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Expert statement on the ICU management of patients with thrombotic thrombocytopenic purpura

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is fatal in 90% of patients if left untreated and must be diagnosed early to optimize patient outcomes. However, the very low incidence of TTP is an obstacle to the development of evidence-based clinical practice recommendations, and the very wide variability in survival rates across centers may be partly ascribable to differences in management strategies due to insufficient guidance. We therefore developed an expert statement to provide trustworthy guidance about the management of critically ill patients with TTP. As strong evidence was difficult to find in the literature, consensus building among experts could not be reported for most of the items. This expert statement is timely given the recent advances in the treatment of TTP, such as the use of rituximab and of the recently licensed drug caplacizumab, whose benefits will be maximized if the other components of the management strategy follow a standardized pattern. Finally, unanswered questions are identified as topics of future research on TTP.

Keywords: Cardiac failure, Auto-immune disease, Thrombocytopenia, Hemolysis, Acute kidney injury, Plasma exchange

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a hematological and critical care emergency, with a 90% mortality rate if left untreated. Thrombotic microangiopathy (TMA) induces severe consumption thrombocytopenia and hemolytic anemia, causing a variable degree of ischemic end-organ damage. The introduction in the late 1970s of early plasma exchange (PEX) combined with corticosteroid therapy significantly reduced the mortality rate, to 9% [1] and 21% [2] in studies of unselected patients. TTP is due to a deficiency in the von Willebrand factor (VWF)-cleaving specific serine metalloprotease ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13) [3–5]. In acquired or immune-mediated TTP, the deficiency is due to the development of anti-ADAMTS13 autoantibodies that either inhibit ADAMTS13 proteolytic activity (neutralizing antibodies) or increase ADAMTS13 clearance (non-neutralizing antibodies) [6, 7]. Due to ADAMTS13 deficiency, VWF exists as uncleaved ultralarge multimers that bind to platelets in high-shear environments. The resulting microthrombi, combined with

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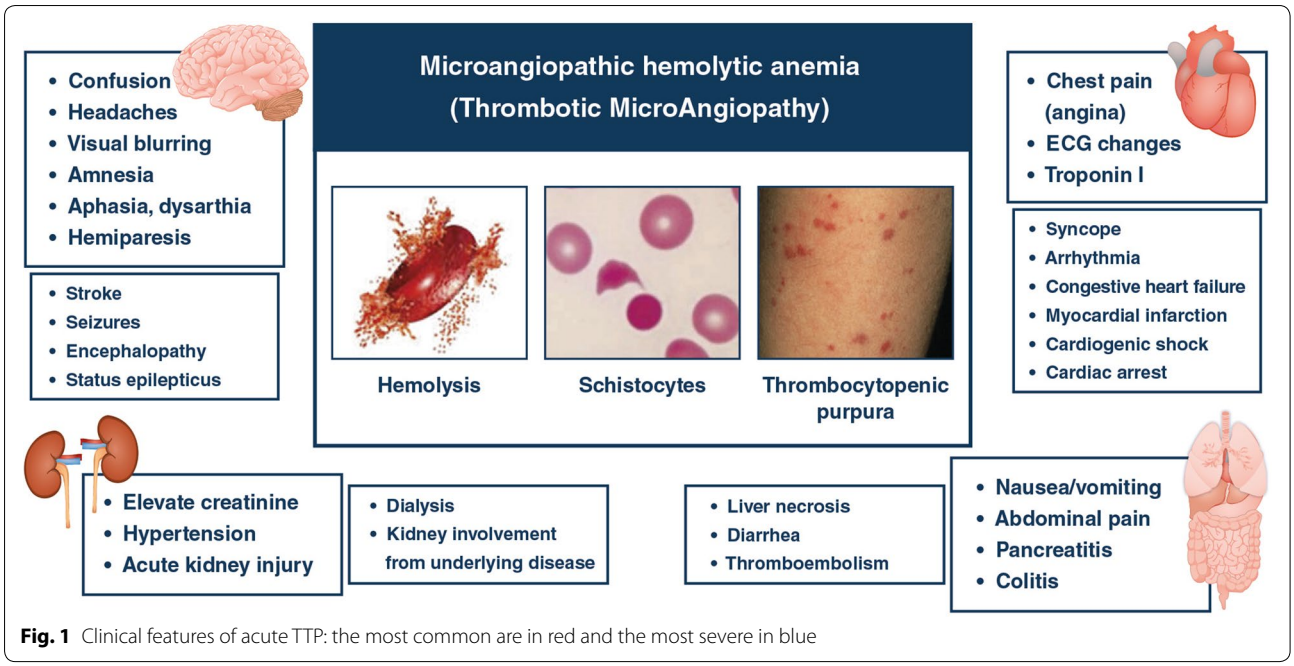

Fig. 1 Clinical features of acute TTP: the most common are in red and the most severe in blue

microangiopathic hemolytic anemia (MAHA), cause microvascular occlusion responsible for organ ischemia [8].

TTP has a prevalence of only 10–15/10^6, a female–male ratio of 2, and a peak incidence before 50 years of age [9]. In adults, immune-mediated TMA with signs of organ ischemia strongly suggests TTP. The initial management focuses on ruling out other causes of TMA, namely, Shiga toxin-related hemolytic and uremic syndrome (STEC-HUS), complement-mediated HUS, and secondary TMA syndromes. The diagnosis of TTP is based on clinical and laboratory findings (Fig. 1). An ADAMTS13 assay showing activity below 10% of that in normal pooled plasma establishes the diagnosis of TTP [4, 10–12]. Anti-ADAMTS13 autoantibodies may be detectable. Importantly, blood sampling for the ADAMTS13 activity assay should be performed immediately, before starting PEX, which should then be initiated without waiting for the results. Diagnostic errors adversely affect outcomes and often lead to the unnecessary use of hospital resources [13]. Thus, delays in PEX initiation have been associated with increased mortality [14, 15], and in severe TTP with advanced organ dysfunction early PEX has been shown to correlate with faster remission [16]. A high level of suspicion for TTP should therefore be maintained.

The severity of TTP varies, and no consensual definition of severe TTP exists. Many patients with TTP require ICU admission [11, 17], either due to severe organ failure or because the ICU is the only place in the hospital where PEX can be performed, a central line inserted, and close monitoring provided around the clock. Close monitoring is crucial, as sudden death can occur at any time during the first days of treatment, chiefly from cardiac microvasculature occlusion, arrhythmia, or cardiogenic shock [18]. In a retrospective study of TMA comparing survivors and nonsurvivors, the main factors associated with death were absence of PEX and cardiac involvement [14].

The very low incidence of TTP is a major obstacle to developing evidence-based management guidelines. It is well recognized that when the existing evidence (supported by RCTs) is insufficient to support formal recommendations, statements developed by experts are valuable means of improving quality of care. Statements for TTP management have been published [10, 19–21]. Nevertheless, mortality rates vary widely across studies (Table 1). Insufficient guidance to establish a standard of care may be among the reasons underlying this variability, although differences in patient populations may also play a role (Table 2). Guiding practices are particularly valuable for rare conditions with which the managing physicians are likely to have little personal experience. Members of the international Nine-i research network therefore developed the scientific statement reported here, both to improve the quality of guidance by using their extensive clinical experience as a supplement to the available evidence and to create a background of standardized care against which newly introduced treatments can be optimally used and evaluated. One such treatment is caplacizumab, an anti-VWF nanobody recently

Table 1 Studies of critically ill patients with TTP

	Zafrani [24]	Mariotte [25]	Darmon [16]	Pene [15]	Gasparović [27]	Knoebl [97]
Country	France	France	France	France	Croatia	Austria
Study design	Retrospective, single center	Retrospective review of prospective single-center registry	Retrospective, single center	Retrospective, multicenter	Retrospective, single center	Retrospective, single center
Period	2001–2013	1997–2011	2000–2003	1998–2001	Not reported	1992–1995
Population (all adults)	ICU patients with TTP	ICU patients with TTP	ICU patients with TMA	ICU patients with TMA	ICU patients with TTP	ICU patients with TTP
No. of patients	92	86	36	63 (21 with TTP)	18	6
Severity	SOFA 6.5 (IQR 5–9)[a]		SAP SII 27 (IQR 13–42)	SAPS II 45 ± 26	–	–
CNS dysfunction	86.9%	79%	50%	Mean GCS score, 12	88.8%	Mild 42%[d] Severe 58%[e]
Renal impairment	Stage 1/2: 10–26%[b] Stage 3: 27.2%	64%	Creatinine clearance < 60 mL/min in 55.4%	Creatinine > 250 µmoL/L in 48%	38.8%	42%
Cardiac involvement	Hypotension: 15.2% Cardiac signs: 50%	Chest pain/CHF: 36% Shock: 5%	Shock: 8.3%	–	–	–
Other clinical features	Digestive signs: 40.2% Fever: 21.7%	Digestive signs: 38% Fever: 30%; Bleeding: 24%; Thrombosis: 12%	–	–	–	Fever: 50%
Organ support	RRT: 15.2%	–	Mechanical ventilation: 30.5%, RRT: 19.4% Vasopressors: 8.3%	–	–	Mechanical ventilation: 50% RRT: 0%
Prognostic factors	Risk of AKI: OR 3.85 per 0.25 unit decrease in C3 level	All deaths were in a group of patients with "unresponsive" TTP[c]	Hospital mortality: IMV (OR 8.3) LODS (OR 1.4/point)	GCS score: HR 0.85; Plasma exchange: HR 0.27	–	–
ICU/Hospital mortality	–/4.3%	8.1%/10.5%	19.4%/19.4%	34.9%/34.9%	–/5.6%	16.7%/33.3%

ICU intensive care unit, *TTP* thrombotic thrombocytopenic purpura, *TMA* thrombotic microangiopathy, *SOFA* Sequential Organ Function Assessment, SAPSII Simplified Acute Physiology Score version II, *CNS* central nervous system, *GCS* Glasgow Coma Scale, *CHF* congestive heart failure, *RRT* renal replacement therapy, *AKI* acute kidney injury, *OR* odds ratio, *IMV* invasive mechanical ventilation, *LODS* Logistic Organ Dysfunction Score, *HR* hazard ratio

[a] Day 1 SOFA score

[b] Defined according to KDIGO 2012 guidelines

[c] Defined as use of second-line treatment, > 15 PEXs, or death due to uncontrolled active TTP

[d] Dizziness, headaches, dysesthesia, vertigo, fatigue, or dysphasia

[e] Vision loss, paresis, seizures, or coma

licensed for use in TTP by the European Medicines Agency and Food and Drug Administration. At the end of this expert statement, unanswered questions are identified as topics of future research into the ICU management of patients with TTP.

