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**Critical Care Expert Statement on the Management of Patients with Thrombotic  
Thrombocytopenic Purpura**

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### **Conflicts of interests**

This statement is the result of an independent effort from the Nine-I investigators. None of the authors received any honoraria or fees for this contribution. The Nine-I has received research grants and sponsors from Gilead, Fisher &Payckle, Jazz Pharma, Ablynx, Baxter, Alexion and Astellas.

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## **Abstract**

Thrombotic thrombocytopenic purpura (TTP) is characterized by a syndrome of thrombotic microangiopathy (TMA), with severe consumption thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), and a variable degree of ischemic end organ damage. Acquired TTP is due to an ADAMTS13 deficiency, a metalloprotease that cleaves the von Willebrand (VWB) factor. TTP patients exhibit uncleaved ultra-large VWF multimers that bind to platelets in high shear environments. Organ ischaemia occurs then as a consequence of microvascular occlusion. The disease carries a 90% mortality rate if left untreated. Misdiagnosis can affect outcomes Initial management focuses on ruling out other potential causes of TMA (shigatoxin-related haemolytic and uremic syndrome (HUS), complement mediated HUS, or secondary TMA syndromes). Despite the lack of consensual definition of severe TTP, a large number of TTP patients are managed in the ICU for either severe organ failure, or to ease management and optimal monitoring. Early plasma exchange (PEX) and corticosteroids significantly reduced mortality. Sudden death can occur anytime within the first days of treatment initiation, mostly from coronary occlusion or cardiogenic shock. Rituximab has been advocated at the earliest phase of severe TTP, along with the just released caplacizumab. In this expert statement written by a group of ICU specialists used to manage patients with TMA syndromes, we sought to inform and guide clinical management of critically ill patients with TTP. Participating experts have agreed and graded items related to diagnostic workup, assessment of patient's severity, standard of care for TTP patients and for second line therapy in patients who are unresponsive to initial treatment. Finally, unanswered questions are raised, leaving a research agenda on the critical care aspects of TTP.

## 1. Introduction (574)

Acquired thrombotic thrombocytopenic purpura (TTP) is a haematological and critical care emergency, with a mortality of 90% if left untreated. The disease is characterized by a syndrome of thrombotic microangiopathy (TMA), with severe consumption thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), and a variable degree of ischemic end organ damage. Early plasma exchange (PEX) and corticosteroids significantly reduced the mortality to about 15%<sup>1,2</sup>. Acquired TTP is due to a deficiency of the von Willebrand factor (VWF) cleaving serine metalloprotease, called ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13)<sup>3-5</sup>. Anti-ADAMTS13 autoantibodies that either inhibit ADAMTS13 proteolytic activity (neutralizing antibodies), or enhance ADAMTS13 clearance (non-neutralizing antibodies) contribute to the pathogenesis of acquired TTP<sup>6,7</sup>. Organ ischaemia occurs as a consequence of MAHA and microvascular occlusion from microthrombi resulting from uncleaved ultra-large VWF multimers that bind to platelets in high sheer environments<sup>8</sup>.

The diagnosis of TTP is based on clinical and biological findings. TTP prevalence is 10-15 cases per million people, with a sex ratio of 2 women for a man, and a peak incidence of disease occurring before the age of 50 years<sup>9</sup>. In adults, acquired TMA syndrome and signs of organ ischemia are highly suggestive of TTP. Initial management focuses on ruling out other potential causes of TMA, namely, shigatoxin-related haemolytic and uremic syndrome (HUS), complement mediated HUS, or secondary TMA syndromes. Once ADAMTS13 activity is found undetectable, with or without anti-ADAMTS13 antibody, TTP diagnosis is then established<sup>4,10-12</sup>. Noteworthy, sampling for ADAMTS13 activity should be collected immediately and prior to any plasma therapy, but clinicians should start PEX without waiting for

ADAMTS13 results. Misdiagnosis can affect outcomes and often leads to unnecessary and excessive use of hospital resources<sup>13</sup>. Along the same line, delay in implementing PEX has been associated with increased mortality<sup>14,15</sup>. Hence, clinicians should maintain a high level of suspicion towards the diagnosis of TTP. Moreover, in the sickest TTP patients with severe organ dysfunction, early PEX correlates with faster remission<sup>16</sup>.

There is no consensual definition of severe TTP. Yet, a large number of TTP patients are managed in the ICU<sup>11,17</sup> for either severe organ failure, or because the ICU is the only place in the hospital where a PEX can be performed, a central line be inserted, or a careful monitoring offered at any time. Indeed, sudden death can occur anytime within the first days of treatment initiation, mostly from coronary occlusion or cardiogenic shock<sup>18</sup>. In a retrospective study comparing TMA patients who died with TMA survivors, lack of PEX implementation and cardiac involvement were the leading causes of death<sup>14</sup>.

Statements or consensus guidelines for the management of TTP patients have previously been published<sup>10,19-21</sup>. In this expert statement written by a group of ICU specialists used to manage patients with TMA syndromes, we sought to inform and guide clinical management of critically ill patients with TTP, with a particular focus on patients with severe organ dysfunction and high risk of sudden death. Moreover, the recent release of caplacizumab, an anti-VWF recently approved in Europe and by the US Food and Drug Administration, motivated our group to review and clarify the basic standard of care, since the optimal benefits of this new treatment will be gauged against a background of high-quality standardized care. Participating experts have agreed and graded items related to diagnostic workup, assessment of patient's severity, standard of care for TTP patients and for second line therapy in patients who are unresponsive to

initial treatment. Finally, unanswered questions are raised, leaving a research agenda on the critical care aspects of TTP to be hopefully conducted in the next five years.

## **2. Search strategy**

A literature search (time between 1978 and 2018) was conducted using the National Library of Medicine database (PubMed) and the Cochrane database using the following search terms: “TTP”, “Thrombotic thrombocytopenic purpura” or “ADAMTS13 deficiency” with search filters of “humans” and “English language”. These terms were combined with additional search terms: “Clinical prediction score”, “prediction”, “score” or “diagnosis” when identifying publications pertaining to definitions and scoring for severe TTP; and “ICU”, “intensive care”, “critical care” or “critical illness” when searching for publications related to TTP in ICU. Additional relevant articles were also included from Internet searches using the same search terms.

Formulation of the guidelines was conducted according to the Grade of Recommendation Assessment, Development and Evaluation methodology <sup>22,23</sup>. A strong agreement was reached on all the recommendations. The guidelines were focused on four 4 areas: diagnostic workup, severity assessment, standard of care and second line therapy.



### 3. TTP in the ICU

We identified six studies that reported on critically ill patients with TTP (Table 2).<sup>15,16,39-42</sup> These populations differed in terms of severity of illness, organ support and mortality, which may be attributable to variation in admission policies across centres. Neurological signs, renal impairment and cardiac abnormalities were commonly observed. However, life sustaining therapies were variably applied with ventilator support reported in 30-50% of patients, and renal replacement therapy in 0-19%. Hospital mortality was reported in all studies and ranged from 4.3% in the study by Zafrani et al.<sup>39</sup> to 34.9% in the study by Pene et al.,<sup>15</sup> where patients were sicker than in other ICU studies.

#### *Why TTP patients should be managed in the ICU?*

In many TTP cases, ICU care may be necessary because of severe organ failure<sup>12</sup> or injury (table 5) such as coma, stroke, seizure, posterior reversible encephalopathy syndrome<sup>47,48</sup>, myocardial infarction, congestive heart failure<sup>49</sup>, arrhythmia,<sup>18</sup> mesenteric ischemia, pancreatitis,<sup>50</sup> or acute kidney injury<sup>39</sup>. Beyond severe organ dysfunction, critical care environment also offers close monitoring to patients at high risk of clinical deterioration, secures catheter placement in patients with profound thrombocytopenia, or facilitates urgent treatment with plasma exchange.<sup>45</sup> Indeed, TTP is a medical emergency that requires rapid recognition and specific treatment as soon as the diagnosis is suspected. At many hospitals, the ICU is the only place where central line placement and plasma exchange can be rapidly initiated with adequate patient's monitoring. For other patients, TTP may not have been diagnosed initially and patients were already in the ICU with presumed alternate diagnosis such as sepsis<sup>51</sup>.

### ***When TTP patients should be managed in the ICU?***

TTP patients should be managed in the ICU upon diagnostic recognition of TMA, to initiate plasma exchange<sup>14,40,41</sup> and to support organ failure with mechanical ventilation, vasopressor support or renal replacement therapy.<sup>15,52</sup> Refractory or relapsing TTP unresponsive to initial management should also be treated in ICU.<sup>40</sup> ICU may also be needed in case of catheter related complications such as bleeding, infection or thrombosis, and in case of plasma transfusion reaction,<sup>53</sup> or worsening neurologic abnormalities after plasma exchange.<sup>54</sup> ICU discharge will depend on the response to treatment and resolution or organ failures. However, hospital facilities (availability of a step down or intermediate care unit), existence of an apheresis department, and hospital organization (monitoring facilities in the wards, availability of a rapid response team) should be taken into account when making the decision of ICU discharge.

### ***Which TTP patients should be managed in the ICU?***

All TTP patients should be managed initially in ICU.<sup>10,14,41,45</sup> Admission to ICU may be elective (e.g. initiation of plasma exchange for a patient in whom diagnosis is strongly suspected or even made), urgent (to confirm the diagnosis and initiate treatment) or emergent (need for intubation and mechanical ventilation, hemodynamic support or renal replacement therapy). Special circumstances (e.g. pregnancy) are especially at risk and deserve ICU admission for optimal multidisciplinary management. Management should be performed preferably in a reference centre by a multidisciplinary team with experience in TTP for both ICU and long term managements.

#### 4. TTP definitions and scoring

TMA diagnosis is based on clinical findings, MAHA with schistocytes, peripheral thrombocytopenia and organ dysfunction<sup>8</sup>.

In 1966, based on a review of 270 cases, Amarosi and Ultman proposed the following "pentad" for the diagnosis of TTP<sup>24</sup>: fever, haemolytic anaemia, purpura or bleeding associated with thrombocytopenia, neurological signs, and renal disease presented with haematuria and/or proteinuria or elevated blood urea nitrogen. However, later studies found that patients diagnosed with TTP were commonly lacking one or more elements of the pentad.

It has since become evident that measurement of ADAMTS13 activity is necessary to confirm the diagnosis of TTP<sup>4,6,7,12</sup>. However, ADAMTS13 analysis may not be immediately available to guide clinical management. As a consequence, almost every TMA syndrome in adults requires urgent plasma therapy, unless evidence for an alternate diagnosis can be quickly gathered (malignant hypertension, vitamin B12 deficiency, metastatic cells in the bone marrow smear, scleroderma renal crisis, etc...).

