CONSENSUS STATEMENT

Immune thrombotic thrombocytopenic purpura: clinical suspicion and basic management in emergency departments — an expert review and consensus statement from the Spanish societies of hematology and hemotherapy (SEHH) and emergency medicine (SEMES)

Cristina Pascual-Izquierdo[1], Pascual Piñera Salmerón[2], Francisco Temboury Ruiz[3], David Valcárcel Ferreiras[4], Sonia Jiménez Hernández[5], Ramón Salinas Argente[6], Carmen del Arco Galán[7], Javier de la Rubia Comos[8]

Acquired or immune thrombotic thrombocytopenic purpura (TTP) are thrombotic microangiopathies associated with high mortality if treatment is not started early. Onset is usually sudden, meaning that the condition is often diagnosed in hospital emergency departments, where TTP must be suspected as early as possible. These guidelines were drafted by specialists in emergency medicine and hematology to cover the diagnosis, referral, and treatment of patients suspected of immune-mediated TTP who require emergency care. Immune TTP should be suspected whenever a patient presents with hemolytic microangiopathy and has a negative Coombs test, and thrombocytopenia, possibly in conjunction with fever and neurologic and cardiac alterations. If one of the existing diagnostic algorithms indicates there is a high probability that the patient has immune TTP, plasma exchange therapy should be started along with immunosuppressants. Treatment with caplacizumab should also be considered. The patient should be referred immediately to the hematology department within the same hospital or a referral hospital.

Keywords: Thrombotic thrombocytopenic purpura. Thrombotic microangiopathy. Plasma exchange therapy. Emergency department. Diagnosis. Treatment.

Púrpura trombocitopénica trombótica inmune: sospecha y manejo básico en los servicios de urgencias. Revisión y consenso de un grupo de expertos de las sociedades científicas SEHH y SEMES

La púrpura trombótica trombocitopénica adquirida o inmune (PTTi) es una microangiopatía trombótica (MAT) con una elevada mortalidad si no se instaura un tratamiento precoz. El inicio habitualmente brusco de la enfermedad hace que, en la mayoría de los pacientes, el diagnóstico inicial se haga en los servicios de urgencias hospitalarios (SUH), donde se debe sospechar esta entidad con la mayor inmediatez posible. Esta guía, elaborada por profesionales de Medicina de Urgencias y de Hematología, establece unas recomendaciones en cuanto al diagnóstico, derivación y tratamiento de los pacientes con sospecha de PTTi en los SUH. Se debe sospechar PTTi en todo paciente que presente una anemia hemolítica microangiopática, prueba de *Coombs* directo negativa y trombocitopenia pudiendo asociar, además, fiebre, alteraciones neurológicas y cardiacas. Si tras la aplicación de alguno de los algoritmos diagnósticos existentes, hay una alta probabilidad de que el paciente presente una PTTi, debería iniciarse tratamiento con recambio plasmático, inmunosupresores y valorar el inicio de caplacizumab. Además, debe gestionarse el traslado inmediato de los pacientes al Servicio de Hematología, bien del mismo centro o a uno de referencia.

Palabras clave: Púrpura trombótica trombocitopénica. Microangiopatía trombótica. Recambio plasmático. Urgencias. Diagnóstico. Tratamiento.

Author Affiliations:
[1]Hematology and Hemotherapy Hemotherapy, Hospital General Universitario Gregorio Marañón, Madrid. Instituto de Investigación Gregorio Marañón, Member of SEHH.
[2]Emergency Department, Hospital General General Universitario Reina Sofía, Murcia, Spain.
[3]Emergency Department, Hospital Universitario Virgen de la Victoria, Málaga, Spain.
[4]Hematology Service, Vall d'Hebron Institut Oncologic (VHIO), Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Spain, Member of SEHH.
[5]Emergency Department, Hospital Clínic, IDIBAPS, Barcelona, Spain.
[6]Banc de Sang i Teixits, Barcelona, Spain. Member of SEHH.
[7]Emergency Department, Hospital Universitario La Princesa, Madrid. Research Institute La Princesa, Madrid, Spain. SEMES Scientific Secretary.
[8]Hematology and Hemotherapy and Hemotherapy, HUP La Fe. Faculty of Medicine, Catholic University of Valencia, Valencia, Spain. Member of SEHH.

Author Contributions:
All authors have confirmed their authorship in the document of author responsibilities, publication agreement and assignment of rights to EMERGENCIAS.

