French National Diagnosis and Care Protocol (PNDS)

Thrombotic Thrombocytopenic Purpura

This French National Diagnosis and Care Protocol (PNDS; *Protocole National de Diagnostic et de Soins*) was coordinated by Prof. Paul Coppo of the French National Reference Center for Thrombotic Microangiopathies (CNR-MAT; *Centre de référence des microangiopathies thrombotiques*) of Hôpital Saint-Antoine, in collaboration with Prof. Agnès Veyradier of Hôpital Lariboisière and Prof. Ygal Benhamou of Hôpital de Rouenunder under the aegis of the French Healthcare Network for Rare Immune Hematological Diseases (MaRIH).

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Abbreviations

ADAMTS13	A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13 (or von Willebrand's factor-cleaving proteinase)
aHUS	Atypical hemolytic uremic syndrome
AI-FFP	Amotosalen-inactivated fresh frozen plasma
ANA	Antinuclear antibody
ANSM	*Agence nationale de sécurité du médicament et des produits de santé* – French National Agency for the Safety of Medicines and Health Products
CBC	Complete blood count
CNR-MAT	*Centre National de Référence des Microangiopathies Thrombotiques* – French National Reference Center for Thrombotic Microangiopathies
COVID-19	Coronavirus disease 2019
cTTP	Congenital thrombotic thrombocytopenic purpura
DDAVP	Desmopressin
DGOS	*Direction Générale de l'Offre de Soin* – General Directorate of Healthcare
DIC	Disseminated intravascular coagulation
FDA	U.S. Food and Drug Administration
FLAIR	Fluid-attenuated inversion-recovery
HAS	*Haute Autorité de Santé* – French National Health Authority
HCG	Human chorionic gonadotropin
HELLP	Hemolysis, Elevated Liver enzymes, Low Platelet count
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTA	Hypertension
HUS	Hemolytic uremic syndrome
IgG	Immunoglobulin G
ISTH	International Society on Thrombosis and Haemostasis
iTTP	Immune-mediated thrombotic thrombocytopenic purpura
LDH	Lactate dehydrogenase
LTC	Long-term care
MA	Marketing Authorization
MAT	Thrombotic microangiopathy
MDPH	*Maisons Départementales des Personnes Handicapées* – Departmental Centers for Disabled People
MDT	Multidisciplinary team meeting

MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
PNDS	French National Diagnosis and Care Protocol
Q-FFP	Quarantine fresh frozen plasma (at least 60 days)
RTU	*Recommandation temporaire d'utilisation* – Temporary recommendation for use
STEC	Shiga toxin-producing Escherichia coli
Stx	Shiga toxin
SD-FFP	Solvent/detergent-treated fresh frozen plasma
TPE	Therapeutic plasma exchange
TTP	Thrombotic thrombocytopenic purpura
VEGF	Vascular endothelial growth factor
vWF	von Willebrand factor

Summary for general practitioners

Thrombotic microangiopathies (TMAs) are pathologies characterized by the association of mechanical hemolytic anemia, peripheral thrombocytopenia due to consumption, and organ damage of varying severity that can affect, in particular, the brain, kidney or heart. The clinical manifestations of TMA syndromes relate to the formation of microthrombi that obstruct the lumen of the capillaries and arterioles of the microcirculation. This leads to tissue hypoxia that is responsible for organ damage. In all cases, diagnosis must be made quickly so that specialized emergency care can be organized.

The various types of TMA comprise thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and other situations when TMA may occur, such as HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome in pregnant women, postpartum TMA, TMA related to cancer or to certain chemotherapies, TMA associated with medications, such as calcineurin inhibitors, particularly systemic autoimmune diseases, allogeneic hematopoietic stem cell transplants, and some infections, especially human immunodeficiency virus (HIV) infection.

The purpose of this PNDS is to describe how to manage the following forms of TTP:

- Immune-mediated TTP (iTTP);

- Congenital TTP (cTTP);

- TTP during pregnancy.

TTP is therefore a specific form of TMA characterized by **severe thrombocytopenia** and **damage to one or more organs, particularly the brain and heart**. TTP is a rare disorder, with an incidence of between one and two cases per million inhabitants per year; its prevalence is 13 cases per million inhabitants. This disorder results from **severe ADAMTS13 deficiency**; ADAMTS13 is the enzyme involved in regulating the size of plasma von Willebrand factor (vWF) multimers. The deficiency can be **congenital** (related to biallelic mutations in the ADAMTS13 gene) or **autoimmune** (linked to anti-ADAMTS13 antibodies). In the autoimmune form, TTP occurs mostly in females (3 females per 1 male) in the fourth decade. Black subjects and North African subjects are more exposed. Anti-ADAMTS13 antibodies occur transiently and disappear permanently or may persist in remission and then inhibit ADAMTS13 over the long term, exposing the patient to approximately 40% risk of relapse up to year 1 and 74% at year 7, if preventive measures are not provided. This emphasizes **the importance of long-term follow-up in patients who have recovered from iTTP to monitor ADAMTS13 activity and recurrence of severe deficiency (ADAMTS13 activity <20%) can be identified before clinical relapse,** which necessitates preventive treatment to correct ADAMTS13 activity. This treatment involves administering monoclonal antibody directed against B cells, typically rituximab. During long-term follow-up, **iTTP patients are at increased risk of developing comorbidities that shorten life expectancy**: cardiovascular diseases, systemic autoimmune diseases occurring in approximately 10% of patients at year 10 of follow-up (typically systemic lupus erythematosus, Sjögren's syndrome, and more

rarely, Still's disease and systemic scleroderma) and malignant diseases. An impact on cognitive function and mood is common.

In the congenital form, the first flare-up may appear at birth (typically look in the patient's health record for an exchange transfusion at birth for jaundice) or in childhood; more rarely, the diagnosis is made in adulthood during visceral complications. **The congenital form can manifest for the first time in pregnant women** (50% of TTP occurring in pregnant women during a first pregnancy are of congenital origin).

TTP is a serious and spontaneously fatal disease, but its prognosis can be excellent if rapid and appropriate management is ensured. Current therapeutic strategies achieve remission rates of more than 95%. **Until the initiation of treatment, however, patients are at risk of sudden death, and the vast majority of TTP-related deaths currently occur in patients who have been unable to receive timely treatment.** It is therefore important that all practitioners who may be faced with this pathology, whether general practitioners or specialists, are aware of this diagnosis despite its rarity and are familiar with first-line treatment.

1. Initial assessment

The initial assessment is multidisciplinary and coordinated by a hospital physician. It is performed by:

- The treating physician who may first suspect the diagnosis of TTP or TMA generally when faced with the clinical picture and laboratory abnormalities;

- The specialist departments receive patients, where the diagnosis is suspected and confirmed, and differential diagnoses are eliminated. Prognosis (based on age and organ damage) will be assessed.

- French National Reference Center for Thrombotic Microangiopathies (CNR-MAT) and/or the constituent centers and centers of expertise, where it will be evaluated based on history, clinical practice and standard laboratory tests if it is an autoimmune or congenital form of the disease.

- The specialists involved based on the type of organ damage.

The clinical picture may include **hemorrhagic syndrome** (purpura/bruising related to thrombocytopenia), **signs of anemia** (dyspnea, pallor) and signs of **visceral pain**; some are nonspecific (headache, abdominal pain), while others reflect central nervous system involvement (confusion, convulsions, focal motor deficit that can vary over time and successively affect different regions of the brain) or kidney involvement (renal failure, rarely oliguria or anuria with high blood pressure). Cardiac involvement, resulting in arrhythmia, is possible. A **prodromal phase** associated with asthenia, arthralgia, myalgia and abdominal and lumbar pain, which can suggest an infectious process, often precedes the onset of TTP by a few days.

Thrombocytopenia, typically severe in TTP (<30 x 10^9/L), in contrast to a normal or elevated leukocyte count with respect to neutrophils. There may be **renal failure**, which is typically moderate in TTP (serum creatinine <200 µmol/L), while it is severe in HUS (serum creatinine ≥ 200 µmol/L).

Anemia is normocytic and regenerative (reticulocytes typically >100 x 10^9/L), and

associated with **signs of hemolysis** (elevated free bilirubin, low or undetectable haptoglobin, elevated LDH). Hemolysis is **mechanical,** i.e., associated with the presence of schistocytes (or fragments of red blood cells) on the blood smear. The **direct antiglobulin test** (formerly known as the direct Coombs test) is usually negative.

Important diagnostic aspects:

The role of treating physicians in the diagnostic process is essential because **they may be the first to see the patient if the patient presents with a hematological picture alone or associated with clinical signs that are still mild. In this context, it is important for the treating physician not to conclude the autoimmune origin of cytopenia and to urgently refer the patient to a hospital to initiate treatment while waiting for the diagnosis of TTP to be established using the ADAMTS13 activity assay.**

It may be necessary consults with the CNR-MAT and/or its constituent centers and centers of expertise (list of centers available on the DGOS website – www.sante.gouv.fr – or CNR-MAT – www.cnr-mat.fr) for a definitive diagnosis.

2. Management of TTP in the acute phase

The initial management of TTP, whether congenital or autoimmune, is only considered in a hospital setting, most often in an intensive care unit. It requires close collaboration between the TMA specialist (intensive care specialist, hematologist, internist, nephrologist, pediatrician) and the nonspecialist hospital physician. In difficult cases, these practitioners should use the regional network of centers of expertise or reference centers for thrombotic microangiopathies.

The objectives of therapeutic management for the treating physician are to help with the urgent initiation of adequate treatment through rapid diagnosis and the organization of emergency hospitalization at the nearest facility to avoid additional morbidity or mortality due to a delay establishing a diagnosis and implementing therapy. In the autoimmune form of the disease, treatment consists of the combination of plasma exchange (TPE) (to provide the ADAMTS13 protein), caplacizumab (to neutralize the proaggregating activity of the vWF) and immunosuppressants (corticosteroids and rituximab, to inhibit the formation of anti-ADAMTS13 antibodies). In the congenital form, it involves providing the ADAMTS13 protein through regular plasma infusions to avoid the presence of cytopenia and hemolysis and to prevent long-term organ damage related to the formation of microthrombi.

3. Specific follow-up of TTP by general practitioners during acute episodes

If the acute phase of the disease is essentially managed in a hospital setting (detailed in the "Summary for specialists" section), **the treating physician has a crucial role in the long-term follow-up of the patient:**

1) For both forms of the disease (autoimmune and congenital):

- The treating physician takes steps to **manage the disease as part of long-term care (LTC)**;

- They promote rapid social and professional reintegration during the TTP episode;

- They provide part of the **psychological support** and must limit the psychological consequences of the disease and its repercussions on the family and the patient's social and professional lives, thus maintaining the highest possible quality of life;

- They **must know the possible triggering factors of an episode** (vaccines, infections, surgical procedures, etc.), especially in the context of known severe ADAMTS13 deficiency, and urgently request a complete blood and platelet count in the case of suspicion of relapse. Thrombocytopenia or cytopenia warrant **referring the patient to an emergency hospital setting**;

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- Regarding vaccination, **the treating physician must discuss with the specialist physician any vaccination plan based on the current recommendations of the French high council for public health**. Since vaccines trigger relapses in patients with severe ADAMTS13 deficiency, it is important not to administer vaccines in the absence of measures to at least partially correct ADAMTS13 activity (ideally at levels >20%). In cTTP, vaccines should be administered immediately after a plasma infusion. In iTTP, vaccines should be preferentially administered when the patient has an ADAMTS13 activity ≥ 20%, and if possible, at a sufficient time after rituximab therapy to achieve optimal vaccine response. Pneumococcal vaccination is recommended, as approximately half of patients may require rituximab treatment repeatedly during follow-up, and some may require splenectomy. This vaccination is based on the Prevenar 13® vaccine followed two months later by the Pneumovax® vaccine; it is important to adhere to the frequency and timing of administration of these two vaccines. The flu vaccination is strongly recommended in adults, especially if repeated treatment with rituximab is used. **TTP is not a contraindication to vaccination against SARS-CoV-2, while requiring the precautions needed for other vaccines.** In children with cTTP, the vaccination schedule should be followed as closely as possible and discussed with the specialist on a case-by-case basis to cover the vaccination injections with a plasma infusion.

- The treating physician should **monitor and manage cardiovascular risk factors early and throughout life**. In this sense, follow-up clinical and laboratory examinations should be performed regularly during monitoring:

  Fasting blood glucose,

  Lipid profile (total cholesterol, HDL and LDL cholesterol, triglycerides),

  Electrocardiogram,

  Depending on the situation and following cardiological advice: cardiac ultrasound, stress test, coronarography, etc.,.

  The frequency of this monitoring must be adjusted based on the underlying risk and the situation.

- Finally, in the period between visits to the specialist, the treating physician treats intercurrent diseases relating to the pathology and situation in collaboration with the specialist or the physician at the reference center and/or center of expertise.

2) For iTTP:

- The treating physician must stress the need for the patient to **adhere to the program for the regular monitoring of ADAMTS13 activity**, organized in a hospital setting, to help prevent relapses;

- They must also detect, prevent and manage infections that may complicate treatment with rituximab, as well as other comorbidities that may occur during follow-up: **systemic autoimmune diseases** and **pathological malignancies**;

- Following gynecological advice, they suggest **contraception and, as a precaution, avoid those containing estrogens,** which has a suspected role in the onset of iTTP.

5) For cTTP:

- The treating physician must look for and prevent the occurrence of progressive organ damage, secondary to chronic ischemic lesions showing insufficient therapeutic plasma intake (neurocognitive disorders and depressive syndrome, renal failure, heart disease, ischemic retinopathy, etc.);

It is important for the treating physician to look for all comorbidities as part of long-term follow-up, since they contribute to a reduction in life expectancy in patients who have survived an episode of TTP in any form.

This follow-up is multidisciplinary and coordinated by a physician specializing in TMA in conjunction with the general practitioner, the local hospital physician and the regional network of centers of expertise or national reference center for the most difficult cases, hospital correspondents from various specialties, and the help of allied health professionals and medical and social professions. Informing patients and their close family and friends about the disease, the risk of relapses and the manifestations that are warning signs is an integral part of therapeutic management.

4. Useful information

All healthcare professionals and patients can be informed of patient advocacy groups.