Methodology

Literature search strategy

The National Library of Medicine database (PubMed) and Cochrane database were searched for relevant articles published between 1978 and 2018. The filters were set to "humans" and "English language". The main search terms of "TTP" OR "thrombotic thrombocytopenic purpura" OR "ADAMTS13 deficiency" were combined with the following additional search terms: "clinical prediction score" OR "prediction" OR "score" OR "diagnosis" to identify publications about definitions and scoring of severe TTP; and "ICU" OR "intensive care" OR "critical care" OR "critical illness" to retrieve publications about the ICU management of patients with TTP. Additional relevant articles were identified by Internet searches using the same search terms.

Table 2 Registry-based studies describing populations with TTP

Author	Mariotte [9]	Kremer Hovinga [47]	Coppo [38]	Scully [46]
Registry	French national TMA registry	Oklahoma TTP registry	French TMA referral center	South East England TTP registry
Period	1999–2013	1989–2008	2000–2007	2002–2006
Number of patients	772	376 (60 patients with documented ADAMTS13 deficiency)	214	176
Age at presentation	43 years	ADAMTS13 < 10%: 41 years ADAMTS13 ≥ 10%: 51 years	ADAMTS13 deficient: 39 years ADAMTS13 detectable: 51 years	42 years
Females	68%	ADAMTS13 < 10%: 82% ADAMTS13 ≥ 10%: 63%	75%	75%
Idiopathic TTP	49%	39%	–	77%
Pregnancy-related TTP	8%	7%	–	2%
Hereditary TTP	3%	–	–	5%
Neurological features	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)
Cardiac involvement	–	–	–	42%
Renal impairment	40%	ADAMTS13 < 10%: 10% ADAMTS13 ≥ 10%: 54%	End-stage renal disease 5%	33%
Other symptoms	Fever, 40% Digestive symptoms, 35%	–	–	Digestive symptoms 35%

Expert statement development

The experts who participated in the development of the statement were selected based on their experience managing TTP in their countries. Of 24 experts invited to participate, 20 accepted. None of the experts had any conflicts of interest related to this work.

The experts first identified the questions relevant to the management of TTP in the ICU and then divided themselves into groups, each of which worked on one question. The questions fell into four main categories: diagnostic workup, severity assessment, standard of care for the initial therapeutic management of TTP, and second-line treatments. TTP during pregnancy was also discussed. The entire group then met face to face during 1 day prior to their annual scientific meeting to discuss the questions, based on the results of the literature search and their own experience, using the PICO (patients, intervention, comparison, outcomes) format.

The level of evidence supplied by each article was carefully evaluated and suggested by four experts (EM, EA, PB and AVD), then submitted and discussed by the entire group.

The quality of the evidence was established by all the experts based on study design, consistency of the results, and directness of the evidence. Strong agreement was achieved for all items. The evidence was, however, difficult to categorize using the GRADE methodology [22, 23] given the rareness of TTP, the scarce number of RCTs in that field, and the paucity of critical care data in the literature.

Expert statement was then reported as follows: "recommend" when the strength of the evidence was strong, or "suggest" when the strength of the evidence was weak, in which case the experts consensually built a statement based on the best management strategies from the available literature and their experience. Alternatively, experts reported having no opinion.

ICU admission of patients with TTP

We identified six studies of critically ill patients with TTP (Table 1) [15, 16, 24–27]. The differences in the populations in terms of illness severity, life-supporting treatments, and mortality may be ascribable to differences in admission policies across centers. Neurological, renal, and cardiac abnormalities were common, whereas the lungs were never involved. Ventilatory assistance was required due to neurological and/or hemodynamic failure in 30–50%, and renal replacement therapy in 0–19% of patients. Hospital mortality ranged from 4.3% [24] to 34.9% [15]. There is some evidence to suggest that differences in illness severity contributed to the differences in mortality. These studies thus illustrate the variability in TTP severity among patients admitted to the ICU.

Severe organ dysfunction is among the main reasons for ICU admission of patients with TTP (Table 3) [12]. TTP may be responsible for coma, stroke, seizures, posterior reversible encephalopathy syndrome [28, 29],

Table 3 Severe organ dysfunction during TTP

Organ	Signs of severity	References
CNS	Acute cerebral MRI changes are common, with predominance of PRES Symptoms of brain ischemia (severe seizures, coma) have been reported during severe ADAMTS13 deficiency but may also occur in other TMA syndromes including STEC-HUS and complement-mediated HUS Cerebral hemorrhage is associated with decreased survival and residual functional impairments Worrisome clinical and brain imaging abnormalities should be interpreted with caution, as complete neurological recovery has been reported	De Marinis [18] Burrus [19]
Heart	Heart involvement is frequent and probably underdiagnosed in TTP. The chest pain/ECG changes/troponin elevation triad must be sought routinely. Echocardiography must be performed routinely Severe myocardial involvement with arrhythmias, severe myocardial infarction, cardiogenic shock, cardiac arrest, and/or Takotsubo cardiomyopathy are rare but can cause early death	Benhamou [6] Balasubramaniyam [20] Fourmont [18]
Kidneys	Development of acute kidney injury is common and may require renal replacement therapy. Renal dysfunction may persist in the long term after severe TTP and in patients with previous renal dysfunction or other comorbidities	Zafrani [23]
GI tract	Acute pancreatitis and severe gastrointestinal bleeding have been reported. Abdominal pain should not be mistaken for pain due to heart ischemia	Hosler [21] Yamamura [22]
Other organs	The adrenal glands, liver, retina, skin, and other organs may be involved	Hosler [21] Yamamura [22]

TTP thrombotic thrombocytopenic purpura, *CNS* central nervous system, *MRI* magnetic resonance imaging, *PRES* posterior reversible encephalopathy syndrome, *TMA* thrombotic microangiopathy, STEC-*HUS* Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome, *GI* gastrointestinal

myocardial infarction, congestive heart failure [30], arrhythmia [18], mesenteric ischemia, pancreatitis [31], and acute kidney injury [24]. Another major reason for ICU admission is that, in many hospitals, the ICU is the only place where a central line can be inserted safely despite profound thrombocytopenia, and PEX initiated rapidly [32]. TTP is an emergency that requires PEX initiation as soon as the diagnosis is suspected. Furthermore, the ICU environment allows the close monitoring needed given the high risk of adverse clinical events during the first few days, including life-threatening cardiac manifestations. Thus, patients with TTP may be admitted to the ICU although they do not exhibit organ failures or meet criteria for severe TTP. The varying proportions of patients with severe organ failure versus with PEX initiation and monitoring as the main reasons for ICU admission can produce widely different case mix. Finally, some patients with TTP are admitted to the ICU with an initial erroneous diagnosis, such as sepsis [33].

Experts suggest that all patients with TTP should be admitted in an ICU

Despite the lack of trial that demonstrate clinical benefit for routine ICU admission, experts suggest that all patients with a suspicion or diagnosis of TTP should be admitted to the ICU for PEX initiation [10, 14, 25, 26, 32] and any necessary life-supporting interventions [15, 34]. Whether the primary reason for ICU admission is life-threatening organ failure or a need for prompt PEX initiation and monitoring dictates the urgency of the admission. If a patient was not admitted to the ICU initially but then proves to have refractory of relapsing TTP [25], catheter-related complications (e.g., bleeding, infection, or thrombosis), plasma transfusion reaction [35], or worsening neurological abnormalities after PEX [36], ICU admission is particularly urgent. Pregnant patients with TTP should also be admitted very quickly. Given the very low incidence of TTP, experts suggest that patients should ideally be admitted to a referral center that has a multidisciplinary team with experience in both the ICU and long-term aspects of management. The time of ICU discharge depends not only on the response to treatment and resolution of organ failures, but also on the availability in the hospital of a step-down or intermediate-care unit, apheresis unit, wards with advanced monitoring equipment, and rapid response team. Follow-up should be provided by a multidisciplinary team including a TTP expert, hematologist, intensivist, and specialists of any impaired organs.

Diagnosis of TTP

The diagnosis is urgent, as the disseminated microthromboses can result in rapidly developing multiorgan failure [13]. However, the diagnosis is now increasingly being made before the development of organ failure. The signs of TTP include fever, purpura, bleeding, MAHA with schistocytes, peripheral thrombocytopenia, laboratory evidence of kidney function impairment (hematuria, proteinuria, blood urea nitrogen elevation), and neurological abnormalities (Fig. 1). However, the schistocytes may be absent initially, raising diagnostic challenges.

