Thrombotic thrombocytopenic purpura: from diagnosis to therapy

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Purpose of review
Thrombotic thrombocytopenic purpura (TTP) is a rare but challenging disease for intensive care specialists. Patients with acute TTP frequently require admission to the intensive care unit because of organ dysfunctions due to the disease or because of the risk of sudden aggravation at the onset of the disease. This review aims at describing recent evolutions in the diagnosis and for the management of TTP for the use of intensive care specialists.

Recent findings
The use of A Disintegrin and Metalloprotease with ThromboSpondin type 1 repeats (ADAMTS13) activity along with clinico-biological features to define TTP by most researchers' teams has led to easier interpretation of the literature. The main issues in TTP treatment in 2015 remain the indication and timing of introduction of anti-CD20 antibody rituximab for the treatment of inaugural TTP and the preemptive use of rituximab in asymptomatic patients with decreasing ADAMTS13 activity.

Summary
The classification of thrombotic microangiopathies has evolved from a clinical to a pathophysiological definition. TTP is characterized by a severe ADAMTS13 deficiency that can be documented *in vitro*, along with anti-ADAMTS13 antibodies in most adult cases. Plasmapheresis and immunosuppressive therapy with steroids remain the standard of care for acute inaugural TTP. Anti-CD20 monoclonal antibody rituximab is safe and indicated in relapsing and/or refractory TTP. Its indication in inaugural TTP remains to be evaluated but is nevertheless recommended by experts. Novel therapies for TTP are still in preclinical phases.

Keywords
ADAMTS13, plasmapheresis, rituximab, thrombotic microangiopathy, thrombotic thrombocytopenic purpura

INTRODUCTION

Thrombotic microangiopathy (TMA) syndrome is a heterogeneous entity defined by the widespread formation of thrombi in the microcirculation [1]. It is usually diagnosed on the association of mechanical hemolytic anemia, peripheral thrombocytopenia and various signs of visceral ischemia.

Thrombotic thrombocytopenic purpura (TTP) is a TMA caused by a severe functional deficiency in Willebrand factor cleaving protease (A Disintegrin and Metalloprotease with ThromboSpondin type 1 repeats) ADAMTS13 documented *in vitro* in more than 90% of the cases [2]. This deficiency can be hereditary in the majority of pediatric cases (Upshaw Shulman syndrome) or acquired through anti-ADAMTS13 antibodies in the majority of adult cases (>95%) [3]. Acquired TTP is a rare disease with an incidence estimated around 3–6/1 000 000, affecting preferentially young women in their fourth decade. The diagnosis of TTP used to rely on clinical symptoms (TMA with predominant neurological involvement) and is now ascertained by the dosage of ADAMTS13 activity [4]. The treatment of TTP relies on the association of plasmatherapy and immunosuppressive therapy resulting in the remission of the disease in more than 80% of cases [5]. The management of refractory and/or relapsing TTP relies on anti-CD20 monoclonal antibody rituximab [6▪]. The treatment of refractory TTP is not clearly codified and depends on local practices and expert recommendations. The

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KEY POINTS

- The classification of the elements of the TMA syndrome has shifted from clinic to pathophysiology.
- Undetectable anti-ADAMTS13 activity is the hallmark of idiopathic TTP.
- Earlier recognition of TMA syndrome in pauci/asymptomatic patients with early introduction of plasma exchange therapy may continue to improve outcome.
- Plasma exchange therapy with cortico steroids still represents the first line of treatment for TTP.
- Early therapeutic intensification with rituximab in patients at high risk of refractory form of TTP or death still has to be evaluated in randomized-controlled studies.

potential severity of organ dysfunctions on diagnosis and the need for urgent treatment with plasmapheresis usually require intensive care unit (ICU) transfer of TTP patients [7].

The aim of this review was to present the state-of-the-art as well as perspectives in terms of diagnosis and treatment of TTP in 2015 with an emphasis on patients admitted to the ICU.

TEXT OF REVIEW

An algorithm for the diagnosis and management of patients with TTP is proposed in Fig. 1.

IDENTIFICATION OF THROMBOTIC MICROANGIOPATHY SYNDROME

TMA is a heterogeneous syndrome defined by the widespread formation of thrombi in the microcirculation [8▪]. TMA is diagnosed on the association of a mechanical hemolytic anemia (anemia, schistocytosis, reticulocytosis, raised lactate dehydrogenase, undosable haptoglobin and negative direct antiglobulin test), peripheral thrombocytopenia and various signs of visceral ischemia (acute organ dysfunctions) in the absence of alternate diagnosis. Elements of the TMA syndrome are illustrated in Fig. 2.

