel. The guideline panel acknowledged that there are no new trials and new reports since those reviewed in 2019, which were considered insufficient for prioritizing a graded question. The guideline panel acknowledged the scant but increasing evidence that antiplatelet therapy or anticoagulant therapy that are needed to treat iTTP patients with concomitant deep vein thrombosis, pulmonary embolism, and ischemic stroke. There are very few cases reported in the literature describing a short-term concomitant administration of caplacizumab and antiplatelets or anticoagulants [108,109]. The guideline panel decided not to issue a GRADE recommendation, but to slightly reword the existing good practice statement (GPS; #19, #30, and #31) [41] while maintaining the previous suggestions not to use antiplatelet agents for prevention or treatment of thrombotic events in patients with iTTP when the platelet count is $< 50 \times 10^9$/L (Table 3).

TABLE 2 Updated summary of recommendations.

2020 ISTH guidelines for treatment of TTP	2025 ISTH guidelines for treatment of TTP
2.1.1 Recommendation 1 For patients with iTTP experiencing a first acute event, the panel recommends the addition of corticosteroids to TPE over TPE alone. (A strong recommendation in the context of very low certainty evidence).	**Recommendation 1**: For patients with iTTP experiencing a first acute event, the Panel recommends the addition of corticosteroids to TPE over TPE alone. (A strong recommendation in the context of very low certainty evidence). **Update**: New evidence was added, but the direction and strength of the recommendation remain the same.
2.1.2 Recommendation 2 For patients with iTTP experiencing their first acute event, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence).	**Recommendation 2:** For patients with iTTP experiencing their first acute event, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence). **Update**: New evidence was added, but the direction and strength of the recommendation remain the same.
2.2.1 Recommendation 3 For patients with iTTP experiencing a relapse, the panel recommends the addition of corticosteroids to TPE over TPE alone. (A strong recommendation in the context of very low certainty evidence).	No change.
2.2.2 Recommendation 4 For patients with iTTP experiencing a relapse, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence).	No change.
2.3.1 Recommendation 5 For patients with iTTP experiencing an acute event (first event or relapse), the panel suggests using caplacizumab over not using caplacizumab. (A conditional recommendation in the context of moderate certainty evidence).	**Recommendation 5:** For patients with iTTP experiencing an acute event (first event or relapse), the panel suggests using caplacizumab over not using caplacizumab. (A conditional recommendation in the context of moderate certainty evidence). **Update**: New evidence was added, but the direction and strength of the recommendations remain the same.
2.4.1 Recommendation 6 For patients with iTTP who are in remission but still have low plasma ADAMTS-13 activity with no clinical signs/symptoms, the panel suggests the use of rituximab over nonuse of rituximab for prophylaxis. (A conditional recommendation in the context of very low certainty evidence).	No change.
2.5.1 Recommendation 7 For patients with cTTP who are in remission, the panel suggests either plasma infusion or a watch-and-wait strategy. (A conditional recommendation in the context of very low certainty evidence).	**Recommendation 7:** For patients with cTTP who are in remission, the panel suggests prophylaxis with plasma infusion over a watch-and-wait strategy. (A conditional recommendation in the context of very low certainty evidence). Update: Change in direction from neutral to in favor of plasma infusion.
2.5.2 Recommendation 8 For patients with cTTP who are in remission, the panel suggests against the use of factor VIII (FVIII) concentrate vs a watch-and-wait strategy. (A conditional recommendation in the context of very low certainty evidence).	**NEW Recommendation 8b**: For patients with cTTP who are in remission, the panel recommends using recombinant ADAMTS-13 over plasma infusion to prevent acute episodes. (A strong recommendation in the context of moderate certainty evidence).
2.6.1 Recommendation 9 For patients with iTTP who are pregnant and have decreased plasma ADAMTS-13 activity but with no clinical signs or symptoms, the panel recommends prophylactic treatment over no prophylactic treatment. (A strong recommendation in the context of very low certainty evidence).	No change.

(Continues)

TABLE 2 (Continued)

2020 ISTH guidelines for treatment of TTP	2025 ISTH guidelines for treatment of TTP
2.6.2 Recommendation 10a For patients with cTTP who are pregnant, the panel recommends prophylactic treatment over no prophylactic treatment. (A strong recommendation in the context of very low certainty evidence).	No change.
2.6.3 Recommendation 10b For patients with cTTP who are pregnant, the panel suggests prophylactic treatment with plasma infusion over FVIII products. (A conditional recommendation in the context of very low certainty evidence).	No change.

cTTP, congenital (or hereditary) thrombotic thrombocytopenic purpura; ISTH, International Society on Thrombosis and Haemostasis; iTTP, immune thrombotic thrombocytopenic purpura; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura

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Prophylactic dosing of anticoagulants, most likely low molecular weight heparin, could be considered for patients with iTTP with recovered platelet counts >50 × 10^9/L, and for those with an increased risk of venous thrombosis (eg, history of recurrent venous thromboembolism [VTE], cancer, and recent surgery).