Identification of ADAMTS13 activity impairment as a major pathophysiological factor in TTP has considerably benefited the early diagnosis, and undetectable ADAMTS13 activity (i.e., < 5–10% according to the

Table 4 Clinical criteria and scoring systems for diagnosing ADAMTS13 deficiency

Clinical predictors of ADAMTS13 deficiency. Coppo et al. [38]	
Creatinine < 200 µmoL/L Platelet count < 30 × 10^9/L Positive antinuclear antibodies	Three criteria predict severe ADAMTS13 deficiency with 98% (94–100%) specificity, 47% (41–53%) sensitivity, 99% (96–100%) positive predictive value, and 39% (36–42%) negative predictive value

Point-based ADAMTS13 deficiency prediction score. Bentley et al. [39, 40]		
	Points	**Probability of severe ADAMTS13 deficiency**
Creatinine > 2.0 mg/dL	− 11.5	
Platelets > 35·10^9/L	− 30	> 30 points, 100%
D-Dimer > 4.0 µg/mL	− 10	20–30 points, 40%
Reticulocytes > 3%	+ 21	< 20 points, 0% probability
Indirect bilirubin > 1.5 µg/mL	+ 20.5	

PLASMIC score. Bendapudi et al. [41]		
	Points	
Platelet count < 30 × 10^9/L	1	Risk of severe ADAMTS13 deficiency
Combined hemolysis variables[a]	1	≤ 4, low
No active malignancy	1	5, intermediate
No history of transplantation	1	6 or 7, risk > 80%
MCV < 9 × 10^{-14} L	1	Median score in patients with confirmed TTP was 7 (IQR 6–7)
INR > 1.5	1	
Creatinine < 2.0 mg/dL	1	

MCV mean corpuscular volume, *INR* international normalized ratio, *IQR* interquartile range

[a] Reticulocytes > 2–5% or undetectable haptoglobin or indirect bilirubin > 2.0 mg/dL

method) is now required to confirm the diagnosis of TTP [4, 6, 7, 12]. A blood sample for an ADAMTS13 assay must be obtained as soon as the diagnosis of TTP is suspected and before the initiation of PEX to avoid false-negative results. However, in one study, ADAMTS13 activity was usually still severely decreased within the first 3 days after PEX initiation in patients with TTP [43–45]. The treatment of TTP, including PEX, should be started before the ADAMTS13 activity assay results become available. More generally, experts recommend that PEX should be started immediately in nearly all adults with TMA diagnosis based on clinical findings, microangiopathic hemolytic anaemia (MAHA) with schistocytes, peripheral thrombocytopenia and organ dysfunction[8], and no obvious evidence of an alternative diagnosis (e.g., malignant hypertension, vitamin B12 deficiency, bone marrow metastases, or scleroderma renal crisis).

In 1966, based on a review of 270 cases, Amorosi and Ultman proposed the following "pentad" for the diagnosis of TTP [37]: fever, hemolytic anaemia, purpura or bleeding associated with thrombocytopenia, neurological signs, and renal disease presenting with hematuria and/or proteinuria or elevated blood urea nitrogen. However, later studies found that patients diagnosed with TTP commonly lacked one or more elements of the pentad. Nowadays, the diagnosis of TTP is being increasingly made in patients with only hematologic features (i.e., before organ dysfunction), as clinicians' awareness for this diagnosis has improved.

Unfortunately, the ADAMTS13 activity assay is not yet widely available, and several days may elapse before the results are available if the sample must be sent to a distant laboratory. Several scoring systems have therefore been developed to predict severe ADAMTS13 deficiency and a diagnosis of TTP (Table 4). One scoring system for predicting severe ADAMTS13 deficiency [38] uses serum creatinine < 200 µmol/L, platelet count < 30 G/L, and positive antinuclear antibody test; when all three criteria are present, the positive predictive value is 99% but the negative predictive value is only 39%, suggesting that these criteria cannot rule out ADAMTS13 deficiency [38]. Moreover, antinuclear antibody testing may not be promptly available. Another scoring system relies on five criteria: creatinine, platelets, D-dimer, reticulocytes, and indirect bilirubin [39]. A validation study [40] demonstrated that a score > 30 predicted TTP and a score < 20 absence of TTP, whereas intermediate scores were difficult to interpret. Finally, the 2017 PLASMIC scoring system uses seven criteria:

platelet count < 30 G/L, hemolysis, no active cancer, no history of solid-organ or stem-cell transplantation, mean corpuscular value < $9{\cdot}10^{-14}$/L, INR < 1.5, and creatinine < 2 mg/dL (177 µmol/L), with one point for each criterion present [41]. Independent external validation of the PLASMIC score was performed in a cohort of 112 patients with TMA: the area under the curve was 0.94 (0.88–0.98), and a score of 6 or 7 predicted severe ADAMTS13 deficiency with 90% sensitivity, 92% specificity, 72% positive predictive value, and 98% negative predictive value [42]. Until ADAMTS13 activity can be reliably determined within a few hours at all centers, scoring systems will continue to be used to guide management decisions. However, no scoring system can serve as a substitute for the ADAMTS13 activity assay, and clinicians should initiate PEX in the absence of a definite alternative diagnosis [10].

If ADAMTS13 activity is not severely decreased (< 5–10%), typical STEC-HUS (rectal swab positive for Shiga toxin), complement-mediated HUS, or a secondary TMA syndrome [32] should be considered.

Expert statement 2: diagnostic workup for TTP

(a) The experts suggest that the following workup is the minimum required in patients with suspected TTP:

- Full clinical screening for organ dysfunctions (chiefly cardiac, neurological, renal, gastrointestinal).
- Laboratory workup to diagnose TMA, including blood cell counts and smear (reticulocytes and schistocytes); blood tests for lactate dehydrogenase (LDH), haptoglobin, bilirubin, direct antiglobulin test to rule out Evans syndrome, basic coagulation tests to rule out disseminated intravascular coagulation; and tests for proteinuria and hematuria; in addition, bone marrow aspiration should be considered in patients with atypical TMA features (e.g., low reticulocyte count or older age) or other diseases (e.g., cancer and/or chemotherapy or immunosuppression).
- Laboratory workup to diagnose TTP, including ADAMTS13 activity and anti-ADAMTS13 antibodies assays in non-heparinized blood samples taken before PEX initiation, studies of the alternative pathway of the complement system (including Bb fragments of factor B activation), and a Shiga toxin PCR on a rectal swab.
- Minimal tests to assess organ function (troponin, ECG, renal function, lipase) and to identify any associated conditions (auto-immunity markers, HIV serology, β-HCG, blood cultures).
- Type and Screen, Cross-matching and hepatitis serologies to prepare for blood transfusion.

(b) The experts suggest that blood samples should probably be obtained before starting plasma therapy.

(c) The experts suggest that the diagnostic workup should not delay PEX.

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

Assessing TTP severity

TTP carries a mortality rate of up to 10% overall in centers equipped to establish the diagnosis and initiate treatment early [9, 46] and of up to 30% among patients who fail to respond to the initial treatment [25]. In addition to an early diagnosis, an accurate assessment of TTP severity contributes to improve outcomes by identifying those patients who require aggressive treatment regimens [10, 58]. Table 6 lists the main factors associated with worse outcomes.

The TTP Clinical Severity Score reported in 1987 stratifies patients based on serum creatinine, platelet count, hemoglobin level, and neurological symptoms [59]. Higher scores were associated with worse outcomes [59]. However, those findings were not replicated subsequently, probably due to the inclusion of patients with HUS in addition to patients with TTP [60].

TTP is characterized by widespread microthrombosis that can rapidly cause severe impairment of multiple organs (Fig. 1, Table 6) including the heart, brain, and kidneys [13]. Transient or partial microvessel occlusion results in intermittent ischemia [8]. Tables 2 and 3 and Fig. 2 list the main manifestations [9, 38, 46, 47]. The high risk of life-threatening cardiac and neurological manifestations in all adults with TTP is a key concern [14, 18, 30].

Cardiac ischemia is among the most common causes of death [18]. Autopsy studies found that widespread myocardial microthrombosis was the rule [14, 50, 61]. Coronary microvessel involvement may manifest as acute myocardial infarction, arrhythmias, heart failure, cardiogenic shock, and troponin elevation [18, 48, 49]. Patients with cardiac involvement are more likely to be unresponsive to treatment [25]. Cardiac troponin elevation, although usually asymptomatic [18, 30], is associated with mortality [48, 62, 63]. Cardiac and cerebral abnormalities including stroke were more common in patients with cardiac troponin I levels above 0.25 µg/L [48]. Chest pain, ECG changes, and troponin must be assessed routinely at presentation then periodically throughout the course of the disease. Transthoracic echocardiography is part of the routine diagnostic workup in ICU patients. Coronary angiography may be reserved for