Corresponding Author:
Cristina Pascual Izquierdo
Hematology and Hemotherapy Service.
Hospital General Universitario Gregorio Marañón
C/ Doctor Esquerdo, 46
28007 Madrid, Spain

Email:
crisizquierdo3@yahoo.es

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Introduction

Acquired thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) of autoimmune origin caused by the development of antibodies against the enzyme ADAMTS13.[1,2] This metalloprotease is essential for fragmenting von Willebrand factor (vWF) multimers and preventing the development of spontaneous thrombosis, especially in small vessels.[3] The decrease of its activity in TTP is associated with an increase of higher molecular weight vWF multimers in the circulation and an increase in the risk of thrombus generation mainly in the microvasculature, which induces the development of thrombocytopenia due to platelet consumption, microangiopathic hemolysis with the appearance of fragmented red blood cells (schistocytes) and ischemic organ damage of variable intensity.[4] It is generally assumed that ADAMTS13 activity of less than 10% is diagnostic of TTP.[1]

TTP is a rare disease, with an incidence in Spain of 2.6 cases/million inhabitants per year.[5] The peak age of presentation is 30-40 years, and it is more frequent in

women and in the black race.[6] The etiology of TTP. is not clearly known. In less than half of the cases it is possible to identify a precipitating factor, such as certain systemic diseases, infections or vaccinations, while in the rest of the cases it is idiopathic.[7] It is a medical emergency that requires early diagnosis, since without specific treatment mortality exceeds 90%[5,8] and up to 20% in the pre-caplacizumab era.[9] Another characteristic of this disease is recurrence in up to 40% of cases.[8] Its low prevalence, together with the wide variety of symptoms and signs with which it can debut, sometimes makes its clinical suspicion very difficult.[10] Currently, treatment consists of a combination of plasma exchange (PE), immunosuppressive therapy with glucocorticoids, with or without associated rituximab, and caplacizumab.[12] PE aims to eliminate the high molecular weight multimers of vWF and autoantibody, in addition to replenishing ADAMTS13. Corticosteroids try to stop the production of the autoantibody and, recently, a new type of treatment, caplacizumab, which is a bivalent nanoantibody that acts by blocking the A1 domain of vWF, preventing its binding to platelets and, therefore, preventing microvascular thrombosis, has been incorporated.[13] It is the only therapy specifically targeted at the treatment of TTP and its early administration[14,15] has been shown to reduce the duration of thrombocytopenia and the risk of presenting a composite event (death, relapse, thromboembolic event) in patients with TTP.[13] These data have recently been corroborated in several real-life studies, underlining the pivotal role of this drug in the treatment of these patients.[16-18]

In the presence of a disease with a high associated life-threatening risk, suspicion and initial management in the ED is required. After the many advances made in recent years in diagnosis and treatment, this review is the result of a group of specialists in emergency medicine and hematology and hemotherapy with extensive experience in the management of TTP. The main objectives of this consensus have been to describe and identify the alarm criteria for rapid intervention in the event of a suspected diagnosis of TTP, and to coordinate with the hematology service the admission of the patient to the center itself or referral to one that provides the necessary resources for early treatment.

Method

Design

In order to carry out the project, a review and analysis of the existing scientific evidence, national and international guidelines, together with the consensus of a group of experts with extensive clinical and research experience in the subject to be developed, was carried out.

Stages of the project

For the development of the document of recommendations and algorithms for diagnosis and referral of TTP, the following stages have been followed as a result of 3 working meetings:

1. Creation of the working group. For the implementation of the project, a multidisciplinary working group was formed with 8 professionals: 4 hematologists and 4 emergency physicians practicing in reference hospitals and other levels, distributed throughout Spain with special links and dedication to the field of TTP and emergency medicine. The participants in this group were chosen from among hematologists who are members of the Spanish Society of Hematology and Hematotherapy (SEHH, acronym in Spanish) of recognized prestige in the diagnosis, treatment, and follow-up of patients with TTP, both from a clinical and curricular point of view, and from among members of the Spanish Society of Emergency Medicine (SEMES) designated by the scientific secretariat for their knowledge of emergency medicine in hospitals at different levels.

2. Identification of key areas. During the development of the project, all the members of the working group participated in structuring the document, establishing its contents and identifying key aspects. At the first meeting, the main objective of the document was established, which was to draw up recommendations aimed at rapid diagnosis, referral and treatment of patients with suspected TTP in the ED. The questions to be answered, methodology, information to be collected, bibliographic criteria and work schedule in the process of drafting the recommendations were also established.

3. Bibliographic search. The key words used for the literature search were: TTP, thrombotic microangiopathy, plasma exchange, ED, diagnosis and treatment, and all national and international clinical practice guidelines for the management of TTP were reviewed. The PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) was used for the literature review, which was limited to articles published between 2001 and 2021.

4. Analysis and synthesis of the scientific evidence. After reading and evaluating the most relevant guidelines and publications,[1,12,19,20,21] two meetings were organized with the experts to pool information. In the first meeting, the existing protocols in the participating centers were analyzed, their efficacy was assessed and areas for improvement were identified. At the second meeting, once the situation had been analyzed, the bases were established for the preparation of a practical guide of recommendations agreed upon by both specialties, as well as the working algorithms for the diagnosis and referral from the ED to the hematology department of patients from hospitals with different health services and resources in a rapid and efficient manner.

