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RECOMMENDATIONS AND GUIDELINES

ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura

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Abstract

Background: Despite an increase in our understandings of pathogenesis of thrombotic thrombocytopenic purpura (TTP), the approaches for initial diagnosis and management of TTP vary significantly.

Objective: The evidence-based guidelines of the International Society on Thrombosis and Haemostasis (ISTH) are intended to support patients, clinicians, and other health care professionals in their decisions about the initial diagnosis and management of acute TTP.

Methods: In June 2018, ISTH formed a multidisciplinary panel that included hematologists, an intensive care physician, nephrologist, clinical pathologist, biostatistician, and patient representatives, as well as a methodology team from McMaster University. The panel composition was designed to minimize the potential conflicts of interests. The panel used the Grading of Recommendations Assessment, Development, and Evaluation approach and the Population, Intervention, Comparison, Outcome framework to develop and grade their recommendations. Public comments were sought and incorporated in the final document.

Results: The panel agreed on three recommendations covering the initial diagnosis with emphasis on the importance of ADAMTS13 testing (eg, activity, anti-ADAMTS13 IgG or inhibitor) and assessment of the pretest probability of TTP by clinical assessment and/or the risk assessment models like the PLASMIC or French score. The panel noted how availability and turnaround time of ADAMTS13 test results might affect early diagnosis and management, in particular the use of caplacizumab.

Conclusions: There is a lack of high-quality evidence to support strong recommendations for the initial diagnosis and management of a suspected TTP. The panel emphasized the importance of obtaining ADAMTS13 testing in a proper clinical context.

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Future research should focus on how to monitor and act on ADAMTS13 levels during remission.

KEYWORDS
ADAMTS13, diagnosis, guidelines, thrombosis, TTP

1 | INTRODUCTION

1.1 | About TTP

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially fatal blood disorder. Its incidence is 2 to 6 per million individuals.[1-4] TTP may be caused by inherited severe deficiency of plasma ADAMTS13 activity resulting from mutations in *ADAMTS13*, referred to as hereditary or congenital TTP (or cTTP)[5,6]; more commonly, TTP is acquired and due to autoantibodies that inhibit plasma ADAMTS13 activity, referred to as immune-mediated TTP (or iTTP).[6,7] More than 95% of all TTP cases are iTTP, whereas cTTP accounts for <5% of cases.[8,9] In some groups, such as young children and pregnant women, cTTP may account for 25% to 50% of all TTP cases.[10] Patients with TTP present with thrombocytopenia, microangiopathic hemolytic anemia, and various degrees of organ damage.[11-14] These signs and symptoms largely overlap with another thrombotic microangiopathy—hemolytic uremic syndrome (HUS)—which includes Shigatoxin-associated HUS[15,16] and complement-mediated HUS.[17,18] The distinction between TTP and HUS relies on the test of plasma ADAMTS13 activity.[6,14,19,20] A plasma ADAMTS13 activity of less than 10 IU/dL (often referred to as 10% of normal ADAMTS13 activity) is the hallmark of TTP; when plasma ADAMTS13 activity is greater than 10 IU/dL, the diagnosis of HUS should be considered after excluding other secondary causes of thrombotic microangiopathy.[6,14,19-21] The distinction between TTP and HUS is crucial for initiation of an appropriate therapeutic strategy. Therapeutic plasma exchange (TPE),[12] in conjunction with corticosteroids, rituximab, and caplacizuamb,[19,22] has significantly reduced the mortality and morbidity rates in iTTP, whereas eculizumab, an anti-complement C5 monoclonal antibody, is a life-saving therapy for complement-mediated HUS.[23,24]

1.2 | About the need for guidelines on TTP

TTP, a life-threatening blood disorder, has considerable morbidity and mortality in the acute phase. In both hereditary and immune-mediated forms, TTP also affects patients' quality of life over the long term owing to exacerbations, relapses, and sustained neurocognitive defects.[4,25-28] Despite recent advances in the diagnosis and treatment, TTP continues to present a serious challenge to health care providers and patients. There is limited and heterogenous evidence on how to best make an early diagnosis, how to differentiate from other forms of thrombotic microangiopathy, and how to manage TTP in acute episode and during remission. Because of the rarity of TTP, most health care providers have very limited experience with managing the disease. Furthermore, there appears to be tremendous variations in practice even among experts who manage these patients frequently.