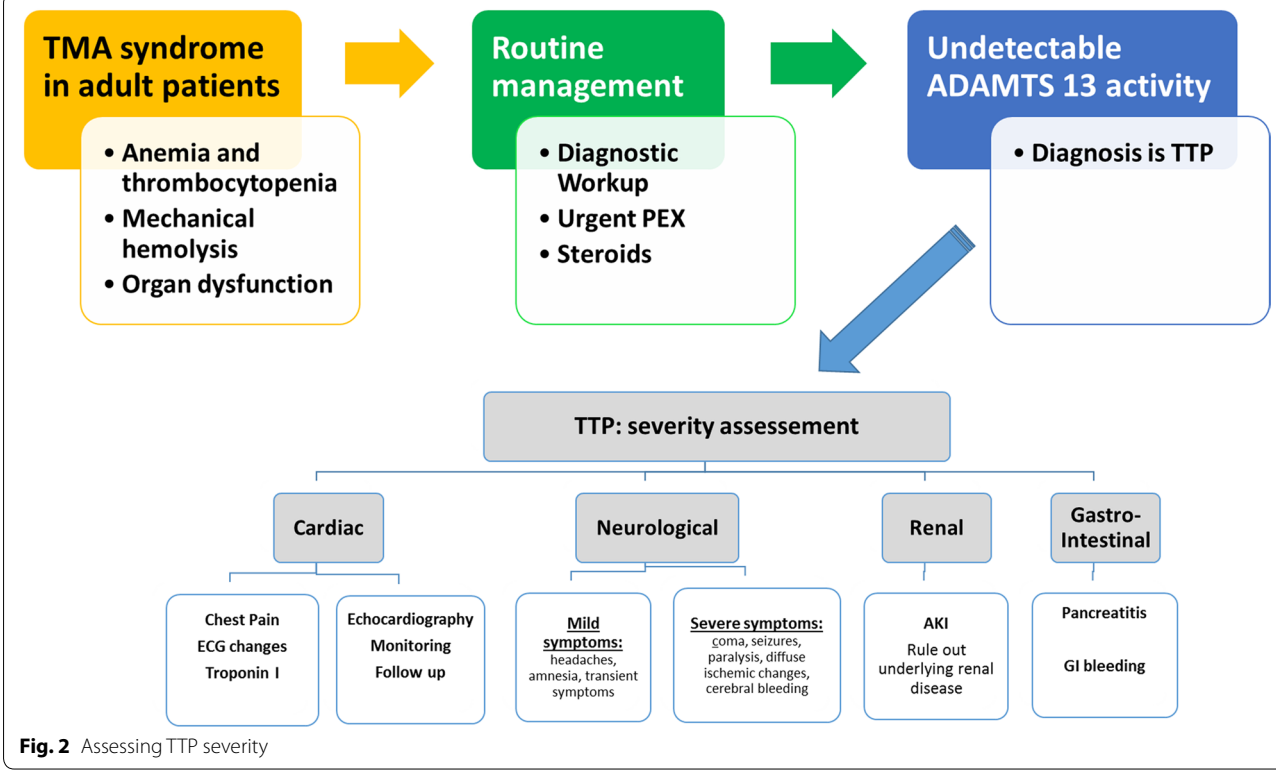

Fig. 2 Assessing TTP severity

patients with risk factors and signs of acute coronary syndrome selected on a case-by-case basis jointly with a cardiologist.

Neurological impairment is common and can produce a wide range of symptoms including headache, personality alterations, cognitive impairment, seizures, transient ischemic attacks, and coma [9, 46]. These symptoms often fluctuate over time due to the formation and dissolution of thrombi in the cerebral microcirculation [8]. Cerebral involvement has been associated with worse outcomes [64] and symptoms of brain ischemia (e.g., severe seizures and coma) with severe ADAMTS13 deficiency [65]. Other factors of adverse prognostic significance include older age [66, 67] and an LDH increase to at least ten times the normal value. However, LDH elevation probably reflects severe multiorgan failure (Tables 5 and 6) [64, 67]. Therefore, when assessing TTP severity, emphasis should be put on the cardiac troponin levels and signs of cardiac and cerebral involvement (Fig. 2).

Several studies suggest that renal involvement may not be a prominent feature of TTP (Tables 1, 2, 3) [38, 40, 51, 52, 53]. However, kidney function may be impaired due to the TTP itself, hemolysis, blood pressure variations, or drug toxicity. In a review of all cases of TTP (with ADAMTS13 activity < 10%) admitted to a single ICU over a 12-year period, acute kidney injury (AKI, defined based on KDIGO 2012) occurred in 58.7% of patients [24]. TTP was the most likely cause of AKI in 96.3% of cases, with potential causes of kidney injury being hypoperfusion (16.7%), acute tubular necrosis (7.4%), nephrotoxicity (9.3%), hemolysis-induced tubulopathy (33.3%), and autoimmune glomerulonephritis (14.8%). Among patients with AKI, 42.6% had chronic kidney disease after 6 months. Similarly high frequencies of AKI were observed in several other ICU studies (Table 1) [9, 15, 16].

Abdominal pain can occur due to acute pancreatitis or to mesenteric ischemia with diarrhea [50].

Platelet transfusions are often administered before the correct diagnosis has been made, and have been associated with clinical deterioration and an increased relapse rate [54–57].

Table 5 Summary of the TTP statement

	Strength	References
(a) Diagnostic workup		
Experts suggest that all patients suspected of having TTP should undergo, at least, the following workup	Weak	
Full clinical screening for organ injury (neurologic, cardiac, renal, gastrointestinal)	Weak	
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, hematuria	Weak	
Biological workup to confirm TTP: non-heparinised samples for ADAMTS13 activity and anti-ADAMTS13 antibodies before PEX, alternative pathway of the complement system study, and PCR on rectal swab for shiga toxin	Weak	
Minimal tests to assess organ involvement (troponin, ECG, renal function, lipase) and to identify possible associated conditions (auto-immunity markers, HIV serology, β-HCG, blood cultures)	Weak	
Type and Screen, Cross-matching before transfusion (blood group, hepatitis serologies)	Weak	
Blood samples should probably be obtained before starting plasma therapy	Weak	[120–122]
Diagnostic workup should probably not delay PEX	Weak	
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	Weak	[38, 40, 41, 118–121]
(b) Assessment of patient's severity		
Organ dysfunction should probably be assessed routinely at presentation and throughout the course of TTP	Weak	[15, 16, 122, 123]
Experts do not provide guidance for the management of organ dysfunction in TTP patients	No opinion	
Experts suggest that the presence of cardiac involvement (i.e., chest pain, ECG and transthoracic echography changes, and troponin) must be assessed routinely at presentation and on a regular basis throughout the course of TTP	Weak	[14–16, 40, 48, 50, 122–124]
Older age, cerebral involvement, and persistently high LDH may help identify TTP patients at increased risk of early death	Weak	[122]
Experts suggest that all patients diagnosed with TTP must be initially admitted to an ICU to monitor and manage organ dysfunctions and to provide urgent plasma exchange therapy	Weak	[14, 125]
Experts suggest that ICU discharge be allowed when PEX can be tapered or stopped, when signs of hemolysis disappear and platelet count increases over 150 G/L, which usually correlates with cardiac and neurological improvements Patients can be discharged from the ICU earlier if there is a PEX unit in the hospital	Weak	[14, 125]
(c) Standard of care in adult patients with a suspicion of TTP		
Therapeutic plasma exchange (PEX)		
PEX must be preferred to plasma infusions in TTP patients. Plasma infusions must be reserved when PEX is not immediately available	Strong	[38]
Experts suggest performing one PEX per day with a dose of plasma of 60 ml/kg (1.5 × blood mass) until platelet count > 150G/L for ≥ 48 h	Weak	[1, 126]
Experts suggest that PEX should be initiated within 6 h of diagnosis	Weak	[14, 15]
If PEX is not available, patients should probably be transferred to another center	Weak	
Corticosteroids		
Prednisone or methylprednisolone should probably be administered in association to PEX in TTP patients	Strong	[48, 123]
Experts suggest a dose of 1 mg/kg/d for 21 days	Weak	[2]
Experts suggest that in case of severe TTP, high-dose pulse steroids (1 g of methylprednisolone) can be given for three consecutive days	Weak	[75]
Monoclonal antibodies		
Rituximab must be used in patients with relapsing autoimmune TTP	Strong	Strong
Rituximab should probably be used as a first-line therapy in severe TTP	Weak	
Experts do not advocate or discourage first-line rituximab in all TTP patients	No opinion	
Caplacizumab must be used as a first-line therapy in severe TTP	Strong	

(a) The experts suggest that organ dysfunction should be assessed routinely at presentation and throughout the course of TTP.

(b) The experts suggest that patients with TTP should be routinely assessed for cardiac involvement (chest pain, ECG and transthoracic echocardiography changes, and troponin levels) at presentation. Clini-

Table 5 (continued)

	Strength	References
Supportive care		
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, gastroduodenal ulcer prophylaxis, prophylaxis against HSV and *Pneumocystis jiroveci* in case of protracted corticosteroid requirement	Weak	[128]
Experts suggest that prophylactic antibiotics should not be administered	Weak	
Platelet transfusion should probably be avoided in TTP patients and be restricted to severe bleeding (i.e., cerebral hemorrhage, etc.)	Weak	
(d) Second-line therapy		
Experts suggest that the lack of platelet normalization by day 5 associated with persistent signs of hemolysis (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	Weak	[9]
Experts suggest that if patients did not receive caplacizumab and rituximab in addition to PEX and steroids, the two medications must then be added	Weak	[20, 126, 129]
Experts suggest that if patients did receive first-line caplacizumab and rituximab in addition to PEX and steroids, twice-daily PEX and high-dose steroid pulses should be started. According to the clinical severity, vincristine or cyclophosphamide can be added	Weak	[17, 82, 103, 127]
Experts suggest that the choice for the second-line therapy depends on the type of underlying condition, if any (pregnancy, AIDS, systemic rheumatic disease…)	Weak	[75, 110, 111, 130]
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	Weak	[131–133]
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	Weak	

a TTP diagnostic workup; b assessment of TTP severity; c standard of care for ICU patients with TTP; d selection of a second-line therapy in TTP patients