- PNDS available on the French National Health Authority website: www.has-sante.fr/, *ALD* (LTC) section;

- French National Reference Center for Thrombotic Microangiopathies (CNR-MAT): www.cnr-mat.fr

- General information: www.orphanet.net/ (Thrombotic Microangiopathies [generic term] section)

- French Society of Hematology (SFH): https://sfh.hematologie.net/

- French National Society of Internal Medicine (SNFMI): https://www.snfmi.org/

- Patient advocacy group: assocadamts13@hotmail.com

- French Healthcare Network for Rare Immune Hematological Diseases (MaRIH): Email: contact@marih.fr – Website: www.marih.fr
  Facebook: @Filiere.MaRIH – Twitter: @Filiere_MaRIH

- Answering TTP Foundation, a Canadian patient advocacy group: https://www.answeringttp.org/

Summary for specialists

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a particular form of thrombotic microangiopathy (TMA) characterized by mechanical hemolytic anemia (associated with the presence of schistocytes), profound peripheral thrombocytopenia and damage to one or more organs (especially the brain and heart), in relation to the formation of thrombi in the vessels of the microcirculation. TTP is a rare disease resulting from severe ADAMTS13 deficiency; ADAMTS13 is the enzyme involved in regulating the size of plasma vWF multimers. This deficiency can be congenital (related to biallelic mutations in the ADAMTS13 gene) or autoimmune (linked to anti-ADAMTS13 antibodies). Advances in the understanding the pathophysiology of TTP now allow us to better understand the effectiveness of certain treatments used to date empirically and to consider targeted therapies. TTP is a serious disease, but its prognosis can be excellent, provided that rapid and appropriate management is ensured. It is therefore important that practitioners who may be confronted with this pathology (treating physicians, hematologists, intensive care specialists, emergency physicians, internists, etc.) are aware of this diagnosis despite its rarity and know the first-line treatment. Better knowledge of this pathology thus represents an important challenge to further improve its prognosis. In all cases, diagnosis must be made quickly so that specialized emergency care can be organized.

Objectives

The objective of this French National Diagnosis and Care Protocol (PNDS) is to explain to the professionals concerned the current optimal diagnostic and therapeutic management and the care pathway for patients with TTP, in its autoimmune and congenital forms and in pregnancy. HUS was the subject of a PNDS written by the CNR-MAT in association with the reference centers for rare kidney diseases. The aim of this PNDS is to optimize and harmonize the management and monitoring of TTP throughout the country. It also makes it possible to identify the propriety medications used for an indication not provided for in the Marketing Authorization (MA), as well as the products, services and propriety medications necessary for patient care but not usually used or reimbursed.

This PNDS serves as a reference for treating physicians (physician designated by the patient to the French national health insurance office) in consultation with the specialist, particularly when establishing the care protocol jointly with the consulting physician and the patient in the case of a request for exemption of copayment for an off-list condition.

However, the PNDS cannot consider all specific cases, comorbidities or complications, therapeutic features, hospital care protocols, etc. It cannot claim the exhaustiveness of possible management practices, nor can it substitute the individual responsibility of the physician to their patient. Various novel drugs are also being developed for TTP, and therapeutic algorithms are expected to change in the coming years. The protocol describes the standard of care for patients with TTP at the date of its publication. It will be updated based on validated new data.

A more detailed document serving as a basis for the development of the PNDS and including

in particular the analysis of the bibliographic information identified (scientific rationale) is available on the reference center's website (http://www.cnr-mat.fr).

Methodology

This PNDS was developed in accordance with the "Method of developing a national protocol for diagnosis and care of rare diseases" published by the French National Health Authority in 2020 (methodological guide available on the HAS website: www.has-sante.fr).

The main sources used to develop the guide were as follows:

- A summary of the main studies and updated data (non-exhaustive review) published in the literature (PubMed) concerning the methods of diagnosis, characteristics and treatment of congenital and autoimmune TTP in adults and children.
- For therapeutic aspects, various grades of recommendations were issued, depending on the data from the literature based on the levels of evidence set out in the table below (reference HAS 2020).
- This document illustrates the experience of French clinicians and clinical pathologies working in teams and networks since May 2000 on the subject of TTP and TMA in general. This experience, which has accumulated for over more than 22 years, is also enriched by a multidisciplinary approach to these pathologies, which our network has always promoted. This document was thus written by hematologists, internists, intensive care specialists and nephrologists.

Epidemiology

TTP represents about 25% of all TMAs. In the autoimmune form (autoimmune TTP, or iTTP), TTP occurs mostly in women (3 females to 1 male) during the fourth decade. Black subjects and North African subjects seem to be more exposed. The incidence of TTP is estimated to be 1 to 2 cases per million inhabitants per year, and its incidence is 13 cases per million inhabitants. Predisposing conditions for iTTP were identified in 50% of cases and included autoimmune diseases (typically systemic lupus erythematosus and Sjögren’s syndrome), pregnancy, HIV infection or, rarely, cancer. Genuine autoimmune TTP has been reported following the use of antiplatelet agents, immunomodulators, such as lenalidomide, in patients with multiple myeloma or checkpoint inhibitors in patients with solid tumors.

In congenital TTP, or cTTP (formerly called Upshaw-Schulman syndrome), nearly 200 mutations of the ADAMTS13 gene have been reported so far. Patients are double heterozygous or homozygous, and the disease is transmitted in an autosomal recessive fashion. The first flare-up of the disease usually occurs before the age of 10 and in more than 50% of cases from birth.

TTP associated with pregnancy accounts for between 10% and 30% of TTP observed in adults. The first episode of TTP in pregnant patients is congenital in 24% to 66% of cases, while the frequency of cTTP in adults with TTP without pregnancy is less than 5%. In cTTP, the first pregnancy almost systematically triggers an episode of TTP, which occurs in the third trimester in 75% of cases.

Pathophysiology

The pathophysiology of TTP is the result of an imbalance between the activity of the ADAMTS13 enzyme and its substrate, the von Willebrand factor (vWF).

VWF is a multimeric glycoprotein that is essential for the adhesion of platelets to the subendothelium and their aggregation after the occurrence of a vascular breach. These properties are exacerbated in the blood microcirculation because the high shear rates of blood flow present in this part of the vascular tree increases the affinity of vWF for platelets. The largest multimers of vWF, known as high-molecular-weight multimers, have the highest adhesive capacity for the subendothelium and platelets. Physiologically, the size of the vWF multimers and their adhesive capacities are regulated by the metalloprotease ADAMTS13 (A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13), which is a protein with the specific function of cleaving vWF high-molecular-weight multimers to lower molecular weight multimers. The ADAMTS13 gene is located on chromosome 9, and its main site of synthesis is the liver (stellar cells, known as Ito cells). Severe functional deficit of ADAMTS13 is insufficient to develop TTP; it is also necessary to activate the endothelium, which leads to an increase in the circulating amounts of vWF secreted by endothelial cells. This endothelial activation is nonspecific and may be secondary to a minor infection, which often precedes the onset of TTP. A seasonal variation in the onset of TTP was thus observed in a series of 100 cases with more episodes occurring during the summer, suggesting the influence of an environmental factor.

Although the significance of environmental factors remains to be determined with precision, these results clearly confirm the major role of ADAMTS13 deficiency in the pathophysiology of TTP. In the absence of ADAMTS13, hyperadhesive multimers released by activated endothelium accumulate and are responsible for the spontaneous formation of microthrombi within the capillaries and arterioles of the microcirculation. Platelets are thus consumed in these microthrombi, explaining thrombocytopenia. These microthrombi are responsible for ischemia and disseminated visceral pain at the origin of the clinical picture of TTP. In addition, red blood cells fragment when they come into contact with these microthrombi, explaining intravascular hemolysis.

Severe ADAMTS13 deficiency is explained by two mechanisms: one congenital (<5% of cases) linked to biallelic mutations of the ADAMTS13 gene, which globally overlaps with rare pediatric forms, and the other acquired (>95% of cases), linked to autoantibodies directed against ADAMTS13 in 75% of cases and that corresponds to the adult forms. Anti-ADAMTS13 antibodies may have an *in vitro* inhibitory effect against ADAMTS13 in 50–80% of cases. The IgG isotype is more common. These antibodies occur transiently and disappear permanently or may persist in remission and then inhibit ADAMTS13 in the long term, exposing the patient to approximately a 40% risk of relapse in the first year and 74% at 7 years, if preventive measures are not taken. This helps us understand the importance of long-term follow-up in patients who have recovered from iTTP in order to monitor ADAMTS13 activity and identify the recurrence of a severe deficiency prior to clinical relapse.

Severe ADAMTS13 deficiency appears to be specific for TTP, since the activity of ADAMTS13 was found to be substantially normal in most HUS cases, as well as in other TMA syndromes, such as HELLP syndrome, catastrophic antiphospholipid syndrome and TMA in the context of allogeneic hematopoietic stem cell transplantation. Severe sepsis is, however, a special situation, since in this context, a large deficit (<10% of activity) could sometimes be found, probably related to protein consumption or cleavage by proteolytic enzymes.

In adults and children, iTTP has been associated with certain loci of the HLA (human leucocyte antigen) system, such as the locus carrying the DRB1*11 and DQB1*03 alleles, which is thus a risk factor. Conversely, other loci, such as DRB1*04, seem to be protective against the disease.

Initial assessment

Main objectives

- Knowing how to identify the signs suggestive of a TMA syndrome and those that can lead to the diagnosis of TTP.

- Implementing an adapted treatment as an emergency.

- Referring the patient toward an appropriate care facility.

Professionals involved

The initial management of patients with TTP is multidisciplinary and coordinated by a hospital physician in connection with the TMA reference center (CNR-MAT) or the center of expertise in the network. Various specialties must be involved, particularly intensive care specialists and emergency physicians, internists, clinical immunologists, hematologists, nephrologists,

physicians of apheresis centers and, depending on the clinical picture, pediatricians, obstetricians, cardiologists and neurologists.

Confirming the diagnosis

Circumstances of discoveries

The diagnosis of TTP should be immediately considered when faced with any TMA syndrome, which is characterized by the association of:

1. Peripheral **thrombocytopenia** (characterized by its association with normal bone marrow cellularity with many megakaryocytes on the myelogram, performed only when there is doubt about the mechanism of thrombocytopenia); and

2. **Hemolytic anemia** (hemoglobin <13 g/dL in men and <12 g/dL in women) (regenerative, with a reticulocyte count of ≥ 120 x 10^9/L, associated with increased free bilirubin and LDH levels, and at a low level of serum haptoglobin or level that cannot be assayed), the mechanism of which is mechanical (i.e., it often is associated with **schistocytes** on the **blood smear**). If schistocytes are absent during an initial blood smear, repeating the test is recommended. If the direct antiglobulin test (formerly known as the direct Coombs test) is usually negative (except in rare situations, such as in lupus patients or in certain pneumococcal infections), it may on rare occasions be positive (lupus, pneumococcal sepsis), which should not lead to the rejection of the diagnosis of TMA syndrome;

3. The association of cytopenia with organ damage (brain, cardiac, renal, digestive, etc.) strengthens the diagnosis, which must then be evident, but **we must not wait for the onset of organ damage before considering the diagnosis of TTP**. It is therefore necessary to try to make the diagnosis of TTP as early as possible, at the hematological stage. **In this context, it is important not to conclude on the autoimmune origin of cytopenia (Evans syndrome being as rare as TTP) and to initiate emergency treatment until you can establish a definitive diagnosis of TTP using the ADAMTS13 activity assay.**

The result of the ADAMTS13 activity is **retrospective to the clinical diagnosis** of a TTP flare-up, and the **severe deficiency confirms the suspicion of the clinical diagnosis**. A period of a few days (generally 24 to 72 hours) for the ADAMTS13 activity results still remains the rule for most centers in the world, which has led to the development of predictive clinical scores of severe ADAMTS13 deficiency that are now used as part of routine care. The two most commonly used diagnostic scores are as follows: **French score**, and more recently the PLASMIC score. **These scores are based on the existence of severe thrombocytopenia (<30 x 10^9/L) and no or moderate kidney damage (serum creatinine <200 µmol/L) in patients who have TMA syndrome with no associated context** (cancer, chemotherapy, pregnancy, sepsis, graft or disseminated intravascular coagulation (**appendix 4**).

Clinical examination

Autoimmune TTP

The onset of the disease is sudden. A prodromal phase combining asthenia, arthralgia, myalgia, abdominal and lumbar pain, which may suggest an infectious process, often precedes the onset of TTP by a few days.

In its typical form, TTP is characterized by visceral involvement (brain, cardiac, gastrointestinal, etc.), mechanical hemolytic anemia and deep peripheral thrombocytopenia (platelets $<30 \times 10^9$/L). TTP must, however, be systematically considered in the case of bicytopenia (anemia and thrombocytopenia) without any apparent organ damage but for which the hemolytic anemia is mechanical (associated with schistocytes). Schistocyte testing should be repeated to increase the sensitivity of the examination. In this context, it is important not to conclude on the autoimmune origin of the cytopenia (see previous section) until a TTP has been definitively ruled out thanks to an ADAMTS13 activity assay.

A moderate fever between 38°C and 38.5°C can accompany this clinical picture in 20% to 30% of cases.

Brain damage is observed in 50% to 92% of cases. It is characterized by its sudden appearance and its transience, since it can reach different territories intermittently, a few hours apart. It can manifest as a clinical picture of confusion with mental fog, headaches, and disorders of consciousness up to coma. A systematic sensory or motor deficit, dysarthria or aphasia may be observed. Stretch reflexes are often brisk. Nearly 20% of patients may have a seizure or even status epilepticus. In the elderly, the neurological picture may be less typical and is more often characterized by delirium, confusion and epilepsy, which can lead to a delayed diagnosis. Nuclear magnetic resonance imaging (MRI) can reveal images suggestive of ischemia or more rarely hemorrhage. Renal failure, typically moderate (serum creatinine <200 µmol/L), is found in 50% to 70% of cases. Kidney involvement can be summed up as proteinuria, with a flow rate generally less than 1.5 g/24 h or 1.5 g/g of creatinine, or hematuria. It regresses from the first days of treatment.

Cardiac involvement is possible and may include myocardial infarction, arrhythmia, congestive heart failure, cardiogenic shock or sudden death. Troponin elevation was observed in 60% of patients and may be associated with a risk of ventricular dysfunction sequelae, disease refractory to standard treatment and increased mortality. The other manifestations show the disseminated nature of TTP. Gastrointestinal involvement is characterized by abdominal pain, vomiting and diarrhea related to digestive ischemia or acute pancreatitis.