To date, two guideline documents have addressed the diagnosis and management of TTP. In 2012, the British Committee for Standards in Haematology sponsored guidelines on the diagnosis and management of TTP and other thrombotic microangiopathic hemolytic anemias (TMAs).[29] The guidelines panel comprised UK-based physicians with expertise in TTP. The evidence informing the guidelines was acquired through a systematic search of Medline and EMBASE, and the recommendations were based on consensus, as well as input from the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology and selected experts. The recommendations were categorized by levels and grades of evidence, using an alphanumeric system. In 2017, the TTP group of Japanese Blood Coagulation Abnormalities Research Team produced national diagnostic and treatment guidelines for TTP.[30] Like the British guidelines, the Japanese guidelines were created by a panel of physicians with TTP expertise. Recommendations were based on consensus and quality of evidence was also ranked using an alphanumeric system.

Since the publication of these guidelines, there has been significant development in the diagnosis and treatment of TTP, and an increase in published data on how management strategies affect the objective health outcomes. International Society on Thrombosis and Haemostasis (ISTH) identified the need for a current, evidence-based TTP guidelines that adhere to the rigorous methodologic standards set by the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (formerly referred as to the Institute of Medicine), the

Guidelines International Network, and the ECRI Guidelines Trust. These guidelines aim at health care providers and policy makers but maintain a focus on the values and priorities of patients. To capture patients' voices, these guidelines incorporated patient consultation and included patients who had TTP on the guidelines panel.

1.3 | How to use these guidelines

The ISTH guidelines apply to the diagnosis and management of adult patients with a suspected TTP.

The target audiences of these guidelines for diagnosis of TTP are the health care providers involved in the diagnosis of TTP, which includes but is not limited to primary care physicians, emergency or critical care physicians, hematologists, nephrologists, neurologists, pathologists or transfusion medicine specialists, surgeons, obstetricians and gynecologists, as well as hospitalists.

These guidelines do not explicitly cover the diagnosis of pediatric patients with TTP and are informed primarily from studies in adult populations. Application of these recommendations to pediatric populations should be done with caution.

No guidelines can account for the unique features of a patient and his or her clinical circumstance, and these guidelines are not meant to replace the clinical judgment.

1.4 | Interpretation of strength of the recommendations

The strength of a recommendation is expressed as either strong ("the guidelines panel recommends…") or conditional ("the guidelines panel suggests…").

A strong recommendation means that the panel is confident that the desirable effects of following the recommendation outweigh the undesirable effects. Most patients would accept the recommended course of action, whereas only a small proportion would not. Most clinicians should follow the recommended course of action, and the recommendation can be adopted as a policy in most situations. Strong recommendations are usually based on high-quality evidence in which we have high confidence. However, in certain paradigmatic situations, strong recommendations are issued in the absence of high certainty evidence[31]; in these instances, the reasoning behind the panel's decision is clearly laid out.

A conditional recommendation means that the panel believes that the desirable effects of following the recommendation probably outweigh the undesirable effects. Most patients would accept the suggested course of action, but many would not. Decision aids might be useful in helping patients make this decision in a way that is consistent with their values and preferences. Clinicians should note that different choices will be appropriate for different patients. Policy making 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, insurance company/payer).

For each recommendation, a report of the systematic review of the literature, an evidence profile summarizing the evidence appraisal, and a comprehensive Evidence to Decision table are available in Appendix S7.

2 | SUMMARY OF GUIDELINES DEVELOPMENT PROCESS

The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach and the Population, Intervention, Comparison, Outcome (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),[32] and the procedures outlined in the Guidelines International Network-McMaster Guidelines Development Checklist.[33]

All panel members have volunteered their time and have not been remunerated apart from the reimbursement of their travel costs to the meeting.

2.1 | Guidelines panel

A multidisciplinary panel was assembled, including hematologists and pathologists with clinical expertise in the diagnosis and management of TTP, as well as clinicians in other relevant disciplines. Additionally, patient representatives are included in the panel. The clinical cochair, Dr. X. Long Zheng, is a professor and department chair of pathology and laboratory medicine at the University of Kansas Medical Center, Kansas City, Kansas. Dr. Zheng is a world-renowned expert in research, diagnosis, and management of TTP, and other related thrombotic microangiopathies. The method cochair, Dr. Sara K. Vesely, a professor of biostatistics and epidemiology at the University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma. She is an expert biostatistician and methodologist with experience in GRADE guidelines development and TTP research.

The guidelines panel continued the work of a preliminary international scoping panel that first identified the need for the guidelines and the key issues the guidelines should address. Detailed panel composition is provided in Appendix S1.

