Blood products and procoagulants in traumatic bleeding: use and evidence

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Purpose of review
Death from uncontrolled haemorrhage is one of the leading causes of trauma-related mortality and is potentially preventable. Advances in understanding the mechanisms of trauma-induced coagulopathy (TIC) have focused attention on the role of blood products and procoagulants in mitigating the sequelae of TIC and how these therapies can be improved.

Recent findings
A host of preclinical and clinical studies have evaluated blood product availability and efficacy in trauma. Recently published randomized controlled trials have investigated the ratio of platelet:plasma:red cell transfusion and the role of early cryoprecipitate in trauma. Demand for readily available plasma has led to changes particularly in the use of thawed group A plasma. Furthermore, ex-vivo and early clinical work has demonstrated variations in the haemostatic activity of different plasma, platelet and whole blood products. A number of multicentre trials are in progress aiming to answer key questions regarding tranexamic acid, procoagulant factor and fibrinogen concentrates and their effect on trauma outcomes.

Summary
There are promising results from ex-vivo studies in manufacturing and storage of blood products to optimize haemostatic activity and availability, particularly with alternative plasma and platelet products and whole blood. There is an urgent need for these products needs to be tested prospectively.

Keywords
blood, haemorrhage, tranexamic acid, transfusion, trauma

INTRODUCTION

Uncontrolled haemorrhage is one of the leading causes of preventable death in major trauma. Most deaths from bleeding occur in the first few hours after injury [1▪]. The present review will cover recent advances in the development and use of blood products and procoagulants in the management of traumatic bleeding.

USE OF BLOOD PRODUCTS IN TRAUMA

Early blood product transfusion is a key component of haemostatic resuscitation (Table 1). Following severe injury and bleeding, 20–40% of patients have trauma-induced coagulopathy (TIC), which is associated with increased mortality [16,17]. TIC is characterized by hypofibrinogenaemia and hyperfibrinolysis [16,17]. This complex process also involves dysregulation of the protein C pathway, endothelial and platelet dysfunction. As understanding of the mechanisms of TIC has advanced, the use of blood products and procoagulants has evolved to target the key drivers of TIC (Table 1). This has also led to developments in blood products to meet the need for timely and effective blood transfusion in the treatment of acute traumatic haemorrhage (Table 2).

The overall aims of blood transfusion are

(1) to provide adequate circulating volume for perfusion and oxygenation of tissues/organs;
(2) to prevent and
(3) to treat coagulopathy.

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Curr Opin Crit Care 2016, 22:598–606
DOI:10.1097/MCC.0000000000000354

KEY POINTS

- Early transfusion of blood products aims to maintain perfusion, prevent and treat coagulopathy.
- Progress has been made in the blood bank to provide readily available plasma for trauma resuscitation but further work is needed to meet the logistic challenges of timely delivery and administration of blood products.
- How storage methods affect the haemostatic activity of different blood products may be clinically relevant and needs to be tested *in vivo*, so we can optimize transfusion management.
- In the next few years, RCTs will be reporting on the effectiveness of early fibrinogen replacement and role of TXA as an antifibrinolytic and anti-inflammatory agent, addressing some of the key unanswered questions in trauma haemorrhage.

RED CELL TRANSFUSION

Red cells are needed for oxygen delivery to vital organs and also contribute to haemostasis by marginalizing platelets along the vessel wall [34].

Age of blood

A systematic review on the age of blood in trauma identified seven studies (6780 patients) [35]. No firm conclusions could be drawn on the effect of age of red cells on mortality. A subsequent subanalysis of trauma patients from the large ABLE trial, a randomized controlled trial (RCT) of over 2000 patients in intensive care, showed no significant difference in mortality between the fresh-blood or standard-blood group [36▪]. However, patients were excluded from the study if they received transfusion prior to admission to intensive care, thereby excluding many patients with acutely bleeding trauma who would have needed transfusion prior to intensive care.

Red cell transfusion thresholds

Red cell transfusion is not without potential harm. In settings outside trauma, such as in upper gastrointestinal bleeding, trials have demonstrated improved outcomes with restrictive transfusion [37]. Subgroup analysis of trauma patients in the Transfusion Requirements in Critical Care Trial (TRICC) showed restrictive red cell transfusion appeared well tolerated in the critically ill patient with haemodynamically stable trauma [38]. Whether results from other patient populations can be extrapolated to trauma patients in the acute or subsequent phases of management is unclear without further evidence.

