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Thrombotic Thrombocytopenic Purpura, Case Report and Literature Review

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ABSTRACT

Background: Thrombotic thrombocytopenic purpura is a rare entity that represents a diagnostic challenge due to clinical manifestations that may be nonspecific. In addition, the diagnostic approach requires expensive and poorly accessible laboratory tests (for example, measurement of ADAMTS13 enzyme activity levels). The first reported case was in 1924, described by Eli Moschcowitz in a 16-year-old girl who died suddenly and in whom the post-mortem biopsy showed thrombi in the kidney, heart and spleen. It is estimated that TTP has an annual incidence of 1.5 to 6 cases per 106 inhabitants, with a prevalence of 10 to 15 cases per 106 inhabitants, and is more frequent in the female sex with a female/male ratio of 2:1. Thrombotic thrombocytopenic purpura (TTP) is characterized by the concomitant appearance of often severe thrombocytopenia, microangiopathic hemolytic anemia, and multiple organ involvement due to ischemia secondary to the formation of thrombi in various parts of the vascular system. The organs most frequently affected are the brain, heart, and kidneys. Currently, it has been identified that the pathophysiology is related to the alteration in the enzyme metalloproteinase with thrombospondin motifs 13 (ADAMTS13), which has protease activity that is responsible for cleaving the ultra-long multimeric chains of the von Willebrand factor (vWF). These alterations can be congenital (recessive mutations of the ADAMTS13 gene) or acquired (formation of antibodies against ADAMTS13). In this review we present the clinical case of a woman from Merida, Yucatan, Mexico, who was admitted to the internal medicine

service due to the presence of tension-type headache and jaundice of more than 1 month of evolution. During her care in the emergency room, laboratory studies documented data of intravascular hemolytic anemia and thrombocytopenia, with no involvement of other organs. An approach to autoimmune hemolytic anemia was started, later she presented clinical worsening, neurological involvement (psychosis), increased hemolysis and thrombocytopenia, empirical treatment with steroids was started without response, she was later evaluated by hematology who, due to the clinical characteristics she presented plus the finding of schistocytes in the peripheral blood smear, an approach for PTT was started requesting ADAMTS13 activity levels, and empirical management with plasmapheresis was started, presenting a favorable response. Days later, the results of the studies were collected, reporting 0% ADAMTS13 activity, confirming the diagnosis of PTT. Methods: A search was performed for literature related to the epidemiology, pathophysiology, clinical manifestations, diagnosis, differential diagnosis and treatment of thrombotic thrombocytopenic purpura, as well as literature related to thrombosis, hemolysis, hemolytic anemia, thrombocytopenia, thrombotic microangiopathy, von Willebrand factor in open access search engines and databases such as PubMed, Springer Link, Science Direct, Web of Science and others. Results: We found and analyzed 80 articles that met the search criteria, of which we selected 34 articles with the most relevant information, and with a publication period of less than 10 years. Conclusions: Thrombotic thrombocytopenic purpura is a rare but potentially fatal disease. Its true incidence is unknown, since the clinical presentation is varied with many pathologies that share the same characteristics. In addition, laboratory tests to confirm the diagnosis are not routinely available. A timely diagnosis can improve the prognosis and survival of patients. Currently, there are more therapeutic alternatives available, reducing mortality, which in the past was over 90%, with plasma exchange being the intervention with the greatest benefit.

Keywords: purpura, thrombosis, hemolysis, hemolytic anemia, microangiopathy, thrombocytopenia, thrombophilia, jaundice, von Willebrand factor, ADAMTS13.

INTRODUCTION

Thrombotic microangiopathies (TMA) represent a heterogeneous group of syndromes characterized by disseminated microthrombi, clinically presenting with the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia and ischemic injury of different organs. Considering that there are multiple syndromes with different pathophysiology that present with the clinical phenotype of TMA, differential diagnosis is often difficult. In this review we focus on thrombotic thrombocytopenic purpura.[1]

Thrombotic thrombocytopenic purpura (also known as Moschcowitz disease) is a potentially life-threatening microcirculatory occlusive disorder characterized by systemic platelet aggregation, organ ischemia (especially of the brain, heart, gastrointestinal tract, and kidneys), profound thrombocytopenia (a low blood platelet count, $<100 \times 10^9$ cells per liter, often $<30 \times 10^9$ cells per liter), and red blood cell fragmentation.[2]

The first reported case was in 1924, described by Eli Moschcowitz in a 16-year-old girl who died suddenly and in the post-mortem biopsy blood clots were observed in the kidney, heart and spleen. The epidemiology of the disease is largely unknown due to the complexity of the

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diagnostic approach; it mainly affects the female sex, with the usual age of presentation before 50 years of age.[3,4]

Current advances in the understanding of physiology (alteration in the function of ADAMTS13) have allowed the creation of therapeutic strategies such as plasma exchange and the use of immunomodulatory drugs, and even at present the usefulness of recombinant ADAMTS13 is being tested for treatment. Despite these advances, mortality continues to be significant. [2,3,4] Below is the clinical case of a patient who was admitted to our internal medicine service and in whom a diagnosis of TTP was established.

CLINICAL CASE

34-year-old female patient, originally from Yucatan. Relevant pathological history includes total hysterectomy in 2023, biopsy of surgical specimen found chronic cystic endocervicitis with extensive tubal metaplasia. Endometrium with complex hyperplasia with atypia. Ovaries with mature cystic teratomas. After surgery, she is maintained with hormonal supplementation based on estradiol/drospinenone. She denies history of blood transfusions or blood products.

The current condition began in August 2024 with intermittent headache of moderate intensity, which was managed with NSAIDs. On September 11, 2024, she presented with intense headache with intolerance to the oral route, she went to an evaluation with a private doctor who requested laboratory tests, in the relevant findings anemia, thrombocytopenia and hyperbilirubinemia were observed.

He entered the emergency room on September 14, 2024, with the laboratory tests mentioned in table 1. An ultrasound of the liver and biliary tract was requested, which reported gallstones with no signs of exacerbation, hepatosplenomegaly, mild hepatic steatosis.

Table 1: Initial Laboratory Studies.

Blood Count. September 14, 2024.	**Blood Chemistry. September 14, 2024.**	**General urine test and urine culture. September 14, 2024.**
Erythrocytes 2.1 x 106/uL. Hemoglobin 7.3 g/dL Hematocrit 21.1 % MCV 100 FL CMHB 34.6 g/dL RDW-CV 22.2 Platelets 42 x 103/uL Leukocytes 8.38 x 103 /uL Neutrophils 5615 u/L Lymphocytes 1844 u/L	Urea 18.6 mg/dl. Creatinine 0.84 mg/dl Total Bilirubin 6.03 mg/dl Direct Bilirubin 0.93 mg/dl ALT 33 U/L AST 56 U/L DHL 949 U/L FA 78 U/L GGT 37 U/L	Appearance: Cloudy. Protein: 30 mg/dl. Bilirubin: Negative. Urobilinogen: 3 mg/dl. pH: 6.0 Nitrites: Positive. Leukocytes: 250 x field. Casts: Few hyalines. Crystals: Does not contain. Urine culture: > 100,000 CFU/ml of Escherichia coli.
Viral Panel. September 15, 2024.	**Others. September 16, 2024.**	**Coagulation Times. September 14, 2024.**
Hepatitis B surface antigen Non-reactive Hepatitis C virus antibodies Non-reactive. HIV Non-reactive VDRL Non-reactive	C-reactive protein < 6 mg/L Globular thirst rate 40 mm/hr Rheumatoid factor < 20 IU/ml	Prothrombin time 12.2 sec Control PT 11.4 sec INR 1.12 sec Partial thromboplastin time 25.8 sec Control PTT 23.3 sec

Initially, given signs of thrombocytopenia and hemolytic anemia, probable Evans syndrome was suspected, for which empirical treatment was started with steroids (dexamethasone for 5 days, then with oral prednisone) while complementary studies were collected (viral panel, immunological panel, direct Coombs, reticulocyte count, urine culture), in addition, antibiotic treatment was given for pathological EGO and urinary symptoms. Despite management, the patient persists with headache, decreased platelet count, jaundice and choluria.

Laboratory tests were collected, finding a polyspecific direct Coombs with a negative result, a rheumatological profile with a negative result (table 2). A CT scan of the chest, abdomen and pelvis was performed without finding neoplasms or metastatic lesions. The patient's condition was slow, and on September 24, 2024, the patient's neurological status deteriorated with indifference to the environment, with no focal data. A CT scan of the head was performed, where the neurology service observed edema in the parietal-occipital region with no signs of acute ischemia.

