Transfusion strategies for major haemorrhage in trauma

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Summary

Trauma is a leading cause of death worldwide in persons under 44 years of age, and uncontrolled haemorrhage is the most common preventable cause of death in this patient group. The transfusion management of trauma haemorrhage is unrecognisable from 20 years ago. Changes in clinical practice have been driven primarily by an increased understanding of the pathophysiology of trauma-induced coagulopathy (TIC), which is associated with poor clinical outcomes, including a 3- to 4-fold increased risk of death. Targeting this coagulopathy alongside changes to surgical and anaesthetic practices (an overarching strategy known as damage control surgery/damage control resuscitation) has led to a significant reduction in mortality rates over the last two decades. This narrative review will discuss the transfusion practices that are currently used for trauma haemorrhage and the evidence that supports these practices.

Keywords: transfusion, trauma, major bleeding, trauma induced coagulopathy.

Globally, trauma is one of the leading causes of death in persons under 44 years of age (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control (2017). It is estimated that, across the world, one person dies every 3 min from injury (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2017) and up to 40% of these deaths are due to uncontrolled bleeding or its consequences (Curry *et al*, 2011). Death from haemorrhage is frequently early – with as many as six in every 10 deaths occurring within the first three hours of injury (Holcomb *et al*, 2013). Additionally, the financial burden of trauma to health systems is large – a cross sectional study conducted in the UK in 2012 estimated the annual cost of treating trauma haemorrhage to be in excess of £148M, and this figure did not include the costs of rehabilitation and lost income from patients not returning to work (Campbell *et al*, 2015).

The transfusion management of trauma haemorrhage is unrecognisable from 20 years ago. The changes in clinical practice have been driven primarily by the increased understanding of the pathophysiology of trauma-induced coagulopathy (TIC). Present in up to a quarter of trauma patients, TIC is associated with significantly poorer clinical outcomes, including increased need for major haemorrhage therapy, increased risk of organ failure and, most importantly, a 3- to 4-fold increase risk of death (Brohi *et al*, 2003; MacLeod *et al*, 2003; Maegele *et al*, 2007). Targeting coagulopathy alongside changes to surgical and anaesthetic practices (an overarching strategy known as damage control surgery/damage control resuscitation) has led to a significant reduction in mortality rates over the last two decades (Cotton *et al*, 2011a).

This narrative review will discuss the transfusion practices that are currently used for trauma haemorrhage and the evidence that supports these practices. We will also discuss the uncertainties that exist and the potential changes that could take place over the next decade.

Traumatic coagulopathy

The understanding of the mechanisms by which TIC develops continues to evolve but it is clear that the condition occurs in the acute phase after major haemorrhage and severe tissue injury independent of fluid resuscitation, which, in itself, can result in an iatrogenic dilutional coagulopathy (Bolliger *et al*, 2010). A detailed description of the changes that take place after injury to the clotting systems and how these are tightly inter-related to inflammatory and immune responses is beyond the scope of this review, and has been reviewed in detail elsewhere (Cohen *et al*, 2013; Lord *et al*, 2014; Davenport & Brohi, 2016).

Briefly, TIC describes the overall failure of the coagulation system to sustain haemostasis after major injury (see Fig 1), and is characterised by both an early endogenous coagulopathy – acute traumatic coagulopathy (ATC) – primarily mediated by protein C activation (Davenport *et al*, 2017), as well

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First published online 27 December 2018
doi: 10.1111/bjh.15737

as a systemic coagulopathy exacerbated by sub-optimal resuscitation (i.e. a dilutional coagulopathy), concomitant acidosis, hypothermia and genetic influences (Cohen *et al*, 2013). Clotting changes evident in ATC include normal to high levels of thrombin generation (Dunbar & Chandler, 2009; Cardenas *et al*, 2014); significant fibrinolysis secondary to the release of tissue plasminogen activator (tPA) from the endothelium (Chapman *et al*, 2016) or other cell surface receptors, e.g. S100A10 (Gall *et al*, 2018); and rapid depletion of fibrinogen (Davenport & Brohi, 2016). High thrombin generation, in concert with tissue hypoxia, leads to activation of the endothelium causing upregulation of thrombomodulin (TM) and subsequent protein C activation. In turn, activated protein C leads to inactivation of factor (F) Va and FVIIIa and depletion of fibrinogen (both effects potentiating a hypocoagulable bleeding state) (Davenport *et al*, 2017), as well as inhibition of plasminogen activator inhibitor-1 (PAI-1) which increases fibrinolysis – a phenomenon known to be significantly activated in many patients after trauma (Brohi *et al*, 2008; Raza *et al*, 2013).

Endothelial activation is central to traumatic coagulopathy, acting as an important link between the coagulation and inflammatory responses. Markers of endothelial activation, such as soluble-TM and syndecan-1, are high (Johansson *et al*, 2011) and are associated with shock and poor clinical outcomes (Kozar *et al*, 2011). Over time, persistent endothelial activation leads to a prothrombotic state, and partly explains the high thrombosis rates in severe trauma (Cap & Hunt, 2014). In addition to endothelial and coagulation dysfunction, platelets are also adversely affected by injury. Several observational studies have demonstrated the presence of platelet dysfunction – most commonly shown by a reduction in aggregation with ADP (Solomon *et al*, 2011; Kutcher *et al*, 2012) although a more global defect has been reported by others (Vuillamy *et al*, 2017). Recent work has shown that platelet dysfunction can increase clot susceptibility to fibrinolysis (possibly due to loss of platelet-stored PAI-1 at the site of injury) (Moore *et al*, 2015). However, much more needs to be learnt about the reasons why, and indeed how, platelet function is altered by severe injury.

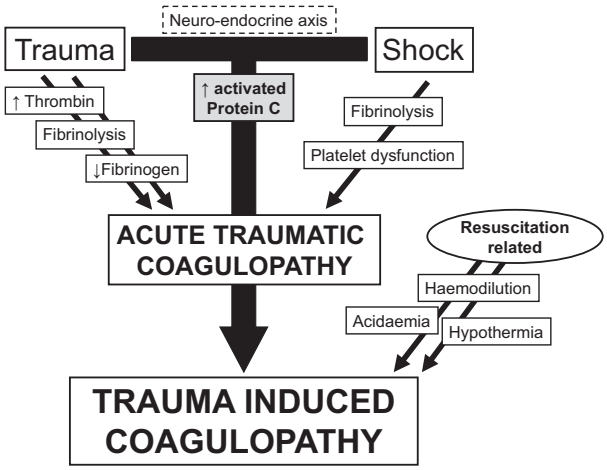

Fig 1. Pathogenesis of trauma-induced coagulopathy. Trauma-induced coagulopathy is the global failure of haemostasis after major trauma haemorrhage. Haemodynamic shock and tissue trauma immediately activate the neuro-endocrine axis and initiate an early endogenous process by the protein C pathway – acute traumatic coagulopathy. Tissue injury leads to increased thrombin generation, fibrinolysis secondary to release of tissue plasminogen activator and early fibrinogen depletion. In the presence of severe shock, these changes result in systemic activation of protein C through the thrombin-thrombomodulin complex. Early changes in coagulation are exacerbated by iatrogenic factors, such as crystalloid infusion leading to haemodilution, which can include inadequate resuscitation with, for example, unbalanced transfusion therapy. Figure reproduced with permission from: Davenport R.A., Brohi K. (2016) Cause of trauma-induced coagulopathy. *Current Opinion in Anesthesiology* **29**: 212–219). https://journals.lww.com/co-anesthesiology/pages/default.aspx.

General clinical management strategies for trauma haemorrhage

Damage control resuscitation

Damage control resuscitation is a key management strategy employed by trauma teams to manage significant haemorrhage after injury. It is defined by rapid surgical or radiological haemorrhage control with an empiric and balanced resuscitation of blood and blood components in high ratios and avoidance of crystalloids (Naumann *et al*, 2018; Pohlman *et al*, 2018). The premise of this haemostatic strategy is to prevent the coagulopathy caused by resuscitation, although it may have a limited effect on reversal of traumatic coagulopathy during active bleeding (Khan *et al*, 2015).

Major haemorrhage protocols

Major haemorrhage protocols (MHP) were introduced to improve the speed and consistency of delivery of red blood cells (RBCs) and other blood components to severely bleeding patients, and have been shown in a number of observational studies to improve outcomes, including mortality (Young *et al*, 2011) [In the US and other countries, the term massive transfusion protocol (MTP) may be used in place of MHP, although this often describes only RBC and blood component therapy, rather than additional adjunctive haemostatic therapy such as tranexamic acid (TXA)]. MHPs provide a clear framework to facilitate a co-ordinated response by a large multi-disciplinary team during a time critical situation (Booth & Allard, 2018). As yet, the optimal MHP strategy remains unknown, and a recent survey of MHP therapy at six large research active level 1 European trauma centres confirmed wide variation in transfusion practice, highlighting the uncertainty that remains over best practice (Schafer *et al*, 2015). A typical UK MHP is provided in Fig 2. Targeted or personalised haemorrhage therapy is an

area of active research but requires a deeper understanding of both the mechanisms which drive TIC and the efficacy of different transfusion therapies on clinical outcomes.

Coagulation testing

Traumatic coagulopathy has been defined by a prolonged prothrombin time (PT) with a threshold international normalised ratio (INR) of 1·2 (Frith *et al*, 2010). More recently, viscoelastic assays definitions (rotational thromboelastometry – ROTEM or thromboelastography – TEG) have been advocated (Meyer *et al*, 2014; Hagemo *et al*, 2015; Moore *et al*, 2017). Early recognition of a coagulopathy and subsequent monitoring is vital to both initiate and maximise resuscitation therapy. British Committee for Standards in Haematology guidelines recommend the use of serial standard laboratory tests (SLTs) taken every 30–60 min to monitor major haemorrhage (Hunt *et al*, 2015). Supporting this idea, a small pilot randomised controlled trial (RCT) reported that SLT-guided transfusion led to less wastage of blood and blood components when compared to an empiric 1:1:1 fixed ratio transfusion practice (Nascimento *et al*, 2013). Notably, viscoelastic haemostatic assays (VHA) were not evaluated in this study.

There are however inherent difficulties with SLTs. Average turn-around-times are between 27 (Cotton *et al*, 2011b) and 77 min (Davenport *et al*, 2011). In direct contrast, VHA can provide clinically useful results within 5 min of test start and provide information about several aspects of the coagulation process, including clot initiation, clot strength and fibrinolysis (Curry *et al*, 2018a). It is important to recognise that VHA are fairly insensitive to mild/moderate fibrinolytic activity (Raza *et al*, 2013) and should not be used to withhold TXA therapy in a bleeding patient (Curry *et al*, 2018a). Despite a large number of observational studies in trauma, high quality evidence supporting the use of ROTEM or TEG in trauma is lacking (Curry *et al*, 2018a) and currently the National Institute for Health and Care Excellence (NICE) does not recommend their use in guiding therapy for bleeding trauma patients (Whiting *et al*, 2015).

