Diagnosis and clinical management of thrombotic thrombocytopenic purpura (TTP): a consensus statement from the TTP Catalan group

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Thrombotic thrombocytopenic purpura (TTP) is a low prevalence disease characterized by severe deficiency of the enzyme ADAMTS13, leading to the development of thrombotic microangiopathy (TMA) and often resulting in severe organ disfunction. TTP is an extremely serious condition and, therefore, timely and appropriate treatment is critical to prevent life-threatening complications.

Over the past 25 years, significant advances in the understanding of the pathophysiology of immune TTP have led to the development of readily available techniques for measuring ADAMTS13 levels, as well as new drugs that are particularly effective in the acute phase and in preventing relapses. These developments have improved the course of the disease.

Given the complexity of the disease and its various clinical and laboratory manifestations, early diagnosis and treatment can be challenging.

To address this challenge, a group of experienced professionals from the Catalan TTP group have developed this consensus statement to standardize terminology, diagnosis, treatment and follow up for immune TTP, based on currently available scientific evidence in the field. This guidance document aims to provide healthcare professionals with a comprehensive tool to make more accurate and timely diagnosis of TTP and improve patient outcomes.

Keywords: ADAMTS13, plasma exchange, thrombotic microangiopathies, thrombotic thrombocytopenic purpura.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a low- prevalence disease, 6 cases per million per year in UK adults (variability ranging from 1.5 to 6 cases per million depending on demographic factors), which presents with a thrombotic microangiopathy (TMA) with the potential for severe organ dysfunction[1,2]. TTP has a mortality rate as high as 90% if appropriate treatment is not initiated promptly[1]. TTP incidence is by far higher in women[2]. Sex/gender differences should be considered in the future research in order to personalize diagnostic and maybe therapeutic approach.

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TTP is characterized by severe deficiency of ADAMTS13 (A Disintegrin and Metalloproteinase with Thrombospondin-1motifs, 13th member of the family), an enzyme responsible for cleaving high molecular weight multimers (HMWM) of the Von Willebrand factor (VWF) secreted by the vascular endothelium[3].

ADAMTS13 deficit may be autoimmune, due to the presence of anti-ADAMTS13 antibodies, usually of the IgG type, or congenital, due to mutations in the ADAMTS13 gene, that prevent its synthesis (Upshaw-Shulman syndrome)[4].

The onset of clinical symptoms of TTP is associated with a severe reduction of ADAMTS13 (<10%), often triggered by a secondary event, such as infections, inflammatory processes, or pregnancy. This deficiency leads to spontaneous and massive platelet aggregation, resulting in the formation of hyaline microthrombi that clog microvessels[5,6].

This obstruction leads to tissue ischemia and damage to various organs and tissues, due to altered tissue perfusion, especially the central nervous system and heart. Renal involvement is usually moderate (creatinine serum <200 umol/L) and normally isolated as proteinuria/hematuria. Acute kidney injury is unusual in TTP. However, a relevant and persistent increase of creatinine is observed in other microangiopathies (as HUS).

Similarly, platelet consumption leads to severe thrombocytopenia (usually platelets 30×10^9/L) with the corresponding bleeding risk. Small vessel obstruction also causes red blood cell lysis and mechanical hemolysis (in the presence of schistocytes). TTP usually occurs in the form of acute episodes, relapses, and exacerbations[5,6].

Because of the overlapping clinical and analytical manifestations, the differential diagnosis of TTP can be challenging and requires exclusion of other possible conditions[7].

Over the past 25 years, the understanding of the physiopathology of immune-mediated TTP has enabled the development of readily accessible techniques for measuring ADAMTS13 levels, as well as new drugs that are particularly useful in the acute phase of the disease, when morbidity and mortality are more elevated (typically within the first 10 days)[8].

The aim of this review is to reach a consensus on the emergency procedures and subsequent management of immune TTP cases by unifying and standardizing terminology, criteria, and clinical practice in all hospitals in Catalonia where emergency plasma exchanges are performed.

The recommendations contained in this document were prepared according to the AGREE methodology. A bibliographic search of the literature published in the last twenty-five years was performed.

MATERIALS AND METHODS

A multidisciplinary team of health care professionals experienced in the TTP field was assembled to develop this consensus statement.