Table 2: Laboratories complementary laboratory studies.

TORCH Profile. **September 17, 2024**	**Immune panel.** **September 19, 2024.**
Ab Anti Toxoplasma gondii IgG Negative. Ab Anti Toxoplasma gondii IgM Negative. Ab Anti Cytomegalovirus IgG Negative. Ab Anti Cytomegalovirus Negative. Ab Anti Rubella IgG Negative. Ab Anti Rubella IgM Negative.	Lupus anticoagulant: 0.62. Antistreptolysin 103 IU/mL. VSG 25mm. CRP 0.43 mg/dL. Rheumatoid Factor <6.3 IU/mL. Ab IgG, IgM and IgA anti-Beta2 Glycoprotein 1 Negative. Ab IgM and IgG anti-Phospholipids Negative. Ab anti cellular by IFI: Negative. Ab anti-cytoplasmic by IFI: Negative. Ab anti-Mitotic by IFI: Negative. Ab anti-Native DNA (DC): Negative. Ab IgG and IgM Anti-Cardiolipin Negative.

She was referred to a third-level unit for evaluation by hematology. During the evaluation, a peripheral blood smear was performed again, in which the presence of schistocytes was reported (figure1). Due to the slow clinical evolution and neurological involvement, the findings in the smear were oriented towards a diagnosis of probable thrombotic thrombocytopenic purpura. Steroid and cyclosporine A treatment was started due to the lack of plasma exchange therapy and she was referred to a highly specialized national center with the capacity to perform plasma exchange.

In this last instance, plasma replacement was started immediately, continuing with the use of steroids, and ADAMT13 enzyme activity levels were requested, which were reported with 0% activity (figure 2). After the first 3 days of plasma replacement therapy, the patient presented an increase in platelet count, a decrease in hemolysis markers (bilirubin s and DHL), as well as an increase in hemoglobin levels. Treatment with caplacizumab was started, and negative antibodies against ADAMTS13 were requested, which is why a possible congenital TPP is attributed. The patient currently remains under surveillance.

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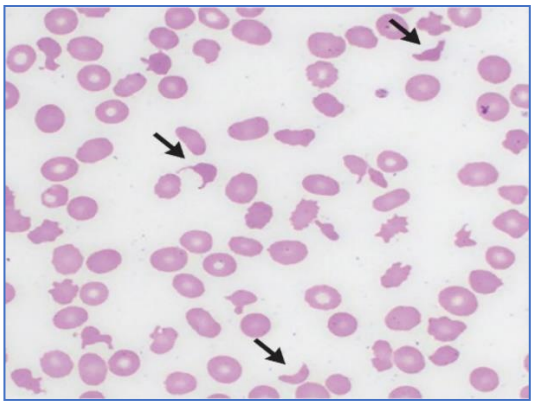

Figure 1: Schistocytes in peripheral blood smear, black dates.

METODOS

To carry out this review, a search of publications related to the key words (purpura, thrombosis, hemolysis, hemolytic anemia, microangiopathy, thrombocytopenia, thrombophilia, jaundice, von Willebrand factor, ADAMS13) was carried out using free search engines. access, within the inclusion and exclusion criteria for the selection of information we consider the following:

Inclusion

- Publication date: publications less than 10 years old were selected.
- Relevance: publications were selected that provided relevant data for understanding the disease or updates on it, the impact factor of the publications and the reliability of the media (journals, platforms, etc.) where they were published.

Exclusion

- Repeated articles.
- Articles published in unreliable or low-impact media.
- Articles published more than 10 years ago.

RESULTS

During our search for information, 80 articles were obtained that were related to the key words, only 34 articles were selected that met all the inclusion criteria (in addition to prioritizing the articles with the most up-to-date information and guidance for diagnosis and treatment), of which the following narrative of the pathophysiology, clinical manifestations, diagnosis and treatment of thrombotic thrombocytopenic purpura is made.

DISCUSSION

Thrombotic thrombocytopenic purpura belongs to a group of known pathologies with thrombotic microangiopathies. It is a rare entity that can cause the death of the patient. Its diagnosis is difficult due to the complexity of the studies necessary to confirm the disease or rule out other pathologies. Below is a summary of the most relevant information on the subject.

Epidemiology

TTP is a rare disorder with an average annual prevalence of about 10 cases per million people and an annual incidence of approximately one new case per million people. Reviews of TTP

have found that this pathology is more common in women with a female/male ratio of 2:1, with an age range of onset between 30 and 50 years.[4,5]

Etiology

The underlying cause may involve the production of unusually large von Willebrand factor (vWF) multimers. These multimers are thought to remain in circulation due to the lack of activity of the vWF-cleaving enzyme, the protease ADAMTS13. The accumulation of vWF multimers facilitates platelet aggregation leading to thrombosis.[6] Based on the mechanism affecting the production or activity of the ADAMT13 enzyme, TTP can be classified into two forms, congenital and acquired. In congenital TTP (cTTP) (also known as Upshaw-Schulman syndrome), severe ADAMTS13 deficiency is caused by homozygous or doubly heterozygous mutations of the gene encoding the enzyme. In acquired or immune-mediated TTP (iTTP), severe ADAMTS13 deficiency is the result of circulating antibodies that inhibit ADAMTS-13 activity or increase its clearance.[7]

Physiopathology

Research has shown that the pathophysiological basis of clinical findings is secondary to alterations in the interaction between vWF and ADAMTS13. The vWF is a multimeric protein that is synthesized in vascular endothelial cells, megakaryocytes and platelets, the gene that encodes it is located on chromosome 12 (12p13.2). There are 2 pathways involved in the secretion of vWF, the constitutive pathway that is related to the synthesis of plasma vWF of endothelial origin that is stored in Weibel-Palade bodies and the regulated pathway, which involves the release of fully multimerized vWF, stored in alpha granules, in megakaryocytes and platelets.[8] ADAMTS13 is a protease-acting enzyme synthesized in hepatic stellate cells. Its only known function is to regulate vWF multimers.[9] Under physiological conditions, ADAMTS13 is in a latent and closed conformation and vWF is in a globular state (Figure 2a).

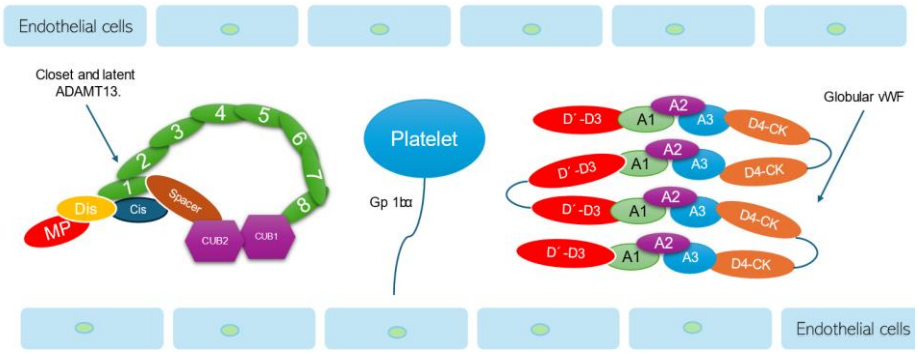

Figure 2a

The proteolytic activity of ADAMTS13 on vWF depends on the conformational change of both proteins. Under shear forces, vWF unravels and exposes its A1 domain allowing interaction with platelets through the Gp Ib/IX/V complex (figure 2b).