SUSPECT THROMBOTIC THROMBOCYTOPENIC PURPURA WITH SIMPLE CLINIC-BIOLOGICAL DATA

TTP is a TMA that may present with various organ involvements. It may be impossible to clinically differentiate TTP from other elements of the TMA syndrome on diagnosis and ADAMTS13 activity

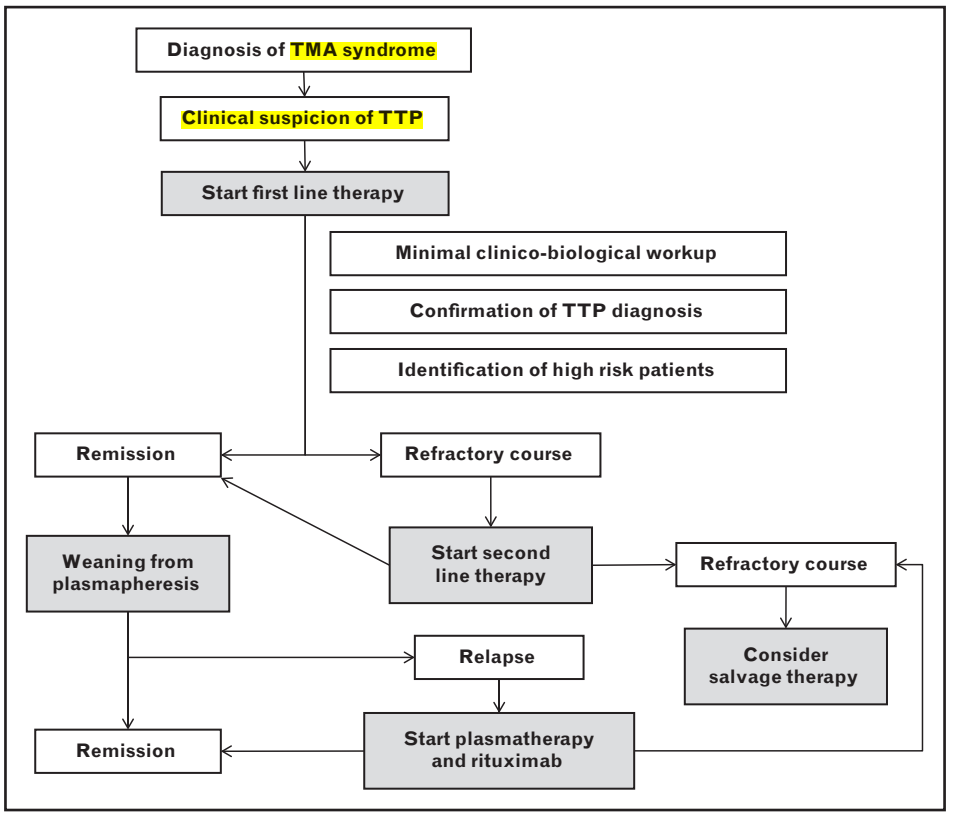

FIGURE 1. Proposition of algorithm for the diagnosis and management of thrombotic thrombocytopenic purpura.

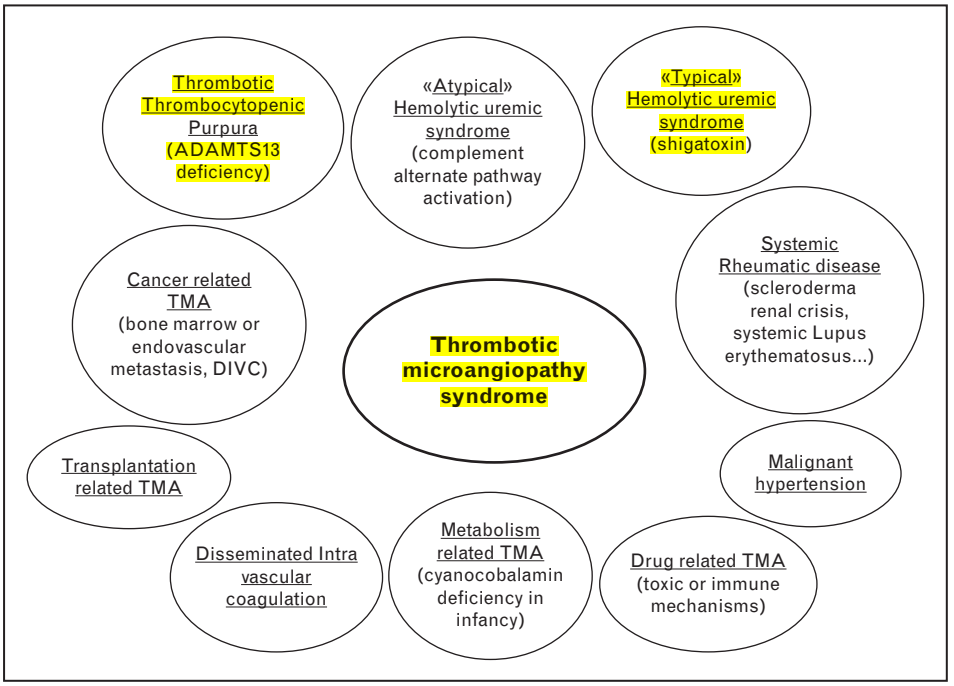

FIGURE 2. Elements of the thrombotic microangiopathy syndrome.