The first step in the development process was a thorough review of the relevant literature published over the last 25 years using electronic databases such as EMBASE, MEDLINE, and the Cochrane Library Central Registry. We excluded letters, and case reports. The key words used were ADAMTS13, plasma exchange, thrombotic microangiopathies and thrombotic thrombocytopenic purpura.

This search included guidelines and consensus statements from international societies, as well as recent studies on TTP diagnosis and management with a particular focus on articles from 2010 to current date.

Next, a series of meetings was held to discuss the literature and to reach consensus on the key points related to TTP diagnosis and treatment. For each statement, panel members voted to agree with the statement, disagree with the statement or the statement should be redefined because of insufficient evidence.

The voters had the opportunity to provide comments or suggestions with their votes.

Consensus was defined as 70% of members responding with agree.

The recommendations contained in this consensus statement were prepared according to the AGREE methodology. The questions were formulated in a structured manner according to the PICO format with the aim to highlighting relevant points and common clinical practice.

The two authors who reported having conflicts of interest recused from decisions concerning caplacizumab.

An initial consensus statement was drafted and then reviewed and corrected by the group members. The final document was edited using the same methodology.

Finally, the consensus statement was finalized and approved by all team members before publication.

RESULTS

Definitions: response, exacerbation, remission, relapse, and refractoriness

The Standardized definitions of response, exacerbation, remission, and relapse were first proposed in 2003 and subsequently amended in 2017[7,9]. They are primarily based on the platelet count to indicate the discontinuation of plasma exchange. With the introduction of new therapeutic strategies, the determination of the activity of ADAMTS13 has become a fundamental tool and, therefore, a new review and standardization is needed[7,9].

Recommended definitions

If clinical exacerbations occur, physicians will be forced to re-initiate TPE. A 10% decrease in platelets count within 24 hours after normalization is considered high-risk for exacerbation and requires close monitoring and extreme precautions (**Table I**).

It is recommended to perform two determinations of ADAMTS13 activity to ensure accurate results (**Table I**).

Diagnosis: emergency response to a suspected thrombotic microangiopathy (TMA)

The suspicion will arise in the presence of: Direct Coombs-negative microangiopathic hemolytic anemia with grade IV thrombocytopenia without other causes.

Recommended diagnostic tests

Analysis (mandatory tests to be performed in hospital emergencies):

- complete blood count with reticulocytes and coagulation (PT, aPTT, fibrinogen);
- direct Coombs test;
- peripheral blood smear with schistocyte count;
- biochemistry with ionogram, kidney and liver function, hemolysis parameters (total bilirubin and LDH);
- urinary sediment;
- troponins (>0.1 microg/L prognostic marker of severity and organic involvement)[10];
- electrocardiogram (EKG);
- ADAMTS13 (activity and antibody detection) before any plasma infusion. Blood sample to be collected before plasma exchange is started (*Online Supplementary Content*, **Table SI**).

The study will be completed with the following determinations:

- daily blood count during the acute phase with peripheral blood smears for periodic counting of schistocytes according to clinical criteria;
- biochemistry: electrolytes, urea, creatinine, liver function and hemolysis parameters (LDH, total, direct, and indirect bilirubin, haptoglobin). The hemolysis parameters should be monitored periodically until they stabilize;
- serologies: HBsAg, anti-HBc, anti-HCV, anti-HIV;
- autoimmunity study: antinuclear antibodies. Expand the autoimmune study if more specific disorders such as lupus or antiphospholipid syndrome are suspected.