Attempts have been made to address this early diagnosis issue, and several scoring systems have been developed to predict severe ADAMTS13 deficiency and diagnosis of TTP (Table 1). However, if these scores are able to stratify patients for a higher likelihood of TTP, none of these can replace ADAMTS13 testing. Based on data from the French TMA Reference Centre, Coppo *et al.* proposed a simple scoring system based on three criteria to predict severe ADAMTS13 deficiency.<sup>27</sup> They included a serum creatinine <200 µmol/L, platelet count <30 x 10<sup>9</sup>/L and positive antinuclear antibody test; when all three criteria are present, the positive predictive value is 99% though the negative predictive value is only 39% suggesting that these criteria cannot

rule out ADAMTS13 deficiency.<sup>27</sup> Moreover, antinuclear antibody testing may not be promptly available either. Bentley *et al* developed another score based on results from 100 patients using five criteria: creatinine, platelets, D-dimer, reticulocytes and indirect bilirubin.<sup>28</sup> This score has since been validated<sup>29</sup> and can be useful at predicting disease when the score is >30, and in ruling out disease when <20, but intermediate scores are difficult to interpret and not discriminative. Finally, the PLASMIC scoring system, published in 2017, uses seven criteria: platelet count <30 x 10<sup>9</sup>/L, haemolysis, no active cancer, no history of solid-organ or stem-cell transplant, mean corpuscular value <9 x 10<sup>-14</sup>L, INR <1.5 and creatinine <2mg/dL (177umol/L) with one point for each positive criterion.<sup>30</sup> An independent external validation of the PLASMIC score was performed in a cohort of 112 patients with TMA: Area under the curve (AUC) was 0.94 (0.88-0.98) and a score of 6 or 7 predicted severe ADAMTS-13 deficiency with a positive predictive value of 72%, a negative predictive value of 98%, a sensitivity of 90% and a specificity of 92%.<sup>31</sup> Hence, until dedicated resources are made available to obtain reliable ADAMTS13 testing within a few hours, scoring systems will continue to be used to stratify patients, but clinicians should understand their limitations and reasons for not initiating plasma therapy within hours of ICU admission should rely on clear and undisputable alternate diagnoses.<sup>10</sup>

If ADAMTS13 activity is detectable, typical HUS (positive shigatoxin on the rectal swab), complement-mediated-HUS) or secondary TMA syndromes<sup>45</sup> should be considered.

As plasma exchanges will remove a significant proportion of plasma proteins, including antibodies and substances bound to albumin [8, 9], they may alter the results of most plasma studies. The initial biological workup should best be retrieved before the onset of plasmapheresis. One study has shown that ADAMTS13 activity is usually,

but not always, still severely decreased in the first 3 days following the onset of PEX  
in patients with TTP. [10]

## 5. TTP and organ dysfunction

TTP is a multisystem disorder. Organ dysfunction occurs as a consequence of widespread microvascular thrombosis (Figure 1). Thrombi occur at high density in the heart, brain and kidney causing transient or partial occlusion of vessels resulting in intermittent ischemia.<sup>8</sup> Several registry-based studies have reported the common signs and symptoms of this condition that are presented in Tables 2 and 3, and in Figure 2.<sup>9,27,32,33</sup> Neurological impairment is common and proteiform, including headache, altered personality, reduced cognition, seizures, transient ischemic attacks and coma.<sup>9,32</sup> These signs and symptoms often fluctuate in presentation and severity, due to the formation and dissolution of thrombi in the cerebral microcirculation.<sup>8</sup> When the coronary vessels are involved patients can experience acute myocardial infarction, arrhythmias, heart failure, cardiogenic shock, and troponin levels are often elevated.<sup>18,34,35</sup> Abdominal pain can occur due to acute pancreatitis or to mesenteric ischemia with resulting diarrhoea.<sup>36</sup>

Several studies have suggested that renal involvement is not a predominant feature of TTP (table 2).<sup>27,29,37,38</sup> However, renal involvement may still occur due to either the TTP itself, haemolysis, blood pressure lability or drug-related renal toxicity. The study by Zafrani et al. reviewed all cases of TTP (with ADAMTS13 activity <10%) admitted to a single ICU over a twelve year period and described the rate of acute kidney injury (AKI).<sup>39</sup> They found that AKI (defined based on KDIGO 2012) was common and affected 58.7% of patients. AKI was ascribed to TTP itself in 96.3% of patients, with potential kidney injuries being hypoperfusion (16.7%), acute tubular necrosis (7.4%), nephrotoxicity (9.3%), haemolysis-induced tubulopathy (33.3%) and autoimmune glomerulonephritis (14.8%). Among those patients with AKI, 42.6% had

chronic kidney disease at 6 months. This high rate of renal injury was also observed in several of the other papers published within the ICU setting ([Table 2](#)).<sup>9,15,16</sup>

**Recommendations for TTP diagnostic workup (table 7A)**

a) *Experts suggest that all patients suspected of having TTP should undergo, at least, the following workup:*

- *Full clinical screening for organ injury (neurologic, cardiac, renal, gastrointestinal).*
- *Biological workup to diagnose TMA: Blood cell count and smear (reticulocytes and schistocytes). Biochemistry: LDH, haptoglobin, bilirubin, Direct Antiglobulin Test to rule out Evans syndrome, basic coagulation tests to rule out DIC, proteinuria, haematuria.*
- *Biological workup to confirm TTP: Non-heparinised samples for ADAMTS13 activity and anti-ADAMTS13 antibodies before TPE, alternative pathway of the complement system study, and PCR on rectal swab for shiga-toxin.*
- *Minimal tests to assess organ involvement (troponin, ECG, renal function, lipase) and to identify possible associated conditions (auto-immunity markers, HIV serology,  $\beta$ -HCG, blood cultures).*
- *Cross-matching before transfusion (blood group, hepatitis serologies).*

**GRADE for a): Expert opinion, Agreement: Strong**

b) *Blood samples should probably be obtained before starting plasma therapy.*

**GRADE for b): 2+, Agreement: Strong**

c) *Diagnostic workup should probably not delay TPE.*

**GRADE for c): 2-, Agreement: Strong**

d) *When ADAMTS13 activity cannot be easily or quickly measured, diagnostic scores (French score, Bentley score, PLASMIC score) should probably be used to assess whether ADAMTS13 is likely to be undetectable.*

**GRADE: 2+, Agreement: Strong**

## 6. Assessing TTP severity

In acquired TTP, microvascular thrombosis translates into ischemic end organ damage so rapid and accurate diagnosis is crucial for survival.<sup>13</sup> Schistocytes may be absent initially; this may distract and delay the diagnosis with severe consequences, especially since the first acute episode is usually more severe than recurrent episodes.<sup>55</sup> Platelet transfusions are often administered before the correct diagnosis has been made, and have been associated with clinical deterioration and increased relapse rate.<sup>56,57</sup>

Urgent (within 4-6 hours of admission) plasma exchange therapy is vital for recovery and should be initiated in the ICU, as TTP patients have increased risk of adverse effects of plasma exchange therapy.<sup>58</sup> Lack of response to plasma exchange therapy is associated with more severe complications, higher consumption of ICU resources, and increased mortality.<sup>40,59</sup> In centres able to perform prompt diagnosis and treatment, mortality is as high as 10% overall,<sup>9,32</sup> and among unresponsive patients, up to 30% die.<sup>40</sup> Mortality is even higher when the diagnosis is missed or the treatment delayed.<sup>14,60</sup> Therefore, it is crucial to identify patients at high risk of mortality or unresponsive disease early (Table 6), in order to be able to offer a more aggressive treatment regimen.<sup>10,61</sup>

By 1987, Rose et al. had developed a “TTP Clinical Severity Score” based on serum creatinine, platelet count, haemoglobin level, and neurologic symptoms, in an attempt to risk stratify patients.<sup>25</sup> In their study, higher scores were associated with worse outcome. However, this finding was not confirmed in further studies, probably due to the inclusion of patients with both TTP and HUS.<sup>26</sup>

One of the most common reasons for death is cardiac ischemia<sup>18</sup> and autopsy studies have found that widespread myocardial microthrombosis is ubiquitous in TTP patients.<sup>14,36,62</sup> Furthermore, patients with cardiac involvement are more likely to be



unresponsive to treatment.<sup>40</sup> Increased cardiac troponin level is associated with mortality<sup>34,63,64</sup> even though most patients with increased cardiac troponin levels are asymptomatic.<sup>18,49</sup> Benhamou *et al.* found that patients with a cardiac troponin I level of  $> 0.25 \mu\text{g/L}$  had more cardiac and cerebral involvement and high levels of troponin were also found in patients with stroke.<sup>34</sup> Chest pain, ECG changes and troponin must be assessed routinely at presentation and on a regular basis throughout the course of the disease. Transthoracic echocardiography is part of the routine diagnostic workup in the ICU. Coronary angiography may be reserved to selected patients with risk factors and signs of acute coronary syndrome, its indication being discussed on a case by case basis along with a cardiologist.

Cerebral involvement has been associated with worse outcome<sup>65</sup> and symptoms of brain ischemia such as severe seizures and coma have been linked to severe ADAMTS13 deficiency.<sup>66</sup> There are other factors associated with worse outcome, such as older age<sup>67,68</sup> and a lactate dehydrogenase (LDH) increase  $\geq 10$  x normal value, although increased LDH level is probably related to severe multiorgan failure (Table 5 and 6).<sup>65,68</sup> Therefore, in stratifying for TTP severity, emphasis should be on measuring cardiac troponin levels and assessing cardiac and cerebral involvement (Figure 2).

General ICU management applies to TTP patients. Namely, this includes early ICU admission, optimal ICU monitoring, increasing awareness that sudden deterioration is possible at any time, standard measures to preserve organs and correct metabolic disturbances. Upon initial management, careful clinical evaluation will assess disease severity. No specific data is available on the management of organ dysfunction in TTP patients (red cell transfusion thresholds, decision to intubate patients with coma or stupor, anti-epileptic prophylaxis, renal replacement therapy, extracorporeal life support, etc...).

In every adult patient with TMA, we advocate to pay specific attention to increased cardiac and neurologic risks<sup>14,18,49</sup>. The disappearance of signs of haemolysis and the platelet count increase over 150G/L usually correlate with cardiac and neurological improvements<sup>10,94,95</sup>, allowing TPE tapering or stop. These markers may be used to decide when to discharge TTP patients from ICU. ICU discharge also depends on the availability of an apheresis unit in the hospital. Follow up should be made by a multidisciplinary team including TTP experts, haematologists, as well as ICU and organ specialists.