VTE rates were reported as 5.5% in the entire iTTP study population (2.9% and 8.1% in caplacizumab and placebo arms, respectively) [110]. In the study by Dutt et al. [111], VTE rate was 5% in caplacizumab group, which was the same in historical controls. A recent *in vitro* study demonstrates that platelet adhesion and aggregation on a collagen-coated surface under shear are significantly increased in the whole blood obtained from patients with iTTP following platelet recovery despite therapeutic dosing of caplacizumab [112]. The platelet threshold for adding anticoagulation therapy is not sufficiently defined in the literature, but a level of 50 × 10^9/L appears to be an acceptable level. For the optimal management of patients with iTTP and major thrombotic events (eg, stroke and acute myocardial infarction), a multidisciplinary team including hematology, neurology, and cardiology should be consulted (Table 3).

6 | ADDITIONAL EVIDENCE FOR PICO QUESTIONS 1, 2, AND 5

Following the initial literature gathering, the methodology team did an additional literature search in early 2025, which yielded 21 more studies reporting on 1435 patients with TTP. One study was added to the EP and GRADE evidence-to-decision [113] framework for Question #1 (steroids plus TPE vs TPE only in patients with iTTP presenting with the first acute event) [114] (Supplementary Material S3). This observational comparative study (13 patients in the TPE plus steroids and 5 patients in the TPE alone) contributes data for all-cause mortality outcome without relevant change to the effect estimate or confidence interval.

Five other observational studies (3 retrospective, comparative [115–117] reporting on 313 patients) were added to Question #2 (Rituximab plus TPE and steroids vs. TPE and steroids) (Supplementary Material S4). The pooled analyses for all-cause mortality, days in hospital, and relapses (1-12 months) were updated, demonstrating a nonsignificant trend toward a reduced mortality rate with rituximab, which does not warrant a change in the strength or directionality of the recommendation.

Moreover, 15 observational studies (6 comparative and 9 single arm) [49,50,53,56,97,100,111,118–123] with a total of 630 patients on caplacizumab and 492 patients on the no caplacizumab arm were added to the EP and evidence-to-decision of Question #5 (Supplementary Material S5). Since the previous analysis included only the 2 available randomized controlled trials, we did not add the comparative studies to the previous comparative evidence, but we generated a pooled event rate in caplacizumab-treated patients for all-cause mortality, relapse (1-12 months), adverse events, and serious adverse events. Therefore, the resulting estimates do not add to the evidence for the relative effect of adding caplacizumab but provide useful estimates of the expected event rate in patients treated with caplacizumab outside of the clinical trial setting. Specifically, the mortality rate for patients treated with caplacizumab in addition to standard-of-care was 0.01 (0.00-0.02), relapse 0.05 (0.01-0.11), all adverse events 0.36 (0.16-0.60), and serious adverse events 0.08 (0.02-0.17).

7 | DISCUSSION

This update focuses on the management of cTTP and concomitant use of antiplatelet or anticoagulants and caplacizumab in patients with iTTP who are at risk of presenting thromboembolic events. Following the GRADE approach and careful assessment of the PICO question for management of cTTP, the guideline panel has issued a new strong recommendation for the use of recombinant ADAMTS-13 over FFP for prophylaxis of cTTP in children and adults. This is a strong recommendation in the context of moderate certainty evidence. Additionally, the guideline panel suggests a change of the previously neutral position to favoring FFP over a watch-and-wait strategy for prophylaxis of cTTP if recombinant ADAMTS-13 is not available. This is a conditional recommendation in the context of very low certainty evidence, primarily derived from the indirect evidence of the trial by

TABLE 3 Updated summary of good practice statements.