dosage is usually not available in critical care setting [9]. When a patient is diagnosed with TMA syndrome, the presence of a very low platelet rate (<30 G/l), moderate renal involvement (creatininemia<200 μmol/l) and positive antinuclear antibodies has been associated with a higher frequency of severely decreased ADAMTS13 activity [10▪]. Nevertheless, the suspicion of TTP in the absence of clear alternative diagnosis warrants the introduction of therapeutic plasma exchange (PEX) therapy and immunosuppressive therapy (systemic corticotherapy) [11].

MINIMAL CLINICAL AND BIOLOGICAL WORKUP

Organ dysfunction may be absent at the earliest phase of acute TTP, so patients may present with microangiopathic anemia and peripheral thrombocytopenia alone. Organ involvement of TTP is also highly variable and can imply any organ, leading to various initial presentations. Clinical and biological anomalies that may be present on diagnosis of TTP are summarized in Table 1 [12–17]. Cardiac involvement must systematically be searched because of its association with increased mortality rate and refractory forms of TTP [10▪].

Initial workup must include the research of conditions associated with TTP (1/3 to 1/2 cases) [18]. The etiologic role of these conditions in the occurrence of TTP bouts is imperfectly understood. Nevertheless, the diagnosis of an associated condition may imply specific therapies. The list of these conditions, possible diagnostic tests and therapeutical implications is displayed in Table 2 [19–30]. In the absence of associated condition, TTP is labeled idiopathic.

Note that the interpretation of most plasmatic markers (e.g. serologies, complement study…) will be uneasy after the onset of plasmatherapy.

START URGENTLY FIRST-LINE THERAPY

Recent recommendations by experts and national scientific societies have insisted on the necessity to begin PEX therapy as soon as possible when TTP is suspected [11,31▪]. This is based on historical data, experts' clinical experience and hints from the comparison of inaugural bouts of TTP to relapses [32]. Time from first clinical manifestation of the disease to the onset of plasmatherapy is thought to be correlated to prognosis of TTP patients, with shorter delays being associated with better outcome.

Therapeutic plasma exchange

The cornerstone of TTP therapy is plasmatherapy. PEXs with donor plasma are preferred to plasma infusions because they allow the administration of higher doses of functional ADAMTS13 without risk of fluid overload along with the removal of ultralarge von Willebrand factor multimers and eventual

Table 1. Possible organ involvement and clinical presentations of acute thrombotic thrombocytopenic purpura

Organ involvement	Clinical presentation	Biological/radiological presentation	References
Neurologic	Cephalalgia	Normal radiology	[12,13]
	Focal deficiency	Ischemic/hemorrhagic stroke	
	Seizure	Posterior reversible encephalopathy syndrome	
	Altered conscience		
Cardiologic	Angina	Nonspecific ECG changes	[14–16]
	Myocardial infarction	Raised cardiac enzymes	
	Cardiac failure	Radiologic/echographic signs of cardiac failure	
Renal	Hypertension	Uremia	[17]
	Oliguria	Hypercreatininemia	
	Proteinuria	Acute renal failure	
	Hemoglobinuria		
Digestive	Abdominal pain	Digestive tract microangiopathy	
	(Bloody) diarrhea	Mesenteric ischemia	

anti-ADAMTS13 antibodies [33]. PEXs have been associated with a higher survival rate in ICU patients with TMA in comparison to plasma infusions [34]. They consist of the administration of 1.5 plasma volumes daily (60 ml/kg/day) until platelet rate is over 150 G/l for at least 48 h. Some experts recommend the administration of 1.5 plasma volume PEX for 48–72 h and then the administration of 1 plasma volume PEX on consecutive days in patients with a good response [11,31▪]. British experts perform

Table 2. Conditions associated with acute thrombotic thrombocytopenic purpura and potential therapeutic implications

Condition	Suggested diagnostic test	Therapeutic implications	References
Pregnancy	β-hcg	Consider transfer to high-risk pregnancy obstetrical facility Consider late onset USS if no anti-ADAMTS13 antibodies	[19,20]
Systemic rheumatic disease	Antinuclear antibodies	Consider early immunosuppressive regimen intensification Consider SRD involvement rather than TMA involvement as the cause of organ dysfunction	[21,22]
HIV	Serology	Consider early antiretroviral therapy introduction Search for opportunistic infection	[23,24]
Infection (non-HIV)	Biological workup depending on clinical symptoms	Treat any ongoing infection as a potential trigger of the TMA	
Drug	Anamnesis	Stop any medication that has been associated with acute TTP	[25,26]
Cancer	Bone marrow smear/biopsy Biological/radiological workup depending on clinical symptoms	Consider treatment of associated cancer or modification of ongoing therapy rather than plasmatherapy	[27,28]
Transplantation	NA	Search for immunosuppressive drug (anticalcineurin) toxicity, search for opportunistic infection	[29,30]