Red cell transfusion and risk of death

The primary aim of the CRASH-2 trial was to evaluate the effect of tranexamic acid (TXA) on mortality [14]. A secondary analysis explored the association of red cell transfusion and death and showed that for patients with less than 20% predicted risk of death, red cell transfusion was associated with increased mortality, whereas for patients with high predicted risk of death the converse was true [39]. Although red cell transfusion was not controlled for in this study and inferences are subject to confounding, this analysis shows that the role of red cell transfusion in non-life-threatening bleeding is less clear and may be potentially harmful.

The recent evidence shows age of transfused blood may not affect outcomes in trauma but there is limited evidence to support a restrictive transfusion approach to transfusion in the acute phase. One of the biggest challenges is how we identify patients at the highest risk of adverse bleeding outcomes, especially those who do not present with classical haemodynamic instability in which red cell transfusion may be harmful [39].

PLASMA

Fresh frozen plasma (FFP) provides a source of procoagulant and anticoagulant proteins and is used to treat and prevent coagulopathy (Table 1). A decrease in coagulation factors (especially FII) usually leads to reduced thrombin generation and increased risk of bleeding [40]. However, in trauma, in the early stages of TIC, thrombin generation is more likely to be normal or elevated, despite low FII levels and questions the role of FFP [40]. Recent work has highlighted the importance of anticoagulants in plasma, especially antithrombin in restoring haemostatic balance following trauma [41].

Plasma transfusion

Observational data have demonstrated survival benefit with ratios of at least 1 : 2 red cell : plasma transfusion [4]. Recent RCT evidence comes from the PROPPR trial, which evaluated efficacy and safety of plasma, platelets, red cell transfusion in a 1 : 1 : 1 versus 1 : 1 : 2 ratio in trauma [5▪▪]. Although overall survival was not improved in the 1 : 1 : 1 group, patients were more likely to reach anatomical haemostasis and less likely to die from exsanguination. There were no significant differences in complications between the two groups.

Table 1. Content and rationale of key components of blood transfusion and procoagulants in trauma

Blood product	Content	Rationale and use	Evidence
Red cells	Red cells from single donor >40 g haemoglobin/unit	Promote haemostasis by marginalizing platelets to vessel wall	Systematic review and meta-analysis of observational studies showed no conclusive survival benefit of prehospital red cells (no RCTs or prospective studies identified) [2]
Fresh frozen plasma	Source of clotting factors, inhibitors of coagulation (protein C, protein S, antithrombin, tissue factor pathway inhibitor) and alpha-2 antiplasmin (antifibrinolytic activity), immunoglobulins, albumin; fibrinogen concentrations can vary from 1 to 3 g/l [3]	Prevent and treat coagulopathy by providing source of clotting factors	Benefit of ratios of at least 1:2 FFP:red cell ratios in observational studies [4]. RCT (PROPPR trial) of 1:1:1 vs 1:1:2 ratio of plasma, platelets, red cells in trauma showed an early survival benefit, fewer deaths from exsanguination at 24 h and a greater likelihood of achieving haemostasis 1:1:1 group [5▪▪]
Platelets	150–510 $\times 10^9$ platelets per adult therapeutic dose; ABO, RhD, HLA and HPA antigens on platelet surface, antibodies in plasma	Mitigate platelet dysfunction in trauma and/or thrombocytopenia caused by dilution or large volume blood loss	No mechanistic prospective studies. Not possible to differentiate effect of platelets or plasma in PROPPR RCT [5▪▪]
Cryoprecipitate	Concentrated source of fibrinogen, FVIII, VWF, FXIII, fibronectin; fibrinogen concentrations vary ~15g/l [6]	Fibrinogen first clotting protein to be depleted to critically low levels and hypofibrinogenaemia key feature of TIC	Feasibility study: RCT evaluating the effects of early administration of cryoprecipitate in major traumatic haemorrhage showed it was feasible to administer cryoprecipitate within 60 min of admission. Larger trial powered for outcomes needed [7▪]
Whole blood	Balanced red cell, platelet and plasma (platelet sparing leucoreduction filters now available)[8]	Single donor product providing balanced haemostatically active red cells, platelets and plasma	The only RCT using modified whole blood in trauma did not use a platelet-sparing filter and platelets were transfused separately (pilot study). Modified whole blood reduced transfusion volumes in patients without brain injury [9]. Single-centre data (Table 2).
Procoagulants			
Prothrombin concentrate complex (PCC)	Four-factor PCC contains FII, VII, IX, X 3-factor PCC contains FII, IX, X	Mainly used for reversal of vitamin K antagonists. Has been used in some centres as an alternative to FFP as no thaw time, accessibility	Observational data – reduction in allogeneic transfusion for PCC and fibrinogen concentrate compared with FFP, although studies have methodological limitations [10]. Need for RCT evidence.
Fibrinogen concentrate	Lyophilized fibrinogen concentrate, 1 g/50 ml	Source of concentrated fibrinogen to prevent or treat coagulopathy. Extra viral inactivation steps compared to cryoprecipitate	Systematic review of observational studies shows fibrinogen concentrate may be associated with reduced blood product requirements [11]. Small RCTs in progress.
DDAVP	Synthetic analogue of vasopressin	Enhances formation of procoagulant platelets and increases VWF and FVIII [12]. Treatment of bleeding on antiplatelet therapy [13]	Not yet prospectively studied in trauma.
Tranexamic acid	1 g IV followed by 1 g infusion	Antifibrinolytic and anti-inflammatory properties. Fibrinolysis key component of traumatic coagulopathy	CRASH-2 trial – reduced death [14,15]. Limited in-vivo studies of non-antifibrinolytic effects.
Aminocaproic acid	Lysine analogue in same class as TXA but with shorter half-life (60–75 vs. 120 min) and less potency than TXA [13]		Not evaluated in an RCT setting in trauma [13].

