Therapeutic plasma exchange-related complications in patients with immune-mediated thrombotic thrombocytopenic purpura

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Background - Daily therapeutic plasma exchange (TPE) is the cornerstone of treatment for immune-mediated thrombotic thrombocytopenic purpura (iTTP). However, TPE is not a risk-free procedure and there is scarce evidence regarding its safety in iTTP. This study aims to describe the TPE-related clinical complications occurred in a cohort of patients hospitalized for an acute iTTP episode.

Materials and methods - In this cross-sectional study, patients hospitalized for an acute iTTP episode at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan) between January 2016 and April 2022 undergoing a central venous catheter (CVC) placement to start TPE were enrolled.

Results - Thirty-three iTTP episodes from 32 patients were included, 20 (61%) first episodes and 2 (6%) complicated with acute exacerbations. Twenty-one episodes (64%) were complicated with at least one major TPE-related complication, 18 (55%) with at least one CVC-related complication, of which 9 (27%) with a major complication. Among major CVC-related complications, 5 were venous thromboses (VTs) requiring heparin treatment and CVC removal, and 3 infections (2 systemic) requiring systemic antibiotic treatment and CVC removal. The 19 CVC-related bleeds (in 16 episodes) were minor bleeds and required only local hemostatic medications. Among the major procedure-related complications, the most common were allergic reactions (present in 16 episodes, 49%), mostly urticarial rashes requiring systemic steroids and antihistamines, and clinical hypocalcemia (in 8 episodes, 24%). The episodes complicated with CVC-related VT or infection required a longer hospitalization and those complicated with CVC-related infection required also a higher number of TPE procedures.

Discussion - TPE procedure was well tolerated in our cohort of acute iTTP patients in the majority of cases, with CVC-related minor bleeds and allergic reactions being the most common complications. The occurrence of CVC-related major complications, as VT or infections, was associated with a longer hospitalization (medians: 30 *vs* 11.5 days).

Keywords: *ADAMTS13, immune thrombocytopenia, thrombosis, thrombotic thrombocytopenic purpura, plasma exchange.*

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INTRODUCTION

Acute immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare life-threatening thrombotic microangiopathy (TMA), requiring urgent treatment[1]. Therapeutic plasma-exchange (TPE), which dramatically reduced disease mortality from 90% to 10-20%[2], is still the cornerstone of acute management and should be initiated as soon as acute iTTP is suspected[3-4]. Although TPE is a life-saving therapy, it is not a risk-free procedure. Considering the urgency of treatment, usually performed empirically (before a confirmed diagnosis), and the hemostatic vulnerability of these patients, who are affected by both thrombotic and bleeding risk, several authors investigated the TPE-related adverse events occurring during acute iTTP management. Overall, findings stemming from these studies, consistently with those involving patients with diseases other than TMAs, confirm that this procedure is well-tolerated in most cases[5-31]. TPE-related adverse events include complications related to the central venous catheter (CVC) insertion (CVC-related) or to the plasma-exchange procedure (procedure-related). The CVC-related complications include local or systemic infections, bleeding episodes, and venous thromboembolisms (VTE), the latter more frequently observed in patients requiring a prolonged TPE therapy and multiple CVC insertions[19]. The most common procedure-related complications are mild allergic reactions as urticaria, citrate-induced hypocalcemia and mild hypotension. The large exchange volume as well as the prolonged duration of therapy increase the risk of major procedure-related complications, such as anaphylaxis or heart failure[18]. In recent years, the progressive reduction of the number of TPE sessions required to achieve clinical remission (as a result of the increasing use of caplacizumab and the early initiation of rituximab), along with the growing use of ultrasound-guided procedures in CVC positioning, have significantly reduced the incidence of these complications[20]. Given the rarity of the disease and the few published data in the field, several questions remain still open. For example, the usefulness of platelet transfusion before CVC insertion in acute iTTP with severe thrombocytopenia is still debated[27-31]. Recently, this topic has gained increasing interest within the scientific and clinical community, driven by growing evidence supporting the efficacy of TPE-free approaches in acute iTTP. Indeed, more and more authors suggest the combination of caplacizumab and immunosuppression as the most appropriate approach in selected cases (based on the TPE-related risk/benefit balance)[32-34]. However, to date, we do not know how identify these patients.

With this background, the present study aims to describe all the TPE-related clinical complications observed during acute management in an Italian cohort of patients hospitalized for an acute episode of iTTP and identify the main related risk factors.

MATERIALS AND METHODS

Study design and patients

In this cross-sectional study, patients hospitalized for an acute iTTP episode at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan between January 2016 and April 2022, who underwent a CVC placement and at least one TPE procedure were enrolled. The diagnosis of iTTP was defined by the presence of both consumptive thrombocytopenia and microangiopathic hemolytic anemia in the absence of alternative causes and confirmed by the severe plasma deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) (activity <10 IU/dL or <10% of normal) and the evidence of anti-ADAMTS13 autoantibodies evaluated using the Technozym ADAMTS13 Inhibitor ELISA kit (Technoclone, Vienna, Austria).

