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Von Willebrand factor as a thrombotic and inflammatory mediator in critical illness

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Abstract

The endothelial exocytosis of high-molecular-weight multimeric von Willebrand factor (vWF) may occur in critical illness states, including trauma and sepsis, leading to the sustained elevation and altered composition of plasma vWF. These critical illnesses involve the common process of sympathoadrenal activation and loss of the endothelial glycocalyx. As a prothrombotic and proinflammatory molecule that interacts with the endothelium, the alterations exhibited by vWF in critical illness have been implicated in the development and damaging effects of downstream pathologies, such as disseminated intravascular coagulation and systemic inflammatory response syndrome. Given the role of vWF in these pathologies, there has been a recent push to further understand how the molecule may be involved in the pathophysiology of related diseases, such as trauma-induced coagulopathy and acute renal injury, which are also known to develop secondarily to critical illness states. Elucidation of the role of vWF across the broader spectrum of generalized pathologies may provide a basis for the development of novel preventative and restorative measures, while also bolstering the scaffold of more widely used treatments, such as the administration of plasma-containing blood products.

SUMMARY

Von Willebrand Factor (vWF), a concatemeric glycoprotein composed of 500-kDa dimeric units, is synthesized within megakaryocytes and endothelial cells and functions as an integral mediator of both hemostasis and inflammation.[1–6] In critical illness states, such as trauma, sepsis, and burns, sympathoadrenal activation and loss of the endothelial glycocalyx may instigate a shift toward a prothrombotic vascular endothelium, leading to large, swift increases in vWF, accompanied by concomitant decreases in the vWF cleaving protease, ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type-1 repeats 13).[7–17] Much of the work that has previously focused on endotheliopathy of critical injury has targeted markers such as syndecan-1, soluble thrombomodulin, and

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plasma adrenaline levels. However, vWF, functioning as an inflammatory anchor to platelets at the hematologic-endothelial junction, emerges as a significant, yet neglected, mediator of the downstream effects of endothelial breakdown and hematologic dysregulation. This review article seeks to unravel the roles of vWF in the development of posttraumatic pathologies and appreciate these functions under the guidance of data that examine its inflammatory, hemostatic, and prothrombotic effects in critical injury as well as the effect of vWF on clinical practices in transfusion.

vWF STORAGE AND REGULATION

Within platelets, vWF is packaged into alpha granules,[18] while the circulatory endothelium stores the protein in Weibel-Palade bodies (WPBs).[19] In addition to vWF, WPBs contain a host of factors that contribute to inflammation and angiogenesis, such as interleukin-6, interleukin-8, and angiopoietin-2.[4] These molecules can be variably packaged, dependent upon cues from their surrounding microenvironment, such as shear force and chemical signaling. By means of packaging vWF into WPBs, vessels are able to respond swiftly and contribute considerably to a broad spectrum of vascular processes, including both subendothelial and endothelial platelet adhesion, platelet aggregation, factor VIII chaperoning, and an immediate inflammatory response to endothelial injury or activation.[1–4]

Deficiency of vWF in type 1 von Willebrand disease (vWD) is the most common inherited disorder of hemostasis and is typically characterized by mild mucosal bleeding.[5] vWF is classically known for its function in platelet adhesion by means of binding platelet glycoprotein 1b via the vWF A1 domain; mutations in glycoprotein 1b lead to congenital bleeding disorders such as Bernard-Soulier and platelet-type vWD.[20] Similarly, mutations in the vWF A1 domain may result in decreased (as in type 2A vWD) or increased affinity for platelets (as in type 2B vWD), leading to a bleeding diathesis, as well.

In static solution, the vWF molecule is coiled on itself in an inactive form; however, vWF responds dynamically to promote hemostasis, elongating and activating as shear rate increases.[21] This environmentally mediated activation promotes the localization of vWF to sites of thrombus formation, as shear rate is elevated due to irregularities in the arterial wall.[22] Interestingly, as vWF grows in multimeric size, it also increases in prothrombotic and proinflammatory effect.[23,24] These size-dependent factors contribute to the deposition of hyaline thrombi that are pathologically seen in the distal arterioles and capillaries in thrombotic thrombocytopenic purpura (TTP), a disease that is caused by a deficiency of ADAMTS13.[25] Notably, TTP highlights the utility of ADAMTS13 within the circulation, given that the inadequate cleavage of vWF leads to the accumulation of these ultra-large vWF forms, which demonstrate increased activity and lead to thrombotic microangiopathy.