Two RCTs evaluating the use of VHA in trauma have been published (Gonzalez *et al*, 2016; Innerhofer *et al*, 2017). In a single centre study, Gonzalez *et al* (2016) reported a significant reduction in death at 28 days with VHA use: 20 deaths SLT (36·4%) vs. 11 VHA (19·6%), with shorter median times to death in the VHA arm (4·2 vs. 10·4 h). This study provides some evidence that VHA-guided transfusion (TEG-5000) may be beneficial in acute bleeding, over and above the empiric 1:1:1 transfusion. A second single centre RCT used ROTEM-guided thresholds to compare fresh frozen plasma (FFP) with single factor concentrates in trauma haemorrhage (Innerhofer *et al*, 2017), with a primary endpoint of multiple organ failure. The study was terminated early due to high treatment failure in the FFP arm. The authors reported an association between clinically relevant bleeding and ROTEM measures, suggesting that ROTEM may be useful to guide trauma haemorrhage therapy. Finally, a multicentre European RCT (iTACTIC; NCT02593877) of nearly 400 patients utilising ROTEM or TEG has just completed recruitment and will report in early 2019. The trial compares SLT-guided transfusion therapy with VHA-guided therapy using a primary endpoint of 24-h survival free from massive transfusion. Derived from prospective coagulation profiles of over 2000 trauma patients (Bakaas-Aasen *et al*, 2018), the VHA and SLT transfusion algorithms will provide further evidence as to the optimal method of guiding coagulation therapy during trauma haemorrhage (iTACTIC trial, NCT02593877).

Transfusion and adjunctive haemostatic therapies for trauma haemorrhage

Tranexamic acid

Fibrinolysis is common after injury, affecting up to 80% of trauma patients admitted to hospital (Raza *et al*, 2013). The landmark trauma trial, CRASH-2 (CRASH-2 trial collaborators, 2010), demonstrated the importance of early modulation of the fibrinolytic pathway in trauma. This study of just over 20,000 patients showed that the administration of TXA (1 g bolus, followed by 1 g infusion over 8 h) reduced overall mortality [14·5% deaths in TXA group vs. 16% in placebo group; relative risk (RR) 0·91, 95% confidence interval (CI) 0·85–0·95; $P = 0·0035$] and reduced risk of death from bleeding (4·9% TXA vs. 5·7% placebo; RR 0·85, 95% CI 0·76–0·96; $P = 0·0077$) (CRASH-2 trial collaborators, 2010). Importantly, subsequent analysis of the data, combined with data from a postpartum haemorrhage trial – the WOMAN study (WOMAN Trial Collaborators, 2017) – showed that the earlier TXA is administered, the greater the outcome benefit. Immediate therapy with TXA was associated with improved survival (Odds ratio 1·72, 95% CI 1·42–2·10; $P < 0·0001$) and the survival benefit then was shown to decrease by 10% for every 15-min delay in treatment, up to 3 h- (Gayet-Ageron *et al*, 2018). Interestingly, mortality benefit is lost when TXA is administered after 3 h of injury, with data from the CRASH-2 trial demonstrating harm for patients treated late, although the pathophysiological mechanisms for increased mortality have yet to be defined. Precisely how TXA improves survival also requires further mechanistic evaluation to clarify the relative effects of reduced bleeding, due to a direct anti-fibrinolytic action, and early modulation of the immune response (TXA activates the innate immune response) possibly altering clinical rates of infection, organ failure or systemic inflammatory response syndrome rates (Lord *et al*, 2014). These questions aside, it is clear that TXA should be given to all trauma patients at risk of bleeding within the first 3 h of injury and, ideally, as quickly as possible (CRASH-2 trial collaborators, 2011).

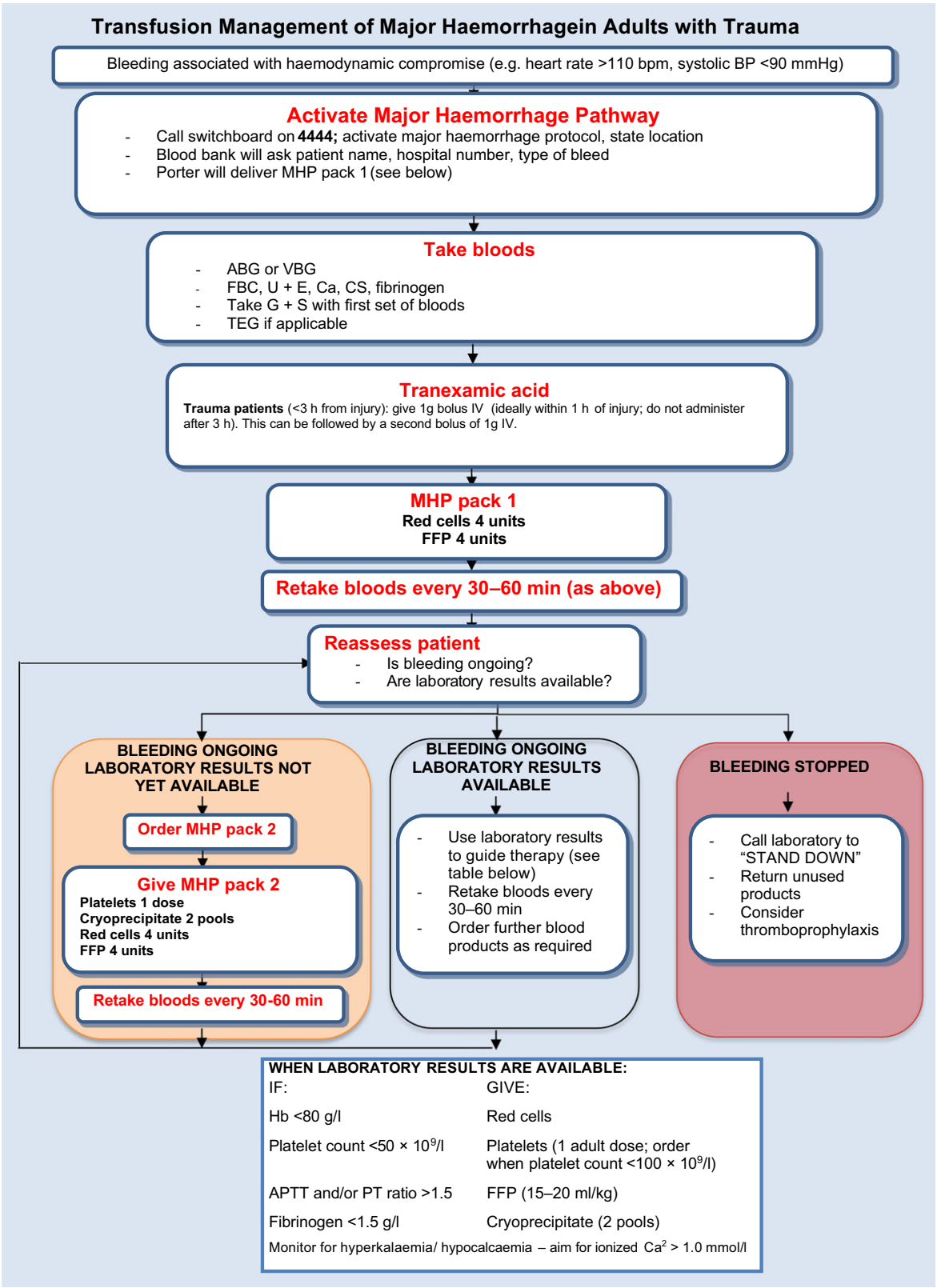

Fig 2. Transfusion management of major haemorrhage in adults with trauma. ABG, arterial blood gas; APTT, activated partial thromboplastin time; BP, blood pressure; Ca, calcium level; CS, clotting screen; FBC, full blood count; FFP, fresh frozen plasma; G+S, group and screen; Hb, haemoglobin concentration; IV, intravenously; MHP, major haemorrhage protocol; PT, prothrombin time; TEG, thromboelastography; U+E, urea and electrolytes; VBG, venous blood gas.

Red blood cells

RBCs provide oxygen carrying capacity, contribute to restoration of adequate circulating volume and may play a role in haemostasis. There are no high-quality data providing evidence for target haemoglobin or haematocrit values during active haemorrhage, but the most recent European trauma guidelines recommend aiming for a haemoglobin of 70–90 g/l (Rossaint *et al*, 2016).

Over the last 5 years there has been increasing use of RBCs in the pre-hospital environment. No RCTs have been published in this setting, although a recent observational study from the London Air Ambulance reported on their use of pre-hospital RBCs (Rehn *et al*, 2018). This retrospective historical cohort study reported a significant reduction in pre-hospital mortality in the group receiving RBCs (42·2% vs. 27·6%), although ultimately no overall survival benefit. A second UK study, comparing pre-hospital RBCs with a historical group receiving pre-hospital crystalloids, reported a reduction in mortality at both 6 h (10% vs. 18%) and 28 days (26% vs. 40%) (Griggs *et al*, 2018). Results from both of these studies must be viewed within the constraints of historical cohorts – where, in these cases, the patients receiving RBCs may have also benefitted from other developments in trauma haemorrhage management.

Fresh frozen plasma

Plasma transfusion is central to the management of trauma haemorrhage. Since 2003, when ATC was found to be associated with increased transfusion need and higher mortality (Brohi *et al*, 2003) there has been extensive interest in the effects of early and/or high dose plasma therapy on clinical outcomes. Many observational studies, both prospective and retrospective, have been published since 2007 evaluating the effects of empiric, high ratio FFP:RBC transfusion strategies. The majority of studies concluded that higher ratios of FFP: RBC were associated with reduced mortality (Zehtabchi & Nishijima, 2009; Murad *et al*, 2010), although many were confounded by survivor bias due to the retrospective nature of the data. Notably, no single FFP:RBC ratio (i.e. 1:1 vs. 1:1·5) was found to be optimal, with few studies providing any mechanistic evidence for effect. FFP provides a source of coagulation factors necessary for thrombin generation although endogenous thrombin potential is maintained in the early phase after injury (Cardenas *et al*, 2014; Davenport *et al*, 2017). The endothelial damage from trauma and restorative effects of plasma on the shed glycocalyx compared to crystalloid is one possible effect (Kozar *et al*, 2011; Watson *et al*, 2016).