Collected variables

Age, sex, ethnicity, triggers, clinical manifestations, laboratory parameters, concomitant chronic diseases and chronic drugs, acute iTTP episode management, episode outcomes, TPE-related features and complications were retrospectively collected from medical records.

Potential triggers of acute TTP episodes were events occurring or drugs taken in the last three months before the episode onset. All clinical manifestations and laboratory parameters were recorded at the time of the acute TTP episode onset. Clinical manifestations were categorized as: systemic, hemorrhagic, cardiovascular, neurological and renal signs/symptoms. Laboratory exams, performed during the acute phase before plasma infusion or TPE start, included platelet count, hemoglobin, white blood cell count, creatinine, lactate dehydrogenase (LDH), total bilirubin, C-reactive protein (CRP) and prothrombin time (PT). Comorbidities were recorded if self-reported or

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inferred from patient's medications. Drugs were recorded if self-reported to be taken daily for at least 90 days. Multimorbidity was defined as the concomitant presence of two or more chronic diseases in the same patient other than TTP. Polypharmacy was defined as five or more medications daily taken for at least 90 days, excluding TTP-related drugs. Concomitant diseases or conditions were grouped into predisposing or not to thrombosis, bleeding and infection. Recorded TTP-related treatments included transfusional treatments (TPE, plasma infusion or immunoglobulins), immunosuppressive treatments (corticosteroids and rituximab), antiplatelet agents or anticoagulants, and caplacizumab. Finally, episode outcomes included death (during the episode or within 30 days from the onset), episode length, clinical response and acute TTP exacerbation. Clinical response was defined as the sustained normalization of platelet count (≥150,000/μL) for at least two consecutive days. Exacerbation of acute TTP was defined as a platelet count decrease (to less than 150,000/μL) occurring after a clinical response and before a clinical remission within 30 days from stopping TPE or caplacizumab. Episode length was expressed in terms of number of TPE sessions and days of TPE required to achieve clinical response and as the number of days of hospitalization (total and in the intensive care unit, ICU).

Definition and classification of the outcomes

The main TPE-related features were collected, including CVC size, type, site and duration, type of fluid and anticoagulant used, and the daily exchanged plasma volume.

All TPE-related (plasma- or CVC-related) complications, time to the complication onset since CVC insertion and their management have been collected.

We defined major clinical complications as those requiring admission to an intensive care unit, an invasive procedure (e.g., CVC replacement), TPE interruption, systemic treatment, or blood transfusion. Hypocalcemia episodes were recorded only when requiring systemic treatment (major), whereas allergic reactions were distinguished into minor or major, based on the need of local or systemic treatment, respectively. For the CVC-related bleeding episodes we also distinguished major, minor and clinically relevant non major bleeds (CRNMB), according to the International Society on Thrombosis and Haemostasis (ISTH) criteria[35]. Bleeds were also categorized into early or late, according to the time of onset after CVC insertion (within 24 hours or after). The platelet count closest to the date of CVC insertion and bleeding, as well as concomitant clinical conditions or drugs predisposing to bleeding, were also recorded. We defined CVC-related VTEs the deep vein thromboses (DVT) occurring in situ (on the central catheter), complicated or not with pulmonary embolism, which were clinically suspected and confirmed by ultrasonography. We distinguished local infections (on CVC site) and CVC-related systemic infections, diagnosed based on positive blood culture. Clinical conditions or drugs predisposing to VTE or infections were also recorded.

Statistical analysis

A descriptive analysis was performed. Categorical variables were expressed as counts and percentages, continuous variables as medians and interquartile ranges (IQR). The analyses were performed by JMP Pro18 (SAS Institute Inc., Cary, NC, USA). A written informed consent was obtained from all subjects, in accordance with the Helsinki Declaration.

RESULTS

Thirty-two patients (33 iTTP episodes) were included in the study, of which 20/33 (61%) were first episodes. The median age at TTP episode was 52 years and the majority of patients were women. The CVCs were replaced in 5 patients, of whom in a patient was replaced twice (for an acute exacerbation requiring hospitalization and for a CVC dysfunction, respectively) and in the other 4 patients for an adverse event (local bleed, CVC-related systemic infection or CVC dysfunction). Therefore, for the 33 iTTP episodes, a total of 39 CVC were placed, of which the majority were in a common femoral vein. These 32 patients were all treated with corticosteroids and TPE with 1-1.5 units of plasma volume. Caplacizumab was used in 11/33 episodes (frontline in 8/11). The main patient and episode-related features are described in **Table I**.