FFP, fresh frozen plasma; DDAVP, desmopressin; HLA, human leukocyte antigen; RCT, randomized controlled trial; RhD, rhesus D; TIC, trauma-induced coagulopathy; TXA, tranexamic acid; VWF, Von Willebrand factor.

Table 2. Blood product developments

Limitations of blood product	Recent developments
Red cells	
35-day shelf-life	Cryopreserved red cells can be stored for 10 years. Recently evaluated in trauma RCT [18]. Rejuvenation solutions to restore ATP and 2,3-DPG levels in stored red cells being tested in cardiac surgery clinical trial (NCT02485366).
Red cell storage lesion (physical and biochemical changes associated with refrigerated, stored red cells) and potential impact on immune and vascular complications	Preservative solutions and storage conditions for red cells in preclinical phase [19,20].
Plasma	
Potential differences in haemostatic function of different plasma products	Preclinical studies – solvent/detergent-treated pooled products have altered thrombin generation kinetics compared with FFP and liquid plasma [21].
Limited availability of universal AB donor	Use of prethawed group A plasma for major haemorrhage prior to group specific FFP.
Time for thaw	Study reported liquid plasma facilitated an early balanced ratio of blood components for super-massive transfusion where patients required >30 units of blood in 24 h [22].
	Lyophilized plasma [23]
Platelets	
Short shelf-life 5–7 days.	Developments in platelet storage methods [24▪]. Cryopreserved (frozen) platelets can be stored for 5 years.
	Lyophilized (freeze-dried) platelets in preclinical studies.
Cold-stored platelets have reduced survival after transfusion	Although cold-stored platelets have shorter survival [25,26], they are haemostatically more active than standard platelets and may still respond to inhibitory signals [27].
	FDA recently approved the storage and use of apheresis platelets at 1–6°C for 3 days for the resuscitation of patients with major bleeding [28▪].
Haemostatic effect of cryopreserved platelets (CPPs)	In-vitro studies compared the haemostatic effect of CPPs with 5-day standard platelets [29,30▪]. CPPs may facilitate a faster onset of thrombin generation and clot formation, but there is no evidence that this is associated with increased thrombotic complications. Increased haemostatic potential may be due to higher levels of microparticles in the CPPs [29].
Cryoprecipitate and fibrinogen concentrate	No recent developments to individual product specification. One study showed preserved haemostatic activity of thawed pooled cryoprecipitate for 72 h [31].
Whole blood	
Nonfunctional platelets	Platelet-sparing leucoreduction filters available. A program of whole blood for civilian trauma is being developed at the University of Pittsburgh (leuco-reduced), Mayo Clinic (non leuco-reduced) [8,31,32▪▪]. Recent study demonstrated *in vivo* platelet viability of platelet concentrate made from stored cold whole blood in healthy volunteers [33].