**Recommendations for assessment of TTP severity (table 7B)**

- a) *Organ dysfunction should probably be assessed routinely at presentation and throughout the course of TTP.*

**GRADE: 2+, Agreement: Strong**

*Experts do not provide guidance for the management of organ dysfunction in TTP patients.*

**Not Graded**

- b) *Experts suggest that the presence of cardiac involvement (ie. chest pain, ECG and trans-thoracic echography changes, and troponin) must be assessed routinely at presentation and on a regular basis throughout the course of TTP.*

**GRADE: Expert opinion, Agreement: Strong**

*Older age, cerebral involvement and persistently high LDH may help identify TTP patients at increased risk of early death.*

**GRADE: 2+, Agreement: Strong**

*Experts suggest that all patients diagnosed with TTP must be initially admitted to an area of Critical Care in order to monitor and manage organ dysfunctions, and to provide urgent plasma exchange therapy.*

**GRADE: Expert opinion, Agreement: Strong**

*Experts suggest that ICU discharge be allowed when TPE can be tapered or stopped, when signs of haemolysis disappear and platelet count increases over 150G/L, which usually correlates with cardiac and neurological improvements. Patients can be discharged from the ICU earlier if there is a TPE unit in the hospital.*

**GRADE: Expert opinion, Agreement: Strong**

## 7. TTP and pregnancy

Pregnancy can be a precipitating cause of TTP and accounts for 2-8% of all TTP cases<sup>9,32</sup>. While hereditary TTP only accounts for 3-5% of TTP cases, an unusually high prevalence of hereditary TTP clustered in the obstetric population was reported. It can represent 25-60% of cases as hereditary TTP often manifests for the first time during pregnancy<sup>43,44</sup>. The presence of severe thrombocytopenia during pregnancy may pose a challenge to physicians given the wide differential diagnosis with many overlapping clinical features. Differentiating pregnancy-associated TTP from incidental causes is paramount to guide management. The differential diagnosis of thrombocytopenia with MAHA during pregnancy include ADAMTS13 deficiency (TTP), complement mediated thrombotic microangiopathy (aHUS), HELLP syndrome (microangiopathic haemolytic anaemia, elevated liver enzymes, low platelet count), and disseminated intravascular coagulopathy (DIC) (table 4). In TTP, intrauterine foetal death may occur due to placental infarction due to thrombus formation in the decidual arterioles. In those cases, the risks to the mother and foetus are minimized with prompt recognition and initiation of plasma therapy.

We advocate for close collaboration and interaction between critical care specialists and TTP experts (haematologists, clinical immunologists, internists, and/or nephrologists). In this specific area of rare diseases, clinicians, biologists and researchers must align skills and knowledge to create a collective experience-based management that goes far beyond the acute care setting and will benefit present and future patients. Hence, multidisciplinary team is the best option to manage TTP.<sup>45</sup> This should translate into improved clinical performances,<sup>46</sup> and improved outcomes. In the setting of pregnancy, early involvement and communication between the intensivist, high-risk obstetric team and haematologists should be pursued to assist with diagnosis

and management. In TTP patients, there is no maternal indication for early delivery, only foetal indications, and the management is similar to the non-pregnant patients with TTP. When there is uncertainty regarding the diagnosis, while awaiting the ADAMTS13 activity results, plasma exchange should be initiated. Platelet transfusions should not be withheld in the setting of severe bleeding.

***GRADE: Expert opinion, Agreement: Strong***

## 8. Therapeutic targets in TTP

Even though first-line TTP therapy has been based on plasma exchange and steroids until recently, several TTP targets exist and could also be considered as first line therapies<sup>61</sup> (Figure 3). This paragraph provides the rationale for the use of available treatments, whereas the next paragraph details the standard of care for first and further line therapy in TTP patients.

### *Replacement therapy*

Therapeutic plasma exchange (TPE) that provides large amounts of functional ADAMTS13 via substitution with fresh frozen plasma, remains today the cornerstone in TTP treatment.<sup>12,69</sup> It prevents excessive binding of ultralarge VWF multimers to platelets, with subsequent aggregation and microthrombi formation within the microvessels. Whether the technique effectively removes anti-ADAMTS13 autoantibodies has not been properly assessed. Plasma infusion alone, although far less effective<sup>1,16,70</sup>, may be provided when expecting delayed initiation of TPE because of hospital organization or availability of an apheresis slot or a TPE machine<sup>1</sup>.

### *Immunomodulation*

Given the autoimmune origin of acquired TTP in adults, there is a rationale for immunomodulation and a variety of treatment strategies exists. Corticosteroid treatment is recommended in the initial phase, together with TPE.<sup>10,19</sup> A trial of corticosteroids in patients with TMA has even demonstrated that in selected cases, they induced prolonged clinical remission.<sup>2</sup> However, this trial published in 1991 did not distinguish among the different clinical entities of TMA, particularly patients with STEC-HUS, aHUS or secondary TMA who do not require corticosteroid. Rituximab, a monoclonal antibody targeting CD20 on B cells, has shown to reduce the relapse rate

in refractory cases of TTP, reduce the level of anti-ADAMTS13 antibody and increase functional ADAMTS13 activity.<sup>71-79</sup> Furthermore, the benefits from several other immunosuppressive and cytostatic drugs in addition to PEX have been reported in smaller studies and case reports as salvage therapy, in refractory cases of TTP. These include vincristine (halting cell division), cyclosporine A (targeting T-cells effector functions), cyclophosphamide (alkylating agent), bortezomib (proteasome inhibitor), and complement (C5) inhibition by eculizumab<sup>80-88</sup>. Splenectomy should only be considered as salvage therapy in patients with severe TTP manifestations unresponsive to all other treatments<sup>83</sup>.

#### *Prevention of VWF binding to platelets*

N-acetylcysteine, by inhibiting platelets adherence to endothelial-anchored ultralarge vWF by reducing their size, has been used successfully in case reports<sup>89</sup>.

In June 2018, the European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended approval of caplacizumab in Europe for the treatment of adults experiencing an episode of acquired TTP. Caplacizumab has also been fast-tracked by the FDA. Marketing Authorisation Application for Caplacizumab has been approved for the treatment of acquired TTP in the US on February 6<sup>th</sup> 2019.

Caplacizumab, an anti-VWF humanized single-variable-domain immunoglobulin (nanobody), inhibits the interaction between ultralarge VWF multimers and platelets by targeting VWF-1b, thereby preventing thrombi formation. Faster platelet count recovery and resolution of organ damage has been demonstrated in TTP patients receiving caplacizumab. In the phase 2 TITAN trial<sup>91</sup>, 75 TTP patients were randomly assigned to caplacizumab (10 mg daily) or placebo. There was a significant improvement in the primary endpoint (39% reduction in median time to

platelet count normalization) in the caplacizumab group. Fewer caplacizumab-treated patients had a major thromboembolic event, a TTP exacerbation, or died versus placebo (11.4% vs. 43.2%)<sup>91</sup>. More recently, in the double-blind, controlled HERCULES trial, 145 patients were randomly assigned to either caplacizumab or placebo during plasma exchange and for 30 days thereafter<sup>17</sup>. The median time to normalization of the platelet count was shorter with caplacizumab than with placebo (2.69 days [1.89-2.83] vs. 2.88 days [2.68-3.56]). Patients who received caplacizumab required less plasma exchange procedures and had a shorter hospitalization than those who received placebo. The percentage of patients with a composite of TTP-related death, recurrence of TTP or a thromboembolic event during the treatment period was lower with caplacizumab than with placebo (12% vs. 49%,  $P < 0.001$ ). Only 12% of the caplacizumab-treated patients underwent TTP recurrence at any time during the trial and none developed a refractory disease (vs. 38% and 4%, respectively). Mild to moderate bleedings were more common with caplacizumab as compared to placebo (54% vs. 38% in the TITAN trial and 65% vs. 48% in the HERCULES trial). Combining TITAN and HERCULES trials, TTP-related deaths were 0% (0/107) in the caplacizumab group versus 4.5% (5/110) in the placebo group. In June 2018, the European Medicines Agency's Committee for Medicinal Products for Human Use has recommended approval of caplacizumab in Europe for the treatment of adults experiencing an episode of acquired TTP. Caplacizumab was approved on August 2018. Caplacizumab was also approved by the US Food and Drug Administration for the treatment of acquired TTP on 06 February 2019.



## 9. Standard of care for treatment of severe TTP (table 7)

Standardizing first-line management of patients with suspected TTP is a challenge<sup>10</sup>. TTP recognition, diagnostic workup, exclusion of differential diagnoses, and first-line patient management must not be delayed (figures 4 and 5).

### *Standard of care for patients with severe TTP*

Whether the first line therapy should be limited to only PEX and corticosteroids, or should include early rituximab and caplacizumab in all ICU patients independently of the severity remains an unresolved issue. Treatment should not be delayed until the diagnostic workup for both TTP and differential diagnoses is complete (figure 2), with emphasis on obtaining a reliable test to ascertain ADAMTS13 blood level before any plasma therapy. The best way to preserve organ function is to implement early a high volume PEX<sup>1,16</sup>. We advocate that every critical care specialist should be able to manage a patient with TMA, diagnose TTP appropriately and promptly, evaluate TTP severity, and implement first line therapy within the first hours of ICU admission. In the following days after ICU admission, we also recommend that a TTP specialist be involved in patient's management, irrespective of the severity, most particularly to provide an expert consult on the underlying condition, share advances in disease understanding and updated therapies and recommendations, prepare ICU discharge and inform patient about long term outcomes. According to patient's severity and organ involvement, appropriate consults might also be called (i.e., cardiologists, neurologists, nephrologists, etc.).

Therapeutic Plasma Exchange (TPE) is urgent and should be initiated within 4-6 hours of TMA diagnosis (figures 4 and 5), as the risk of death is maximal before TPE onset<sup>14,15</sup>. TPE is superior to plasma infusions in terms of morbidity and mortality<sup>1,16</sup>. Plasma infusions should only be used when TPE is not immediately available, until the

patient is transferred to another centre. The experts suggest to perform one TPE per day with a dose of plasma of 60 ml/kg (1.5 x estimated plasma volume) until platelet count is above 150G/L for  $\geq 48$  hours. TPE should be repeated every day until remission (see definition below). When no alternative is available, placement of a central venous catheter should be performed by an experienced operator, under ultrasound guidance, without platelet transfusions<sup>96</sup>. Indeed, platelets transfusion and medications that may induce microvascular injury (desmopressin, vasopressin, tranexamic acid, etc...) should be avoided, unless a life threatening haemorrhage occurs<sup>10</sup>. It should however be noted that despite profound thrombocytopenia, TTP is far more an ischemic than a haemorrhagic disease. Plasma availability should be checked with the blood bank, and all pre-transfusion requirements should be applied<sup>97</sup>.

Initial immunosuppression includes methylprednisolone (1 mg/kg) or equivalent<sup>2,10,98</sup> and may be given for 21 days. Corticosteroids may also reduce side effects often observed with PEX<sup>99</sup>. In case of severe TTP, high dose pulse corticosteroids (e.g. 1 g of methylprednisolone) may be given daily for three consecutive days<sup>100</sup>

Rituximab is used off-label in TTP, but is very effective to eradicate the autoantibodies<sup>72,73</sup>. Rituximab is given in patients with relapsing TTP<sup>40,75,77,101</sup>. The slow onset of action, about 10-14 days, makes it unlikely to manage effectively TTP severity at the initial phase and prevent early deaths. However, it may prevent delayed exacerbations and relapses<sup>98</sup>. There are no studies comparing upfront (empirical) vs. individualized (ADAMTS13-based) use of rituximab. Scully et al. reported faster TTP remission with rituximab compared to historical controls,<sup>77</sup> a finding confirmed by the French study group<sup>75</sup>. Despite the lack of a proper clinical trial in patients with severe TTP, rituximab may however be overall beneficial<sup>73,75,77,78</sup>. We recommend that in

critically ill TTP patients, rituximab be used as a first line agent in all patients. Standard lymphoma doses should be used, but shorter regimen based on B-cell depletion may be considered as well <sup>72,102</sup>. Some have suggested a twice weekly schedule administration of rituximab in acute TTP due to the removal of the molecule by PEX<sup>72</sup>.