Thirty episodes (91%) were complicated with at least one TPE-related clinical complication, 64% with at least a major one. Overall, we observed 32 CVC-related complications and 75 procedure-related complications. The most common CVC-related complications were mild cutaneous bleeds on CVC site (No.=19 in 16 episodes). They required treatment with hemostatic medications and occurred within 24 hours from CVC insertion in approximately

Table I - *Main patient- and iTTP episode-related features*

	All iTTP episodes (No.=33)
First iTTP episode, No. (%)	20 (60.6)
Age, years, median (IQR)	52.0 (40-59.3)
Female, No. (%)	20 (60.6)
White ethnicity, No. (%)	31 (93.9)
Concomitant autoimmune disease, No. (%)	11 (33.3)
Platelet count, 10^6/L, median (IQR)[1]	13,000 (9,000-24,500)
Hemoglobin, g/dL, median (IQR)[2]	9.3 (8.2-11.8)
LDH, IU/dL, median (IQR)[3]	657 (420-1,426)
Creatinine, mg/dL, median (IQR)[4]	1.2 (1.1-1.5)
Total bilirubin, mg/dL, median (IQR)[5]	2.2 (1.7-3.0)
Systemic signs/symptoms, No. (%)	26 (78.8)
Hemorrhagic signs/symptoms at onset, No. (%)	24 (72.7)
Neurological signs/symptoms at onset, No. (%)	22 (66.7)
Cardiovascular signs/symptoms, No. (%)	8 (24.2)
Renal signs/symptoms, No. (%)	8 (24.2)
TPE and corticosteroids, No. (%)	33 (100)
Frontline caplacizumab, No. (%)[1]	8 (25)
Rituximab, No. (%)	14 (42.4)
Hospital stay, days, median (IQR)	14 (10-23)
Clinical response, No. (%)	33 (100)

[1]available for 31 episodes; [2]available for 32 episodes; [3]available for 30 episodes; [4]available for 24 episodes; [5]available for 25 episodes. Hospital stay included the two exacerbations (a bleed and a systemic infection occurred during exacerbations). The patient who had a relapse has been considered at two different times. Systemic signs/symptoms: fatigue, fever, abdominal pain, headache, vomiting, jaundice (defined as total bilirubin levels ≥2.5 mg/dL); neurological signs/symptoms: ischemic stroke, transient ischemic attack, epileptic seizures, coma, personality disorders, and focal neurological signs; hemorrhagic signs/symptoms: skin bleeding (purpura, bruising), mucosal bleeds (including epistaxis), hematuria, meno-metrorrhagia, gastrointestinal hemorrhages; cardiovascular signs/symptoms: acute coronary syndrome, electrocardiographic ischemic changes; renal signs/symptoms: acute renal failure, increased creatinine level (>1.3 mg/dL), anuria, need for dialysis, emoglobinuria, proteinuria, oliguria.
Frontline caplacizumab: administered within the first 48 hours since TPE start.
IQR: interquartile range; iTTP: immune-mediated thrombotic thrombocytopenic purpura; LDH: lactate dehydrogenase; TPE: therapeutic plasma-exchange.

one third of episodes (6/16, 37.5%). No major CVC-related bleeds were observed. As regards the other CVC-related complications, a total of 10 major complications occurred in 9 TTP episodes. In particular, we observed 5 VTs (major), 5 CVC dysfunctions (2 major requiring CVC replacement), 1 local infection (major) and 2 CVC-related systemic infections (major).

All the CVC-related venous thromboses occurred in a common femoral vein (3 extended to external iliac vein) and were treated with CVC removal and heparin. Infectious episodes, occurred in 3 cases (9%), included 2 methicillin-resistant *Staphylococcus aureus* (MRSA)-related systemic infections, treated with vancomycin/daptomycin and piperacillin-tazobactam, and 1 *Staphylococcus epidermidis* local infection at the catheter exit site, which required CVC removal and systemic antibiotic therapy with amoxicillin-clavulanic acid.

The most commonly observed procedure-related adverse events were allergic reactions (urticarial rash) requiring systemic treatment with antihistamines and corticosteroids (No.=45 in 16 episodes), and hypocalcemia episodes treated with intravenous calcium gluconate (No.=23 in 8 episodes). Moreover, 5 episodes of hypotension and 2 of acute hypervolemic heart failure were observed (**Table II**).

Table II - *CVC/TPE-related features and clinical complications*

	All iTTP episodes (No.=33)
CVC duration, days, median (IQR)	11 (10-22)
Total number of TPE, median (IQR)	8 (7-14)
At least one TPE-related clinical complication, No. (%)	30 (90.9)
At least one major TPE-related clinical complication, No. (%)	21 (63.6)
CVC-related	
At least one major CVC-related clinical complication, No. (%)	9 (27.3)
At least one bleeding episode, No. (%)	16 (48.5)
Time from CVC insertion to bleeding, days, median (IQR)	5.5 (1-8.3)
VT, No. (%)	5 (15.2)
Time from CVC insertion to VT, days, median (IQR) [1]	18 (14.5-22.5)
Local infection, No. (%)	1 (3)
Systemic infection, No. (%)	2 (6)
Time from CVC insertion to infection, days, median (IQR)	11 (8-11)
CVC dysfunction, No. (%)	5 (15.2)
Pneumothorax, No. (%)	0
Procedure-related	
At least one major procedure-related clinical complication, No. (%)	16 (48.5)
At least one allergic reaction, No. (%)[2]	16 (48.5)
At least one clinical hypocalcemia, No. (%)[3]	8 (24.2)
Hypotension or heart failure, No. (%)	7 (21.2)

