Nephrol Dial Transplant (2022) 37: 1229–1234
https://doi.org/10.1093/ndt/gfac034
Advance Access publication date 23 February 2022

SPECIAL REPORT

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

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

Kathrin Eller[1], Paul Knoebl[2], Sevcan A. Bakkaloglu[3], Jan J. Menne[4], Paul T. Brinkkoetter[5], Leonie Grandt[6], Ursula Thiem[6], Paul Coppo[7], Marie Scully[8] and Maria C. Haller[6]

[1]Division of Nephrology, Medical University of Graz, Graz, Austria, [2]Division of Haematology and Haemostasis, Department of Medicine I, Medical University of Vienna, Vienna, Austria, [3]Department of Paediatric Nephrology, Gazi University, Faculty of Medicine, Ankara, Turkey, [4]KRH Klinikum Mitte – Location Siloah, Hannover, Germany, [5]Department II of Internal Medicine and Centre for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany, [6]Department of Medicine III - Nephrology, Ordensklinikum Linz Elisabethinen, Linz, Austria, [7]Department of Haematology, Reference Centre for Thrombotic Microangiopathies, Saint-Antoine University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France and [8]Department of Haematology, University College London Hospitals, London, UK

Correspondence to: Kathrin Eller; E-mail: kathrin.eller@medunigraz.at

ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease that is caused by severe ADAMTS-13 deficiency. Immune-mediated TTP develops due to autoantibodies against ADAMTS-13, whereas congenital TTP is caused by mutations in the ADAMTS13 gene. Diagnostic possibilities and treatment options in TTP have emerged in recent years, which prompted the International Society on Thrombosis and Haemostasis (ISTH) to publish clinical practice guidelines for the diagnosis and treatment of TTP in 2020. In this article, the European Renal Best Practice Working Group endorsed the ISTH guidelines and emphasizes a number of considerations, including the importance of rapid ADAMTS-13 activity testing, the use of rituximab and anti-von Willebrand factor therapies such as caplacizumab, that enhance the clinical applicability of the guidelines in Europe.

Keywords: AKI, guidelines, plasma exchange, systematic review, thrombotic microangiopathy

CHAPTER 1. INTRODUCTION

The International Society on Thrombosis and Haemostasis (ISTH) published clinical practice guidelines for the diagnosis and treatment of thrombotic thrombocytopaenic 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 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) 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 ultralarge multimers of von Willebrand factor (vWF). In the absence of ADAMTS13, the ultralarge vWF multimers persist in the circulation, unfold and expose their A1 domains upon enhanced blood flow shear forces, thereby becoming hyperadhesive for platelets, which results in microthrombi obstructing microcirculation, leading to thrombotic microangiopathy (TMA) with ischaemic organ injury [3]. Important improvements in the diagnosis and treatment of TTP have been made in recent years. First, ADAMTS13 activity measurement is available not only for the diagnosis of TTP, but also for the response to therapy as

well as the risk for recurrence of the disease [5–7]. Second, immunosuppressive medications, especially rituximab, have been successful in reducing anti-ADAMTS13 antibodies, which shortens the 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, while not based on randomized controlled trials, which may still be relevant for the treatment of patients with TTP.

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

CHAPTER 2. METHODS

The 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, rigour 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 >70%. Domain scores can be used to identify the 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 >70% (94% for scope and purpose, 88% for stakeholder involvement, 74% for rigour 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 h (to 72 h) after the suspicion of TTP to ensure appropriate therapy [2]. PLASMIC (Platelet count; combined hemoLysis variable; absence of Active cancer; absence of Stem-cell or solid-organ transplant; MCV; INR; Creatinine) 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 immunoglobulin G 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 immunoglobulin subtypes that are not detected by the immunoassay used [2]. If congenital TTP (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 a high suspicion for iTTP, caplacizumab might be started before receiving ADAMTS13 activity results. We nevertheless urge that rapid ADAMTS13 activity evaluation, ideally within 24 h (to 72 h) 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 <10%, caplacizumab should be started according to the Phase III Trial with Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura (HERCULES) 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 guidelines [1], we urge not starting caplacizumab if ADAMTS13 activity testing is not available. Overall, it is important to receive ADAMTS13 results as quickly as possible and/or to transfer the patient with high suspicion of TTP to an experienced centre.

