Donat R. Spahn
Professor
Institute of Anaesthesiology
University and University Hospital Zurich
Zurich, Switzerland

donat.spahn@usz.ch

Key decisions in a goal-directed coagulation management approach

An individualised goal-directed approach to managing coagulopathy is recommended to treat bleeding trauma patients.

Severe trauma is a great burden to society, with millions of victims worldwide. If trauma patients are hazardly bleeding, surgical bleeding requires the surgeon to fix the problem, while coagulopathy requires management with an algorithm that includes monitoring and specific treatment. About 30% of all major trauma patients have a significant coagulopathy at hospital admission (Maegele 2010).

In most trauma patients low fibrinogen concentration is a key element of their coagulopathy. Fibrinogen is central to the coagulation system as it is vital for platelet aggregation and a key substrate of plasmatic coagulation (Spahn et al. 2013). Fibrinogen is the coagulation 'element' that becomes critically reduced first in many clinical situations, including trauma. The critical level of fibrinogen may be < 1.5-2.0g/L or a maximum clot firmness (MCF) in FIBTEM of < 7mm, or even < 10mm, as measured by a point-of-care rotational thromboelastometry (ROTEM) device.

Unlike red blood cells (RBCs) and platelets there are no fibrinogen stores in the body that might be mobilised. When bleeding lasts a long time and lost volume is replaced with crystalloids and/or colloids, haemoglobin goes down exponentially. At a certain stage it does not go down anymore despite ongoing blood loss, because RBCs are mobilised. Platelets can also go down, but they can be stabilised or increased at a later stage since also platelets can be mobilised. This is not the case for fibrinogen. The more bleeding is ongoing the more likely the need to replace fibrinogen with exogenous fibrinogen.

Fibrinogen replacement

Fresh frozen plasma

A systematic review of randomised controlled trials using fresh frozen plasma (FFP) concluded that for most clinical situations the evidence for clinical efficacy is limited (Stanworth et al. 2004). FFP is an important source of factor V in demonstrable multi-factor deficiency with severe bleeding (Stanworth et al. 2004), but there is limited data on use in liver bleeding. Guidelines state that whether and how much FFP to use to treat a patient with massive blood loss should be guided by timely tests of coagulation, including near-patient tests. Formulae to guide replacement strategies should not be used (Stanworth et al. 2004).

FFP transfusions are associated with major adverse outcomes, including increased mortality (Welsby et al. 2010), increased multi-organ failure (Watson et al. 2009), increased infection (Sarani et al. 2008), increased transfusion-associated lung injury (TRALI) (Silliman et al. 2005; Rana et al. 2006; Eder et al. 2007; Chaiwat et al. 2009), transfusion-associated circulatory overload (TACO) (Rana et al. 2006) and, most importantly, inefficacy in treating coagulopathy (Weber et al. 2012; Innerhofer et al. 2017; Stein et al. 2017a).

The more bleeding there is, the more likely the need to replace fibrinogen from other sources to achieve a minimum fibrinogen concentration of 1.5 to 2 g/L. Sources of fibrinogen are FFP, fibrinogen concentrate and cryoprecipitate. The range of fibrinogen concentration in FFP is 1 to 3 g/L, and is highly variable between units (Levy and Goodnough 2015).

Pathogen inactivation reduces fibrinogen concentration further and consistently to a concentration below 2g/L. If several units of FFP are transfused at a time a vicious cycle starts (**Table 1**).

Fibrinogen replacement therapy

There is guidance on how to use fibrinogen replacement therapy in acquired bleeding (Levy and Goodnough 2015; Theusinger et al. 2017; Garrigue et al. 2018).

Fibrinogen concentration measurement

In a goal-directed approach to coagulation management, it is essential to measure and monitor fibrinogen concentration. However, laboratory measurement of fibrinogen concentration is difficult. Solomon et al. (2014) showed that six laboratories had differences of fibrinogen concentration measurements of 80% between them for 30 patient samples, before, during and after cardiopulmonary bypass. The first international standard established by the World Health Organization for fibrinogen concentrate is 10.4 g/L (National Institute for Biological Standards and Control 2008); the results in this study varied from 2-12 g/L. In addition, the laboratory value takes at least 30 to 60 minutes to reach the doctor ordering the test.