In an attempt to definitively answer the FFP:RBC ratio question, a large multicentre RCT evaluating the use of two transfusion regimens in adult trauma haemorrhage patients – the PROPPR trial (Holcomb *et al*, 2015) – was conducted at 12 Level 1 trauma centres in North America. An FFP:-platelets:RBC ratio of 1:1:1 was compared to 1:1:2 in 680 participants with a combined primary endpoint of 24-h and 30-day mortality (see Table I). The study was powered to detect a 10% difference in 24-h mortality (11% vs. 21%) and a 12% difference in 30-day mortality (23% vs. 35%), with 95% and 92% power, respectively. Mortality was not shown to be significantly different between arms, either at 24 h (12·7% in 1:1:1 group vs. 17·0% in 1:1:2 group; $P = 0{\cdot}12$) or at 30 days (22·4% vs. 26·1%, respectively; $P = 0{\cdot}26$), although the Kaplan Meier survival curves show a clear separation from 3 h of injury. However, the intervention was reported to significantly reduce the secondary endpoint of death due to bleeding, the most common cause of death up to 24 h (1:1:1 group 9·2% vs. 14·6% in 1:1:2 group; $P = 0{\cdot}03$). In addition, more patients in the 1:1:1 group achieved haemostasis (as defined by a study-specific haemorrhage assessment tool) than in the 1:1:2 group (86% vs. 78%, respectively; $P = 0{\cdot}006$). The 1:1:1 group received more plasma (median of 7 units vs. 5 units, $P < 0.001$) and platelets (12 units vs. 6 units, $P < 0{\cdot}001$) and similar amounts of red blood cells (9 units) over the first 24 h. No significant differences were reported for adverse events, in particular organ failure, transfusion-related adverse events, sepsis and thromboembolism (Holcomb *et al*, 2015).

These data have been used by many to inform local transfusion practice for trauma, because they are the highest quality data available around early FFP use, although the results are inconclusive – with many UK centres following NICE guidance, which recommends FFP:RBC in the ratio of 1:1 (National Clinical Guideline Centre 2016). However, the use of immediate platelet transfusion in a 1:1:1 ratio is not universally accepted, with many physicians unclear about how to adopt the results of PROPPR, where two interventions were evaluated simultaneously, e.g. high ratio FFP and early platelet administration (see below).

Following the PROPPR study, research has focussed on even earlier delivery of plasma with two prehospital RCTs published this year (Table I). The COMBAT study was a single centre RCT that compared 2 units of frozen plasma (thawed in the land ambulance) with normal saline in 144 trauma patients with haemorrhagic shock (Moore *et al*, 2018). There was no difference in 28-day mortality, safety profiles or transfusion use; however; prehospital times were short (median times from injury to admission were under half an hour) and just over half of patients required further transfusion in hospital. In contrast, the PAMPer Study, a larger, multi-centre, cluster-randomised study, compared 2 units AB, or A with low anti-B titre, thawed plasma with standard of care - where crystalloids were the resuscitation fluid of choice (Sperry *et al*, 2018). In the 501 patients randomised, mortality was significantly lower in the plasma group vs. control (23·3% vs. 33·0%, $P = 0{\cdot}03$). The separation in mortality rates was first

Table I. Summary of blood and plasma therapy randomised controlled trial trauma studies.

Study	Transfusion intervention evaluated	Pre- or in-hospital single or multi-centre	Intervention	Comparator	Primary endpoint	Primary endpoint result	Secondary endpoints			
							Transfusion	VTE	Organ failure	Other
Plasma studies										
PROPPR: Holcomb *et al* (2015)	FFP and plts	In-hospital Multi-centre	FFP:plts: RBC = 1:1:1 (n = 338)	FFP:plts: RBC = 1:1:2 (n = 342)	Mortality at 24 h and 30 days	NS difference in mortality at 24 h and 30 days	Intervention group received more plasma at 24 h (7U vs. 5U) and platelets (12U vs. 6U) NS difference in RBC at 24 h	NS	NS	Reduction in death from bleeding at 24 h (9·2% vs. 14·6%) More participants achieved haemostasis (86% vs. 78%)
PAMPer: Sperry *et al* (2018)	FFP	Pre-hospital Multi-centre	Plasma (n = 230)	Standard-care resuscitation (n = 271)	Mortality at 30 days	Reduction in mortality (23·3% vs. 33·0%)	Plasma group received fewer RBC at 24 h (3U vs. 4U)	NR	NS	Median PTr lower in plasma group (1·2 vs. 1·3) upon arrival at hospital
COMBAT: Moore *et al* (2018)	FFP	Pre-hospital Single centre	FFP (n = 65)	Normal saline (n = 60)	Mortality at 28d	NS difference in mortality	NS difference in RBC, FFP, plts or cryoprecipitate at 24 h	NS	NS	
TRAUCC: Garrigue *et al* (2017)	LyoPLAS	In-hospital Single centre	F-LyP (n = 24)	FFP (n = 24)	Fibrinogen level at 45 min	Higher fibrinogen level (mean difference 0·29 g/l)	NS difference in RBC, plasma, platelets at 24 h	NR	NR	F-LyP reduced the time to 1st unit of plasma (14 vs. 77 min) F-LyP improved PTr, FII and FV levels at 45 min and 6 h No difference in mortality
Whole blood studies										
Cotton *et al* (2013)	Modified WB	In-hospital Single centre	Modified WB (n = 55)	RBC + plasma (n = 52)	24-h transfusion volumes	NS differences	Excluding TBI patients – WB group received less RBC (3U vs. 6U), FFP (4U vs. 6U) and plts (0U vs. 3U) at 24 h	NR	NS	

F-LyP, French lyophilised plasma; FFP, fresh frozen plasma; NR, not reported; NS, not significant; Plts, platelets; PTr, prothrombin time ratio; RBC, red blood cells; TBI, traumatic brain injury; U, unit(s); VTE, venous thromboembolism, WB, whole blood.

Table II. Lyophilised plasma characteristics.

Product	F-LyP	LyoPlas N-w	Bioplasma FDP
Use	From 1994: French Military From 2011: Civilian	General population – Germany	General population – South Africa and surrounding countries
Manufacture	Lyophilised	Lyophilised	Lyophilised
	Pooled apheresis FFP (<11 donors)	Single donor	Pooled (up to 1,500 donors)
	All volunteer donors	Donor screening	All volunteer donors
	Donor screening	Haemovigilance programme	Donor screening
	Haemovigilance programme	Frozen for donor retest	Comprehensive testing
	Leucoreduced	Leucoreduced	Haemovigilance programme
	No HLA Ab+ women	No HLA Ab+ women	SD for PI
	Amotosalen for PI		
Plasma characteristics	Normal clotting factor levels	Normal clotting factor levels	Clotting factor levels ≥0·40 iu/ml
	ABO-universal	ABO type specific	ABO-universal
Shelf-life	2 years at RT	15 months at 2–25°C	To be stored below 25°C
Safety	No adverse events reported since 1994	No increase in adverse events	Contraindicated in severe protein S deficiency No increase in adverse events

Ab, antibody; FFP, fresh frozen plasma; HLA, human leucocyte antigen; PI, pathogen inactivation; RT, room temperature; SD, solvent detergent.

evident at 3 h from injury and persisted to 30 days. In addition, the median PT ratio (PTr) was lower in the plasma group vs. control [1·2 [interquartile range (IQR), 1·1–1·4] vs. 1·3 (IQR, 1·1–1·6), $P < 0·001$]. No differences were seen in adverse event rates or transfusion requirements and, of interest, patients with traumatic brain injury patients seemed to benefit more from early FFP than other groups.

These data are likely to direct mainstream clinical practice and, certainly, some UK helicopter emergency medical services (HEMS) already carry plasma on board. Nevertheless, thawed FFP has a relatively short shelf life once thawed (3–5 days) (3 days in the UK and up to 5 days in Canada and the US) and this confers practical challenges to blood banks and HEMS services. Additionally, it is known that levels of labile coagulation factors, such as FVIII and FV, fall during storage of thawed plasma. Lyophilised and dried plasmas have been evaluated in an attempt to avoid these difficulties.

Lyophilised plasma

The obvious advantage of using lyophilised plasma is the lack of need for refrigeration (a challenge particularly for military settings). Lyophilised plasma is most commonly manufactured by first freezing the plasma, then dehydrating it by sublimation under vacuum for several days. Less commonly, plasma can be spray dried by atomising the liquid plasma and exposing it briefly to a stream of hot, dry gas (Pusateri *et al*, 2016). Currently there are three available lyophilised plasmas (Table II): (i) French Lyophilised Plasma (F-LyP), produced by the French Military Blood Institute; (ii) LyoPlas N-w, a single donor product produced by the German Red Cross; (iii) Bioplasma FDP, produced by National Bioproducts Institute, South Africa. Lyophilised plasma has been used both in military (Shlaifer *et al*, 2017) and austere civilian (Sunde *et al*, 2015) settings. A small ($n = 48$) single centre open label RCT (NCT02750150, TRAUCC – Transfusion for Trauma-induced Coagulopathy and Fibrinogen Concentration trial) compared F-LyP with FFP on arrival at hospital for treatment of trauma haemorrhage and TIC (Garrigue *et al*, 2017) (Table I). The authors reported that F-LyP achieved a significantly higher fibrinogen level at 45 min [baseline-adjusted mean difference, 0·29 g/l; 95% confidence interval (CI), 0·08–0·49, $P = 0·006$] and at 6 h (baseline-adjusted mean difference, 0·51 g/l; 95% CI, 0·14–0·88, $P = 0·008$) and a greater improvement in coagulation factors FII and FV and PTr, both at 45 min and 6 h. F-LyP also reduced fibrinogen concentrate use and 30-day mortality was 22% (F-LyP) and 29% (FFP). A UK multicentre pre-hospital trauma study is currently ongoing (RePHILL, Resuscitation with Pre-Hospital Blood Products, EME 14/152/14) and is comparing 2 units RBCs and 2 units LyoPlas N-w vs. crystalloid resuscitation in 490 patients using a primary endpoint of lactate clearance and mortality in hospital.

