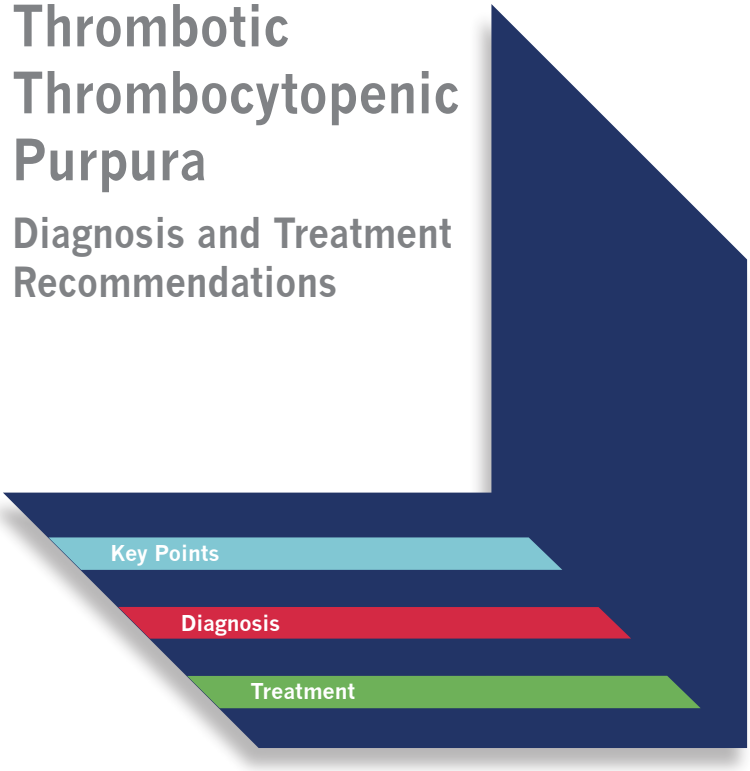
ISTH®

International Society on
Thrombosis and Haemostasis

Thrombotic Thrombocytopenic Purpura

Diagnosis and Treatment Recommendations



INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS:

CABLIVI (caplacizumab-yhdp) is indicated for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.

CONTRAINDICATIONS:

CABLIVI is contraindicated in patients with a previous severe hypersensitivity reaction to caplacizumab-yhdp or to any of its excipients. Hypersensitivity reactions have included urticaria.

WARNINGS AND PRECAUTIONS:

Hemorrhage:

- CABLIVI increases the risk of bleeding. In clinical studies, severe bleeding adverse reactions of epistaxis, gingival bleeding, upper gastrointestinal hemorrhage, and metrorrhagia were each reported in 1% of subjects. Overall, bleeding events occurred in approximately 58% of patients on CABLIVI versus 43% of patients on placebo.
- In the postmarketing setting cases of life-threatening and fatal bleeding were reported in patients receiving CABLIVI.
- The risk of bleeding is increased in patients with underlying coagulopathies (e.g. hemophilia, other coagulation factor deficiencies). It is also increased with concomitant use of CABLIVI with drugs affecting hemostasis and coagulation.
- Avoid concomitant use of CABLIVI with antiplatelet agents or anticoagulants. If clinically significant bleeding occurs, interrupt use of CABLIVI. Von Willebrand factor concentrate may be administered to rapidly correct hemostasis. If CABLIVI is restarted, monitor closely for signs of bleeding.
- Withhold CABLIVI for 7 days prior to elective surgery, dental procedures or other invasive interventions. If emergency surgery is needed, the use of von Willebrand factor concentrate may be considered to correct hemostasis. After the risk of surgical bleeding has resolved, and CABLIVI is resumed, monitor closely for signs of bleeding.

ADVERSE REACTIONS:

The most common adverse reactions (>15% of patients) were epistaxis (29%), headache (21%) and gingival bleeding (16%).

CONCOMITANT USE OF ANTICOAGULANTS OR ANTIPLATELET AGENTS:

Concomitant use of CABLIVI with any anticoagulant or antiplatelet agent may increase the risk of bleeding. Avoid concomitant use when possible. Assess and monitor closely for bleeding with concomitant use.

PREGNANCY:

There are no available data on CABLIVI use in pregnant women to inform a drug associated risk of major birth defects and miscarriage.

- **Fetal/neonatal adverse reactions:** CABLIVI may increase the risk of bleeding in the fetus and neonate. Monitor neonates for bleeding.
- **Maternal adverse reactions:** All patients receiving CABLIVI, including pregnant women, are at risk for bleeding. Pregnant women receiving CABLIVI should be carefully monitored for evidence of excessive bleeding.

Please see accompanying full Prescribing Information.