Table 1. Clinical consequences of fresh frozen plasma administration

Fibrinogen concentration ➡ or ⬇
Haemoglobin concentration ⬇ and platelet count ⬇
➡ coagulopathy
RBC transfusion
Coagulation potential ⬇
Further FFP administration - triggers a vicious cycle

Therefore, it is best to base the coagulation algorithm on a ROTEM or thrombelastography (TEG) monitoring device. In 10 minutes there is a clear answer if there is something wrong with the coagulation and what is wrong. There are concerns that this technology is expensive. However, the UK National Health Service found consistent cost savings in viscoelastic point-of-care testing compared with standard lab tests to assist with diagnosis, management and monitoring of haemostasis in cardiac surgery and particularly trauma (Whiting et al. 2015). Their systematic review of 31 trials (11 in cardiac surgery with 1089 patients) showed reduction in blood product use [RBC RR 0.88 (0.80-0.96); FFP RR 0.47 (0.35-0.65)] and platelets RR 0.72 (0.58-0.89). And it is efficacious. A prospective study that randomised patients after heparin reversal following cardiopulmonary bypass compared coagulation management based on conventional laboratory analyses with two algorithms, intra- and postoperative, based on ROTEM. The ROTEM group received fewer RBCs and did not receive FFP; platelets were about the same, fibrinogen usage was the same, there was no rFVIIa anymore and the cost of haemotherapy (including cost of monitoring, blood products and factor concentrate) was about half. The patients in the ROTEM group had better survival at 6-months (Weber et al. 2012).

Some have suggested that practice in trauma patients should be based on the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) study, believing that it proved that 1:1:1 (platelets:FFP:RBC) is better than 1:1:2 (Holcomb et al. 2015). However, the primary outcome, 24h-30 day mortality, was similar between the two formulae. Nascimento et al. (2013) showed that a 1:1:1 ratio is inferior to a control group treated based on a laboratory-based algorithm.

The European guideline on management of major bleeding and coagulopathy following trauma recommends that routine practice includes early and repeated monitoring of coagulation, using either a traditional laboratory determination of fibrinogen concentration [prothrombin time (PT), activated partial thromboplastin time (APTT) platelet counts and fibrinogen] and/or a viscoelastic method (ROTEM or TEG) (Rossaint et al. 2016). Measurement is required after each treatment to ensure that fibrinogen remains.

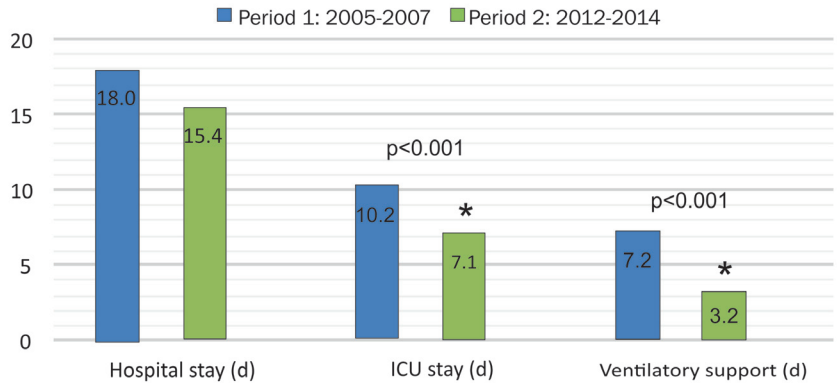

Figure 1. Outcome of patient cohorts managed traditionally (2005-2007) and with coagulation algorithm (2012-2014) (Stein et al. 2017a)