Platelets

Platelet dysfunction is common after trauma and it would make sense intuitively to transfuse platelets to improve haemostatic potential in bleeding patients. However, to date, the effects of platelet transfusion remain unclear. For example, there are few observational studies that show benefit solely from platelet transfusion (Perkins *et al*, 2009; Inaba *et al*, 2010; Shaz *et al*, 2010) and, notably, all three of these studies suffered from significant survivorship bias (Hallet *et al*, 2013), whereas the two observational studies evaluating platelet effect that were deemed of higher quality, i.e. without survivor bias (Cotton *et al*, 2008; del Junco *et al*, 2013) were unable to show an overall mortality benefit. Looking more mechanistically, Vuillamy *et al* (2017) reported on the haemostatic effects of transfused platelets in 161 UK trauma patients who were actively bleeding, and showed that platelet transfusion was associated with increased PAI-1, reduced tPA and a decrease in ROTEM lysis measurements, but no improvement in platelet aggregation parameters. These results suggest platelet transfusion given during active bleeding may mitigate the fibrinolysis commonly seen. At present in the UK, many centres are using platelets in their second haemorrhage 'pack' and advising their use early within this pack (authors own unpublished observations).

Aside from the, as yet, unclear role that platelets have during traumatic bleeding, there are also practical issues. In many smaller hospitals, as well as in austere military settings, the ability to provide standard platelet concentrates (PCs) is challenging, mostly due to their short shelf life (between 5–7 days) and their specific storage requirements i.e. room temperature and continuous agitation.

Cryopreservation and cold storage techniques have been proposed as potential methods to prolong PC shelf life by reducing platelet metabolism and bacterial proliferation. Cryopreservation involves suspending platelets in dimethyl sulfoxide followed by frozen storage at −80°C, with subsequent thawing and resuspension in either plasma or saline (Marks, 2018). The wars in Iraq and Afghanistan highlighted the need for a safe PC with a long shelf life, and cryopreserved platelets (CRYO-PLT) have been issued since 2011 by the Netherlands Military Blood Bank (Lelkens *et al*, 2006), with promising clinical results (a reduction in mortality rates with higher platelet ratios) (Noorman *et al*, 2016).

However, CRYO-PLT appear more activated than standard PCs, with higher CD62P expression and increased phosphatidylserine exposure (Johnson *et al*, 2014), leading to concerns about the hypercoagulability of this product. *In vitro* studies have demonstrated that CRYO-PLTs contain 15 times as many microparticles as platelets stored at room temperature (RT-PLTs) and the microparticles confer the most haemostatic effect (Raynel *et al*, 2015). However, clinical studies so far have reported positive outcomes with good haemostatic efficacy and no increased thrombotic risk (Noorman *et al*, 2016). Nevertheless, even if CRYO-PLTs are established as safe and effective in civilian settings, there are significantly greater preparation times and equipment costs associated with PC cryopreservation, and thawing may be a barrier to widespread use. To date, CRYO-PLTs are approved for general use in France and for military operations in the Netherlands and Germany (Dumont *et al*, 2014), with other countries developing their use (Marks, 2018).

Cold-stored PCs (2–6°C) are an alternative to CRYO-PLTs and are easier to prepare and store. Cold-stored PCs have decreased bacterial contamination risks and improved haemostasis compared with RT-PLTs (Nair *et al*, 2014; Pidcoke *et al*, 2014). However, cold platelets are cleared from the circulation more rapidly than RT-PLTs, with an average life span of 1·3 days (vs. 3·9 days for RT-PLTs)(Reddoch *et al*, 2014). However, it could be argued that, for rapidly bleeding trauma patients, the most important objective is to arrest life-threatening bleeding rather than preserve platelet longevity *in vivo*. Indeed, in 2015, the US Food and Drug Administration (FDA) approved cold-stored PCs for resuscitation of bleeding patients in the US and data on their clinical efficacy in this setting are awaited. This development may lead to blood banks routinely storing platelets both at room temperature and at 2–6°C, depending on the indication for transfusion.

Lyophilised platelets are the fourth and final type of PC that are currently being evaluated. There are some promising pre-clinical studies using lyophilised platelets with good haemostasis achieved in a porcine model using species-specific lyophilised platelets (Inaba *et al*, 2014) but there have been no clinical studies demonstrating efficacy in trauma yet (Cap & Perkins, 2011).

Fibrinogen replacement

Fibrinogen is critical for effective haemostasis. It is the precursor of fibrin and is an important mediator of platelet aggregation, via the platelet receptor glycoprotein IIb/IIIa. Once cleaved by thrombin, fibrinogen forms a network of insoluble polymerised fibrin strands that act as a 'mesh' to support the formation of a stable clot. Both cryoprecipitate and fibrinogen concentrate are given during major haemorrhage to ameliorate hypofibrinogenaemia, and the choice of the blood component used depends commonly on the country of the treating physician (see Table III) (Wong & Curry, 2018).

Observational data support the importance of fibrinogen supplementation and have shown that low fibrinogen levels are an independent predictor of mortality (Rourke *et al*, 2012), as well as bleeding (Schöchl *et al*, 2011a). Despite it being known for over 20 years that fibrinogen is one of the first clotting factors to fall to clinically low levels (Hiippala *et al*, 1995), the central importance of fibrinogen replacement for effective haemostasis in major bleeding has only recently been recognised. This shift in thinking is likely to be a major reason behind the reports of increased cryoprecipitate use

Table III. Comparison of cryoprecipitate and fibrinogen concentrate.

	Cryoprecipitate	Fibrinogen concentrate (Riastap)
Manufacture	Europe: • SD plasma UK: • SD plasma • MB treated (given in UK to patients born after 1/1/1996)	Pooled human plasma (30–60 000 donors)
Concentration	15–17 g/l	20 g/l
Other factors	FVIII: mean 1·01 iu/ml Fn: 1500 μg/ml FXIII: mean 0·80 iu/ml VWF: mean 2·60 iu/ml	Not published
Variability	High	Standardised product
Cost	£181 per 2 g fibrinogen	£680 per 2 g fibrinogen
Volume for 2 g dose	~150 ml	100 ml
Viral inactivation	Nil in standard cryoprecipitate	Pasteurisation 60°C for 20 h Fibrinogen adsorption/ precipitation also removes virus
Adverse events	TRALI, TTI	TTI, thrombosis
Shelf-life	4–6 h once defrosted	24 h once reconstituted
Storage	12 months at −25°C or colder	5 years at room temperature
Speed of reconstitution/availability	17–20 min to thaw	~10 min
Blood group compatibility	Requires consideration	Not applicable
Recovery *in vivo*	4 g fibrinogen raises blood fibrinogen level by 1·0 g/l	

FFP, fresh frozen plasma; Fn, fibronectin; FVIII, factor VIII; FXIII, factor XIII; iu, international units; LyoPLAS, single donor lyophilised plasma; S/D, solvent detergent; TRALI, transfusion-related acute lung injury; TTI, transfusion-transmitted infection; VWF, von Willebrand factor.

(22% rise between 2011 and 2013 in UK), and increased fibrinogen concentrate use in Europe.

Higher quality data from RCT data are scarce – with only three pilot/feasibility studies having been published so far (Curry *et al*, 2015, 2018b; Nascimento *et al*, 2016), and one RCT comparing speed of delivery of fibrinogen concentrate to cryoprecipitate reporting preliminary data at a trauma conference this month (FEISTY, NCT02745041). The three pilot studies evaluated the feasibility of administering (i) CRYOSTAT-1 (ISRCTN55509212): 4 g fibrinogen (as 2 pools of cryoprecipitate); (ii) FiiRST (NCT02203968): 6 g fibrinogen concentrate and (iii) EFIT-1 (ISRCTN67540073): 6 g fibrinogen concentrate at timescales of 90, 60 and 45 min. Together the data show that the average time to fibrinogen delivery is between 45–60 min from admission and those patients in the intervention arms maintained their fibrinogen levels much higher during active bleeding than in the comparator arms (Table IV). The studies do not show an increase in thromboembolic risk with fibrinogen replacement, and overall no significant effect on mortality. These data provide preliminary data showing that early fibrinogen is safe and it is feasible to give it in a challenging clinical environment, however, none of the studies provide clinical efficacy outcome data.

CRYOSTAT-2 (ISRCTN 14998314) is a multicentre, international (UK-wide and selected US sites) trauma trial evaluating whether 6 g of early fibrinogen replacement (3 pools of cryoprecipitate) reduces mortality at 28 days in adults with major trauma haemorrhage (Marsden *et al*, 2018). Target recruitment is 1568 patients and is due to be completed in 2020. This trial will report for the first time whether fibrinogen replacement affects mortality and will undoubtedly bring about changes in transfusion practice and how fibrinogen is prioritised during active haemorrhage. Until then, it is likely that fibrinogen replacement will continue to be given empirically (or to maintain a fibrinogen level more than 1·5 g/l) as part of the MHP for trauma haemorrhage, based on consensus and observational data.

What about the differences between cryoprecipitate and fibrinogen concentrate (Table III)? The FEISTY study has directly compared speed of delivery of the two products in trauma and full results are awaited. Given the costs and logistics of a head-to-head trial, for the time-being it appears that industry is unlikely to fund a direct comparison between

Table IV. Comparisons of fibrinogen replacement trauma trials.

	E-FIT-1		FiiRST		CRYOSTAT-1	
	(ISRCTN67540073)		(NCT02203968)		(ISRCTN55509212)	
	FgC	Placebo	FgC	Placebo	CRYO	No CRYO
Feasibility of delivery						
Aim of study	45 min		60 min		90 min	
% achieved (95% CI)	69 (52–83)		85 (72–98)		85 (69–100)	N/A
Feasibility achieved?	No		Yes		Yes	
Speed of delivery of fibrinogen source (mean (standard deviation))						
Time from admission to administration of study intervention (min)	39 (14)	46 (25)	50 (8)	51 (9)	67 (21)	N/A
Fibrinogen blood level post therapy (mean (standard deviation- where available))						
Fibrinogen level (g/l)	2·8 (1·3) at 2 h	1·8 (0·6) at 2 h	2·7 g/l at 2 h	1·7 g/l at 2 h	2·5 g/l at 4 units RBC	1·5 g/l at 4 units RBC
Thrombotic complications						
Arterial %	1/20 (5·0%)	2/19 (10·5%)	0	0	0	1 (4·6%)
Symptomatic VTE %	2/20 (10·0%)	0	2 (9·5%)	1 (4·2%)	0	3 (14·3%)
Clinical outcomes						
Mortality %	10/24 (42%)	7/24 (29%)	2/20 (10%)	1/24 (4·2%)	2/20 (10%)	6/21 (28·6%)

CI, confidence interval; CRYO, cryopreservation; FgC, fibrinogen concentrate; N/A, not applicable; RBC, red blood cell.

these two products in a clinical trial powered for patient outcomes. Nevertheless, many view fibrinogen concentrate as a superior product to cryoprecipitate with reasons including: standardisation of production – vials contain a known fibrinogen concentration; lyophilisation making it easily portable and not requiring storage or thawing in blood bank; viral inactivation; and a consideration for the UK is a probable lower risk for variant Creutzfeldt-Jakob disease transmission (Wong & Curry, 2018). Gram for gram, fibrinogen concentrate is four times the cost of cryoprecipitate. On average it takes at least 10 min to reconstitute fibrinogen concentrate (Innerhofer *et al*, 2017) and once reconstituted, it must be administered within 24 h. By way of contrast, cryoprecipitate takes 17–20 min to defrost and once defrosted, it has a shelf-life of 4 h, increasing its potential for wastage. Blood services have been addressing this particular issue by exploring the effects of extended post-thaw shelf-life, both to 24 h (Sheffield *et al*, 2016) and 72 h (Green *et al*, 2016). In both studies, no significant reductions in fibrinogen, FVIII, FXIII or von Willebrand factor were found after storage at 20–24°C at either time point and ROTEM parameters were similar at 72 h – suggesting maintenance of haemostatic potential (Green *et al*, 2016). However, there remains concern about bacterial contamination in thawed cryoprecipitate, which would be stored at room temperature, and this potential risk currently prohibits the extension of the shelf-life.