SRD, systemic rheumatic disease; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; USS, Upshaw Schulman syndrome.

twice daily PEX with 1.5 blood mass for 72 h in patients with severe neurologic or cardiac involvement [35▪]. These strategies have not been evaluated in randomized controlled studies.

IMMUNOSUPPRESSIVE THERAPY

As most adult-acquired TTP cases are autoimmune diseases with detectable anti-ADAMTS13 antibodies, an immunosuppressive treatment is associated with PEX therapy in order to control the anti-ADAMTS13 autoimmune response.

First line of immunosuppressive therapy usually consists of systemic corticosteroid therapy. This class of drugs has historically shown efficiency as single therapy in TMA patients with mild neurological involvement, before the era of plasmatherapy [36].

Dosage, modalities of administration and duration of treatment are loosely codified. Some authors recommend the administration of high-dose corticosteroid bolus at the beginning of treatment with [37] or without [35▪] high-dose maintenance therapy. One study suggests that high-dose steroid therapy (10 mg/kg/day methylprednisolone for 3 days followed by 2 mg/kg/day methylprednisolone) could be associated with higher remission rates at day 23 in idiopathic TTP patients in comparison with lower dose steroid therapy (1 mg/kg/day methylprednisolone) [37]. If patients present with signs of ongoing infection at diagnosis of TTP, the introduction of steroid therapy can be delayed.

SUPPORTIVE CARE

Supportive care for TTP bout consists of red cells transfusion and oxygenotherapy in case of symptomatic anemia, folate supplementation to help regeneration of the hemolytic anemia and gastroduodenal ulcer prevention [11]. Strict blood pressure control is recommended for TTP patients, as arterial hypertension has been associated with poorer outcomes in TMA patients [38]. Prevention of thromboembolic venous disease must be started early (usually as soon as the platelet rate reaches 50 G/l) as TTP patients are especially prone to deep vein thrombosis under PEX therapy [39]. Deep vein thrombosis prophylaxis may be obtained via mechanical (compression stocking) and/or pharmacological means (heparin). Prevention of coronary ischemic disease is also recommended in patients diagnosed with cardiac involvement of the TMA at presentation or under therapy [11]. This is usually obtained with oral antiplatelet therapy (aspirin) started as soon as the platelet rate reaches 50 G/l.

Platelet transfusions have an uncertain efficiency in the context of peripheral thrombocytopenia [40] and have been associated with sudden exacerbations of TTP [41]. Platelets are usually contra-indicated prophylactically (particularly before central venous access insertion [42▪]) and should only be used in the case of severe hemorrhagic manifestations not controllable by mechanical means [31▪].

CONFIRMATION OF THE DIAGNOSIS OF THROMBOTIC THROMBOCYTOPENIC PURPURA

Confirmation diagnosis of TTP will be obtained through ADAMTS13 study performed on plasma samples retrieved before the introduction of plasmatherapy.

ADAMTS13 activity

The confirmation of a diagnosis of acute TTP will be obtained by the dosage of ADAMTS13 activity in the patient's plasma retrieved before the onset of plasmatherapy [43].

ADAMTS13 will be undetectable (<10%) in nearly all patients with idiopathic TTP and a variable proportion of patients with a clinical diagnosis of TTP associated with other conditions [3]. Several techniques allow the determination of ADAMTS13 activity. Most validated methods assess the ability of the patient's plasma to cleave von Willebrand factor, whether full length or short fragments [44]. These dosages should be performed in expert centers as the performance and reproducibility of different commercial tests have not thoroughly been evaluated [45,46].

If ADAMTS13 is found detectable in a patient with a clinical diagnosis of acute TTP, an exhaustive workup is mandatory to rule out other entities of the TMA syndrome, with particular attention to complement-mediated TMA (formerly known as atypical hemolytic uremic syndrome).

The persistence of an undetectable ADAMTS13 activity is possible in patients who are in clinical remission of the disease. This has been associated with a higher risk of recurrence of the TTP [43,47].