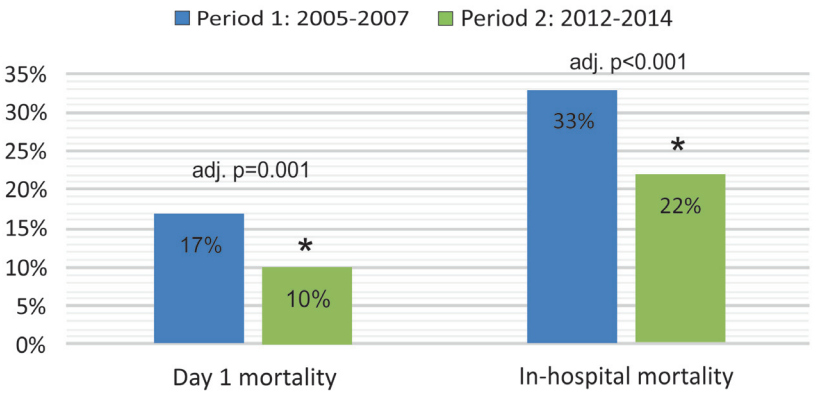

Figure 2. Mortality of patient cohorts managed traditionally (2005-2007) and with coagulation algorithm (2012-2014) (Stein et al. 2017a)

Tranexamic acid

The European guideline recommends that tranexamic acid be administered as early as possible to the trauma patient who is bleeding or at risk of significant haemorrhage at a loading dose of 1g infused over 10 minutes, followed by an IV infusion of 1g over 7 hours (Rossaint et al. 2016).

In a prospective, multicentre observational study (*TXA in the EMS on the Helicopter and the Ambulance*, NCT 02354885), our group gave 1g of tranexamic acid intravenously early on scene to 70 trauma patients (Stein et al. 2018). The control group (n=38) did not receive tranexamic acid. The coagulation of these control patients deteriorated until hospital admission. In contrast, patients who received tranexamic acid on scene had clot stabilisation on arrival at the emergency department (ED). There were four cases with documented hyperfibrinolysis on-scene in the tranexamic acid group; in all these cases there was no sign of hyperfibrinolysis detectable at hospital admission.

Therefore, 90 minutes after the initial dose of 1g tranexamic acid re-dosing is required with an individualised goal-directed strategy to keep the fibrinogen level to a minimum of 1.5 to 2.0 g/L.

In a recent prospective multicentre observational study in major trauma patients receiving tranexamic acid on scene, plasma concentration was measured at hospital admission (Grassin-Delyle et al. 2018). The study authors propose a dosing scheme to maintain a specific target blood concentration.

The European guidelines recommend treatment with fibrinogen and cryoprecipitate if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less

Table 2. Coagulation algorithm

Detect low fibrinogen	
MCF in FIBTEM ≤ 7mm	Fibrinogen 2-4 g IV (after 6 g of fibrinogen, administer Factor XIII 15 U/kg IV)
Detect fibrinolysis	
EXTEM/INTEM: Clot lysis after MCF and APTEM: normal = hyperfibrinolysis	Tranexamic acid • Bolus: 15 mg/kg IV (consider empiric use) • Consider continuous infusion 1-2 mg/kg/h
Ongoing bleeding	
Factor XIII < 60%	Factor XIII 15 U/kg IV
Platelet count/function • EXTEM/INTEM MCF < 40mm • Platelet count ≤ 50,000/µl (≤ 100,000/ µl in cardiac surgery or traumatic brain injury)	Platelet concentrate
• Platelet function (impedance aggregometry)	Consider desmopressin 0.3 µg/kg (max 16 µg) in case of aspirin (like) platelet dysfunction
• INR > 2.3 (Quick's value < 30%)	Four-factor prothrombin complex concentrate (slow continuous infusion of small repeated doses - e.g. 500 IU)
• Factor V < 20%)	FFP (2-4 units)
Detect heparin	
INTEM (CT/CFT) or ACT prolonged and HEPTEM or heparinase-ACT normal	Protamine (1:1) to antagonise heparin

Source: Stein et al. 2017b

than 1.5-2.0 g/L (Rossaint et al. 2016).