There are theoretical reasons why cryoprecipitate may confer advantages over fibrinogen concentrate in trauma haemorrhage – for example increased levels of FXIII and alpha-2-anti-plasmin may confer increased clot resistance to fibrinolysis. These theories have not yet been explored, and in the UK, at present, cryoprecipitate remains the only licensed product for fibrinogen replacement in acquired bleeding.

Whole blood

There have been on-going questions about the role of whole blood in the management of trauma haemorrhage for many years. Many clinicians advocate its use because it provides a balanced product and returns to the patient 'what has been lost'. There are several forms of whole blood: fresh whole blood (FWB), cold stored whole blood (CWB) and cold fresh whole blood (CFWB), a product used within 48 h of collection (Table V). Whole blood that has been stored and tested for transfusion-transmitted infections (TTI) has been approved for use in the US by the FDA for massive blood loss. FWB is not licensed, however, due to its potential risks, which include TTI (a report of 10 000 FWB transfusions confirmed 1 hepatitis C virus and 1 human T-lymphotropic virus seroconversion and one death from transfusion-associated graft-versus-host disease) and the increased risk of ABO-mismatched blood being provided (Cap *et al*, 2018).

RCT evidence for the use of WB in trauma comes from a single centre study of 107 patients who were randomised

Table V. Comparisons of types of whole blood.

	FWB	CWB	LTOWB
Storage /shelf-life conditions	22°C for up to 8 h Maximum of an additional 24 h at 4°C	1–6°C: 21 days (if stored in non-adenine- anticoagulation) 35 days in CPDA-1	1–6°C: 21 days Collected in CPD
Process for collection	Collected from pre-tested donor pool Retrospective TTI testing	Leucodepleted TTI testing	Male donors Leucodepleted with a platelet sparing filter Low titre (<50) anti-A and anti-B donations only TTI testing
Haemostatic potential	Considered to be maximal	Haemostatic function may vary Supplementation with platelets may be required when CWB transfused after 14 days of storage	A moderate reduction in thrombin generation and clot strength measures using VHA following leucoreduction
ABO matching required	Yes	Yes	No
Associated risks	Higher risk of TTI Speed of process may increase risk of ABO incompatible transfusion		
Indication for use	Used only in military settings	FDA approved CWB for treatment of life-threatening bleeding	

CPD, citrate phosphate dextrose; CPDA-1, citrate phosphate dextrose adenine-1; CWB, cold stored whole blood; FDA, US Food and Drug Administration; FWB, fresh whole bloodLTOWB, low-titre, group O positive, leucoreduced, cold stored whole blood; TTI, transfusion-transmitted infection; VHA, viscoelastic assay.

to receive modified WB (where platelets were removed during leucofiltration) or standard blood component therapy (Cotton *et al*, 2013) (Table I). The primary endpoint, 24-h transfusion volume, was not different between arms, although in a subgroup analysis there was significant reduction in transfusion need in patients without traumatic brain injury.

FWB has been used in military operations, especially in austere or far forward environments (Daniel *et al*, 2016), and evidence from the battlefield has shown favourable outcomes when compared to component therapy (Nessen *et al*, 2013). The military use an emergency donor panel for collection and delivery of FWB (Strandenes *et al*, 2014), and this provides rapid access to warm FWB in the vicinity of the patient, without need for storage, transport or refrigeration. The blood is collected from pre-screened donors but does not undergo full TTI-testing prior to transfusion. This approach only allows for a small number of donations from each volunteer, invalidates the donor from giving further donations for 6–8 weeks, and needs high-quality systems to facilitate its conduct. Ideally, provision of FWB requires screening to avoid transmission of blood-borne infections (Spinella *et al*, 2007). Furthermore, FWB transfused without leucoreduction, in an attempt to maintain platelet function, may lead to an increase in the risk of acute lung injury and graft-versus-host disease (Gilstad *et al*, 2012).

Pre-screened, leucoreduced CWB may be a safer product, but these modifications impair platelet function and clotting capacity (Siletz *et al*, 2017). However, there is some evidence that CWB can be collected and stored for up to 14 days without detriment to its haemostatic function (Strandenes *et al*, 2015). After 2 weeks storage it seems that the haemostatic function becomes much more variable and, in particular, platelet function seems to be lost (Cap *et al*, 2018).

An additional practical issue that limits easy use of WB is the need to transfuse ABO-compatible blood. More recently, work has been undertaken to look at the safety of low-titre, group O positive, leucoreduced, CWB (LTOWB) as a universal WB product. This is particularly attractive for use in the pre-hospital or military setting. An observational civilian study of 172 bleeding trauma patients (102 non-group O and 70 group O) who received between 1–4 units of LTOWB was recently reported (Seheult *et al*, 2018). No increased haemolysis markers (lactate dehydrogenase, haptoglobin, bilirubin) were noted in the non-group O when compared with the group O patients and no adverse transfusion reactions were reported (Seheult *et al*, 2018). This study has led to the use of LTOWB units in 6 US study sites as standard clinical practice. In the UK, the National Health Service Blood and Transplant has recently embarked on the clinical evaluation of a "Red Cell and Plasma" product (leucodepleted and platelet filtered) for use with the London Air Ambulance and work continues on developing a platelet rich, leucodepleted product quality assured for UK practice.

Non-fibrinogen factor concentrates

Single (e.g. recombinant activated FVII, rFVIIa, FXIII) and combined factor concentrate therapies (e.g. prothrombin complex concentrates, PCC) have been used for traumatic bleeding. Two RCTs have been published looking at the effectiveness of rFVIIa in trauma (Boffard *et al*, 2005; Hauser *et al*, 2010). The primary endpoint in the first trial was transfusion requirement; the second trial, powered for mortality, was closed early due to slow recruitment and futility. Both reported a reduction in RBC use following rFVIIa administration in blunt trauma but no improvement in mortality. A systematic review of the rFVIIa RCT literature, including trauma, indicated no evidence to support rFVIIa as standard treatment for traumatic bleeding and raised concerns about increased risks of thrombotic events (Simpson *et al*, 2012). The RETIC trial (Innerhofer *et al*, 2017) compared FFP with factor concentrates (including fibrinogen and FXIII) using ROTEM-guided triggers. It was not possible to differentiate the effect of FXIII in this study and no other RCT has evaluated FXIII in the trauma setting.

PCC are plasma-derived coagulation factor concentrates that contain 3 or 4 vitamin K-dependent factors at high concentration and are commonly used to reverse vitamin-K antagonist therapy. PCC has been used also as first line therapy for TIC in some countries. Two observational European cohort studies described the use of PCC in trauma, as an adjunct to fibrinogen concentrate, and reported reduced transfusion need in one but no mortality improvement in either study (Nienaber *et al*, 2011; Schöchl *et al*, 2011b). A US group compared 4-factor PCC (4-PCC) plus FPP ($n = 40$) with FFP alone ($n = 80$) in an observational study and reported reduction in RBC (7 vs. 9units) and FFP (5 vs. 7 units) use, as well as a lower mortality (25% vs. 33%) in the PCC plus FFP arm. No difference was seen in thromboembolic events (2·5% vs. 1·2%) (Jehan *et al*, 2018). No RCT data are available, and there remain unanswered questions about the safety of PCC in this setting, particularly in relation to thrombotic events (Grottke *et al*, 2011).

Future directions

The transfusion strategies that have been employed to date have focussed on 'replacing what is lost/missing' and this could be thought of as a simplistic view. Certainly, it is an important part of the resuscitation process, and significant improvements in mortality have been linked to this approach. There is much more work that is currently ongoing, looking at how to maximise the potential of the blood and blood components that are available both in pre-clinical or clinical settings, including better storage methods. The increase in numbers of small and large RCTs is also encouraging, as these studies provide clinicians with high quality evidence about how to improve clinical practice and patient outcomes. One important strategy that will continue to support high quality trauma research is a focus on strengthening collaborative approaches, using international networks such as the International Trauma Research Network (INTRN) or the Biomedical Excellence for Safer Transfusion (BEST) collaborative. These types of international networks will facilitate and guide large, well-co-ordinated, high quality studies in how best to treat major trauma haemorrhage with transfusion and haemostatic therapies.

However, using a 'replace what is missing' strategy alone fails to address the endothelial activation (the 'endotheliopathy' of trauma) that goes hand-in-hand with the physiological changes of shock and severe haemorrhage (Naumann *et al*, 2018). An additional focus for both civilian and military settings will be to address these endothelial changes, and the inflammatory processes, as well as direct transfusion therapy towards a more personalised approach. The added focus for military settings will also be on the delivery of haemostatic products that do not require refrigeration, are temperature stable, lightweight, safe and can be carried easily.

Conclusions

The world of trauma transfusion has seen an explosion of high quality small and large RCTs which have led to marked practice changes and improved mortality globally. The next few years will probably see further significant shifts in the management of haemostatic resuscitation.

Author contributions

NC and RD conceived and wrote the manuscript. Both authors reviewed and approved the final version of the manuscript before submission.

References

Bakaas-Aasen, K., Van Dieren, S., Balvers, K., Juffermans, N.P., Noess, P.A., Rourke, C., Eaglestone, S., Ostrowski, S.R., Stensballe, J., Stanworth, S., Maegele, M., Goslings, C., Johansson, P.I., Brohi, K. & Gaarder, C.; the TACTIC/INTRN collaborators. (2018) Data-driven development of ROTEM and TEG algorithms for the management of trauma haemorrhage. A prospective observational multicentre study. *Annals of Surgery*, [e-pub, ahead of print] https://doi.org/10.1097/sla.0000000000002825

Boffard, K.D., Riou, B., Warren, B., Choong, P.I., Rizoli, S., Rossaint, R., Axelsen, M. & Kluger, Y.; NovoSeven Trauma Study Group. (2005) Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *Journal of Trauma*, **59**, 8–18.