5. Writing of recommendations. The members of the group of experts proceeded to formulate specific recommendations based on the scientific evidence and their clinical experience. A consensus was reached and all the information compiled was written up and, by means of a common discussion, a recommendations

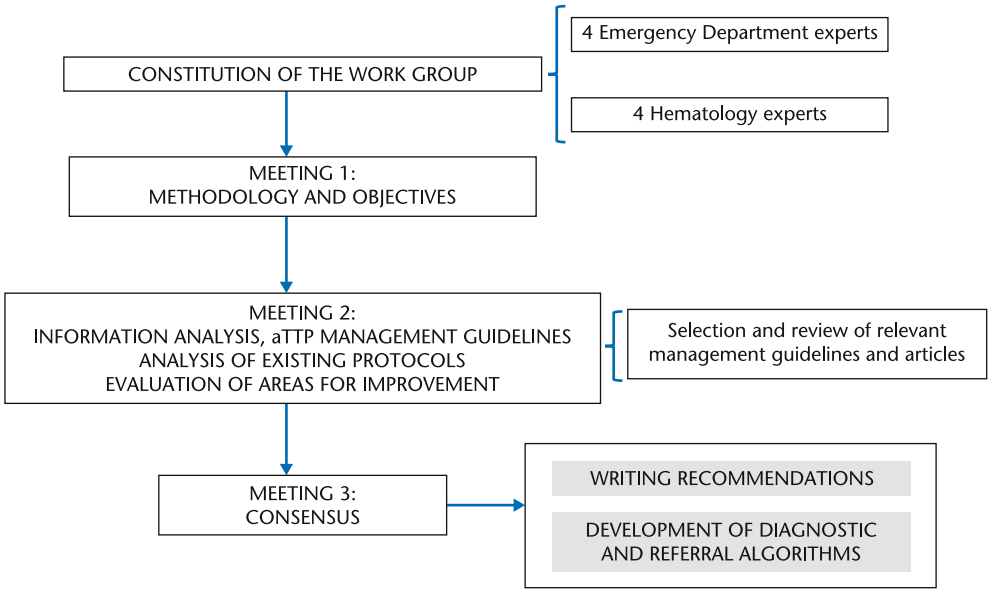

Figure 1. Flowchart of the work developed by the expert group for the diagnosis and management of acquired thrombotic thrombocytopenic purpura in the ED. aTTP: acquired thrombotic thrombocytopenic purpura.

guide was drawn up in which both specialties established the criteria for clinical suspicion, complementary tests, diagnosis, criteria for referral and treatment in the ED, according to the characteristics of the hospital receiving the patient with suspected TTP/MAT.

6. Elaboration of algorithms. Finally, the algorithms for the diagnosis and referral of patients with TTP or suspected TTP were drawn up based on the recommendations previously agreed and drafted. These algorithms are intended to be a tool to assist the ED in the rapid identification and initial management of this rare and fatal pathology.

The flow chart of the work carried out is included in Figure 1. This document has the scientific endorsement of both scientific societies. Approval by the Ethics Committee was not required as it does not deal with patient data.

Results

Clinical suspicion

The classic debut, with the classic presentation described in this disease, consisting of hemolytic anemia with negative direct Coombs, thrombocytopenia, fever, neurological symptoms, and renal failure, only appears in 10% of patients[22] and does not include damage to organs with known repercussions in TTP, such as the heart. Therefore, TTP should be considered as an option in any patient presenting with negative direct Coombs, hemolytic anemia and thrombocytopenia.

Hemolysis is associated with an anemic syndrome (e.g. asthenia, dyspnea, dizziness), jaundice and choluria. Thrombocytopenia is associated with hemorrhagic symptoms of variable intensity ranging from mild mucocutaneous bleeding to intraparenchymal cerebral hemorrhage. Fever appears in approximately 10% of patients,[8] together with other general symptoms such as myalgias and arthralgias.

Thrombus formation in the microvasculature leads to ischemia of different tissues.[10] Cerebral ischemia is the most frequent (60%); it is associated with varied symptoms such as dizziness, motor/sensory focality or even coma,[23] depending on the vascular territory and area affected. The neurological symptoms are usually fluctuating and tend to be recurrent.[23] Although up to 69% may present with nonspecific gastrointestinal symptoms, 35% of patients present with mesenteric ischemia manifested as abdominal pain or sometimes diarrhea.[23] Ischemic cardiac damage is also frequent (25%) and may be asymptomatic (detected by complementary tests such as elevated myocardial enzymes) or develop a complete acute coronary syndrome.[24] Renal injury usually manifests only as isolated proteinuria or hematuria and renal failure is rare (10-27%) and if it occurs, it is usually mild or moderate, unlike that present in hemolytic-uremic syndrome, which is usually more severe. Patients with renal failure may present associated serious complications, such as severe pancreatitis or malignant hypertension.[8]