The experience of this group with caplacizumab is limited to the participation for some of its members into the two published RCTs<sup>17,90</sup>, or off label in temporary authorization programs. Thus, none of the members of this group has a large personal experience with caplacizumab given under real-life conditions. The current approved use of caplacizumab is for the treatment of adult patients with acquired TTP, in combination with PEX and immunosuppressive therapy. We suggest that, in critically ill patients with severe TTP and high risk of thromboembolic events, exacerbations, relapse, prolonged PEX and death, caplacizumab be given systematically, as a first line therapy in addition to PEX, corticosteroids and rituximab. A registry of every case treated with caplacizumab and further evaluation are warranted to confirm or not the potential benefit of this drug in combination with other first line therapies.

The best standard of care of ICU management should be provided, including deep vein thrombosis and peptic ulcer prophylaxis, as well as limited use of red cells transfusions<sup>10</sup>. Folate replacement should be administered over the first two weeks<sup>98</sup>. Anti-platelet therapy are quite broadly used in patients with severe cardiac or brain involvement, and once platelet count reaches 50G/l. However, evidence supporting such practice remains poor <sup>103</sup>. Moreover, the use of caplacizumab raises concerns for its combination with anti-platelet agents. However, trials assessing the efficacy of caplacizumab did not recommend to withdraw anti-platelet agents, even though we cannot assess whether the combination of the two was associated with increased bleeding rates<sup>17,103</sup>. Attention should be paid to prevent and monitor the dialysis catheter

for thrombosis or infection, to maintain adequate blood pressure control, and to provide prophylaxis against herpes simplex virus and *Pneumocystis jirovecii* in case of protracted corticosteroid requirement. Experts suggest that prophylactic antibiotics should not be administered. As stated before, platelet transfusion should be avoided as it may worsen microvascular injury and should be limited to severe bleeding (i.e., cerebral haemorrhage, etc...) <sup>56,96</sup>.

To optimize efficacy, every treatment should be given after PEX, and therapeutic drug monitoring should be adjusted where appropriate.

Daily blood cell count, troponin level and haemolytic activity should be performed. These experts also recommend to perform an ECG every day. ADAMTS13 activity and anti-ADAMTS13 inhibitors should be assessed every week until remission, then every two weeks for one month, then monthly for three months. Low ADAMTS13 activity identifies a group of patients at high risk of unresponsiveness to treatment or relapse <sup>11,104,105 106</sup>. This can occur despite the use of rituximab and/or caplacizumab<sup>17,90,104,107</sup>. Last, standard of care should also include usual measures to prevent, diagnose and treat infections in immunocompromised patients.

### ***Recommendations for a standard of care for patients with severe TTP (Table 7C)***

#### ***a) Therapeutic plasma exchanges***

1. *TPE must be preferred to plasma infusions in TTP patients. Plasma infusions must be reserved when TPE is not immediately available.*

**GRADE: 1+, Agreement: Strong**

2. *Experts suggest to perform one TPE per day with a dose of plasma of 60 ml/kg (1.5 x blood mass) until platelet count > 150G/L for ≥48 hours.*

**GRADE: Expert opinion, Agreement: Strong**

3. *Experts suggest that TPE should be initiated within 6 hours of diagnosis.*

**GRADE: Expert opinion, Agreement: Strong**

4. *If TPE is not available, patients should probably be transferred to another centre where TPE is available.*

**GRADE: 2+, Agreement: Strong**

**b) Steroids**

1. *Prednisone or methylprednisolone should probably be administered in association to TPE in TTP patients.*

**GRADE: 2+, Agreement: Strong**

2. *Experts suggest a dose of 1 mg/kg/d for 21 days.*

**GRADE: Expert opinion, Agreement: Strong**

3. *Experts suggest that in case of severe TTP, high dose pulse steroids (1 g of methylprednisolone) can be given for three consecutive days.*

**GRADE: Expert opinion, Agreement: Strong**

**c) Monoclonal antibodies**

1. *Rituximab must be used in patients with relapsing autoimmune TTP.*

**GRADE: 1+, Agreement: Strong**

2. *Rituximab should probably be used as a first line therapy in severe TTP*

**GRADE: 2+, Agreement: Strong**

3. *Experts do not advocate nor discourage first-line rituximab in all TTP patients.*

**GRADE: Expert opinion, Agreement: Strong**

4. *Caplacizumab must be used as a first line therapy in severe TTP*

**GRADE: 1+, Agreement: Strong**

**d) Supportive care**

1. *Experts suggest folate supplementation, prophylactic anticoagulation and antiplatelet agents as soon as platelet count reaches 50G/L, monitoring of the central venous catheter for thrombosis or infection, tight blood pressure control, gastro-duodenal ulcer prophylaxis, prophylaxis against HSV and Pneumocystis jirovecii in case of protracted corticosteroids requirement.*

**GRADE: Expert opinion, Agreement: Strong**

2. *Experts suggest that prophylactic antibiotics should not be administered*

**GRADE: Expert opinion, Agreement: Strong**

3. *Platelet transfusion should probably be avoided in TTP patients and be restricted to severe bleeding (i.e., cerebral haemorrhage, etc...).*

**GRADE: Expert opinion, Agreement: Strong**

### ***Recommendations for a second line therapy in patients with severe TTP (Table 7C)***

Clinical remission is defined by a haematological response, resolution of haemolysis and resolution of organ dysfunction. Haematological response is defined by the normalization of platelet count (>150G/L for 2 consecutive days). In case of bone marrow dysfunction, return to baseline platelet count is required. Haemolysis should be unapparent despite TPE interruption. Lastly, improvement in cardiac, renal and neurologic functions can be rapid, even though in the most severe cases recovery can be delayed with persistent or residual organ impairment reported<sup>35,39,49,108</sup>.

Unresponsive or refractory TTP can be defined by persistent thrombocytopenia and haemolysis after at least 7 days of standard treatment<sup>40,94</sup>. In practice, the lack of platelet normalization by day 5 associated with persistent signs of haemolysis (LDH level) and/or severe cardiac or neurological manifestations defines a group of patients at high risk of poor outcomes and who need treatment intensification<sup>94</sup>. Kidney involvement may take longer to recover, especially in patients requiring renal replacement therapy<sup>39</sup>. It is known that surgery, extracorporeal circulation, transfusions or sepsis can generate high shear stress rates from the release of ultra large VWF multimers and may trigger TTP exacerbations<sup>70</sup>.

Disease exacerbation or TTP flare refers to a recurrence of thrombocytopenia and other TTP manifestations either during TPE or within 30 days after stopping TPE, whereas TTP relapse refers to TTP recurrence later than 30 days after TPE therapy has been completed<sup>94</sup>.

Immunologic response is however not based on clinical findings or standard biology. It is defined by the recovery of normal ADAMTS13 activity and complete clearance of anti-ADAMTS13 antibodies<sup>9,27,104,105</sup>.

Patients in clinical and haematological remission may still have a low ADAMTS13 activity and therefore a high risk of relapse. These patients require careful monitoring and prolonged rituximab administration until ADAMTS13 activity recovers and remains stable over time<sup>104,107</sup>. Caplacizumab may have a special role in these patients with persistent high risk of thromboembolic events for a longer time, at least until ADAMTS13 becomes detectable again.

Triggers for exacerbation (most particularly infection, thrombosis and error in treatment delivery) must be looked for and treated<sup>70</sup>. A personalized approach must be given priority. No study has properly evaluated therapeutic strategies for TTP exacerbation or for patients who are unresponsive to a first line therapy that includes TPE and corticosteroids<sup>85</sup>.

If patients did not receive caplacizumab and rituximab in addition to PEX and corticosteroids, the two may be added in combination with twice-daily PEX<sup>110,111</sup>, and intensification of immunosuppression with higher dose or pulse corticosteroids<sup>100</sup>. Rituximab onset of action is delayed and can be expected by day 7-10 at best<sup>75</sup>. If patients received first line caplacizumab and rituximab in addition to PEX and steroids, twice-daily PEX and high dose corticosteroid pulses should be started. According to the clinical severity, vincristine or cyclophosphamide may be added. Vincristine has provided fast, effective and sustained clinical and biological responses<sup>84,112</sup>, and cyclophosphamide has been used with success<sup>74,83,113</sup>. Other drugs such as bortezomib, cyclosporine, mycophenolate mofetil, N-Acetylcysteine, eculizumab, daratumumab or immunoadsorption have been more rarely used. The choice of a second line therapy

depends on the type of underlying condition, if any (pregnancy, AIDS, systemic rheumatic disease...). As stated above, we suggest caplacizumab as a first line agent in all severe TTP patients, especially with a high and prolonged risk of thromboembolic events and sudden death<sup>17,103</sup>. In case of failure of rituximab, ofatumumab might be an option<sup>109</sup>. It has also been suggested that in patients unresponsive to treatment, centrifugation devices might be preferred over plasma filters (lower shear stress rates).

Finally, salvage splenectomy remains an alternative for those patients who either show no clinical and biological response to all of the previous strategies, and/or have a clinical emergency based on cardiac or neurological thromboembolic events<sup>83,85,114,115</sup>. Splenectomy may be beneficial and hamper the autoimmune process by eliminating helper-T-cells, however this procedure should be a last resort treatment after failure of first and second line therapies.

For all TTP patients, advice should be obtained from a TTP specialist. More particularly, in unresponsive cases, the second-line therapy should be discussed with TTP specialists, including biologists and immunologists.