Bolliger, D., Görlinger, K. & Tanaka, K.A. (2010) Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *Anesthesiology*, **113**, 1205–1219.

Booth, C. & Allard, S. (2018) Major haemorrhage protocols. *ISBT Science Series*, **13**, 219–228.

Brohi, K., Singh, J., Heron, M. & Coats, T. (2003) Acute traumatic coagulopathy. *Journal of Trauma*, **54**, 1127–1130.

Brohi, K., Cohen, M.J., Ganter, M.T., Schultz, M.J., Levi, M., Mackenersie, R.C. & Pittet, J.F. (2008) Acute traumatic coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *Journal of Trauma*, **64**, 1211–1217.

Campbell, H.E., Stokes, E.A., Bargo, D.N., Curry, N., Lecky, F.E., Edwards, A., Woodford, M., Seeney, F., Eaglestone, S., Brohi, K., Gray, A.M. & Stanworth, S.J. (2015) Quantifying the healthcare costs of treating severely bleeding major trauma patients: a national study for England. *Critical Care*, **19**, 276.

Cap, A.P. & Hunt, B. (2014) Acute traumatic coagulopathy. *Current Opinion in Critical Care*, **20**, 638–645.

Cap, A.P. & Perkins, J.G. (2011) Lyophilized platelets: challenges and opportunities. *Journal of Trauma*, **7** (5 Suppl), S59–S60.

Cap, A.P., Beckett, A., Benov, A., Borgman, M., Chen, J., Corley, J.B., Doughty, H., Fisher, A., Glasberg, E., Gonzales, R., Kane, S.F., Malloy, W.W., Nessen, S., Perkins, J.G., Prat, N., Quesada, J., Reade, M., Sailliol, A., Spinella, P.C., Stockinger, Z., Strandenes, G., Taylor, A., Yazer, M., Bryant, B. & Gurney, J. (2018) Whole blood transfusion. *Military Medicine*, **183**, 44–51.

Cardenas, J.C., Rahbar, E., Pommerening, M.J., Baer, L.A., Matijevic, N., Cotton, B.A., Holcomb, J.B. & Wade, C.E. (2014) Measuring thrombin generation as a tool for predicting haemostatic potential and transfusion requirements following trauma. *Journal of Trauma and Acute Care Surgery*, **7**, 839–845.

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) Fatal Injury Data. (2017). Available at: https://www.cdc.gov/injury/wisqars/fatal.html (accessed 13 October 2018).

Chapman, M.P., Moore, E.E., Moore, H.B., Gonzalez, E., Gamboni, F., Chandler, J.G., Mitra, S., Ghasabyan, A., Chin, T.L., Sauaia, A., Banerjee, A. & Silliman, C.C. (2016) Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in severely injured trauma patients. *Journal of Trauma and Acute Care Surgery*, **80**, 16–23.

Cohen, M.J., Kutcher, M., Redick, B., Nelson, M., Call, M., Knudson, M.M., Schreiber, M.A., Bulger, E.M., Muskat, P., Alarcon, L.H., Myers, J.G., Rahbar, M.H., Brasel, K.J., Phelan, H.A., del Junco, D.J., Fox, E.E., Wade, C.E., Holcomb, J.B., Cotton, B.A. & Matijevic, N.; PROMMTT Study Group. (2013) Clinical and mechanistic drivers of acute traumatic coagulopathy. *Journal of Trauma and Acute Care Surgery*, **75** (Suppl), S40–S47.

Cotton, B.A., Gunter, O.L., Isbell, J., Au, B.K., Robertson, A.M., Morris, J.A. Jr, St Jaques, P. & Young, P.P. (2008) Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *Journal of Trauma*, **64**, 1177–1182.

Cotton, B.A., Reddy, N., Hatch, Q.M., LeFebyre, E., Wade, C.E., Kozar, R.A., Gill, B.S., Albarado, R., McNutt, M.K. & Holcomb, J.B. (2011a) Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. *Annals of Surgery*, **254**, 598–605.

Cotton, B.A., Faz, G., Hatch, Q.M., Radwan, Z.A., Podbielski, J., Wade, C., Kozar, R.A. & Holcomb, J.B. (2011b) Rapid thrombelastography delivers real-time results that predict transfusion within 1 hour of admission. *Journal of Trauma*, **71**, 407–417.

Cotton, B.A., Podbielski, J., Camp, E., Welch, T., del Junco, D., Bai, Y., Hobbs, R., Scroggins, J., Hartwell, B., Kozar, R.A., Wade, C.E. & Holcomb, J.B. (2013) A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. *Annals of Surgery*, **258**, 527–532.

CRASH-2 trial collaborators. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*, **376**, 23–32.

CRASH-2 trial collaborators. (2011) The importance if early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*, **377**, 1096–1101.

Curry, N.S., Hopewell, S., Doree, C., Hyde, C., Brohi, K. & Stanworth, S. (2011) The acute management of trauma hemorrhage: a systematic review of randomized controlled trials. *Critical Care*, **15**, R92.

Curry, N., Rourke, C., Davenport, R., Beer, S., Pankhurst, L., Deary, A., Thomas, H., Llewelyn, C., Green, L., Doughty, H., Nordmann, G., Brohi, K. & Stanworth, S. (2015) Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. *British Journal of Anaesthesia*, **115**, 76–83.

Curry, N.S., Davenport, R., Pavord, S., Mallett, S.V., Kitchen, D., Klein, A.A., Maybury, H., Collins, P.W. & Laffan, M. (2018a) The use of viscoelastic haemostatic guidelines in the management of major bleeding: a British Society for Haematology Guideline. *British Journal of Haematology*, **182**, 789–806.

Curry, N., Foley, C., Wong, H., Mora, A., Curnow, E., Zarankaite, A., Hodge, R., Hopkins, V., Deary, A., Ray, J., Moss, P., Reed, M.J., Kellett, S., Davenport, R. & Stanworth, S. (2018b) Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT-1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. *Critical Care*, **18**, 164.

Daniel, Y., Habas, S., Malan, L., Escarment, J., David, J.S. & Peyrefitte, S. (2016) Tactical damage control resuscitation in austere military environments. *Journal Royal Army Medical Corps*, **162**, 419–427.

Davenport, R.A. & Brohi, K. (2016) Cause of trauma-induced coagulopathy. *Current Opinion in Anaesthesiology*, **29**, 212–219.

Davenport, R., Manson, J., De'Ath, H., Platton, S., Coates, A., Allard, S., Hart, D., Pearse, R., Pasi, K.J., MacCallum, P., Stanworth, S. & Brohi, K. (2011) Functional definition and characterization of acute traumatic coagulopathy. *Critical Care Medicine*, **39**, 2652–2658.

Davenport, R.A., Guerreiro, M., Rourke, C., Platton, S., Cohen, M., Pearse, R., Thiemermann, C. & Brohi, K. (2017) Activated protein C drives the hyperfibrinolysis of acute traumatic coagulopathy. *Anesthesiology*, **126**, 115–127.

Dumont, L.J., Slichter, S.J. & Reade, M.C. (2014) Cryopreserved platelets: frozen in a logjam? *Transfusion*, **54**, 1907–1910.

Dunbar, N.M. & Chandler, W.L. (2009) Thrombin generation in trauma patients. *Transfusion*, **49**, 2652–2660.

Frith, D., Goslings, J.C., Gaarder, C., Maegele, M., Cohen, M.J., Allard, S., Johansson, P.I., Stanworth, S., Thiemermann, C. & Brohi, K. (2010) Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. *Journal of Thrombosis and Haemostasis*, **8**, 1919–1925.

Gall, L.S., Vulliamy, P., Gillespie, S., Jones, T.F., Pierre, R.S.J., Breukers, S.E., Gaarder, C., Juffermans, N.P., Maegele, M., Stensballe, J., Johansson, P.I., Davenport, R.A. & Brohi, K.; Targeted Action for Curing Trauma-Induced Coagulopathy (TACTIC) partners. (2018) The S100A10 pathway mediates an occult hyperfibrinolytic subtype in trauma patients. *Annals of Surgery*. https://doi.org/10.1097/SLA.0000000000002733

Garrigue, D., Godier, A., Glacet, A., Labreuche, J., Kipnis, E., Paris, C., Duhamel, A., Resch, A., Bauters, A., Machuron, F., Renom, P., Goldstein, P., Tavernier, B., Sailliol, A. & Susen, S. (2017) French lyophilised plasma versus fresh frozen plasma for the initial management of trauma-induced coagulopathy: a randomized open-label trial. *Journal of Thrombosis and Haemostasis*, **16**, 481–489.

Gayet-Ageron, A., Prieto-Merino, D., Ker, K., Shakur, H., Ageron, F.X., Roberts, I. & Collaboration, Antifibrinolytics Trials (2018) Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet*, **3910**, 125–132.

Gilstad, C., Roschewski, M., Wells, J., Delmas, A., Lackey, J., Uribe, P., Popa, C., Jardeleza, T. & Roop, S. (2012) Fatal transfusion-associated graft-versus-host disease with concomitant immune hemolysis in a group A combat trauma patient resuscitated with group O fresh whole blood. *Transfusion*, **52**, 930–935.

Gonzalez, E., Moore, E.E., Moore, H.B., Chapman, M.P., Chin, T.L., Ghasabyan, A., Wohlauer, M.V., Barnett, C.C., Bensard, D.D., Biffl, W.L.,

Burlew, C.C., Johnson, J.L., Pieracci, F.M., Jurkovich, G.J., Banerjee, A., Silliman, C.C. & Sauaia, A. (2016) Goal-directed hemostatic resuscitation of trauma-induced coagulopathy a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. *Annals of Surgery*, **263**, 1051–1059.

Green, L., Backholer, L., Wiltshire, M., Platton, S., Stanworth, S.J. & Cardigan, R. (2016) The hemostatic properties of thawed pooled cryoprecipitate up to 72 hours. *Transfusion*, **56**, 1356–1361.

Griggs, J.E., Jeyanathan, J., Joy, M., Russell, M.Q., Durge, N., Bootland, D., Dunn, S., Sausmarez, E.D., Wareham, G., Weaver, A. & Lyon, R.M.; on behalf of Kent, Surrey & Sussex Air Ambulance Trust. (2018) Mortality of civilian patients with suspected traumatic haemorrhage receiving pre-hospital transfusion of packed red blood cells compared to pre-hospital crystalloid. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, **26**, 100.