Table I - *Recommended definitions*

Clinical response	The platelet count remains >125×10^9/L + LDH <1.5 upper limit of normal (ULN) after discontinuation of therapeutic plasma exchange (TPE) without evidence of new organ damage or worsening of already existing organ damage. The platelet count should be considered according to each patient's situation
Clinical exacerbation	A fall in the platelet count <125×10^9/L after achieving clinical response (in the absence of other causes of thrombocytopenia) with or without evidence of new organ damage or worsening of already existing organ damage, within 30 consecutive days of the last TPE or anti-VWF administration
Clinical remission	Clinical response maintained beyond 30 days of the last TPE and last dose of anti-VWF, or achievement of complete or partial activity of ADAMTS13 (whichever happens first)
ADAMTS13 partial remission	Clinical remission and ADAMTS13 activity ≥20% (threshold related to protection against clinical relapse)
ADAMTS13 complete remission	Clinical remission and normal ADAMTS13 activity
ADAMTS13 relapse	Decrease in ADAMTS13 level <20% after achieving ADAMTS13 remission (partial or complete)
Clinical relapse	A fall in the platelet count <125×10^9/L after achieving clinical remission (in the absence of other causes of thrombocytopenia) with or without evidence of new organ damage or worsening of already existing organ damage. Confirmation of severe ADAMTS13 deficiency is required
Refractoriness	Platelets <50×10^9/L after the first 5 TPE or clinical or analytical worsening during daily treatment with TPE

Adapted from from Cuker A *et al.*[9]

The following additional studies are recommended in cases where there is a significant renal involvement, a recent (i.e., less than 1 year previous) cancer or transplant, or clinical presentation of diarrhea:

- a complement study, for aHUS evaluation of C5b9 deposit on endothelial cells is useful for diagnosis and, especially, to assess response to treatment;
- shiga toxin;
- stool cultures;
- additionally, a neoplasm screening is often necessary.

When obtaining a patient's medical history, it is important to rule out the use of the following drugs:

- thienopyridines (ticlopidine, clopidogrel);
- calcineurin inhibitors (cyclosporine, tacrolimus);
- mTOR inhibitors (sirolimus, everolimus);
- antineoplastics (mitomycin, gemcitabine);
- quinine;
- interferon;
- estrogens, progesterone;
- recently, other drugs such as bevacizumab, carfilzomib, ixazomib, and palbociclib.

We will suspect the possibility of an acute episode of immune-mediated TTP that needs prompt treatment when:

- we are faced with suggestive clinical symptoms, altered hemolysis parameters, platelet counts $<30\times10^9$/L, microangiopathic hemolytic anemia with presence of schistocytes with negative direct combs (DC) test results, with no other obvious cause);
- we encounter suggestive symptoms in a person with a history of immune TTP episodes;
- clinical signs and symptoms can be vague and overlapping with other TMA.

For the measurement of ADAMTS13 activity we use:

- the PLASMIC Score, which is a simple algorithm that calculates the probability of measuring less than or equal to 10% ADAMTS13 activity in a patient with microangiopathic anemia and thrombocytopenia. A high score (6-7) correlates with a sensitivity of 90% and a specificity of 92%[11,12] (*Online Supplementary Content*, **Table SII**);
- measurement of ADAMTS13 activity and anti-ADAMTS13 antibodies should be considered a priority, and performed prior to plasma infusion, with results available within a maximum of 24-48 hours.

Treatment: for a first episode of immune-mediated TTP (Figure 1)

Recommended treatment and monitoring in case of high clinical-analytical suspicion or high PLASMIC Score

We would like to highlight that PLASMIC Score is not intended to replace the ADAMTS13 dosing, but is a helpful tool to orient physicians[13-16].

Recommendations for first- line treatment

Given the severity of the disease during the acute phase and the intrinsic pathogenesis, we recommend first-line treatment with: therapeutic plasma exchange + immunosuppressive treatment + caplacizumab.

A) *Therapeutic plasma exchange (TPE)- enables the elimination of the antibody and replenishment of ADAMTS13*

- TPE should be initiated as soon as possible, ideally within 4 hours and never later than 10 hours , in patients with an intermediate or high probability PLASMIC Score. It is necessary to inform the specialists of each hospital who handle a possible TTP as well as the Blood and Tissue Bank;
- in cases where a delay in treatment is anticipated (transfer or other situations that may prevent treatment from starting within 10 hours), plasma should be infused immediately (ideally a minimum of 20 mL/kg, depending on tolerance). The patient should be transferred with a medicalized ambulance to a center where emergency apheresis treatment can be performed;
- between 1 and 1.5 volumes of plasma should be replaced (there is no clear consensus on this);
- when treated concomitantly with caplacizumab, it is necessary to perform daily procedure until the platelet count reaches $>125\times10^9$ for two consecutive days, normalization of LDH and clinical improvement or stabilization if there was stablished or expected sequels. Subsequently, the TPEs can be stopped.