2020 ISTH GPS for treatment of TTP	2025 Update of ISTH GPS for treatment of TTP
3.1 Statement 1 Clinicians generally consider a diagnosis of TTP in individuals presenting with thrombocytopenia and microangiopathic hemolytic anemia. Patients may be critically ill or may have relatively minor and nonspecific complaints. Importantly, the classic signs of TTP (eg, hemolytic anemia, thrombocytopenia, fever, neurologic abnormalities, and renal abnormalities) also known as "Raynaud's Pentad" are present in only 40% of patients; therefore, the historical pentad are only seen in the more severe forms of the disease, or in patients left without appropriate treatment resulting from a delayed diagnosis. The prevalence of this catastrophic presentation has decreased in past few decades as the result of better awareness of the disease among practitioners. Therefore, the presence of thrombocytopenia and microangiopathic hemolytic anemia without other explanation should prompt a suspicion of TTP in the differential diagnosis.	No change.
3.2 Statement 2 An initial laboratory evaluation of presumptive TTP should include a complete blood count with careful review of a peripheral blood film for lack of platelets and presence of fragmented red blood cells (or schistocytes), serum lactate dehydrogenase, and creatinine, testing to demonstrate hemolysis (eg, low haptoglobin, increased indirect bilirubin), coagulation testing (which is expected to be relatively normal in TTP unless it is a severe form of the disease and there is a concomitant disseminated intravascular coagulation). A direct Coombs test is expected to be negative in TTP but may be positive in autoimmune hemolytic anemia. Troponin I and electrocardiogram should be systematically performed to identify subclinical cardiac involvement. Computed tomography/magnetic resonance imaging of the brain may also be included in the initial evaluation for TTP if there are symptoms and signs suggestive of brain injury.	No change.
3.3 Statement 3 If the index of suspicion for TTP is high, clinicians should consider the emergency initiation of TPE and corticosteroids. Because of the severity and instability of their illness, and the foundational role of TPE in the treatment of TTP, patients experiencing an acute event of TTP are usually urgently transferred to a facility that can perform TPE, ideally overseen by a clinician who has expertise in the management of TTP. Most of these patients (>95%) if plasma ADAMTS-13 activity is <10 IU/dL (or <10% of normal) are immune-mediated TTP or iTTP. For a suspected iTTP, a blood sample should be obtained for plasma ADAMTS-13 testing (eg, activity and inhibitors or anti-ADAMTS-13 IgG) before the initiation of TPE. Daily TPE is generally initiated as soon as possible with fresh frozen plasma, or cryo-poor plasma, or solvent detergent-treated plasma as a replacement fluid. The volume of the replacement fluid is usually 1.0 to 1.5 times of patient's plasma volume (ie, 40-60 mL/kg) every 24 hours until normalization of patient's platelet counts and serum lactate dehydrogenase. Patients with a suspected or confirmed cTTP are generally treated with plasma infusion (10-15 mL/kg) at a frequency of every 1 to 3 weeks for maintenance therapy or daily for a symptomatic patient until the symptoms resolve, and normalization of platelet counts.	No change.
3.4 Statement 4 Because of the severity and instability of their illness, TTP patients experiencing an acute event are often managed in a setting with critical/intensive care capabilities, including continuous monitoring of neurologic status, cardiac status, and oxygen saturation. Initial management in a critical/intensive care setting is considered appropriate on the grounds that TTP patients may deteriorate quickly and have a high risk of severe organ dysfunction such as coma, ischemic stroke, seizures, myocardial infarction, congestive heart failure, arrhythmias, mesenteric ischemia, pancreatitis, and acute kidney injury. All these complications require early detection, intensive care monitoring, and rapid therapeutic interventions; furthermore, TPE is associated with rare adverse effects, such as anaphylactic reactions that are best managed in the critical/intensive care setting.	No change.
3.5 Statement 5 In general, the clinical evaluation of patients with TTP at the time of hospital admission and regularly thereafter emphasizes cardiac and neurological assessment. Specifically, cardiac troponin levels are measured at diagnosis, followed by serial troponin levels, electrocardiography, and echocardiography as clinically indicated. Increased cardiac troponin (>0.25 μg/L) appears to be associated with increased cardiac and cerebral involvement, ischemic stroke, and mortality in TTP, although most patients with an increased level of cardiac troponin remain asymptomatic.	No change.

(Continues)

TABLE 3 (Continued)