More rarely, eye damage, such as retinal detachment, has been described. Sometimes, there is no obvious organ damage. TTP is thus purely hematological and reveals itself through a hemorrhagic syndrome with purpura, bruises, hematomas or even recent onset of asthenia in the context of anemic syndrome.

Predisposing conditions for autoimmune TTP were identified in 50% of cases, such as systemic autoimmune diseases (typically disseminated lupus erythematosus or Sjögren's syndrome, more rarely Still disease or systemic sclerosis), pregnancy, HIV infection, medications or, more rarely,

cancer. The presence of other associated contexts, such as transplantation, chemotherapy or extensive progressive cancer, should instead point to secondary TMA, for which the ADAMTS13 activity is usually ≥ 20% and for which management is different.

Particularities of TTP in HIV-infected patients

HIV infection is a risk factor for the onset of thrombotic microangiopathy (TMA) in general. TMA occurring during HIV infection brings together two large, distinct entities. HIV^+ TTP is characterized by its sudden onset in patients who have moderate immune deficiency with little history of opportunistic pathologies and severe ADAMTS13 deficiency with autoimmune mechanism. Patients with HIV^+ TTP have a clinical presentation close to that of patients with HIV^- TTP. In particular, the frequency of brain involvement, the intensity of cytopenia and the low frequency of renal failure are comparable between these two populations. The diagnosis of HIV^+ TTP involves the initiation of emergency treatment combining daily TPE, caplacizumab (despite the lack of data in this patient population), immunomodulators and antiretroviral therapy. Its prognosis is comparable to that of HIV^- TTP.

TTP and medications

Clinical pictures of TMA have been described in combination with antiplatelet agents. In 2011, the Food and Drug Administration (FDA) reported 97 cases of TMA associated with ticlopidine, 197 associated with clopidogrel and 14 associated with prasugrel.

Ticlopidine: genuine TTP, associated with severe ADAMTS13 deficiency linked to anti-ADAMTS13 antibodies, has been described in patients treated with ticlopidine, typically 3 to 14 days after taking the medication. The antibodies inhibit ADAMTS13 independently of the medication, suggesting that they are autoantibodies and not immunoallergic antibodies. A study also reported the cytotoxic effect of ticlopidine or its metabolites on the endothelium, which led to apoptosis. The prognosis is generally good under TPE, with a response rate greater than 80%, and relapses are rare.

Clopidogrel: clopidogrel-induced TMA has a higher HUS profile since ADAMTS13 activity can be detected and renal failure is severe. This clinical picture develops within three months of initiating treatment, and sometimes within the first few days, suggesting a direct toxicity of clopidogrel to the endothelium rather than an immunological mechanism. The response to TPE is not as good, and relapses are more frequent.

Prasugrel: the mechanisms of TMA syndrome induced by prasugrel have yet to be clarified, although cases associated with severe autoimmune ADAMTS13 deficiency have been reported.

Immunomodulators: genuine autoimmune TTP has also been reported following the use of immunomodulators, such as lenalidomide, in patients with multiple myeloma or checkpoint inhibitors in patients with solid tumors.

Congenital TTP

In cTTP (formerly called Upshaw-Schulman syndrome), nearly 200 mutations in the ADAMTS13 gene have been reported so far. Patients are double heterozygous or homozygous, and the disease is transmitted in an autosomal recessive fashion. The first flare-up of the disease usually occurs before the age of 10 and in more than 50% of cases from birth. Renal involvement is of variable intensity (proteinuria, hematuria, renal failure of variable severity). In newborns, unexplained hemolysis and thrombocytopenia are sometimes the reason for an exchange transfusion. At first, flare-ups are entirely regressive, but after a few years of development and in the absence of optimal prophylactic plasma therapy, chronic renal failure (which can mislead the diagnosis of HUS) and other chronic visceral pain, related to repeated ischemic episodes, may appear. As development progresses, cardiovascular complications become more frequent: stroke, myocardial infarction, atherosclerosis, etc. A clinical picture associated with abdominal pain, chronic fatigue, headache, mood disorders, epilepsy, etc., may also be observed. Often, hematological involvement is also chronic and associates moderate hemolysis with thrombocytopenia. Diagnosis can be delayed for several years. In pregnant women, cytopenia should suggest the diagnosis of TTP, particularly cTTP, which represents 25% to 66% of TTP (see next section).

Family history sometimes uncovers similar damage or clinical pictures of fatal neonatal hemolysis in siblings. On the other hand, parents are in good health because they do not have a severe ADAMTS13 deficiency, given the recessive nature of the disease.

TTP and pregnancy

TTP associated with pregnancy is very often the first manifestation of the condition. This strong association between TTP and pregnancy can be explained by age and general female predominance in TTP and the progressive imbalance during pregnancy between increasing vWF levels and decreasing ADAMTS13 levels. The latter is corroborated by the fact that TTP occurs mainly in the last trimester or sometimes in the postpartum period, but very rarely in the first trimester.

In cTTP, the first pregnancy almost systematically triggers an episode of TTP, which occurs in the third trimester in 75% of cases; plasma therapy is associated with a good maternal prognosis, but the fetal prognosis is always poor. In pregnant patients with iTTP, the disease occurs during a woman's first pregnancy in 82% of cases, after the 20th week since her last menstrual period (LMP) in 70% of cases; TPE treatment is also associated with good maternal prognosis, and the fetal prognosis is good in two thirds of cases and correlated with the later term of pregnancy. Overall survival in patients is 80% and 60% in fetuses.

The diagnosis of TTP during pregnancy is often difficult, as most of the time, it occurs in patients with no history of the disease and is not associated with specific clinical or biological signs other than severe ADAMTS13 deficiency. In the absence of treatment, the poor prognosis warrants that a pregnant patient presenting with thrombocytopenia associated with hemolytic anemia, without any other etiology, should be considered to have TTP until proven otherwise. In particular, in patients with severe HELLP syndrome, only ADAMTS13 activity makes it possible to definitely rule out TTP. While awaiting this result, it is recommended to perform TPE under the assumption of TTP. In this context, fetal extraction should be discussed with the obstetric team.

Differential diagnosis

This is discussed for a hospitalized patient. They are of two types: **differential diagnoses of TMA syndrome** and **differential diagnoses of TTP in a patient with a specific TMA syndrome**:

The main **differential diagnoses of TMA syndrome** are as follows:

- Evans syndrome;
- Severe sepsis;
- Antiphospholipid syndrome;
- Vitamin B12 deficiency unrelated to congenital cobalamin C deficiency;
- Type 2 heparin-induced thrombocytopenia.

Differential diagnoses of TTP in patients with TMA are as follows:

- Any type of HUS: STEC+ or atypical;
- TMA associated with cancer or chemotherapy;
- TMA associated with a systemic autoimmune disease flare-up;
- TMA associated with infection, particularly HIV (some represent genuine TTP);
- TMA associated with an allogeneic hematopoietic stem cell transplantation;
- TMA in combination with a medication (mitomycin, gemcitabine, calcineurin inhibitors, rapamycin, anti-VEGF, tyrosine kinase inhibitors, etc.);
- Hemolysis and thrombocytopenia on a valve prosthesis;

- Scleroderma renal crisis;
- Malignant hypertension, with primary malignant nephroangiosclerosis or secondary to previously uncontrolled hypertension, isolated or associated with chronic nephropathy;
- Decompensated uncontrolled severe hypertension.

Additional examinations (appendix 5).

Peripheral thrombocytopenia is constant and often (~90% of cases) <30 x 10^9/L.

Anemia is severe and regenerative (reticulocyte levels typically ≥ 100 x 10^9/L). The blood smear reveals **schistocytes**, reflecting the mechanical character of hemolysis. Schistocyte testing should be repeated to increase the sensitivity of the examination, as these may appear delayed compared to cytopenia. The identification of schistocytes shows variable sensitivity from one cytologist to another, and the identification of schistocytes must correspond to rigorous morphological criteria allowing them to be counted in the most replicable way possible. The direct antiglobulin test is usually negative. Sometimes, however, such as in systemic lupus erythematosus or pneumococcal infection, the Coombs test may be positive and should not challenge the diagnosis of TMA.

Hemolysis is characterized by elevated serum free bilirubin and LDH levels (elevated LDH levels are also related to visceral pain) and by serum haptoglobin levels that are low or cannot be assayed.

Neutrophil polynucleosis is common (typically <20 x 10^9/L).

Other routine complementary tests include **serum creatinine** with an estimated glomerular filtration rate, complete **blood electrolytes**, **troponin assay**, liver function tests (transaminases, alkaline phosphatases and gamma GT), urinary electrolytes with creatinine levels, **protein/creatinine ratio** and urinary sediment.

A **spine examination** (bone marrow aspiration) is rarely necessary but sometimes useful to rule out a central component to cytopenia (myelodysplastic syndrome in particular) when anemia is aregenerative or more generally when there is doubt about the anemia mechanism.

Antinuclear antibodies indirectly demonstrate the autoimmune character of the disease and have no particular prognostic value for the acute phase. If positive, testing for anti–native DNA antibodies and an exploration of the complement (C3, C4, CH50) make it possible to test for lupus. This assessment must be carried out before starting TPE.

As treatment with rituximab in the acute phase or as a preventive measure is now systematic, it is necessary to perform **serum protein electrophoresis** and a weight-based measurement of serum immunoglobulins to check for hypogammaglobulinemia. Similarly, **phenotyping of circulating B lymphocytes** may be useful to assess the response to rituximab.

Testing for a **site of infection** (which may have been the triggering factor and may sustain the TMA process) is systematic.

HIV serology should be routine, as well as **hepatitis B virus serology** in preparation for rituximab treatment.

Plasma **beta-HCG** testing is systematic in patients of childbearing age.

Assessing ADAMTS13 activity:

This confirms the diagnosis of TTP, most often retrospectively. ADAMTS13 assessment is based on reference tests evaluated in international studies. However, commercial kits make it possible to detect ADAMTS13 activity <10%, but with 12% false negatives. Plasma samples with ADAMTS13 activity and anti-ADAMTS13 autoantibodies are taken at diagnosis before the start of TPE (**appendix 6**).

The ADAMTS13 activity assay may be particularly worthwhile in patients with apparent idiopathic thrombocytopenic purpura or Evans syndrome who do not respond to conventional therapies. Indeed, some patients may have genuine TTP, and the demonstration of undetectable ADAMTS13 activity thus makes it possible to correct the diagnosis.

Assessing ADAMTS13 activity must be systematically performed when faced with any TMA syndrome in children to avoid overlooking cTTP. **In adults, the indications are as follows (appendix 7):**

- **At diagnosis,** when faced with any TMA syndrome, including associated TMA (progressive cancer, chemotherapy, allogeneic hematopoietic stem cell transplantation). In severe ADAMTS13 deficiency, negative anti-ADAMTS13 IgG (and possibly the circulating anti-ADAMTS13 inhibitory activity) may suggest the diagnosis of cTTP. A genetic assessment of ADAMTS13 is then performed if ADAMTS13 activity (in the absence of detectable anti-ADAMTS13 autoantibodies) remains stably <10% in remission. On the contrary, positive anti-ADAMTS13 IgG makes it possible to make the diagnosis of iTTP at the outset.

- **After achieving remission**. The rise of ADAMTS13 activity to a detectable level, i.e., >10%, then gradually increasing beyond the lower limit of normal (>50%) shows an acquired deficit. Monitoring ADAMTS13 activity makes it possible to assess the risk of relapse, which was historically (in the absence of preventive treatment) 40% at 1 year and 74% at 7 years in the case of persistent severe deficit.

- **In the context of TTP in pregnancy**, it is essential to include a complete assessment of ADAMTS13 (activity, antigen and IgG anti-ADAMTS13 testing) in the follow-up of patients in remission to distinguish congenital cases (cTTP) from autoimmune forms (iTTP) of TTP. Indeed, these two entities pose a risk of recurrence and require different management during a subsequent pregnancy.

- In all cases, severe persistent ADAMTS13 deficiency during follow-up and when anti-ADAMTS13 antibodies have not been found warrants testing for genetic variants of ADAMTS13 under the assumption of cTTP (sequencing is done using the Sanger® technique and will soon be done using (next generation sequencing (NGS)).

Pretransfusion testing is carried out: blood group, complete Rhesus phenotyping, irregular agglutinins, serology and viremia for the hepatitis B and C viruses.

Assessing the degree of severity and prognosis

TTP is a disease that must always be considered serious, with **the patient being at a risk of sudden death until treatment is initiated**. The prognosis of a TTP diagnosis can be assessed based on the existence **of brain and cardiac involvement**, **age** and a **very high level of LDH** (>10 times normal), reflecting organ damage. Thus, patients with brain involvement, with a very high level of LDH and who are aged 60 years or older have a high risk of death, ranging from 39% to 66%. Conversely, patients without any of these severity factors have a risk of death of 3% to 5%. The determination of cardiac troponin is also predictive of a fatal outcome or refractory disease. However, these prognostic scores were established before the era of caplacizumab use, which appears to have largely eliminated these historical poor prognostic factors. The prognosis of TTP should therefore be redefined in light of the most recent therapeutic strategies.

ADAMTS13 activity in clinical remission makes it possible to assess the risk of relapse. In the case of persistent severe ADAMTS13 deficiency or in the case of relapse of severe ADAMTS13 deficiency, patients are at a 40% risk of clinical relapse in the first year and 74% at 7 years if preventive measures are not taken.

Regarding prognosis in the medium or long term, **cognitive sequelae** may be observed during an episode of TTP in 75% to 88% of cases and concern various language, attention, dexterity and memory tests. These sequelae probably relate to cerebral infarction that is sometimes clinically silent. Similarly, the quality of life in patients who survived an episode of TTP is lower than in the general population. There is an increased risk of severe depression after an episode of TTP, and life expectancy is reduced due to an increase in comorbidities in these patients, particularly

cardiovascular (ischemic stroke, myocardial infarction) and malignant pathologies.

Therapeutic management

Main objectives

Treatment of autoimmune or congenital TTP is always an emergency (**appendix 8**). The frequency of visceral pain in the acute phase and the potentially serious course of this makes it preferable to hospitalize patients in an **intensive care unit** until the platelet count normalizes.

The objectives are as follows:

- **urgently** initiate appropriate treatment and avoid additional morbidity and mortality related to delayed diagnosis and initiation of treatment;

- achieve complete remission;

- assess the risk of relapses and prevent them;

- limit and reduce disease-related sequelae;

- reduce adverse reactions and treatment-related sequelae;

- promote rapid social and professional reintegration during the TTP episode;

- prevent the increased risk of early death associated with a high prevalence of comorbidities in these patients, which include obesity, high blood pressure, diabetes and higher risk of systemic autoimmune diseases and neoplastic pathologies.