2,3-DPG, 2,3-diphosphoglycerate; ATP, adenosine triphosphate; FFP, fresh frozen plasma; RCT, randomized controlled trial.

Approaches for rapid provision of plasma

Improved outcomes with more balanced plasma:red cell transfusion has focused attention on approaches to facilitate rapid provision of plasma and alternatives to universal plasma. Universal AB plasma is limited by shortage in the available donor pool (only 4% of the population is group AB), which means it is not kept defrosted. In patients with life-threatening haemorrhage, delays in thawing plasma may be critical and the risk of clinically significant haemolysis is likely to be low [42]. To overcome this potential delay and increase supply, alternatives to standard FFP such as prethawed group A plasma, liquid and lyophilized plasma have been developed (Table 2).

Prethawed group A plasma, prior to type-specific FFP, has been adopted in countries including the United States and United Kingdom, to increase availability of readily thawed plasma for major haemorrhage [43]. Group A plasma is compatible with over 85% of the patient population and there have not been any concerns with safety so far [42,44]. In the PROPPR RCT, a total of 141 group A plasma units were transfused to AB and B patients without evidence of haemolysis or other reactions [45▪].

Table 3. Ongoing/recently completed randomized controlled trials in trauma

Intervention	Current studies
Red cells and plasma	RePHILL trial (prehospital red cell and lyophilized plasma EudraCT2015–001401-13) PUPTH RCT evaluating the effectiveness of early prehospital thawed plasma in traumatic haemorrhage (NCT02303964).
Plasma/coagulation factor concentrates	RETIC trial: Reversal of trauma induced coagulopathy using coagulation factor concentrates or FFP (NCT01545635).
Fibrinogen	There are five small RCTs in trauma which are evaluating fibrinogen concentrate (NCT01475344, NCT02203968, NCT02344069, NCT01545635), (EudraCT2015-000875-28), and another in set-up (NCT02745041).
TXA	PATCH study (NCT02187120). Prehospital TXA STAAMP – prehospital TXA within 2 h of injury (NCT02086500). TAMPITI comparing two doses of TXA (NCT02535949).

FFP, fresh frozen plasma; RCT, randomized controlled trial; TXA, tranexamic acid.

Liquid plasma is derived from whole blood, which has never been frozen and can be stored for up to 26 days with retention of most coagulation factors [46]. In ex-vivo studies, liquid plasma had superior clot strength and thrombin generation compared with thawed plasma but the labile factors V, VIII and protein S were significantly reduced (see Table 2) [46,47]. Another study showed reductions in factor V and protein S levels on day 15 suggesting use of liquid plasma past 15 days is not optimal for trauma [48].

Fresh frozen plasma and the endothelium

In addition to providing a source of coagulation factors, FFP may also promote endothelial stability [25,28▪]. During endothelial damage, syndecan-1 is shed and in trauma patients with haemorrhagic shock, levels are elevated [49▪]. In a study of FFP transfusion prior to invasive procedure in nonbleeding critically ill patients, a FFP decreased syndecan-1 and may stabilize the endothelium [49▪].

Advances have been made particularly with readily available Group A thawed plasma to enable rapid provision of FFP as part of haemostatic resuscitation. Liquid or lyophilized plasma are not widely available but may be additional therapeutic options for the future, to manage supply of plasma. Future studies could compare these plasma products in trauma resuscitation on bleeding endpoints and effect on the endothelium.

CRYOPRECIPITATE AND FIBRINOGEN CONCENTRATE

Fibrinogen is the first clotting protein to be depleted to critically low levels in major bleeding [50] and hypofibrinogenaemia is a key feature of TIC [51]. This has focused attention to the role of specific early fibrinogen replacement in traumatic bleeding [51].

The two main sources of fibrinogen replacement are cryoprecipitate and fibrinogen concentrate. A systematic review summarized the RCT evidence for fibrinogen concentrate in traumatic bleeding. Fibrinogen concentrate reduced transfusion requirements but the quality of trials was low with high risk of bias [11] and we await completion of a number of trials evaluating fibrinogen concentrate (Table 3). The only published RCT of cryoprecipitate in trauma is a pilot study (CRYOSTAT) [7▪]. This demonstrated feasibility of early cryoprecipitate transfusion and a follow-up trial has been proposed to evaluate cryoprecipitate powered for mortality [7▪].