2.2 | Methodology team

McMaster University provided the methodological support for the guidelines development process, including conducting systematic literature reviews to inform the guidelines questions, providing

training to the guidelines panel members, guiding the discussion at panel meetings, and preparing the final evidence report. The methodology team was led by Dr. Menaka Pai and Dr. Alfonso Iorio. Detailed composition of the methodology team is also provided in Appendix S1.

2.3 | Patient advisory panel

A patient advisory panel consisting of TTP patients from various organizations around the world, which provided a broader patient perspective to the guidelines, particularly for the value patients place on the outcomes of interest.

2.4 | Conflict of interest management

Members of the guidelines panel disclosed all financial and nonfinancial relationships from 12 months before guidelines initiation to the date of submitting manuscript for publication. Financial conflicts included commercial entities with interests related to guidelines recommendations and nonfinancial conflicts such as the involvement in TTP/Thrombotic microangiopathy research. Individuals with major conflicts of interest with respect to an individual PICO were required to abstain from formulating and voting on a corresponding recommendation. They were allowed, however, to contribute to the discussion leading up to the final vote. The conflicts of each individual panelist were declared verbally and presented on screen at the start of each PICO discussion. The detailed conflict of interest policy is reported in Appendix S2.

2.5 | Panel meetings

The guidelines panel met twice in person betweeen 2018 and 2019. In the first meeting, PICO questions for identifying and finalizing the outcomes of interest were developed in a 2-day meeting, June 21-22, 2018. Three diagnostic pathways relevant to diagnosis and early management of TTP, particularly the immune-medidated TTP (iTTP), were identified for a full appraisal (Appendix S3). In the second meeting on May 17-18, 2019, the panel was to review the evidence profiles, discuss the evidence for the recommendations, issue the final recommendations, and clinical practice implication, as well as the future research priorities.

2.6 | Public comment

This document, in its final version approved by all panelists, was made available on the ISTH website for public comments for 30 days. All ISTH members were invited to provide comments, so were the patient representatives, a selected number of TTP experts, and the TTP registry representatives. Comments received were reviewed by the panelists and the methodology team, addressed, and incorporated in the final guidelines when appropriate.

2.7 | Dissemination

A version of this guidelines document will be posted on the ISTH website after peer-reviewed publication. The major reports and/or this unabridged document will be submitted to ECRI Guidelines Trust, a publicly available repository of clinical guidelines.

2.8 | Developing PICO questions

The PICO questions in the guidelines were finalized during the guidelines panel meeting in Toronto, Canada, June 2018. Starting from the scoping document, the panel identified three questions relevant to the diagnosis and early management of TTP, agreed on their PICO components, and moved to considering them as three diagnostic and early management pathways.

The panel decided to prioritize the initial diagnostic steps involved in confirming TTP during the first acute episode, for the purpose of providing optimal initial treatment to the appropriate patient population.

The panel agreed to follow the specific GRADE approach for diagnosis.[34-36] In brief, it is a two-step process starting with the appraisal of the test characteristics of the diagnostic test of interest and continuing with modeling of the impact on patient important outcomes of adopting different diagnostic pathways for patients with different pretest probabilities of the disease of interest and availability of ADAMTS13 testing. During the first in-person panel meeting, the following potential diagnostic pathways were identified for a full appraisal:

Scenario A: a pathway where ADAMTS13 activity measurement is readily available (ie, within 72 hours).
Scenario B: a pathway where ADAMTS13 measurement is NOT available.
Scenario C: a pathway where ADAMTS13 activity measurement is available with a delay (ie, after 72 hours but less than 7 days).

All three scenarios were thought to potentially apply to patients presenting with a clinical picture of TMA and suspected TTP. The population of interest would therefore be defined as: patients with thrombocytopenia ($<100 \times 10^9$/L), microangiopathic hemolytic anemia (eg, hemoglobin and hematocrit below the lower limit of the reference range, low haptoglobin, elevated lactate dehydrogenase, the presence of schistocytes in peripheral blood smear), and relatively preserved renal function.[6,19] The panel discussed the additional value of using a clinical risk assessment model, such as the PLASMIC score[37,38] or the French score.[39] (Table 1) Appraising the evidence for these two specific risk assessment models was felt to be out of scope for the guidelines at this time. The panel agreed that any diagnostic strategy would have to start with a thoughtful assessment of

TABLE 1 PLASMIC score or French score predicts the likelihood of severe ADAMTS13 deficiency in a suspected TTP