Professionals involved

Management of patients with TTP includes comprises specifics that depend on whether it is the congenital or autoimmune form.

In all cases, the severity of TTP in the acute phase, whatever its form, requires knowing how to quickly recognize it in order to initiate emergency treatment **(appendix 8)**. Specialists who treat this type of patient must therefore be aware of the diagnosis and treatment. They include reception and emergency services physicians, intensive care specialists, internists, hematologists, physicians at apheresis centers, neurologists and nephrologists. In all cases, management requires close collaboration between the varied specialists. In difficult cases, it is strongly recommended, at the regional level, to seek the expertise of constituent centers and centers of expertise or even the French National Reference Center for Thrombotic Microangiopathies.

During the acute phase, **close collaboration is required between the treating physician and the specialist physician** to manage possible comorbidities, monitor ADAMTS13 activity and arrange preventive treatment, if necessary.

If necessary, seeking the assistance of allied health professionals is possible:
- Nurses;
- Dietitians, in the case of overweight patients or those with other cardiovascular risk factors, which are common in this patient population;
- Psychologists and social workers to support the adaptation of the patient's life plan and to manage neurological and cognitive sequelae and their consequences;
- School physicians for children, occupational physicians for adults.

Curative treatment of iTTP

Several propriety drugs mentioned in this PNDS for the therapeutic management of children and adults are used for an indication or under conditions of use not provided for in the MA.

As a reminder:

- Prescribing a propriety drug is possible[1] in the absence of an appropriate alternative medication if the indication (or the conditions of use) has been the subject of a Temporary Recommendation for Use (RTU) or if the prescriber considers the use of the propriety drug essential to improve or stabilize the patient's clinical condition in light of the scientific data. In this case:
  - The patient must be informed of the off-label nature of the prescription, "the absence of appropriate alternative medication, the risks incurred and the likely constraints and benefits of the medication," as well as the conditions of health insurance coverage;
  - The wording "Off-label prescription" must appear on the prescription;
  - The reason for the prescription must appear in the patient's medical record;
- The French National Agency for the Safety of Medicines and Health Products (ANSM) can use the PNDS to develop an RTU for the propriety drug for the off-label indication if there is no appropriate alternative medication.[2]

The proprietary drug may be covered or reimbursed by health insurance for the off-label indication by way of derogation and for a limited period after consulting with the HAS, provided that it has previously been the subject of an RTU and that its use is essential to improve the patient's health or prevent its worsening.[3]

1 Article L.5121-12-1 of the French Public Health Code
2 Article L.5121-12-1 of the French Public Health Code.
3 Article L.162-17-2-1 of the French Social Security Code (CSS).

1) Plasma therapy

In iTTP, treatment is based on performing **therapeutic plasma exchange (TPE)** that provide large volumes of plasma (and therefore ADAMTS13). TPE may also subtract high-molecular-weight VWF multimers, anti-ADAMTS13 antibodies and inflammatory cytokines, but these assumptions have never been demonstrated. The plasma volume exchanged is **1.5 plasma mass**, which corresponds to ~60 mL/kg. In general, the replacement fluid is only plasma.

The three types of plasma most conventionally used are quarantine fresh frozen plasma, solvent/detergent-treated fresh frozen plasma (plasma-derived medicinal product) or psoralen/UV. Retrospective studies have led to the conclusion that there is **no inferiority of one plasma compared to the others**. Quarantine fresh frozen plasma has been associated with more allergic adverse reactions than the others. Overall, the three types of plasma can be prescribed indifferently to patients with TTP at diagnosis.

TPE is generally performed with a continuous-flow blood cell separator using the centrifugation technique (the efficiency of plasma purification is better than the filtration technique). Whenever possible, the choice of venous access favors peripheral veins if they are of good caliber to avoid the insertion of central catheters as much as possible, especially since the risk of venous thrombosis is high in patients with TTP, especially when thrombocytopenia begins to correct itself. The use of peripheral veins is impossible if the exchange is carried out by the filtration technique.

If TPE cannot be performed urgently, **while awaiting TPE**, infusions of large volumes of plasma (20 mL/kg/day) can be initiated.

TPE should continue **daily** until the disappearance of organ damage and until the **normalization of platelet count** (>150 × 10^9/L). Reticulocytes and LDH should be normal or **decreasing**. Since the systematic use of caplacizumab, the number of TPE sessions required to achieve complete clinical response has halved. TPE can be stopped completely as soon as platelet counts normalize (the gradual decrease of TPE, which was performed for 3 to 4 weeks to prevent exacerbations, which are sometimes severe, has become unnecessary since the use of caplacizumab).

2) Caplacizumab

This is used from diagnosis in conjunction with TPE. Caplacizumab is a bivalent nanobody of approximately 28 kD composed of two variable domains of immunoglobulin heavy chains linked by 3 alanine residues. It received orphan drug status in 2009 and was approved in Europe in August 2018 (European MA) and in the United States in February 2019 for the treatment of autoimmune TTP. The MA states that caplacizumab is indicated in adult and adolescent patients aged over 12 years who weigh over 40 kg with a clinical diagnosis of iTTP, in conjunction with TPE and immunosuppressive therapy.

Caplacizumab binds to the A1 domain of vWF and thus inhibits the interaction between vWF and its platelet receptor glycoprotein 1b under conditions of high shear forces, **preventing the formation of platelet microthrombi induced by high-molecular-weight vWF multimers**. This mechanism of action protects patients from the deleterious effects of microthrombi in the acute phase by stabilizing platelets until immunomodulation with rituximab corrects ADAMTS13 activity to thresholds that protect patients.

Caplacizumab has so far been evaluated in two international therapeutic trials, one phase 2 (TITAN) and one phase 3 (HERCULES). Caplacizumab, compared to placebo, resulted in a **significant reduction in the incidence of a composite objective including TTP-related death, exacerbations and the onset of macrothrombotic events** (12.7% vs. 49.3%). Caplacizumab also resulted in **halving TPE treatment**, as well as a **shorter ICU stay and hospitalization**.

Caplacizumab is prescribed upon admission as follows: 1 × 10 mg ampoule intravenously before the first plasma exchange, then 1 ampoule after the subcutaneous plasma exchange; then one ampoule daily subcutaneously at the end of each plasma exchange. Once TPE is suspended, daily caplacizumab injections are continued at least until ADAMTS13 activity reaches an empirically defined protective threshold of 20%. Indeed, while the caplacizumab summary of product characteristics (SmPC) currently (March 2023) recommends a treatment duration of 30 days, data from the literature (see in particular Coppo *et al.*, Blood 2021) suggest that a protective threshold of the ADAMTS13 activity of 20% identified based on weekly monitoring from the end of plasma exchange may allow caplacizumab to be stopped earlier than D30 in some patients. This hypothesis is being evaluated in France in a National Clinical Research Hospital Program (ClinicalTrials.gov Identifier: NCT04720261), and similar studies are being conducted in Europe. In practice, in all patients treated with caplacizumab, ADAMTS13 activity is currently monitored weekly until confirmation of ADAMTS13 activity ≥ 20% in two consecutive samples. ADAMTS13 activity is then monitored at 1 month and then every 3 months for years.

Adverse reactions were reported in more than 50% of patients treated with caplacizumab. They are essentially related to the mechanism of action of the medication, which is responsible for an equivalent of type 2M von Willebrand disease. The most common adverse reactions are bleeding (33% of patients), the risk of occurrence of which is not related to the duration of treatment: gingivalgia, epistaxis, bruising and hematoma (especially at the injection site), metrorrhagia, and more rarely gastrointestinal bleeding. In rare cases, more severe bleeding caused hemorrhagic shock or required red blood cell transfusions. A case of cerebral and meningeal hemorrhage has been reported in the literature. In these cases, infusions of von Willebrand factor concentrates may be considered in consultation with the reference center team in addition to discontinuing caplacizumab.

In less than 10% of cases, an urticaria inflammatory reaction, sometimes significant, may occur at the injection site. This manifestation typically occurs at the end of treatment. Finally, thrombocytosis with up to more than 1 million platelets has been reported in 20% to 25% of patients; it does not seem to be associated with increased risk of venous thromboembolism.

Caplacizumab does not prevent thromboembolic events, which may be observed in up to 12% of patients without prophylaxis. Therefore, as soon as patients reach 50,000 platelets/mm^3, it is recommended to **initiate prophylactic anticoagulant therapy with low-molecular-weight heparin** (continuing caplacizumab), **until hospital discharge** (and until the patient recovers normal mobility).

The use of caplacizumab is not recommended in patients requiring continued anticoagulation therapy at an effective dose consistent with their histories (typically patients with a heart valve prosthesis or patients with high-risk emboligenic arrhythmia). Based on the first real-life experiences reported with the use of caplacizumab, the combination of caplacizumab with antiplatelet therapy does not appear to be associated with increased bleeding complications compared to caplacizumab alone. However, the available experience on the use of caplacizumab concomitantly with anticoagulants or antiplatelet agents is currently very limited and will be subject to formal recommendations at a later stage.

3) Immunosuppressive therapy

a. Systemic corticosteroid therapy

Given the long-suspected autoimmune mechanism in TTP, corticosteroids have been used to treat the disease for many years. Despite a low level of evidence, there is a strong consensus on systematically combining them with TPE at the dose of 1 to 1.5 mg/kg/day during the acute phase (for 2 to 3 weeks) decreasing over 1 week. The benefit of higher doses of corticosteroids compared to standard corticosteroid therapy has been suggested. However, the current recommendation, although empirical, is to administer standard corticosteroid therapy. Cortisone osteoporosis should not be treated preventively if corticosteroid therapy is less than one month old (which should be the rule).

Corticosteroids are initially administered intravenously immediately at the end of TPE, and then orally.

b. Rituximab

Rituximab is a monoclonal antibody directed against the B lymphocyte antigen CD20; it thus allows a transient depletion of B lymphocytes from the blood, and partly from the lymphoid organs. By causing a depletion of anti-ADAMTS13 B lymphocytes, it normalizes the activity of the protein. Rituximab was initially used as adjuvant therapy for TPE in cases of suboptimal response; given its effectiveness in preventing relapses in the year following an acute episode (which were historically 40%), it is now prescribed **systematically as first-line therapy in combination with corticosteroid therapy**.

The regimen of rituximab administration in the acute phase is empirical and based on the fact that 50% to 60% of the active substance is subtracted by plasmapheresis. Thus, traditionally, **4 infusions of 375 mg/m2 IV are administered in only 2 weeks, on D1, D4, D8 and D15**. The infusions should be performed immediately after TPE, leaving, if possible (if the patient's clinical picture so allows), 18 to 24 hours between the end of the rituximab infusion and the subsequent TPE. Lighter regimens (**375 mg/m^2 IV on D1, D4 and ± D15 depending on the persistence of B lymphocytes in peripheral blood on D14**) were found to be comparable in terms of effectiveness. Both regimens can therefore be used, the choice being left to the clinician.

The indication for rituximab or its biosimilars in iTTP is off-label, but it has benefited from a Temporary Recommendation for Use (RTU) issued by the ANSM in adults and children.

In this context, rituximab also shortened treatment time in slow responders. The remission rate is >90% in less than 4 weeks. On the other hand, the effectiveness of rituximab is not immediate and requires an **average period of 2 weeks**; it has therefore only slightly improved the survival of TTP in the acute phase, since most deaths occur within the first 10 days of treatment. However, relapses can be observed after 12 to 18 months following the administration of rituximab and happen at the same time as immune reconstitution.
B. It is therefore important to monitor ADAMTS13 activity during the acute episode (see the "Prevention of relapses" section).

The tolerance profile is satisfactory. Initial fears about the risk of JC virus infection of the central nervous system (progressive multifocal leukoencephalopathy [PML]) reported in other autoimmune diseases in patients previously treated with heavy and prolonged immunosuppressive therapy have not been confirmed in iTTP where this risk is probably exceptional (no cases described so far, probably several thousand patients treated for 20 years).

The use of rituximab in pregnant women is not recommended. However, in severe life-threatening forms of iTTP during pregnancy, the risk/benefit balance should be assessed and the decision to introduce rituximab should be left to the clinician. Similarly, in a patient with severe ADAMTS13 deficiency acquired and isolated during pregnancy, exposing the patient to a high risk of clinical relapse and fetal loss, the indication for a preventive injection of rituximab rather than the use of another

immunosuppressant should be assessed by the clinician in consultation with the patient. These situations should also be discussed with a member of the reference center.

Known adverse reactions of rituximab are as follows:

- During administration of the product: a rare and potentially serious allergic risk requiring close hemodynamic monitoring during and for a few hours after infusion, especially at the time of the first injection. This risk is partially prevented by the administration of premedication with 100 mg methylprednisolone intravenously, which should be routinely administered in the absence of contraindications. An antihistamine treatment with Polaramine (5 mg; 1 ampoule) should also be given. There is also a rare risk of serum sickness during the infusion.

- A risk of delayed neutropenia, which is usually transient and not symptomatic. This risk is rare when rituximab is used in autoimmune diseases.

- Hypogammaglobulinaemia, sometimes prolonged and sometimes delayed for several years after the injection, has been described especially in patients with immune thrombocytopenia (ITP). However, hypogammaglobulinemia has been shown to be most often related to a common variable immunodeficiency (CVID) in adults, and autoimmune lymphoproliferative syndrome (ALPS) in children, which had gone unnoticed until then. It is thus recommended to perform serum protein electrophoresis or weight-based measurement of serum immunoglobulins on an annual basis for a few years.

- A low risk of infection requiring prolonged posttreatment follow-up, especially in patients regularly treated with rituximab, or receiving intensive treatment. There is a risk of viral replication in patients with hepatitis B virus; therefore, prior antiviral therapy should be initiated in these patients (e.g., tenofovir 245 mg/day or entecavir 0.5 mg/day, to be continued for 1 year after completion of rituximab therapy). Lamivudine is associated with more mutant virions; therefore, its use is limited to situations in which the duration of immunosuppression is short, whereas iTTP patients may require repeated rituximab injections over time in more than 50% of cases. The use of tenofovir is therefore preferred. Verification of the serological status against hepatitis B virus is therefore necessary before treatment. Preventive antiviral treatment is also recommended when the patient has anti-HBc antibodies.