Types of exchange solution

The Blood Bank offers three types of plasma that can be used interchangeably:

1. fresh frozen plasma inactivated with methylene blue or with amotosalen;
2. quarantined plasma;
3. cryoprecipitate supernatant (combined with one of the other two and monitoring of clotting factors).

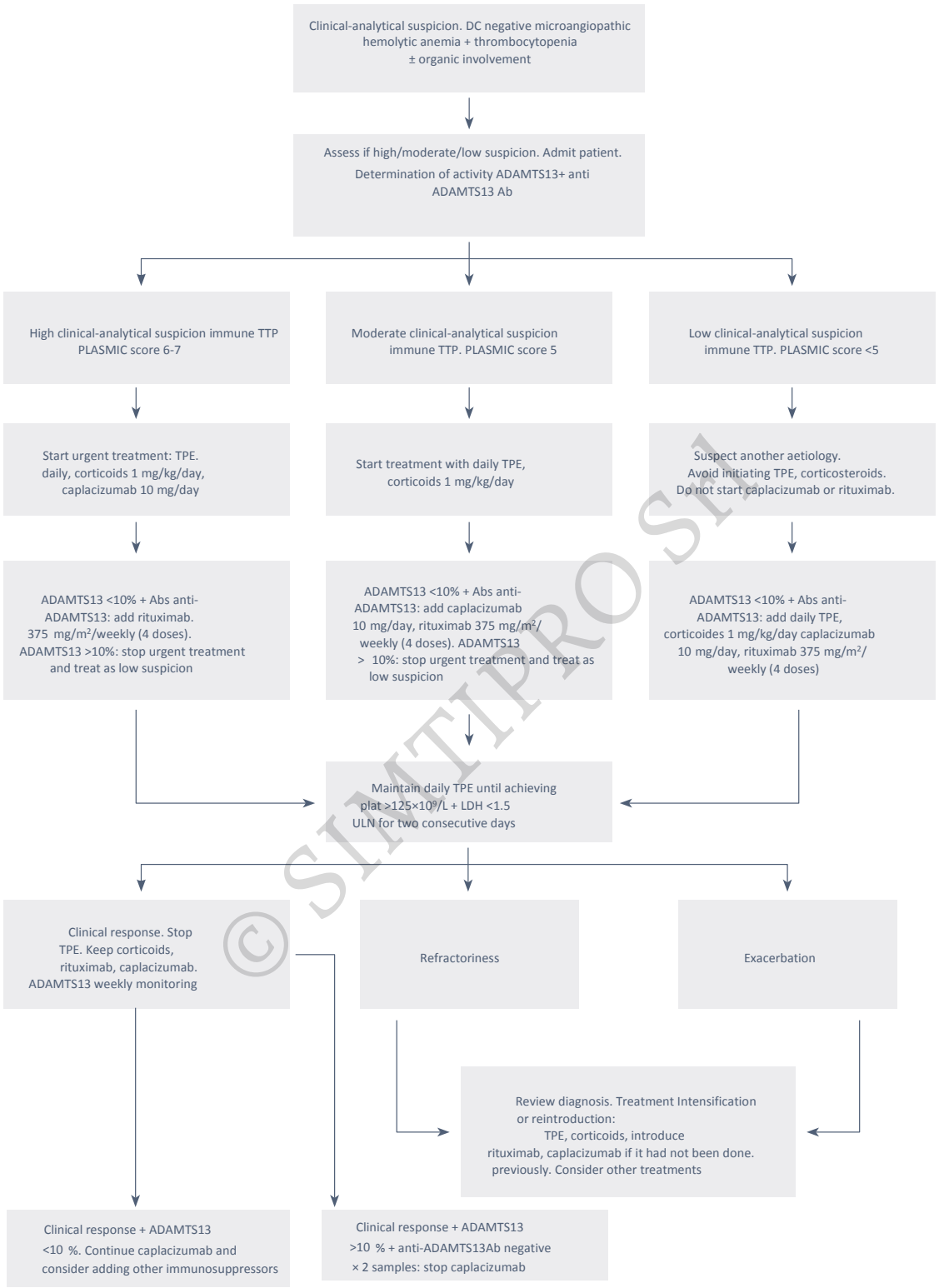

Figure 1 - Diagnostic-therapeutic algorithm for immune TTP
Figure based on previous publications and our own experience. Ab: antibodies; DC: direct coombs; LDH: Lactate dehydrogenase; TPE: therapeutic plasma exchange; TTP: thrombotic thrombocytopenic purpura.