2020 ISTH GPS for treatment of TTP	2025 Update of ISTH GPS for treatment of TTP
3.6 Statement 6 Patients with TTP often need a central venous access secured urgently. Rapid placement of central venous access allows TPE to be initiated as soon as possible. The type of central venous access depends on the modality of TPE: centrifugal apheresis vs membrane filtration. Centrifugal apheresis involves lower blood flow rates, and enables the use of catheters with smaller diameters, and more flexible walls (such as peripheral catheters or standard triple lumen central venous catheters). Conversely, membrane filtration involves higher blood flow rates, which require the use of larger diameter, stiffer catheters (such as standard dialysis catheters or single lumen central venous catheters). Clinicians should be aware of or consult the appropriate service for what modality of TPE is used at their center, so appropriate central venous access can be secured before initiation of TPE.	No change.
3.7 Statement 7 The risk of catheter-related complications such as bleeding, thrombosis, and sepsis is increased in patients with TTP. We did not systematically search and review the evidence on strategies to reduce the risk of bleeding around catheter placement. Depending on local practice and resource availability, procedures to minimize the risk of bleeding may be considered, including placement by an experienced clinician, ultrasound-guided placement, and internal jugular vein or femoral vein access (rather than subclavian vein access). Once the platelet counts increase and the patient is stable, clinicians usually regularly review whether lines need to be changed and whether VTE prophylaxis should be considered.	No change.
3.8 Statement 8 We did not systematically search and review the evidence on the beneficial or harmful effects of platelet transfusions in TTP. Platelet transfusions are usually avoided and considered unnecessary in most cases of TTP. However, platelet transfusion is often carried out before a correct diagnosis of TTP has been made. There are case reports in patients with TTP of the association between platelet transfusions and arterial thrombosis, clinical deterioration, and increased relapse rate. However, the causative role of platelet transfusion is not clear. In general, prophylactic platelet transfusions are avoided in nonbleeding TTP patients because their effect is not clear and they carry the potential risk of adverse events, especially when transfusions are repeated. However, platelet transfusions are sometimes used in TTP patients with serious bleeding or in TTP patients undergoing invasive procedures with a high risk of bleeding. However, whether platelet transfusion should be performed before central line placement depends on the experience of the individual placing the line and the patient's overall bleeding risk.	No change.
3.9 Statement 9 Based on indirect evidence in other critically ill patients, patients with TTP usually receive VTE prophylaxis. Nonpharmacologic VTE prophylaxis (ie, ambulation as tolerated, graduated compression stockings, intermittent pneumatic compression devices) is usually used while the platelet count is $<50 \times 10^9$/L. Once the platelet count is $>50 \times 10^9$/L, pharmacologic VTE prophylaxis such as low molecular weight heparin should be considered.	No change.
3.10 Statement 10 We did not systematically search and review the evidence on long-term complications of TTP. In patients who have recovered from an acute TTP episode, the panel acknowledged the importance of monitoring for the development of mood disorders, neurocognitive symptoms (including short-term memory issues), and hypertension, which may develop during remission. Specific recommendations regarding screening for long-term complications cannot be made at this time, but serial follow-up and monitoring for these complications should be considered part of routine follow-up.	No change.
3.11 Statement 11 We did not systematically search and review the evidence on the role of support groups for TTP patients. Health care providers may consider offering patients with TTP professional online resources and/or support groups for this rare disease. Several established support groups exist for individuals with TTP who are going through or have gone through similar experiences.	No change.

(Continues)

TABLE 3 (Continued)

2020 ISTH GPS for treatment of TTP	2025 Update of ISTH GPS for treatment of TTP
4.1 Statement 12 We did not systematically review the evidence on triggers for relapse. However, several potential triggers for relapse have been suggested in patients with TTP who have achieved clinical remission. Any illness or a special health condition can trigger a relapse; however, the most discussed triggers include: • Infections, including influenza, community-acquired pneumonia, periodontal and dental infections, and gastroenteritis • Pregnancy • Major trauma or surgery • Intake of oral contraceptives • Cocaine and other recreational drugs • Intake of other drugs, including quinine, ticlopidine, clopidogrel, checkpoint inhibitors, cyclosporine, and tacrolimus. • Pancreatitis **Clinicians usually counsel patients on triggers for relapse and encourage them to seek medical attention for concerning signs and symptoms of any illness**.	No change.
4.2 Statement 13 We did not systematically search and review the evidence on the role of ADAMTS-13 monitoring in TTP patients in remission. Patients in remission are usually assessed regularly during follow-up (typically every mo for the first 3 mo, then every 3 mo for the first year, then every 6-12 mo if stable). If available, ADAMTS-13 activity is usually measured serially during each follow-up assessment, and more frequently if levels begin to drop. Durably stable ADAMTS-13 activity close to the lower limit of normal is usually a reassuring finding. Conversely, patients with persistently low ADAMTS-13 activity (<10 IU/dL or 10% of normal) may be at risk for relapse, which may be prevented by administration of rituximab.	No change.
5.1 Statement 14 We did not systematically search and review the evidence on vincristine for TTP patients. Patients with refractory TTP unresponsive to standard treatments may be considered for other immunosuppressive treatments (with scant supporting evidence), such as vincristine. In these cases, vincristine (2 mg) is usually administered intravenously, at a slow rate of infusion. Typically, a single dose is used because additional doses can cause neurotoxicity and bone marrow suppression.	No change.
5.2 Statement 15 We did not systematically search and review the evidence on cyclosporine A for TTP patients. Patients with refractory TTP unresponsive to standard treatments may be considered for other immunosuppressive treatments (with scant supporting evidence), such as cyclosporine A. In these cases, cyclosporine A is usually administered orally (300 mg/d) or intravenously (2-3 mg/kg/d, divided twice daily). The appropriate duration of therapy is unknown, although administration of this drug for several months, followed by tapering, has been reported.	No change.
5.3 Statement 16 We did not systematically search and review the evidence on cyclophosphamide for TTP patients. Patients with refractory TTP unresponsive to standard treatments may be considered for other immunosuppressive treatments (with scant supporting evidence), such as cyclophosphamide. In these cases, cyclophosphamide (500 mg/d) is usually administered intravenously over 2 hours. Typically, a single dose is used because additional doses may cause severe bone marrow suppression.	No change.
5.4 Statement 17 We did not systematically search and review the evidence on splenectomy for TTP patients. This procedure has been largely superseded by other treatments such as rituximab. It is generally not used but may still have a role in selected TTP patients as a prophylactic/treatment strategy.	No change.
5.5 Statement 18 We did not systematically search and review the evidence on azathioprine for TTP patients. Clinicians may sometimes consider azathioprine to inhibit anti-ADAMTS-13 autoantibody production, which leads to normalization of plasma ADAMTS-13 activity and prevents relapse in patients with refractory disease unresponsive to standard treatments.	No change.