The relative urgency with which rituximab is indicated in iTTP patients makes it difficult to administer pneumococcal vaccination, especially since ADAMTS13 activity is typically undetectable in this context, and vaccination could be a triggering factor for relapse. However, these vaccinations can be performed when the patient reaches 20% protective ADAMTS13 activity by waiting 6 months after rituximab administration to enable effective seroconversion. The vaccination schedule is Prevenar 13® followed 2 months later by an injection of Pneumovax®; subsequently, combine vaccination against *Haemophilus influenzae* [ActHIB ®] and against the different serotypes of meningococcal disease in young subjects. Attenuated viral vaccines are contraindicated during treatment with rituximab.

4) Antiplatelet and other agents

There is insufficient data on the efficacy of antiplatelet agents, such as aspirin. In addition, they increase the risk of bleeding. Their mechanism of antiaggregating distinct from the mechanism of platelet hyperaggregation involved in TTP is reason for not introducing them. They should be discussed during the acute phase based on the underlying cardiovascular risk factors.

Other treatments, such as heparin, fibrinolytic, prostacyclin and vitamin E infusions, are unnecessary and can be dangerous to some patients.

5) General regimen

The modern treatment of autoimmune TTP consists of a "triplet" regimen combining (1) TPE, (2) immunomodulation with corticosteroids and rituximab and (3) caplacizumab (**appendix 8**), which thus makes it possible to correct the three pathophysiological aspects of the disease: severe ADAMTS13 deficiency, production of anti-ADAMTS13 antibodies and hyperadhesion of vWF to platelets. TPE, corticosteroids and caplacizumab are initiated upon strong clinical suspicion of the diagnosis of iTTP, based on the French score (score of 1 or 2). Rituximab can be initiated immediately when the French score is 2; some practitioners prefer to wait for confirmation of the diagnosis of TTP based on undetectable ADAMTS13 activity. The therapeutic algorithm is detailed in **appendix 9**.

Symptomatic or adjuvant treatment

- Correct any arterial hypertension (rare in TTP).

- **Folic acid** supplementation is systematically administered in these patients with significant bone marrow regeneration.

- Transfusions of erythrocyte concentrates are administered in the case of **poorly tolerated anemia**.

- Thromboprophylaxis with low-molecular-weight heparin is indicated once a platelet count of ≥ 50 x 10^9/L is reached. Its prescription depends on the patient's bleeding risk and renal function (prescription allowed up to a clearance of 20 mL/min according to the Cockcroft-Gault equation).

- In the absence of serious bleeding threatening immediate life, **platelet transfusions are contraindicated** because they may maintain and even increase the formation of microthrombi or thrombosis of the large vessels.

- Treatment of a possible triggering factor is necessary (anti-infective treatment, antiretroviral treatment in the case of HIV infection, discontinuation of an attributable immunomodulatory drug, etc.).

- It is recommended to prescribe a proton pump inhibitor for prophylaxis of a stress ulcer in these patients who are often hospitalized in intensive care, thrombocytopenic and receiving corticosteroid therapy;

- Intensive care measures should be systematically provided in the case of organ failure, which may be reversible.

Refractory iTTP

Refractory iTTP is defined as the **absence of doubling platelet counts after 5 days of well-conducted treatment**, or **clinical and/or laboratory worsening following the start of response to treatment (despite continued intensive treatment)**. These refractory forms have become exceptional since the systematic use of caplacizumab. As a guide, the following strategies could be proposed in the case of a refractory situation with caplacizumab. They are inspired by those proposed before the era of caplacizumab. In all cases, the management of refractory iTTP must involve an expert center and will be discussed on a case-by-case basis.

- Intensive TPE twice daily;

- Vincristine: 1.5 mg/m^2/week, strictly intravenous due to the risk of skin necrosis in the case of extravasation of the product, maximum 2 mg per dose in total, for 3 to 4 weeks;

- Cyclophosphamide (Level 4): 600 mg/m^2 D1-D15-D28 then D1-D28, with 6 infusions in total.

- Splenectomy. This is performed after discussion with the regional reference center or center of expertise. Splenectomy is managed by TPE. Temporary suspension of caplacizumab should be discussed to avoid increased risk of bleeding. Transfusion of platelets before the procedure can be avoided and depending on the surgeon's experience, the laparoscopic approach is preferred over laparotomy. The spleen is systematically analyzed in anatomic pathology.

- Intravenous polyvalent immunoglobulins. There is insufficient evidence to prescribe polyvalent immunoglobulins for iTTP.

- Immunoadsorption. The effectiveness of immunoadsorption columns in patients with ADAMTS13 autoimmune deficiency has not been evaluated to date, but some clinical cases suggest potential effectiveness of immunoadsorption with a filtration cascade enabling depletion of anti-ADAMTS13 IgG correlated with increased ADAMTS13 activity (CNR-MAT data). This technique could be used in absolutely exceptional situations of refractory iTTP.

Clinical and biological relapse of iTTP, or ADAMTS13 relapse

Clinical relapse is defined as **reappearance of clinical signs and laboratory abnormalities** associated with <10% ADAMTS13 activity, occurring within **≥ 30 days after the disappearance of clinical signs and the normalization of platelet count. A relapse is *sensu stricto* a new episode of the disease (before the 30th day, it is an exacerbation, which belongs to the same episode).**

A biological relapse (now called "ADAMTS13 relapse") is defined as reappearance of **severe ADAMTS13 deficiency (activity <20%)** (without clinical signs or an abnormal complete blood and platelet count), **following a partial correction** (ADAMTS13 activity ≥ 20% but <50%) or complete (ADAMTS13 activity ≥ 50%) ADAMTS13 activity.

During clinical relapse, these patients can be treated in the same way as at diagnosis. To prevent further relapses, long-term monitoring of ADAMTS13 activity and preventive immunomodulatory therapy should always be provided during an ADAMTS13 relapse (see next section).

Prevention of relapses

Preventive treatment of clinical relapse should be systematically provided during a biological relapse (ADAMTS13 <20%). It is based on the following treatments:

1) Rituximab

The effectiveness of rituximab in preventing relapse at 1 year justified its gradual use as first-line therapy in combination with TPE and corticosteroids, and now with caplacizumab. Rituximab, effective in nearly 85% of cases, thus allows these patients to prevent the vast majority of clinical relapses at 1 year by normalizing ADAMTS13 activity stably. However, **beyond 12 to 18 months, nearly half of patients may have a further decrease in ADAMTS13 activity, which exposes them to relapses** (74% of relapses in cumulative incidence at 7 years). Preventive treatment with rituximab thus allows ADAMTS13 activity to be corrected in most cases. Therefore, **preventive treatment with rituximab in patients with severe ADAMTS13 deficiency (defined here as <20% activity) during their follow-up is not strongly recommended.** This indication benefited from an RTU.

Preventive treatment with rituximab consists of a single infusion of 375 mg/m^2 IV, which normalizes ADAMTS13 activity in 3 to 4 weeks.

In patients experiencing adverse reactions with the use of rituximab, other anti-CD20 monoclonal antibodies, such as **obinutuzumab** and **ofatumumab** (off-label), can be offered and therefore need to be evaluated.

In the event of failure, defined as persistence of severe ADAMTS13 deficiency at 3 months after rituximab infusion, **intensive rituximab treatment**, based on the proposed maintenance regimens in indolent B-cell lymphoma, may be proposed: **rituximab 375 mg/m^2/week x4 IV, followed by an infusion every 3 months for 2 years**.

The use of **1400 mg rituximab subcutaneously** to reduce the burden of care on the patient and care team; this may be considered in patients requiring an intensive therapeutic regimen.

In patients receiving multiple rituximab infusions (intensive 2-year regimen or regular infusions every 12 to 18 months), **prophylactic anti-infective treatment may** be offered. It combines valaciclovir 500 mg twice daily with cotrimoxazole 800 mg three times weekly. This treatment should be continued throughout the period of rituximab treatment and prolonged for one year after the end of treatment.

In the case of persistent failure, or a contraindication to this intensive regimen with rituximab, alternative immunomodulatory strategies may be considered (see following points).

2) Ciclosporin, azathioprine and mycophenolate mofetil

Immunomodulatory therapy with ciclosporin, azathioprine or mycophenolate mofetil is indicated for iTTP with severe autoimmune ADAMTS13 deficiency **in the event of failure of rituximab therapy**. To date, ciclosporin is the preferred medication.

3) Splenectomy

In patients with **persistent acquired severe ADAMTS13 deficiency despite rituximab and the possible use of other immunosuppressants (including other anti-CD20 monoclonal antibodies)**, splenectomy may be considered during clinical remission. This indication has become rare since the systematic use of rituximab; it must therefore be systematically discussed in a national multidisciplinary team meeting. Splenectomy is performed after the usual vaccinations against encapsulated pathogens (pneumococcus, haemophilus, meningococcus), ideally at a time when ADAMTS13 activity reaches a protective threshold $\geq 20\%$. Secondary prophylaxis with oral amoxicillin or penicillin V is considered for a period for which a consensus has not been reached. The patient should be informed of the risk of severe infections and the need to start antibiotics promptly in the case of fever.

4) Special cases of iTTP associated with HIV infection:

Since the development of highly active antiviral treatments, cases of iTTP associated with HIV infection have become much rarer. The treatment is based on standard measures for any iTTP, significantly associated with control of viral replication by antivirals. Rituximab should be used with caution in patients with Kaposi sarcoma.

Congenital TTP

In the vast majority of cases, cTTP is detected in childhood or in the neonatal period. Long-term plasma therapy is the standard treatment to prevent both acute episodes and long-term organ complications.

In newborn babies, an **exchange transfusion** is often necessary when faced with significant hyperbilirubinemia (this can suggest the diagnosis when associated with thrombocytopenia and mechanical hemolytic anemia). In children, the curative treatment at diagnosis or in the case of a flare-up consists of **plasma infusions of 10 mL/kg daily.** This generally allows a cessation of hemolysis within 24–72 hours and a correction of thrombocytopenia within 1 week.

Treatments performed only in the case of cTTP flare-ups do not prevent the risk of long-term brain, heart or kidney damage. **Patients not receiving plasma therapy develop more cardiovascular, brain and renal complications**, clearly impacting life expectancy and quality of life over time. **There is therefore a tendency to offer prophylactic plasma therapy to any patient with cTTP, whether the flare-ups of the disease are frequent or less frequent.** The soon availability of recombinant ADAMTS13 protein should make this long-term management easier, especially in patients with less frequent relapses over time and who are not inclined to accept prophylactic treatment.

At present, **prophylactic treatment consists in performing plasma infusions at a volume of 10 mL/kg every 2 or even 3 weeks**. In practice, the interval between 2 plasma infusions can be chosen based on the time taken to decrease the platelet count to below 150,000/mm^3. Most patients do not relapse on this regimen, and failures are mainly due to insufficient plasma intake or excessive interval between 2 infusions. To date, no anti-ADAMTS13 alloimmunization has been formally documented.

cTTP patients are at risk of relapse in the case of a triggering factor, which can be any situation that activates the endothelium and results in the release of sufficiently large amounts of vWF. It is therefore recommended that children be closely monitored during **infection** or **vaccination** and that plasma therapy be initiated as soon as the platelets count falls below 150,000/mm^3. In the case of **surgical intervention and vaccination with some particularly pyrogenic vaccines**, it is preferable to manage the procedure with prophylactic plasma therapy. Finally, young women leaving the pediatric community must be informed, as well

as their parents, treating physician and gynecologists and obstetricians, of the risk of **recurrence during pregnancy**. If possible, pregnancy should be planned, with close monitoring and prophylactic plasma intake (see next section).

Management of women with a history of TTP planning to become pregnant

The recommendations below are based on the clinical experience of the reference center and the ISTH recommendations published in 2020. The management of these patients in this context absolutely requires **discussion of the approach with a member of the regional reference center and/or competence center.** As experience in this context is still limited, these recommendations remain empirical.

1) Patients with known cTTP:

To obtain an **ADAMTS13 activity of approximately 15%**, it is necessary to administer plasma from conception in the following way:

- 1st trimester: 20 mL/kg/14 days

- 2nd trimester and beginning of 3rd trimester: 20 mL/kg/7 days

- 3rd trimester: 20 to 30 mL/kg/7 days or TPE

- Postpartum: 10 to 20 mL/kg/7 days for to 3 weeks; then discontinuation in the absence of cytopenia or hemolysis.

Monitoring is as follows:

- Complete blood and platelet counts, reticulocytes, LDH, haptoglobin, transaminases and residual ADAMTS13 activity to adjust plasma volumes;

- At delivery: placental histology, complete blood count + ADAMTS13 activity at birth in the newborn;

- If fetal death *in utero*: placental and fetal histology; fetal DNA collection.

There is not enough data to date to systematically offer aspirin treatment.

2) Patients with a history of iTTP:

The approach depends on the ADAMTS13 activity when the woman plans to become pregnant (appendix 9):

- If activity is normal (≥ 50%):

Pregnancy can be considered; it is closely managed in a multidisciplinary manner;

- In case of undetectable (<20%) or low (<50%) activity:

- There is a significant risk of relapse. In the case of undetectable activity, it is therefore recommended to perform a single infusion of rituximab and to check the increase in ADAMTS13 activity remotely (typically at 2 months) then at 6 months to check that normal ADAMTS13 activity is maintained. At 6 months, after observation of the reappearance of B lymphocytes indicating disappearance of circulating rituximab, and the appearance of detectable ADAMTS13 activity, pregnancy can be considered. In the case of low but detectable activity, the risk of severe ADAMTS13 deficiency worsening during pregnancy is high and may warrant preventive treatment in situations where activity is close to 20%.

In all cases, the monitoring of pregnant patients is as follows:

- Complete blood count, reticulocytes, LDH, haptoglobin, transaminases, uricemia, urinary dipstick 1 time/month initially then 2 times/month in the 3rd trimester;

- Assessment of ADAMTS13 activity monthly, then every 2 weeks during the third trimester depending on the decrease in activity, which may also be physiological;

- Close maternal and fetal monitoring by the obstetric team.

3) Patients with a history of iTTP and undetectable ADAMTS13 activity during pregnancy monitoring:

- Weekly laboratory monitoring or more if there are clinical warning signs;

- Plan for a scheduled delivery;

- A preventive infusion of rituximab may be discussed to sustainably normalize ADAMTS13 activity (transplacental passage of rituximab from the second trimester onward). An alternative is to offer treatment with ciclosporin A or azathioprine;

- After delivery: Placental histology

  Complete blood count on D0 and D7

  ADAMTS13 activity

- In the case of fetal death *in utero*: placental and fetal histology and blood sampling.