Anti-ADAMTS13 antibodies

Functional tests aiming at the determination of the ability of a patient's plasma to inhibit the ADAMTS13 activity of a pool of normal plasma have been used to look for anti-ADAMTS13 antibodies. These tests can be time-consuming. Newer simple ELISA tests are currently used to detect anti-

ADAMTS13 antibodies (immunoglobulin G isotype) in the plasma of TTP patients. Most patients with inaugural adult-acquired TTP will present with anti-ADAMTS13 antibodies [48,49]. These antibodies may persist at significant rate in patients in clinical remission of the disease and have inconstantly been associated with an increased risk of recurrence [50]. The absence of anti-ADAMTS13 antibody will raise the suspicion of late-onset Upshaw Schulman syndrome, especially in young women in their first pregnancy [51].

IDENTIFY PATIENTS AT RISK OF REFRACTORY THROMBOTIC THROMBOCYTOPENIC PURPURA

Normal time from the beginning of therapy to improvement of TTP manifestations usually varies in a range between hours and 2–3 days after the onset of PEX therapy.

In most studies, the response to plasmatherapy is judged on the platelet rate that must begin to increase before 4–7 days since the beginning of plasmatherapy. A lack of improvement of the thrombocytopenia 4–7 days after the onset of plasmatherapy or clinical/biological deterioration of any parameter during first-line therapy defines refractory TTP in most studies.

Identification of refractory TTP prompts the research of a cause of aggravation and the intensification of immunosuppressive therapy and/or PEX therapy. Factors that have been associated with refractory TTP and death from TTP are summarized in Table 3 [10▪,52–56].

PLASMA EXCHANGE WEANING SCHEDULE IN RESPONSIVE THROMBOTIC THROMBOCYTOPENIC PURPURA

Remission of the TTP is usually defined by the normalization of the platelet rate during at least 48 h. When patients reach remission, PEXs are progressively tapered over 1–2 weeks in most European centers but publications from British and US authors

Table 3. Features associated with refractory course and death in thrombotic thrombocytopenic purpura patients

Feature	Association	Population	References
Troponin (cTnI) >0.25 μg/l	Mortality rate during acute phase of TTP	*N* = 133	[10▪]
	Refractoriness = absence of platelet rate doubling after four full days of treatment with persistently elevated LDH levels	TTP	
		ADAMTS13 <10%	
Age >60 years	Refractoriness = requirement for therapeutic intensification (aside from PEX+steroids)	*N* = 86	[52]
Cardiac involvement		TTP	
Mild neurological involvement		ADAMTS13 <10% (84%)	
Platelet rate <15 Giga/l at day 2			
Platelet recovery rate <5 Giga/l/day from day 1 to 3	1-year mortality rate	*N* = 64	[53]
	Refractoriness = failure to obtain remission with PEX	TTP	
		ADAMTS13 <10% (41%)	
Cerebral involvement	30 days mortality rate	*N* = 281 (analysis cohort) and 66 (validation cohort)	[54]
Age (40–60 years; >60 years) LDH >10N		TTP, ADAMTS13 <10%	
Elevated creatininemia (median 2.9 mg/dl)	3-month mortality	*N* = 60	[55]
High anti-ADAMTS13 activity inhibitor >2 BU		TTP, ADAMTS13 <10%	
Age >40 years	6-month mortality	*N* = 86	[56]
Hemoglobin <9g/dl Fever >38.5°C		TTP/HUS	

HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

Table 4. Second-line and salvage therapy for nonresponsive thrombotic thrombocytopenic purpura

Therapy	Dosage	Delay of action (days)	References
Rituximab	375 mg/m^2/week for 4 weeks 375 mg/m^2 D1-4-7-14	7–10	[6▪,57]
High-dose methylprednisolone bolus	1 g or 10 mg/kg/day for 3 days	<7	[37]
Vincristine	1.4 mg/m^2 (max 2 mg)/week	<7	[59]
Cyclophosphamide pulse	500–750 mg/m^2/week	>7	[60]
Splenectomy	NA	<7	[60]
Twice-daily PEX	1.5 PV/12 h	<7	[11,31▪,61]

PEX, plasma exchange.

suggest that PEX can be stopped at once with no increased risk of TMA re-evolutivity [11,31▪].

TREATMENT OF REFRACTORY THROMBOTIC THROMBOCYTOPENIC PURPURA

Rituximab

Anti-CD20 monoclonal antibodies are approved by different agencies for the treatment of refractory and relapsing TTP. Rituximab has proved its efficacy in this situation [57]. In patients with inaugural TTP, rituximab has neither demonstrated the efficiency to increase the response rate nor to decrease the duration of PEX therapy [6▪]. One study showed a decrease in the duration of hospitalization in TTP patients receiving rituximab after exclusion of patients requiring ICU admission [58]. However, rituximab is used off label with an increasing frequency in patients with inaugural TTP presenting with severe symptoms and/or characteristics associated with refractoriness/high risk of death [11]. The validity of this approach has yet to be studied.

Others

In cases of refractory TTP, the therapeutic arsenal is detailed in Table 4 [6▪,11,31▪,37,57,59–61].