Interpretation of the Certainty in Evidence of Effects using the GRADE framework

H = High	We are very confident that the true effect lies close to that of the estimate of the effect.
M = Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
L = Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
VL = Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Interpretation of Strong and Conditional Recommendations using the GRADE framework

Implications	S = Strong recommendation	C = Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared-decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

* Strong recommendations are indicated by statements that lead with "recommend", while conditional recommendations are indicated by statements that lead with "suggest"

Key Points

- **Remarkable advances have been made in recent years towards our understanding of the pathophysiology of thrombotic thrombocytopenic purpura (TTP), which has led to advancements in novel therapies.**
- **Despite an increase in our understandings of pathogenesis of TTP, the approaches for initial diagnosis and management of TTP vary significantly.**
- **The guidelines are intended to support patients, clinicians, and other healthcare professionals in their decisions about the initial diagnosis and management of acute TTP.**

Diagnosis

- **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 (See Table 1). (C-L)**

Table 1. Diagnosis in settings with timely access to plasma ADAMTS13 activity testing and for patients with a *HIGH* clinical suspicion of immune TTP

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).

Note: 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).

➤ **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 (See Table 2). (C-L)**

Table 2. Diagnosis in settings with timely access to plasma ADAMTS13 testing and for patients with *INTERMEDIATE* or *LOW* clinical suspicion of iTTP

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 ≥20% of normal) (a negative result).

Note: Clinical judgement is required for continuing or stopping TPE and corticosteroids, or adding caplacizumab or rituximab when plasma ADAMTS13 activity is between 10 and 20 IU/dL.

➤ **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. (C-L).**

- TPE and steroids, plus rituximab may still be offered in the scenario.

Table 3. PLASMIC score or French score predicts the likelihood of severe ADAMTS13 deficiency in a suspected TTP

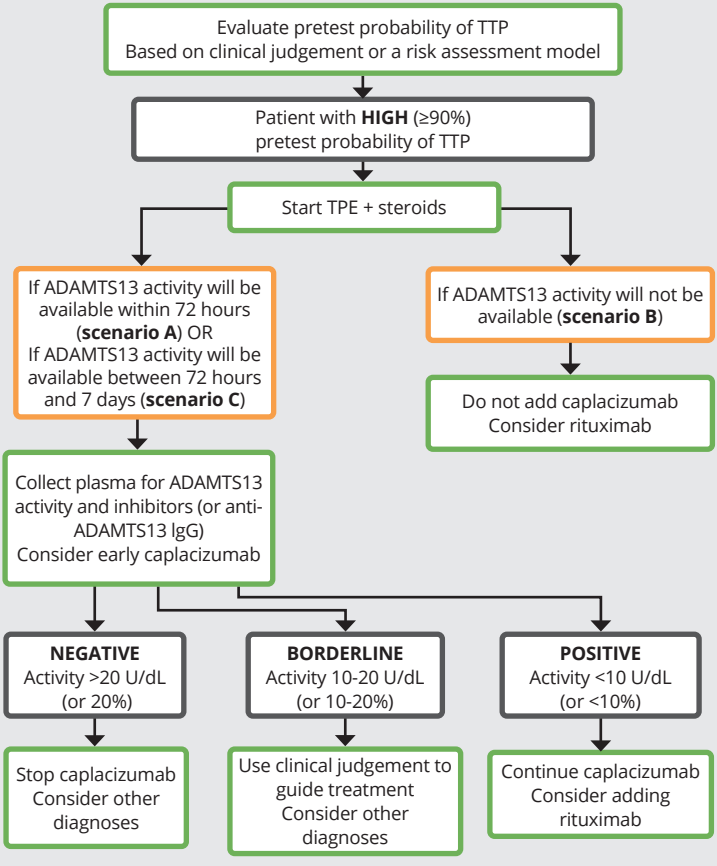
Parameters	French Score	PLASMIC Score
Platelet count	$<30 \times 10^9$/L (+1)	$<30 \times 10^9$/L (+1)
Serum creatinine level	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis		
Indirect bilirubin >2 mg/dL	*	+1
or reticulocyte count >2.5 %		
or undetectable haptoglobin		
No active cancer in previous year	*	+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).

*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.

