

Solvent detergent treated pooled plasma and reduction of allergic transfusion reactions

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BACKGROUND: Thrombotic thrombocytopenic purpura (TTP) patients have increased risk for allergic transfusion reactions (ATR) due to the number of plasma products they require. This study evaluated the efficacy of solvent detergent treated plasma (S/D treated plasma) to reduce ATRs.

STUDY DESIGN AND METHODS: All TTP patients who presented from April 2014 to February 2015 and experienced a moderate–severe ATR to untreated plasma with TPE were switched to S/D treated plasma (Octaplas) for their remaining procedures and included in the study. Patient records were retrospectively reviewed.

RESULTS: The overall ATR rate per procedure decreased from 35.0% (95% CI = 15.4%–59.2%) with untreated plasma to 1.4% ([1/73] 95% CI = 0.0%–7.4%) with S/D treated plasma. The moderate–severe ATR rate decreased from 20.0% ([4/20] 95% CI = 5.7%–43.7%) with untreated plasma to 0.0% ([0/73] 95% CI = 0.0%–4.9%) with S/D treated plasma. The overall ATR rate per plasma unit decreased from 2.6% (95% CI = 1.0%–5.1%) with untreated plasma to 0.1% (95% CI = 0.0%–0.4%) with S/D treated plasma. No patients experienced VTE while receiving untreated plasma. Four patients experienced VTE events while receiving S/D treated plasma. All patients who experienced a VTE had additional risk factors for VTE.

CONCLUSION: S/D plasma has promise as an effective product to reduce the risk of ATRs in TTP patients. Given the high risk of ATR in TTP patients, consideration of S/D plasma instead of untreated plasma for TPE in these patients may be warranted, especially for patients with a history of moderate to severe ATR. More extensive studies are needed to confirm these findings.

In thrombotic thrombocytopenic purpura (TTP), a protease named ADAMTS13 (an acronym for A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, member 13), is central to the pathophysiology of the disease. ADAMTS13 is a normal constituent of plasma and cleaves von Willebrand factor (vWF) multimers secreted from vascular endothelial cells. In TTP, ADAMTS13 levels are severely diminished and ADAMTS13 antibodies are often present. Without normal levels of ADAMTS13 abnormally large vWF multimers are found in the plasma in increased amounts. These large multimers have increased affinity for platelets and induce platelet aggregation, leading to formation of the platelet thrombi that characterize this disease. If left untreated, TTP has an extremely high mortality rate of 90%.¹ Therapeutic plasma exchange (TPE) is the established first-line therapy of choice and drastically improves the mortality rate to 7.5%–20%.^{2,3} TPE treatment with plasma products as the replacement fluid is the

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TABLE 1. Allergic symptoms with untreated plasma versus S/D treated plasma

	Symptoms with untreated plasma	Symptoms with S/D treated plasma
Patient 1	Itching, hives, oropharyngeal edema (multiple episodes); SOB	Itching, eyelid swelling (1 episode)
Patient 2	Respiratory distress, threatened intubation	None
Patient 3	Acute onset of rapid, dry cough	None
Patient 4	Chest tightness, itching	None
Patient 5	Hives, chest tightness, SOB prior to transfer*	None
Patient 6	Hives, chest tightness, SOB prior to transfer*	None

* Per patients' report.
SOB = shortness of breath.

standard of care for TTP treatment; it works by removing ADAMTS13 antibody, and the plasma replacement fluid replenishes ADAMTS13 levels.^{2,4,5}

The large amount of plasma exposure per procedure and number of TPE procedures required places TTP patients at heightened risk of an allergic transfusion reaction (ATR). ATRs can manifest anywhere on a spectrum from mild reactions, such as pruritus and urticaria, to severe or life-threatening reactions such as dyspnea, angioedema and shock.^{6,7} ATRs occur in 1% to 3% of all transfusions, yet 65.8% of TTP patients experience an ATR over the course of their plasma exchange treatments.⁸⁻¹¹ When TTP patients experience moderate to severe ATRs during TPE, the optimal way to proceed with treatment while avoiding the risk of life-threatening ATR is yet to be defined.