Some express caution over giving fibrinogen to patients as it may induce higher than normal plasma fibrinogen levels after major trauma. However, in their study of the time course of plasma fibrinogen, Schlimp and colleagues (2016) showed that fibrinogen concentrate treatment at admission does not lead to higher fibrinogen, concentration levels post-trauma beyond that occurring naturally due to the acute phase response.

Prothrombin complex concentrate

The European guidelines recommend early use of prothrombin complex concentrate (PCC) for the emergency reversal of vitamin K-dependent oral anticoagulants (Rossaint et al. 2016).

One study showed that using four-factor PCC compared to plasma had much faster vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions (Goldstein et al. 2015), which is key in traumatised patients. PCCs are also indicated according to the European guidelines, if there is evidence of delayed initiation of coagulation using viscoelastic monitoring (CT in EXTEM), but the condition is that fibrinogen has been normalised. Therefore, we normalise fibrinogen first and give PCCs only if the CT remains elevated after fibrinogen administration.

Coagulation algorithm

Traditional management of coagulopathy was compared with an individualised goal-directed coagulation and transfusion protocol during two time periods (Stein et al. 2017a). During the first period (2005-2007) we used traditional management and in the second period (2012-2014) a protocol that included primary whole-body CT, tranexamic acid, restrictive fluid therapy (preferably crystalloids), permissive hypovolaemia/hypotension and damage control surgery, according to the European guidelines. The outcome was the comparison between the observed and the Trauma Associated Severe Haemorrhage (TASH)-predicted massive transfusion rate to ICU admission. The simple coagulation algorithm is shown in **Table 2** (Stein et al. 2017b).

In the second period the goal-directed protocol resulted in half the expected massive transfusion rate predicted, the same platelet count and fibrinogen, more tranexamic acid and no rFVIIa (Stein et al. 2017a). ICU length of stay (LOS) was reduced by 3 days, ventilatory support reduced by 4 days (**Figure 1**). Also mortality was reduced (**Figure 2**). ■

Abbreviations

FFP fresh frozen plasma
MCF maximum clot firmness
PCC prothrombin complex concentrate
RBC red blood cells
ROTEM rotational thromboelastometry
TEG thromboelastography

Key Points

- Fibrinogen is the coagulation element that becomes critically reduced first in many instances
- In trauma and cardiac surgery patients, the critical level is 1.5 to 2.0 g/L
- Immediate viscoelastic coagulation monitoring is key for individualised goal-directed coagulation algorithms
- Coagulation algorithms should be available in every hospital
- Compliance with the European trauma treatment guidelines improves survival

References

Chaiwat O, Lang JD, Vavilala MS et al. (2009) Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. Anesthesiology, 110(2): 351-60.

Eder AF, Herron R, Strupp A et al. (2007) Transfusion-related acute lung injury surveillance (2003-2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. Transfusion, 47(4): 599-607.

Garrigue D, Godier A, Glacet A et al. (2018) French lyophilized plasma versus fresh frozen plasma for the initial management of trauma-induced coagulopathy: a randomized open-label trial. J Thromb Haemost, 16(3): 481-9.

Goldstein JN, Refaai MA, Milling TJ Jr et al. (2015) Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet, 385(9982): 2077-87.

Grassin-Delyle S, Theusinger OM, Albrecht R et al. (2018) Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. Anaesthesia, 73(6): 719-29.

Holcomb JB, Tilley BC, Baraniuk S et al.; 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. JAMA, 313(5): 471-82.

Innerhofer P, Fries D, Mittermayr M et al. (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 Haematol, 4(6): e258-e271.

Levy JH, Goodnough LT (2015) How I use fibrinogen replacement therapy in acquired bleeding. Blood, 125(9): 1387-93.

For full references, please email editorial@icu-management.org or visit https://iii.

Evidence for using first-line coagulation factor concentrates for trauma-induced coagulopathy

Petra Innerhofer
Professor
Department of Anaesthesia and Intensive Medicine
Medical University Innsbruck
Innsbruck, Austria

petra.innerhofer@tirol-kliniken.at

Fibrinogen limits coagulopathy and massive bleeding, has less transfusion requirements and thereby decreases the risk of multi-organ failure in trauma patients.

