

European Renal Best Practice endorsement of guidelines for diagnosis and therapy of thrombotic thrombocytopenic purpura published by the International Society on Thrombosis and Haemostasis

A European Renal Best Practice (ERBP) endorsement of ISTH Guidelines for Treatment of Thrombotic Thrombocytopenic Purpura (TTP) with some refinements for Europe

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CHAPTER 1. INTRODUCTION

The International Society on Thrombosis and Haemostasis (ISTH) has published clinical practice guidelines for the diagnosis and treatment of thrombotic thrombocytopenic purpura (TTP) in 2020 (1, 2). These guidelines were necessary due to the important innovations made in the field of TTP including diagnostics using ADAMTS13 as well as therapy with caplacizumab. TTP can be differentiated into immune-mediated TTP (iTTP), caused by autoantibody-mediated inhibition of ADAMTS13, and congenital TTP, caused by mutations in the ADAMTS13-gene (3, 4). ADAMTS13 cleaves the ultra-large multimers of von Willebrand factor (vWF). In the absence of ADAMTS13, the ultra-large vWF multimers persist in the circulation, unfold and expose their A1 domains upon enhanced blood flow shear forces, thereby becoming hyper-adhesive for platelets, which results in microthrombi obstructing microcirculation leading to thrombotic microangiopathy (TMA) with ischemic organ injury (3). Important improvements in the diagnosis and treatment of TTP have been made in the past years. First, ADAMTS13 activity measurement is available not only for the diagnosis of TTP, but also for the response to therapy as well as risk for recurrence of disease (5-7). Second, immunosuppressive medications, especially rituximab, have been successful in reducing anti-ADAMTS13 antibodies, which shortens time to remission and limits the risk for exacerbation and relapse (8-12). Third, caplacizumab, a nanobody directed against A1 binding domains of vWF, has been approved for the treatment of iTTP together with therapeutic plasma exchange (TPE) (13, 14).

The 2020 ISTH Guidelines on TTP have now been evaluated by the European Renal Best Practice (ERBP) Working Group and are herewith endorsed. Recommendations of the 2020 ISTH guidelines on TTP are summarized in Table 1. However, the Working Group argued that some recommendations need refinement from a European perspective. This endorsement highlights and expands on certain elements of the rationale following each recommendation. It also includes some comments on the treatment, whilst not based on randomized controlled trials, may still be relevant for the treatment of patients with TTP.

We further shortly discuss relevant issues in diagnosis and treatment of TTP and try to make recommendations for clinical practice in Europe.

CHAPTER 2. METHODS

ERBP assigned a working group consisting of experts in TTP and guideline development to evaluate the 2020 ISTH guidelines on TTP for endorsement. We evaluated the methodological quality of the ISTH guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument (15). AGREE II is an internationally validated and widely accepted clinical practice guideline evaluation tool assessing six domains of guideline development: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Four members of the ERBP working group independently scored each item from 1 (Strongly Disagree) to 7 (Strongly Agree). We calculated each domain score using the formula provided by the AGREE II instrument by summing up all scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The threshold to determine high quality within a domain was set at a domain score above 70%. Domain scores can be used to identify strengths and limitations of guidelines, to compare methodological quality between guidelines, or to select high quality guidelines for endorsement.

For the 2020 ISTH Guidelines on TTP all domains received a score above 70% (94% for scope and purpose, 88% for stakeholder involvement, 74% for rigor of development, 83% for clarity of presentation, 72% for applicability and 88% for editorial independence), and thus the ERBP working group classified the 2020 ISTH guideline on TTP as high-quality guidelines.

CHAPTER 3. DIAGNOSIS OF TTP

The ERBP working group urges the availability of rapid ADAMTS13 activity testing across Europe since it is not only necessary for diagnosing TTP, but also to guide therapy and to monitor clinical remission. In all European countries ADAMTS13 activity testing should be available ideally within 24 (to 72) hours after the suspicion of TTP to ensure appropriate therapy (2). PLASMIC or French scores (Table 2) are both useful to evaluate pretest probability for TTP in patients with features of TMA and no associated conditions (in particular pregnancy, cancer or chemotherapy, transplantation, severe sepsis) (16, 17). Furthermore, measuring ADAMTS13 inhibitors or anti-ADAMTS13 IgG to underline the diagnosis of iTTP is important, although negative inhibitor results can also occur in some cases of early iTTP or be false negative in the case of Ig subtypes that are not detected by the immunoassay used (2). If cTTP is suspected, genetic analysis of ADAMTS13 should be performed.