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- It is possible to consider using 5% albumin for TPE once the platelet count reaches >125×10^9 platelets on two consecutive occasions. In these cases, the administration of IV immunoglobulins (100 mg/kg post-TPE or 200 mg/kg every 2 TPE) may also be considered.

B) *Immunosuppressive treatment*

- Corticoids (immunosuppressant)
  Immediate start. 1 mg/kg EV Methylprednisolone to be administered after TPE. Tapering according to clinical criteria.
- Rituximab (B lymphocytes modulation)
  Originally, its use was suggested for patients who responded poorly to initial treatment. The British group showed a decrease in relapses and a shorter hospital stay when using it as first line therapy. These results were confirmed by the French reference group and the Oklahoma registry[17,18].
  Dosage: 375 mg/m^2 on a weekly basis for 4 weeks; it is crucial to administer it 24 hours prior to the TPE or immediately after the therapy is completed.
  Rituximab should be initiated when a severe deficiency in ADAMTS13 activity and the presence of anti-ADAMTS13 antibodies have been confirmed.
  Prior to administering rituximab, it is important to check for HBV serologies (and consider antiviral prophylaxis if the patient is HBV core positive).

C) *Caplacizumab (ALX-0081 inhibition of platelet-VWF interaction)*

Caplacizumab (ALX-0081) is a nanoantibody that targets the A1 region of VWF and specifically inhibits the interaction between this domain and platelet glycoprotein Ib. Clinical trials, such as TITAN (phase II)[19] and HERCULES (phase III)[20], have demonstrated its effectiveness and safety in treating immune TTP for the first time. Its use has been linked to faster platelet count recovery, fewer TPEs, shorter hospital stays, reduced severe and early thromboembolic events and prevents refractoriness. The most common side effects include mucocutaneous and gynecological bleedings. Careful consideration is needed when using caplacizumab in fragile patients, or those taking oral anticoagulants or antiplatelet medications[21].

It was approved by the EMA (September 2018) and the US FDA (February 2019) as a first line treatment for adults with immune TTP associated with TPE and immunosuppressive treatment. It is recommended to deliver and review the appropriate material with the patient to minimize the associated risks of its use[22].

Dosage

Day 1: 10 mg intravenous Initial loading dose prior to TPE. Subsequently, 10 mg will be administered subcutaneously after the TPE.

The 10 mg subcutaneous daily dose (post-TPE, if done) will be maintained until ADAMTS13 activity is at least higher than 10% and autoantibodies are negative in two consecutive samples.

It is proposed that a stock of caplacizumab is made available at hospital pharmacies to ensure immediate treatment initiation.

Recommendations for monitoring

Monitoring of ADAMTS13 and anticoagulants during an acute episode (a sample of plasma will be collected in a citrate tube and all samples will be sent to the hospital's hemostasis laboratory for analysis (see *Online Supplementary Content*, **Table SI** for details):

- a sample of plasma should be taken at time 0 (it is crucial that this is done before any plasma infusion);
- up to day +7;
- up to day +14;
- up to day +21;
- up to day +28;
- every week up until the 56th day after the last plasma exchange[23].

Recommendations for treatment in case of refractoriness/exacerbation/clinical relapse

Approximately 10-15% of patients will not respond well to the combined treatment with TPE + corticosteroids, and between 15-53% of patients with an acute episode may experience an exacerbation[21].

The data currently available suggests that using a triple treatment approach (TPE+ immunosuppressive therapy + anti-VWF) as first-line treatment can significantly reduce the rates of exacerbations, relapses, and mortality in the acute phase, compared to historical cohort data[24,25].

In a situation of refractoriness, it is necessary to re-evaluate the diagnosis with a new determination of ADAMTS13 + inhibitor activity and rule out potential triggering factors such as sepsis, underlying neoplasms, and basic treatments. It is necessary to tailor the treatment to each individual patient based on the specific situation.