Both recipient and donor factors play a role in the likelihood of a patient to develop an ATR and many methods have been attempted to address these factors.¹²⁻¹⁵ One such method, the use of diphenhydramine premedication to prevent ATRs, has deep historical roots. Unfortunately, there is significant evidence that diphenhydramine is ineffective at preventing ATRs when used as a premedication.¹⁶ Other practitioners have

focused on reducing the volume of plasma in transfused components through the blood component concentration, washing, or the use of platelet additive solution platelets in order to reduce ATRs. Several studies have demonstrated reducing the volume of plasma in transfused components does effectively reduce the incidence of ATRs.^{12,14,17,18} However, since plasma is integral to the standard of care for TTP patients and diphenhydramine premedication may be ineffective at preventing ATRs, other strategies to reduce ATRs need to be investigated in this patient population.

Use of solvent detergent treated plasma (S/D treated plasma) in lieu of conventional, untreated plasma is an intriguing strategy to reduce the likelihood of further ATRs, especially moderate to severe ATRs, in this patient population. S/D treated plasma is prepared from a pool of 630-1520 single-donor plasma units; pooling of plasma from many donors would logically reduce ATRs caused by a high dose of allergen from a single donor.¹⁹⁻²³ Indeed, multiple prior studies, including hemovigilance data from several European countries, report a lower rate of ATRs with S/D treated plasma transfusion.^{5,24-26} In addition, the successful use of S/D treated plasma replacement fluid to prevent further severe ATRs in one TTP patient with a history of anaphylaxis while undergoing TPE with untreated plasma was recently reported.²⁷

However, a suggestion to use S/D treated plasma would be incomplete without also addressing the products' history, which may partly correspond to a resistance of its more widespread use in the United States. The first formulation of S/D treated plasma in the United States (V.I. Technologies [VITEX]) was discontinued due to concerns about bleeding and, conversely, thrombotic episodes.²⁸⁻³² One study showed S/D treated plasma has lower levels of clotting factors while others reported decreased levels of inhibitors of clot lysis. However, several studies failed to show a difference in efficacy between S/D treated plasma and untreated plasma in coagulopathic patients.³²⁻³⁶ The first formulation of S/D treated plasma in the United States had nearly absent levels of protein S which may have increased its thrombotic potential. The European formulation of S/D treated plasma has always had only

TABLE 2. Premedication details per procedure with untreated plasma and S/D treated plasma, respectively.

Untreated Plasma					Solvent/Detergent (S/D) Treated Plasma								
Patient 1	Proc.#	1-9 D 25	10 D 50 M 125	Total: 10	Proc.#	1-3 D 50 M 150	4-11,13 D 25 M 125	12 D 50 M 125	14 D 50 M 100	16 None	15, 17-23 D 25	24-25 D 50	Total: 25
Patient 2	Proc.#	1 D 25		Total: 1	Proc.#	1-2,4,12,14-15 D 25	5-11,16 None	- -	- -	- -	- -	- -	Total: 16
Patient 3	Proc.#	1-6 D 25		Total: 6	Proc.#	1-2,9 D 25	3-8 None	- -	- -	- -	- -	- -	Total: 9
Patient 4	Proc.#	1-3 D 25		Total: 3	Proc.#	1-2,4-11,13-23 D 25	3,12 D 50	- -	- -	- -	- -	- -	Total: 23
Patient 5	Proc.#	Unknown -		Total: Unknown	Proc.#	1-3,5-19 D 25	4 None	- -	- -	- -	- -	- -	Total: 19
Patient 6	Proc.#	Unknown -		Total: Unknown	Proc.#	1-5, 7-13 D 25	6,14 None	- -	- -	- -	- -	- -	Total: 14

Proc.=procedure, D=diphenhydramine, M=methylprednisolone, R=ranitidine. All dosages displayed as a number; all dosages given in units of milligrams.

modestly decreased levels of protein S; the VTE rate associated with its use is similar to those reported in patients with TTP or hemolytic uremic syndrome who received untreated plasma or cryoprecipitate.^{5,33–35,37,38} The current formulation of S/D treated plasma in the United States (Octaplas, Octapharma), is quality controlled to have only modest decreases in protein S risks.^{28–32} Further, large studies in Norway and Ireland have demonstrated that use of S/D treated plasma is safe.^{39,40}

Further, S/D treated plasma has the same levels of ADAMTS13 as untreated plasma, and numerous studies have demonstrated S/D treated plasma to be effective in the treatment of TTP.^{4,41} Therefore, this study sought to determine whether use of S/D treated plasma for TPE reduced the occurrence of ATR in TTP patients with a history of moderate to severe ATRs to untreated plasma, particularly a reduction in further moderate–severe ATRs, as well as report on its safety in these patients.