What stops the bleeding?

Haemostatic therapy aims to stop the bleeding, but is it a concentration of coagulation factors, mainly assessed by international normalised ratio (INR) readings that works, or is it fibrinogen/fibrin, which are the precondition for stable clot formation? We conducted a study in patients with polytrauma and those with isolated brain injury (Tauber et al. 2011) to find out what the most predominant pathology was (**Figure 1**). The red bars refer to polytrauma patients. There is significant increase in the frequency of low fibrinogen, low fibrinpolymerization and consequently low clot firmness, in 20-30%, while a significant and prolonged INR of about 1.5 was found in only about 14%. Clot firmness and fibrin polymerization were independently associated with mortality and also with blood loss as measured by early transfusion requirements. In addition patients had tremendously increased molecular markers of thrombin generation, regardless of the INR readings. It's not the main interest to increase it more by substituting plasma, because very huge thrombin levels do not benefit trauma patients. It may cause endothelial injury and also activate other receptors and inflammation and so on.

Further results confirm these findings, e.g. in a study that included more than 4,000 patients, with injury severity scores (ISS) considerably lower than in our patient population, fibrinogen deficiency occurred frequently and fibrinogen levels < 1.5g/L were associated with increased mortality (McQuilten et al. 2017). Hagemo et al.'s study investigating 1,133 patients in a multicentre trial, found that increased mortality was associated with fibrinogen levels < 2.29 g/L, which is barely below normal (Hagemo et al. 2014). The INR was not independently associated with mortality.

Coagulation factor substitutes

Plasma

Plasma refers to 6-8% protein solution and 92-94% water. It was introduced in clinical practice mainly for volume substitution but later to treat coagulation disorders. It contains all procoagulants and also anticoagulants. It's easy to use, is considered safe regarding thrombosis, and relatively low-cost. However, plasma transfusion is time-consuming and requires planning.

The concentration of coagulation factors and especially fibrinogen are rather low in plasma and vary depending on the individual donor and the type of processing. Plasma efficacy can be questioned and partial requirements correction is not possible. It may also induce transfusion-associated circulatory overload (TACO), transfusion-associated lung injury (TRALI), transfusion-associated immunomodulation (TRIM), multi-organ failure (MOF), immunosuppression, lung injury.

Fibrinogen concentrate

There are several concentrates on the market:

1. Fibrinogen concentrate
2. FXIII concentrate
3. PCC (FII, VII, IX, X)
4. vWF concentrate
5. rVIIa, PCCa
6. FVIII, IX, X, XI concentrate

No factor V concentrate is available.

Concentrates are immediately ready to use, contain defined and high concentration of the factor, no volume expansion is needed,

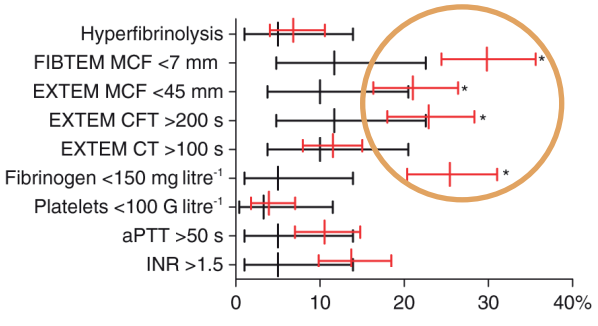

Figure 1

Source: Tauber et al. (2011)

so there will be an effective rise in concentration, making targeted therapy possible. There will be no TACO, TRALI or TRIM and the concentrates are virus-inactivated.

The main problem is cost; they are more expensive than plasma. Some may be concerned about the risk of thromboembolism, and this may occur if thrombin formation is increased by use of PCC and activated PCC and rFVIIa. It is not a problem with fibrinogen, which is also called antithrombin I, as fibrinogen and fibrin are able to capture free-flowing thrombin, and thrombin is the one that initiates thrombosis. Authors of reviews and meta-analyses also criticise the fact that currently there are only a few high-quality studies in trauma patients showing a benefit with coagulation factor concentrates.