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 nine eligible studies [10]. Most of the studies treated patients with 375 mg/m^2 weekly for one to four 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 ≥150 × 10^9/L and lactate dehydrogenase <1.5 times the upper limit of normal and no clinical evidence of new or progressive ischaemic organ injury [18], is achieved. A clinical response should be critically differentiated from a clinical remission,

Table 1. Summarized ISTH guideline recommendations. Adapted from Zhang *et al.* [1, 2]

Chapter	Recommendation	Setting	Intervention	Strength
Diagnosis	Recommendation 1	Access to ADAMTS13 testing and patients with a high clinical suspicion of iTTP[a]	Step 1: Plasma sample for ADAMTS13 testing before an initiation of TPE or use of any blood product Step 2: TPE and corticosteroids without waiting for the results of ADAMTS13 testing Step 3: Consider early administration of caplacizumab before receiving plasma ADAMTS13 activity results Step 4: If ADAMTS13 test is positive[b]: continue caplacizumab If ADAMTS13 test is negative[c]: stop caplacizumab and consider other diagnoses 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	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[d]	Step 1: Plasma sample for ADAMTS13 testing 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: No caplacizumab until the result of plasma ADAMTS13 activity is available Step 4: If ADAMTS13 test is positive[b]: consider adding caplacizumab and rituximab If ADAMTS13 test is negative[c]: do not start caplacizumab and consider other diagnoses	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 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 non-use 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 non-use of rituximab for prophylaxis	A conditional recommendation in the context of very low certainty evidence

Table 1. Continued

Chapter	Recommendation	Setting	Intervention	Strength
	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 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

[a]High clinical suspicion of TTP: ≥90% pretest probability of iTTP based on clinical assessment or a formal clinical risk assessment method such as PLASMIC score or French score.
[b]Positive result: ADAMST13 activity <10 IU/dL (or <10% of normal).
[c]Negative result: ADAMTS13 activity >20 IU/dL (or >20% of normal).
[d]Intermediate or low clinical suspicion: based on clinical assessment or a formal clinical risk assessment method such as PLASMIC score or French score.

Table 2. French and PLASMIC scores to predict the likelihood of severe ADAMTS13 deficiency. Adapted from Zhang *et al.* [2]

Parameters	French score	PLASMIC score
Platelet count	$<30 \times 10^9$/L (+1)	$<30 \times 10^9$/L (+1)
Serum creatinine	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Haemolysis	–[a]	(+1)
Indirect bilirubin >2 mg/dL or reticulocyte count >2.5% or undetectable haptoglobin		
No active cancer in the previous year	–[a]	(+1)
No history of solid organ transplantation or stem cell transplantation	–[a]	(+1)
INR <1.5	–[a]	(+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%

INR, international normalized ratio; MCV, mean corpuscular value.
[a]French score considered patients with thrombotic microangiopathy that included haemolysis 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. N/A: not incorporated in the French score.

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% of the lower limit of normal (LLN), whereas complete ADAMTS13 remission is reached when ADAMTS13 is greater than or equal to the 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 to $<150 \times 10^9$/L with or without evidence of new ischaemic organ injury after a clinical remission. Other causes of thrombocytopaenia need to be ruled out and the

clinical relapse needs to be confirmed by detection of severe ADAMTS13 deficiency. An ADAMTS13 relapse is defined as ADAMTS13 levels <20% after an ADAMTS13 complete or partial remission [18]. According to the ISTH guidelines [1], starting 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 favour preemptive rituximab treatment in such situations to reinduce 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 guidelines [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 being conducted (registered at www.clinicaltrials.gov as NCT03393975 and NCT03922308), which are expected to have a 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 should be treated for TTP by experienced specialists. 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 are 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 favours 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 foetus [21]. For pregnant patients with cTTP in remission, the ERBP working group endorses the recommendation of the ISTH guidelines to prophylactically treat patients with plasma infusions [1].

CONCLUSION

Not only treatment regimens, but also diagnostic approaches, have dramatically changed in TTP in recent years. The 2020 ISTH guidelines 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 thrombocytopaenic purpura [1, 2]. However, the ERBP working group wants to draw attention to a number of considerations that enhance the clinical applicability of the guidelines in Europe.

First we urge establishing ADAMTS13 activity measurements in TTP centres across Europe to shorten the time to TTP diagnosis and to prevent a clinical relapse in the follow-up period.

Second, TPE and corticosteroids remain cornerstones of acute iTTP treatment, but the addition of 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].

Third, caplacizumab improved therapy of acute iTTP treatment by reducing unfavourable outcomes such as the risk of refractoriness and acute clinical exacerbation [14]. Recombinant ADAMTS13 may be added to the iTTP armamentarium for the treatment of acute episodes and is currently being tested in clinical studies.