Parameters	French Score	PLASMIC Score
Platelet count	<30 × 10^9/L (+1)	<30 × 10^9/L (+1)
Serum creatinine level	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis		
Indirect bilirubin >2 mg/dL	[a]	+1
or reticulocyte count >2.5%		
or undetectable haptoglobin		
No active cancer in previous year	[a]	+1
No history of solid organ or SCT	[a]	+1
INR < 1.5	[a]	+1
MCV < 90 fL	NA	+1
Likelihood of severe deficiency of ADAMTS13 activity (<10%)	0: 2%	0-4: 0%-4%
	1: 70%	6: 5%-24%
	2: 94%	6-7: 62%-82%

Note: Each item is associated with 1 point (+1). The table is adapted from Joly BS.[53]

Abbreviations: INR, international normalized ratio; MCV, mean corpuscular value; SCT, stem cell transplantation.

[a]French score considered patients with thrombotic microangiopathy that included hemolysis and schistocytes in their definition and assumed that there was no history or clinical evidence for associated cancer, transplantation, or disseminated intravascular coagulation. Therefore, these items were intrinsic to the scoring system. NA in MCV: not incorporated in the French score.

the patient's pretest probability of having TTP and the use of a formal risk assessment or pretest probability assessment model would not be inappropriate. However, they noted that both the PLASMIC and the French scores were designed for adult populations with no comorbid conditions (eg, pregnancy, cancer, sepsis, organ/tissue transplantation, etc.), which may not be reliable in assessing children[37,39,40] and patients with other comoridities. The logical framework for the process is described in Appendix S6.

The diagnostic tests of interest for three pathways are centered on the measurement of plasma ADAMTS13 activity and the identification or quantification of inhibitor or anti-ADAMTS13 IgG. Judging on the impact of a diagnostic pathway requires to assume the effect of the treatment to be adopted in patients identified as positive, and not to be adopted (or alternative treatment) in patients identified as negative.

To this scope, the panel decided to consider, as the management option for patients with a confirmed TTP, those interventions recommended in the treatment guidelines (eg, specifically TPE, corticosteroids, rituximab, and caplacizumab). Accordingly, similar outcomes of such interventions were also considered. Essentially, the questions to be addressed in the diagnostic recommendations were framed as: "For patients with a specified probability of having TTP, what is the impact on patient important outcomes (eg, disease recurrence and mortality) of adopting a specific diagnostic pathway (ie, availability or not of the ADAMTS13 testing) and consequent appropriate management?"

The diagnostic characteristics or accuracy of four different ADAMTS13 tests for which evidence is appraised summarized in the Appendices.

3 | RECOMMENDATIONS

3.1 | Recommendation 1

In settings with a timely access to plasma ADAMTS13 activity testing and for patients with a high clinical suspicion (≥90% pretest probability) of iTTP (eg, based on clinical assessment or a formal clinical risk assessment method), the panel suggests the following diagnostic strategy. (A conditional recommendation in the context of low certainty evidence.)

Step 1: Acquire a plasma sample for ADAMTS13 testing (eg, ADAMTS13 activity and inhibitors or anti-ADAMTS13 IgG) before an initiation of TPE or use of any blood product.
Step 2: Start TPE and corticosteroids without waiting for the results of ADAMTS13 testing (see Recommendation 1 in Treatment Guidelines).
Step 3: Consider early administration of caplacizumab (see Recommendation 5 in Treatment Guidelines) before receiving plasma ADAMTS13 activity results.
Step 4: When the result of plasma ADAMTS13 activity is available, continue caplacizumab if ADAMTS13 activity is less than 10 IU/dL (or <10% of normal) (a positive result) or stop caplacizumab and consider other diagnoses if ADAMTS13 activity is >20 IU/dL (or >20% of normal) (a negative result).
Step 5: For patients with plasma ADAMTS13 activity less than 10 IU/dL (or <10% of normal) (a positive result), also consider adding rituximab as early as possible, as a majority of these adult patients (>95%) have autoantibodies against ADAMTS13 (see Recommendation 2 in Treatment Guidelines)

However, clinical judgment is required for continuing or stopping treatments (eg, TPE, corticosteroids, rituximab, caplacizumab) when plasma ADAMTS13 activity is between 10 and 20 IU/dL (or 10%-20% of normal) (an equivocal result).