In 51% of patients presenting with TTP,[7] it is triggered by an underlying process, so any secondary symptom can be associated with the primary disease (Table 1), and the most frequent are autoimmune diseases and bacterial infections. Female sex, black race, obesity and the presence of the HLA DRB1*11 locus are well known predisposing factors.[24-26]

The clinical history should be exhaustive, specifically asking about previous similar episodes, autoimmune diseases, consumption of new drugs, occurrence of intercurrent infections and a rigorous anamnesis by appa-

Table 1. Known triggers of acquired thrombotic thrombocytopenic purpura (aTTP)

TTP desiccants
Idiopathic (50%)
Secondary to underlying process (50%)
– Autoimmune diseases.
– Bacterial infections.
– Pregnancy.
– Cancer.
– HIV infection.
– Drugs.
– Solid organ and hematopoietic progenitor transplantation.
– Others: pancreatitis, surgery.

HIV: human immunodeficiency virus.

ratus and systems. The physical examination should be complete, including vital signs, search for mucocutaneous haemorrhagic lesions, cardiopulmonary auscultation, abdominal and neurological examination.

Complementary tests

An initial basic laboratory study can already point to a clinical suspicion of TTP.[26] The hemogram usually shows moderate anemia with a mean hemoglobin of 8.5 g/dL (range 5.4-14 g/dL), although sometimes the anemia is mild-moderate, which makes diagnosis difficult, with severe thrombocytopenia with a mean platelet count of 25 x 10^9/L (range 5-120 x 10^9/L) without leukopenia.[5,8] This is a hemolytic anemia, so, if available, reticulocytes will be increased, and mean corpuscular volume may also be increased. As mentioned above, the CD is usually negative. The hemostasis study is normal, both in basic times (prothrombin time and activated partial thromboplastin time) and in derived fibrinogen and D-dimer, although the latter may occasionally be slightly elevated. In basic blood biochemistry there is an elevation of total bilirubin based on increased indirect bilirubin and LDH (lactate dehydrogenase). Renal failure with or without ionic disturbances may occur in 20-25% of patients.[21] Finally, liver function tests (ASAT, ALAT, GGT, alkaline phosphatase) are usually normal. Table 2 details the laboratory tests available or not available in emergency laboratories.

In the presence of such a clinical and laboratory picture, the existence of TMA should be considered a diagnostic possibility that must be ruled out as quickly as possible, so the corresponding hematology service should be contacted urgently to complete the study. First of all, a peripheral blood smear should be performed to search under the light microscope for schistocytes, which in the case of TMA will be present in > 1% (1 schistocyte for every 100 red blood cells observed). Schistocytes are red cell fragments resulting from intravascular destruction of red cells (Figure 2), so although indicative, they are not specific for TTP. Other analytical alterations that support the picture of hemolytic anemia may be an undetectable haptoglobin.

In all patients with suspected TTP it is recommended to request troponin and pro-BNP,[27] since more than half of the patients may present elevations of these markers although only half of them present chest pain and 60% present electrocardiogram (ECG) alterations.[24] The changes described in the ECG can range from subtle and early, such as changes in the T wave or sinus tachycardia, to ST elevations that usually appear in later phases. The study with transthoracic echocardiography is not usually necessary in the early phases.

Table 2. Laboratory tests

Test	EMERGENCY Laboratory	ROUTINE Laboratory
Heomgram	X	
Peripheral blood smear	X	
APTT, PT, fibrinogen derivative, D-Dimer	X	
Creatine	X	
Total bilirubin	X	
LDH	X	
ALAT/ASAT	X	
Troponin	X	
Reticulocytes		X
Direct Coombs		X
Thrombin time		X
Haptoglobin		X
Indirect bilirubin		X

APTT: activated partial thromboplastin time; PT: prothrombin time; LDH: Lactatodehydrogenase.

In urinalysis, the appearance of hematuria and isolated proteinuria are less frequent and indicate renal damage. Other complementary tests that can be performed are urgent HIV serology, pregnancy test, simple chest X-ray, as well as blood and urine cultures if there is associated fever. In case of neurological symptoms, a cranial computed tomography (CT) with contrast should be performed, but in the absence of this, its suitability should be assessed according to the clinical stability of the patient and prioritizing other tests or techniques. Finally, depending on the patient's symptoms or history, other studies such as serum lipase and amylase can be associated to rule out the existence of associated pancretitis.

Patient referral

The management of TTP should be carried out in centers with access to the technical means that allow adequate treatment. Therefore, when this entity is suspected in the ED, the hematology department of the center should be contacted urgently to evaluate the patient and continue with the diagnostic and therapeutic process through hospital admission. The algorithm proposed by the group of experts for the referral of patients with suspected TTP is included in Figure 3.