[1]available in 3/5 VT episodes; [2]with a median of 3 allergic reactions (range: 1-7); [3]with a median of 3 clinical hypocalcemia (range: 1-6).
For patients with two CVC-related bleeds (No.=3) the time from CVC insertion to the first bleed has been considered. For patients undergoing more than one CVC placement (e.g., for exacerbation or CVC-related major complications), the total duration was defined as the sum of the duration of each placed CVC. The two exacerbation required additional 9 and 5 TPE procedures, respectively.
CVC: central venous catheter; IQR: interquartile range; iTTP: immune-mediated thrombotic thrombocytopenic purpura; TPE: therapeutic plasma-exchange; VT: venous thrombosis.

Episodes complicated with major CVC-related complications (e.g., VTs and infections) were characterized by a significant longer CVC duration and length of hospitalization. Also after adjusting for age and sex, length of hospitalization was confirmed to be significantly associated with major CVC-related complications in a multivariate logistic regression model (unitary OR: 1.30 [95% CI: 1.11-1.71], p<0.001). We observed higher LDH levels in episodes with CVC-related major complications, with no other difference on the main patient and episode-related features between the two groups (**Table III**).

When comparing patient- and episode-related features according to the specific type of CVC-related complication (bleed, VT or infection), no significant difference was found among the three groups, except for the total number of TPE procedures (which was higher in the episodes complicated with CVC-related infections) and length of hospitalization (higher in episodes complicated with CVC-related VT or infection) (*Online Supplementary*, **Table SI**). Moreover, after comparing episodes with vs. without CVC-related bleeding (16 *vs* 17), we observed that CVC-related bleeds occurred in patients with a significantly higher number of comorbidities and higher proportion of polypharmacy and conditions predisposing to bleeding (e.g., chronic liver disease, hematological cancer, antiplatelet drug/anticoagulants). No association was found between platelet count level at CVC placement and the incidence of CVC-related bleeds (p=0.91).

We also compared the prevalence of TPE-related complications between episodes treated with and

Table III - *Patient- and episode-related features in iTTP episodes with and without major CVC-related clinical complications*

	iTTP episodes without major CVC-related complications (No.=24)	iTTP episodes with at least one major CVC-related complication (No.=9)	p-value
1st iTTP episode, No. (%)	15 (62.5)	5 (55.6)	NS
Age, years, median (IQR)	49.8 (33.9-59.2)	57.0 (45.8-63.1)	NS
Female, No. (%)	14 (58.3)	6 (66.7)	NS
Number of comorbidities, median (IQR)	3 (2-5.8)	4 (2.5-8)	NS
Polypharmacy, No. (%)	6 (25.0)	4 (44.4)	NS
Concomitant autoimmunity, No. (%)	9 (37.5)	2 (22.2)	NS
Known allergy to plasma or drugs, No. (%)	9 (37.5)	4 (44.4)	NS
Chronic disease/drug predisposing to bleed, No. (%)	9 (37.5)	5 (55.6)	NS
Chronic disease/drug predisposing to VTE, No. (%)	12 (50)	7 (77.8)	NS
Chronic disease/drug predisposing to infection, No. (%)	13 (54.2)	4 (44.4)	NS
Infectious trigger of acute TTP, No. (%)[1]	12 (54.5)	4 (44.4)	NS
PT, median (IQR)[2]	1.1 (1-1.2)	1.2 (1.1-1.3)	NS
Platelet count, 10^6/L, median (IQR)[3]	13,000 (10,000-28,000)	9,500 (7,500-14,250)	NS
Hb, g/dL, median (IQR)[4]	9.3 (8.1-12.3)	9.1 (8.5-9.6)	NS
Creatinine, mg/dL, median (IQR)[5]	1.2 (1-1.7)	1.2 (1.1-1.3)	NS
LDH, IU/dL, median (IQR)[6]	537 (345-920)	1,552 (1,086-1,716)	**0.0556**
Total bilirubin, mg/dL, median (IQR)[7]	2.1 (1.5-2.8)	2.5 (2.2-3.5)	NS
Hemorrhagic signs/symptoms at onset, No. (%)	18 (75)	6 (66.7)	NS
Neurological signs/symptoms at onset, No. (%)	16 (66.7)	6 (66.7)	NS
Total number of TPE, median (IQR)	8 (7-13)	13 (6-15)	NS
CVC duration, days, median (IQR)	10 (9-16.8)	24 (14.5-30.5)	**0.0123**
Hospital lenght of stay, days, median (IQR)	11.5 (9-16.8)	30 (20.5-39.5)	0.0317

[1]available in 22 and 9 episodes, respectively; [2]available in 21 and 6 episodes; [3]available in 23 and 8 episodes; [4]available in 24 and 8 episodes; [5]available in 16 and 8 episodes; [6]available in 23 and 7 episodes; [7]available in 18 and 7 episodes.