Grottke, O., Braunschweig, T., Spronk, H.M., Esch, S., Rieg, A.D., van Oerle, R., ten Cate, H., Tolba, R. & Rossaint, R. (2011) Increasing concentrations of prothrombin complex concentrate induce DIC in a pig model of coagulopathy with blunt liver injury. *Blood*, **118**, 1943–1951.

Hagemo, J.S., Christiaans, S.C., Stanworth, S.J., Brohi, K., Johansson, P.I., Goslings, J.C., Naess, P.A. & Gaarder, C. (2015) Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. *Critical Care*, **19**, 97.

Hallet, J., Lauzier, F., Mailloux, O., Trottier, V., Archambault, P., Zarychanski, R. & Turgeon, A.F. (2013) The use of higher platelet: RBC transfusion ratio in the acute phase of trauma resuscitation: a systematic review. *Critical Care Medicine*, **41**, 2800–2811.

Hauser, C.J., Boffard, K., Dutton, R., Bernard, G.R., Croce, M.A., Holcomb, J.B., Leppaniemi, A., Parr, M., Vincent, J.L., Tortella, B.J., Dimsits, J. & Bouillon, B.; CONTROL Study Group. (2010) Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. *Journal of Trauma*, **69**, 489–500.

Hiippala, S.T., Myllylä, G.J. & Vahtera, E.M. (1995) Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesthesia and Analgesia*, **81**, 360–365.

Holcomb, J., del Junco, D.J., Fox, E.E., Wade, C.E., Cohen, M.J., Schreiber, M.A., Alarcon, L.H., Bai, Y., Brasel, K.J., Bulger, E.M., Cotton, B.A., Matijevic, N., Muskat, P., Myers, J.G., Phelan, H.A., White, C.E., Zhang, J. & Rahbar, M.H.; PROMMTT Study Group. (2013) The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *Journal of the American Medical Association Surgery*, **148**, 127–136.

Holcomb, J., Tilley, B.C., Baraniuk, S., Fox, E.E., Wade, C.E., Podbileski, J.M., del Junco, D.J., Brasel, K.J., Bulger, E.M., Callcut, R.A., Cohen, M.J., Cotton, B.A., Fabian, T.C., Inaba, K., Kerby, J.D., Muskat, P., O'Keeffe, T., Rizoli, S., Robinson, B.R., Scalea, T.M., Schreiber, M.A., Stein, D.M., Weinberg, J.A., Callum, J.L., Hess, J.R., Matijevic, N., Miller, C.N., Pittet, J.F., Hoyt, D.B., Pearson, G.D., Leroux, B. & van Belle, G.; PROPPR Study Group. (2015) Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma. The PROPPR randomized clinical trial. *Journal of the American Medical Association*, **313**, 471–482.

Hunt, B.J., Allard, S., Keeling, D., Norfolk, D., Stanworth, S.J. & Pendry, K.; on behalf of the BCSH. (2015) A practical guideline for the haematological management of major haemorrhage. *British Journal of Haematology*, **170**, 788–803.

Inaba, K., Lustenberger, T., Rhee, P., Holcomb, J.B., Blackbourne, L.H., Shulman, I., Nelson, J., Talving, P. & Demetriades, D. (2010) The impact of platelet transfusion in massively transfused trauma patients. *Journal of the American College of Surgeons*, **211**, 573–579.

Inaba, K., Barmparas, G., Rhee, P., Branco, B.C., Fitzpatrick, M., Okoye, O.T. & Demetriades, D. (2014) Dried platelets in a swine model of liver injury. *Shock*, **41**, 429–434.

Innerhofer, P., Fries, D., Mittermayr, M., Innerhofer, N., von Langen, D., Hell, T., Gruber, G., Schmid, S., Friesenecker, B., Lorenz, I.H., Strohle, M., Rastner, V., Trubsbach, S., Raab, H., Treml, B., Wally, D., Treichl, B., Mayr, A., Kranewitter, C. & Oswald, E. (2017) Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. *Lancet Haematology*, **4**, e258–e271.

Jehan, F., Aziz, H., O'Keefe, T., Khan, M., Zakaria, E.R., Hamidi, M., Zeeshan, M., Kulvatunyou, N. & Joseph, B. (2018) The role of four-factor prothrombin complex concentrate in coagulopathy of trauma: a propensity matched analysis. *Journal of Trauma and Acute Care Surgery*, **85**, 18–24.

Johansson, P.I., Stensballe, J., Rasmussen, L.S. & Ostrowski, S.R. (2011) A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. *Annals of Surgery*, **254**, 194–200.

Johnson, L., Coorey, C.P. & Marks, D.C. (2014) The haemostatic activity of cryopreserved platelets is mediated by phosphatidylserine-expressing platelets and platelet microparticles. *Transfusion*, **54**, 1917–1926.

del Junco, D.J., Holcomb, J.B., Fox, E.E., Brasel, K.J., Phelan, H.A., Bulger, E.M., Schreiber, M.A., Muskat, P., Alarcon, L.H., Cohen, M.J., Cotton, B.A., Wade, C.E., Myers, J.G. & Rahbar, M.H.; on behalf of the PROMMTT Study Group. (2013) Resuscitate early with plasma and platelets or balance blood products gradually: findings from the prospective, observational, multicenter, major trauma transfusion (PROMMTT) study. *Journal of Trauma and Acute Care Surgery*, **75** (Suppl) , S24–S30.

Khan, S., Davenport, R., Raza, I., Glasgow, S., De'Ath, H.D., Johansoon, P.I., Curry, N., Stanworth, S., Gaarder, C. & Brohi, K. (2015) Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma haemorrhage. *Intensive Care Medicine*, **41**, 239–247.

Kozar, R.A., Peng, Z., Zhang, R., Holcomb, J.B., Pati, S., Park, P., Ko, T.C. & Paredes, A. (2011) Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesthesia and Analgesia*, **112**, 1289–1295.

Kutcher, M.E., Redick, B.J., McCreery, R.C., Crane, I.M., Greenberg, M.D., Cachola, L.M., Nelson, M.F. & Cohen, M.J. (2012) Characterization of platelet dysfunction after trauma. *Journal of Trauma and Acute Care Surgery*, **73**, 13–19.

Lelkens, C.C., Koning, J.G., de Kort, B., Floot, I.B. & Noorman, F. (2006) Experiences with frozen blood products in the Netherlands military. *Transfusion Apheresis Science*, **34**, 289–298.

Lord, J.M., Midwinter, M.J., Chen, Y.-F., Belli, A., Brohi, K., Kovacs, E.J., Koenderman, L., Kubes, P. & Lilford, R.J. (2014) The systemic immune response to trauma: an overview of pathophysiology and treatment. *Lancet*, **384**, 1455–1465.

MacLeod, J.B., Lynn, M., McKenny, M.G., Cohn, S.M. & Murtha, M. (2003) Early coagulopathy predicts mortality in trauma. *Journal of Trauma*, **55**, 39–44.

Maegele, M., Lefering, R., Yucel, N., Tjardes, T., Rixen, D., Paffrath, T., Simanski, C., Neugebauer, E. & Bouillon, B.; AG Polytrauma of the German Trauma Society (DGU). (2007) Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury*, **38**, 298–304.

Marks, D. (2018) Cryopreserved platelets: are we there yet? *Transfusion*, **58**, 2092–2094.

Marsden, M., Benger, J., Brohi, K., Curry, N., Foley, C., Green, L., Lucas, J., Rossetto, A., Stanworth, S., Thomas, H. & Davenport, R.; on behalf of the CRYOSTAT-2 investigators. (2018) Coagulopathy, cryoprecipitate and CRYOSTAT-2: realising the potential of a nationwide trauma system for a national clinical trial. *British Journal of Anaesthesia*. https://doi.org/10.1016/j.bja.2018.10.055

Meyer, A.S., Meyer, M.A.S., Sorensen, A.M., Rasmussen, L.S., Hansen, M.B., Holcomb, J.B., Cotton, B.A.C., Wade, C.E., Ostrowski, S.R. & Johansson, P.I. (2014) Thrombelastography and rotational thromboelastometry early amplitudes in 182 trauma patients with clinical suspicion of severe injury. *Journal of Trauma and Acute Care Surgery*, **76**, 682–690.

Moore, H.B., Moore, E.E., Chapman, M.P., Gonzalez, E., Slaughter, A.L., Morton, A.P.,

D'Alessandro, A., Hansen, K.C., Sauaia, A., Banerjee, A. & Silliman, C.C. (2015) Viscoelastic measurements of platelet function, not fibrinogen function, predicts sensitivity to tissue-type plasminogen activator in trauma patients. *Journal of Thrombosis and Haemostasis*, **13**, 1878–1887.

Moore, H.B., Moore, E.E., Chapman, M.P., Huebner, B.R., Einersen, P.M., Oushy, S., Silliman, C.C., Banerjee, A. & Sauaia, A. (2017) Viscoelastic tissue plasminogen activator challenge predicts massive transfusion in 15 minutes. *Journal of the American College of Surgeons*, **225**, 138–147.

Moore, H.B., Moore, E.E., Chapman, M.P., McVaney, K., Bryskiewicz, G., Blechar, R., Chin, T., Burlew, C.C., Pieracci, F., West, F.B., Fleming, C.D., Ghasabayan, A., Chandler, J., Silliman, C.C., Banerjee, A. & Sauaia, A. (2018) Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. *Lancet*, **392**, 283–291.

Murad, M.H., Stubbs, J.R., Gandhi, M.J., Wang, A.T., Paul, A., Erwin, P.J., Montori, V.M. & Roback, J.D. (2010) The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. *Transfusion*, **50**, 1370–1383.

Nair, P.M., Pidcoke, H.F., Cap, A.P. & Ramasubramanian, A.K. (2014) Effect of cold storage on shear induced platelet aggregation and clot strength. *Journal of Trauma and Acute Care Surgery*, **77**, S88–S93.

Nascimento, B., Callum, J., Tien, H., Rubenfeld, G., Pinto, R., Lin, Y. & Rizoli, S. (2013) Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory-results-guided transfusion in patients with severe trauma: a randomized feasibility trial. *Canadian Medical Association Journal*, **185**, E583–E589.

Nascimento, B., Callum, J., Tien, H., Peng, H., Rizoli, S., Karanicolas, P., Alam, A., Xiong, W., Selby, R., Garzon, A.-M., Colavecchia, C., Howald, R., Nathens, A. & Beckett, A. (2016) Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. *British Journal of Anaesthesia*, **117**, 775–782.