MATERIAL AND METHODS

From April 2014 to February 2015, all patients who experienced a moderate to severe ATR to untreated plasma with TPE were switched to S/D treated plasma (Octaplas, Octapharma, Hoboken, New Jersey) for the remainder of their procedures and were included in the study. Patient records were retrospectively reviewed for the number of S/D treated and untreated plasma units received, number and severity of ATRs, occurrence of venous thromboembolism (VTE), number of VTE events and whether they received VTE prophylaxis. Two of the patients were transferred to our hospital from another institution (Patients #5 and #6). Patient #5 and #6 received all of their TPE with untreated plasma at the outside hospital (OSH); the number of TPE, volume of plasma received, number of ATRs, number of VTE events and whether they received VTE prophylaxis prior to transfer was unknown for these two patients. Line days at the time of VTE could not be determined retrospectively. VTE timing was therefore calculated and reported as TPE procedure number at time of VTE discovery as well as the number of days from the date of first TPE to the date of line removal (if this date could be found and was documented immediately prior to VTE discovery).

For all ATRs that occurred within our institution, the diagnosis of ATRs was documented at the time of reaction by transfusion medicine physicians in consultation with the clinical teams. ATRs were clinically diagnosed by the definitions provided in the AABB Technical Manual and the National Healthcare Safety Network Biovigilance definitions.^{11,42} All diagnosed ATRs were within 4 hours of transfusion and other potential etiologies of an allergic reaction (e.g., medication, food, etc.) were excluded. Only ATRs with imputability categories of definite and probable were counted.

Quantitative analyses were restricted to four patients (Patients #1–4), in whom data on both S/D treated and untreated plasma transfusion and occurrence of ATRs for the entire duration of their hospitalization were known. Individual patient ATR rates per procedure and per plasma

TABLE 3. Overall allergic transfusion reaction (ATR) rate per procedure and per plasma unit received with untreated plasma and S/D treated plasma

Patient	Untreated plasma					Solvent/detergent (S/D) treated plasma				
	No. overall ATR	No. moderate–severe ATR	No. procedures	No. units	ATR per procedure rate (%)	ATR per unit rate (%)	No. overall ATR	No. moderate–severe ATR	No. procedures	No. units
Patient 1	4	1	10	147	40.0	2.7	1	0	25	510
Patient 2	1	1	1	7	100.0	14.3	0	0	16	301
Patient 3	1	1	6	80	16.7	1.3	0	0	9	160
Patient 4	1	1	3	40	33.3	2.5	0	0	23	440
Patient 5*	–	–	–	–	–	–	0	0	9	255
Patient 6*	–	–	–	–	–	–	0	0	17	338
Overall†	7	4	20	274	35.0	2.6	1	0	73	1411

* S/D Patients #5 and #6 received all of their TPE with untreated plasma at the OSH; the exact number of TPE procedures and ATRs prior to transfer was unknown.

† Overall values only include Patients #1–4, in whom data on plasma transfusion and occurrence of ATRs was available for the entire duration of their hospitalization. ATR = allergic transfusion reaction; No. = number; mL = milliliter.

TABLE 4. Details of number, prophylaxis and/or treatment, type, timing and risk factors for VTE occurring with untreated and S/D treated plasma procedures

	Untreated plasma				Solvent/Detergent (S/D) treated plasma					
	No. VTE	Prophylaxis/ Treatment	Total No. procedures	VTE risk factors	No. VTE	VTE Type/ Location	VTE Prophylaxis/ Treatment	Total No. procedures	VTE timing (Days, procedure No.)	VTE risk factors
Patient 1	0	None	10	Indwelling catheter	1	Catheter associated/RIJ	None	25	13, 21	Indwelling catheter
Patient 2	0	Heparin (SC)	1	Indwelling catheter	1	Catheter associated/RIJ	None [‡]	16	5, 4	Indwelling catheter, 7 days without VTE prophylaxis [‡]
Patient 3	0	None	6	History of stroke, outpatient warfarin stopped [§] Complete immobilization	4	1. PICC line associated/RIJ 2. Non-catheter/LIJ 3. Non-catheter/RF 4. PE	None None None Low dose heparin drip × 4 days [¶]	9	<u>VTE #1-3: 18, 5</u> <u>VTE #4: 22, 8</u>	History of stroke, outpatient warfarin stopped, [§] complete immobilization Only low dose heparin started for VTE treatment [¶]
Patient 4	0	TEDS	3	Indwelling catheter, obesity	0	–	TEDS	23	–	Indwelling catheter, obesity
Patient 5	–	Unknown	–	Unknown	0	–	None	9	–	Indwelling catheter
Patient 6	–	Unknown	–	Unknown	1	Catheter associated/RIJ	None	17	23,18	Indwelling catheter
Overall**	0	–	20	–	7	4 line associated, 3 non-catheter	–	99	–	–

VTE = venous thromboembolism; RIJ = right internal jugular; SC = subcutaneous; PICC = peripherally inserted central catheter; LIJ = left internal jugular; RF = right distal femoral vein; PE = pulmonary embolus; TEDS = thromboembolic deterrent stockings.