The panel considered the probability of TTP high when estimated at above 90% (9 in 10 patients are usually found to be positive). The panel considered ADAMTS13 activity test with results available in less than 72 hours to be ideal, and the results available between 72 hours and 7 days acceptable. The panel did not review the evidence for any

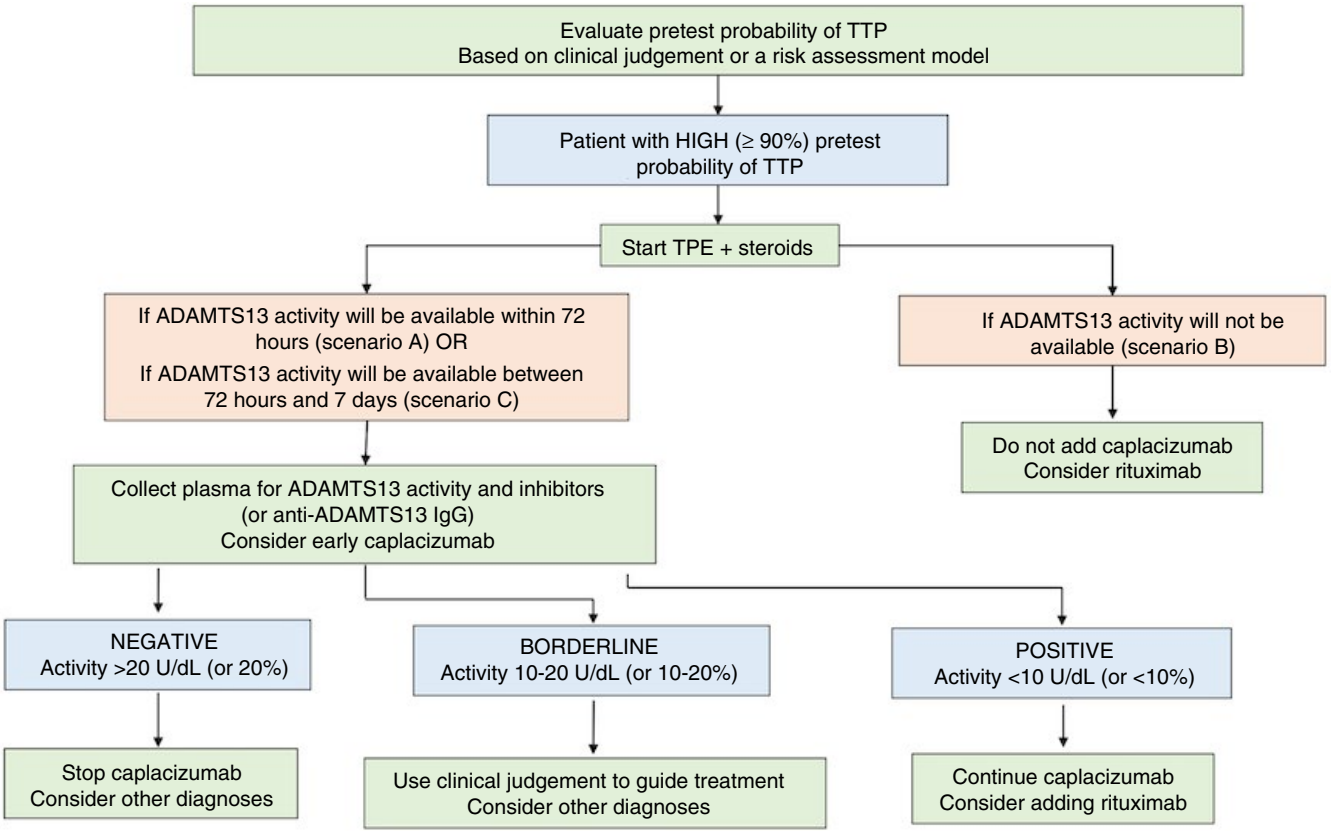

FIGURE 1 A suggested diagnostic and early management strategy for patients with HIGH (≥90%) pretest probability of TTP. Pretest probability of TTP should be determined based on clinical parameters (eg, PLASMIC score or French score). If the pretest probability of TTP is high, start TPE and corticosteroids, and collect plasma samples for ADAMTS13 testing (eg, ADAMTS13 activity and inhibitors, anti-ADAMTS13 IgG) before therapy. Consider caplacizumab if ADAMTS13 test results are expected within 72 hours; if ADAMTS13 test results are not available, do not start caplacizumab; if ADAMTS13 <10 IU/dL (or 10% of normal), continue caplacizumab and rituximab. If ADAMTS13 is ≥20 IU/dL (or 20% of normal), consider stop caplacizumab and seek other diagnoses. However, if ADAMTS13 activity is in borderline (10-20 IU/dL or 10%-20% of normal), clinical judgment is required for continuing therapies or seeking other alternative diagnoses (All are conditional recommendations in the setting of low certainty of evidence). Here "treatment" includes caplacizumab and other therapies (eg, TPE and steroids)

specific score available for stratification of risk in patients; therefore, no specific scoring system is recommended. The recommendation applies regardless of the timing of ADAMTS13 testing and availability of results. The panel underscored the importance of consulting a clinician with experience in the management of TTP early on in the process (see Figure 1).