Chronic disease/drug predisposing to bleed included chronic liver disease, hematological cancer, antiplatelet drug/anticoagulants. Chronic disease/drug predisposing to VTE included chronic liver disease, thrombophilia, obesity, hematological cancer, history of TPE, SLE or connective tissue disease. Chronic disease/drug predisposing to infection included history of bone marrow transplantation, hematological cancer, chronic liver disease, COPD, bronchiectasis, type 2 diabetes, chronic steroids or other immunosuppressive therapy, having a vascular or orthopedic prosthesis. Total number of TPE, CVC duration and hospital length of stay included the two exacerbations (a bleed and a systemic infection occurred during exacerbations).

All clinical manifestations and laboratory parameters were recorded at the time of the acute TTP episode onset. Laboratory exams were recorded before plasma infusion or TPE start.

CVC: central venous catheter; IQR: interquartile range; iTTP: immune-mediated thrombotic thrombocytopenic purpura; LDH: lactate dehydrogenase; NS: not significant; SLE: systemic lupus erythematosus; TPE: therapeutic plasma-exchange; VTE: venous thromboembolism.

without frontline caplacizumab (8 *vs* 24). We observed that the episodes treated with caplacizumab within the first 48 hours since TPE start showed a slightly lower proportion of major TPE-related complications (4/8, 50% *vs* 16/24, 66.7%), despite a slightly higher proportion of major CVC-related complications (3/8, 37.5% *vs* 5/24, 20.8%). Indeed, the lower proportion of major TPE-related complication was mostly secondary to the lower proportion of major procedure-related complications (2/8, 25% *vs* 14/24, 58.3%). As regards CVC-related minor bleeds, these were more prevalent in patients treated with frontline caplacizumab (5/8, 62.5% *vs* 10/24, 41.7%).

As regards major procedure-related complications, we did not find any difference comparing the main patient- and episode- related features between the two groups (with and without these complications: 16 *vs* 17) (*data not shown*).

DISCUSSION

In the present study, we evaluated the safety of TPE procedures in 33 acute iTTP episodes.

Among major CVC-related complications, we observed 5 VTs and 3 infections (2 systemic), although the most common CVC-related complications were mild mucocutaneous bleeds. Among major TPE-related complications, the most common were allergic reactions. We found that iTTP episodes complicated with CVC-related VT or infection required a longer hospitalization.

The rationale behind TPE is the replenishment of the deficient protease ADAMTS13 and the removal of the ultra-large multimers of Von Willebrand factor (VWF) and of anti-ADAMTS13 autoantibodies. Although several real-world studies (case series and a retrospective case-control study[32-34]) have been reporting the efficacy of TPE-free approaches, TPE is still considered the cornerstone of acute iTTP management. The TPE-related complications are well described in other diseases. However, data on TPE-related complications in patients with iTTP are still scarce. A study from the Oklahoma TTP registry prospectively reported complications secondary to TPE in patients enrolled from 1996 to 2011[20]. Of 302 patients treated with TPE for an acute episode of TTP or hemolytic uremic syndrome (HUS), 72 (24%) had major TPE-related complications. As regards the 66 patients with severe deficiency of ADAMTS13 activity (<10%), the analysis of the 5 consecutive enrollment cohorts, each lasting three years, showed a significant reduction of the frequency of major TPE-related complications in the most recent years. Authors explained this favorable trend considering the significant progressive reduction of the length of TPE treatment (because of the increased use of rituximab and caplacizumab) and the increasing use of ultrasound-guided maneuvers in CVC placement, reducing the need for CVC replacements. In particular, referring to the most recent cohort of that study (2008-2011, No.=53), which is the time period closest to our study, 11 major complications (in 8 patients, 17%) were observed, including 8 CVC-related ones and 3 procedure-related. The 8 major CVC-related complications included 5 (9.4%) systemic infections, 1 (1.9%) local infections, 1 (1.9%) local hematoma, and 1 (1.9%) CVC dysfunction requiring replacement. No venous thromboses were observed. Among the 3 procedure-related major complications, 2 patients suffered from hypoxia and acute respiratory distress and 1 patient had volume overload. Compared with the study of Som et al, we observed a similar prevalence of systemic infections, but a much higher proportion of CVC-related thromboses and bleeds. However, our data are only partially comparable with those reported by Som *et al.*, because in that study only 22% of the patients (66/302) had a confirmed diagnosis of TTP by evidence of severe ADAMTS13 deficiency.