Although ADAMTS13 is thought to be the primary protease that affects vWF, it should be noted that multiple other proteases are capable of its cleavage. Specifically, leukocytes release factors following their activation that lead to vWF degradation at or near the ADAMTS13 cleavage site within the A2 domain.[26] These cleavage sites become important when examining vWF as a molecule that is active not only in hemostasis but at the frontlines of inflammation as well. vWF's functionality in the immune response is

emphasized in both a vWF-deficient and an anti-vWF–injected mouse model of immune complex vasculitis, where cutaneous leukocyte recruitment could be reduced by 50% to 65% when compared to wild-type mice.[6] Interestingly, the recruitment of leukocytes, especially neutrophils, appears to function as a mechanism by which vWF may be further actuated at the site of inflammation. Under shear stress, vWF is sensitive to oxidative compounds, such as hypochlorous acid, which are generated following recruitment and activation of neutrophils. These molecules oxidize accessible sulfur-containing residues, including methionine and cysteine. Importantly, one such methionine residue is included in the vWF Tyr1605-Met1606 scissile bond; once converted into a methionine sulfoxide, the vWF molecule is provided resistance to cleavage and inactivation by ADAMTS13.[27] Thus, an important balance of vWF-driven inflammation is likely maintained by means of the oxidative environment, preventing vWF cleavage, and the vWF breakdown that is produced by leukocyte proteases at sites of vWF deposition.

SYSTEMIC ROLE OF vWF IN COAGULOPATHY AND INFLAMMATION FOLLOWING CRITICAL INJURY

Disseminated intravascular coagulation (DIC) may appear in critically ill patients, particularly sepsis, as a devastating coagulopathy that is characterized by the widespread thrombosis of the small vasculature due to hyperactivation of coagulation and inflammatory responses.[28,29] This hyperactivation leads to factor consumption and increased fibrin degradation products, contributing to platelet malfunction and leading to profuse hemorrhaging from various sites. Notably, vWF levels were increased 4.5-fold, while ADAMTS13 activities were decreased threefold in all-cause DIC when compared to healthy patients.[30] These data suggest that vWF is excessively released due to systemic endothelial activation. These persistently increased levels of vWF result in platelet sequestration with subsequent formation of microthrombi, impairing blood flow and exacerbating ischemic injury.[31] The depressed ADAMTS13 activity levels have also been shown to be a prognostic biomarker of poor outcomes in those with DIC secondary to severe sepsis.[32] In addition to supportive care, replenishment of ADAMTS13, as well as fibrinogen and other coagulation factors, via therapeutic plasma exchange has been shown to have a positive impact on coagulopathy and survival in these critically ill patients.[33,34]

Rusu et al.[35] have previously demonstrated that the interaction between soluble N-ethylmaleimide sensitive factor-attachment protein alpha (αSNAP) and guanine nucleotide-binding alpha-subunit 12 (Gα12) is necessary for both the basal and thrombin-induced secretion of vWF from endothelial cells. Recently, Rusu et al. have reported that, through the generation of an inhibitory peptide targeted against αSNAP, the direct interaction between αSNAP and Gα12 could be hindered.[36] By preventing this interaction, the researchers demonstrated decreased membrane fusion events of WPBs and, therefore, less vWF secretion. When the inhibitory peptide was tested in mice that had undergone a cecal ligation and puncture (CLP) to induce sepsis, there were both reduced plasma vWF levels and markers of microvascular thrombosis of the kidney.[35,36] Furthermore, it was found that while all wild-type mice had died by 96 hours in the CLP model, homozygous Gα12 knockouts demonstrated reduced vWF levels and 100% survival. Thus, given the positive

impact of vWF exocytotic inhibition in this sepsis model of DIC, it appears that vWF may play a direct role in the downstream damage that is caused by coagulopathy of critical injury.[36]

Specific to traumatic injury, trauma-induced coagulopathy (TIC) appears to stem from various factors including shock, hemodilution, hypothermia, inflammation, and acidemia.[37] In addition, there are unique, trauma-derived mechanisms that result in an endogenous coagulopathy, making TIC a separate disease entity from DIC.[38,39] Nevertheless, in some patients after severe injury, the pathophysiology of TIC largely resembles DIC, including decreased fibrinogen levels and antithrombin III, in addition to increased prothrombin time and thrombin–antithrombin III complexes. As such, some have argued that TIC is simply "DIC with a fibrinolytic phenotype." However, DIC may be juxtaposed with TIC in that it leads to low platelet counts and normal to low peak thrombin generation, suggesting that the two pathologies can be categorized and evaluated as distinct entities.[38,40–43]