***Recommendations for second line therapy in TTP patients (table 7D)***

1. *Experts suggest that the lack of platelet normalization by day 5 associated with persistent signs of haemolysis (LDH level) and/or severe cardiac or neurological manifestations define unresponsive or refractory TTP. The Kidney involvement may take longer to recover, especially in patients requiring renal replacement therapy.*

**GRADE: Expert opinion, agreement: Strong**

2. *Experts suggest that if patients did not receive caplacizumab and rituximab in addition to TPE and steroids, the two medications must then be added.*

**GRADE: Expert opinion, agreement: Strong**

3. *Experts suggest that if patients did receive first-line caplacizumab and rituximab in addition to TPE and steroids, twice-daily TPE and high dose steroid*



*pulses should be started. According to the clinical severity, vincristine or cyclophosphamide can be added.*

**GRADE: Expert opinion, agreement: Strong**

4. *Experts suggest that the choice for the second line therapy depends on the type of underlying condition, if any (pregnancy, AIDS, systemic rheumatic disease...).*

**GRADE: Expert opinion, agreement: Strong**

5. *Experts suggest that splenectomy should probably remain an alternative therapy for unresponsive TTP; however, with appropriate and timely TTP management it should be reserved as a salvage therapy.*

**GRADE: Expert opinion, agreement: Strong**

6. *Experts suggest that for all TTP patients, an advice should be sought from a TTP specialist. More particularly, in unresponsive cases, the second-line therapy should be discussed with a TTP specialist.*

**GRADE: Expert opinion, agreement: Strong**

## **Unanswered clinical questions – and research agenda about TTP in the ICU**

Despite improvements in our understanding of TTP pathophysiology, the advent of new therapeutic agents, and optimal ICU management, there are still specific needs and unanswered clinical questions when caring for TTP patients.

### ***Initial TTP management***

- Can deep learning allow to identify variables that predict ADAMTS13 activity and inhibitor testing with a close-to 100% sensitivity?
- Would the use of clinical algorithms and artificial intelligence application improve TTP recognition, and exclude alternate diagnosis?
- Would the use of therapeutic algorithms translate into better outcomes?
- Are there risk-stratification models that would allow early ICU discharge in patients at low risk of clinical deterioration (delta-platelet rate? troponin?)?
- Should we standardize the definition of severe TTP and suggest tailored standard of care for these specific patients?

### ***At the onset of TTP treatment***

- We have advocated for a full quadruple initial therapy combining upfront PEX, corticosteroids, rituximab and caplacizumab for all patients. An ideal goal would be to prevent early deaths, and limit the number of severe thromboembolic events. We realize that some patients will be cured with corticosteroids only<sup>64</sup>, some with PEX and corticosteroids<sup>70</sup>, and others with adding rituximab<sup>75,77</sup>. Patients unresponsive to PEX and corticosteroids represent a substantial subgroup of patients that could be identified early after ICU admission<sup>40</sup>. Whether the full quadruple therapy should be limited to those patients with cardiac and

neurological involvement, or those with low platelet count at day 2, remains an unresolved question and deserves to be addressed in another trial. For that to be done, updating factors associated with mortality in the era of comprehensive management of TTP patients is required.

- What is the optimal level of cardiac and neurologic monitoring?
- Should we develop a patient's leaflet mentioning all the risk encountered in TTP, particularly the risk of bleeding with caplacizumab? Guidelines for specific monitoring of von Willebrand factor ristocetin cofactor activity (vWf:RiCo) ratio could be provided and disseminated.
- What is the role of anti-platelet therapy in TTP patients receiving caplacizumab? Should it be administered to all patients or to those with severe neurologic or cardiac involvement?
- Should we consider adjuvant therapy with minor side effects for every patient with the hope that it will ultimately allow to reduce the number of days requiring TPE (N-acetylcystein, magnesium sulfate, etc.)

#### ***Specific questions regarding TTP treatments***

- Access to TPE depends on countries, hospitals and uses. However, studies have never controlled for factors such as devices (centrifuge-based systems vs. plasma filters), anticoagulation (citrate versus heparin) or plasma volume that vary from one study to another.
- What is the best regimen for corticosteroids and rituximab in TTP? Some experts recommend of routine pulse corticosteroids for three days followed by 1mg/kg of methylprednisolone, others recommend rituximab in doses and timing depending on B-cell data.

- Should second line therapy be standardized? In patients not receiving initial rituximab and caplacizumab, second line therapy should include these two drugs, possibly associated with pulse corticosteroids and twice-daily TPE. However, what would be the standard therapy in patients unresponsive to total therapy? If these patients are clinically stable, treatments such as vincristine, cyclophosphamide, and cyclosporine may be initiated. However, if they are sicker, strategies that can provide faster resolution should be considered.
- In patients who are unresponsive to total therapy and severe thromboembolic events, should splenectomy be considered as a second line therapy? There is no doubt that this clinical vignette embodies patients at very high risk of early death. In that case, splenectomy would still remain limited to a small number of patients, but may allow faster recovery in these very high risk patients.
- In patients unresponsive to therapy, should proactive strategies to clear anti-ADAMTS13 inhibitors be attempted (immunoadsorption, new membranes to clear antibodies etc.)?

***Questions about specific organ involvement and treatments***

- Should patients with severe cardiac involvement (ST elevation, high troponin) and cardiovascular risk factors routinely undergo cardiac catheterization, angioplasty and stenting if appropriate?
- Should we consider specific management in patients with cerebral deterioration? Fibrinolytic therapy in large stroke, specific monitoring of cerebral edema and seizure in patients with coma, specific drugs in status epilepticus?
- Should we tailor red cell transfusion thresholds to myocardial and neurological involvement?

- Can we still ascribe organ dysfunction to TTP when ADAMTS13 levels have reached a certain level? Should ADAMTS13 concentrations be the main criteria for discontinuing plasma therapy, rituximab and caplacizumab?
- What are the long term outcomes of neurologic and cardiac involvement? What are the actual rates of cognitive disorders one year after ICU discharge? Depression rates? Cardiac insufficiency rates?
- In the years to come, will caplacizumab be changing the standard of care? (TPE intensity, ICU admission, intensity of immunosuppression)?

## **Conclusion**

TTP is a life threatening disease that benefited from significant diagnostic and therapeutic advances over the last decade. A standardized management protocol allows to both optimizing initial care and avert morbidity and mortality, and also to strengthening the impact of new therapeutic strategies such as rituximab and caplazimuab. Large ICU registries are needed to validate reliable clinical and biological markers that allow to stratify TTP patients at high risk of initial cardiovascular and neurological complications, but also to recognize low acuity TTP patients in whom management could be rapidly be de-escalated or even streamlined.

## Writing committee

All the authors have significantly contributed to building the outline of this statement, as well as to writing, editing and validating the submitted version.

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Figure 1: Clinical features and signs in acute TTP: Symptoms in red are the most frequent whereas symptoms in blue are the most severe.