If the center where the patient has arrived does not have a hematology service that can take charge of the patient, urgent referral of the patient to the referral center should be managed by activating an immediate transfer code red. In cases where the patient presents severe neurological symptoms, acute coronary syndrome, or hemodynamic instability, it will be necessary to transfer the patient to the intensive care unit.[26]

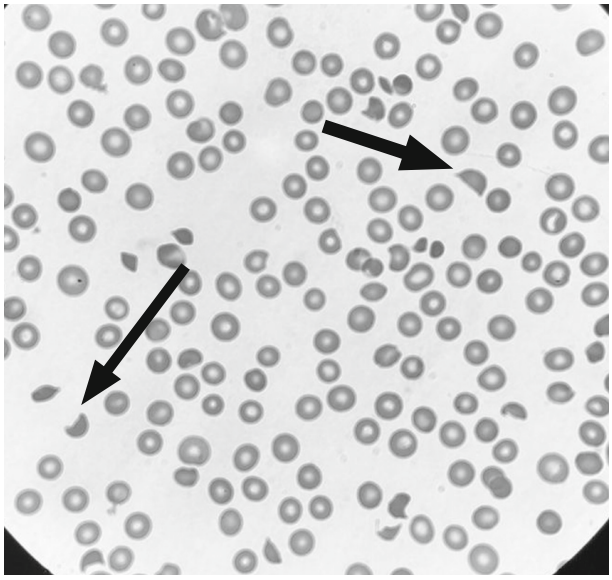

Figure 2. Optical microscope image (100x) of peripheral blood smear with presence of schistocytes (arrows). On loan from the Hematology Service-HGUGM.

Diagnosis

Confirmatory diagnosis of TTP requires the determination of plasma ADAMTS13 activity and the detection and titration of anti-ADAMTS13 antibodies. This technique is not available in the ED and is only performed in certain specialized centers. The diagnostic algorithm proposed by the expert group is included in Figure 4.

Several scoring systems are currently available to aid in the diagnosis of TTP in the context of TMA. We consider the most appropriate to be those developed by the French microangiopathy group[29] and PLASMIC,[29,30] which predict with high sensitivity and specificity a suspected TTP and should be applied whenever ADAMTS13 results are not immediately available (Table 3).[19]

In those patients in whom the score obtained indicates a pretest probability of severe ADAMTS13 activity deficit, the diagnosis of TTP should be assumed and treatment should be initiated early. On the other hand, if the score is intermediate or low, the therapeutic decision should be individualized.

Another novel prognostic model, the AHC,[31] is able to identify patients with poorer prognosis TTP with a high probability of being refractory to treatment. It is based only on age, hemoglobin and serum creatinine at diagnosis, and could change the therapeutic approach in the coming years in these patients.

If the patient is at the center where the diagnostic and treatment strategy is to be continued, samples should be collected in a tube with citrate anticoagulant and after centrifugation the plasma obtained should be frozen at -40°C to confirm in a second time the decrease in ADAMTS13 activity and, therefore, the diagnosis of TTP.[19,32] Ideally, samples for the study of ADAMTS13 activity should be obtained before starting treatment with PE to avoid interference.

In addition, samples should be saved to complete the study and rule out other causes of TMA, such as vitamin B12 and erythrocyte folate, autoimmunity studies, viral serologies or complement studies.

Treatment[20,33,34]

Treatment should be initiated in all patients with a high suspicion of TTP (French scale score and high probability PLASMIC). Treatment should be early, since 50% of TTP deaths occur in the first 24 hours.[10,22] The main treatments and their dosage are summarized in Table 4.

PE should be instituted as soon as possible, preferably within 4-8 hours of suspicion, and securized fresh frozen plasma (FFP) should be used as a replacement solution. PE should be performed daily and aims to remove circulating anti-ADAMTS13 antibodies in the patient and to replenish part of the ADAMTS13 concentration with the infused plasma. PE will be performed by any of the procedures available at the center (ultracentrifugation or ultrafiltration). It is recommended to exchange 1.5 plasma volemia daily, although in the case of life-threatening conditions, an increase in the frequency or volemia in the PE could be considered. If PE cannot be started within the recommended time, FFP transfusion (25-30 ml/kg) should be initiated. PE requires cannulation of a high caliber central venous catheter. Prior to this, platelet transfusion may be used if there is severe thrombocytopenia.[20,33]

In case of allergic reactions to plasma, or if a compatible plasma is not available (e.g. severe IgA deficiency), the best available alternative as a replacement solution should be discussed with the hematology department. PE sessions should be maintained until 48 hours after a complete clinical response, defined as a platelet count > 150 x 10^9/L, has been achieved. Drugs that can be eliminated by plasma exchange should be administered after the end of plasma exchange.