4) Positive diagnosis of iTTP in pregnant women:

- Standard treatment with TPE and corticosteroids;

- Rituximab recommended if unfavorable course. Azathioprine or ciclosporin may also be discussed. Relief must be discussed based on the term.

Contraindication to certain treatments:

Treatment with plasma therapy is imperative. There may rarely be contraindications to certain types of plasma when faced with allergic phenomena, despite appropriate premedication.

With regard to concomitant treatments, particularly immunosuppressants, it is necessary to check for possible infection before prescribing them. Rituximab is contraindicated in uncontrolled, progressive viral hepatitis B.

The administration of desmopressin (DDAVP) is formally contraindicated in patients with ADAMTS13 deficiency (hereditary or acquired). DDAVP triggers release of very high-molecular-weight multimers and decrease in ADAMTS13 levels and can thus trigger a TTP flare-up.

Estrogen-based contraception could promote TTP flare-ups by stimulating vWF synthesis or by playing an immunomodulatory role. As a precaution, it is therefore preferable to contraindicate its use. The safety of progestogen contraception also remains to be demonstrated.

Patient education and lifestyle changes

Patient education is the set of activities designed to help patients (and their close family and friends) to understand the disease and treatments, participate in care, manage their state of health, and encourage, as far as possible, a return to normal activities. Currently, a **patient education program is underway within the coordinating reference center**, which has been validated by the Regional Health Agency. It includes **information** that may relate specifically to:

1. The autoimmune form:

- Above all, the risk of clinical relapse of the disease, which may occur unpredictably; this risk persists many years after the acute episode, which explains why lifelong follow-up is likely to be essential for these patients. It is therefore important for the patient to understand the importance of regular monitoring of ADAMTS13 activity, typically every three months during the first few years with less frequent monitoring considered only if ADAMTS13 activity remains stable in a normal manner.

- The other important point is to raise the patient's awareness of the control of cardiovascular risk factors (type 2 diabetes, high blood pressure, overweight, dyslipidemia, etc.) and testing for other comorbidities (systemic autoimmune diseases, malignant pathologies), which are more frequent in this population and which have a negative impact on quality of life, as well as life expectancy.

2. The congenital form:

- It is important to educate the patient and parents about long-term complications, especially in the case of difficulties in adherence to prophylactic plasma therapy. The current recombinant ADAMTS13 protein is in an advanced stage of development and should eventually be administered at home and subcutaneously. It should significantly improve compliance and better prevent complications in the long term: stroke, myocardial infarction, neurocognitive disorders, chronic renal failure, etc.

- Similarly, given the worsening of these complications with age, it is important for patients to be aware of the need to control cardiovascular risk factors as much as possible.

- Genetic counseling. cTTP is an unusual autosomal recessive disorder. Diagnosis can be made early at birth during subsequent pregnancies in families in which one child is already affected, thus allowing appropriate care.

Information on the mode of transmission is given with a theoretical risk of 1 child in 4 being affected, 2 in 4 being carriers of a mutated allele and 1 in 4 being free from the disease.

Prenatal screening is not offered in view of the current impossibility of assessing the prognosis of the disease, which does not correlate with the genetic abnormalities found; in addition, some patients may have a first flare-up of TTP only late in adulthood. This screening can be discussed on a case-by-case basis depending on the parents' wishes.

Screening by ADAMTS13 activity assay is systematically offered to siblings, supplemented by complete genotyping of the ADAMTS13 gene in the case of abnormality. The interview seeks possible cases in the family (especially in the case of inbreeding), with screening offered, if necessary.

The parents of a cTTP patient are asymptomatic and not at risk of developing the disease themselves (each parent carries a single mutated allele of the ADAMTS13 gene, and it is an autosomal recessive disorder). An ADAMTS13 activity assay can nevertheless be performed at home at their request or be offered as part of a systematic family investigation.

3. Vaccination

Any vaccination plan should be discussed with the specialist based on the current recommendations of the French high council for public health. Since vaccines trigger relapses in patients with severe ADAMTS13 deficiency, it is important not to administer vaccines in the absence of measures to at least partially correct ADAMTS13 activity (ideally at levels >20%). In cTTP, vaccines should be administered immediately after a plasma infusion. In iTTP, the vaccine should be preferentially administered when the patient has ADAMTS13 activity ≥ 20% and, if possible, at a sufficient distance from rituximab therapy to allow optimal vaccine response (typically 6 months from the last injection).

Pneumococcal vaccination is recommended, as approximately half of patients may require rituximab treatment repeatedly during follow-up, and some may require splenectomy. This vaccination is based on the Prevenar 13® vaccine followed two months later by the Pneumovax® vaccine; it is important to respect the sequence and timing of administration between these two vaccines. The flu vaccination is strongly recommended in adults, especially if repeated treatment with rituximab is used. **TTP does not represent a contraindication to COVID-19 vaccination, while requiring the precautions needed for other vaccines. As a precaution, an mRNA vaccine should be preferred, without thrombotic risk.** In children with cTTP, the vaccination schedule should be followed as closely as possible and discussed with the specialist on a case-by-case basis to cover the vaccination injections with a plasma infusion.

4. Patient information regardless of TTP type

Informing patients and their close family and friends about the disease, the risk of relapses and the manifestations that are warning signs is an integral part of therapeutic management. Patients should therefore learn the early warning signs of relapse that should prompt urgent consultation: fever, neurological signs, unusual abdominal pain, diarrhea, hematomas and/or purpura and jaundice.

Patients must carry a **personalized card** issued by the reference center and all its sites specifying the diagnosis, type of TTP, history, treatments received and place of care, as well as the methods of emergency care, contraindicated actions and corresponding physicians.

It is important that **the patient inform the treating physician and the specialist of a planned pregnancy**, **planned intervention** or **the need for vaccination**, which should be organized based on ADAMTS13 activity. The method of contraception should also be discussed in consultation with the specialist and gynecologist.

All healthcare professionals and patients may be informed of the existence of patient advocacy groups whose contact information appears in this document. The treating physician or medical specialists can provide the patient with the information documents on TTP published by the reference center and downloadable from the website www.cnr-mat.fr.

Follow-up of patients with TTP

Objectives

It is important to educate and **make sure that patients are aware of the risk of relapse** (especially during pregnancy). Follow-up of patients must be standardized and prolonged to obtain better epidemiological knowledge of the natural course of the disease, possible sequelae and the appearance of systemic autoimmune diseases.

iTTP has been associated with multiple systemic autoimmune diseases, particularly systemic lupus erythematosus and Sjögren's syndrome (more rarely Still disease and systemic scleroderma), which may occur during follow-up (around 10% of cases at 10 years).

Another important aspect is **testing for and prevention of cardiovascular risk factors** and **screening for malignant pathologies**, which are more frequent in this population (a chronic ADAMTS13 deficiency could also be a factor favoring the occurrence of cardiovascular events, such as stroke and myocardial infarction).

Finally, it is necessary to look for signs showing **cognitive sequelae** that can impact quality of life. All these complications may also have a negative impact on life expectancy.

In cTTP, chronic and severe ADAMTS13 deficiency, especially if it is insufficiently supplemented by plasma infusions, is associated with chronic injury in several organs, leading to the deterioration of their function: chronic renal failure, neurocognitive disorders, heart disease, ischemic stroke, epilepsy, coronary heart disease and myocardial infarction, retinopathy, etc. These patients must therefore be monitored and receive an assessment of these various organs as proposed in patients with sickle cell disease.

Professionals involved

Follow-up takes place jointly between the hospital physician of the center that has taken care of the patient, and the treating physician. The assistance of a cardiologist, neurologist or psychiatrist may be required. The role of the treating physician in the optimal management of cardiovascular risk factors is crucial.

Frequency and content of specialized consultations

iTTP-specific monitoring:

The frequency of consultations is once every 3 months in the first year, every 6 months in the second year, and then every year thereafter.

The hospital physician checks for the absence of **obvious clinical signs of relapse and checks that the quarterly ADAMTS13 activities remain within the protective thresholds (≥ 20%).** Together with the treating physician, they look for the appearance of possible clinical signs suggesting a **systemic autoimmune disease** or **malignant pathology**. An assessment of **cardiovascular risk factors** is necessary, typically on a yearly basis (the frequency is adapted to the risk and the situation, after consultation with the cardiologist, if necessary). **Neurocognitive sequelae** are also tested. The details of these examinations are specified in the following section, "Assessment of cardiovascular risk factors and neurocognitive sequelae (all types of TTP)."

Additional examinations

- **Standard laboratory tests**: Complete blood count, platelet count, serum creatinine, estimated glomerular filtration rate, LDH, protein/creatinine ratio;

- Assessment of **ADAMTS13 activity** and anti-ADAMTS13 antibodies; this examination is central insofar as the severe ADAMTS13 deficiency is the first abnormality to appear, followed by others (cytopenia, hemolysis and organ damage);

- Assessment of **residual CD19+ B lymphocytes in peripheral blood** in patients treated with rituximab. This research is only indicated in patients who have failed preventive rituximab therapy to check that the treatment failure is unrelated to a defect in B cell depletion. In this context, rituximab should deplete patients of blood B lymphocytes (<1% of B lymphocytes detectable by flow cytometry), which is a prerequisite for achieving normalization of ADAMTS13 activity.

Frequency of laboratory monitoring:

1. ADAMTS13 activity assay (and antibody testing by ELISA if ADAMTS13 activity is less than 10%) and standard laboratory monitoring are indicated as follows:

- Every week after platelet normalization (and cessation of TPE) until partial normalization of ADAMTS13 activity at levels of 20–30%; thereafter, a new 28-day control is performed to confirm normalization (ideally at a level of ≥ 50%).

- Thereafter, every 3 months for several years, with, in principle, monitoring for life.

- It is only after several years of normal ADAMTS13 activity (≥ 50%) that monitoring once every 6 months or once a year can be considered.

2. Patients with severe ADAMTS13 deficiency in remission receive preventive infusions of rituximab. In this case, monitoring (standard laboratory tests and ADAMTS13 activity) is controlled at one month of infusion, and once normalization of activity is achieved, a monitoring rate of once every 3 months is resumed.

3. In all patients with clinical or laboratory signs suggesting relapse of iTTP, an additional assessment of ADAMTS13 is offered.

4. In any patient with a history of iTTP, an assessment of ADAMTS13 activity is also performed in the case of planned pregnancy or scheduled surgery.

cTTP-specific monitoring:

The frequency of consultations is one every 3 to 6 months; they can be less frequent thereafter. This follow-up must take place in conjunction with the treating physician. In all cases, patients are regularly hospitalized in a day hospital (typically every 14 to 21 days) to receive prophylactic plasma infusions.

An **interview and clinical examination** should determine whether there have been **intercurrent episodes** (particularly neurological events) since the last consultation or plasma administration. It is also necessary to assess the existence of **clinical manifestations related to persistent deficiency insufficiently supplemented with ADAMTS13**: chronic headaches, persistent fatigue, neurocognitive disorders (see "Assessment of cardiovascular risk factors and neurocognitive sequelae (all types of TTP)"), abdominal pain, dizziness, etc.

Additional examinations:

The following are systematically indicated **before each plasma infusion**:

- **Standard laboratory tests**: Complete blood count, including platelets, serum creatinine, blood electrolytes, estimated glomerular filtration rate, LDH, serum haptoglobin;

On a regular basis (once a year to once every three years depending on the situation and the patient's age), the **impact of the disease on organs must be assessed** more specifically:

- **Heart**: electrocardiogram, cardiac ultrasound, stress test;

- **Brain**: brain MRI

- **Eye**: fundus of the eye.

Finally, **cardiovascular risk factors** should be assessed and managed (see next section).

Assessment of cardiovascular risk factors and neurocognitive sequelae (all types of TTP):

The following are indicated to assess cardiovascular risk factors:

- Fasting blood glucose, hemoglobin A1c,

- Lipid profile (total cholesterol, HDL and LDL cholesterol; triglycerides),

- Electrocardiogram,

- According to the opinion of the cardiologist: echocardiogram, stress test, coronary angiography, etc.

The frequency of this monitoring should be adapted to the underlying risk, situation and cardiologist's opinion, if necessary (once every three years in the youngest patients to once a year in the oldest patients). It can sometimes be performed by the treating physician.

For the assessment of neurocognitive sequelae, the following are indicated:

The systematic assessment of these sequelae is only recent in TTP, but it should become rapidly widespread. The most frequently studied scales are as follows:

- PCL-S (Posttraumatic Stress Disorder Checklist Scale), which tracks signs of posttraumatic stress disorder;

- HADS (Hospital Anxiety and Depression Scale) questionnaire, which assesses the presence of a depressive or anxious state;

- SF36 questionnaire, which assesses quality of life associated with health.

Social and professional aspects and renewal of LTC insurance

There is a significant risk of neurocognitive sequelae in survivors of an episode of TTP (63% to 75%) after the acute episode. The impact of these deficits (especially memory disorders) likely contributes to shortening of life expectancy in these patients. Two studies found deterioration in the physical and mental quality of life in most patients compared to a reference population. The data are currently insufficient to assess the social and economic impact in the short and long terms (the social and professional impact of the disorder can be significant, especially in the case of repeated relapses). A professional reclassification or disability classification may therefore be necessary. It is often essential to stop work during the first 3 months of treatment. Due to the duration of the initial conventional treatment (1 month minimum on average) and the prolonged risks of relapse that require long-term monitoring (for at least 10 years), the allocation of an LTC status can take place for renewable periods of 5 years.

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The following people participated in developing the PNDS:

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Conflict of Interest Statement

All participants in the development of the PNDS completed a Conflict of Interest Statement, detailed below (**see HAS**).

Paul Coppo is a member of the Scientific Advisory Board and has received funding for research projects from Sanofi, Alexion, Takeda and Janssens. He has received funding for research projects from Roche, Amgen, Sandoz and AstraZeneca.

Agnès Veyradier is a member of the French Scientific Advisory Board for caplacizumab (Sanofi) and for ADAMTS13 recombinant therapy (Takeda).

Ygal Benhamou is a member of the French Scientific Advisory Board for caplacizumab (Sanofi) and for ADAMTS13 recombinant therapy (Takeda).

Jean-Michel Halimi received fees for consulting or conference activities from Alexion, Sanofi and AstraZeneca.