TREATMENT OF RELAPSING THROMBOTIC THROMBOCYTOPENIC PURPURA

Under first line of therapy, more than 80% of inaugural TTP patients will reach remission. They may relapse during the following months/years with an increased frequency if they keep an undetectable ADAMTS13 activity at clinical remission of the disease and detectable anti-ADAMTS13 antibodies (inhibitory or not *in vitro*) [43,50]. ADAMTS13 activity monitoring is routinely performed in TTP patients in clinical remission of the disease. Clinical relapse of the disease is usually preceded by a drop in ADAMTS13 activity. Preemptive treatment of severely decreased ADAMTS13 activity in asymptomatic patients has been proposed but not yet evaluated prospectively [62▪].

In the presence of a clinical relapse (TTP re-evolutivity after a period of remission of at least 30 days), PEX therapy and corticosteroid are resumed with the early adjunction of rituximab to prevent further relapses in the following year [58]. A study demonstrated that early administration (<3 days after admission) of rituximab in this indication leads to reduced number of PEX needed to reach remission and shorter hospital stay in comparison with late administration (>3 days after admission) [63].

PERSPECTIVE

Novel therapies for TTP include inhibition of the adhesion of Willebrand factor multimers to platelets via anti-Willebrand factor nanobodies (caplacizumab) and ADAMTS13 substitution by recombinant ADAMTS13. These new therapies are not yet available in clinical practice and their role in the treatment of adult-acquired TTP remains to be established [64▪].

CONCLUSION

The improvement in the comprehension of TMAs' pathophysiology during the past decades has led to a better classification of patients between the different elements of the TMA syndrome. Studies using ADAMTS13 activity as a diagnostic and therapeutic marker for TTP have given new insights and better quality evidence. Outcome of patients admitted to the ICU with a diagnosis of TTP has improved and may get even better with promising new therapeutic tools to come.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Moake JL. Thrombotic microangiopathies. N Engl J Med 2002; 347:589–600.
2. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood 2008; 112:11–18.
3. Kremer Hovinga JA, Lammle B. Role of ADAMTS13 in the pathogenesis, diagnosis, and treatment of thrombotic thrombocytopenic purpura. Hematology Am Soc Hematol Educ Program 2012; 2012:610–616.
4. Coppo P, Veyradier A. Thrombotic microangiopathies: towards a pathophysiology-based classification. Cardiovasc Hematol Disord Drug Targets 2009; 9:36–50.
5. Crawley JT, Scully MA. Thrombotic thrombocytopenic purpura: basic pathophysiology and therapeutic strategies. Hematology Am Soc Hematol Educ Program 2013; 2013:292–299.
6. ■ Lim W, Vesely SK, George JN. The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura. Blood 2015; 125:1526–1531.

State-of-the-art for the use of rituximab in TTP with exhaustive review of the literature on the topic.

7. Dutt T, Scully M. A proposal: the need for thrombotic thrombocytopenic purpura Specialist Centres – providing better outcomes. Br J Haematol 2015; 170:737–742.
8. ■ George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med 2014; 371:654–666.

A nice review detailing the concept and different elements of the TMA syndrome.

9. Veyradier A, Meyer D. Thrombotic thrombocytopenic purpura and its diagnosis. J Thromb Haemost 2005; 3:2420–2427.
10. ■ Benhamou Y, Boelle PY, Baudin B, *et al.* Cardiac troponin-I on diagnosis predicts early death and refractoriness in acquired thrombotic thrombocytopenic purpura. Experience of the French Thrombotic Microangiopathies Reference Center. J Thromb Haemost 2015; 13:293–302.

A retrospective study demonstrating the impact of a detectable troponin level at diagnosis on mortality in TTP patients (odds ratio for death 3.03).