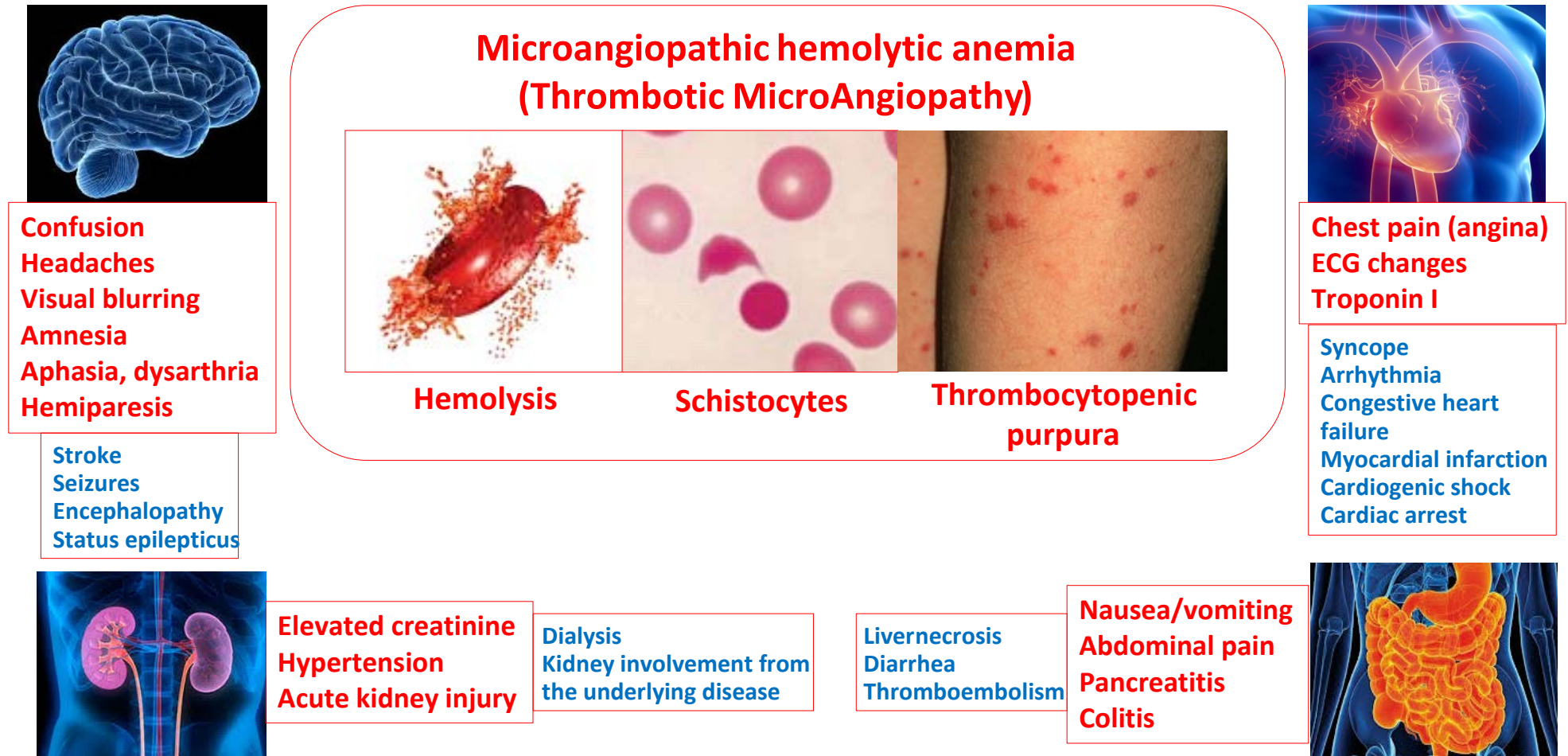
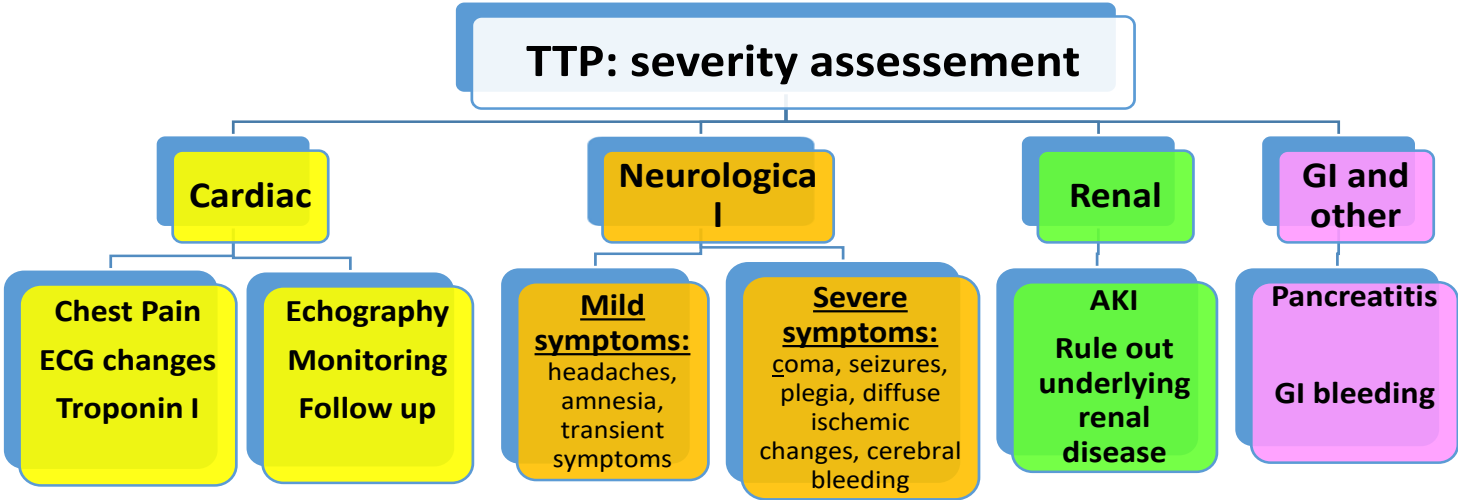
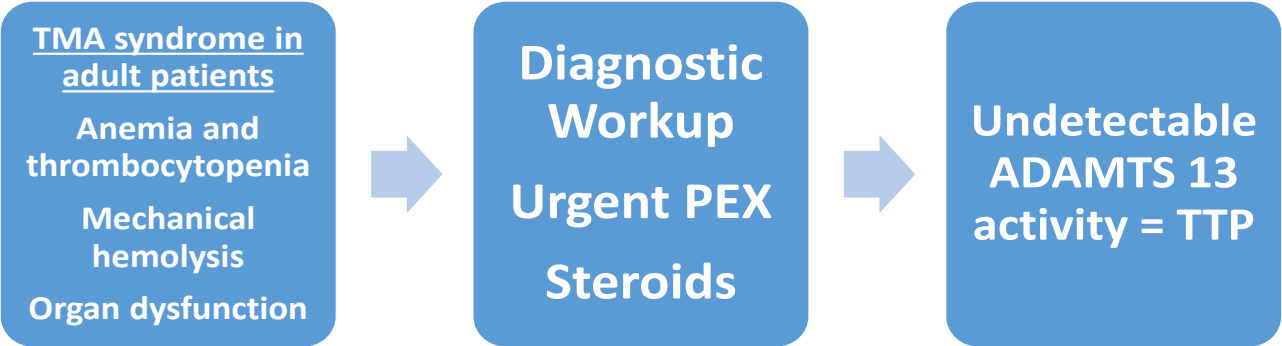
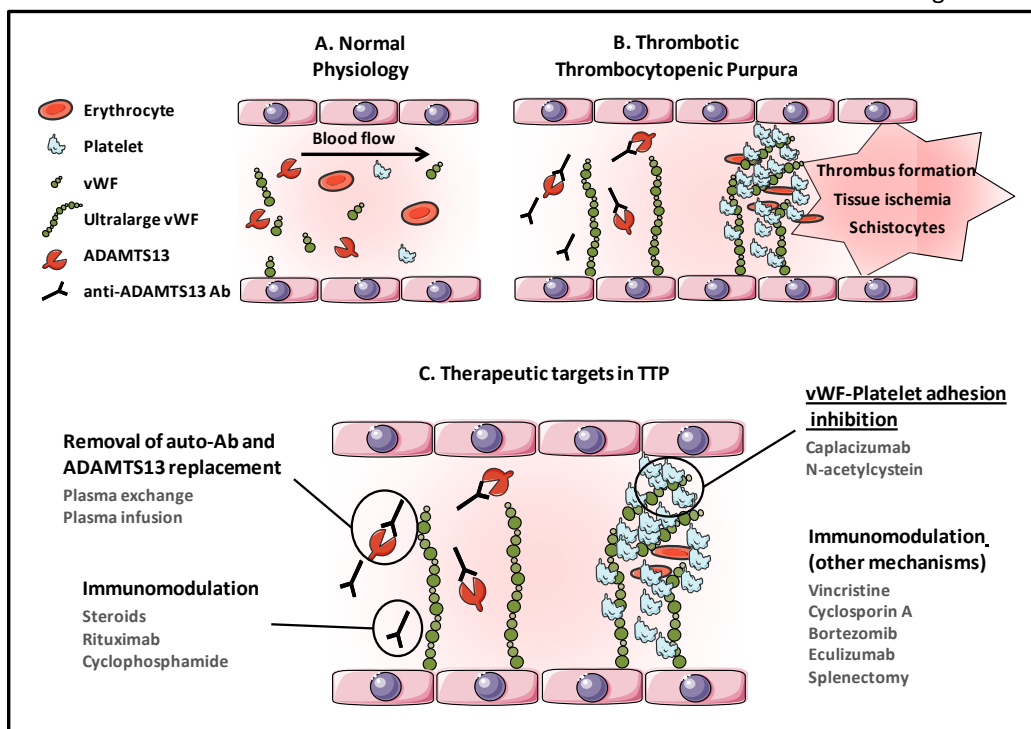


Figure 2: Assessing TTP severity

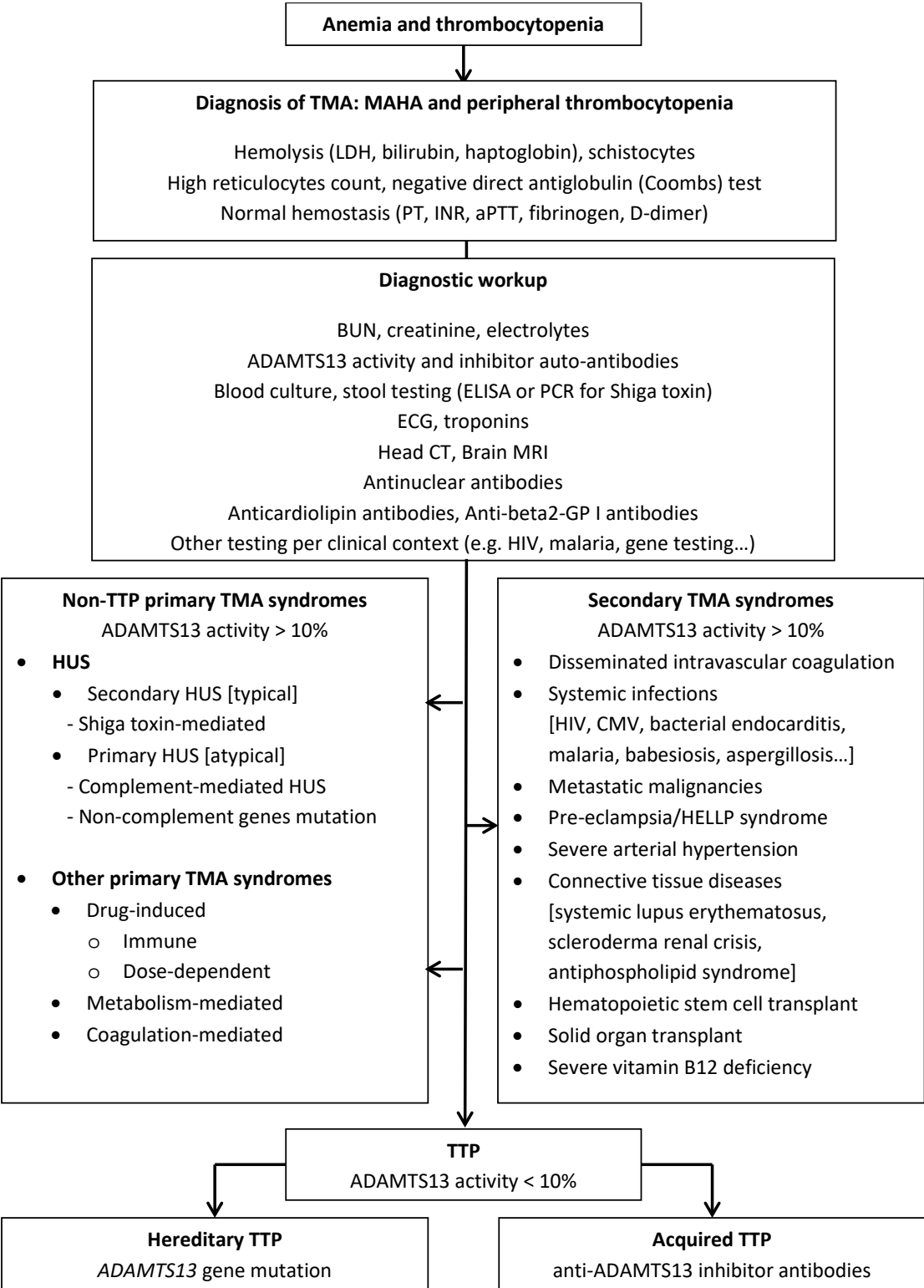


**Figure 3. TTP pathophysiology and therapeutic targets.** (A) In physiologic conditions, ultralarge vWF multimers that are hyperadhesive to platelets are cleaved by ADAMTS13 to smaller, less adhesive multimers. (B) In TTP, low ADAMTS13 activity (often caused by auto-antibody inhibition) facilitates spontaneous binding of ultralarge vWF multimers to platelets, promoting aggregation, platelet consumption and microthrombi formation within the capillary microvessels. (C) The treatment is based on removal of auto-antibodies and replacement of ADAMTS13 by plasma exchange and immunomodulation. Corticosteroids are recommended in the initial phase together with TPE, whereas other additional immunomodulatory strategies are optional. Inhibition of the interaction between ultralarge vWF multimers and platelets by caplacizumab is becoming approved.