Table 6 Factors associated with worse outcome in TTP patients

Variable	Nature of the association	References
1. Age	Outcomes worsen as age increases, notably after 60 years of age	Goel [10] Chaturvedi [7] Benhamou [8]
2. Cardiac troponin elevation	Serum troponin I elevation is associated with increased treatment refractoriness and mortality and warrants a high level of suspicion for myocardial ischemia. Monitoring is crucial to identify patients at higher risk of early death	Brazelton [5] Benhamou [6]
3. CNS involvement	Unlike headaches, stupor, seizures, and coma are associated with poor outcomes. Although TTP is a thrombotic disease, cerebral bleeding may occur, with deleterious effects on survival and functional outcomes	Chaturvedi [7] Benhamou [8] Rose [9]
4. Delayed diagnosis	Failing to recognize TMA syndrome, to perform a complete clinical and laboratory diagnostic workup, and to obtain an ADAMTS13 assay to diagnose TTP is associated with adverse outcomes. Importantly, schistocytes may not be seen initially, DAT is positive in rare cases, and the reticulocyte response may be delayed	Grall [11]
5. Platelet transfusions	Platelet transfusions are associated with clinical deterioration and a higher relapse rate. A delayed diagnosis increases the risk of platelet transfusions [12, 13]	Benhamou [12] Yoshii [13]
6. LDH elevation	LDH elevation at admission and/or after two plasma exchanges is associated with worse outcomes	Chaturvedi [7] Benhamou [8]
7. Refractory TTP	Unresponsiveness to plasma exchange and steroids and need for second-line therapy are associated with worse outcomes. Age > 60 years, neurological or cardiac manifestations at diagnosis, and day 2 platelet count $< 15 \times 10^9$/L are associated with refractory TTP	Mariotte [14]
8. Acute disease vs. relapse	Recurrent TTP episodes are usually less severe than the first acute episode, but should always be regarded as potentially fatal	Veyradier [15] Lotta [16]
9. Ethnicity	Patients of black African or Caribbean descent are at highest risk for TTP, but may have better outcomes than Caucasians with TTP. Underlying systemic disease must be diagnosed and treated	Martino [17]
10. Other factors	Cardiac arrest; pancreatitis; HIV infection; Comorbid conditions	

CNS central nervous system, *LDH* lactate dehydrogenase, *TTP* thrombotic thrombocytopenic purpura, *TMA* thrombotic microangiopathy, *DAT* direct antiglobulin test (Coomb's test)

Figure X

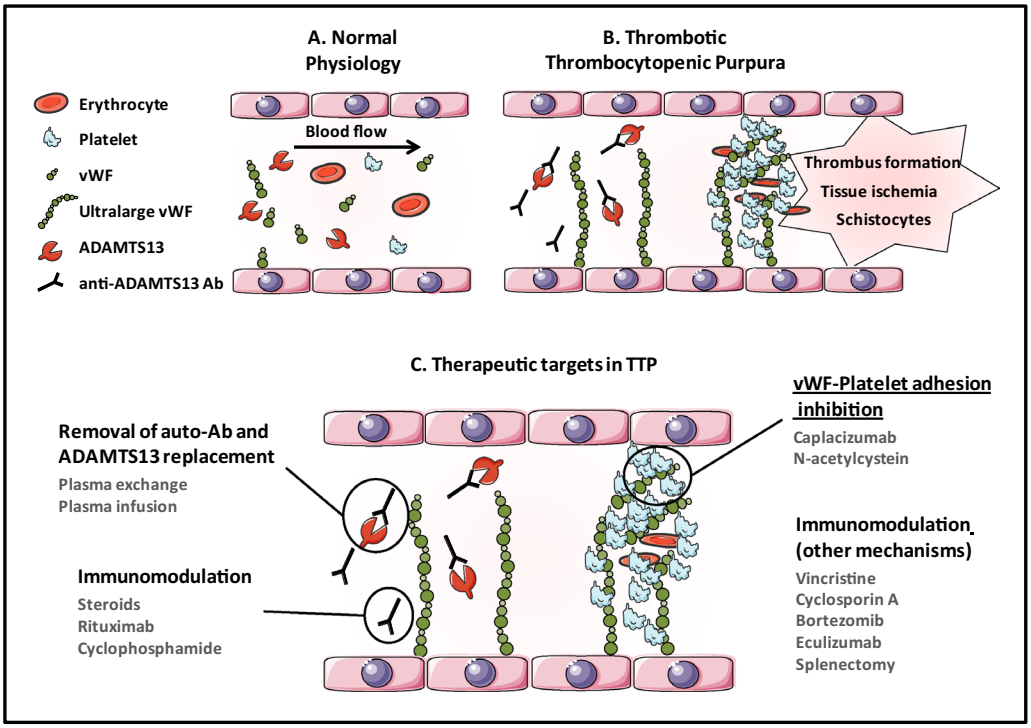

Fig. 3 TTP pathophysiology and therapeutic targets. **a** Ultralarge von Willebrand factor (vWF) multimers that are hyperadhesive to platelets are normally cleaved by ADAMTS13 to smaller, less adhesive multimers. **b** In TTP, low ADAMTS13 activity (often caused by inhibiting autoantibodies) facilitates spontaneous binding of ultralarge vWF multimers to platelets, promoting aggregation, platelet consumption, and microthrombi formation within the capillary network. **c** The conventional treatment consists in supplying ADAMTS13 and removing the autoantibodies by plasma exchange (PEX) and corticosteroids. Caplacizumab to inhibit vWF-platelet interactions and rituximab to suppress autoantibody formation were introduced recently for the treatment of immune-mediated TTP. Other immunosuppressors may be used in refractory forms. Splenectomy is a treatment of last resort

cal assessment is also needed at least daily throughout the course of the disease.

(c) The experts suggest that older age, cerebral involvement, cardiac troponin elevation, and persistent LDH elevation may help to identify TTP patients at increased risk of early death.

Standard of care for the initial therapeutic management of TTP

Specific treatments available

Until very recently, PEX to supply functional ADAMTS13 and corticosteroid therapy to suppress the autoimmune response were the main first-line treatments available for TTP. Rituximab and caplacizumab now also deserve to be considered as part of the first-line treatment strategy [58] (Fig. 3).

Replacement therapy: PEX

PEX with fresh frozen plasma provides large amounts of functional ADAMTS13 and remains the cornerstone of TTP treatment [12, 73]. The enzyme cleaves the ultralarge vWF multimers, thereby preventing microthrombus formation. Whether PEX also effectively removes anti-ADAMTS13 autoantibodies has not been properly assessed. Plasma infusion alone, although far less effective [1, 16, 74], can be used when PEX must be delayed due to organizational or technical difficulties [1].

Immunomodulation: corticosteroids, rituximab, other immunosuppressants, and splenectomy

Corticosteroid treatment is recommended in combination with PEX as the first-line treatment of TTP [10, 19]. A cohort study reported in 1991 suggested an association of corticosteroid therapy with prolonged clinical remission, but did not focus specifically on TTP [2]. In a randomized controlled trial, the complete response rate was higher with high-dose pulse methylprednisolone than with standard-dose methylprednisolone [75].

The monoclonal antibody rituximab targeting CD20 on B cells decreased the 1-year relapse rate in patients with suboptimal responses to standard treatment (including

those with refractory or relapsing TTP), decreased anti-ADAMTS13 antibody titers, and increased functional ADAMTS13 activity [76–84]. Several other immunosuppressive and cytostatic drugs used in combination with PEX produced benefits in small studies and anecdotal case reports when used as salvage therapy in refractory TTP. These drugs include vincristine (to disrupt cytoskeletal microtubules and thereby platelet function), cyclosporine A (to target T cell effector functions), cyclophosphamide (an alkylating agent), bortezomib (a proteasome inhibitor that targets B cells), and eculizumab (to inhibit complement C5) [85–93]. Splenectomy should be considered only as salvage therapy in patients unresponsive to all other treatments [88].

Prevention of vWF binding to platelets

N-acetylcysteine decreases the size of endothelial cell-anchored ultralarge vWF multimers, thereby inhibiting their interaction with platelets, and has been described as effective in anecdotal case reports [94].

Caplacizumab, an anti-vWF humanized single-variable-domain immunoglobulin nanobody, inhibits the interaction between the vWF-A1 domain of ultralarge vWF multimers and platelet GPIb, thereby preventing thrombus formation. Proven effects of caplacizumab include faster platelet count recovery and organ damage resolution. In the phase II TITAN trial [95], 75 patients with TTP were randomly assigned to caplacizumab (10 mg daily) or placebo. There was a significant improvement in the primary end point of median time to platelet count normalization, which was 39% shorter with caplacizumab than with the placebo. Fewer caplacizumab-treated patients had a major thromboembolic event, a TTP exacerbation, or died (11.4% vs. 43.2% with the placebo) [95]. More recently, in the double-blind, controlled HERCULES trial, 145 patients were randomly assigned to either caplacizumab or placebo throughout PEX and for 30 days after PEX discontinuation [17]. Median time to platelet count normalization was shorter with caplacizumab (2.69 days [1.89–2.83] vs. 2.88 days [2.68–3.56] with the placebo). Patients who received caplacizumab required fewer PEX sessions and had shorter hospital stays compared to those given the placebo. The percentage of patients with a composite of thromboembolic event, TTP recurrence, or TTP-related death during treatment was lower with caplacizumab (12% vs. 49% with the placebo, $P<0.001$). Only 12% of caplacizumab-treated patients experienced TTP recurrence at any time during the trial, and none developed refractory disease (vs. 38% and 4%, respectively, with the placebo). Mild-to-moderate bleeding was more common with caplacizumab compared to the placebo (54% vs. 38% in the TITAN trial and 65% vs. 48% in the HERCULES trial). Caplacizumab therapy was associated with an increased risk of mucocutaneous bleeding reminiscent of von Willebrand disease. The most common treatment-emergent adverse events were epistaxis and gingival bleeding, which were generally mild or moderate and did not usually require treatment [96, 97]. Pooling the TITAN and HERCULES trial populations yields TTP-related mortality rates of 0% (0/107) with caplacizumab and 4.5% (5/110) with the placebo. Moreover, caplacizumab was associated with a significant reduction in health-care resource use (ICU and hospital stay lengths, number of PEX sessions, and volume of plasma required to achieve a remission).