11. Scully M, Hunt BJ, Benjamin S, *et al.* Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012; 158:323–335.
12. Burrus TM, Wijdicks EF, Rabinstein AA. Brain lesions are most often reversible in acute thrombotic thrombocytopenic purpura. Neurology 2009; 73:66–70.
13. Meloni G, Proia A, Antonini G, *et al.* Thrombotic thrombocytopenic purpura: prospective neurologic, neuroimaging and neurophysiologic evaluation. Haematologica 2001; 86:1194–1199.
14. Perez L, Ramappa P, Guzman JA. Myocardial injury in thrombotic thrombocytopenic purpura: a frequent, perplexing complication. Int J Cardiol 2008; 128:257–260.
15. Hawkins BM, Abu-Fadel M, Vesely SK, *et al.* Clinical cardiac involvement in thrombotic thrombocytopenic purpura: a systematic review. Transfusion 2008; 48:382–392.
16. Nichols L, Berg A, Rollins-Raval MA, *et al.* Cardiac injury is a common postmortem finding in thrombotic thrombocytopenic purpura patients: is empiric cardiac monitoring and protection needed? Ther Apher Dial 2015; 19:87–92.
17. Zafrani L, Mariotte E, Darmon M, *et al.* Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity. J Thromb Haemost 2015; 13:380–389.
18. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med 2006; 354:1927–1935.
19. Delmas Y, Helou S, Chabanier P, *et al.* Incidence of obstetrical thrombotic thrombocytopenic purpura in a retrospective study within thrombocytopenic pregnant women. A difficult diagnosis and a treatable disease. BMC Pregnancy Childbirth 2015; 15:137.
20. von Auer C, von Krogh AS, Kremer Hovinga JA, *et al.* Current insights into thrombotic microangiopathies: thrombotic thrombocytopenic purpura and pregnancy. Thromb Res 2015; 135 (Suppl 1):S30–S33.
21. Matsuyama T, Kuwana M, Matsumoto M, *et al.* Heterogeneous pathogenic processes of thrombotic microangiopathies in patients with connective tissue diseases. Thromb Haemost 2009; 102:371–378.
22. Jiang H, An X, Li Y, *et al.* Clinical features and prognostic factors of thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus: a literature review of 105 cases from 1999 to 2011. Clin Rheumatol 2014; 33:419–427.
23. Hart D, Sayer R, Miller R, *et al.* Human immunodeficiency virus associated thrombotic thrombocytopenic purpura: favourable outcome with plasma exchange and prompt initiation of highly active antiretroviral therapy. Br J Haematol 2011; 153:515–519.
24. Brecher ME, Hay SN, Park YA. Is it HIV TTP or HIV-associated thrombotic microangiopathy? J Clin Apher 2008; 23:186–190.
25. Al-Nouri ZL, Reese JA, Terrell DR, *et al.* Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood 2015; 125:616–618.
26. Reese JA, Bougie DW, Curtis BR, *et al.* Drug-induced thrombotic microangiopathy: experience of the Oklahoma Registry and the BloodCenter of Wisconsin. Am J Hematol 2015; 90:406–410.
27. Lechner K, Obermeier HL. Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine (Baltimore) 2012; 91:195–205.
28. Ducos G, Mariotte E, Galicier L, *et al.* Metastatic cancer-related thrombotic microangiopathies: a cohort study. Future Oncol 2014; 10:1727–1734.
29. Kim SS, Patel M, Yum K, *et al.* Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. Transfusion 2015; 55:452–458.
30. George JN, Terrell DR, Vesely SK, *et al.* Thrombotic microangiopathic syndromes associated with drugs, HIV infection, hematopoietic stem cell transplantation and cancer. Presse Med 2012; 41 (3 Pt 2):e177–e188.
31. ■ Sarode R, Bandarenko N, Brecher ME, *et al.* Thrombotic thrombocytopenic purpura: 2012 American Society for Apheresis (ASFA) consensus conference on classification, diagnosis, management, and future research. J Clin Apher 2014; 29:148–167.

Proceedings of the ASFA 2012 consensus conference from respected experts in the field of TTP.

32. Forzley BR, Sontrop JM, Macnab JJ, *et al.* Treating TTP/HUS with plasma exchange: a single centre's 25-year experience. Br J Haematol 2008; 143:100–106.
33. Rock GA, Shumak KH, Buskard NA, *et al.* Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 1991; 325:393–397.
34. Pene F, Vigneau C, Auburtin M, *et al.* Outcome of severe adult thrombotic microangiopathies in the intensive care unit. Intensive Care Med 2005; 31:71–78.
35. ■ Blombery P, Scully M. Management of thrombotic thrombocytopenic purpura: current perspectives. J Blood Med 2014; 5:15–23.

A presentation of the application of the British Committee for Standards in Haematology recommendations for the management of TTP by British experts.

36. Bell WR, Braine HG, Ness PM, *et al.* Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. N Engl J Med 1991; 325:398–403.
37. Balduini CL, Gugliotta L, Luppi M, *et al.* High versus standard dose methylprednisolone in the acute phase of idiopathic thrombotic thrombocytopenic purpura: a randomized study. Ann Hematol 2010; 89:591–596.
38. Dierkes F, Andriopoulos N, Sucker C, *et al.* Indicators of acute and persistent renal damage in adult thrombotic microangiopathy. PLoS One 2012; 7:e30886.
39. Camous L, Veyradier A, Darmon M, *et al.* Macrovascular thrombosis in critically ill patients with thrombotic micro-angiopathies. Intern Emerg Med 2014; 9:267–272.
40. Zhou A, Mehta RS, Smith RE. Outcomes of platelet transfusion in patients with thrombotic thrombocytopenic purpura: a retrospective case series study. Ann Hematol 2015; 94:467–472.
41. Harkness DR, Byrnes JJ, Lian EC, *et al.* Hazard of platelet transfusion in thrombotic thrombocytopenic purpura. JAMA 1981; 246:1931–1933.
42. ■ Riviere E, Saint-Leger M, James C, *et al.* Platelet transfusion and catheter insertion for plasma exchange in patients with thrombotic thrombocytopenic purpura and a low platelet count. Transfusion 2015; 55:1798–1802.