The complications we observed in our TTP cohort are consistent with those observed in other diseases. Data stemming from other disease cohorts showed that the most common procedure-related complications are usually mild, including fever, urticarial, mild hypotension and clinical hypocalcemia, although major complications, such as sepsis, VTE, anaphylaxis and acute pulmonary edema may occur[5-11]. Also in case of coagulopathies bleeds are usually mild and do not require specific approaches or prophylaxes before CVC insertion[12-16].

Although in iTTP platelet transfusion is contraindicated unless a life-threatening bleeding episode occurs because of the risk of thrombotic complications, the beneficial or harmful role of platelet transfusion before CVC insertion is still debated[27-31]. Our data do not provide a clear answer to this discussed topic. However, in the present study, all bleeds occurring after CVC placement were mild despite the severe thrombocytopenia and platelet count was not associated with the risk of CVC-related bleeds.

We observed that episodes treated with frontline caplacizumab had a slightly higher proportion of CVC-related minor bleeds and CVC-related VTEs, with a lower proportion of procedure-related complications, likely because of the lower number of procedures and exchanged plasma volumes. However, this comparison has to be taken with caution because of the study period including many patients treated in the pre-caplacizumab era or in the first months of caplacizumab era, when disease severity (e.g., with or without organ damage) influenced physician decision to start this drug. In particular, among the 14 episodes occurred after September 2018 (in the caplacizumab era) and not treated with caplacizumab, in 3 cases caplacizumab was not started for the occurrence of severe bleeding manifestations at onset (a case with

subarachnoid hemorrhage and 2 cases with severe macrohematuria), in 4 cases patients were transferred from other hospitals where caplacizumab was not available yet, and in the other 7 cases for clinical decision. Moreover, the very small number of patients treated with caplacizumab and of CVC-related VTEs limits any analyses and final concluding messages.

We found that iTTP episodes complicated with CVC-related major complications (e.g., VTEs, infections) were those where CVC remained in site for more days and required a longer hospitalization. These complications occurred at a median of 11 days (infection) and 18 days (VT) after CVC insertion and likely contributed to further prolong the length of hospital stay.

This is not surprising, considering that these complications may often occur during hospitalizations and are frequently associated with a higher length of hospitalization also in no TTP patients.

Moreover, the three episodes complicated with CVC-related infections required a higher number of TPE procedures. This is consistent with the known strong association between infection and the risk of TTP refractoriness and exacerbation[36-38].

The present study has limitations. Among the main ones, the limited sample size and the retrospective nature of data collection. Despite the aforementioned limits, considering the rarity of the disease and the limited evidence in this field, our findings provide useful information on the safety of TPE in acute iTTP, even more useful considering the changing landscape in acute iTTP management. While TPE remains an effective cornerstone of treatment, our data highlight the occurrence of potentially severe complications, emphasizing the need for strategies to mitigate these risks. Approaches such as premedication with antihistamines (e.g., cetirizine), optimizing catheter management, and careful patient selection may help to reduce adverse events. Notably, the anti-vWF nanobody caplacizumab has shown to be able to reduce the plasma volumes exchanged during TPE procedures and the overall number of needed TPE procedures, leading to a shorter hospital stay. Therefore, there is a growing scientific interest in understanding the possible adverse events related to TPE procedures and in identifying the main patient characteristics associated with a higher risk of complications as well as in exploring alternative therapeutic approaches. Patients with an unfavorable benefit-risk profile may be candidates for these alternative approaches.

In this context, ongoing phase 3 trials, including MAYARI (evaluating caplacizumab plus immunosuppressive drugs without TPE) and VITA (investigating recombinant ADAMTS13, rADAMTS13), aim to further redefine the treatment paradigm for acute iTTP, potentially reducing or even eliminating the need for TPE in selected patients.

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Data sharing statement

For original, deidentified data, please contact the corresponding Author.

Authorship contributions

PA, IM and FP designed the study. PA, CC and CB collected data. PA analysed the data and wrote the first draft of the manuscript. PA, IM, AA, CC, PDL, CB, AT, BF, JAG, NNF, MCM, DP and FP interpreted the data and carefully revised the manuscript.

Disclosure of conflicts of interest

PA received honoraria for participating as a speaker at educational meetings organized by Sanofi. IM received honoraria for participating as a speaker at educational meetings organized by Instrumentation Laboratory and Sanofi. FP has received honoraria for participating as a speaker in education meetings organized by Takeda and Sanofi, and she is member of scientific advisory boards of CSL Behring, Biomarin, Roche, Sanofi, Sobi, Pfizer. DP is Section Editor of Blood Transfusion but had no role in the peer-review process or editorial decision. The other Authors have not conflicts of interest.