3.2 | Recommendation 2

In settings with a timely access to plasma ADAMTS13 testing and for patients with intermediate or low clinical suspicion of iTTP (eg, based on clinical assessment or a formal clinical risk assessment method), the panel suggests the following diagnostic strategy. (A conditional recommendation in the context of low certainty evidence.)

Step 1: Acquire a plasma sample for ADAMTS13 testing (eg, ADAMTS13 activity and inhibitor or anti-ADAMTS13 IgG) before an initiation of TPE or use of any blood product.
Step 2: Consider starting TPE and corticosteroids, depending on the clinician's judgment and assessment of the individual patient.
Step 3: Do not start caplacizumab until the result of plasma ADAMTS13 activity becomes available.
Step 4: When the result of plasma ADAMTS13 activity testing is available, consider adding caplacizumab and rituximab (see Recommendation 2 in Treatment Guidelines) if ADAMTS13 activity is less than 10 IU/dL (or <10% of normal) with inhibitors or an elevated level of anti-ADAMTS13 IgG (a positive test result), but do not start caplacizumab and consider other diagnoses if ADAMTS13 activity is greater than 20 IU/dL (or >20% of normal) (a negative result).

The panel judges that for patients with an intermediate or low clinical suspicion of TTP, the balance of benefit, risk, cost, and resource use does not justify the use of caplacizumab. Therefore, a positive ADAMTS13 activity test result (<10 IU/dL or <10% of normal) is required before the initiation of caplacizumab treatment. The panel also noted that ADAMTS13 testing was not a prerequisite for inclusion of TTP patients into the clinical trials for caplacizumab.[41,42] The panel does not review the evidence for any specific clinical score available for stratification of the risk of a suspected TTP, although either the