Patients with TIC tend to have ratios of peak thrombin generation to isolated thrombin activity that are two- to sixfold higher than healthy patients and trauma patients who do not develop TIC.[44] However, at the same time, these patients have functional reductions in clot generation and clot strength.[45] Similar to the shift that is seen in DIC with increased levels of prothrombotic vWF, these changes suggest an imbalance in the pro- versus anticoagulant axis, where procoagulants that drive TIC, including vWF, tissue factor, phospholipids, collagen, and platelet-derived extracellular vesicles are released into the circulation.[46–48] As suggested above, patients with TIC also demonstrate a hyperfibrinolytic phenotype that appears to be primarily characterized by fivefold normal levels of activated protein C.[49] Importantly, TIC was attenuated in transgenic mice that lacked the capability to activate protein C, underlining its importance in the pathology. Interestingly, recent data have demonstrated that there is a sustained increase in vWF antigen, vWF activity, and proportion of high-molecular-weight vWF forms in the days following traumatic injury, suggesting movement toward a prothrombotic and proinflammatory phenotype within the circulation[50]; furthermore, low ADAMTS13 levels have been linked to worse outcomes in these patients.[51] While knowledge regarding the contribution of vWF to the development of TIC is rather limited, advances with respect to understanding TIC following traumatic brain injury (TBI) are highlighted later in this article and may provide insight into the role that vWF is playing.[14–16]

In addition to the procoagulant and prothrombotic states that may be generated due to critical injury, such as DIC and TIC, a widespread reaction known as systemic inflammatory response syndrome (SIRS) may develop as well. This syndrome is characterized by increased levels of proinflammatory cytokines and complement, causing the excessive activation of immune cells, increasing the risk of organ damage and death.[52] vWF is well known to be increased in SIRS, and has been noted at levels 11-fold greater than healthy subjects.[17] More recent evidence indicates that while the stimulated release of vWF in SIRS is not predictive of mortality, levels of vWF found in an active conformation may be used prognostically to predict 28-day mortality in patients suffering from SIRS.[53]

Although discrete entities, TIC, DIC, and SIRS, exist on an excessively complex axis that spans the bounds of hemostasis and inflammation. While vWF has been implicated within these processes, its mechanistic contributions within the pathologies are still in need of evaluation. For these reasons, the following sections will specifically examine the current data surrounding the effects of vWF in various areas of medicine. We will first evaluate how methodologies of transfusion-based treatments have evolved due to recent research that focuses on vWF and ADAMTS13. We will then examine vWF contributions to coagulopathy and inflammation, subsequent to an inciting event such as TBI. Finally, we will expand on how, in addition to its systemic effects, vWF may mediate end-organ damage, secondary to various critical injuries.

EFFECT OF vWF ON CLINICAL MANAGEMENT WITH BLOOD PRODUCTS

In traumatic injury with hemorrhage, hemostatic resuscitation with agents containing coagulation factors, including vWF, can mitigate bleeding.[54,55] Similarly, other diseases that result in excessive endothelial injury and inflammation, such as severe sepsis or burns may interfere with the normal release and processing of vWF, causing microvascular thromboses and altering the hemostatic response.[56] In this section, blood products that impact vWF concentrations or metabolism in various conditions with altered vWF profiles will be reviewed.

Plasma-containing blood products have varying amounts of vWF present in them. When addressing issues with the vWF-platelet-ADAMTS13 axis, four blood products may be considered for transfusions: plasma, cryoprecipitate, platelets, and whole blood (see Table 1). Plasma, by definition, contains normal physiologic amounts of vWF and ADAMTS13 in addition to all other coagulation factors; as it is almost always an acellular product and typically frozen prior to being thawed for transfusion, no platelets are present.[57] Cryoprecipitate that is produced from slowly thawed plasma and then refrozen contains enriched quantities of vWF and ADAMTS13 activity, albeit in a smaller volume; it is also an acellular blood product and contains increased concentrations of factors VIII and XIII, fibronectin, and fibrinogen, but has lower amounts of other coagulation factors.[58] Platelets that are immersed in plasma contain at least 3.0×10^{11} platelets per apheresis-collected unit, along with other coagulation factors typically present in plasma.[59] Whole blood also contains plasma and all of its normal coagulation factors.[60] The decision to transfuse these particular blood products depends on specific clinical situation and precise vWF derangement. Importantly, vWF formulations that are risk reduced from an infectious disease perspective exist if vWF replacement is required.