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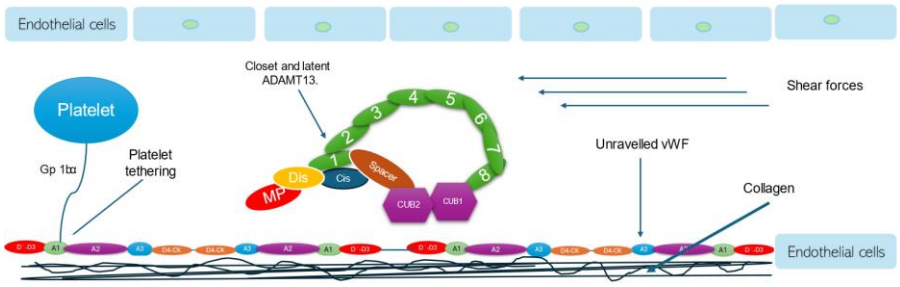

Figure 2b

In this unwound state, the A2 domain of vWF elongates and exposes the ADAMTS13 binding sites. The initial interaction of the domains allosterically activates ADAMTS13, inducing an open conformation (Figure 2c).[2,5,9]

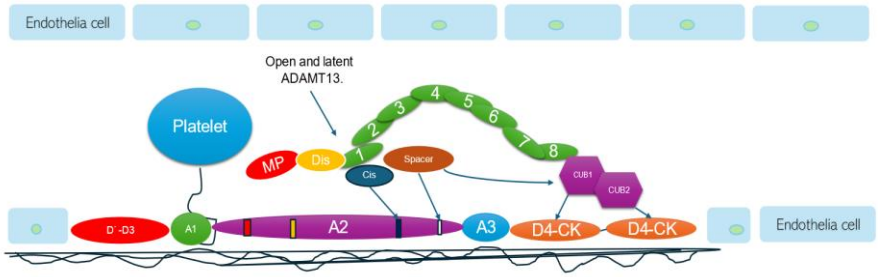

Figure 2c

Sequential interactions ultimately trigger proteolysis (Figure 2d). When there is severe ADAMTS13 deficiency (<10%), ultra-long von Willebrand factor multimers (ULvWF) can accumulate, leading to dysregulated platelet adhesion and aggregation, resulting in TTP with disseminated microthrombi and organ ischemia (Figure 2e). [2,5,9]

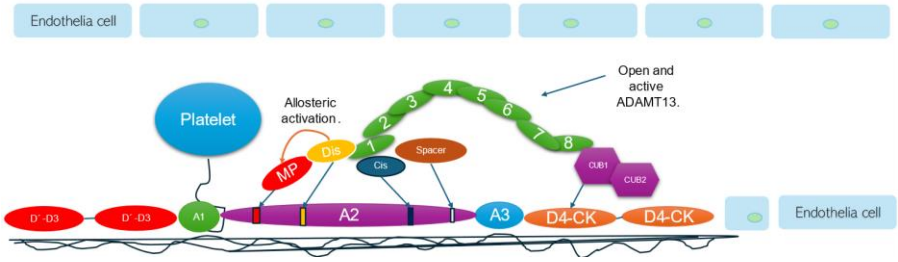

Figure 2d

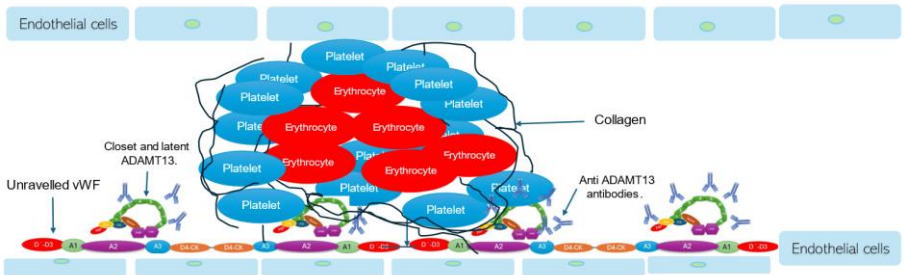

Figure 2e

Although severe ADAMTS13 deficiency is necessary for the development of TTP, enzyme deficiency alone may not be sufficient to induce the clinical syndrome. Complement system activation has also been suggested to play a role in acute TTP. Indeed, ULVWF multimers serve as a scaffold for the assembly and activation of the alternative pathway of the complement system.[2,5,9]

As mentioned, the deficiency can be congenital (cTTP) due to mutations in the gene encoding ADAMTS13 or acquired (iTTP) due to the formation of antibodies. Anti-ADAMTS13 autoantibodies are divided into two categories: inhibitory and non-inhibitory. Inhibitory antibodies neutralize the proteolytic activity of ADAMTS13, and non-inhibitory antibodies bind to the protease, accelerating its elimination from the plasma.[2,9] The most common isotype class of anti-ADAMT13 autoantibodies is IgG, followed by IgA and IgM (20% of cases).[2,5,9]

Likewise, iTTP can be subdivided into primary, when no associated underlying disease can be determined, and secondary, when a defined underlying disorder is identified. In most cases, iTTP is primary. Secondary iTTP can be associated with various infectious diseases, but a greater association with HIV has been demonstrated.[2,5,9]

Diagnosis:

Clinical Presentation:

Previously, TTP was defined by a clinical "pentad" consisting of fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic deficits, and renal failure. However, the pentad was reported at a time when the efficacy of plasma-based therapy for treating TTP had not been firmly established (less than 10% of patients have these 5 findings). Today, the presence of thrombocytopenia and hemolytic anemia alone, without an alternative explanation, should prompt serious consideration of the diagnosis of TTP or other TMA.[9]

Acute TTP almost uniformly presents severe thrombocytopenia (typically <30 109/L) and microangiopathic hemolytic anemia, often with evidence of red blood cell fragmentation on the peripheral blood smear (schistocytes). Other classic parameters of hemolysis are frequently also present: low haptoglobin concentration, elevated reticulocytes, elevated total bilirubin (at the expense of indirect bilirubin), elevated lactate dehydrogenase (LDH). The Coombs test is usually negative, and coagulation parameters are not severely abnormal in TTP. [9,10,11]

Symptoms usually appear in the age range of 30-50 years, appearing earlier in patients with cPTT. These patients have 2 periods of greater risk in which the disease can be activated: the first days after birth and pregnancy. In addition, other situations such as significant alcohol consumption and infections also increase the risk of activating the disease.[11]

Signs and symptoms secondary to organ ischemia are variable, with up to 60% of patients having neurological manifestations that vary widely from mild confusion to stroke, seizures, or coma.[5,9,13] Gastrointestinal ischemia is present in 35% of patients, can cause abdominal pain, nausea, diarrhea and in severe cases pancreatitis may occur.[5,9] Evidence of myocardial ischemia is present in one-quarter of patients with acute TTP and may be characterized by electrocardiographic changes, or more commonly, elevated troponins. Symptoms of congestive heart failure or myocardial infarction may also be present.[5,9,13] Renal injury is common in TTP, although acute renal failure requiring renal replacement therapy is quite rare. Hematuria and

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proteinuria are the most frequently observed renal manifestations. Although mild renal failure may occur, most patients have a creatinine below 2 mg/dl.[5,13] Some clinical findings in patients with TTP are presented in Figure 3.

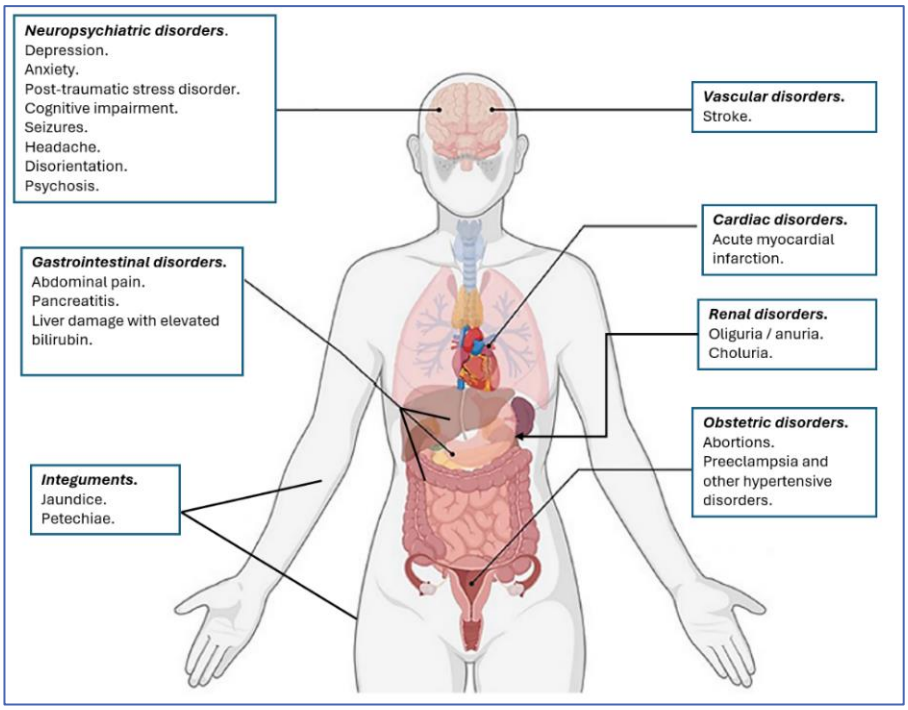

Figure 3: Clinical manifestations in patients with TTP.