Figure X



**Figure 4: Diagnostic workup in patients with thrombotic microangiopathy syndromes**



**Table 1: Clinical criteria and scoring systems for diagnosing ADAMTS-13 deficiency**

<b>Clinical criteria to predict ADAMTS13 deficiency. Coppo et al. 2010 <sup>1</sup></b>		
<b>Creatinine &lt; 200 µmol/L</b>		<i>Three criteria predict severe ADAMTS13 deficiency with a 98% (94-100) specificity, 47% (41-53) sensitivity, 99% (96-100) positive and 39% (36 – 42) negative predictive values</i>
<b>Platelet count &lt; 30 x 10<sup>9</sup>/L</b>		
<b>Positive Antinuclear antibodies</b>		
<b>Point-based ADAMTS13 deficiency prediction score. Bentley et al. 2010 <sup>2,3</sup></b>		
	<u>Points</u>	
<b>Creatinine &gt; 2.0 mg/dL</b>	-11.5	<i>A score &gt;30 points corresponds to a 100 % probability of severe ADAMTS13 deficiency</i>
<b>Platelets &gt; 35 x 10<sup>9</sup>/L</b>	-30	
<b>D-dimer &gt; 4.0 µg/ml</b>	-10	<i>A score between 20 and 30 points corresponds to a 40% probability of severe ADAMTS13 deficiency</i>
<b>Reticulocyte &gt;3%</b>	+21	
<b>Indirect bilirubin &gt; 1.5 µg/ml</b>	+20.5	<i>A score below 20 points corresponds to a 0% probability of severe ADAMTS13 deficiency</i>
<b>The PLASMIC score. Bendapudi et et al. 2016 <sup>4</sup></b>		
	<u>Points</u>	
<b>Platelet count &lt; 30 x 10<sup>9</sup>/L</b>	1	<i>A score ≤4 corresponds to a low risk for severe ADAMTS13 deficiency</i>
<b>Combined hemolysis variables*</b>	1	
<b>Absence of active neoplasia</b>	1	<i>A score of 5 corresponds to an intermediate risk for severe ADAMTS13 deficiency</i>
<b>Absence of transplant</b>	1	
<b>MCV &lt; 9 x 10<sup>-14</sup> L</b>	1	<i>A score of 6 or 7 corresponds to a high risk (&gt;80%) for severe ADAMTS13 deficiency. Patients with confirmed TTP had a median score of 7 (IQR 6–7).</i>
<b>INR &gt; 1.5</b>	1	
<b>Creatinine &lt; 2.0 mg/dL</b>	1	

\* Combined hemolysis variables are defined as reticulocyte count >2-5%, undetectable haptoglobin, or indirect bilirubin >2.0 mg/dl

MCV: Mean corpuscular value; INR: international normalized ratio

TTP: thrombotic thrombocytopenic purpura

**References for table 1:**

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**Table 2: Studies reporting on critically ill patients with TTP**

	Zafrani	Mariotte	Darmon	Pene	Gasparovic	Knobl
<b>Country</b>	France, single centre	France, single centre	France, single centre	France, multicentre	Croatia	Austria, single centre
<b>Study type</b>	Retrospective	Prospective registry	Retrospective	Retrospective	Retrospective	Retrospective
<b>Period</b>	2001 – 2013	1997 – 2011	2000 – 2003	1998 – 2001	Not reported	1992 – 1995
<b>Population</b>	ICU patients with TTP	ICU patients with TTP	ICU patients with TMA	ICU patients with TMA	ICU patients with TTP	ICU patients with TTP
<b>N patients</b>	92	86	36	63 (21 with TTP)	18	6
<b>Severity</b>	SOFA 6.5 (IQR 5-9) <sup>a</sup>		SAPSII 27 (IQR 13-42)	SAPS II 45±26	-	-
<b>CNS dysfunction</b>	86.9%	79%	50%	Mean Glasgow Coma scale (GCS) 12	88.8%	Mild 42% <sup>d</sup> Severe 58% <sup>e</sup>
<b>Renal impairment</b>	Stage 1/2: 10-26% <sup>b</sup> Stage 3: 27.2%	64%	Creatinine Clearance <60mL/min in 55.4%	Creatinine >250 µmol/l in 48%	38.8%	42%
<b>Cardiac involvement</b>	Hypotension: 15.2% Cardiac signs: 50%	Chest pain/ CHF: 36% Shock: 5%	Shock: 8.3%	-	-	-
<b>Other clinical features</b>	Digestive signs: 40.2% Fever: 21.7%	Digestive signs: 38% Fever: 30%; Bleeding: 24%; Thrombosis: 12%	-	-	-	Fever: 50%
<b>Organ support</b>	RRT: 15.2%	-	Mechanical ventilation: 30.5%, dialysis: 19.4% Vasopressors: 8.3%	-	-	Mechanical ventilation: 50% dialysis: 0%
<b>Prognostic factors</b>	Risk of AKI: OR 3.85 per 0.25 unit decrease in C3 levels	All deaths were in a group of patients with "unresponsive" TTP <sup>c</sup>	Hospital mortality: IMV (OR 8.3) LOD (OR 1.4/point)	GCS: HR 0.85; Plasma exchange: HR 0.27	-	-
<b>ICU/Hospital mortality</b>	- / 4.3%	8.1% / 10.5%	19.4% / 19.4%	34.9% / 34.9%	- / 5.6%	16.7% / 33.3%

Thrombotic microangiopathy (TMA); Creatinine clearance (CrCl); Congestive heart failure (CHF); invasive mechanical ventilation (IMV); renal replacement therapy (RRT); acute kidney injury (AKI); plasma exchange (PEX). <sup>a</sup>Day 1 SOFA score. <sup>b</sup>Defined as per KDIGO 2012 guidelines; <sup>c</sup>Defined as use of second line treatment, >15 PEXs or death due to uncontrolled active TTP. <sup>d</sup>Dizziness, headaches, dysesthesia, vertigo, fatigue or dysphasia. <sup>e</sup>Vision loss, paresis, seizures or coma. LOD: logistic organ dysfunctions score

**Table 3: Registry based studies describing TTP population**

Author	Mariotte (2016)	Hovinga (2010)	Coppo (2010)	Scully (2008)
<b>Registry</b>	French national registry for TMA	Oklahoma TTP registry	French TMA reference center	South East England TTP registry
<b>Years</b>	1999 – 2013	1989 – 2008	2000 – 2007	2002 – 2006
<b>Number of patients</b>	772	376 (60 patients with measured ADAMTS13 deficiency)	214	176
<b>Age at presentation</b>	43 years	ADAMTS13 <10%: 41 years ADAMTS13 ≥10%: 51 years	ADAMTS13 deficient: 39 years ADAMTS13 detectable: 51 years	42 years
<b>Females</b>	68%	ADAMTS13 <10%: 82% ADAMTS13 ≥10%: 63%	75%	75%
<b>Idiopathic TTP</b>	49%	39%	-	77%
<b>Pregnancy-related TTP</b>	8%	7%	-	2%
<b>Congenital TTP</b>	3%	-	-	5%
<b>Neurological features</b>	61% (Headache or confusion 30%) (Severe symptoms 31%)	ADAMTS13 <10%: 50% ADAMTS13 ≥10%: 44%	Focal deficit 23% Headache 21%; Coma 21%; Confusion 18%; Seizure 12%;	78% (including 10% with coma)
<b>Cardiac involvement</b>	-	-	-	42%
<b>Renal impairment</b>	40%	ADAMTS13 <10%: 10% ADAMTS13 ≥10%: 54%	End stage renal disease 5%	33%
<b>Other symptoms</b>	Fever 40% Digestive symptoms 35%	-	-	Digestive symptoms 35%



**Table 4: differential diagnoses of thrombocytopenia with microangiopathic hemolytic anemia during pregnancy**

	ASSOCIATED WITH PREGNANCY			CAUSED BY PREGNANCY		
	TTP	Atypical-(complement mediated)-HUS	Idiopathic thrombocytopenia purpura	HELLP	DIC	Acute fatty liver of pregnancy
<b>Timing</b>	Trimesters 1-3 post partum	Trimesters 1-3 post partum ++	Trimesters 1-3 post partum	>20 weeks, post partum	Trimesters 2 & 3	Trimester 3
<b>Platelets (/microL)</b>	Typically <30,000	Typically <100,000	<50,000	50,000-100,000	Mild drop	Mild drop
<b>Schistocytes</b>	+++	+++	-	- / +	- / +	-
<b>Additional hematologic changes</b>	MAHA high LDH low haptoglobin	MAHA high LDH low haptoglobin	No	MAHA high LDH low haptoglobin	Prolonged PT & aPTT Low fibrinogen (overt DIC)	Possible prolonged PT & aPTT low fibrinogen
<b>DIC</b>	No	No	No	In 10% of cases	+++ Beware of normal fibrinogen in setting of inflammation	No
<b>ADAMTS13 Activity</b>	<10%	≥ 10%-normal	≥ 10%-normal	≥ 10%-normal	≥ 10%-normal	≥ 10%-normal
<b>Hepatic Changes</b>	None or mild elevation in enzymes	No	No	Elevated liver enzymes**	Possible	Markedly abnormal liver enzymes, liver synthetic dysfunction
<b>Renal Changes</b>	Mild	Severe	No	None-Mild	Possible ATN	Possible
<b>Neurologic Changes</b>	Often present***	Rare	No	Pre-eclampsia+++	Possible	Encephalopathy
<b>Other Features</b>	Elevated troponin Unresponsive TMA that may worsen after delivery	Unresponsive TMA that may worsen after delivery	/	80-85% have concurrent preeclampsia	Presence of a trigger (i.e.: amniotic fluid embolism, fetal demise, PPH)	Hypoglycemia, Potential multisystem organ failure
<b>Management</b>	Plasma therapy; immunosuppression	Anti-complement therapy (Eculizumab)	Glucocorticoids IVIG immunosuppression	Delivery	Treat underlying cause; Supportive care with blood products	Delivery, Early involvement of liver transplant team
<b>Delivery</b>	Not curative; Only indicated for fetal issues	Not curative; Only indicated for fetal issues	Not curative	Curative Timing determined by OB and ICU	Curative if HELLP related DIC or fetal demise	Curative May need transplant

\*Pregnancy may unmask these conditions

**\*\* Liver enzymes might be markedly elevated in severe cases of intrahepatic hemorrhage, subcapsular hematoma or hepatic infarcts.**

**\*\*\* Stroke, seizures, weakness, aphasia, mental status changes etc. AFLP Acute fatty liver of pregnancy; ATN Acute tubular necrosis; cTMA complement mediated thrombotic microangiopathy; DIC Disseminated intravascular coagulopathy; HELLP Hemolytic anemia, Elevated Liver enzymes, Low Platelets; LDH Lactate dehydrogenase; ITP Idiopathic thrombocytopenia purpura; MAHA microangiopathic hematologic anemia; PT, aPTT prothrombin and activated partial prothrombin time; TTP Thrombotic thrombocytopenic purpura**

**As a reminder, other conditions of severe thrombocytopenia in pregnancy that are not pregnancy-related include antiphospholipid antibody syndrome, systemic lupus erythematosus, drug induced thrombocytopenia, sepsis, and malignancy.**

**Table 5. Manifestations of severe organ dysfunction in TTP**

<b>CNS</b>	In brain MRI acute changes are often seen; most commonly PRES. Symptoms of brain ischemia (severe seizures, coma) have been associated to severe ADAMTS13 deficiency but might be encountered in other TMA syndromes including STEC-HUS and complement-mediated HUS. Brain hemorrhage is associated with decreased survival and altered functional outcomes. Worrisome clinical status and brain imaging need to be interpreted with caution as complete neurological recovery has been reported.	<i>De Marinis</i> <sup>18</sup> <i>Burrus</i> <sup>19</sup>
<b>Heart</b>	Heart involvement is frequent and probably under-diagnosed in TTP. The triad chest pain/ECG changes/increased troponin must be routinely sought. Echocardiography alterations must be routinely excluded. Severe myocardial involvement with arrhythmias, severe myocardial infarction, cardiogenic shock, cardiac arrest, Takotsubo cardiomyopathy rarely occurs but is responsible for early deaths.	<i>Benhamou 2015</i> <sup>6</sup> <i>Balasubramaniyam 2013</i> <sup>20</sup> <i>Fourmont 2018</i>
<b>Kidneys</b>	Development of acute kidney injury is common and renal replacement therapy might be required. Long term renal outcome might be altered in severe TTP patients, and in those with previous renal insufficiency or other comorbidities.	<i>Zafrani 2015</i> <sup>23</sup>
<b>GI-tract</b>	Acute pancreatitis and severe gastrointestinal bleeding have been reported. Abdominal pain should not be mixed up with cardiac angina.	<i>Hosler 2003</i> <sup>21</sup> <i>Yamamura 1998</i> <sup>22</sup>
<b>Other Severe organ involvement</b>	Adrenal glands, liver, retina, skin ...	<i>Hosler 2003</i> <sup>21</sup> <i>Yamamura 1998</i> <sup>22</sup>