One of the unanswered questions is whether cryoprecipitate and fibrinogen concentrate have equal efficacy in trauma and this has not been evaluated in any head to head trials in trauma. A recently published systematic review compared cryoprecipitate and fibrinogen concentrate in bleeding patients [52]. Four studies were included (one RCT in cardiac surgery and three observational). There were no differences in the fibrinogen increment; transfusion requirement; thromboembolic complications or bleeding between the two products; mortality was not published in the studies included.

In-vitro and ex-vivo work has also shown that these two blood products lead to similar improvements in coagulopathy during trauma haemorrhage and the effects are dependent on fibrinogen concentration rather than the formulation [51]. A theoretical model elegantly demonstrated that when deciding on the optimal form of fibrinogen replacement, consideration should be given to the concentration of the source, as it is impossible to achieve a target fibrinogen level above the concentration of the fibrinogen source [53]. Cryoprecipitate is one quarter of the cost per gram of fibrinogen and a recent economic evaluation confirmed that even after cryoprecipitate wastage, fibrinogen concentrate is at least twice as expensive [54].

In conclusion, at present there is no firm evidence that either cryoprecipitate or fibrinogen concentrate is superior as specific replacement for fibrinogen in trauma haemorrhage. We await results of studies evaluating the early use of fibrinogen replacement.

PLATELETS

A number of studies using platelet aggregometry, platelet mapping and microfluidics have shown evidence of platelet dysfunction early on hospital admission following trauma [55–57]. However, the mechanisms of platelet dysfunction are not well understood. Using microfluidics to investigate platelet function in trauma, a recent study showed defects in platelet adherence to collagen and secondary platelet aggregation indicating possible lack of ADP or thromboxane A2-mediated clot growth [57]. Flow-based assays of global haemostasis and platelet function may be an area for further development to guide management of coagulopathy in trauma.

Platelet transfusion

The PROMMT study, an observational study, showed higher plasma and platelet ratios early in resuscitation were associated with decreased mortality [58]. This led onto the PROPPR trial (described earlier) where in the 1 : 1: 1 group patients achieved haemostasis earlier and platelet transfusion was given first [5▪▪]. The design of the trial meant it was not possible to distinguish between the relative therapeutic benefits of plasma and platelets.

In a study of transfusion practice in trauma in the United Kingdom, the median time to first platelet transfusion in patients with major haemorrhage was 120 min in a major trauma centre and 144 min in a trauma unit [1▪]. Although there were also delays to the provision of other blood products and room for improvement in transfusion practice, this does highlight the great contrast between real-world practice in both large and small trauma centres and optimal clinical trial settings. In the PROPPR trial, the participating tertiary trauma centres were able to provide upfront platelet transfusion but this model is logistically challenging for many trauma-receiving hospitals and may not be appropriate for all. Although studies have shown platelet dysfunction is present, the evidence for upfront platelet transfusions or a specific red cell: platelet ratio is not conclusive [59].

In addition to laboratory and clinical studies on platelets in trauma, there have also been developments in platelet storage methods to improve their shelf-life and efficacy (see Table 2). Cryopreserved or cold-stored platelets have improved haemostatic efficacy and are of particular interest in trauma care [24▪].

Management of bleeding in patients on antiplatelet therapy

The effectiveness of platelet transfusion for bleeding in patients in receipt of antiplatelet therapy has not been established. An important RCT by the PATCH investigators evaluated the effectiveness of platelet transfusion in spontaneous intracranial haemorrhage for patients on antiplatelet therapy [60▪▪]. Nearly 200 patients were randomized to receive platelet transfusion or standard of care (no transfusion). Unexpectedly, the odds of death or dependence at 3 months were higher in the platelet transfusion group than in the standard care group (odds ratio 2.05; 95% CI, 1.18–3.56; $P = 0.0114$). Although this trial was in patients with nontraumatic intracerebral haemorrhage, it does question the role of platelet transfusion in major bleeding and highlight the paucity of evidence in this area.