CHAPTER 4. TREATMENT OF THE FIRST EPISODE OF iTTP

In all patients with suspected iTTP, TPE and steroid treatment should be started immediately. In patients with high suspicion for iTTP, caplacizumab might be started before receiving ADAMTS13 activity results. We nevertheless urge that rapid ADAMTS13 activity evaluation ideally within 24 (to 72) hours of admission (2) would improve the treatment of iTTP patients and limit critical side effects of caplacizumab, such as bleeding. In case of ADAMTS13 activity below 10%, caplacizumab should be started according to the HERCULES study protocol (10 mg intravenously immediately, followed by 10 mg subcutaneously (s.c.) after each TPE, followed by daily s.c. injections (14). Caplacizumab needs to be continued until stable recovery of ADAMTS13 activity >10-20%, since earlier discontinuation leads to a high risk of TTP exacerbation. As recommended in the 2020 ISTH guideline (1), we urge not to start caplacizumab in case ADAMTS13 activity testing is not available at all. Overall, it is important to receive ADAMTS13 results as quick as possible and/or to transfer the patient with high suspicion of TTP to an experienced center.

The ERBP working group strongly supports adding rituximab to the treatment protocol as early as possible if iTTP is suspected. TTP patients receiving rituximab display significantly decreased mortality rates as well as relapse rates as shown in a meta-analysis including 570 patients recruited in 9 eligible studies (10). Most of the studies treated patients with 375 mg/m² weekly for 1 to 4 doses in total (10). Since rituximab is very effective in treating iTTP, tapering steroids rapidly and limiting steroid treatment to 3-4 weeks seems reasonable.

In general, TPE may be discontinued soon after a clinical response, defined by a sustained platelet count $\geq 150 \times 10^9/L$ and LDH <1.5 times of the upper limit of normal and no clinical evidence of new or progressive ischemic organ injury (18), is achieved. A clinical response should be critically differentiated from a clinical remission that has been defined as a sustained clinical response without TPE and caplacizumab treatment for 30 days or with attainment of ADAMTS13 remission (partial or complete), whichever occurs first (18). A partial ADAMTS13 remission is achieved when ADAMTS13 activity is 20% to < lower limit of normal (LLN), whereas complete ADAMTS13 remission is reached when ADAMTS13 is \geq LLN (18). Testing for ADAMTS13 activity should be repeated to confirm ADAMTS13 remission (18). As per the HERCULES protocol, ADAMTS13 activity should be measured weekly in patients treated with caplacizumab and treatment should be discontinued once an ADAMTS13 remission has been achieved rather than stopping after an arbitrary interval (5, 7, 18, 19). Importantly, the ERBP working group emphasizes that ADAMTS13 activity testing during TPE should be avoided since results might be influenced by plasma exchange.

CHAPTER 5. TREATMENT OF A RELAPSING EVENT OF iTTP

A clinical relapse has been recently defined as a decrease of platelets $<150 \times 10^9/L$ with or without evidence of new ischemic organ injury after a clinical remission. Other causes of thrombocytopenia need to be ruled out and the clinical relapse needs to be confirmed by detection of severe ADAMTS13 deficiency. An ADAMTS13 relapse is defined in case ADAMTS13 levels decrease below 20% after an ADAMTS13 complete or partial remission (18). According to the ISTH guidelines (1), start of TPE, corticosteroids, rituximab and caplacizumab in case of a clinical relapse is recommended. When an ADAMTS13 relapse without a clinical relapse is diagnosed, the working group and others favor preemptive rituximab treatment in such situations to reinduce an ADAMTS13 remission thereby reducing the risk of a clinical relapse (8-12, 18).

CHAPTER 6. TTP IN REMISSION

For iTTP the ERBP working group advocates regular testing of ADAMTS13 activity during ADAMTS13 remission to detect ADAMTS13 relapse. The ERBP working group supports the recommendation of the ISTH guideline (1) to use rituximab preemptively in case of ADAMTS13 relapse as outlined in chapter 5. In patients with cTTP in remission the ERBP working group supports the recommendation of the ISTH guideline to use prophylactic plasma infusions (1), but emphasizes that trials using recombinant ADAMTS13 in cTTP and iTTP are currently performed (registered at www.clinicaltrials.gov as #NCT03393975 and #NCT03922308), which are expected to have relevant impact on treatment strategies not only in cTTP, but also iTTP.