Risk Factors:

There are various factors that have been linked to a higher probability of presenting the disease. These factors are presented in table 3.[6]

Table 3: Risk factors for PTT.

Strong association	Weak association
Black Ethnicity: The relative incidence among blacks is nine times higher than among non-blacks. Female Sex: Between 65% and 75% of patients with TTP are women. Obesity: 55% of patients have a BMI >30 kg/m^2. Pregnancy (term or postpartum): TTP is diagnosed during pregnancy or the postpartum period in 12% to 25% of cases, and 75% of these episodes occur around the time of delivery. Anticancer Therapies: TTP develops in <1% of patients receiving mitomycin. Associations are also seen with cyclosporine, gemcitabine, and tacrolimus.	-HIV infection -Bone marrow transplant. -Antiplatelet agents (clopidogrel and ticlopidine), -Quinine.

Laboratory Studies:

The initial approach is carried out with the available laboratories, in which data compatible with thrombotic microangiopathy are intentionally sought, since more specific studies are not always available, decisions must be made based on the clinical symptoms and the findings found.[14] Table 4 summarizes the initial laboratories to request and the results most frequently found in patients with TTP.

Table 4: Initial laboratory studies for the diagnostic approach to PTT

Lab study	Result.
Platelets.	Decreased. The degree of decrease is variable, but a decrease in platelets is required as part of the diagnosis; up to 95% of cases have a platelet count less than 20x109/l.
Hemoglobin.	Decreased. Anemia can be found in 80% of cases, and generally with levels less than 8 g/dl.
Haptoglobin.	Decreased. Haptoglobin is markedly decreased during acute episodes due to intravascular hemolysis.
Peripheral blood smear.	Blood smear with schistocytes. Schistocytes may not be present on the blood smear during the first 24 to 48 hours but are usually present on blood smear examination at the time of presentation.
Reticulocyte count.	Increased. Reticulocyte counts are typically elevated in patients with TTP.
Urea and creatinine.	Elevated. However, severe renal failure only occurs in 5% of patients.
Urine test.	Proteinuria. Proteinuria and mild-moderate renal injury occur in 40% of patients.
Coombs direct.	Negative. It is negative in patients with PTT. However, it is used to rule out the presence of hemolytic anemia.
Others.	Coagulation times (usually normal), liver function tests (elevated bilirubin at the expense of indirect bilirubin), viral panel for hepatitis (to rule out a precipitating infectious process), blood levels of vitamin B12, iron and folate (to rule out deficiency anemia), immunological panel (for example, anti-nuclear antibodies, complement levels, to rule out immunological diseases).

When TTP is suspected, it is necessary to determine the activity levels of ADAMTS13 to confirm or rule out the diagnosis. An activity of less than 10% is confirmatory. If the diagnosis is confirmed, the next step is to rule out the presence of antibodies against ADAMTS13 to determine whether TTP is congenital or acquired. If antibodies are documented, it is relevant to subclassify them, since they are prognostic factors of response to treatment and mortality. For example, the presence of IgA is associated with a higher mortality rate.[9] Currently, various techniques are available for measuring ADAMTS13 activity. Some techniques for measuring the activity and presence of antibodies are described in table 5.

Table 5: Techniques for detecting ADAMTS13 activity and presence of anti-ADAMTS13 antibodies.

ADAMTS13 Activity	Severe deficiency is defined as being less than 10% of the activity. Although there are different ways to measure it, the standardized technique by the WHO is the FRETS-VWF73-based assay (FRETS, fluorescence resonance energy transfer). The assay is based on the degradation of full-length VWF or synthetic VWF peptides by ADAMTS13 in the plasma sample being analyzed, and the degradation products are then measured. [2,7]
Anti-ADAMTS13 Autoantibodies	After identifying an ADAMTS13 activity of less than 10%, the next step is to rule out the presence of antibodies (inhibitors/non-inhibitors) to distinguish between congenital and acquired PTTA. The main antibody found is the IgG1 type. Detection can be performed by ELIZA (detects inhibitory and non-inhibitory antibodies) or the Bethesda test (detects only inhibitory antibodies). [7]
ADAMTS13 Antigen	The ADAMTS13 antigen can be measured by ELISA but is not yet part of routine clinical practice. In one study, the relationship between antigen levels and mortality was analyzed, and an inverse relationship was found: higher antigen levels resulted in lower mortality. [15]

Diagnostic Algorithm and Differential Diagnoses:

TTP is a complex diagnosis, requiring special studies to confirm the diagnosis and, if possible, support from the hematology service. There are no pathognomonic findings in routine

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laboratory tests. Part of the diagnostic approach consists of excluding other pathologies in which ADAMTS13 levels are available, and even medical management should be started immediately based empirically on the clinical picture and without waiting for the results of ADAMT13 activity.[14] The main differential diagnoses that should be ruled out include pathologies within the group of so-called thrombotic microangiopathies, and the approach to rule out these entities should be started in patients who present the following findings:

- Microangiopathic hemolytic anemia.
- Thrombocytopenia with purpura.
- Acute renal failure (generally less marked in TTP than in hemolytic uremic syndrome).
- Neurological abnormalities (generally more marked in TTP than in hemolytic uremic syndrome).

Figure 4 presents an algorithm for the diagnostic approach to thrombotic thrombocytopenic purpura and other thrombotic microangiopathies and table 6 presents the main differential diagnoses of TTP. [2,9]

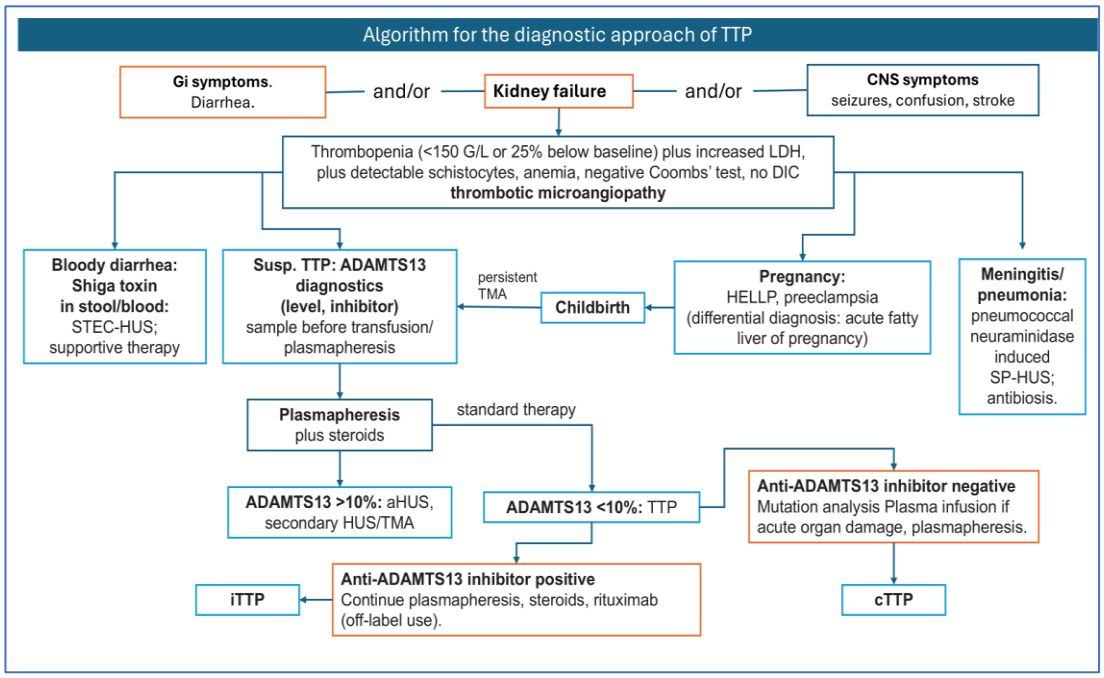

Figure 4: Algorithm for the diagnostic approach to PTT.

Table 6: Main differential diagnoses of TTP.

Disease	Pathophysiology	Differences from TMA	Therapy
Vitamin B12 deficiency, pseudo-TTP	Vitamin B12 deficiency with appearance of schistocytes and neurological symptoms, high homocysteine levels with defective endothelium.	Reduced levels of reticulocytes, extremely high LDH levels (>5000 U/L), elevated levels of methylmalonate.	Vitamin B12 substitution.
Acute pregnancy-induced fatty liver	Hereditary defects of fat metabolism with liver failure.	Nausea, abdominal pain, hypoglycemia, elevated transaminases, increased bilirubin levels, reduced ATIII, reduced coagulation factors.	Childbirth, supportive therapy.