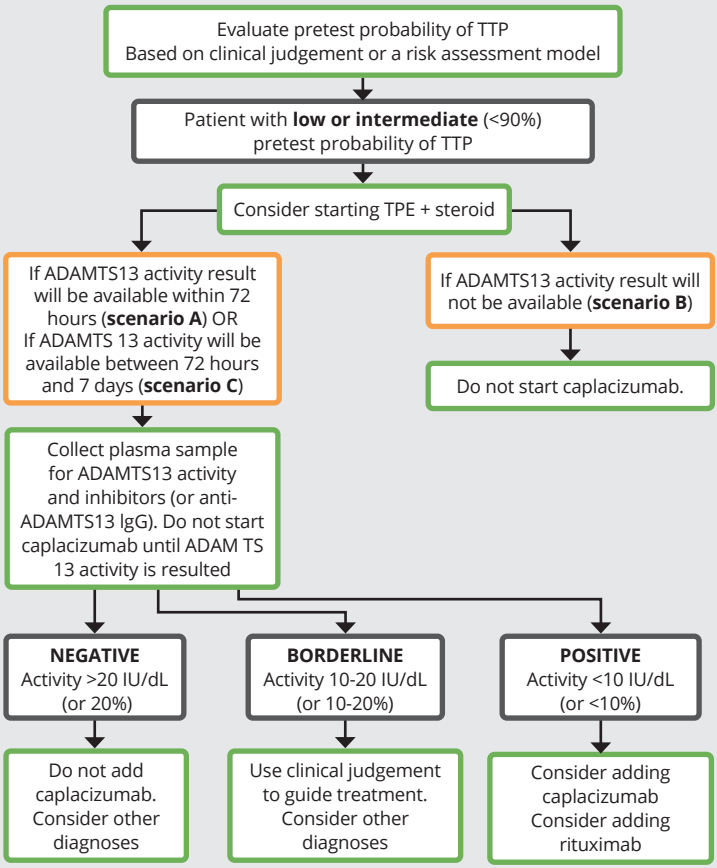
The table is adopted from Joly B.S. *Expert Rev Hematol*. 2019;12:383-95.

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.)

Treatment

Immune-mediated TTP (iTTP)

- For patients with iTTP experiencing a first acute event, the panel recommends the addition of corticosteroids to therapeutic plasma exchange (TPE) over TPE alone. (S-VL)
- 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. (C-VL)
- For patients with iTTP experiencing a relapse, the panel recommends addition of corticosteroids to TPE over TPE alone. (S-VL)
- For patients with iTTP experiencing a relapse, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (C-VL)
- For patients with iTTP experiencing an acute event (first event or relapse) the panel suggests using caplacizumab over not using caplacizumab. (C-M)
- For patients with iTTP who are in remission, but still have low plasma ADAMTS13 activity with no clinical signs/symptoms, the panel suggests the use of rituximab over non-use of rituximab for prophylaxis. (C-VL)

Hereditary or Congenital TTP (cTTP)

- For patients with cTTP who are in remission, the panel suggests either plasma infusion or a watch and wait strategy. (C-VL)
- For patients with cTTP who are in remission, the panel suggests against the use of factor VIII concentrate infusions versus a watch and wait strategy. (C-VL)
- For patients with iTTP who are pregnant and have decreased plasma ADAMTS13 activity but with no clinical signs/symptoms, the panel recommends prophylactic treatment over no prophylactic treatment. (S-VL)
- For patients with cTTP who are pregnant, the panel recommends prophylactic treatment over no prophylactic treatment. (S-VL)
- For patients with cTTP who are pregnant, the panel suggests prophylactic treatment with plasma infusion over FVIII products. (C-VL)

Abbreviations

cTTP, hereditary or congenital TTP; **FVIII**, factor VIII; **INR**, international normalized ratio; **iTTP**, immune-mediated TTP; **MCV**, mean corposcular value; **SCT**, stem cell transplantation; **TMA**, thrombotic microangiopathy; **TPE**, therapeutic plasma exchange; **TTP**, thrombotic thrombocytopenic purpura

The guidelines provide evidence-based recommendations that have been developed using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology. GRADE involves structured literature review, systematic reviews and meta-analyses of combined data, and expert discussion to assess the certainty in the evidence and determine the strength of each recommendation.

Source

X. Long Zheng, Sara K. Vesely, Spero R. Cataland, et al. ISTH Guidelines for the Diagnosis of Thrombotic Thrombocytopenic Purpura. *Journal of Thrombosis and Haemostasis*. 2020 July doi:10.1111/jth.15006.

X. Long Zheng, Sara K. Vesely, Spero R. Cataland, et al. ISTH Guidelines for Treatment of Thrombotic Thrombocytopenic Purpura. *Journal of Thrombosis and Haemostasis*. 2020 July doi:10.1111/jth.15010.

Disclaimer

This pocket guide attempts to define principles of practice that should produce high-quality patient care. It is applicable to specialists, primary care, and providers at all levels. This pocket guide should not be considered exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment concerning the propriety of any course of conduct must be made by the clinician after consideration of each individual patient situation.
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ISTHTTP09203

MAT-US-2020589-v2.0-03/2022