A proposition of algorithm for platelet infusion in TTP patients.

43. Peyvandi F, Lavoretano S, Palla R, *et al.* ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission. Haematologica 2008; 93:232–239.
44. Peyvandi F, Palla R, Lotta LA, *et al.* ADAMTS-13 assays in thrombotic thrombocytopenic purpura. J Thromb Haemost 2010; 8:631–640.
45. Mackie I, Langley K, Chitolie A, *et al.* Discrepancies between ADAMTS13 activity assays in patients with thrombotic microangiopathies. Thromb Haemost 2013; 109:488–496.
46. Thouzeau S, Capdenat S, Stepanian A, *et al.* Evaluation of a commercial assay for ADAMTS13 activity measurement. Thromb Haemost 2013; 110:852–853.

47. Jin M, Casper TC, Cataland SR, *et al.* Relationship between ADAMTS13 activity in clinical remission and the risk of TTP relapse. Br J Haematol 2008; 141:651–658.
48. Rieger M, Mannucci PM, Kremer Hovinga JA, *et al.* ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. Blood 2005; 106:1262–1267.
49. Ferrari S, Mudde GC, Rieger M, *et al.* IgG subclass distribution of anti-ADAMTS13 antibodies in patients with acquired thrombotic thrombocytopenic purpura. J Thromb Haemost 2009; 7:1703–1710.
50. Bettoni G, Palla R, Valsecchi C, *et al.* ADAMTS-13 activity and autoantibodies classes and subclasses as prognostic predictors in acquired thrombotic thrombocytopenic purpura. J Thromb Haemost 2012; 10:1556–1565.
51. Moatti-Cohen M, Garrec C, Wolf M, *et al.* Unexpected frequency of Upshaw-Schulman syndrome in pregnancy-onset thrombotic thrombocytopenic purpura. Blood 2012; 119:5888–5897.
52. Mariotte E, Blet A, Galicier L, *et al.* Unresponsive thrombotic thrombocytopenic purpura in critically ill adults. Intensive Care Med 2013; 39:1272–1281.
53. Liu C, Kallogjeri D, Dynis M, *et al.* Platelet recovery rate during plasma exchange predicts early and late responses in patients with thrombotic thrombocytopenic purpura. Transfusion 2013; 53:1096–1107.
54. Benhamou Y, Assie C, Boelle PY, *et al.* Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. Haematologica 2012; 97:1181–1186.
55. Kremer Hovinga JA, Vesely SK, Terrell DR, *et al.* Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood 2010; 115:1500–1511; quiz 1662.
56. Wyllie BF, Garg AX, Macnab J, *et al.* Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome: a new index predicting response to plasma exchange. Br J Haematol 2006; 132:204–209.
57. Froissart A, Buffet M, Veyradier A, *et al.* Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. Crit Care Med 2012; 40:104–111.
58. Scully M, McDonald V, Cavenagh J, *et al.* A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood 2000; 118:1746–1753.
59. Ziman A, Mitri M, Klapper E, *et al.* Combination vincristine and plasma exchange as initial therapy in patients with thrombotic thrombocytopenic purpura: one institution's experience and review of the literature. Transfusion 2005; 45:41–49.
60. Beloncle F, Buffet M, Coindre JP, *et al.* Splenectomy and/or cyclophosphamide as salvage therapies in thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. Transfusion 2012; 52:2436–2444.
61. Nguyen L, Li X, Duvall D, *et al.* Twice-daily plasma exchange for patients with refractory thrombotic thrombocytopenic purpura: the experience of the Oklahoma Registry, 1989 through 2006. Transfusion 2008; 48:349–357.
62. Hie M, Gay J, Galicier L, *et al.* Preemptive rituximab infusions after remission ■ efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. Blood 2014; 124:204–210.
A retrospective study on the interest of preemptive rituximab infusion in TTP patients with persistent undetectable ADAMTS13 activity during clinical remission of the disease.
63. Westwood JP, Webster H, McGuckin S, *et al.* Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. J Thromb Haemost 2013; 11:481–490.
64. Cataland SR, Wu HM. Acquired thrombotic thrombocytopenic purpura: new ■ therapeutic options and their optimal use. J Thromb Haemost 2015; 13 (Suppl 1):S223–S229.
A good focus on the place of rituximab and the potential place of new therapies (recombinant ADAMTS13 and caplacizumab) in the management of TTP.