Corticosteroid treatment should be initiated simultaneously with PE. Classically, prednisone or methylprednisolone (MTP) at a dose of 1 mg/kg/day is used, although higher doses can also be considered: MTP boluses of 1000 mg or 10 mg/kg/24 hours for 3 days and then 2.5 mg/kg/day, although there is no consensus on the doses used.[20,21,35,36]

Both the ISTH[12] and the recently published Spanish guidelines[21] recommend the use of caplacizumab in the first line when there is a high clinical suspicion of TTP (90%) according to the clinical score,[12,19] when there is an acute event (first episode or relapse) or an exacerbation and refractoriness of the disease. In patients who initiate treatment with caplacizumab, given a high suspicion of TTP, it is necessary to confirm the diagnosis by means of ADAMTS13 plasma activity within a maximum of 7 days. In patients with low or intermediate probability, it is not recommended to start treatment with caplacizumab until confirmation of the diagnosis by determination of ADAMTS13 concentration. To initiate treatment with caplacizumab, a first intravenous

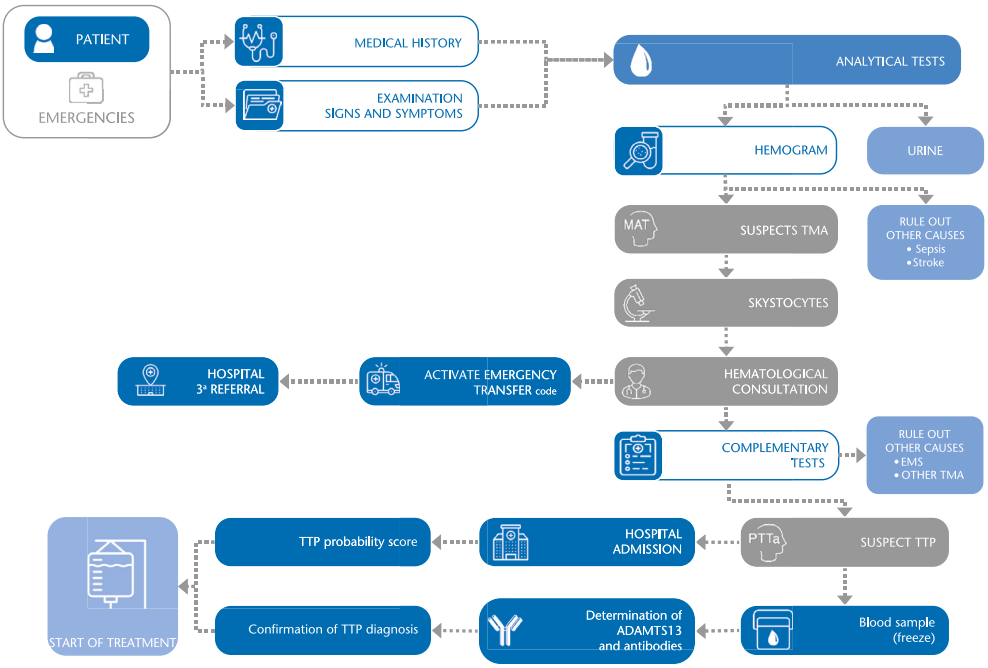

Figure 3. Referral algorithm for acquired thrombotic thrombocytopenic thrombocytopenic purpura proposed by the SEMES and SEHH expert group. TTP: acquired thrombotic thrombocytopenic thrombocytopenic purpura; SEMES: Spanish Society of Emergency Medicine; SEHH: Spanish Society of Hematology and Hemotherapy; TMA: thrombotic microangiopathy; HUS: hemolytic uremic syndrome.

dose of 10 mg should be administered before the first PE and, subsequently, a subcutaneous dose of 10 mg daily after each PE for as long as these are maintained and until 30 days after the last refill. The efficacy and safety of caplacizumab in patients who have had an episode of TTP has been studied in two randomized, controlled clinical trials (TITAN[37] and HERCULES[13,38]). The results showed a reduction in the number of days to normalization in the number of platelets, number of deaths, vascular events, exacerbations, recurrences, refractoriness and days of treatment with PE.[13,37,38] The main adverse effects associated with caplacizumab are hemorrhagic complications, most of the time mild and not requiring discontinuation of treatment, and no serious life-threatening effects have been found associated with the administration of the drug.[13-15]

Rituximab is an anti-CD20 monoclonal antibody. Although it is not approved for use in TTP, its administration in early stages of the disease is associated with a lower risk of early relapse.[22] Although the optimal dose is not known, the most administered dose is 375 mg/m^2 IV/week for 4 weeks. It should be administered after PE and infusion reactions are its most frequent complication.[34,39] Before administering rituximab, the patient should undergo a hepatitis B serological study, due to the risk of reactivation associated with its use. Another complication associated with rituximab is immunosuppression secondary to the depletion of B lymphocytes from the circulation.