CHAPTER 7. TTP during pregnancy

The ERBP working group advocates that patients with iTTP in remission and pregnancy are treated by experienced specialists for TTP. During pregnancy ADAMTS13 activity should be measured frequently. For the ERBP working group the evidence basis for clear treatment recommendations for pregnant patients with ADAMTS13 relapse is too scarce. In this condition, prophylactic TPE and/or steroids or other immunosuppressants might be considered. In case of a clinical relapse, the ERBP working group favors treatment with TPE and steroids. Treatment with rituximab might also be considered in case of refractory disease (20). At present, the use of caplacizumab cannot be recommended in pregnant patients due to the proven bioavailability across the placental barrier and the lack of clinical data on potential side effects affecting the fetus (21). For pregnant patients with cTTP in

remission the ERBP working group endorses the recommendation of ISTH guidelines to prophylactically treat patients with plasma infusions (1).

CONCLUSION

Not only treatment regimens, but also diagnostic approaches, have dramatically changed in TTP within the past years. The 2020 ISTH Guideline group reviewed all available evidence on the management of TTP in a rigorous way and the ERBP working group endorsed the 2020 ISTH guidelines for the diagnosis and treatment of thrombotic thrombocytopenic purpura (1, 2). However, the ERBP working group wants to draw attention to a number of considerations that enhance the clinical applicability of the guideline in Europe.

- We do urge to establish ADAMTS13 activity measurements in TTP centers across Europe to shorten time to TTP diagnosis and to prevent a clinical relapse in the follow-up period.
- TPE and corticosteroids remain cornerstones of acute iTTP treatment, but additional rituximab improves the time to ADAMTS13 remission and the number of clinical relapses in acute iTTP (10). Furthermore, rituximab is a recommended preemptive strategy in patients with an ADAMTS13 relapse to prevent a clinical relapse (1, 18).
- Caplacizumab improved therapy of acute iTTP treatment by reducing unfavorable outcomes such as the risk of refractoriness and acute clinical exacerbation (14). Recombinant ADAMTS13 will be added to the iTTP armamentarium for the treatment of acute episodes and is currently tested in clinical studies.

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CONFLICT OF INTEREST STATEMENT

KE is member of advisory boards for and received speaker fees from Sanofi-Genzyme and Alexion. PK received consultancy and speaker fees, research and travel grants from: Ablynx, Sanofi-Genzyme, Shire (a Takeda company), Alexion, CSL Behring, Roche, Novo Nordisk, Sobi. JJM received speaker and consultant fees from Ablynx, Sanofi-Genzyme and Alexion. PTB is member of advisory boards for and received speaker honoraria from Alexion, Sanofi-Genzyme, Bayer, Vifor, Astra Zeneca and Pfizer. PC is member of advisory boards for and received speaker fees from Sanofi, Alexion, Janssen, and Takeda. MS is member of advisory boards for and received speaker fees from Sanofi, Takeda, Octapharma, Novartis, Alexion. MCH, SAB, LG and UT report no conflict of interest.

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Table 1.

Chapter	Recommendation	Setting	Intervention	Strength
Diagnosis	Recommendation 1	Access to ADAMTS13 testing and patients with a high clinical suspicion of iTTP*	<p>Step 1: Plasma sample for ADAMTS13 testing before an initiation of TPE or use of any blood product</p> <p>Step 2: TPE and corticosteroids without waiting for the results of ADAMTS13 testing</p> <p>Step 3: Consider early administration of caplacizumab before receiving plasma ADAMTS13 activity results</p> <p>Step 4:</p> <p>If ADAMTS13 test is positive***: continue caplacizumab</p> <p>If ADAMTS13 test is negative****: stop caplacizumab and consider other diagnoses</p> <p>Step 5: For patients with a positive ADAMTS13 inhibitor testing, also consider adding rituximab as early as possible, as a majority of these adult patients (>95%) have autoantibodies against ADAMTS13</p>	A conditional recommendation in the context of low certainty evidence