Caplacizumab was approved by the European Medicines Agency for the treatment of adults with immune-mediated TTP in August 2018. The US Food and Drug Administration approved caplacizumab for immune-mediated TTP in February 2019.

Defining the first-line standard of care for patients with severe TTP

Standardizing the first-line management of patients with suspected TTP is a challenge, as several issues remain unsettled, notably regarding the use of recently introduced medications [10]. The diagnosis must be made early, and treatment should not be delayed until the diagnostic workup for TTP and differential diagnoses is complete (Fig. 2). A blood sample for an ADAMTS13 assay should be collected before starting plasma therapy (Fig. 4). Obtaining advice from a TTP specialist is helpful, irrespective of disease severity. Depending on the clinical presentation, advice from other specialists such as a cardiologist, neurologist, or nephrologist may also be useful.

PEX combined with immunomodulation via corticosteroid therapy is the cornerstone of the treatment of immune-mediated TTP. Whether early rituximab and caplacizumab should be used routinely, i.e., independently of TTP severity, remains unresolved. Early high-volume PEX may be the best means of preserving organ function [1, 16].

The experts recommend that PEX be initiated within 4–6 h after the diagnosis of TMA (Fig. 4) to decrease the risk of death [14, 15]. PEX is superior over plasma infusions in decreasing morbidity and mortality [1, 16]. Plasma infusions should be used only when PEX is not immediately available, until the patient is transferred to another center. The panel experts suggest one PEX session per day, with 60 mL/kg of plasma (1.5 times the estimated plasma volume), until the platelet count has remained above 150 G/L for at least 48 h. A central venous catheter should be placed by an experienced operator, under ultrasound guidance, without platelet transfusions [98]. Despite the profound thrombocytopenia, ischemia is a far greater risk than bleeding

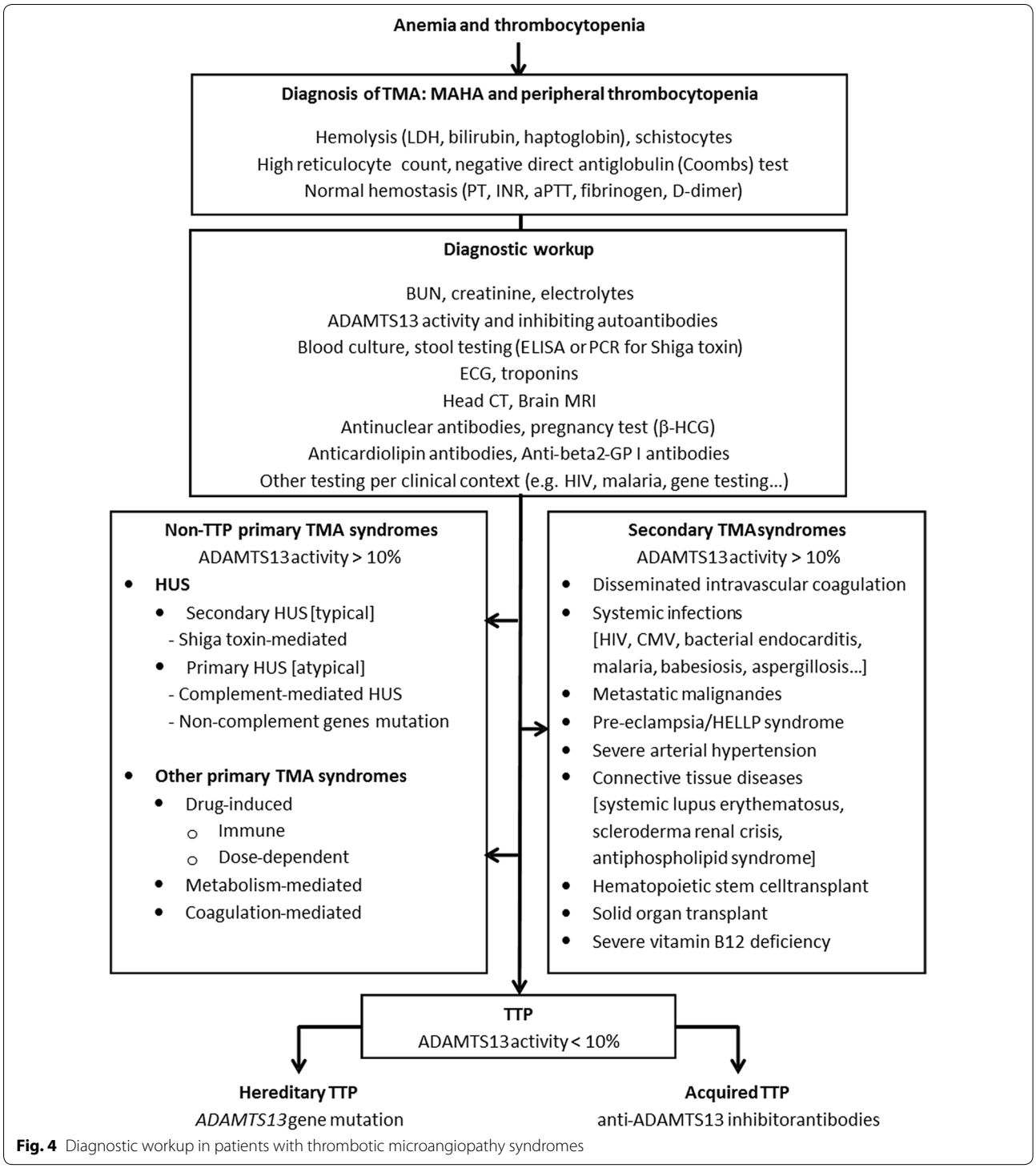

Fig. 4 Diagnostic workup in patients with thrombotic microangiopathy syndromes

during TTP. Plasma availability should be assessed with the blood bank, and all pre-transfusion requirements should be met [99].

To suppress anti-ADAMTS13 antibody formation, experts recommend that methylprednisolone (starting at 1 mg/kg) or equivalent [2, 10, 100] should be given for 21 days. This treatment may also decrease the side effects often observed with PEX [101]. In patients with severe TTP, high-dose pulse corticosteroid therapy (e.g., 1 g of

methylprednisolone) may be given daily for three consecutive days [75].

Rituximab is used off-label in TTP, but is very effective in suppressing anti-ADAMTS13 autoantibody formation [77, 78]. No randomized controlled trials of rituximab in patients with severe TTP exist, but substantial data suggest an overall beneficial effect [78, 80, 82, 83]. Rituximab has been used chiefly to treat relapsing TTP [10, 25, 80, 82]. The slow onset of action of about 10–14 days argues against an ability of rituximab to decrease disease severity at the initial phase and to prevent early deaths. However, rituximab may prevent exacerbations and relapses [100]. Scully et al. reported faster TTP remission with rituximab started within the first 3 days compared to historical controls [82]. In a prospective study of patients with a poor response to first-line therapy, add-on rituximab was associated with faster remission and fewer relapses [80]. The panel experts suggest that rituximab be included in the first-line treatment of all patients with severe TTP. Standard lymphoma dosages should be used, but the treatment may be shortened based on the level of B-cell depletion [77, 102]. A twice weekly administration schedule has been suggested for acute TTP to compensate for rituximab removal by PEX [77].

Experience of the panel with caplacizumab is limited to the participation of some of its members in the two published RCTs [17, 103] and to off-label use within the framework of temporary authorizations. Caplacizumab is now approved for adults with immune-mediated TTP, in combination with PEX and immunosuppressive therapy. The panel experts recommend first-line caplacizumab therapy, in addition to PEX, corticosteroids, and rituximab, in critically ill patients with severe TTP. In the randomized controlled trials [17, 103], bleeding was more common with caplacizumab than with the placebo. The reasons for this difference are still unclear. Severe bleeding during caplacizumab therapy can be managed using plasma-derived vWF concentrate (pure vWF or mixed FVIII-vWF depending on the country). Caution is in order with the newly developed recombinant vWF in patients with TTP, as it contains ultralarge vWF multimers not found in plasma-derived vWF concentrates.

A registry of all patients given caplacizumab to treat immune-mediated TTP should be established to further evaluate the efficacy and safety. Of special interest will be the safety profile of caplacizumab in critically ill patients requiring invasive procedures.

The best standard of ICU management should be provided, including deep vein thrombosis and peptic ulcer prophylaxis, as well as limited use of red cell transfusions [10]. Folate supplements should be administered over the first 2 weeks [100]. The use of antiplatelet agents in patients with severe cardiac or cerebral involvement, and after the platelet count rises above 50 G/L, is common but not supported by sound evidence [104]. Moreover, whether caplacizumab can be safely given in combination with antiplatelet agents is unclear. The protocols of the TITAN and HERCULES trials did not require antiplatelet agent withdrawal, but whether the combination was associated with increased bleeding rates cannot be assessed based on the available data [17, 103]. Careful attention should be given to the prevention and early detection of PEX-catheter thrombosis and infection and to maintain adequate blood pressure control. The usual measures for preventing, diagnosing, and treating infections in immunocompromised patients should be applied, including prophylaxis against herpes simplex virus and *Pneumocystis jiroveci* infection if prolonged corticosteroid therapy is required. The panel of experts suggests refraining from prophylactic antibiotic therapy. Platelet transfusions and medications that may induce microvascular injury (e.g., desmopressin, vasopressin, and tranexamic acid) should not be given in the absence of life-threatening bleeding, and it should be borne in mind that, despite the profound thrombocytopenia, ischemia is a far greater risk than bleeding during TTP [10, 54, 98].

