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ISTH Guidelines for the Diagnosis of Thrombotic Thrombocytopenic Purpura

Running title: ISTH Guidelines for Diagnosis of TTP

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Summary

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 of Thrombosis and Haemostasis (ISTH) are intended to support patients, clinicians, and other healthcare professionals in their decisions about the initial diagnosis and management of acute TTP. *Methods*: In June 2018, ISTH formed a multidisplinary panel that included hematologists, 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 GRADE approach and PICO framework to develop and grade their recommendations. Public comments were sought and incorporated in the final document. *Results*: The panel agreed on 3 recommendations covering the initial diagnosis with emphasis on the importance of ADAMTS13 testing (e.g. activity and anti-ADAMTS13 IgG or inhibitor) and assessment of the pretest probability of TTP by clinical assessment and/or the risk assessment models like PLASMIC or French score. The panel noted how availability and turn-around-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. Future research should focus on how to monitor and act on ADAMTS13 levels during remission.

Section 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 congential 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] Over 95% of all TTP cases are iTTP, while cTTP accounts for less than 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 conjuction with corticosteroids, rituximab, and caplacizuamb,[19, 22] has signicantly reduced the mortality and morbidity rates in iTTP, while eculizumab, an anti-commplement 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 (BCSH) 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 BCSH 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 of 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 (HMD) of the National Academies of Sciences, Engineering, and Medicine (formerly referred as to the Institute of Medicine), the Guidelines International Network (GIN), 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 judgement.

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, while 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 (e.g. patients, treating physicians, and 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 (ETD) Table are available in Appendix G.

Section 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 (HMD) of the National Academies of Sciences, Engineering, and Medicine (formerly called the Institute of Medicine),[45] and the procedures outlined in the GIN-McMaster Guidelines Development Checklist.[46]

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 co-chair, Dr. X. Long Zheng, is a Professor and Chair of Pathology and Laboratory Medicine at the University of Kansas Medical Center, Kansas City, Kansas, U.S.A. Dr.

Zheng is a world-renown expert in research, diagnosis, and management of TTP, and other related thrombotic microangiopathies. The method co-chair, Dr. Sara K. Vesely, a Professor of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, U.S.A.. 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 which first identified the need for the guidelines and the key issues the guidelines should address. Detailed panel composition is provided in **Appendix A**.

2.2. Methodology team

McMaster University provided the methodological support for the guidelines process, including conducting systematic literature reviews to inform the guidelines questions, providing training to the Guidelines panel members, guiding discussion at panel meetings, and preparing this final evidence report. The methods team was led by Dr. Menaka Pai, and Dr. Alfonso Iorio. Detailed composition of the method team is also provided in **Appendix A**.

2.3. Patient advisory panel

A patient advisory panel consisting of TTP patients from various organizations around the world 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 non-financial relationships from 12 months prior to guidelines initiation through to publication. Financial conflicts include commercial entities with interests related to guidelines recommendations and non-financial conflicts are the involvement in TTP/TMA research. Individuals with major conflicts of interest (COI) with respect to the individual PICO were required to abstain from the formulation of and voting on the corresponding recommendations. They were allowed,

however, to contribute to the discussion leading up to the final vote. The conflicts of each individual panalist were declared verbally and presented on screen at the start of each PICO discussion. The detailed COI policy is reported in **Appendix B**.

2.5. Panel meetings

The guidelines panel met twice in person. In the first meeting, PICO questions to identify and finalize the outcomes of interest were developed in a two-day meeting June 21-22, 2018. Three diagnostic pathways relevant to diagnosis were identified for full appraisal (**Appendix C**).

In the second and final meeting, the panel met May 17-18, 2019 to review the evidence profiles, to discuss the evidence for the recommendations, and to issue the final recommendations, including clinical practice implication, and future research priorities.

2.6. Public comment

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

2.7. Dissemination

A version of this document may be posted on the ISTH website after peer reviewed publication of the main report(s). 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 to be covered by the guidelines were finalized during the guidelines panel meeting in Toronto, Canada, in June 2018. Starting from the scoping document the

panel identified 3 questions relevant to the diagnosis of TTP, agreed on their PICO components and moved to considering them as three diagnostic pathways.

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

The panel agreed to follow the specific GRADE approach for diagnosis.[32-34] In brief, this 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 the adoption of different diagnostic pathways, for patients with different pretest probabilities of the disease of interest. During the first in-person meeting of the panel, the following three potential diagnostic pathways were identified as relevant, and selected for full appraisal:

Scenario A: a pathway where ADAMTS13 activity measurement is readily available (i.e., 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 (i.e., after 72 hours but less than 7 days)

All three scenarios were thought to potentially apply to patients presenting with a clinical picture of thrombotic microangiopathy (TMA) and suspected to have TTP. The population of interest would therefore be defined as: patients with thrombocytopenia (<150 $x10^9$/L), microangiopathic hemolytic anemia (e.g., hemoglobin and hematocrit below the lower limit of the reference range, low haptoglobin, elevated lactate dehydrogenase (LDH) and the presence of schistocytes in peripheral blood smear, etc.), 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 [35, 36] or the French score.[37] (**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 the patient's pretest probability of having TTP and the use of a formal risk assessment or protest 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 (e.g., pregnancy, cancer, sepsis, transplant), which may not be reliable in assessing children. [35, 37, 38] The logical framework for the process is described in **Appendix F**.