Hyperfibrinolysis with DIC	Fibrin consumption e.g. for APL, prostate cancer, gastric cancer.	Reduced fibrinogen, blasts with Auer rod formation in PB (APL), leucoerythroblastic blood hemogram.	Specific therapy valve
Heart valve–induced hemolysis	Mechanical fragmentation of red blood cells with consumption of platelets.	Medical history of cardiac valve prosthesis, valve defect TEE.	Correction of defective heart.
Endocarditis	Bacteremia with sepsis with a valve vegetation.	Blood culture, TEE.	Targeted antibiotic therapy.
Evans syndrome	Immune thrombocytopenia with Coombs-positive autoimmune hemolysis.	Coombs' test, lack of schistocytes.	Immunosuppressio n.
Sepsis with DIC	Consumption coagulopathy.	Blood culture, procalcitonin.	Sepsis therapy, antibiotic therapy.
Catastrophic antiphospholipid syndrome	Arterial and venous thrombi, secondary endothelial damage.	Prolonged aTTP, cardiolipin antibody, aβ2GPI-Ab.	Heparin, possibly plasmapheresis, (eculizumab)
Malaria, babesiosis	Intracellular parasites with hemolysis and thrombopenia.	Morphology of peripheral blood.	Antiparasitic therapy.
Hemorrhagic fever, viral infections	Dengue virus, filoviridae, hantavirus	No hemolysis, clinical history of exposure.	Supportive therapy.
aβ2GPI-Ab: anti-beta2-glycoprotein I antibody; APL: acute promyelocytic leukemia; ATIII: antithrombin III; aPTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulopathy; LDH: lactate dehydrogenase; PB: peripheral blood; TEE: transesophageal echocardiography; TMA: thrombotic microangiopathy; TTP: thrombotic thrombocytopenic purpura. Adapted from reference 34.			

When specific studies are not available to confirm the diagnosis (ADAMTS13 activity level and the time at which the results are reported), the initiation of medical management can be assessed based on the clinical picture, the patient's history and laboratory findings. In addition, prognostic scales can be used to assess the probability of risk for ADAMTS13 activity deficiency. The first scoring system in this sense was the Bentley scale, and later the French score and the PLASMIC score were developed, the latter being the most widely used due to its greater sensitivity.[16]

The PLASMIC Score was derived by Bendapudi et al and externally validated in a study with an independent cohort of 112 consecutive hospitalized patients with suspected thrombotic microangiopathy and appropriate ADAMTS-13 testing (including 21 patients with TTP diagnosis). The PLASMIC model predicted severe ADAMTS-13 deficiency with a c statistic of 0.94 (0.88-0.98). When dichotomized at high (scores 6-7) vs. low-intermediate risk (scores 0-5), the model predicted severe ADAMTS-13 deficiency with positive predictive value 72%, negative predictive value 98%, sensitivity 90% and specificity 92%.[16,17] The tables 7 and 8 present the variants necessary to use the PLASMIC Score and the interpretation of the results.

Table 7: PLASMIC Score variants.

Variable	**0 points**	**1 point**
Platelet count <30 x 109/L	No	Yes
Hemolysis*	No	Yes
Active cancer**	Yes	No
History of solid-organ or stem-cell transplant	Yes	No
MCV <9.0 x 10-14 L (<90 fL)	No	Yes
INR <1.5	No	Yes

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Creatinine <2.0 mg/dL (176.8 µmol/L)	No	Yes
*Reticulocyte count >2.5%, haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL (34.2 µmol/L). **Treated for cancer within the past year.		

Treatment

TTP is a medical emergency that threatens the patient's life, currently the first-line management is plasma exchange, which considerably reduces mortality when available, however, as this is a therapy that is not accessible in all cases, use should be made of the second-line therapies that are available and refer promptly to a third level unit, figure 5 presents the initial algorithm for patients with suspected TTP, the following paragraphs summarize the available treatment alternatives, dividing the management into two stages, initial treatment or acute phase (on which greater emphasis will be placed) and long-term treatment (follow-up).

Table 8: interpretation of PLASMIC score results.

PLASMIC Score	**Risk group**	**Risk of severe ADAMTS13 deficiency***
0-4	Low	0%
5	Intermediate	6%
6-7	High	72%
***Severe deficiency was defined as ADAMTS13 activity level <15%.**		

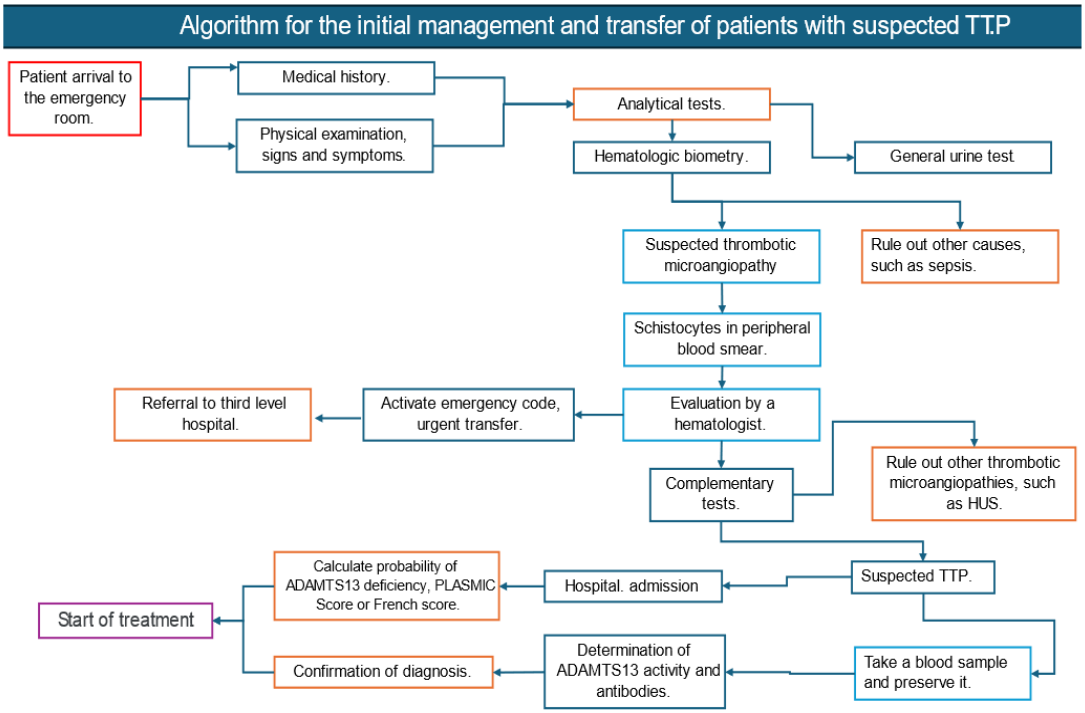

Figure 5: Algorithm for transferring patients with suspected TTP to third-level units or centers with plasma exchange

Treatment During the Acute Phase:

Most guidelines and related articles on the management of TTP mention plasma exchange as a first-line treatment, if possible, immediately within the first 48 hours of the onset of clinical symptoms, as well as the importance of referring the patient to a specialized unit.[14,18]

Currently, studies are being developed that compare the clinical results of immunomodulators, for example caplacizumab or rituximab, as first-line therapy vs. plasma exchange, obtaining similar results in terms of clinical response, refractoriness, mortality and prognosis.[19] The general management of acute TTP will be described below, with greater emphasis on iTTP. Also, the management of TTP in special conditions such as pregnancy and other concomitant diseases will be mentioned. The figure 6 presents an algorithm that summarizes the initial management of patients with suspected/diagnosed TTP in the acute phase.