(Continues)

TABLE 3 (Continued)

2020 ISTH GPS for treatment of TTP	2025 Update of ISTH GPS for treatment of TTP
5.6 Statement 19 We did not systematically search and review the evidence on antiplatelet agents for TTP patients. Antiplatelet agents have been used in nonpregnant patients with TTP, particularly in the setting of macrothrombotic complications (eg, ischemic stroke and myocardial infarction). Otherwise, antiplatelets are not generally recommended in TTP; their role in preventing relapse is not supported in the literature, and they may be harmful in the acute phase of TTP when the platelet count is low (e.g., $<50 \times 10^9$/L). Inputs from cardiologists, neurologists, and/or other vascular medicine specialists are usually sought if antiplatelet agents are considered in the treatment of TTP-related complications.	**Statement 19**. Prophylactic dosing of anticoagulants, most likely low molecular weight heparin, could be considered for patients with iTTP with recovered platelet counts $>50 \times 10^9$/L, and for those with an increased risk of venous thrombosis (eg, history of recurrent VTE, cancer, and recent surgery). For the optimal management of patients with iTTP and major thrombotic events (eg, stroke, acute myocardial infarction), a multidisciplinary team including hematologists, neurologists, and cardiologists should be consulted.
5.7 Statement 20 We did not systematically search and review the evidence on anti-C5 monoclonal antibody (eg, eculizumab) for TTP patients. Increased complement activation has been demonstrated in patients with acute TTP. Therefore, clinicians sometimes consider eculizumab in very selected patients with refractory disease or those unresponsive to all other treatment options. This strategy should be pursued with caution.	No change.
5.8 Statement 21 We did not systematically search and review the evidence on intravenous immunoglobulin for TTP patients. Intravenous immunoglobulin is generally not used in TTP. Its efficacy is unknown, and adverse reactions to this product mimic thrombotic, neurologic, and renal manifestations of TTP.	No change.
5.9 Statement 22 We did not systematically search and review the evidence on corticosteroid dosage, dose adjustment, or tapering in TTP. In patients with TTP, high-dose corticosteroids (eg, prednisone, 1 mg/kg/d, orally, or methylprednisolone, 125 mg, intravenous, 2-4 times daily) are usually used as the initial regimen. If the platelet count does not increase within 3-4 d of treatment, a higher dose of corticosteroids is usually used. High doses of corticosteroids are usually continued until the platelet count is recovered and TPE is stopped. When platelet count recovery is sustained (eg, after 5-7 d), corticosteroids are usually tapered and discontinued over 3 wk. Tapering may be delayed or slowed based on platelet count, ADAMTS-13 test results, and/or neurological symptoms.	No change.
6.1 Statement 23 Women with a history of TTP who are planning for pregnancy usually receive preconception counseling. The panel acknowledged the importance of offering counseling to all women with a history of TTP who are considering pregnancy. The risks of TTP with a somewhat unpredictable course must be discussed during the counseling. The patient's values and preferences must also be considered. Pregnancy can trigger TTP relapse, resulting in an increased risk of maternal and fetal mortality and morbidity. It is difficult to predict who may experience a relapse during pregnancy. A normal plasma ADAMTS-13 activity at the onset of pregnancy in patients with a history of TTP may be associated with a reduced risk of immediate relapse, while a low (eg, <10 IU/dL) plasma ADAMTS-13 activity at the onset of pregnancy may be associated with an increased risk of relapse.	No change.
6.2 Statement 24 In some institutions, women with decreased ADAMTS-13 activity (eg, <10 IU/dL) before or at the onset of pregnancy are offered a prophylactic rituximab therapy, with a goal to eliminate anti-ADAMTS-13 autoantibodies and normalize plasma ADAMTS-13 activity before conception. Evidence of normal ADAMTS-13 activity may be associated with a lower risk of relapse in women with a history of TTP.	No change.
6.3 Statement 25 Patients treated with rituximab are usually asked to wait for 6 to 12 mo following rituximab administration before trying to conceive; normalization of CD19 lymphocyte levels and undetectable serum rituximab levels are often used as evidence of "drug washout." Global drug safety databases suggest that rituximab is associated with few congenital malformations or neonatal infections. However, scant case reports of its use in patients with TTP did not report maternal or neonatal toxicity. Nevertheless, women should be informed that the evidence about the safety and efficacy of rituximab in pregnancy is extremely limited and inconclusive.	No change.