The diagnostic tests of interest for the three pathways are centered on the measurement of plasma ADAMTS13 activity and the identification or quantification of anti-ADAMTS13 antibodies. Judging on the impact of a diagnostic pathway requires to assume the effect of the treatment adopted in patients identified as positive and not adopted (or alternative treatment) in patient 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 section of the guidelines (specifically TPE, corticosteroids, rituximab, and caplacizumab, etc.). Accordingly, similar outcomes 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 (e.g., disease recurrence and mortality) of adopting a specific diagnostic pathway (i.e. availability or not of ADAMTS13 testing) and consequent appropriate management?"

The diagnostic characteristics or accuracy of four different ADAMTS13 tests for which evidence is appraised and summarized in **Appendicies**.

Section 3. Recommendations

Recommendation 1. In settings with timely access to plasma ADAMTS13 activity testing and for patients with a high clinical suspicion of immune TTP (e.g., based on clinical assessment or a formal clinical risk assessment method), the panel suggests the following diagnostic strategies. (A conditional recommendation in the context of low certainty evidence)

Step 1. Acquire a plasma sample for ADAMTS13 testing (e.g. ADAMTS13 activity and inhibitors or anti-ADAMTS13 IgG) before an initiation of therapeutic plasma exchange (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 Management Guidelines**).

Step 3. Consider early administration of caplacizumab. (see **Recommendation 5 in Management Guidelines**) before receiving 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 less than 10% of normal) (a positive result) or stop caplacizumab and consider other diagnoses if ADAMTS13 activity is greater than 20 IU/dL (or greater than 20% of normal) (a negative result).

Step 5. For patients with plasma ADAMTS13 activity less than 10 IU/dL (or less than 10% of normal) (a positive result), consider adding rituximab as early as possible, as a majority of these patients (>95%) have autoantibodies against ADAMTS13 (see **Recommendation 2 in** Management Guidelines).

However, clinical judgement is required for continuing or stopping treatments (e.g., TPE, corticosteroids, rituximab, and caplacizumab, etc.) 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 immune 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 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**).

Recommendation 2. In settings with timely access to plasma ADAMTS13 testing and for patients with intermediate or low clinical suspicion of iTTP (e.g., based on clinical assessment or a formal clinical risk assessment method), the panel suggests the following diagnostic strategies. (A conditional recommendation in the context of low certainty evidence)

Step 1. Acquire a plasma sample for ADAMTS13 testing (e.g., 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 judgement and assessment of the individual patient.

Step 3. Do not start caplacizumab until the result of plasma ADAMTS13 activity is available.

Step 4. When the result of plasma ADAMTS13 activity testing is available, consider adding caplacizumab and rituximab (see **Recommendation 2 in Management Guidelines**) if ADAMTS13 activity is less than 10 IU/dL (or less than 10% of normal) with an inhibitor or elevated 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 greater than 20% of normal) (a negative result).

The panel judges that for patients with an intermediate or low clinical suspicion of iTTP, the balance of benefit, risk, cost, and resource use does not justify the use of caplacizumab. Therefore, a positive ADAMTS13 activity test result less than 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 prerequsite for inclusion of TTP patients into clinical trials of caplacizumab.[39, 40] The panel does not review the evidence for any specific clinical score available for stratification of risk of a suspected TTP, although either the PLASMIC score or the Frensh score may be used. The recommendation applies 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. (see **Figure 2**).

However, clinical judgement is required for continuing or stopping TPE and corticosteroids, or additing 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 probabilities of having TTP.

Recommendation 3. In settings of no reasonable access to plasma ADAMTS13 testing, the panel suggests that caplacizumab not be used, regardless of the pretest probability of immune 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 settings where plasma ADAMTS13 activity results cannot not be obtained. This was however not the case in the HERCULES clinical trials.[39] The panel emphasized that the importance of providing clinicians with timely access to plasma ADAMTS13 activity and antibody testing for the optimal care of patients with iTTP (see **Figures 1** & **2**).

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

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 modelling scenarios considered by the panel are reported in **Appendices**.

While 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 methologies developed over the years and their performance characteristics are carefully evaluated during the panel discussion.