The coordinator of the work (P. Coppo) and the two collaborators (Y. Benhamou and A. Veyradier) met four times to consolidate some aspects of the PNDS. The document was submitted to all reviewers by email.

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TTP Patient Advocacy Group:

ADAMTS13 Association: President: Ms. Sandra Da Silva 3 Rue

Salvador Allende – 91120 Palaiseau

Phone: +33 (0)6 09 24 67 16

Email: assocadamts13@hotmail.com – Website: http://asso.orpha.net/ADAMTS13/

- Answering TTP Foundation, a Canadian patient advocacy group: https://www.answeringttp.org/

Appendix 3. Management in Emergency Situations

1. Abnormalities requiring emergency hospitalization

These are abnormalities suggesting a relapse of TTP, whether autoimmune (iTTP) or congenital (cTTP):

Clinically:

Any clinical manifestation suggesting the formation of microthrombi responsible for organ damage:

- Clinical picture of transient or composite stroke: focal deficit (limb, hemibody, aphasia/dysarthria, amaurosis);
- Confusion, coma;
- Seizure;
- Unusual headaches;
- Unusual abdominal pain that may reflect pancreatic or intestinal involvement (mesenteric ischemia);
- Lipothymia, severe dizziness or fatigue, which may indicate anemia or cardiac distress;

- Hemorrhagic syndrome related to thrombocytopenia: purpura, ecchymosis, etc.

Laboratory tests:

These are peripheral cytopenia and abnormalities showing organ damage:

- Any thrombocytopenia; in iTTP and sometimes in cTTP, thrombocytopenia is classically the second abnormality chronologically in the onset of the clinical relapse, after severe ADAMTS13 deficiency;
- Hemolytic anemia often associated with the presence of schistocytes on the blood smear;
- These abnormalities can typically be associated with elevated LDH levels, as well as serum creatinine and cardiac troponin.

In a patient monitored regularly (typically every 3 months), the onset of a severe ADAMTS13 deficiency (activity <10%) is predictive of a clinical relapse that can occur at any time, the severity of which cannot be accurately estimated. This situation therefore represents a relative emergency requiring the implementation of preventive treatment (most often with rituximab) to correct the ADAMTS13 activity (see "Prevention of relapses").

2. Management

- In a patient with a clinical picture of relapse (clinical and laboratory signs, or only laboratory signs but which can suddenly include organ damage or even sudden death especially in the autoimmune form), it is essential for them to be hospitalized as a matter of urgency to initiate standard treatment as soon as possible (see "Therapeutic management").

a. At the doctor's office:
   - **Perform urgently**: complete blood count and platelet count, testing for schistocytes, reticulocytes, LDH, free bilirubin and serum creatinine, troponin.
   - The patient should be referred urgently to the nearest hospital to confirm the diagnosis of relapse and to initiate the first therapeutic measures.

b. At the hospital:
   - **Urgently**: confirm cytopenia, mechanical hemolytic anemia (testing for schistocytes; free bilirubin, haptoglobin, LDH), and look for the presence of organ damage (clinical examination, serum creatinine and troponin); take a sample to assess ADAMTS13 activity.
   - The medical team contacts a regional center of expertise of the CNR-MAT or the CNR-MAT itself to discuss the diagnosis of relapse and the treatment to be implemented. In the coming years, strategies based on the emergency administration of caplacizumab alone or with low volumes of therapeutic plasma and in combination with immunosuppressive therapy should be evaluated. Pending these evaluations, the current first-line therapy is still plasma therapy through TPE.

- In the case of a biological relapse identified during the monitoring of a patient in clinical remission (recurrence of severe ADAMTS13 deficiency), hospitalization in a day hospital must be organized quickly to initiate preventive treatment from the outset (if the previous ADAMTS13 activities were already in kinetics of decrease) or to confirm the severe ADAMTS13 deficiency in a new sample (if previous activity was normal) before implementing preventive rituximab.

Useful contacts in case of emergency:

CNR-MAT: Hôpital Saint-Antoine, AP-HP.6 – Sorbonne University, Paris;

184, rue du Faubourg Saint-Antoine 75571 Paris Cedex 12

Emergency number: +33 (0)1 71 97 00 82

Other useful numbers: Secretary's

office: + 33 (0)1 49 28 34 39

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paul.coppo@aphp.fr

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raida.bouzid-saadaoui@aphp.fr

Appendix 4. Predictive Score of Severe Acquired ADAMTS13 Deficiency

Parameter	French Score	PLASMIC Score
Platelets	<30 x 10^9/L (+1)	<30 x 10^9/L (+1)
Serum creatinine	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis Free bilirubin >2 mg/dL or reticulocytes >2.5% or undetectable haptoglobin	a	+1
No progressive cancer over the past year	a	+1
No context of organ or stem cell transplantation	a	+1
INR <1.5	a	+1
MCV <90 fl	a	+1
Probability of severe (<10%) ADAMTS13 deficiency	**0: 2%** **1: 70%** **2: 94%**	**0–4: 0–4%** **5: 5–24%** **6–7: 62–82%**

Abbreviations: INR: international normalized ratio; MCV: mean corpuscular volume.

a: These items are not useful in the French score, for which the presence of thrombotic microangiopathy syndrome without associated context (for which the absence of severe ADAMTS13 deficiency is usual) is a prerequisite.

Appendix 5. Additional Tests for the Diagnosis and Follow-up of TTP

Test	Special Situations
Complete blood and platelet counts	Participates in diagnosis Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Blood smear when testing for schistocytes	Participates in diagnosis Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Reticulocyte assay	Participates in diagnosis Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Hemolysis assessment: LDH, haptoglobin, free bilirubin	Participates in diagnosis Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Coombs test	Initial assessment
aPTT-PT-thrombin time-fibrinogen	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Complete blood electrolytes with serum creatinine	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Urine electrolytes with creatinine	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Urine sediment	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Protein/creatinine ratio	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Total protein, serum protein electrophoresis	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event, or treatment with rituximab
Immunofixation of serum protein	In the case of hyper- or hypogammaglobulinemia detected by serum protein electrophoresis
Troponin	Initial assessment, and in case of need or intercurrent event
C reactive protein (CRP)	If infectious syndrome, and in case of intercurrent event
Liver function tests (AST, ALT, GGT, alkaline phosphatase, total and conjugated bilirubin)	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Vitamin B12 assay	At diagnosis, before erythrocyte transfusion
Urine culture	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Blood culture	If fever
Stool culture	Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
HIV, HCV, HBV serology	At diagnosis
Pretransfusion assessment	At diagnosis and before transfusion
Bone marrow differential cell count	At diagnosis, if aged ≥ 60 years or if doubt about the central nature of cytopenia
ADAMTS13 activity assay	If clinical picture of TTP: Initial assessment, therapeutic management and follow-up, and in case of need or intercurrent event
Anti-ADAMTS13 antibody testing	If clinical picture of TTP: Initial assessment, therapeutic

	management and follow-up, and in case of need or intercurrent event
Testing for *Escherichia coli* STX+ and toxin in stools or swab	If diarrhea – Initial assessment, therapeutic management
Antinuclear antibodies – If positive: anti-DNA antibodies native and C3-C4-CH50	At diagnosis and follow-up
Cardiolipin/anti-β2GP1 antibody	At diagnosis and follow-up
Beta-HCG	In women of childbearing age, initial assessment, therapeutic management and follow-up
Pretransfusion assessment	
ABO-RH1 blood group	Before 1st transfusion (established twice)
RH-KEL1 phenotype	Before 1st transfusion (established twice)
Testing for irregular agglutinins (screening)	Before each transfusion
Laboratory monitoring of TTP treatments, in accordance with the MA	Corticosteroids: serum potassium, serum calcium, blood phosphorus, fasting blood glucose, etc. (refer to LTC 8 Diabetes if applicable), testing for dyslipidemia immunosuppressants: Complete blood and platelet counts
Long-term laboratory monitoring of iTTP to prevent clinical relapses	Complete blood and platelet counts, serum creatinine, blood electrolytes, estimated glomerular filtration rate, LDH, ADAMTS13 activity
Long-term monitoring of comorbidities during TTP (autoimmune or congenital)	- Fasting blood glucose, hemoglobin A1c, - Lipid profile (total cholesterol, HDL and LDL cholesterol; triglycerides), - Electrocardiogram, - According to the opinion of the cardiologist: echocardiogram, stress test, coronary angiography, etc. The frequency of this monitoring must be adjusted based on the underlying risk and the situation.
Long-term monitoring of comorbidities occurring specifically during cTTP	On a regular basis (once a year to once every three years depending on the situation and the patient's age), the impact of the disease on organs must be assessed more specifically: - Heart: electrocardiogram, echocardiogram, stress test - Brain: brain MRI - Eye: fundus of the eye

Appendix 6. Assessment of ADAMTS13 Activity, Anti-ADAMTS13 Antibody Testing, ADAMTS13 Gene Sequencing

When faced with a clinical picture suggesting TTP,
BEFORE ANY PLASMA TREATMENT (INFUSIONS OR EXCHANGES)
Collect: 1 dry 5 mL tube or 1 citrate tube (for the biochemical study of ADAMTS13 = ADAMTS13 activity and anti-ADAMTS13 IgG titration) and 1 EDTA 5 mL tube (for the genetic study of ADAMTS13) (consent should be obtained from the patient or parents).

Processing the samples:
- **Centrifuge the dry tube** for 15 minutes, at 4°C, between 1300g and 2500g.
- Aliquot the serum into Eppendorf tubes (500 µL per tube); freeze at −20°C or −80°C.
- **Centrifuge the citrate tube** for 15 minutes, at 4°C, 2000g to 2500g.
- **Freeze the EDTA tube** (do not centrifuge) at –20°C or –80°C until shipping.

For all CHU de Paris-IDF hospitals and for CHU de Régions regional hospitals whose local laboratories do not perform ADAMTS13 testing, the samples should be sent on dry ice (by AP-HP courier for the Paris-IDF centers or by DHL for regional centers) **to the reference laboratory:**

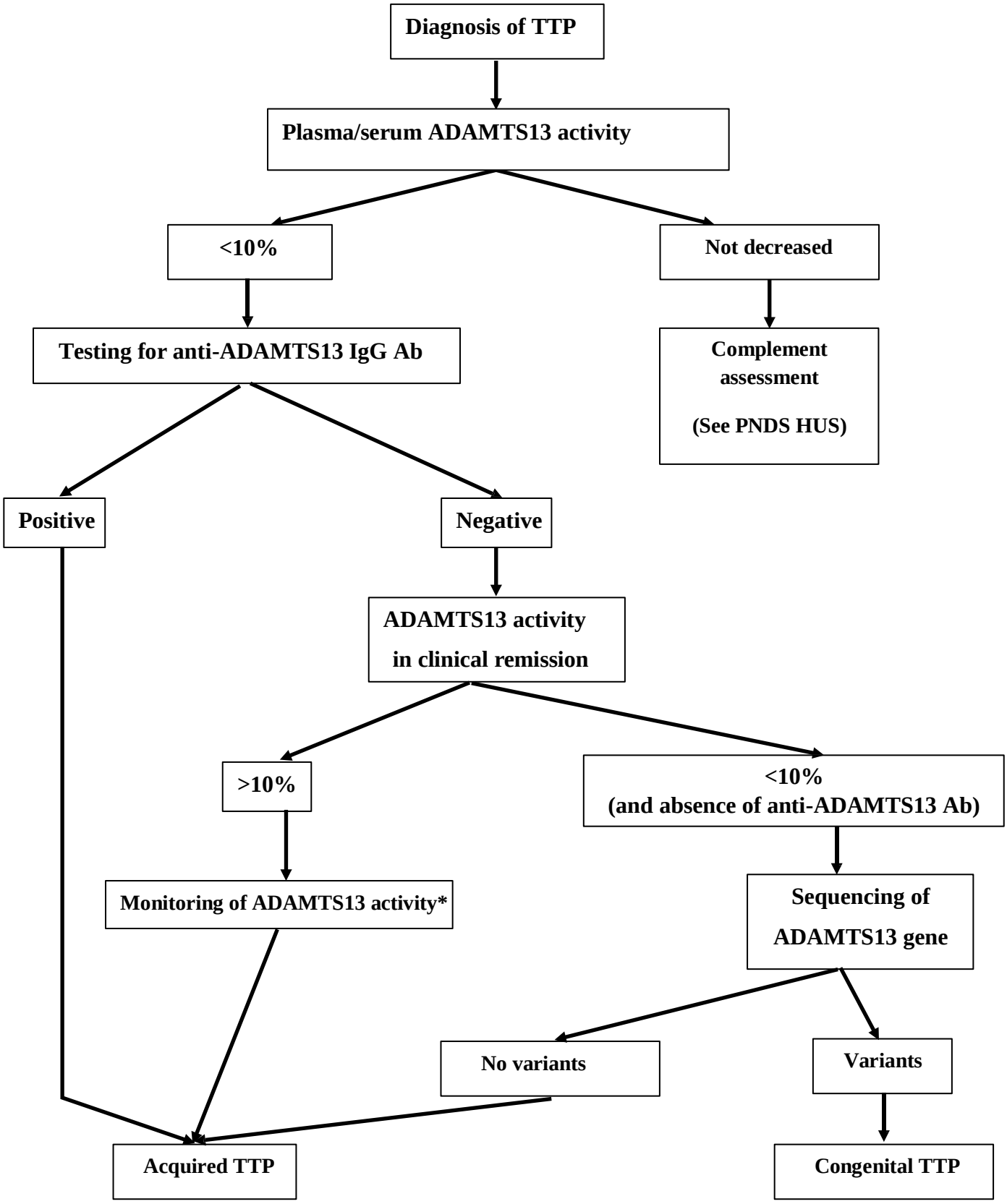
Prof. A. Veyradier – Dr. B. Joly – Dr. A. Stepanian Hôpital Lariboisière,