(Continues)

TABLE 3 (Continued)

2020 ISTH GPS for treatment of TTP	2025 Update of ISTH GPS for treatment of TTP
6.4 Statement 26 Pregnant women with a history of TTP are usually closely monitored by a hematologist and an obstetrician with experience in maternal-fetal medicine/perinatology. The panel supports the involvement of clinicians with expertise in TTP in the care of pregnant women with a history of TTP. Complete blood counts are usually monitored at least monthly. Plasma ADAMTS-13 activity is usually monitored monthly or every 2 to 3 mo at least. (More frequent monitoring tends to occur if the ADAMTS-13 activity begins to drop during pregnancy.)	No change.
6.5 Statement 27 TTP presenting in pregnancy generally merits a transfer to a more specialized center with hematologists, obstetricians, and transfusion medicine specialists, and TPE capabilities, for comprehensive and definitive care. As in the case of TTP in nonpregnant patients, daily TPE is generally needed as soon as possible with fresh frozen plasma, cryo-poor plasma, or solvent detergent-treated plasma as a replacement fluid. The volume of replacement fluid is usually 1.0-1.5 times of patient's plasma volume (ie, 40-60 mL/kg) every 24 h.	No change.
6.6 Statement 28 Women with a history of TTP require close monitoring by a hematologist with experience in TTP and maternal-fetal medicine throughout pregnancy. Their risk of relapse is generally considered to be high if they enter pregnancy with plasma ADAMTS-13 activity below the normal range. If plasma ADAMTS-13 activity falls significantly (eg, usually <30 IU/dL or 30% of normal) even in the absence of clinical signs/symptoms, TPE and corticosteroids (or azathioprine) are often considered. It is a good practice to monitor ADAMTS-13 activity throughout pregnancy and during the postpartum period. Induction of labor at 36 to 37 wk gestation is commonly suggested. In the absence of other obstetrical indications for cesarean section, vaginal delivery is considered a preferred method of delivery in pregnant women with a history of TTP. This statement also applies to women with a history of either cTTP or iTTP.	No change.
6.7 Statement 29 Women with a history of TTP who are planning pregnancy usually receive preconception counseling. Pregnant women with a history of TTP have a high risk of serious complications during pregnancy. They receive plasma infusion, at a dose of 10 to 15 mL/kg weekly or every 2 wk, or TPE, depending on the symptoms. Beginning in the second or early third trimester, the frequency of infusion is usually increased to weekly or twice weekly or TPE. Women with a history of TTP require close monitoring by a hematologist with experience in maternal-fetal medicine throughout pregnancy. Induction of labor at 36 to 37 wk gestation is commonly suggested. In the absence of other obstetrical indications for cesarean section, vaginal delivery is considered the preferred method of delivery in pregnant women with a history of TTP. These statements apply to women with a history of either cTTP or iTTP.	No change.
6.8 Statement 30 We did not systematically search and review the evidence on the effect of aspirin in pregnant women with TTP. Largely based on indirect evidence from other populations, pregnant women with a history of TTP are usually not offered low-dose aspirin throughout pregnancy.	No change.
6.9 Statement 31 We did not systematically search and review the evidence on the effect of antithrombotic therapy in pregnant women with TTP. Largely based on indirect evidence from other populations, pregnant women with a history of TTP and a history of venous thrombosis are usually offered low molecular weight heparin at prophylactic doses throughout pregnancy, to prevent the formation of placental microthrombi and insufficiency, as well as preventing recurrent venous thrombosis. Offering antithrombotic therapy to women with a history of TTP-associated pregnancy loss, but not venous thrombosis, remains controversial.	No change.
6.10 Statement 32 We did not systematically search and review the evidence on the effect of hormonal preparations, particularly those containing estrogen, as a potential trigger for relapse in women with TTP. Women with a history of TTP are usually counseled that nonhormonal methods of contraception and progestin-only preparations are preferred over estrogen-containing preparations that may promote production of autoantibodies against ADAMTS-13.	No change.

(Continues)

TABLE 3 (Continued)

2020 ISTH GPS for treatment of TTP	2025 Update of ISTH GPS for treatment of TTP
7.1 Statement 33 (32 in document—typo) We did not systematically search and review the evidence on alternatives to blood products in TTP patients. Patients with TTP refusing blood products (eg, Jehovah's Witnesses) generally will not accept TPE with replacement of plasma. Clinicians should explore patients' values and preferences to determine if they will accept albumin and other purified protein fractions because these products are sometimes acceptable. This strategy can, at minimum, help remove ADAMTS-13 autoantibodies and other potential harmful inflammatory mediators. Clinicians may empirically consider the use of corticosteroids, rituximab, and caplacizumab, as well as erythropoietin and folic acid (to promote erythropoiesis). If the patient will accept plasma derivatives, FVIII concentrates containing enough ADAMTS-13 may be considered instead of plasma. If the patient will accept albumin, TPE with albumin as the replacement fluid may be considered.	No change.

cTTP, congenital (or hereditary) thrombotic thrombocytopenic purpura; FVIII, factor VIII; ISTH, International Society on Thrombosis and Haemostasis; iTTP, immune thrombotic thrombocytopenic purpura; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; VTE, venous thromboembolism.