* Data regarding VTE events while patients were receiving untreated plasma was not available for patients #5 and #6, whom received all TPE with untreated plasma at OSHs.

† Calculated as first day of therapeutic plasma exchange to date of VTE diagnosis.

‡ SC heparin discontinued for 7 days prior to VTE because patient was discharged home.

§ Outpatient warfarin stopped due to presence of subarachnoid hemorrhage (SAH) on admission.

|| Patient was intubated and sedated for the duration of hospital admission.

¶ Low dose heparin started after VTE #1-3 and administered for 4 days prior to subsequent VTE. Low dose selected over standard dose given concurrent SAH.

** Overall values only include patients #1-4, in whom data on VTE events and prophylaxis was available for the entire duration of their hospitalization.

unit were calculated as the number of ATRs divided by the number of procedures or number of plasma units, respectively. ATR rates were calculated separately for procedures using untreated plasma versus procedures using S/D treated plasma. The overall ATR rates per procedure and per plasma unit were calculated as the number of ATRs experienced by all of the patients divided by the total number of procedures or total units of plasma received, respectively. Total plasma volumes received by each patient could not be obtained retrospectively. Therefore, the total TPE procedure volumes, inclusive of the volume of saline and citrate infused, were utilized to calculate the total volumes of untreated and treated plasma received. Exact 95% confidence intervals (95% CI) were calculated from a binomial distribution. VTE data were descriptively described. The study was approved by the Johns Hopkins Medical Institutions Institutional Review Board.

RESULTS

Allergic symptoms in all patients with TTP who were switched to S/D treated plasma replacement following a moderate to severe ATR to untreated plasma are reported in Table 1. Patients #5 and #6 both reported moderate to severe ATR symptoms to untreated plasma prior to transfer from an OSH; both patients received S/D treated plasma for their entire TPE course at our institution. Patients #1-4 received between 7 and 147 untreated plasma units before switching to S/D treated plasma and between 160 and 510 units of S/D treated plasma. Patients #1-4 each received a greater number of TPE procedures with S/D treated plasma than untreated plasma and a greater number of S/D treated plasma units than untreated plasma units. In addition, Patients #1-4 each received a greater volume of S/D treated plasma (122,198 mL, 68,510 mL, 36,996 mL, 106,856 mL, respectively) than untreated plasma (51,127 mL, 2573 mL, 28,730 mL and 14,214 mL, respectively).

Patients received premedication with 25 mg of diphenhydramine for the majority of their procedures, before and after switching to S/D treated plasma. They also received premedication with other dosages of diphenhydramine, alone and in combination with other medications for many procedures. For a minority of procedures, before and after switching to S/D treated plasma, patients received no premedication (Table 2).

For Patients #1-4 at an individual level, ATRs occurred in 16.7%-100% of their untreated plasma TPE procedures versus 0%-4% of their S/D treated plasma TPE procedures (Table 3). The overall ATR rate per procedure decreased from 35.0% (95% CI = 15.4%-59.2%) with untreated plasma replacement to 1.4% (95% CI = 0.0%-7.4%) with S/D treated plasma replacement. The overall ATR rate per plasma unit decreased from 2.6% (95% CI: 1.0%-5.2%) with untreated plasma to 0.1% (95% CI: 0.0%-0.4%) with S/D treated plasma. The moderate-severe ATR rate per procedure with

untreated plasma was 20.0% ([4/20] 95% CI = 5.7%-43.7%) and 0.0% after switching to S/D treated plasma ([0/73], 95% CI = 0.0%-4.9%). Only one patient (Patient 1) had a mild ATR after switching to S/D treated plasma (Table 1); this occurred during their 32nd procedure (out of 35 total); for this procedure, Patient 1 had received premedication consisting of 25 mg diphenhydramine and symptoms resolved with additional provision of 25 mg IV diphenhydramine during the procedure.