National Clinical Guideline Centre. (2016) Major trauma: assessment and initial management. NICE Guideline NG39 ©2016 National Clinical Guideline Centre. Available at: www.nice.org.uk/guidance/ng39/evidence/full-guideline-2308122833 Pages 236-239 (accessed 14 October 2018)

Naumann, D.N., Khan, M.A., Smith, J.E., Rickard, R. & Wooley, T. (2018) Future strategies for remote damage control resuscitation after traumatic haemorrhage. *Journal of Trauma*. https://doi.org/10.1097/TA.0000000000002080)

Nessen, S.C., Eastridge, B.J., Cronk, D., Craig, R.M., Berseus, O., Ellison, R., Remick, K., Seery, J., Shah, A. & Spinella, P.C. (2013) Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets. *Transfusion*, **53** (Suppl 1), 107S–113S.

Nienaber, U., Innerhofer, P., Westermann, I., Schöchl, H., Attal, R., Breitkopf, R. & Maegele, M. (2011) The impact of fresh frozen plasma vs. coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. *Injury*, **42**, 697–701.

Noorman, F., van Dongen, T.T., Plat, M.J., Badloe, J.F., Hess, J.R. & Hoencamp, R. (2016) Transfusion: -80 degrees C frozen blood products are safe and effective in military casualty care. *Public Library of Science One*, **11**, e0168401.

Perkins, J.G., Cap, A.P., Spinella, P.C., Blackbourne, L.H., Grathwohl, K.W., Repine, T.B., Ketchum, L., Waterman, P., Lee, R.E., Beekley, A.C., Sebesta, J.A., Shorr, A.F., Wade, C.E. & Holcomb, J.B. (2009) An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients. *Journal of Trauma*, **66**, S77–S84.

Pidcoke, H.F., Spinella, P.C., Ramasubramanian, A.K., Strandenes, G., Hervig, T., Ness, P.M. & Cap, A.P. (2014) Refrigerated platelets for the treatment of acute bleeding: a review of the literature and re-examination of current standards. *Shock*, **41** (Suppl), S51–S53.

Pohlman, T.H., Fecher, A.M. & Arreola-Garcia, C. (2018) Optimizing transfusion strategies in damage control resuscitation: current insights. *Journal of Blood Medicine*, **9**, 117–133.

Pusateri, A.E., Given, M.B., Schreiber, M.A., Spinella, P.C., Pati, S., Kozar, R.A., Khan, A., Dacorta, J.A., Kupferer, K.R., Prat, N., Pidcoke, H.F., Macdonald, V.W., Malloy, W.W., Sailliol, A. & Cap, A.P. (2016) Dried plasma: state of the science and recent developments. *Transfusion*, **56** (Suppl), S128–S139.

Raynel, S., Padula, M.P., Marks, D.C. & Johnson, L. (2015) Cryopreservation alters the membrane and cytoskeletal protein profile of platelet microparticles. *Transfusion*, **55**, 2422–2432.

Raza, I., Davenport, R., Rourke, C., Platton, S., Manson, J., Spoors, C., Khan, S., De'Ath, H.D., Allard, S., Hart, D.P., Pasi, K.J., Hunt, B.J., Stanworth, S., MacCallum, P.K. & Brohi, K. (2013) The incidence and magnitude of fibrinolytic activation in trauma patients. *Journal of Thrombosis and Haemostasis*, **11**, 307–314.

Reddoch, K.M., Pidcoke, H.F., Montgomery, R.K., Fedyk, C.G., Aden, J.K., Ramasubramanian, A.K. & Cap, A.P. (2014) Hemostatic function of apheresis platelets stored at 4°C and 22°C. *Shock*, **41** (Suppl), S54–S61.

Rehn, M., Weaver, A., Brohi, K., Eshelby, S., Green, L., Roislien, J. & Lockey, D.J. (2018) Effect of pre-hospital red blood cell transfusion on mortality and time of detah in civilian trauma patients. *Shock*. https://doi.org/10.1097/SHK.0000000000001166

Rossaint, R., Bouillon, B., Cerny, V., Coats, T.J., Duranteau, J., Fernandez-Mondejar, E., Filipescu, D., Hunt, B.J., Komadina, R., Nardi, G., Neugebauer, E.A.M., Ozier, Y., Riddez, L., Schultz, A., Vincent, J-L. & Spahn, D.R. (2016) The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Critical Care*, **20**, 100.

Rourke, C., Curry, N., Khan, S., Taylor, R., Raza, I., Davenport, R., Stanworth, S. & Brohi, K. (2012) Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *Journal of Thrombosis and Haemostasis*, **10**, 1342–1351.

Schafer, N., Driessen, A., Frohlich, M., Sturmer, E.K., Maegele, M.; TACTIC partners. (2015) Diversity in clinical management and protocols for the treatment of major bleeding trauma patients across European level 1 Trauma Centres. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, **23**, 74.

Schöchl, H., Cotton, B., Inaba, K., Nienaber, U., Fischer, H., Voelckel, W. & Solomon, C. (2011a) FIBTEM provides early prediction of massive transfusion in trauma. *Critical Care*, **15**, R265.

Schöchl, H., Nienaber, U., Maegele, M., Hochleitner, G., Primavesi, G., Steitz, B., Arndt, C., Hanke, A., Voelckel, W. & Solomon, C. (2011b) Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Critical Care*, **15**, R83.

Seheult, J.N., Bahr, M., Anto, V., Alarcon, L.H., Corcos, A., Sperry, J.L., Triulzi, D.J. & Yazer, M.H. (2018) safety profile of uncrossmatched, cold-stored, low-iter, group O+ whole blood in civilian trauma patients. *Transfusion*, **58**, 2280–2288.

Shaz, B.H., Dente, C.J., Nicholas, J., MacLeod, J.B., Young, A.N., Easley, K., Ling, Q., Harris, R.S. & Hillyer, C.D. (2010) Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. *Transfusion*, **50**, 493–500.

Sheffield, W.P., Bhakta, V. & Jenkins, C. (2016) Stability of coagulation protein activities in single units or pools of cryoprecipitate during storage at 20-24°C for up to 24 h. *Vox Sanguinis*, **110**, 12–19.

Shlaifer, A., Siman-Tov, M., Radomislensky, I., Peleg, K., Shina, A., Baruch, E.N., Glassberg, E. & Yitzhak, A. (2017) Prehospital administration of freeze-dried plasma, is it the solution for trauma casualties? *Journal of Trauma and Acute Care Surgery*, **83**, 675–682.

Siletz, A., Burruss, S., Gruber, T., Ziman, A., Marder, V. & Cryer, H.M. (2017) Leukocyte filtration lesion impairs functional coagulation in banked whole blood. *Journal of Trauma and Acute Care Surgery*, **83**, 420–426.

Simpson, E., Lin, Y., Stanworth, S., Birchall, J., Doree, C. & Hyde, C. (2012) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews*, **14**, CD005011.

Solomon, C., Traintinger, S., Ziegler, B., Hanke, A., Rahe-Meyer, N., Voelckel, W. & Schochl, H. (2011) Platelet function following trauma. A

multiplate electrode aggregometry study. *Thrombosis Haemostasis*, **106**, 322–330.

Sperry, J.L., Guyette, F.X., Brown, M.H., Yazer, M.H., Triulzi, D.J., Early-Young, B.J., Adams, P.W., Daley, B.J., Miller, R.S., Harbrecht, B.G., Claridge, J.A., Phelan, H.A., Witham, W.R., Putnam, A.T., Duane, T.M., Alarcon, L.H., Callaway, C.W., Zuckerbraun, B.S., Neal, M.D., Rosengart, M.R., Forsythe, R.M., Billiar, T.R., Peitzman, A.B. & Zenati, M.S.; for the PAMPer Study Group. (2018) Prehospital plasma during air medical transport in trauma patients at risk for haemorrhagic shock. *New England Journal of Medicine*, **379**, 315–326.

Spinella, P.C., Perkins, J.G., Grathwohl, K.W., Repine, T., Beekley, A.C., Sebesta, J., Jenkins, D., Azarow, K. & Holcomb, J.B. (2007) Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital. *Critical Care Medicine*, **35**, 2576–2581.

Strandenes, G., De Pasquale, M., Cap, A.P., Hervig, T.A., Kristoffersen, E.K., Hickey, M., Cordova, C., Berseus, O., Eliassen, H.S., Fisher, L., Williams, S. & Spinella, P.C. (2014) Emergency whole-blood use in the field: a simplified protocol for collection and transfusion. *Shock*, **41** (Suppl 1), 76–83.

Strandenes, G., Austlid, I., Apelseth, T.O., Hervig, T.A., Sommerfelt-Pettersen, J., Herzig, M.C., Cap, A.P., Pidcoke, H.F. & Kristoffersen, E.K. (2015) Coagulation function of stored whole blood is preserved for 14 days in austere conditions: a ROTEM feasibility study during a Norwegian antipiracy mission and comparison to equal ratio reconstituted blood. *Journal of Trauma and Acute Care Surgery*, **78** (6 Suppl 1), S31–S38.

Sunde, G.A., Vikenes, B., Strandenes, G., Flo, K.C., Hervig, T.A., Kristoffersen, E.K. & Heltne, J.K. (2015) Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation. *Journal of Trauma and Acute Care Surgery*, **78** (6 Suppl 1), S26–S30.

Vuillamy, P., Gillespie, S., Gall, L.S., Green, L., Brohi, K. & Davenport, R.A. (2017) Platelet transfusions reduce fibrinolysis but do not restore platelet function during trauma haemorrhage. *Journal of Trauma and Acute Care Surgery*, **83**, 388–397.

Watson, J.J., Pati, S. & Schreiber, M.A. (2016) Plasma transfusion: history, current realities, and novel improvements. *Shock*, **46**, 468–479.

Whiting, P., Al, M., Westwood, M., Corro Ramos, I., Ryder, S., Armstrong, N., Misso, K., Ross, J., Severens, J. & Kleijnen, J. (2015) Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. *Health Technology Assessment*, **19** ISSN 1366-5278, 1–228. https://doi.org/10.3310/hta19580

WOMAN Trial Collaborators. (2017) Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*, **389**, 2105–2116.

Wong, H. & Curry, N. (2018) Do we need cryoprecipitate in the era of fibrinogen concentrate and other specific factor replacement options? *Vox Sanguinis*, **13**, 23–28.

Young, P.P., Cotton, B. & Goodnough, L.T. (2011) Massive transfusion protocols for patients with substantial haemorrhage. *Transfusion Medicine Reviews*, **25**, 293–303.

Zehtabchi, S. & Nishijima, D.K. (2009) Impact of transfusion of fresh-frozen plasma and packed red blood cells in a 1:1 ratio on survival of emergency department patients with severe trauma. *Academic Emergency Medicine*, **16**, 371–378.