The general principles of organ support apply to patients with TTP, including early ICU admission, optimal ICU monitoring, awareness that sudden deterioration is possible at any time, standard organ-protective measures, and correction of metabolic disturbances. Disease severity should be assessed at the same time that initial treatment measures are applied. No specific data are available on the management of organ dysfunction in TTP patients, regarding for instance the red cell transfusion threshold, criteria for intubation of patients with impaired consciousness, seizure prophylaxis, renal replacement therapy, and extracorporeal life support.

To optimize efficacy, all medications should be given after the PEX session, and therapeutic drug monitoring should be performed to allow dosage adjustment.

The panel of experts suggests that monitoring tests should include a daily blood cell count, troponin assay, hemolytic activity assessment, and ECG. After collecting the first blood sample for the diagnostic ADAMTS13 activity assay, ADAMTS13 activity and anti-ADAMTS13 antibodies should be monitored at least at discharge, then every 3 months for 1 year, and once or twice a year subsequently. Caplacizumab treatment may modify ADAMTS13 activity levels at the acute phase of TTP. The panel experts suggest weekly monitoring after caplacizumab initiation to identify patients with rapid recovery of detectable ADAMTS13 activity, in whom caplacizumab treatment may be shortened to less than 20 days. Patients whose ADAMTS13 activity remains undetectable on day 30 should be kept on caplacizumab.

Persistently low ADAMTS13 activity despite first-line treatment is associated with a high risk of treatment unresponsiveness or relapse [11, 105–107] and can occur despite rituximab and/or caplacizumab therapy [17, 103, 105, 108]. In treated patients, triggers for a further exacerbation (notably infection, thrombosis, and error in treatment delivery) must be sought and corrected [74]. A personalized approach must be given priority.

Expert statement 4: first-line treatment of severe TTP

Place of admission

The experts suggest that all patients with TTP must be initially admitted to an intensive care unit, for monitoring, organ dysfunction management, and immediate PEX.

PEX

1. The experts recommend that PEX must be preferred over plasma infusions in patients with immune-mediated TTP. Plasma infusions must be used only when PEX is not immediately available.
2. The experts recommend one PEX session per day with a plasma volume of 60 mL/kg (1.5 times the estimated blood mass) until the platelet count remains above 150 G/L for at least 48 h.
3. The experts recommend that PEX should be initiated as soon as possible and no later than 6 h after the diagnosis.
4. If PEX is not available, the experts suggest that patients should be transferred to another center where PEX is available.

Corticosteroids

1. The experts recommend prednisone or methylprednisolone to be administered in combination with PEX.
2. The experts suggest a starting corticosteroid dose of 1 mg/kg/d of prednisone equivalent for a total of 21 days.
3. The experts suggest that patients with severe TTP should receive high-dose pulse corticosteroid therapy (1 g of methylprednisolone) for three consecutive days.

Monoclonal antibodies

1. The experts recommend that rituximab must be used in patients with relapsing autoimmune TTP.
2. The experts suggest that rituximab should probably be used as part of the first-line treatment of severe TTP.
3. The experts have no opinion about first-line rituximab therapy in all TTP patients regardless of disease severity.
4. The experts recommend that caplacizumab must be used as part of the first-line treatment of severe TTP.

Supportive care

1. The experts suggest folate supplementation, prophylactic anticoagulation using low-molecular-weight heparin (if renal function is normal) and antiplatelet agents as soon as the platelet count reaches 50 G/L, monitoring of the central venous catheter for thrombosis and infection, tight blood pressure control, gastroduodenal ulcer prophylaxis, and prophylaxis against herpes simplex virus and *Pneumocystis jiroveci* infection in patients requiring protracted corticosteroid therapy.
2. The experts suggest that prophylactic antibiotics should not be administered.
3. The experts suggest reserving platelet transfusion for those patients who have severe bleeding (e.g., cerebral hemorrhage).

ICU discharge

The experts suggest the following criteria for ICU discharge: PEX tapered or stopped, resolution of evidence of hemolysis, and platelet count above 150 G/L. These criteria usually correlate with cardiac and neurological improvements. Patients can be discharged from the ICU earlier if they can receive PEX elsewhere in the hospital.

Standard of care for the second-line treatment of TTP

Patients requiring second-line treatment

Clinical remission is defined as platelet count recovery (>150 G/L for 2 consecutive days), hemolysis resolution persisting after PEX discontinuation, and recovery of previous organ function. In patients with bone marrow dysfunction, a return to the baseline platelet count is required. Cardiac, renal, and neurological functions can improve rapidly, although delayed recovery with residual organ function impairment has been reported [24, 30, 49, 109]. Immunological remission is defined as recovery of normal ADAMTS13 activity and complete clearance of anti-ADAMTS13 antibodies [9, 38, 105, 106].

Refractory TTP requiring second-line treatment is defined as persistent thrombocytopenia and hemolysis after 7 days of first-line treatment [25, 68]. In practice, however, persistent thrombocytopenia with persistent hemolysis (LDH elevation) and/or severe cardiac or neurological manifestations on day 5 is associated with a high risk of poor outcomes and requires treatment

intensification [68]. Kidney involvement may recover more slowly, notably in patients requiring renal replacement therapy [24].

TTP exacerbation is defined as recurrent thrombocytopenia with other TTP manifestations, either during PEX or within 30 days after PEX discontinuation. TTP relapse is recurrent TTP more than 30 days after PEX discontinuation [68]. Exacerbations and relapses may be associated with identifiable triggers, such as surgery, extracorporeal circulation, blood transfusions, and sepsis [74]. Patients in clinical remission who have failed to achieve an immunological remission (i.e., who have low ADAMTS13 activity) are at high risk for relapse. They should be monitored closely and may require preemptive rituximab therapy until stable ADAMTS13 activity is recovered [105, 108]. Prolonged caplacizumab therapy may deserve consideration to decrease the risk of thromboembolic events until the recovery of ADAMTS13 activity.

Second-line treatments

No study has properly evaluated therapeutic strategies for TTP refractory to first-line treatment including PEX and corticosteroids or for TTP exacerbation or relapse [90]. Advice should be obtained from TTP specialists including biologists and immunologists.

The experts suggest that patients whose first-line treatment did not include caplacizumab and rituximab may be given these two drugs in combination [110, 111]. However, rituximab has a time to action of 7–10 days [80]. Immunosuppression can be intensified by increasing the corticosteroid dosage or using a pulse administration regimen [75]. The PEX session frequency can be increased to two per day in patients with life-threatening complications.

In patients given first-line caplacizumab and rituximab in addition to PEX and corticosteroid therapy, PEX could be performed twice daily in combination with high-dose pulse corticosteroid therapy. If rituximab fails to achieve remission, ofatumumab might be an option [114]. If dictated by clinical severity, vincristine or cyclophosphamide may be added. Vincristine has provided fast, effective, and sustained clinical and biological responses [89, 112], and cyclophosphamide has also been found beneficial [79, 88, 113]. Other drugs such as bortezomib, cyclosporine, mycophenolate mofetil, *N*-acetylcysteine, eculizumab, and immunoadsorption have been used only rarely. Finally, in patients unresponsive to treatment, centrifugation devices may be preferred over plasma filters, as they generate less shear stress. However, these devices are not universally available and the level for such evidence is low, leaving the experts with no opinion about this.

The choice of the second-line therapy also depends on the underlying condition, if any (e.g., pregnancy, AIDS, or systemic rheumatic disease).

Finally, salvage splenectomy remains an option for patients who show no clinical and biological response and/or experience life-threatening cardiac or neurological thromboembolic events despite optimal treatment [88, 90, 115, 116, 117]. Splenectomy is a treatment of last resort after failure of all first- and second-line treatments.

Expert statement 5: second-line treatment of severe TTP

1. The experts suggest that refractory TTP (i.e., TTP unresponsive to treatment) should be defined based on persistent thrombocytopenia and hemolysis (LDH elevation) and/or severe cardiac or neurological manifestations on day 5 after PEX initiation. Kidney involvement may take longer to resolve, notably in patients requiring renal replacement therapy.
2. The experts suggest that patients with refractory TTP who did not receive first-line caplacizumab and rituximab in addition to PEX and corticosteroids should be given add-on treatment with both drugs.
3. The experts suggest that patients with refractory TTP who received first-line caplacizumab and rituximab in addition to PEX and corticosteroids should have their number of PEX sessions increased to two per day and their corticosteroid regimen switched to high-dose pulse therapy. If dictated by clinical severity, vincristine or cyclophosphamide may be added.
4. The experts suggest that the underlying condition, if any (e.g., pregnancy, AIDS, or systemic rheumatic disease) should be taken into consideration when selecting the second-line treatment.
5. The experts suggest that splenectomy should be reserved for patients with TTP refractory to all other treatment options and that early optimal first- and second-line treatment should considerably restrict the use of splenectomy.
6. The experts suggest that advice should be sought from TTP specialists about the best second-line treatment.

TTP in pregnant women

Pregnancy is among the causes of immune-mediated TTP. Of all TTP cases, 2–8% occur in pregnant women [9, 46]. TTP due to recessively inherited ADAMTS13 deficiency (Upshaw–Schulman syndrome) accounts for only 3–5% of TTP cases overall, but is responsible for a higher proportion of cases during pregnancy. Among patients with hereditary TTP, 25–60% experience their first TTP episode during pregnancy [70, 71].