Transfusions of blood components should be individualized according to the patient. Transfusion of packed red blood cells (RBC) should be considered if hemoglobin levels are < 7 g/dL or < 8 g/dL if clinical manifestations recommend it. Platelet transfusion should be avoided even in severe thrombocytopenia, although it can be performed on an isolated basis in case of severe hemorrhagic symptoms or prior to an invasive procedure such as placement of a central line for ROP, without evidence that it increases the thrombotic risk.[40,41]

The use of anticoagulation is highly debated. Although the systematic use of antiplatelet therapy or anticoagulation is not recommended in patients with TTP, treatment should be individualized in the case of intercurrent thrombotic events and the experience of each center. Therefore, some groups recommend the administration of anticoagulant therapy, generally with low-molecular-weight heparins (LMWH) in prophylactic doses, as long as the patient reaches a platelet count of 50 x 10^9/L[42].

Discussion

The proposals referred to by the group of experts for the diagnosis and treatment of TTEP are the first consensus document focused on recommendations in the ED. The practical guide for the urgent treatment of TMA published by the "Grupo de Microangiopatía Trombótica del Hospital Universitario y Politécnico de La Fe (Valencia)",[34] focuses on the detection and treatment of TMA within the first hours of suspicion. Unlike

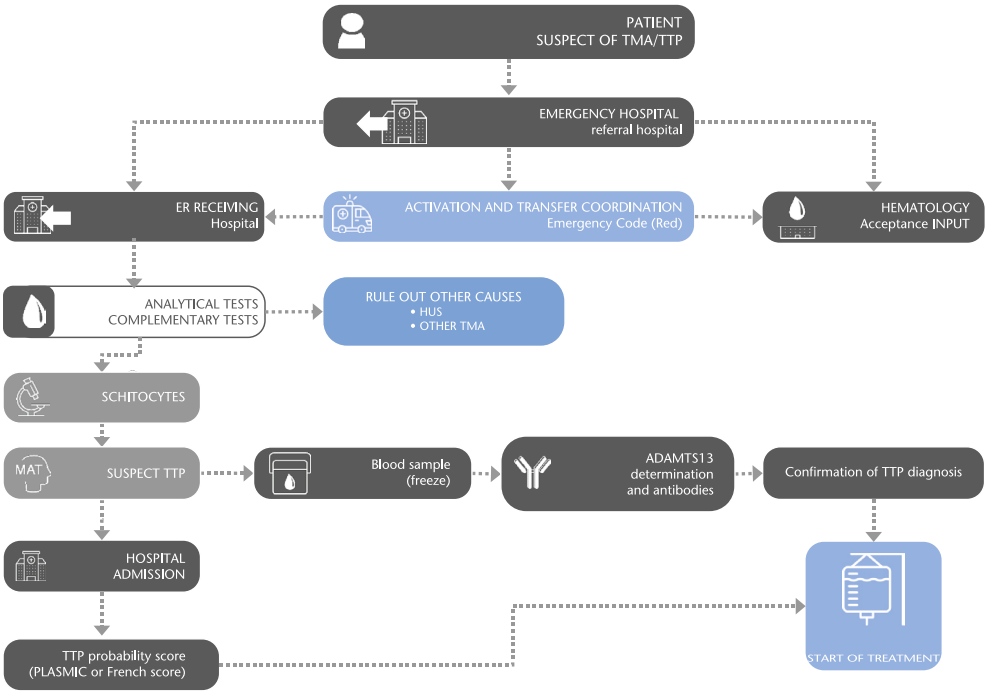

Figure 4. Diagnostic algorithm for acquired thrombotic thrombocytopenic thrombocytopenic purpura proposed by the SEMES and SEHH expert group.
TTP: acquired thrombotic thrombocytopenic purpura; SEMES: Spanish Society of Emergency Medicine; SEHH: Spanish Society of Hematology and Hemotherapy; TMA: thrombotic microangiopathy; HUS: hemolytic uremic syndrome; HUS: hemolytic uremic syndrome.

our work, it does not include TTP diagnostic probability scores or the use of drugs such as rituximab or caplacizumab. The most important step for the correct management of these patients is early clinical suspicion, since the risk of serious complications is especially high in the first hours.[43,44] The experience published by Sawler et al. shows that up to 60% of the cases of TTP treated in the ED received the first PE within 8 hours of the first medical contact, although only the cases with a delay in the initiation of PE greater than 24 hours from the first medical contact had a higher mortality and development of thrombotic events.[45]

Therefore, in any patient with hemolytic anemia, thrombocytopenia and negative CD, the diagnosis of TMA should be suspected. The differential diagnosis between TTP and other TMA should be streamlined as management varies greatly between the different entities.