Thrombosis and adverse events

None of the four patients who underwent plasma exchange with untreated plasma at our hospital experienced a VTE. Four of the six patients (66.7%) who underwent plasma exchange with S/D treated plasma at our hospital experienced at least one VTE while receiving S/D treated plasma replacement. One of these six patients (16.7%), whom had significant VTE risk factors (Patient #3), experienced two non-catheter associated VTE events. The remainder of VTE events were line associated (Table 4).

DISCUSSION

As diphenhydramine has no proven efficacy in decreasing the risk of ATRs, other strategies, including those focused on donor-based factors, warrant consideration.¹⁶ This is particularly important in TTP patients given their heightened risk of ATRs and their reliance on plasma, which eliminates volume mitigation strategies as a means to decrease ATR risk. Pooling strategies, such as those devised in S/D treated plasma, remain a viable donor product-based strategy to reduce ATR risk in plasma dependent patients. This study demonstrates a correlation between the use of S/D treated plasma for replacement fluid in TPE and a substantially reduced rate of both mild and moderate ATRs in TTP patients.

In our study, 0 out of 4 patients experienced a VTE event while receiving untreated plasma and 4 out of 6 patients experienced line associated VTE events while receiving S/D treated plasma. We therefore cannot rule out the possibility that the line associated VTE events were correlated with S/D treated plasma. However, it is worth noting that each patient had indwelling catheters, which are a known risk factor for VTE in general, and none of these patients were receiving VTE prophylaxis at the time of the VTE event.³⁷ Further, all patients received more procedures with S/D treated plasma and a higher overall volume of S/D treated plasma than untreated plasma at the time their VTE was noted. It is possible their VTE events were merely temporally associated, rather than correlated, with S/D treated plasma replacement. Importantly, the line-associated VTE events were all successfully treated without complication. Non-line associated VTE events occurred only in one patient (Patient #3); whom experienced two non-catheter

associated VTE events. We cannot rule out that these two non-catheter associated VTE events were correlated with S/D treated plasma. However, Patient #3 was not receiving VTE prophylaxis at the time of the first non-catheter associated VTE event, received 4 days of only low dose heparin (as treatment for the first non-catheter associated VTE) at the time of the second non-catheter associated VTE event, had significant additional risk factors for VTE, and the two non-catheter associated events in this patient were clinically attributed to those additional risk factors.

Given the small number of patients in our study and the difficulty in concluding a relationship between VTE events and S/D plasma, it is worth noting that reservations both for increased risk of thrombosis and conversely, increased risk of bleeding, with S/D treated plasma have not withstood critical review within the literature at large.^{11,24,25,42,43} The reports of thrombotic episodes in nine patients which led to withdrawal of the first formulation of S/D plasma (VITEX) were attributed to the nearly absent levels of protein S in that formulation.²⁸⁻³⁰ However, this issue has been addressed in the newest formulation of S/D plasma (Octaplas, Octapharma) for which protein S level is quality controlled (must be equivalent to ≥ 0.4 International Units (IU)/mL or $\geq 40\%$ of the normal range).^{31,32} In addition, a large Norwegian study including neonates and liver transplant patients showed no adverse events related to S/D treated plasma administration.³⁹ Data from Ireland following adoption of exclusive use of S/D treated plasma demonstrates it is safe.⁴⁰ Conversely, concerns regarding bleeding risks have stemmed from reports of decreased levels of procoagulants in S/D plasma products. One study showed that S/D treated plasma has lower levels of clotting factors, increased prothrombin time and activated prothrombin time compared to untreated plasma. Others have also reported alpha-2 antiplasmin (also known as plasmin inhibitor, an inhibitor of clot lysis) is selectively decreased in S/D treated plasma by about 80%. However, several studies have failed to demonstrate a clinical difference in efficacy between untreated plasma and S/D treated plasma in coagulopathic patients, including patients undergoing open heart surgery, with liver disease or undergoing liver transplantation or with prolonged prothrombin times.^{25,44-48} In addition Norwegian and Irish data support the clinical efficacy of S/D treated plasma.^{39,40}