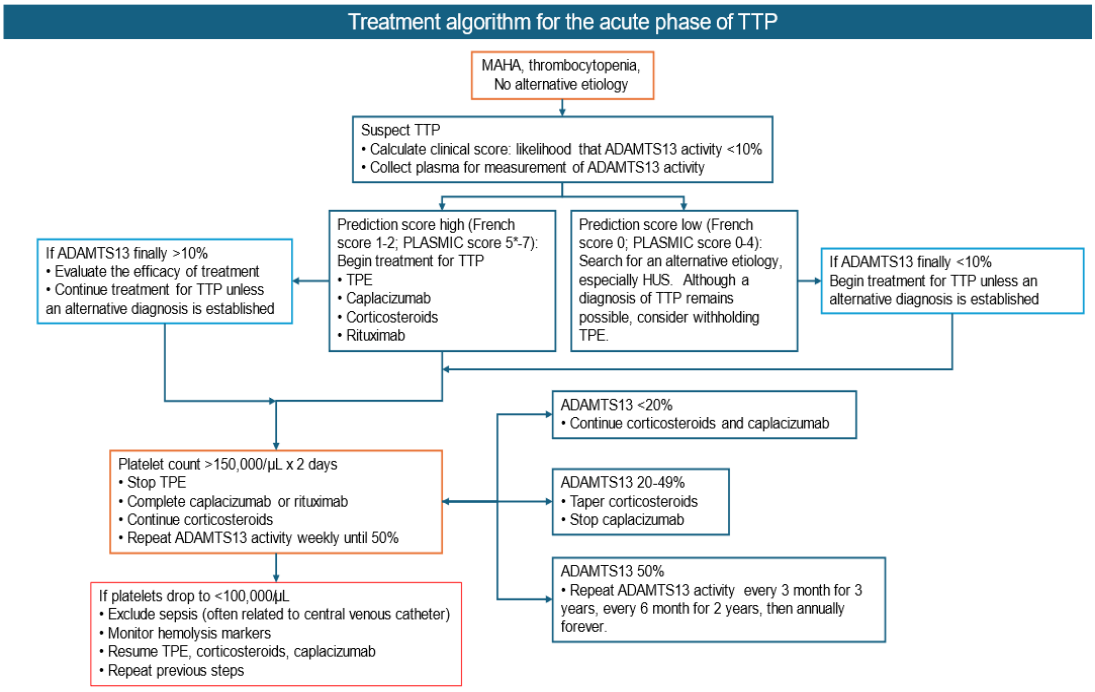

Figure 6: Treatment algorithm for the acute phase of TTP

Management of Acute iTTP:

In the case of patients with acquired iTTP, it is not necessary to distinguish between primary or secondary for management, since the management is the same, and many times this distinction cannot be made quickly.

Plasma Exchange:

Therapeutic plasma exchange (TPE) with fresh frozen plasma (FFP) is the basis of first-line therapy for TTP and should be started within the first 4 to 8 hours of the onset of clinical symptoms.[14,19] The proposed mechanism for TPE is that it provides adequate levels of ADAMTS13 while eliminating circulating anti-ADAMTS13 autoantibodies. Delays in therapy may result in early mortality, which can be prevented by rapid initiation of TPE.[9] Typically, 1 to 1.5 plasma volumes (PV) are exchanged for the first three days, followed by 1 PV exchange every day thereafter. While there is no optimal duration of therapy or prespecified number of procedures required, therapy should be continued daily until a clinical response is achieved and maintained for two days. In patients with refractory TTP or evidence of progressive end-organ damage, more intensive therapy such as twice-daily TPE may be considered. Daily TPE is estimated to reduce initial mortality from 90% to 10-20% mortality.[14]

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Drugs Against von Willebrand Factor:

Caplacizumab: is a humanized immunoglobulin originating from llamas, which targets the A1 domain of VWF and thus prevents its interaction with platelets, is the first drug specifically approved to treat TTP. In the recent Phase 2 TITAN and Phase 3 HERCULES trials, caplacizumab in addition to TPE and immunosuppression significantly reduced the time to normalization of platelet count and the rate of exacerbations compared to placebo. Caplacizumab is well tolerated and has a good safety profile, with the most common side effect being minor bleeding, which is often easily controlled.[9,14,20] The initial dose is 10 mg administered intravenously before the first TPE, followed by 10 mg daily and subcutaneously thereafter until 30 days after completion of TPE. In patients with a body weight <40 kg, a daily dose of 5 mg should be used.[14] As a novel agent, one limitation of the incorporation of caplacizumab into current standard practice is its high cost. In addition, it is noteworthy that it improves platelet count by decreasing VWF activity, but does not resolve the deficiency in ADAMTS13 activity, and is therefore associated with relapses upon discontinuation of the drug.[9,12,14,19,22]

N-acetylcysteine: N-acetylcysteine (NAC) is a mucolytic that is predominantly used to treat pulmonary diseases. Its efficacy in TTP has been examined, since VWF multimers polymerize in a similar manner to mucins. NAC was found to degrade ULVWF multimer chains and inhibit VWF-dependent platelet aggregation and collagen binding in vitro. NAC has been effective in some cases of severe, refractory iTTP, but only a few case reports exist to date.[9] The recommended dose of 150 mg/kg IV bolus followed by 150 mg/kg over 17 hours.[22]

Immunosuppressive Therapy:

Corticosteroids: Steroids are widely used in conjunction with TPE at the initiation of therapy for acute iTTP. Although there are no randomized clinical trials comparing TPE with steroids versus TPE alone, there is high biological plausibility for concurrent immunosuppression given the autoimmune nature of the condition. A small prospective randomized controlled trial comparing prednisone with cyclosporine A as an adjunct to TPE demonstrated that prednisone was superior in the initial treatment of iTTP.[9,21]

The most common regimen is prednisone (PRD) 2.5 mg/kg/day or methylprednisolone 1 g/day for 3 days followed by PRD 1 mg/kg/day tapered based on response. When platelets have recovered, taper treatment after 5-7 days and discontinue in 3 weeks.[12,22]

Rituximab: is a monoclonal antibody against CD20, which specifically targets B cells. Rituximab is most frequently administered during the acute phase of iTTP, usually during the first few days of hospitalization (within the first 3 days). In some studies, rituximab has been shown to be effective as a first-line drug for iTTP (if the presence of anti-ADAMTS13 antibodies has been previously confirmed), and it also appears to be effective in patients with refractory TTP or poor response to TPE. The standard dose of rituximab is 375 mg/m2 administered weekly for a total of four doses, which is recommended for both initial episodes of iTTP and the acute phase of relapse episodes.[9,14,22]

Other immunosuppressive therapies: In patients with contraindications to steroids or with refractory disease, cyclosporine A may be effective. Mycophenolate mofetil has also been used successfully in some case reports. Prior to the use of rituximab, vincristine was used for refractory disease but is no longer preferred. Bortezomib, a proteasome inhibitor that targets

plasma cells, has been used successfully as an alternative agent to rituximab. Cyclophosphamide and/or splenectomy are also options for refractory or chronically relapsing cases.[9,14]

Emerging Therapy:

Recombinant ADAMTS13, still in phase III trials, some studies have shown its efficacy as a first line treatment but focused on cTTP.

Platelet Transfusion:

Although the most recent series of patients do not show a worse prognosis in patients who receive platelet transfusions in TTP, it is advisable to restrict their use to situations of severe or life-threatening bleeding, or prior to the implantation of a central catheter or interventional procedure.[22]

Operational Definitions of Treatment Responses

Before continuing, it is important to mention the operational definitions of treatment responses according to the International Working Group for Thrombotic Thrombocytopenic Purpura.[23]

1. Clinical response: Normalization of platelet count to a level greater than the lower limit of the established reference range (150 x 10^9/L) and LDH level to <1.5 x the upper limit of normal (ULN). If the initial presentation is severe with evidence of significant target organ damage, stabilization of these parameters with improvement in function should also be required to qualify as a clinical response.[9,22,23]
2. Clinical remission: sustained clinical response that is maintained for >30 days after cessation of plasma exchange.[9,23]
3. Exacerbation: Decreased platelet count with increased LDH and need to restart plasma exchange therapy within 30 days of cessation after an initial clinical response is observed.[9.22,23]
4. Relapse: Fall of platelet count below the lower limit of the established reference range (~150 x 10^9/L), with or without clinical symptoms, during a clinical remission that requires restarting therapy. ADAMTS13 activity will likely be <10%.[9,22,23]
5. Refractory TTP: Persistent thrombocytopenia (platelet count <50 x 10^9/L, without increase) and persistently elevated LDH (>1.5 x ULN) despite five plasma exchange therapies along with adequate steroid treatment. If the platelet count remains <30 x 10^9/L, it is classified as severe refractory TTP.[9,22,23]

Treatment of the Acute Phase of cTTP and TTP Associated with Comorbidities:

Treatment of cTTP:

The cTTP, also known as Upshaw-Schulman syndrome, is defined by 3 documented findings in patients which are: ADAMTS13 activity <10 IU/dl, absence of anti-ADAMTS13 autoantibodies and confirmatory variants in the ADAMTS13 gene.[14] cTTP accounts for 2% to 10% of all TTP cases, with an incidence of 1/million.20 Presentation may occur in neonates/children with severe neonatal jaundice, thrombocytopenia, and red cell fragmentation on blood smear. Inheritance of cTTP is autosomal recessive, patients with cTTP may remain asymptomatic until a precipitating event results in a frank episode of TTP.[24,25]***c***TTP may be misdiagnosed as chronic immune thrombocytopenia, Evans syndrome, or atypical hemolytic uremic syndrome. Precipitating events include pregnancy (most common), febrile episodes, infections, and vaccinations.[24,25] Acute episodes in patients with known cTTP can be successfully treated with

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plasma infusions (FFP, 10–15 mL/kg/day). Treatment is continued until clinical response is achieved.[11] In patients with a recurrent cTTP phenotype, prophylactic plasma infusions may be required. Prophylactic plasma infusions have also been shown to improve chronic symptoms unrelated to an acute episode. In patients receiving chronic plasma infusions, the half-life of ADAMTS13 activity has been reported to be 2.5–5.4 days. Consequently, ADAMTS13 activity is expected to return to baseline activity after approximately 5–10 days. Treatments are typically administered every 2–3 weeks, depending on clinical symptoms, platelet counts, and patient preference.[26,27]

Treatment of TTP During Pregnancy:

TTP in the pregnant patient presents many difficulties and challenges. These patients should be managed by a multidisciplinary team that usually includes hematologists, high-risk obstetricians, and occasionally neonatologists. Prompt recognition and differentiation from preeclampsia or HELLP syndrome followed by appropriate treatment is critical, as maternal/fetal morbidity and mortality are high if not recognized.[28] Pregnancy can trigger acute episodes in patients with cTTP who have previously been asymptomatic. Approximately 25-30% of all obstetric TTP cases were due to cTTP. Therefore, a high suspicion of cTTP in pregnant patients is warranted and an appropriate diagnostic workup should be performed if there is no evidence of an inhibitor or anti-ADAMTS13 autoantibodies.[14] Acute treatment of cTTP in pregnancy includes plasma infusions, but more severe cases may require TPE.[9] Caplacizumab is currently not recommended for use during pregnancy because it can cross the placenta and there is a risk of bleeding associated with severely reduced von Willebrand factor activity levels. Low-dose aspirin and prophylactic LMWH should be considered for all women with acute TTP during pregnancy when the platelet count is >50 × 10^9/L. In refractory or relapsed TTP, additional immunosuppression may be necessary. Options include prednisolone, azathioprine, cyclosporine, and rituximab. [9,14,29] In most cases, termination of pregnancy is not necessary. Careful fetal monitoring with regular assessment of fetal growth and placental function is recommended. Antenatal care and delivery should be performed in specialized tertiary obstetric and fetomaternology units and a regional TTP center.[14] An algorithm for the management of patients with TTP during pregnancy is presented in figure 7.

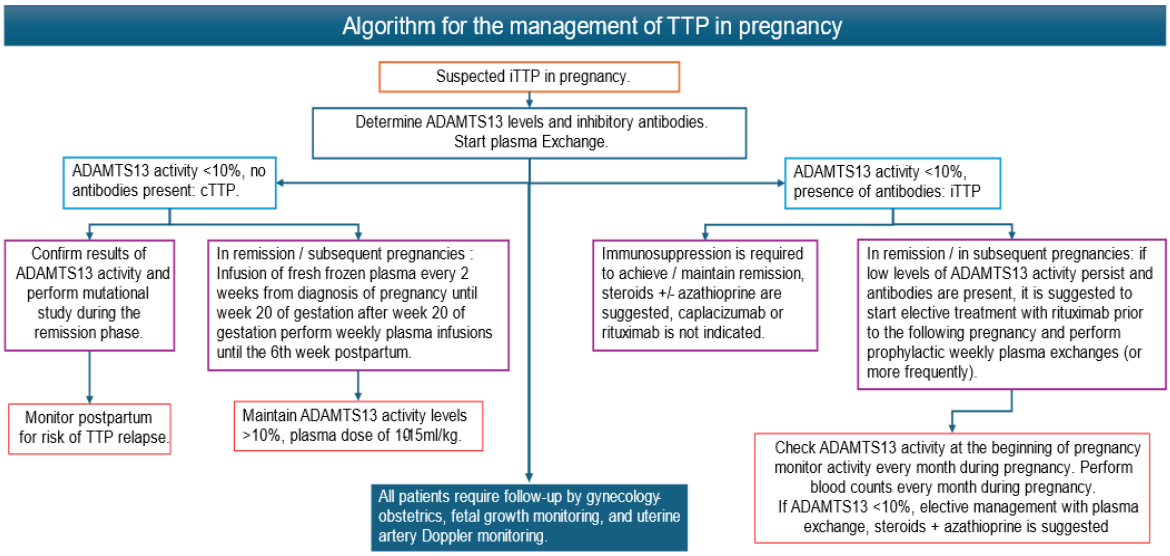

Figure 7: algorithm for the treatment of TTP in pregnancy.

Treatment of the Acute Phase of TTP in Patients with HIV:

TTP is associated with HIV most often when the patient presents with a high viral load. Presentation with de novo TTP and relapse can also occur in those treated with antiretroviral therapy and may indicate non-compliance or drug resistance. Most cases appear to respond to TPE/corticosteroids and HAART, therefore additional immunomodulatory therapy may not be required. When TTP presents with undetectable viral loads or if unresponsive to first-line therapy, treatment with rituximab may be used. Early involvement of the infectious disease team is recommended to ensure robust follow-up. As with other medications for those receiving TPE the timing of administration of HAART and TPE should aim to ensure maximum exposure to the medication. In patients with low/undetectable viral load, ADAMTS13 relapse or clinical relapse should be treated as standard iTTP.[14,30]

Treatment of TPP Associated with Other Autoimmune Diseases:

Immune-mediated TTP may occur in the setting of other autoimmune disorders (e.g., SLE/Sjögren's) and is frequently associated with the presence of other autoantibodies. Management of acute TTP will not be altered in this setting; however, long-term management and monitoring will require input from other relevant medical specialists (e.g., rheumatologist/renal physician).[14]

Treatment of TPP Associated with Cancer:

People with cancer have several reasons for developing TMA and presenting as TTP. The most prevalent cancer is adenocarcinoma, typically gastric, breast, prostate or lung, and in most cases, these were metastatic. ADAMTS13 activity is not severely reduced in patients with cancer-associated TMA and therefore there is no role for TPE in this patient group.[14] There is no standard therapy, management should be life-sustaining therapy and treating the underlying cancer. [22]

Treatment of TPP Associated with Transplants:

TPP is associated with solid organ and stem cell transplantation and, while heterogeneous in its presentation and end-organ effects, the underlying pathology is primarily related to self-propagating endothelial injury and complement activation. ADAMTS13 activity levels are not severely reduced and TPE is not indicated. Elucidation of the role of complement has led to a move toward treatment with terminal complement blocking agents.[14,31]

Treatment of TPP in Jehovah's Witnesses and Other Groups That Do Not Accept Blood Component Transfusion:

Jehovah's Witnesses may not accept exogenous blood products for religious or other reasons. As TPE is the mainstay of treatment for acute episodes, this presents a unique challenge in the treatment of these patients. Several regimens have been previously tested, including vincristine and plasma exchange with albumin or cryosupernatant replacement. With the use of caplacizumab in conjunction with enhanced immunosuppressive therapy, successful treatment without TPE has been described not only in this patient population but also in other selected patients, including one with anaphylaxis to plasma.[9,14,32,33]

Treatment Options and Actions to Be Taken in Case of Treatment Failure

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Table 9 presents treatment alternatives for patients in whom treatment objectives are not achieved or in those patients who are asymptomatic but who maintain persistently low levels of ADAMTS13 activity.

Treatment of Patients After the Acute Episode (Long-Term Follow-Up)

Close clinical and biological monitoring should be carried out in all patients who have had an acute episode of iTTP. This includes, apart from the complete blood count and hemolysis parameters, the determination of ADAMTS13 activity and the presence of the inhibitor. Regarding the frequency of the check-ups, a possible scheme would be weekly, in the first month; monthly, during the following quarter, and quarterly, until the first year is completed. Subsequently, every 6 months until the second year and annually from the third year onwards.[22]

Table 9: Treatment options for treatment failure or asymptomatic cases with persistently low levels of ADAMTS13 activity.