REFERENCES

1. Scully M, Cataland S, Coppo P, La Rubia J de, Friedman KD, Kremer HJ et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J. Thromb. Haemost. 2017; 15: 312-322. doi: 10.1111/jth.13571.
2. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, 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. doi: 10.1056/NEJM199108083250604.
3. Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, et al. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J. Thromb. Haemost. 2020; 18: 2486-2495. doi: 10.1111/jth.15006.
4. Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020; 18(10): 2496-2502. doi: 10.1111/jth.15010.
5. Shemin D, Briggs D, Greenan M. Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures. J Clin Apher. 2007; 22(5): 270-276. doi: 10.1002/jca.20143.
6. Yeo FE, Bohen EM, Yuan CM, Sawyers ES, Abbott KC. Therapeutic plasma exchange as a nephrological procedure: a single-center experience. J Clin Apher. 2005; 20(4): 208-216. doi: 10.1002/jca.20059.
7. Lemaire A, Parquet N, Galicier L, Boutboul D, Bertinchamp R, Malphettes M, et al. Plasma exchange in the intensive care unit: Technical aspects and complications. J Clin Apher. 2017; 32(6): 405-412. doi: 10.1002/jca.21529.
8. Sengul Samanci N, Ayer M, Gursu M, Ar MC, Yel K, Ergen A, et al. Patients treated with therapeutic plasma exchange: a single center experience. Transfus Apher Sci. 2014; 51(3): 83-89. doi: 10.1016/j.transci.2014.10.006.
9. Lu J, Zhang L, Xia C, Tao Y. Complications of therapeutic plasma exchange: A retrospective study of 1201 procedures in 435 children. Medicine (Baltimore). 2019; 98(50): e18308. doi: 10.1097/MD.0000000000018308.
10. Erkurt MA, Kuku I, Kaya E, Ozgen U, Berber I, Koroglu M, et al. Therapeutic plasma-exchange in hematologic disease: results from a single center in Eastern Anatolia. Transfus Apher Sci. 2013; 48(3): 335-339. doi: 10.1016/j.transci.2013.04.012.
11. Baumann Kreuziger L, Jaffray J, Carrier M. Epidemiology, diagnosis, prevention and treatment of catheter-related thrombosis in children and adults. Thromb Res. 2017; 157: 64-71. doi: 10.1016/j.thromres.2017.07.002.
12. Doerfler ME, Kaufman B, Goldenberg AS. Central venous catheter placement in patients with disorders of hemostasis. Chest. 1996; 110(1): 185-188. doi: 10.1378/chest.110.1.185.
13. DeLoughery TG, Liebler JM, Simonds V, Goodnight SH. Invasive line placement in critically ill patients: do hemostatic defects matter? Transfusion. 1996; 36(9): 827-831. doi: 10.1046/j.1537-2995.1996.36996420763.x.
14. van de Weerdt EK, Biemond BJ, Zeerleder SS, van Lienden KP, Binnekade JM, Vlaar APJ; Study collaborative. Prophylactic platelet transfusion prior to central venous catheter placement in patients with thrombocytopenia: study protocol for a randomised controlled trial. Trials. 2018; 19(1): 127. doi: 10.1186/s13063-018-2480-3.
15. van de Weerdt EK, Biemond BJ, Baake B, Vermin B, Binnekade JM, van Lienden KP, et al. Central venous catheter placement in coagulopathic patients: risk factors and incidence of bleeding complications. Transfusion. 2017; 57(10): 2512-2525. doi: 10.1111/trf.14248.
16. Kander T, Frigyesi A, Kjeldsen-Kragh J, Karlsson H, Rolander F, Schött U. Bleeding complications after central line insertions: relevance of pre-procedure coagulation tests and institutional transfusion policy. Acta Anaesthesiol Scand. 2013; 57(5): 573-579. doi: 10.1111/aas.12075.
17. McGuckin S, Westwood JP, Webster H, Collier D, Leverett D, Scully M. Characterization of the complications associated with plasma exchange for thrombotic thrombocytopaenic purpura and related thrombotic microangiopathic anaemias: a single institution experience. Vox Sang. 2014; 106(2): 161-166. doi: 10.1111/vox.12090.
18. Reutter JC, Sanders KF, Brecher ME, Jones HG, Bandarenko N. Incidence of allergic reactions with fresh frozen plasma or cryo-supernatant plasma in the treatment of thrombotic thrombocytopenic purpura. J Clin Apher. 2001; 16(3): 134-138. doi: 10.1002/jca.1025.
19. Benhamou Y, Sauvètre G, Grangé S, Veyradier A, Coppo P. [Venous thrombo-embolism during immune-mediated thrombotic thrombocytopenic purpura is prevalent in patients with a prolonged treatment with therapeutic plasma exchange]. Rev Med Interne. 2020; 41(12): 809-813. doi: 10.1016/j.revmed.2020.06.014. [in French.]