Scully et al. [74]. The potential risks of long-term organ damage resulting from the absence of circulating ADAMTS-13 in cTTP [124,125] outweigh the side effects of FFP, despite a report from the International Hereditary TTP registry that did not show a reduction of acute events in patients with plasma prophylaxis regimens compared with those without [125]. This may be largely confounded by insufficient volume, infrequent or sporadic infusion of FFP, and data that were reported to the registry rather than directly assessed by investigators in this diverse cohort of patients.

The strong recommendation for prophylactic treatment of cTTP with recombinant ADAMTS-13 drew evidence from the pivotal, prospective, randomized, crossover, and phase 3 trial [74]. The trial included 48 patients randomly assigned to receive 6-month prophylaxis with recombinant ADAMTS-13 (40 IU/kg body weight, intravenous) or standard-of-care with plasma-derived products, followed by 6 months of the alternate treatment and another 6 months of extended recombinant ADAMTS-13 treatment. While none of the arms reported acute TTP events (primary outcome), patients who received recombinant ADAMTS-13 showed a trend for lower incidence of TTP-related manifestations (eg, thrombocytopenia, elevated lactate dehydrogenase, neurological symptoms, and abdominal pain) than those who received the standard-of-care. Additionally, patients who received recombinant ADAMTS-13 achieved much higher plasma levels of ADAMTS-13 activity and were exposed to a longer duration of plasma ADAMTS-13 levels above 10 IU/dL (or 10%) than those who received the standard-of-care. Plasma ADAMTS-13 activity above 10 IU/dL (or 10%) appears to be protective for TTP exacerbation or relapse in iTTP [103,104]. Also, the age of onset and long-term complications (eg, cardiovascular diseases, end-stage renal disease, silent ischemic stroke) are associated with the residual levels of plasma ADAMTS-13 activity in cTTP [82,125].

The approval of recombinant ADAMTS-13 for cTTP has changed how cTTP patients are managed. The drug can be administered in any clinic without the need for sophisticated equipment, infusion resources, and expertise as is required for plasma infusion or TPE. Patients who received recombinant ADAMTS-13 therapy reported adverse events (including neurological) but fewer than those treated with plasma. Severe reactions frequently seen in plasma infusion including allergic reactions, anaphylaxis, volume overload, and infections, which rarely occurred in patients who received recombinant ADAMTS-13 [71–75,126].

Because the previously used plasma infusion protocol (eg, irregular and prolonged interval) does not appear to provide sufficient ADAMTS-13, the treatment did not appear to significantly reduce or eliminate the long-term complications [82,125], leading to the neutral position for the recommendation of plasma infusion vs watch-and-wait strategy in the 2020 guidelines [40]. The standard-of-care arm in the prospective phase 3 trial, following the regular infusion of plasma at a pre-defined dosage and interval, did prevent acute TTP events, as did recombinant ADAMTS-13 infusion [74], suggesting that plasma infusion remains effective in prophylaxis of cTTP when recombinant ADAMTS-13 is not available. Currently, recombinant ADAMTS-13 is only approved for use in cTTP in the USA, Europe, and Japan.

Patients with cTTP during pregnancy have significantly increased risk of maternal mortality (10%) and fetal loss (>50%) [127]. Those who did not receive prophylaxis may also develop an early onset of preeclampsia [128]. Thus, prophylactic treatment of cTTP during pregnancy should be considered to reduce acute events and perinatal mortality. There is no specific recommendation for the use of either FFP or recombinant ADAMTS-13 in the management of cTTP during pregnancy because pregnant women were excluded from phase 3 trial [74]. However, several case reports indicate that recombinant ADAMTS-13 is highly efficacious and safe either as a monotherapy or in combination with plasma in patients with cTTP during pregnancy [75,126,129]. This prophylactic strategy has resulted in live births and avoided maternal mortality. If, however, recombinant ADAMTS-13 is not available, regular plasma prophylaxis at higher dose and shorter interval (eg, 30-40 mL/kg/wk) should be considered in patients with cTTP early during pregnancy with close monitoring of platelet counts, the ADAMTS-13 activity (when available), and fetal health conditions.

Such a strategy has been shown as effective, achieving term delivery in 75% of pregnancies and live birth in 89% of patients [130–132].

The guideline panel did not make any change to the recommendation for management of iTTP, either in the directionality and strength despite additional new information that contributes to the body of evidence but does not change our confidence in the direction and balance of risks and benefits. Since the initial publication of the TTP guidelines, increasing observational data, meta-analyses, and other literature have been accumulated. Caplacizumab added to TPE and immunosuppression is associated with a mortality rate of <5% [48,49,52,53,55,56,101,109]. This is a remarkable accomplishment in the field. In all these reports, patients receiving triple therapy (eg, caplacizumab, TPE, and immunosuppressives) experienced faster platelet count normalization, less disease exacerbations, and received fewer TPE sessions and lower plasma volumes. Additionally, patients had shorter stays in the intensive care units and hospital. Once stable platelet normalization is achieved, patients may be safely discharged to complete caplacizumab administration and immune suppressive treatment at home. All these data are retrospective and non-comparative with a potential for selection bias.