Potential treatment options in case of refractoriness, exacerbation, relapse and persistently low levels of ADAMTS13 activity in iTTP.	
Scenery.	**Treatment option**
Refractoriness	**Re-assess ADAMTS13 activity and presence of inhibitor.** In the meantime: •→Intensify PRs to 1.5 plastic volumes. •→Intensify steroid regimen (e.g., methylprednisolone 1 g/day IV for 3 days). •→Start rituximab 375 mg/m^2/dose (after checking for anti-ADAMTS13 antibodies). Two possible dosing schedules: weekly on days 1, 7, 14, 21 or days 1, 4, 7, 14. •→Add caplacizumab if not used first-line or resume if discontinued (1st dose 10 mg IV, then 10 mg/day SC within first 4 hours after TPE). **Evaluate adding according to clinical-analytical evolution:** •→Vincristine 1 g/m^2 (maximum 2 g) IV. •→Cyclophosphamide PO or IV 500 mg/2 week (6 total doses). •→Bortezomib 1.3 mg/m^2, 2 times a week for 2 weeks. •→N-acetylcysteine 150 mg/kg IV daily for 17 hours. •→Cyclosporine, 300 mg/day PO or 2-3 mg/kg/day •→Splenectomy, as a last resort.
Exacerbation	**Rule out any cause of exacerbation, especially catheter-related sepsis** •→Add rituximab, if not used. •→Resume TPE, if not already discontinued. •→Intensify steroid regimen. •→Add caplacizumab (if not given initially or if discontinued).
Relapse	**•→Start RP 1-1.5 plastic volumes** •→Immunosuppression with glucocorticoids: methylprednisolone 1 g/day for 3 days, 1 mg/kg/day. •→Rituximab 375 mg/m^2/d weekly on days 1, 7, 14, 21 or days 1, 4, 7, 14 •→Caplacizumab (1st dose 10 mg IV, then 10 mg/day subcutaneously in the first 4 hours after TPE). •→Splenectomy if the patient presents multiple recurrences.
Asymptomatic patient with persistently low levels of ADAMTS13 activity in iTTP.	Rituximab 375 mg/m^2/week is recommended for 1-4 weeks, especially in cases where a decrease in ADAMTS13 activity and the appearance of anti-ADAMTS13 antibodies are detected during follow-up. Aim to achieve 10-20% ADAMTS13 activity with rituximab; once the goal is achieved, measure activity levels every 15 days until normal (depending on the laboratory), then follow up every 3 months in the first year, every 6 months in the second year, and an annual measurement thereafter.

ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; IV: intravenous; PO: oral (per os); iTTP: acquired thrombotic thrombocytopenic purpura; TPE: therapeutic plasma exchange. Adapted from reference 22.

For pregnant women with a history of iTTP, it is recommended that platelet count and ADAMTS13 activity be monitored at least once per trimester. Recurrent iTTP during pregnancy should be treated with plasmapheresis and corticosteroids; rituximab should be postponed until after pregnancy given the potential effects on the fetus. If ADAMTS13 activity falls to 10-20% in the absence of thrombocytopenia and other signs of microangiopathy, low-dose corticosteroids may be considered to increase ADAMTS13 activity. If ADAMTS13 activity falls below 10%, prophylactic plasmapheresis may be considered. Low-dose aspirin therapy should be considered as prophylaxis for preeclampsia.[10]

It is important to intentionally search for and adequately monitor long-term complications that patients may experience after an acute episode of TTP. The main sequelae that patients may experience are:

- Mental/psychiatric (depression) and cognitive disorders
- Diagnosis of systemic lupus erythematosus and other autoimmune diseases.
- Renal injury with microalbuminuria and high blood pressure.
- Higher risk of death from cardiovascular events such as stroke and ischemic heart disease compared to the general population.

The figure 8 describes some of the actions to reduce complications in patients with TPP.[10]

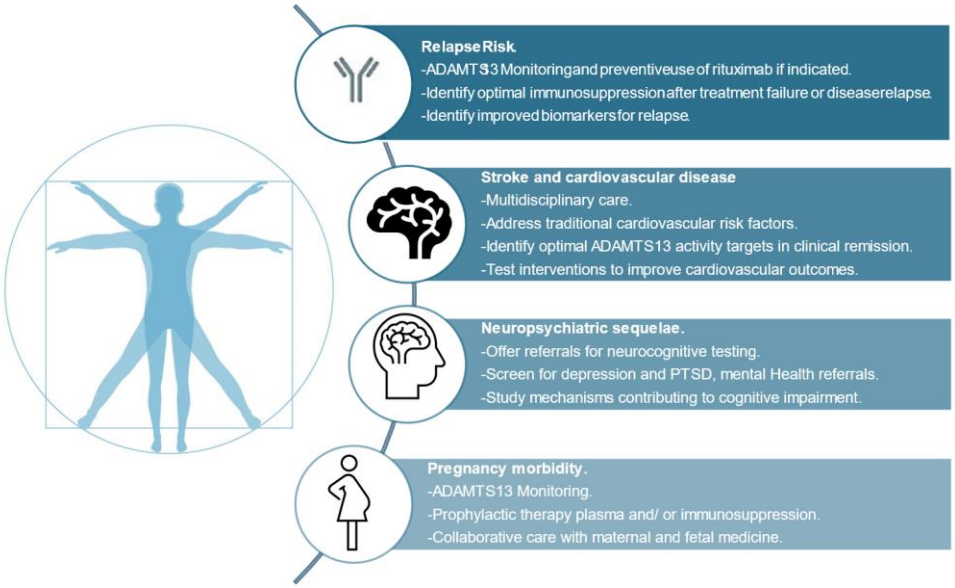

Figure 8: Interventions to reduce the risk of complications in patients with TTP.

Prognosis

The patient's prognosis is optimal when a timely diagnosis is made, and treatment is initiated as soon as possible. Neurologic or cardiac involvement at presentation, need for intubation, and advanced age are poor prognostic factors. signs. Race also influences prognosis, with nonwhite

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individuals having a higher risk of exacerbation or relapse but lower mortality. With the use of plasma exchange, mortality has decreased from >90% to between 10% and 30%. Approximately 90% of patients will respond to plasma exchange within 3 weeks, and most will respond within 10 days. Although it cannot be predicted who will respond, it appears that those without severe deficiency of ADAMTS13 activity and without evidence of ADAMTS13 inhibitors are more likely to have transient or incomplete responses to therapy. Other laboratory tests (eg, platelet count) are not by themselves predictive; however, refractory disease is associated with a worse prognosis. Those with a severe ADAMTS-13 deficiency are more likely to have a relapsing course.[14] The table 10 summarizes some of the prognostic factors in patients.

Table 10: Prognostic factors for relapse and mortality in patients with TTP.

Prognostic factors for relapses and mortality in patients with iTTP	
Relapse	Mortality
young.	Delay in diagnosis and initiation of treatment.
Blood group different from O+.	Advanced age.
Previous recurrence.	Elevated levels of lactic dehydrogenase.
ADAMTS13 activity <10% during follow-up.	Elevated troponin levels.
	Low levels of ADAMTS13 activity with high levels of antibodies against ADAMTS13.
	Lack of rapid response to treatment with plasma exchange.

CONCLUSION

Thrombotic thrombocytopenic purpura is a potentially fatal pathology that is difficult to diagnose. The clinical presentation is nonspecific, so an adequate approach must be taken to rule out other pathologies within the group of thrombotic microangiopathies. Unfortunately, it is not always possible to have all the human resources (for example, hematologists) or materials (specialized laboratory studies) in all medical care units, which delays the diagnosis and initiation of treatment, and thus management, increasing mortality and complications in the patient.

There should be a protocol in the local hospital network for the approach, transfer and initiation of management of patients with suspected TTP, since very few units have TPE (therapy which has reduced initial mortality from close to 90% to 10-20% if it is available and is started in the first hours of the onset of the clinical picture). Although the current trend is the use of drugs such as Caplacizumab or rituximab as first-line drugs that can replace TPE, their high cost limits their access to patients.

It is extremely important that after the resolution of an acute episode, control of modifiable risk factors and monitoring of complications is carried out. Likewise, patients should be referred to the mental health area, since among the main sequelae after an episode of PTT are those related to depression and/or post-traumatic stress, both conditions affecting the quality of life and productivity of patients.

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Declarations

Conflict of interest: No conflicts of interest.

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