	Recommendation 2	Access to ADAMTS13 testing and patients with intermediate or low clinical suspicion of iTTP**	<p>Step 1: Plasma sample for ADAMTS13 testing before an initiation of TPE or use of any blood product</p> <p>Step 2: Consider starting TPE and corticosteroids, depending on the clinician's judgment and assessment of the individual patient</p> <p>Step 3: no caplacizumab until the result of plasma ADAMTS13 activity is available</p> <p>Step 4:</p> <p>If ADAMTS13 test is positive***: consider adding caplacizumab and rituximab</p> <p>If ADAMTS13 test is negative****: do not start caplacizumab and consider other diagnoses</p>	A conditional recommendation in the context of low certainty evidence
	Recommendation 3	No access to plasma ADAMTS13 activity testing	No caplacizumab regardless of the pretest probability of TTP	A conditional recommendation in the context of low certainty evidence
Treatment	Recommendation 1	iTTP, first acute event	Addition of corticosteroids to therapeutic plasma exchange (TPE) over TPE alone	A strong recommendation in the context of very low certainty evidence
	Recommendation 2	iTTP, first acute event	Addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone	A conditional recommendation in the context of very low certainty evidence

	Recommendation 3	Relapse of iTTP	Addition of corticosteroids to TPE over TPE alone	A strong recommendation in the context of very low certainty evidence
	Recommendation 4	Relapse of iTTP	Addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone	A conditional recommendation in the context of very low certainty evidence
	Recommendation 5	Acute event of iTTP (first event or relapse)	Use of caplacizumab over nonuse of caplacizumab	A conditional recommendation in the context of moderate certainty evidence
	Recommendation 6	iTTP in remission, but low plasma ADAMTS13 activity and no clinical signs/symptoms	Use of rituximab over nonuse of rituximab for prophylaxis	A conditional recommendation in the context of very low certainty evidence
	Recommendation 7	cTTP in remission	Either plasma infusion or a watch and wait strategy	A conditional recommendation in the context of very low certainty evidence
	Recommendation 8	cTTP in remission	No use of factor VIII (FVIII) concentrate but a watch and wait strategy	A conditional recommendation in the context of very low certainty evidence
	Recommendation 9	Pregnant patients with iTTP and decreased plasma ADAMTS13 activity but with no clinical signs/symptoms	Prophylactic treatment over no prophylactic treatment	A strong recommendation in the context of very low certainty evidence
	Recommendation 10A	Pregnant patients with cTTP	Prophylactic treatment over no prophylactic treatment	A strong recommendation in the context of very low certainty evidence

	Recommendation 10B	Pregnant patients with cTTP	Prophylactic treatment with plasma infusion over FVIII products for prophylaxis	A conditional recommendation in the context of very low certainty evidence
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*High clinical suspicion of TTP: $\geq 90\%$ pretest probability of iTTP based on clinical assessment or a formal clinical risk assessment method such as PLASMIC score or French score

** Intermediate or low clinical suspicion: based on clinical assessment or a formal clinical risk assessment method such as PLASMIC score or French score

*** Positive result = ADAMST13 activity less than 10 IU/dL (or $< 10\%$ of normal)

**** Negative result = ADAMTS13 activity > 20 IU/dL (or $> 20\%$ of normal)

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Table 2. French and PLASMIC Score to predict the likelihood of severe ADAMTS13 deficiency. Adapted from (2).

Parameters	French Score	PLASMIC Score
Platelet count	< 30 x 10 ⁹ /L (+1)	< 30 x 10 ⁹ /L (+1)
Serum-creatinine	< 2.26 mg/dL (+1)	< 2.0 mg/dL (+1)
Hemolysis indirect bilirubin > 2 mg/dL or reticulocyte count >2.5% or undetectable haptoglobin	*	(+1)
No active cancer in the previous year	*	(+1)
No history of solid organ transplantation or stem cell transplantation	*	(+1)
INR < 1.5	*	(+1)
MCV < 90 fl	N/A	(+1)
Likelihood of severe deficiency of ADAMTS13 activity (<10%)	0: 2% 1: 70% 2: 94%	0-4: 0-4% 5: 5-24% 6-7: 62-82%

Abbreviations: INR, international normalized ratio; MCV, mean corpuscular value;

* 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.