The development of severe thrombocytopenia with MAHA during pregnancy can indicate a wide range of diagnoses including immune-mediated or hereditary

Table 7 Causes of thrombocytopenia with microangiopathic hemolytic anemia during pregnancy

	Associated with pregnancy			Caused by pregnancy		
	TTP	Atypical-(complement-mediated)-HUS	Idiopathic thrombocytopenic purpura	HELLP	DIC	Acute fatty liver of pregnancy
Timing	Trimesters 1-3 Postpartum	Trimesters 1-3 Postpartum ++	Trimesters 1-3 Postpartum	> 20 weeks, Postpartum	Trimesters 2 and 3	Trimester 3
Platelets (/μL)	Typically < 30,000	Typically < 100,000	< 50,000	50,000-100,000	Mild drop	Mild drop
Schistocytes	+++	+++	–	−/+	−/+	–
Additional hematological changes	MAHA High LDH low haptoglobin	MAHA High LDH Low haptoglobin	No	MAHA High LDH Low haptoglobin	PT and aPTT prolongation Low fibrinogen (overt DIC)	Possible PT and aPTT prolongation Low fibrinogen
DIC	No	No	No	In 10% of cases	+++ Beware of normal fibrinogen coinciding with systemic inflammation	No
ADAMTS13 activity	< 10%	≥ 10% normal	≥ 10%-normal	≥ 10%-normal	≥ 10%-normal	≥ 10%-normal
Liver tests	Normal or mild enzyme elevation	Normal	Normal	Elevated liver enzymes[b]	Possible liver enzyme elevation	Markedly abnormal liver enzymes, liver synthetic dysfunction
Renal tests	Mild abnormalities	Severe abnormalities	Normal	Normal Mild abnormalities	Possible acute tubular necrosis	Possible abnormalities
Neurological abnormalities	Common[c]	Rare	None	Pre-eclampsia+++	Possible	Encephalopathy
Other features	Elevated troponin Unresponsive TMA that may worsen after delivery	Unresponsive TMA that may worsen after delivery	/	80%–85% have concurrent pre-eclampsia	Presence of a trigger (i.e., amniotic fluid embolism, fetal death, postpartum bleeding)	Hypoglycemia, Potential multiorgan failure
Management	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
Delivery	Not curative; Indications based solely on fetal prognosis	Not curative; Indications based solely on fetal prognosis	Not curative	Curative Timing determined by obstetrician and intensivist	Curative if HELLP related DIC or fetal death	Curative Liver transplant may be required

Other causes of severe thrombocytopenia in pregnancy that are not pregnancy related include antiphospholipid antibody syndrome, systemic lupus erythematosus, drug-induced thrombocytopenia, sepsis, and malignancy

TTP thrombotic thrombocytopenic purpura, *HUS* hemolytic uremic syndrome, *HELLP* hemolysis-elevated liver enzymes–low platelet count syndrome, *DIC* disseminated intravascular coagulopathy, *MAHA* microangiopathic hemolytic anemia, *LDH* lactate dehydrogenase, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *IVIG* intravenous gammaglobulin

[a] Pregnancy may unmask these conditions

[b] Liver enzymes may be markedly elevated in severe cases of intrahepatic hemorrhage, subcapsular hematoma, or hepatic infarction

[c] Stroke, seizures, weakness, aphasia, mental status changes, etc.

ADAMTS13 deficiency (TTP), complement-mediated thrombotic microangiopathy (atypical HUS), HELLP syndrome (microangiopathic hemolytic anemia, elevated liver enzymes, and low platelet count), and disseminated intravascular coagulopathy (Table 7).

TTP during pregnancy may result in placental infarction with fetal death. An early diagnosis promptly followed by plasma therapy initiation minimizes the risks to the fetus and mother. Intensivists, obstetricians, neonatologists, and TTP experts (hematologists, clinical immunologists, internists, and/or nephrologists) should work in close collaboration to manage pregnant patients with TTP [32, 72].

The experts suggest that the management of TTP in pregnant patients is similar to that of TTP in non-pregnant patients. Delivering the fetus does not improve maternal outcomes, in contrast to experience with other forms of TMA during pregnancy, such as pre-eclampsia and HELLP syndrome. Consequently, decisions about delivery should be based on the fetal prognosis. Death in utero is common when TTP occurs early during pregnancy. Early PEX is the best means of increasing the chances of fetal survival. PEX should be started before the ADAMTS13

assay results become available. Platelet transfusions may be required in patients with severe bleeding.

Unanswered clinical questions and research agenda for TTP in the ICU

Despite improvements in our understanding of TTP pathophysiology, the advent of new therapeutic agents, and advances in ICU management, several clinical issues remain unsettled.

Shortening the time to diagnosis is of critical importance to improving patients' outcomes. Progress is needed in the identification of predictors of TTP, in understanding ADAMTS13 activity, and anti-ADAMTS13 antibody production. However, the best means of improving the early diagnosis is dissemination of knowledge about TTP within the health-care community.

One of the most pressing issues is defining the optimal first-line treatment. The panel of experts suggests that PEX, corticosteroids, rituximab, and caplacizumab should be given in combination to all patients who meet criteria for severe TTP. However, experience is limited with rituximab and, even more so, with caplacizumab. Combining PEX with corticosteroid therapy is known to provide recovery in many patients [63, 69, 80, 82]. The early, reliable identification of patients not responding to PEX and corticosteroid therapy alone would limit the use of rituximab and caplacizumab therapy, thereby decrease the risk of side effects and limiting costs [25]. For instance, early cardiac and neurological monitoring might identify patients who would benefit from rituximab and caplacizumab. Caplacizumab was highly effective in randomized trials, and its use may impact the other components of the treatment strategy, for instance by decreasing PEX and immunosuppressant requirements. The development of a caplacizumab registry will provide the opportunity to monitor this point. Also, new anti-ADAMTS13 antibody clearance methods, such as immunoadsorption, are being evaluated and, if proven effective and safe, may further change the therapeutic landscape. Some uncertainty continues to surround the optimal corticosteroid and rituximab dosages and administration regimens. Thus, routine pulse corticosteroid therapy for 3 days, followed by 1 mg/kg of methylprednisolone has been recommended. Determining the rituximab dosage and dosing schedule based on B-cell data may improve efficacy while minimizing side effects. Finally, in patients with highly refractory TTP, the efficacy and safety of immunosuppressants such as vincristine and cyclophosphamide needs further evaluation.

Whether antiplatelet aspirin therapy should be given to all patients receiving caplacizumab or reserved for those with severe neurological or cardiac involvement needs to be determined. Also, the ability of well-tolerated adjunctive treatments such as *N*-acetylcysteine and magnesium sulfate to shorten PEX therapy duration deserves further evaluation. The impact of specific PEX modalities (e.g., use of a centrifuge-based system vs. a plasma filter, use of citrate vs. heparin for anticoagulation, and plasma volume) on the therapeutic and adverse effects should be investigated.

Bleeding was more common in the caplacizumab-treated groups than with the placebo in both randomized controlled trials of caplacizumab. With caplacizumab, vWF-ristocetin cofactor activity drops below 20% within 24 h [103]. However, whether vWF-ristocetin cofactor activity correlates with the bleeding risk is unclear.

Advances are needed in the management of the organ dysfunctions caused by TTP. The role for cardiac catheterization, angioplasty, and stenting in patients with cardiac involvement should be refined. Similarly, specific treatments might improve outcomes of patients with cerebral involvement. However, caution is in order. Indeed, in patients with massive stroke, fibrinolytic therapy may seem appealing, but carries a high risk of bleeding and may consume the ADAMTS13 provided by PEX. In comatose patients, the role for cerebral edema and seizure activity monitoring deserves attention, as does the optimal drug therapy for status epilepticus. Another issue of interest is whether red cell transfusion thresholds should be altered in patients with cardiac and/or neurological involvement.

The optimal criteria for discontinuing TTP therapy overall, or specific components thereof, need to be studied. For instance, the relative roles for the platelet count, ADAMTS13 activity level, and anti-ADAMTS13 antibody titers should be assessed. Long-term studies will be important to determine whether the initial treatment affects the subsequent risk of relapse and of residual neurological and cardiac impairments.

Conclusion

TTP is a life-threatening disease that has been the subject of significant diagnostic and therapeutic advances over the last decade. The widespread use of a standardized management protocol can be expected to optimize the effectiveness not only of conventional treatments (PEX and corticosteroids), but also of rituximab and caplacizumab. Exhaustive ICU registries should be established to monitor the effectiveness and safety of new drugs and to identify reliable clinical and laboratory markers associated with either a high risk of early cardiovascular and neurological complications or, on the opposite, a low risk of morbidity and mortality consistent with a less intensive treatment strategy. The management of TTP is a rapidly changing scene that will require an update of these guidelines within a few years.

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Author contributions
All experts contributed significantly to developing the statement and to writing and revising the manuscript. All experts have approved the final submitted version.

Compliance with ethical standards

Conflicts of interest
This statement is the result of independent work carried out by members of the Nine-i network of investigators. None of the authors received any honoraria or fees for this work. The Nine-i network has received research grants and sponsorships from Gilead, Fisher&Payckle, Jazz Pharma, Ablynx, Baxter, Alexion, and Astellas. Financial ties unrelated to this work are as follows. Over the last 3 years, EA received honoraria or travel expense reimbursements from Alexion, Baxter, MSD, Ablynx, Pfizer, and Gilead. IML has received honoraria or travel expense reimbursements from Biomerieux, MSD, and Gilead. AV sits on the advisory boards of Ablynx-Sanofi-Genzyme, Roche-Chugai, and Shire-Takeda. PC sits on the advisory boards of Alexion, Sanofi-Genzyme, Roche-Chugai, Octapharma, and Shire-Takeda. PP received honoraria or travel expense reimbursements from Pfizer and Orion. DB has received grants from Gilead, Astellas, Fisher-Paykel, Baxter, Alexion, and Fresenius Kabi. SC sits on the advisory boards of Alexion, Sanofi-Genzyme, and Shire-Takeda. FP and JGM have received fees from Alexion. None of the other authors has any potential conflicts of interest to declare.

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