Although not specific to patients with critical injuries, it is important to highlight the extremes of vWF derangements that are demonstrated by vWD and TTP, so that more subtle alterations in other conditions can be appreciated. While multiple subtypes of vWD exist, with each having their own unique clinical and laboratory presentations, the unifying theme is bleeding or elevated risk of bleeding that requires correction by increasing vWF concentrations (either endogenously or exogenously).[61] On the other end of the vWF dysregulation spectrum, as exemplified by TTP, abnormal increases in vWF due to decreased ADAMTS13 enzyme activity leads to platelet-vWF–rich microthrombi

that impair blood flow throughout the body, causing ischemic injury to all major organ systems.[62] Management of TTP includes administration of ADAMTS13 via plasma transfusion (therapeutic plasma exchange for acquired TTP versus plasma transfusion for congenital TTP).[33] In severe sepsis or traumatic injury, elements of either bleeding, clotting, or both may be present and need to be addressed.

In traumatic injury, coagulation factors are lost or consumed due to hemorrhage and its attendant effects.[39] The tenets of hemostatic resuscitation in the care of trauma patients appropriately emphasize replacement of these lost coagulation factors with plasma products. All of the plasma-containing blood products can be transfused at various times in various ratios as part of resuscitating these patients.[54,55] However, unlike many other coagulation factors, vWF concentrations can be variable depending on the mechanism and severity of injury.[63] In those with severe traumatic injury and elevated vWF levels, associated depressed ADAMTS13 activity levels and need for platelets have also been observed, again demonstrating the interrelated nature of the vWF-ADAMTS13-platelet axis.[64] While early and increased transfusions with plasma-containing blood products have been associated with clinical benefits, specific interventions to directly address the abnormal elements of the vWF-ADAMTS13-platelet axis in trauma injury have not been performed to date.

Cryoprecipitate has previously shown mild clinical utility, typically as a second- or third-line agent, in a variety of pathologies, such as hypodysfibrinogenemia, vWD, hemophilia A, and factor XIII deficiency. Recently, the usage of cryoprecipitate in the CRYOSTAT-1 study, a feasibility study that assessed the effects of early high-dose cryoprecipitate in adults with major traumatic hemorrhage, demonstrated sustained fibrinogen levels in the treatment arm along with a suggestion of decreased mortality.[65,66] These data may demonstrate benefits from the integration of vWF into fibrin clots, leading to the mitigation of hemorrhage as an explanation for some of the observed findings[67]; furthermore, it is noteworthy that cryoprecipitate contains the highest concentration of ADAMTS13 activity of any blood product.[68] While the vWF-ADAMTS13-platelet axis was not specifically investigated in the CRYOSTAT-1 study, encouraging findings in this feasibility study may also be partly due to the positive effects of ADAMTS13 administration to cleave vWF and reestablish microvascular blood flow. Continuing investigations are being performed in the ongoing CRYOSTAT-2 study, extending the previous analysis of 43 patients in the CRYOSTAT-1 trial to 1568 trauma patients with severe bleeding. It is important to note that, while there are increased ADAMTS13 levels in cryoprecipitate, a recent secondary analysis of the data from the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial demonstrated that posttraumatic administration of cryoprecipitate was independently linked to the development of venous thromboembolism; this association may be partly due to excessive levels of fibrinogen and vWF within cryoprecipitate.[69] Ultimately, given findings such as these, there is abundant promise in the continued characterization of the role of vWF in critical injury, and, for this reason, further investigations into accompanying vWF-specific interventions are increasingly necessary.

THE ROLE OF vWF IN COAGULOPATHY AND INFLAMMATION AFTER TBI

In TBI, direct endothelial damage and cytokine activation of the blood-brain barrier result in the excessive release of stored vWF from WPBs.[14,70,71] Studies have investigated the impact of this response and established vWF as an important biomarker of outcomes after severe TBI. De Oliveira et al.[16] demonstrated that a vWF plasma concentration of greater than 234 IU/dL, 24 hours after injury, is sensitive and specific for mortality in patients with severe TBI, and Kumar et al.[14] showed that patients with the highest mortality from TBI have both increased vWF antigen levels and vWF collagen binding activity with minimal changes in the vWF antigen to collagen binding ratio.[14–16] Furthermore, both studies found a concomitant decrease in ADAMTS13 levels in patient populations with the highest mortality, potentially emphasizing the procoagulant and inflammatory vWF functions due to impaired cleavage of high-molecular-weight multimers.[14]