Department of Biological Hematology –

2, Rue Ambroise Paré, 75010 Paris

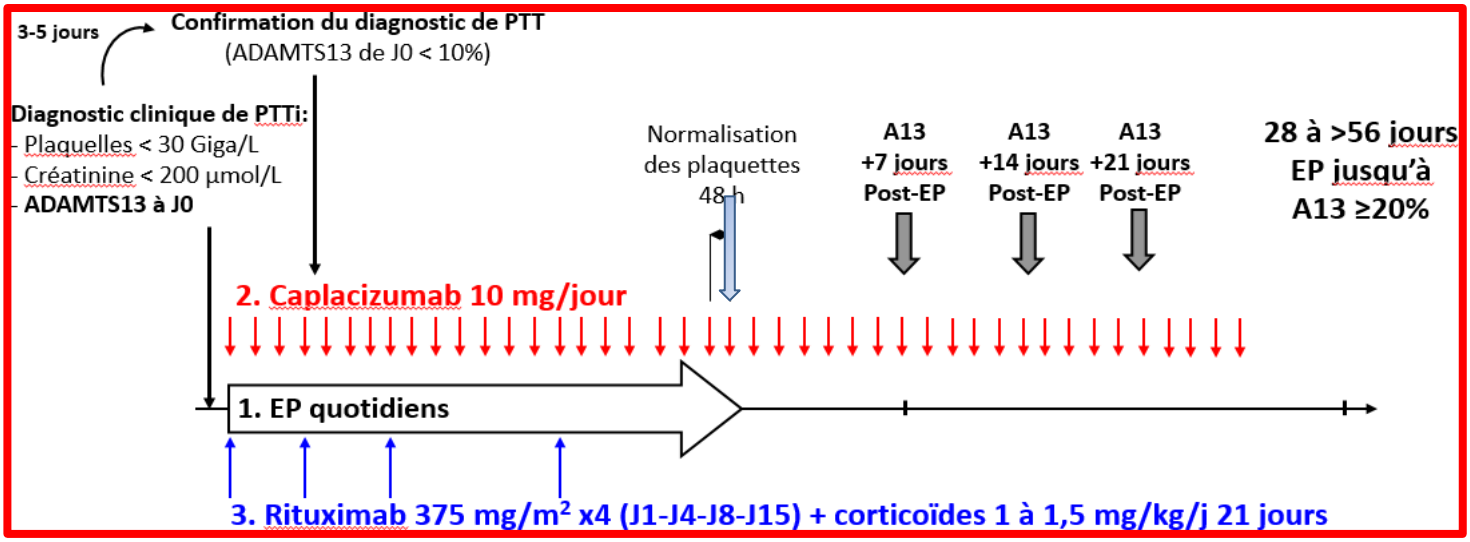
(Administration: Tel.: +33 (0)1 49 95 64 11; Fax: +33 (0)1 49 95 81 81)

Appendix 7. Decision Tree for the Biological/Genetic Diagnosis of TTP in the Acute Phase



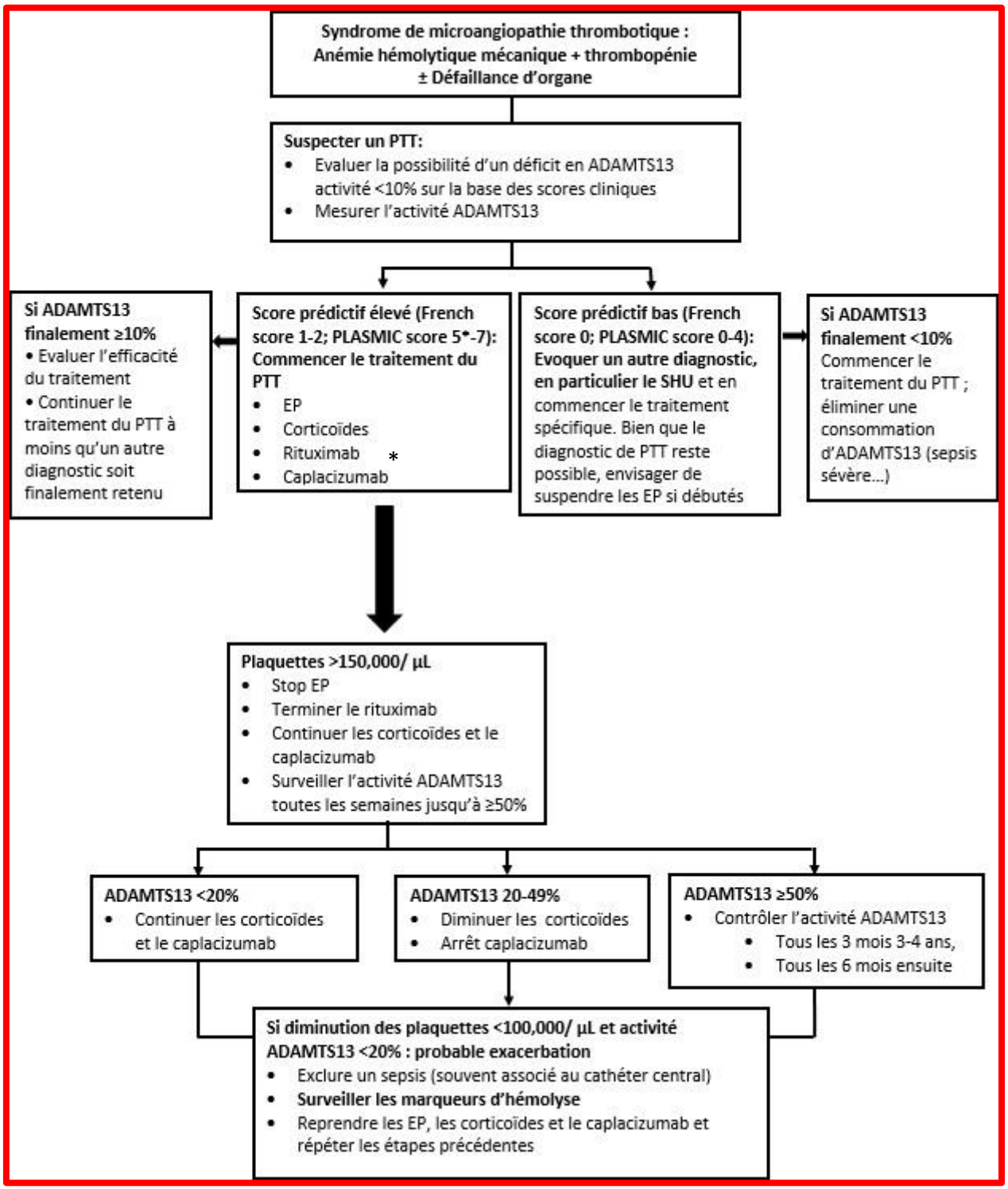
* When monitoring ADAMTS13 activity in remission, which has become detectable at a rate >10%, it should be ensured that the values continue to increase to levels >30% (within a period typically of 1 year) to be able to assert the acquired character of the deficiency. Otherwise, sequencing of the ADAMTS13 gene can be discussed, looking for a monoallelic mutation (heterozygous) or an association of polymorphisms that may explain why ADAMTS13 activity is not increasing at a rate >50%.

Appendix 8. Treatment Regimen for iTTP in the Acute Phase ("Triplet Regimen")



Abbreviations: TPE: therapeutic plasma exchange; D: day; h: Hours; A13: ADAMTS13.

Appendix 9. Algorithm for the Treatment of iTTP in the Acute Phase



Given the urgency of initiating adequate treatment, a clinical diagnosis score calculated from baseline clinical characteristics is most often used to assess the likelihood of severe ADAMTS13 deficiency (activity <10%) (**appendix 4**). When the clinical score is strongly suggestive of severe ADAMTS13 deficiency (French score of 2), it is therefore important to initiate complete treatment of iTTP (according to the "triplet" regimen) immediately. Rituximab can be initiated immediately when the French score is 2; some practitioners prefer to wait for confirmation of the diagnosis of TTP based on undetectable ADAMTS13 activity. If the likelihood of severe ADAMTS13 deficiency is intermediate (for example, a French score of 1; **appendix 4**), treatment of iTTP should be empirically started with at least TPE given the risk of the rapidly unfavorable outcome of untreated or delayed treatment of iTTP. This emergency treatment should subsequently be supplemented with immunomodulatory therapy and caplacizumab when, and only if, severe ADAMTS13 deficiency is identified and measured. If ADAMTS13 activity is eventually found to be ≥ 10%, the diagnosis of iTTP is much less likely and the discontinuation of TPE treatment should be discussed, unless there is a clearly favorable outcome under TPE (as cases of iTTP with a detectable ADAMTS13 activity are rare).

When the clinical score is low in favor of severe ADAMTS13 deficiency, it should be discussed whether treatment for iTTP should be suspended if it has been initiated; however, the diagnosis of iTTP cannot be completely ruled out at this stage. In these patients, it is important to look for another etiology to mechanical hemolytic anemia and thrombocytopenia, such as, in particular, postinfectious or atypical (or complement-mediated) hemolytic and uremic syndrome, especially when there is predominant renal failure. If ADAMTS13 activity is eventually <10%, treatment for TTP should be continued or initiated urgently if not yet initiated, unless another etiology for severe acquired ADAMTS13 deficiency is retained (e.g., severe sepsis, severe DIC or malignant disease).

The diagnosis of TTP is based on the clinical assessment, as well as the ADAMTS13 activity assay. Corticosteroid therapy consists of administering prednisone, 1 to 1.5 mg/kg/day. In addition, diagnostic boluses have been proposed in the most severe patients before the era of caplacizumab (methylprednisolone IV, 1000 mg/day for 3 days). Rituximab is used according to the following regimen: 375 mg/m^2, 4 doses over 2 to 3 weeks. Studies have reported that lower doses (2 to 3 injections instead of 4, or lower dose per injection) have comparable effectiveness. Caplacizumab has now been granted Market Authorization for the treatment of iTTP at diagnosis. After platelet normalization, patients may maintain isolated severe ADAMTS13 deficiency; therefore, ADAMTS13 activity should be monitored weekly until normalization (activity ≥ 50%), while continuing caplacizumab therapy (until ADAMTS13 activity reaches 20%*) to avoid exacerbations

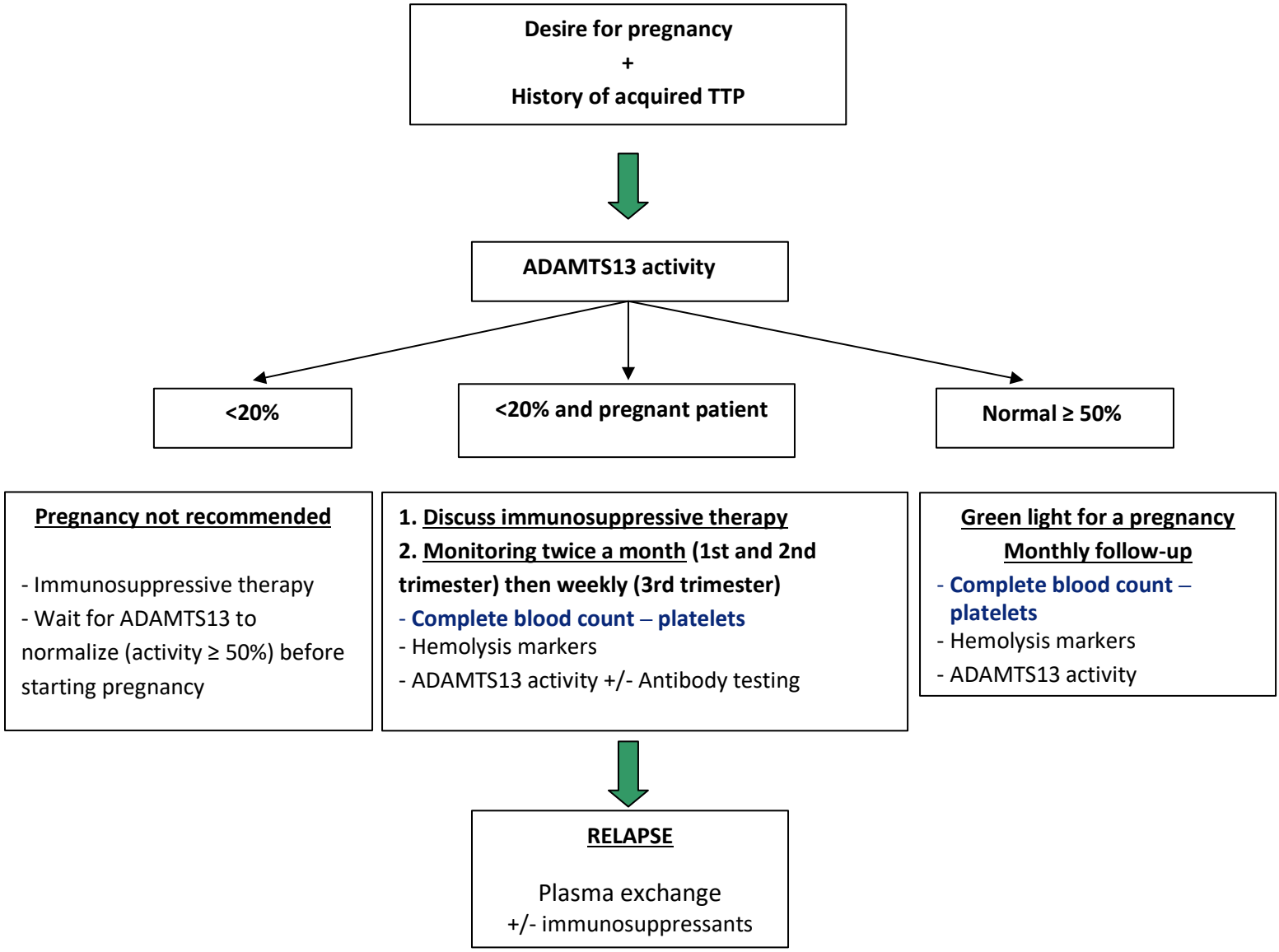
or relapses of the disease. It is also necessary to optimize immunomodulatory treatment if the ADAMTS13 activity is not corrected. Once ADAMTS13 activity is normalized, it is necessary to continue monitoring activity every 3 months for 3 to 4 years; if the activity remains normal during this period, monitoring may be less frequent (once every 6 months), but it is likely to be continued for life, given the risk of relapse that can occur many years after the initial episode.

*The relevance of discontinuation of caplacizumab before D30 on the basis of an ADAMTS13 threshold of 20% is being assessed in several clinical studies conducted in France and abroad.

Abbreviations: TPE: therapeutic plasma exchange; TTP: thrombotic thrombocytopenic purpura; iTTP: immune TTP.

Appendix 10. Desire for Pregnancy in Women with a History of iTTP

Discussions of these situations take place on a case-by-case basis as part of a national multidisciplinary consultation meeting, especially for cases where ADAMTS13 activity before conception or at the start of pregnancy is between 10% and 50%.



Appendix 11. References