The differential diagnosis with other TMA is complex,[46,47] especially in HUS, although clinical and analytical features can help to discriminate the most important entities. Hemolytic uremic syndrome usually appears after hemorrhagic diarrhea caused by Shiga toxin-producing *Escherichia coli,*[48] and is characteristically associated with oligoanuria, arterial hypertension, microangiopathic anemia, thrombocytopenia, and renal failure. Therefore, the presence of renal failure, diarrhea and Shiga toxin are highly suggestive findings.

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Table 3. French and PLASMIC scores for screening patients with suspected thrombotic thrombocytopenic purpura

Parameters	Scoring according to the French TMA study group	PLASMIC score
Platelets	< 30 x 10^9/L (+1)	< 30 x 10^9/L (+1)
Creatinine	< 2,26 mg/dL (+1)	< 2 mg/dl (+1)
Hemolysis: Bb ind > 1 mg/dL, or reticulocytes > 2.5%, or undetectable haptoglobin	*	+1
No active cancer in the last year	*	+1
No TOS/TPH	*	+1
INR < 1.5	*	+1
MCV < 90fl	*	+1
Probability of severe deficit of ADAMTS13 activity (<10%)	0 points: 2%. 1 point: 70%. 2 points: 94%.	0-4 points: 0-4%. 5 points: 5-24%. 6-7 points: 62-82%

*The French scale score can only be applied in patients with hemolytic anemia with schistocytes and without active cancer, transplantation or disseminated intravascular coagulation.
Bb ind: indirect bilirubin; INR: international normalized ratio; SOT: solid organ transplantation; HSCT: hematopoietic stem cell transplantation; MCV: mean corpuscular volume.

Table 4. Main treatments in acquired thrombotic thrombocytopenic purpura (aTTP), when to initiate and dosage of administration

Treatment	Starting time	Dosage
Plasma exchange	< 4-8 hours since suspicion	1.5 volemia refill with FFP
Corticosteroids	< 4-8 hours from suspicion	MTP 1 mg/kg/24 hours, or boluses of MTP 1,000 mg or 10 mg/kg/24 hours for 3 days and thereafter 2.5 mg/kg/day
Caplacizumab	If high probability score and ADAMTS13 activity results in < 7 days	10 mg IV prior to 1st PE 10 mg sc after each PE 10 mg sc up to 30 days after end of of PEs
Rituximab	Always after PE	375 mg/m^2 IV x 4 weekly doses

PE: plasma exchange; MTP: methylprednisolone; IV: intravenous; FFP: fresh frozen plasma.

failure. Therefore, the presence of renal failure, diarrhea and Shiga toxin are highly suggestive findings. Although TTP may present with renal failure, this is rare and generally less severe. Different TMA can occur during pregnancy, such as HELLP syndrome and TTP, and thrombocytopenia (LP), presents with hemolytic anemia (HA), elevated liver enzymes (ELE) and thrombocytopenia (LP). It is usually associated with generalized edema and vomiting. It is more frequent in the third trimester of pregnancy, and in these cases it is recommended to terminate the pregnancy, although up to 30% may occur in the puerperium. In addition, eclampsia and other autoimmune diseases precipitated by pregnancy can produce TMA, making diagnosis difficult in pregnant women. Other TMA, such as those secondary to drugs or post-transplant solid organ and hematopoietic progenitor transplantation, require joint management with the relevant specialist due to the great complexity of the cases. Although more cases need to be evaluated, there are already cases of TMA caused by infection associated with SARS-CoV-2.[50]

Disseminated intravascular coagulation (DIC), a condition secondary to clot formation in the microvasculature due to uncontrolled activation of the coagulation cascade and fibrinolysis, should be appropriately ruled out. DIC is associated with consuming anemia and thrombocytopenia with decreased clotting factors, lengthening of basic clotting times (PTTA and PT), and low or inappropriately normal fibrinogen levels with elevated D-dimer. Megaloblastic anemia, due to folic acid or vitamin B12 deficiency, can produce a picture characterized by pancytopenia (anemia, thrombocytopenia and neutropenia) with elevated LDH, bilirubin and haptoglobin consumption by intramedullary abortion, with occasional schistocytes in the peripheral blood smear.[52] However, in this case the reticulocyte count will not be increased.

Once the diagnosis of TMA has been established, the application of the French or PLASMIC scales is of great help in establishing the probability that it is due to TTP. In patients with a high probability of TTP, treatment with PE and immunosuppressants should be started early and, if available, caplacizumab should be added.[53]

In conclusion, this article seeks to assist emergency physicians in the early diagnostic suspicion of TTP with the intention of reducing initial mortality as much as possible. It proposes an algorithm for the referral of patients to hematology services to optimize their management. The presence of CD-negative hemolytic anemia, thrombocytopenia and the application of prognostic scales should be the focus of clinical suspicion. Treatment with PR and corticosteroids should not be delayed and, if indicated, new drugs such as caplacizumab can improve the outcome in these patients.

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