*Abbreviations: ADAMTS13: A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13, MRI: magnetic resonance imaging, PRES: posterior reversible encephalopathy syndrome, TTP: thrombotic thrombocytopenic purpura.*

**Table 6. Factors associated with worse outcome in TTP patients**

<b>Variable</b>	<b>Nature of the association</b>	<b>Reference</b>
<b>1. Age</b>	Increasing age is associated with increasingly bad prognosis. This is especially true in the age group > 60 years.	<i>Goel 2016</i> <sup>10</sup> <i>Chaturvedi 2013</i> <sup>7</sup> <i>Benhamou 2012</i> <sup>8</sup>
<b>2. Increased cardiac troponin level</b>	Increased serum troponin I is associated with increased treatment refractoriness and mortality; monitoring is crucial and could maintain a high level of suspicion for myocardial ischemia and identify patients with a higher risk of early death.	<i>Brazelton 2016</i> <sup>5</sup> <i>Benhamou 2015</i> <sup>6</sup>
<b>3. Cerebral involvement</b>	Unlike headaches, symptoms such as stupor, seizures and coma are associated with poor outcomes. Although TTP is a thrombotic disease, cerebral bleeding may occur and impacts survival as well as functional outcomes.	<i>Chaturvedi 2013</i> <sup>7</sup> <i>Benhamou 2012</i> <sup>8</sup> <i>Rose 1987</i> <sup>9</sup>
<b>4. Delayed diagnosis</b>	Failing to recognize TMA syndrome, to perform complete clinical and biological diagnostic workup, and to obtain ADAMTS13 to ascertain TTP is associated with adverse outcomes. For instance, clinicians must be aware that schistocytes might not be seen initially, that in rare situations DAT could be positive, or that reticulocytes might be delayed.	<i>Grall 2017</i> <sup>11</sup>
<b>5. Platelet transfusions</b>	Platelet transfusions are associated with clinical deterioration and increased relapse rate. Delayed diagnosis increases the risk of platelet transfusions <sup>12,13</sup>	<i>Benhamou</i> <sup>12</sup> <i>Yoshii</i> <sup>13</sup>
<b>6. Increased LDH</b>	An increased LDH at admission, as well as persistent LDH elevation after two plasma exchanges, are associated with worse outcomes.	<i>Chaturvedi 2013</i> <sup>7</sup> <i>Benhamou 2012</i> <sup>8</sup>
<b>7. Unresponsive/refractory TTP</b>	Lack of response to plasma exchange and steroids, and need for a second line therapy are associated with worse outcomes. Age >60y, neurological or cardiac manifestations at diagnosis, and day 2 platelet count <15.10 <sup>9</sup> /L have been associated with unresponsive TTP.	<i>Mariotte 2013</i> <sup>14</sup>
<b>8. Acute disease vs. relapse</b>	Recurrent episodes of TTP are usually less severe than the first acute episode, however should always be regarded as a potentially fatal condition.	<i>Veyradier 2016</i> <sup>15</sup> <i>Lotta 2010</i> <sup>16</sup>
<b>9. Ethnicity</b>	Patients from Black African or Caribbean origins are at highest risk for TTP, but may have better outcome than white patients with TTP. Underlying systemic disease always needs to be diagnosed and treated.	<i>Martino 2016</i> <sup>17</sup>
<b>10. Other factors</b>	Cardiac arrest; Pancreatitis; HIV infection; Comorbid conditions beyond age	

**Abbreviations: DAT: Direct anti-globulin test (Coomb's test), LDH: lactate dehydrogenase, TTP: thrombotic thrombocytopenic purpura.**

**Table 3.A. GRADES for the TTP diagnostic workup**

	GRADE	Ref
<b>A. Diagnostic workup</b>		
<p><b>a) Experts suggest that all patients suspected of having TTP should undergo, at least, the following workup</b></p> <ul style="list-style-type: none"> <li>• Full clinical screening for organ injury (neurologic, cardiac, renal, gastrointestinal).</li> <li>• Biological workup to diagnose TMA: Blood cell count and smear (reticulocytes and schistocytes). Biochemistry: LDH, haptoglobin, bilirubin, Direct Antiglobulin Test to rule out Evans syndrome, basic coagulation tests to rule out DIC, proteinuria, haematuria.</li> <li>• Biological workup to confirm TTP: Non-heparinised samples for ADAMTS13 activity and anti-ADAMTS13 antibodies before TPE, alternative pathway of the complement system study, and PCR on rectal swab for shiga-toxin.</li> <li>• Minimal tests to assess organ involvement (troponin, ECG, renal function, lipase) and to identify possible associated conditions (auto-immunity markers, HIV serology, <math>\beta</math>-HCG, blood cultures).</li> <li>• Cross-matching before transfusion (blood group, hepatitis serologies).</li> </ul>	Expert Opinion	
<b>b) Blood samples should probably be obtained before starting plasma therapy.</b>	2+	[1, 2] [3]
<b>c) Diagnostic workup should probably not delay TPE.</b>	2-	
<b>d) When ADAMTS13 activity cannot be easily or quickly measured, diagnostic scores (French score, Bentley score, PLASMIC score) should probably be used to assess whether ADAMTS13 is likely to be undetectable.</b>	2+	[4] [5, 6] [7–10]

**Table 3.B. GRADES for the assessment of TTP severity**

	<b>GRADE</b>	<b>Ref</b>
<b><u>B. Assessment of patient's severity</u></b>		
a) Organ dysfunction should probably be assessed routinely at presentation and throughout the course of TTP.	2+	[11–14]
b) Experts do not provide guidance for the management of organ dysfunction in TTP patients.	Not graded	
c) Experts suggest that the presence of cardiac involvement (ie. chest pain, ECG and trans-thoracic echography changes, and troponin) must be assessed routinely at presentation and on a regular basis throughout the course of TTP.	Expert opinion	[6, 11, 11, 12, 14–18]
d) Older age, cerebral involvement and persistently high LDH may help identify TTP patients at increased risk of early death.	2+	[11]
e) Experts suggest that all patients diagnosed with TTP must be initially admitted to an area of Critical Care in order to monitor and manage organ dysfunctions, and to provide urgent plasma exchange therapy.	Expert opinion	[16, 19]
f) Experts suggest that ICU discharge be allowed when TPE can be tapered or stopped, when signs of haemolysis disappear and platelet count increases over 150G/L, which usually correlates with cardiac and neurological improvements. Patients can be discharged from the ICU earlier if there is a TPE unit in the hospital.	Expert opinion	[16, 19]

**Table 3.C. GRADES for the standard of care for ICU patients with TTP**

	GRADE	Ref
<b>C. Standard of care in adult patients with a suspicion of TTP</b>		
<b>a) Therapeutic Plasma Exchange (TPE)</b>		
1. TPE must be preferred to plasma infusions in TTP patients. Plasma infusions must be reserved when TPE is not immediately available.	1+	[4] [20, 21]
2. Experts suggest to perform one TPE per day with a dose of plasma of 60 ml/kg (1.5 x blood mass) until platelet count >150G/L for ≥48 hours.	Expert opinion	[12, 16]
3. Experts suggest that TPE should be initiated within 6 hours of diagnosis.	Expert opinion	
4. If TPE is not available, patients should probably be transferred to another centre.	2+	
<b>b) Steroids</b>		
1. Prednisone or methylprednisolone should probably be administered in association to TPE in TTP patients.	2+	[14, 18] [22]
2. Experts suggest a dose of 1 mg/kg/d for 21 days.	Expert opinion	[23]
3. Experts suggest that in case of severe TTP, high dose pulse steroids (1 g of methylprednisolone) can be given for three consecutive days.	Expert opinion	
<b>c) Monoclonal antibodies</b>		
1. Rituximab must be used in patients with relapsing autoimmune TTP.	1+	[24–27]
2. Rituximab should probably be used as a first line therapy in severe TTP.	2+	
3. Experts do not advocate nor discourage first-line rituximab in all TTP patients.	Expert opinion	
4. Caplacizumab must be used as a first line therapy in severe TTP.	1+	

<b>d) Supportive care</b>		
1. Experts suggest folate supplementation, prophylactic anticoagulation and antiplatelet agents as soon as platelet count reaches 50G/L, monitoring of the central venous catheter for thrombosis or infection, tight blood pressure control, gastro-duodenal ulcer prophylaxis, prophylaxis against HSV and Pneumocystis jirovecii in case of protracted corticosteroids requirement.	Expert opinion	[28]
2. Experts suggest that prophylactic antibiotics should not be administered	Expert opinion	
3. Platelet transfusion should probably be avoided in TTP patients and be restricted to severe bleeding (i.e., cerebral haemorrhage, etc...).	2-	



**Table 3.D. GRADES for the selection of a second-line therapy in TTP patients**

	GRADE	Ref
<b>D. Second line therapy</b>		
1. Experts suggest that the lack of platelet normalization by day 5 associated with persistent signs of haemolysis (LDH level) and/or severe cardiac or neurological manifestations defines unresponsive or refractory TTP. The Kidney involvement may take longer to recover, especially in patients requiring renal replacement therapy.	Expert opinion	[29]
2. Experts suggest that if patients did not receive caplacizumab and rituximab in addition to TPE and steroids, the two medications must then be added.	Expert opinion	[21, 30, 31]
3. Experts suggest that if patients did receive first-line caplacizumab and rituximab in addition to TPE and steroids, twice-daily TPE and high dose steroid pulses should be started. According to the clinical severity, vincristine or cyclophosphamide can be added.	Expert opinion	[24–26, 32]
4. Experts suggest that the choice for the second line therapy depends on the type of underlying condition, if any (pregnancy, AIDS, systemic rheumatic disease...).	Expert opinion	[23, 33–35]
5. Experts suggest that splenectomy should probably remain an alternative therapy for unresponsive TTP, however, with appropriate and timely TTP management it should be reserved as a salvage therapy.	Expert opinion	[36–38]
6. Experts suggest that for all TTP patients, an advice should be sought from a TTP specialist. More particularly, in unresponsive cases, the second-line therapy should be discussed with a TTP specialist.	Expert opinion	

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