Although tissue factor and protein C pathways have long been implicated in TBI-induced TIC,[72–76] recent translational and animal-based studies have identified that vWF may be a potential key mediator of TBI-induced impairments, including in vitro platelet aggregation, increased microvascular thrombosis, leukocyte recruitment, and endothelial permeability.[77–79] In a prospective study of TBI patients, the platelet-vWF-factor VIII axis was examined using assays of in vitro platelet aggregation and coagulation factor activity. Kornblith et al.[77] found that platelet aggregation in response to ristocetin stimulation, but not to other agonists, was reduced and associated with increased factor VIII activity. Ristocetin induces platelet aggregation by forming complexes with vWF; therefore, impaired aggregation in response to ristocetin suggests a functional or quantitative vWF deficit. Given that prior work had demonstrated increased vWF antigen levels in TBI,[16] the authors proposed that vWF-platelet binding had already occurred, thereby decreasing availability of functional vWF to enable ristocetin-stimulated aggregation in vitro. Furthermore, the increase in factor VIII activity,[77] which has been correlated with decreased vWF antigen levels, may have implications for the higher rate of thromboembolic complications associated with TBI.[80]

The proposed mechanisms by which vWF mediates coagulopathy and inflammation in TBI has been further delineated in several small animal studies. In a rat model of TBI, secondary ischemic injury was associated with the development of delayed thrombi rich in vWF and platelets.[81] Reduction of plasma vWF antigen and platelet factor-4 levels (using an 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor) decreased the extent of these processes, supporting that release and rapid consumption of vWF may indeed explain the impairments in vWF-mediated platelet aggregation in TBI.[77,81] VWF also weakens the integrity of endothelial tight junctions,[79] and antibodies against vWF effectively reduced vascular permeability and leukocyte recruitment in a murine model.[82]

A further advance in our understanding of the role of vWF in coagulopathy and endothelial injury was assessed in a fluid percussion model of TBI in mice.[78] Following injury, the release of vWF both activated platelets and led to formation of procoagulant and vWF-bound platelet-derived microvesicles. In addition to triggering consumptive coagulopathy, these vWF-bound microvesicles adhered to endothelium, initiating release

of additional hyperadhesive vWF multimers and increased vascular permeability. To further elucidate vWF's pathologic role, mice were then treated with recombinant ADAMTS13 to inactivate vWF. These mice were protected from coagulopathy and vascular damage, suggesting a relative ADAMTS13 deficiency in the setting of massive vWF release. Finally, administration of lactadherin, which promotes microvescicle clearance, also prevented endothelial injury and coagulopathy, further supporting a role for microvesicles in this context.[78]

Ultimately, findings from several recent translational and animal studies suggest that excessive release of vWF in the context of TBI-induced endothelial damage may play an integral role in the development of altered platelet behavior, coagulopathy, and increased vascular permeability after TBI. Active research in this area surrounds the biologic role and potential therapeutic benefits of ADAMTS13 and other therapies that may regulate the vWF axis or promote clearance of microvesicles.

EFFECT AND FUNCTIONAL VARIATION OF vWF IN ACUTE AND CHRONIC KIDNEY INJURY

Reported incidences of acute kidney injury (AKI) range from 16% to 67% of patients in the adult intensive care unit; more specific analyses suggest that 1% to 50% of patients with traumatic injuries and 4% to 53% of sepsis patients will develop AKI, dependent upon severity.[83–87] The commonly cited mechanisms of AKI following critical illness are renal hypoperfusion, rhabdomyolysis, direct renal injury, compartment syndrome, and nephrotoxicity of other therapies; these effects lead to tubular cell dysfunction and damage that primarily effects the metabolically active parts of the nephron.[88–91] However, the role of vWF in AKI has been a topic of speculation, as renal failure is a pillar of the pentad seen in TTP, where prothrombotic ultra-large vWF is generated, leading to microthrombosis of the distal capillaries, consumption of platelets, and a bleeding diathesis. However, indication that AKI secondary to critical illness may be a process that overlaps with thrombotic microangiopathies following systemic inflammation is a relatively novel assertion that requires further study of the surrounding physiological influences.