Possible options include:

- intensify treatment with TPE (process 1.5 plasma volumes) or reintroduce if it had stopped;
- intensify treatment with corticosteroids (methylprednisolone 1 g/day IV for 3 days);
- start rituximab if it has not been done in the first line (check the antibodies detection beforehand);
- start caplacizumab if it has not been done in the first line. We will reintroduce the treatment with caplacizumab if this has already been suspended (the same doses).

Recommendations in case of non-response to the previous treatment options

Consider the use of cyclophosphamide, vincristine, bortezomib, N-acetylcysteine, cyclosporine, mycophenolate mofetil (MMF), daratumumab or splenectomy. These options are also valid for situations of exacerbation and relapse.

Recommendations on other relevant points

- It is necessary to assess the need for TPE in a critical care setting or in the emergency room with monitoring in case there is no intensive care bed available.
- Supportive treatment will be given if necessary and the transfusion of red blood cells will be consider based on clinical and laboratory criteria.
- Platelet transfusion will be contraindicated prophylactically, it should only be considered in cases of severe bleeding with stage IV thrombocytopenia and/or the need for invasive procedures. The transfusion of prophylactic platelets prior to the placement of a central line will be considered according to the risk/benefit ratio and, we recommend that it should only be considered if platelet counts are below 15×10^9/L.
- The administration of prophylactic low -molecular-weight heparin is recommended if platelet count is equal or greater than 50×10^9/L.
- Peripheral venous access will be assessed and, if feasible, will be prioritized. If a CVC is necessary, it should be double lumen (8 to 12.5 F).
- It would be desirable to have a minimum stock of caplacizumab available at hospital pharmacies to ensure its use in the critical phase of the disease.

Recommendations in case of moderate/low clinical-analytical immune TTP suspicion

The patient must be admitted to hospital for further evaluation. This includes completing the TMA study (with analytical monitoring) and performing additional tests.

It is necessary to determine ADAMTS13 activity and anti-ADAMTS13 antibodies.

The PLASMIC Score should be applied:

- if the score is 5 or higher and there is clinical justification, TPE and treatment with corticosteroids can be initiated. The use of caplacizumab should also be considered when ADAMTS13 results are pending;
- a score of less than 5 should lead us to suspect another underlying etiology;
- it should be noted that this score may be less effective in cases associated with systemic erythematous lupus, primary HIV infection or in pregnant women.

Follow-up: for immune TTP outpatients

Once the patient is discharged, it is recommended to establish regular follow-up appointments to monitor their clinical and laboratory progress (**Table II**).

Table II - *Outpatient follow-up*

Outpatient follow-up	ADAMTS13 activity/antibody	Blood count/ hemolysis parameters
1st month	Weekly	Weekly
2nd-3rd month	Monthly	Every 2 weeks
3rd-6th month	Quarterly	Monthly
6th-12th month	Quarterly	Semesterly
1st-2nd year	Semesterly	Semesterly
>2nd year	Semesterly	Annual

Long-term side effects of TTP have been described, mainly psychiatric complications (such as depression), cognitive impairment, hypertension, and microalbuminuria. These should be closely monitored[26].

CONCLUSIONS

This clinical consensus statement is intended to serve as a valuable tool for health care professionals to standardize the diagnosis, treatment and follow up of immune TTP. It is based on the latest published evidence and the collective experience of skilled professionals in the field. It is expected that its implementation will lead to more accurate and timely diagnosis and improved patient outcomes.

It is also important to note that further research and updates are needed to further improve the understanding and management of this complex disease.

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DISCLAIMER

The Authors of this consensus statement have made every effort to ensure the accuracy and reliability of the information provided in this document. However, the Authors do not assume any liability for any errors, omissions, or inaccuracies that may be contained in this document.

AUTHORS' CONTRIBUTIONS

NG led the development of the consensus statement, coordinated the consensus process, and wrote the initial draft of the manuscript. All other Authors contributed to the development of the consensus statement, reviewed the literature and provided input on the manuscript.
All Authors read and approved the final manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST

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NG, SO, XS, JC, MD, ABM, ÁA, MS, IH, JMS, AL, JG, LE, LM, GJF, JL, RC, JAD, VP, DV and JRG declare that there are no conflicts of interest relevant to this article.

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