Importantly, given the mechanism of action of caplacizumab (inhibiting VWF and platelet interaction and blocking thrombus formation immediately in the absence of ADAMTS-13 function), one should start caplacizumab as early as possible (ideally within 3 days). A delayed administration of caplacizumab or use of caplacizumab as salvage treatment in refractory iTTP may not be as effective as the upfront use because disseminated microvascular thrombosis and ischemic injury to the major organ tissues will have already occurred [56,101]. Caplacizumab does not disrupt any preformed microthrombi but prevents the formation of new VWF-platelet rich thrombi under flow [112,133]. Whether caplacizumab can be used with immunosuppressives without TPE remains to be further investigated. Kuehne et al. [58] reported the success of using caplacizumab and immunosuppressives alone without TPE, with rapid control of thrombotic microangiopathy and achievement of a sustained clinical response in iTTP. The rate of platelet normalization with the double therapy is the same as seen with the triple therapy. This observation needs confirmation by larger studies, including a more complete spectrum of iTTP severity. If so, it will dramatically alter how we treat iTTP.

To date, the adverse events reported in patients with cTTP receiving recombinant ADAMTS-13 are mostly mild to moderate, and include headache, migraine, nasopharyngitis, and diarrhea. No hypersensitivity reactions were reported in patients receiving recombinant ADAMTS-13. No neutralizing antibodies were detected in any patient with cTTP, and no instance of increased levels of binding antibodies were observed [71,73–75]. Despite this, long-term monitoring of therapeutic efficacy and alloantibody against recombinant ADAMTS-13 should be considered.

The major adverse event of caplacizumab for treatment of iTTP is the increased risk of bleeding, which is consistent with its pharmacological action of disrupting VWF and platelet interaction. Most bleeding episodes are mild to moderately severe, including epistaxis, gingival bleeding, and gastrointestinal bleeding [74,101]. However, severe bleeding such as intracranial bleeding may occur [134], so caplacizumab may be contraindicated for patients with a risk of, or presenting with, hemorrhagic stroke.

In conclusion, the discovery of ADAMTS-13 and better understanding of the pathophysiology of TTP have enabled the development of rapid and accurate diagnostic and monitoring tools, as well as targeted therapies such as recombinant ADAMTS-13 and caplacizumab. Recombinant ADAMTS-13 is now approved for the treatment of cTTP with better efficacy and safety. Caplacizumab, added to TPE and immunosuppression, has accelerated platelet recovery and drastically reduced disease exacerbation and relapse, as well as mortality rates in iTTP. We hope that the updated guidelines will provide guidance to health care providers for how to best manage TTP with available resources. Further studies are needed to optimize these novel therapeutics in different clinical settings to reduce the long-term complications associated with both cTTP and iTTP.

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AUTHOR CONTRIBUTIONS

X.L.Z., S.R.C., P.C., B.G., A.I., A.K., C.M., M.M., K.R.M., J.M., R.A.M., Z.A.H., F.P., L.R., R.T. and S.K.V., analyzed the data, participated in panel discussion, as well as wrote and revised manuscript. All authors reviewed and approved the final version of the manuscript.

DECLARATION OF COMPETING INTERESTS

X.L.Z. is a cofounder of Clotsolution that provides consultation and advisory service to Sanofi and Takeda; S.K.V. is a biostatistician for the Oklahoma Thrombotic Thrombocytopenic Purpura (TTP) registry; S.R.C. is a consultant for Sanofi and Takeda, serving study steering committee for Roche, a consultant for Novartis, and received research grants from Takeda, Sanofi, and Roche; P.C. is a consultant for Sanofi, Alexion, Janssen, and Takeda, received research grants from Sanofi and Takeda, and serving the head and founder of the French Reference Center for Thrombotic Microangiopathies; B.G. is an employee of Regeneron Pharmaceuticals and owns stock in Regeneron and Merck, and serves on Editorial Boards; F.G. has no active conflict of interest to declare. In the past 3 years, F.G.'s institution (McMaster University) received research funding from NovoNordisk, Roche, Takeda, Bayer, Pfizer, BioMarin, and CSL; C.M. served on an advisory board for Sanofi; M.M. received royalty interest from Alfressa Pharma and research grants from Roche and Alexion; K.R.M. serves on data safety boards for Sanofi and Argenx and on advisory board for Novartis; J.M. is a founder of TTPNetwork, received funding and sponsorship from Sanofi and Takeda; F.P. received research grants from Sanofi and Takeda; and A.I., A.K., R.A.M., Z.A.H., L.R., and R.T. declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

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