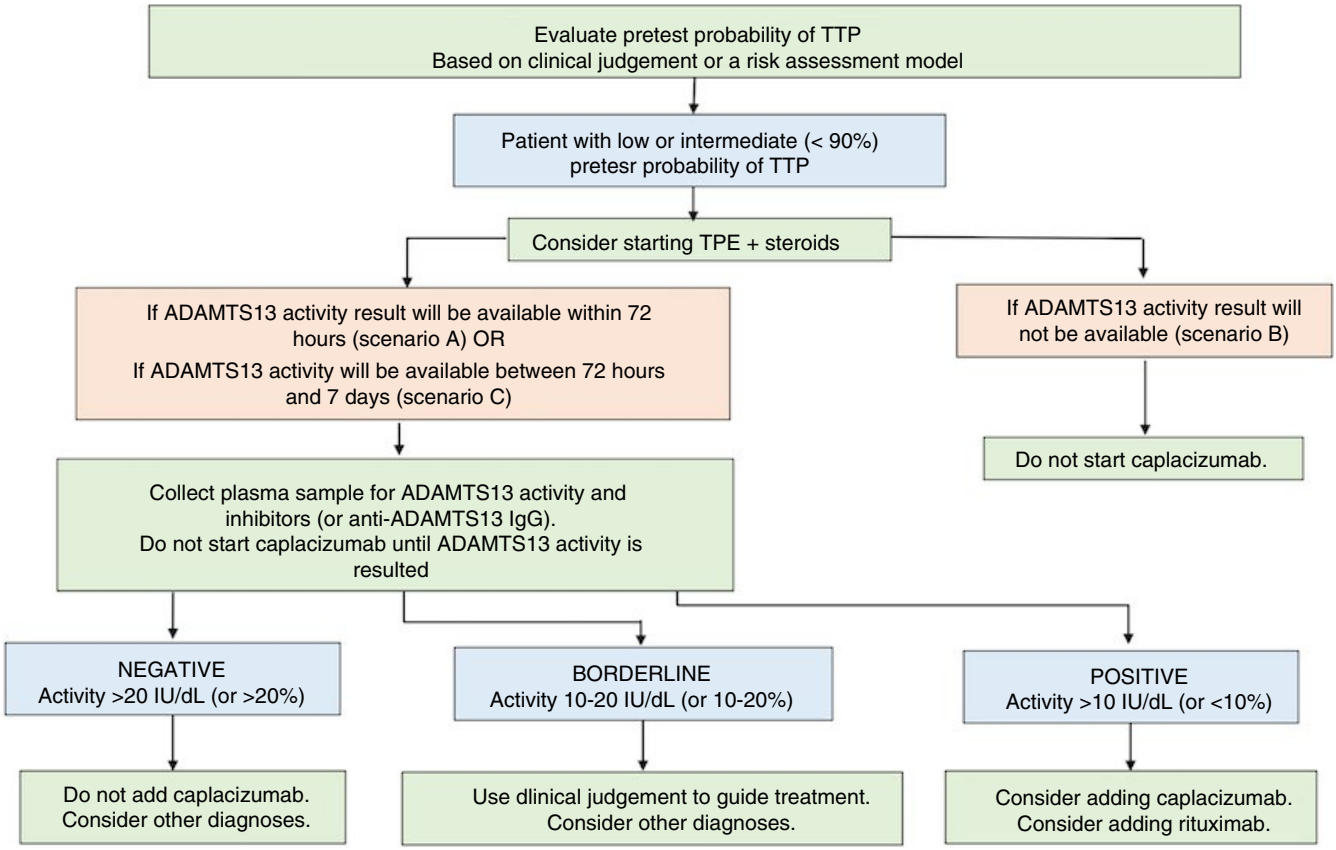

FIGURE 2 A suggested diagnostic and management strategy for patients with LOW or INTERMEDIATE pretest probability of TTP. Pretest probability of TTP should be determined based on clinical presentation and laboratory results. If probability of TTP is low or intermediate, still consider TPE and corticosteroids, but withhold caplacizumab until plasma ADAMTS13 test results are available. If ADAMTS13 test is not available, no caplacizumab should be started; if ADAMTS13 activity is <10 IU/dL (or 10% of normal), consider adding caplacizumab and rituximab; if ADAMTS13 activity is ≥20 IU/dL (or 20% of normal), no caplacizumab should be used and other diagnoses should be actively sought; if ADAMTS13 activity falls borderline between 10 and 20 IU/dL (or 10%-20% of normal), consider other diagnoses. Further treatments in these patients should be based on physician's own clinical judgment (Note: All are conditional recommendations in the setting of low certainty of evidence)

PLASMIC score or the French score may be used. The recommendation applies to the diagnosis and early management of TTP regardless of the timing of ADAMTS13 testing and availability of results. The panel underscored the importance of involving a physician with experience in management of TTP early on in the process (Figure 2).

However, clinical judgment is required for continuing or stopping TPE and corticosteroids, or adding caplacizumab or rituximab when plasma ADAMTS13 activity is between 10 IU/dL and 20 IU/dL (or 10%-20% of normal) (an equivocal result), particularly in those with low or intermediate pretest probabilities of TTP.

3.3 | Recommendation 3

In settings of no reasonable access to plasma ADAMTS13 activity testing, the panel suggests that caplacizumab not be used, regardless of the pretest probability of TTP. (A conditional recommendation in the context of low certainty evidence.)

The panel judged that the potential benefits of caplacizumab, relative to its incremental bleeding risk, cost, and resource use, do not justify its use in the settings where plasma ADAMTS13 activity cannot not be obtained. This was, however, not the case in the HERCULES clinical trials.[41] The panel emphasized that the importance of providing clinicians with a timely access to plasma ADAMTS13 activity (and inhibitor or anti-ADAMTS13 IgG) testing for the optimal care of patients with TTP (Figures 1 and 2).

The panel unanimously judged that management of TTP relapses for a patient previously diagnosed could be safely undertaken on clinical grounds without the need for a confirmatory ADAMTS13 test.

4 | DISCUSSION

This is the first evidence-based guidelines developed by the ISTH TTP guidelines panel for the diagnosis and initial management of TTP. These guidelines differ from the 2012 British[29] and 2017 Japanese[30] TTP guidelines, which were created by a panel of physicians with TTP expertise. The recommendations were made on the basis of consensus with the quality of evidence ranked with an

alphanumeric system. The ISTH TTP guidelines use the GRADE system to present the summaries of evidence in a structured way, which is transparent in describing how the guidelines panel has used the evidence to make the recommendations. Also, these guidelines do not provide recommendations for testing based solely on the review of the evidence of diagnostic accuracy of the available tests. The guidelines appraise the impact on patient important outcomes of a diagnostic pathway by considering the net clinical benefits, patient preferences and values, and cost. Such costs include those resulting from incorrect diagnosis and inappropriate treatment provided to the patients. Details about the modeling scenarios considered by the panel are reported in the Appendices.