Of 23 studies, eight reported the use of a flourescence energy transfer (FRET) assay for 599 patients. The pooled assay sensitity and specificity in the diagnosis of TTP with ADAMTS13 activity <10% as the cutoff were 94% and 99%, respectively.[41-47] Four studies with 168 patients reported the use of a collagen-binding assay (CBA) 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 (RICO) 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], while 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 complexicty and the lack of reproducibility in the moderately ADAMTS13-deficient samples.

The availability and turn-around-time of ADAMTS13 activitiy 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 inititiation of TPE and corticosteroids in all patients regardless of the availability of ADAMTS13 testing. TPE alone is a life-saving procedure and should be provided to all patients with a suspected immune TTP. (ref) However, the use of caplacizumab depends on the pretest probability for immune TTP, and the availability and turn around time of the

ADAMTS13 activity test results. When the pretest probability is high (>90%), based on clinical judegment or risk assessment scores, 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 proability is low (e.g., <20%), many more patients without immune TTP, for whom caplacizumab treatment is not indicated, would have been treated in the absence of a confirmatory ADAMTS13 activity test. Therfore, having an ADAMTS13 test available either immediately (less than 72 hours) or with a reasonable delay (less than 7 days) would reduce the number of patients to be treated with caplacizumab based on the modeling as shown in the **Appendicies**.

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

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Conflicts of interest disclosure

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

Authorship statement

X. L. Zheng, S. K. Vesely, S. Cataland, P. Coppo, A. Iorio, M. Pai, and F. Peyvandi analyzed the data, participated in the panel discussion, and wrote the manuscript; B. Geldziler, M.

Matsumoto, R. Mustafa, G. Rock, L. Russell, R. Tarawneh, and J. Valdes analyzed the data, participated in the panel discussion, and revised manuscript. All authors approved the final version of the manuscript.

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	<30x10^9/L (+1)	<30x10^9/L (+1)
Serum creatinine level	<2.26mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis		
Indirect bilirubin > 2 mg/dL	*	+1
or rculocyte count > 2.5 %		
or undetectabel haptoglobin		
No active cancer in previous year	*	+1
No history of solid organ or SCT	*	+1
INR < 1.5	*	+1
MCV < 90 fL	NA	+1
Likelihood of severe deficiency of ADAMTS13 activity (<10 %)	0: 2% 1: 70% 2: 94%	0-4: 0-4% 6: 5-24% 6-7: 62-82%

Each item is associated with one point (+1); INR, international normalized ratio; MCV, mean corposcular value; SCT, stem cell transplanation; *French score considered patients with thrombotic microangiopathy (TMA) 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, MCV was not incorporated in the French score. The table is adopted from Joly B.S.[53]

Figure Legends

Figure 1. A suggested diagnostic and management strategy for patients with HIGH pretest probability of immune TTP. Pretest probability of TTP should be determined based on clinical parameters (e.g. PLASMIC or French score). If probability of TTP is high, start TPE and corticosteroids and collect plasma samples for ADAMTS13 testing (e.g. activity and inhibitors or 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 judgement is required for continuing therapy and other alternative diagnostic approaches (All are conditional recommendations in the setting of low certainty of evidence). Here “treatment” includes caplacizumab and other therapies (such as TPE and steroids).

Figure 2. A suggested diagnostic and management strategy for patients with LOW or INTERMEDIATE pretest probability of immune TTP. Pretest probability of immune 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 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 is ≥ 20 IU/dL (or 20% of normal), no caplacizumab should be used and other diagnoses should be sought; If ADAMTS13 falls borderline 10-20 IU/dL (or 10-20% of normal), consider other diagnoses and further treatments should be based on clinician’s own clinical judgement (All are conditional recommendations in the setting of low certainty of evidence).

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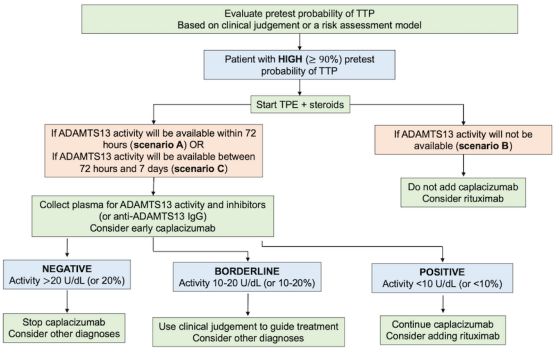

Figure 1

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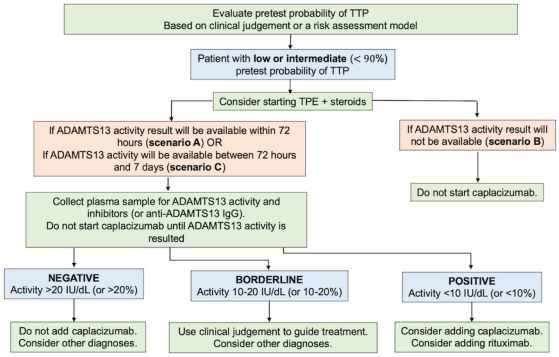

Figure 2

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