20. Som S, Deford CC, Kaiser ML, Terrell DR, Kremer Hovinga JA, Lämmle B, et al. Decreasing frequency of plasma exchange complications in patients treated for thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, 1996 to 2011. Transfusion. 2012; 52(12): 2525-2532; quiz 2524. doi: 10.1111/j.1537-2995.2012.03646.x.
21. Rizvi MA, Vesely SK, George JN, Chandler L, Duvall D, Smith JW, et al. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome. Transfusion. 2000; 40(8): 896-901. doi: 10.1046/j.1537-2995.2000.40080896.x.
22. McClain RS, Terrell DR, Vesely SK, George JN. Plasma exchange complications in patients treated for thrombotic thrombocytopenia purpura-hemolytic uremic syndrome: 2011 to 2014. Transfusion. 2014; 54(12): 3257-3259. doi: 10.1111/trf.12917.
23. McMinn JR Jr, Thomas IA, Terrell DR, Duvall D, Vesely SK, George JN. Complications of plasma exchange in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: a study of 78 additional patients. Transfusion. 2003; 43(3): 415-416. doi: 10.1046/j.1537-2995.2003.00336.x.
24. Nguyen L, Terrell DR, Duvall D, Vesely SK, George JN. Complications of plasma exchange in patients treated for thrombotic thrombocytopenic purpura. IV. An additional study of 43 consecutive patients, 2005 to 2008. Transfusion. 2009; 49(2): 392-394. doi: 10.1111/j.1537-2995.2008.02030.x.
25. Colling M, Sun L, Upadhyay V, Ryu J, Li A, Uhl L, et al. Deaths and complications associated with the management of acute immune thrombotic thrombocytopenic purpura. Transfusion. 2020; 60(4): 841-846. doi: 10.1111/trf.15721.
26. Howard MA, Williams LA, Terrell DR, Duvall D, Vesely SK, George JN. Complications of plasma exchange in patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Transfusion. 2006; 46(1): 154-156. doi: 10.1111/j.1537-2995.2006.00687.x.
27. Swisher KK, Terrell DR, Vesely SK, Kremer Hovinga JA, Lämmle B, George JN. Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. Transfusion. 2009; 49(5): 873-887. doi: 10.1111/j.1537-2995.2008.02082.x.
28. Otrock ZK, Liu C, Grossman BJ. Platelet transfusion in thrombotic thrombocytopenic purpura. Vox Sang. 2015; 109(2): 168-172. doi: 10.1111/vox.12274.
29. Riviere E, Saint-Léger M, James C, Delmas Y, Clouzeau B, Bui N, et al. Platelet transfusion and catheter insertion for plasma exchange in patients with thrombotic thrombocytopenic purpura and a low platelet count. Transfusion. 2015; 55(7): 1798-1802. doi: 10.1111/trf.13041.
30. Duffy SM, Coyle TE. Platelet transfusions and bleeding complications associated with plasma exchange catheter placement in patients with presumed thrombotic thrombocytopenic purpura. J Clin Apher. 2013; 28(5): 356-358. doi: 10.1002/jca.21279.
31. Ong M, Veillon D, Cotelingam J. Is platelet transfusion necessary prior to a central venous catheter placement in thrombotic thrombocytopenic purpura patients? J La State Med Soc. 2012; 164(5): 283-284. PMID: 23362594.
32. Capecchi M, Gazzola G, Agosti P, De Leo P, Mancini I, Ferrari B, et al. Treatment of immune-mediated thrombotic thrombocytopenic purpura without plasma exchange. Haematologica. 2024; 109(6): 2019-2023. doi: 10.3324/haematol.2023.284438.
33. Völker LA, Brinkkoetter PT, Knöbl PN, Krstic M, Kaufeld J, Menne J, et al. Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab. J Thromb Haemost. 2020; 18(11): 3061-3066. doi: 10.1111/jth.15045.
34. Kühne L, Knöbl P, Eller K, Thaler J, Sperr WR, Gleixner K, et al. Management of immune thrombotic thrombocytopenic purpura without therapeutic plasma exchange. Blood. 2024; 144(14): 1486-1495. doi: 10.1182/blood.2023023780.
35. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015; 13(11): 2119-2126. doi: 10.1111/jth.13140. PMID: 26764429.
36. Hussein EA. Idiopathic TTP in the Middle East: Epidemiology and clinical outcomes in infection associated episodes. Transfus Apher Sci. 2020; 59(6): 102916. doi: 10.1016/j.transci.2020.102916.
37. Kanj NA, Mikati AR, Kfoury Baz EM. Early relapse of thrombotic thrombocytopenic purpura during therapeutic plasma exchange associated with Acinetobacter anitratus bacteremia. Ther Apher Dial. 2003; 7(1): 119-121. doi: 10.1046/j.1526-0968.2003.00016.x.
38. Niv E, Segev A, Ellis MH. Staphylococcus aureus bacteremia as a cause of early relapse of thrombotic thrombocytopenic purpura. Transfusion. 2000; 40(9): 1067-1070. doi: 10.1046/j.1537-2995.2000.40091067.x. PMID: 10988308.