There is some evidence that desmopressin (DDAVP), a synthetic analogue of vasopressin, can reverse platelet dysfunction in patients who are taking antiplatelet agents. It has been recommended in the European Trauma Guidelines for patients treated with antiplatelet therapy with intracerebral bleeding and in trauma patients with von Willebrand disease [13]. However, it is not recommended for all trauma patients because of lack of evidence but further work could explore whether DDAVP may have a more extended role.

WHOLE BLOOD AND CELL SALVAGE

There has also been renewed interest in whole blood transfusion. Recent developments suggest that issues such as risk of haemolytic transfusion reactions if group O whole blood is used in nongroup O patients and potential reduced haemostatic effect of whole blood platelets can be overcome [7▪,49▪] (Table 2). A single-centre study reported the feasibility and safety of transfusion of two units of cold-stored low-titre group O uncrossmatched whole blood for trauma [32▪▪]. Clinically significant haemolysis was not observed in patients receiving uncrossmatched whole blood [32▪▪]. Studies using rapid thromboelastography have shown platelets in cold-stored leuco-reduced whole blood retain platelet function but definitive confirmation of platelet function using specific platelet function analysis is awaited [61].

Cell salvage

Cell salvage can reduce allogeneic blood transfusion but can be logistically challenging and there are concerns with risk of infection. A systematic review identified one RCT ($n = 44$) in emergency trauma surgery [62,63]. This study showed cell salvage reduced blood transfusion in the 24 h after injury with no increase in postsurgery infection and could be an area for further research.

PROCOAGULANTS

Prothrombin complex concentrates

Prothrombin complex concentrates (PCCs) are mainly used for reversal of vitamin K antagonists in major bleeding. Four-factor PCCs containing FII, VII, IX, X are more effective at coumarin reversal compared with three-factor PCCs [64,65]. However, the evidence for PCC as an adjunct or to replace FFP in trauma coagulopathy is limited to retrospective or observational studies [10]. There are concerns that prothrombotic effects of PCC may last for several days in trauma and increase risk of thrombosis [66]. Until we have more robust evidence on the efficacy and safety profile of PCC, a more cautious approach may be needed.

ANTIFIBRINOLYTICS

Hyperfibrinolysis is a key component of TIC, associated with a high mortality rate [16,67]. This has led to much interest in TXA as an antifibrinolytic [68].

Tranexamic acid

TXA inhibits fibrinolysis by preventing the binding of plasminogen to fibrin and also inhibits the enzymatic activation of plasminogen to plasmin [68]. The hypothesis that TXA would reduce bleeding and mortality from trauma was tested in the CRASH-2 trial [14]. This pivotal trial demonstrated a 9% reduction in all-cause mortality in the TXA group compared to the non-TXA group without a significant increase in thrombotic events [14]. Further analysis showed increased death from bleeding when TXA was given after 3 h and the greatest benefit when given early [15]. However, there is debate about the role of TXA in trauma haemorrhage. Concerns have been raised regarding some of the knowledge gaps in the timing and indications for TXA in trauma and understanding biologically how TXA reduces mortality [68,69].

Emerging evidence shows that TXA may have effects outside the direct antifibrinolytic effect [70,71]. The extended beneficial effects of TXA may be mediated through its inhibition of plasmin. Studies have shown plasmin is pro-inflammatory and plays a role in innate immunity [72,73]. Plasmin may also modify permeability of the blood–brain barrier [71]. Ongoing studies are seeking to address some of the knowledge gaps in the use of TXA such as off-target effects (on pro-inflammatory mediators, the complement pathway, inflammatory cell activation), dosing and role in traumatic brain injury [70,74] (Table 3).

CONCLUSION

The past few years have seen advances in optimizing trauma haemorrhage care. As we begin to understand the mechanisms of TIC, the order and priority of blood product transfusion is evolving with much more interest in (early) fibrinogen replacement. There have also been developments to blood products to provide readily available plasma and platelets with optimal haemostatic function. To improve outcomes in trauma haemorrhage, further collaborative work could evaluate the mechanisms of platelet dysfunction, hypofibrinogenaemia and the potential extended role of TXA to optimize and individualize therapy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

N.C. is on the advisory board for LFB and has received an investigator led research grant from CSL Behring. S.J.S. has received an investigator led research grant from CSL Behring. H.W. is involved in an investigator led study funded by CSL Behring.

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