Although diagnosis of TTP relies on a high index of suspicion, based on clinical presentation and laboratory results, the panel recognized that the importance of having an ADAMTS13 activity test in the diagnosis and initial management process. There are a number of testing methodologies developed over the years and their performance characteristics are carefully evaluated during the panel discussion.

Of 23 studies, eight reported the use of a fluorescence energy transfer assay for 599 patients. The pooled assay sensitivity and specificity in the diagnosis of TTP with ADAMTS13 activity <10% as the cutoff were 94% and 99%, respectively.[32,33,43-47] Four studies with 168 patients reported the use of a collagen-binding assay with a pooled sensitivity and specificity of 93% and 100%, respectively.[48-51] Four other studies with 441 patients reported on an immunoassay with a pooled sensitivity and specificity of 69% and 97%, respectively.[48-51] Two studies with 81 patients reported on the use of a ristocetin-cofactor assay; the results could not be pooled owing to the lack of false positivity rate in either study. Bohm et al reported a sensitivity of 91% and specificity of 100%,[52] whereas Studt et al reported a sensitivity of 83% and specificity of 100%.[51] The latter three assay methodologies are rarely used for diagnosis clinically owing to the complexity and the lack of reproducibility in the moderately ADAMTS13-deficient samples.

The availability and turnaround time of plasma ADAMTS13 activity test may directly affect how we manage our patients with a suspected TTP. The panel has focused on delineating the initial pathway based on three different scenarios. The panel conditionally recommends the initiation of TPE and corticosteroids in all patients regardless of the availability of ADAMTS13 testing. TPE alone can be a life-saving procedure and should be provided to all patients with a suspected TTP.[11,12] However, the use of caplacizumab depends on the pretest probability for TTP, and the availability and turnaround time of the ADAMTS13 activity test results. When the pretest probability is high (≥90%), based on clinical judgment or a formal risk assessment score, the chance of treating a patient with a wrong diagnosis of immune TTP with caplacizumab is low regardless of test availability; however, when the pretest probability is low (eg, <20%), many more patients without TTP, for whom caplacizumab treatment is not indicated, would have been treated in the absence of a confirmatory plasma ADAMTS13 activity test. Therefore, having an ADAMTS13 test available either immediately (<72 hours) or with a reasonable delay (<7 days) would reduce the number of patients to be treated with caplacizumab based on the modeling as shown in the Appendices.

In conclusion, there is still insufficient high-quality evidence to support strong recommendations for the diagnosis and initial management in a patient with suspected TTP. The panel emphasizes the importance of obtaining ADAMTS13 tests (eg, ADAMTS13 activity, inhibitors, or anti-ADAMTS13 IgG) while starting a patient on treatment with TPE and corticosteroids. Rituximab and caplacizumab should be considered for the patients with a high pretest probability of TTP and those with obtainable ADAMTS13 test results. Alternative diagnoses should always be sought in patients with plasma ADAMTS13 activity between 10 and 20 IU/dL (or 10-20% of normal). Further research is necessary to develop more rapid and accurate ADAMTS13 activity and antibody tests and to more broadly assess how ADAMTS13 testing would impact short- and long-term outcomes.

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CONFLICTS OF INTEREST

Dr. Zheng is a speaker and/or a consultant for Alexion, Sanofi-Genzyme, and Takeda, as well as a cofounder of Clotsolution; Dr. Vesely is a biostatistician for the Oklahoma TTP registry; Dr. Cataland is a consultant for Sanofi-Genzyme and Takeda and served on an advisory board for Alexion; Dr. Coppo is a consultant for Sanofi-Genzyme, Alexion, and Takeda; Dr. Matsumoto has received royalty interest from Alfressa Pharma; Dr. Peyvandi is a speaker for Spark Therapeutics, Sobi, Bioverativ, Grifols, Takeda, and Sanofi-Genzyme; and Dr. Geldziler is an employee of Merck Pharmaceuticals. Dr. Iorio's institution received a project-based funding via research or service agreements from Bayer, CSL, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark, and Takeda; Dr. Pai and other authors whose names are not specifically mentioned in this section declare no conflict of interest.

AUTHOR CONTRIBUTION

X. L. Zheng, Sara K. Vesely, Spero Cataland, P. Coppo, Alfonso Iorio, Menaka Pai, and Flora Peyvandi analyzed the data, participated in the panel discussion, and wrote the manuscript; Brian Geldziler,

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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