ACKNOWLEDGEMENTS

This article was written on behalf of the ERBP, which is an official body of the European Renal Association.

CONFLICT OF INTEREST STATEMENT

K.E. is a member of advisory boards for and received speaker fees from Sanofi-Genzyme and Alexion. P.K. received consultancy and speaker fees and research and travel grants from Ablynx, Sanofi-Genzyme, Shire (a Takeda company), Alexion, CSL Behring, Roche, Novo Nordisk and Sobi. J.J.M. received speaker and consultant fees from Ablynx, Sanofi-Genzyme and Alexion. P.T.B. is a member of advisory boards for and received speaker honoraria from Alexion, Sanofi-Genzyme, Bayer, Vifor, AstraZeneca and Pfizer. P.C. is a member of advisory boards for and received speaker fees from Sanofi, Alexion, Janssen and Takeda. M.S. is a member of advisory boards for and received speaker fees from Sanofi, Takeda, Octapharma, Novartis, Alexion. M.C.H., S.A.B., L.G. and U.T. report no conflicts of interest.

REFERENCES

1. Zheng XL, Vesely SK, Cataland SR *et al.* ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2020; 18: 2496–2502
2. Zheng XL, Vesely SK, Cataland SR *et al.* ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2020; 18: 2486–2495
3. Kremer Hovinga JA, Coppo P, Lammle B *et al.* Thrombotic thrombocytopenic purpura. *Nat Rev Dis Primers* 2017; 3: 17020
4. Scully M, Cataland S, Coppo P *et al.* Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost* 2017; 15: 312–322
5. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: toward targeted therapy and precision medicine. *Res Pract Thromb Haemost* 2019; 3: 26–37
6. Jin M, Casper TC, Cataland SR *et al.* Relationship between ADAMTS13 activity in clinical remission and the risk of TTP relapse. *Br J Haematol* 2008; 141: 651–658

7. Mazepa MA, Masias C, Chaturvedi S. How targeted therapy disrupts the treatment paradigm for acquired TTP: the risks, benefits, and unknowns. *Blood* 2019; 134: 415–420
8. Hie M, Gay J, Galicier L *et al.* Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. *Blood* 2014; 124: 204–210
9. Jestin M, Benhamou Y, Schelpe AS *et al.* Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. *Blood* 2018; 132: 2143–2153
10. Owattanapanich W, Wongprasert C, Rotchanapanya W *et al.* Comparison of the long-term remission of rituximab and conventional treatment for acquired thrombotic thrombocytopenic purpura: a systematic review and meta-analysis. *Clin Appl Thromb Hemost* 2019; 25: 1076029618825309
11. Westwood JP, Thomas M, Alwan F *et al.* Rituximab prophylaxis to prevent thrombotic thrombocytopenic purpura relapse: outcome and evaluation of dosing regimens. *Blood Adv* 2017; 1: 1159–1166
12. Westwood JP, Webster H, McGuckin S *et al.* Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. *J Thromb Haemost* 2013; 11: 481–490
13. Peyvandi F, Scully M, Kremer Hovinga JA *et al.* Caplacizumab for acquired thrombotic thrombocytopenic purpura. *N Engl J Med* 2016; 374: 511–522
14. Scully M, Cataland SR, Peyvandi F *et al.* Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med* 2019; 380: 335–346
15. Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting, and evaluation in health care. *Prev Med* 2010; 51: 421–424
16. Bendapudi PK, Hurwitz S, Fry A *et al.* Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol* 2017; 4: e157–e164
17. Coppo P, Schwarzinger M, Buffet M *et al.* Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. *PLoS One* 2010; 5: e10208
18. Cuker A, Cataland SR, Coppo P *et al.* Redefining outcomes in immune TTP: an international working group consensus report. *Blood* 2021; 137: 1855–1861
19. Volker LA, Kaufeld J, Miesbach W *et al.* Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. *Blood Adv* 2020; 4: 3085–3092
20. Perrotta K, Kiernan E, Bandoli G *et al.* Pregnancy outcomes following maternal treatment with rituximab prior to or during pregnancy: a case series. *Rheumatol Adv Pract* 2021; 5: rkaa074
21. Kuhne L, Volker LA, Hagmann H *et al.* First use of the anti-VWF nanobody caplacizumab to treat iTTP in pregnancy. *Br J Haematol* 2022; 196: e30–e33

Received: 6.1.2022; Editorial decision: 19.1.2022