Further, European reports include data to support the efficacy of S/D treated plasma in reducing ATRs. Hemovigilance data from Norway, Finland, France and United Kingdom (which maintains a dual inventory of S/D treated plasma and untreated plasma) demonstrate a lower rate of ATRs with S/D treated plasma.^{24,25,49} An individual British center reported similar findings in their TTP patients; they found a 9.3% rate of ATR with TPE performed with cryo-poor plasma and a 3.1% rate in patients receiving S/D treated plasma.⁵ In our study, the overall ATR rate in patients with a history of moderate-severe ATR to untreated plasma decreased by 96.1% and the rate of moderate-severe ATR decreased from 20.0 to 0% when

switched to S/D treated plasma. This is particularly interesting as studies have previously observed that ATRs tend to recur in some patients but not others, suggesting that some patients have greater susceptibility to ATRs.¹⁵ Thus, our patients who had a history of moderate-severe ATR to untreated plasma should be at higher risk for recurrent ATR but nonetheless, their ATR rate decreased when switched to S/D treated plasma and they experienced no further moderate-severe ATRs.

There are a few limitations to this study. The total TPE run volume was used as the volume of untreated and S/D treated plasma, even though this volume includes the volume of citrate and saline. Therefore, this volume overcalculates the volume of plasma received by each patient, but would be expected to affect both the untreated volume of plasma and S/D treated volume of plasma. Further, while exact volumes (exclusive of citrate and saline) of untreated and S/D treated plasma could not be obtained, it is clear from the greater number of procedures with S/D treated plasma that patients #1-4 received much higher volumes of S/D treated plasma than untreated plasma in line with the total volumes reported. While we saw a marked reduction in overall ATRs and no further moderate-severe ATRs after switching to S/D treated plasma, the number of patients is limited and the data presented may not be generalizable. Demonstration of a change in rate of mild ATRs is limited by inconsistent reporting for mild ATRs; however, this would affect patients prior to and following the switch to S/D treated plasma and would bias results to the null. Moderate-severe ATRs are more accurately reported and confirm the results. In addition, a recent analysis of the Trial to Reduce Alloimmunization to Platelets (TRAP) study demonstrated that risk of ATR reactions reduces with increasing numbers of transfusions.⁵⁰ We therefore cannot say if the reduced rate of ATRs in patients receiving S/D treated plasma was correlated with S/D treated plasma replacement or was merely temporally associated. Data on the number of ATRs that transfer patients experienced prior to transfer was also unable to be obtained. In addition, diphenhydramine premedication was used inconsistently for the majority of the patients' procedures, and other premedication such as steroids were used inconsistently, making it impossible to exclude their contribution to reduction in ATR symptoms. However, diphenhydramine is unlikely to explain the reduced rate of ATR in that diphenhydramine premedication was provided both before and after switching to S/D treated plasma and has no proven efficacy at preventing ATRs in multiple studies.¹⁶ In addition, while we observed higher rates of line-associated VTE events while patients were receiving S/D treated plasma replacement fluid, the presence of several confounding variables (indwelling catheters, lack of VTE prophylaxis in these patients, higher number of procedures with and volume of S/D treated plasma received at the time of VTE event), makes it difficult to conclude whether these VTE events were correlated with S/D treated plasma, the patients' VTE risk factors, or merely temporally associated with S/D plasma administration. In addition, for catheter-associated VTEs we were unable to determine the line days at the time of

VTE discovery. While the date from time of catheter insertion to either VTE discovery or line removal could be calculated, we were unable to exclude the possibility that a catheter had been removed and replaced during that time. This makes it difficult to assess the degree of VTE risk expected from this specific confounding variable. While one patient experienced two non-catheter associated VTE events while receiving S/D treated plasma; it is difficult to conclude whether these were correlated with S/D treated plasma or the patients other VTE risk factors, to which the clinical team attributed these VTE events. However, several studies have reported that S/D treated plasma is safe; it has completely replaced untreated plasma in Ireland, and is used by at least some centers as their first-line replacement of choice for TPE in TTP patients.^{5,39,40}

From available research and our small data set, S/D treated plasma appears to have promise as a safe, effective product to reduce the risk of ATR in TTP patients with a history of ATR to untreated plasma products. Given the high risk of ATR in patients with TTP, consideration of standard use of S/D treated plasma instead of untreated plasma for TPE in these patients may be warranted in patients without significant risk factors for VTE. Even in centers where standard use of S/D treated plasma is not practical, S/D treated plasma should be utilized for patients with a history of moderate-severe ATR without significant risk factors for VTE. As most patients with TTP are expected to have risk for VTE related to the prothrombotic state of TTP, indwelling central venous catheters and immobility; use of VTE prophylaxis should be considered regardless of whether or not S/D treated plasma is utilized.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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