Not only was early AKI following trauma associated with a twofold increase in mortality, but critically ill patients who developed AKI also demonstrated an increased vWF to ADAMTS13 ratio.[11–13] Ono et al.[12] found that in sepsis-induced DIC, ADAMTS13 levels were inversely correlated with the development of renal failure, suggesting that the insufficient cleavage of vWF leads to a more severe inflammatory state. A study that evaluated dogs presenting with AKI showed that the ratio of vWF antigen to collagen binding activity was increased, while collagen-activated platelet aggregation was decreased in AKI when compared to healthy controls.[92] These data are increasingly interesting in light of the evaluation of vWF in patients with chronic renal disease, another physiological state characterized by systemic inflammation.[93] In a consistent pattern with the Kornblith study on TBI,[77] patients with uremia demonstrated both elevated vWF levels and a decreased ratio of ristocetin cofactor activity to vWF antigen. They further explained the decreased activity to antigen ratio by demonstrating the consumption of highly prothrombotic, high-

molecular-weight vWF forms.[17,94,95] In a similar study that evaluated vWF in patients with chronic renal failure beginning dialysis, the ratio of vWF antigen to collagen binding activity was increased, collagen-activated platelet aggregation was decreased, and there was once again an absence of the large, prothrombotic vWF forms when compared to healthy controls.[96] Altogether, these studies in acute and chronic renal injury suggest that the inflammatory state both accompanied and driven by uremia fuels the consumption of the prothrombotic high-molecular-weight multimeric forms of vWF, likely through a mechanism that increases their activity. However, studies are still required to demonstrate whether these prothrombotic alterations to vWF may function in a way that fuels renal injury by means of microthrombotic insults, similar to what is seen in DIC. It must first be proven that the loss of high-molecular-weight vWF is not simply an artifactual consequence of a primary uremic process, leading to coagulopathy.

CONCLUSIONS

vWF is active in a broad spectrum of physiological insults where there is an associated systemic endotheliopathy that leads to a relative excess of hyperinflammatory and -thrombotic vWF forms. A few broad diseases that share this general pathologic progression include DIC, TIC, and SIRS, commonly developing secondary to critical illness. It is thought that coagulopathic diseases that commonly occur following injuries, such as TBI, follow distinct pathways that lead to their development. Unfortunately, the exact pathways that these pathologies use are still poorly understood. This dearth of well-defined data leads to a lack of clarity with respect to the effects of transfusing a variety of vWF- and ADAMTS13-containing blood products; additional complications arise given that vWF and ADAMTS13 testing is not routinely done in the critical care setting, despite marked alterations in circulating concentrations of these molecules following critical injury. Furthermore, current data surrounding vWF demonstrates promise with respect to the molecule acting as a mediator of systemic damage seen in critical illness. Further investigation of vWF and ADAMTS13 will not only provide a better understanding of the physiological manifestations of these prothrombotic and proinflammatory pathologies, but it will also begin to build a basis for the pharmacological nature of the vWF found in blood products, which are commonly used in the treatment of critical illness.

CONFLICT OF INTEREST

WEP, ZAM, and LZK have disclosed no conflicts of interest. JSR was an investigator for the HERCULES Phase III randomized controlled trial investigating caplacizumab in acquired TTP; MAR is an advisory board member for Bayer, Inc. and Novo Nordisk, Inc. MDN receives research support from Accriva Diagnostic, Janssen Pharmaceuticals, and Haemonetics as well as serving on an advisory board for CSL Behring and Haima Therapeutics.

ABBREVIATIONS:

AKI	acute kidney injury
CLP	cecal ligation and puncture
DIC	disseminated intravascular coagulation

Gα12	guanine nucleotide-binding alpha-subunit 12
SIRS	systemic inflammatory response syndrome
αSNAP	soluble N-ethylmaleimide sensitive factor-attachment protein alpha
TBI	traumatic brain injury
TIC	trauma-induced coagulopathy
TTP	thrombotic thrombocytopenic purpura
vWF	von Willebrand factor
WPBs	Weibel-Palade bodies

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Table 1.

Contents of plasma-containing blood products

	Fibrinogen (mg/dL)	vWF (IU/dL)	ADAMTS13 activity (%)	Platelets
Plasma	200	100	120	None
Cryoprecipitate	1000	1000	240	None
Platelets, apheresis	200	100	120	3×10^{11}
Whole blood (plasma fraction)	200	100	120 (estimated)	5.5×10^{10}

Fibrinogen, vWF, ADAMTS13, and platelet levels of commonly transfused plasma containing blood products.