The European guideline (Rossaint et al. 2016) recommends the use of standard coagulation tests and/or viscoelastic tests (level of evidence 1C). Viscoelastic testing gives a timely and more comprehensive picture. The guideline recommends use of plasma together with RBC at least 1:2 or use of fibrinogen concentrate with RBC and PCC and factor XIII in selected cases.

Evidence for fibrinogen concentrate

The most frequently cited studies using coagulation factor concentrates in trauma patients are summarised in **Table 1**. All show promising results: lower mortality than predicted, lower transfusion requirements, and lower multi-organ failure. Fibrinogen was maintained within a normal range even if much fibrinogen had been administered. There were fewer transfusions of red blood cells (RBCs) and platelets. In the study by Wafaisade and colleagues (2013), early mortality was also reduced. These patients received fibrinogen and also had massive transfusions of plasma.

Meta-analyses on plasma efficacy in bleeding patients have concluded that there is no clear benefit for blood loss, transfusion and mortality (Stanworth et al. 2004; Casbard et al. 2004; Yang et al. 2012; Kozek-Langenecker et al. 2011; Desborough et al. 2015). However, there are several reports in trauma patients showing improved survival with early aggressive transfusion without any blood measurements. Administration of 1:1 ratios is recommended, but there are studies that found no difference and studies that found that mortality did not change and coagulopathy was not corrected (**Table 2**). Before massive transfusion of plasma, reported mortality in many centres was about 50 percent. Now the rate is between 21% and 35% (**Table 3**). This mortality is considerably higher than studies using a targeted correction of coagulopathy and using coagulation factor concentrates, especially fibrinogen concentrate.

RETIC trial comparing plasma and coagulation factor concentrates

Our study group conducted the first randomised controlled trial comparing the effect of a plasma-based strategy to the use of coagulation factor concentrate in severe

Table 1. Are CFCs useful in trauma patients?

Author	Design	n/ISS	Products	Main result
Schöchl 2010	Retrospective	131 38 ± 15	FC (128) PCC (98) FFP (12)	Mortality lower than predicted
Schöchl 2011	Retrospective	681 35 ± 11	CFC n=80 FFP n=601	Fewer RBC and PC with CFC
Nienaber 2011	Retrospective matched pair	311 44 (38,50)	CFC n=18 FFP n=293	Fewer RBC, lower MOF with CFC
Schlimp 2013	Retrospective	157 29 (23,41)	FC n=85 FC+PCC n=63 FC+PCC+FFP n=9	Fibrinogen maintained, within normal range at 24h ICU
Innerhofer 2013	Observational	144 37 (29,50)	CFC n=66 CFC +FFP n=78	Fewer RBC and PC with CFC alone, lower MOF
Wafaisade 2013	Retrospective matched pair	588 37 ± 13	FC 294 no FC 294	Reduced 6h mortality and MOF with FC

CFC coagulation factor concentrate FC fibrinogen concentrate FFP fresh frozen plasma MOF multi-organ failure PCC prothrombin complex concentrate RBC red blood cells

Table 2. Massive transfusion: Fixed ratio RBC: FFP: PC

Pro 1:1		Indifferent		Con	
Study	Type	Study	Type	Study	Type
Hirshberg et al. 2003	Mathematical model	Rangarajan et al. 2011	Retrospective	Scalea et al. 2008	Prospective
Maegele et al. 2008	Retrospective	Dirks et al. 2010	Retrospective	Nienaber et al. 2011	Matched pair analysis
Gonzalez et al. 2007	Retrospective	Magnotti et al. 2011	Registry - selection bias!	Johnson et al. 2010	Prospective
Duchesne et al. 2009	Retrospective	Snyder et al. 2009	Retrospective - selection bias!	Edens et al. 2010	Prospective
Teixeira et al. 2009	Retrospective	Holcomb et al. 2015	Only early death (secondary endpoint)	Kashuk et al. 2008	Prospective
Mitra et al. 2010	Retrospective			Rourke et al. 2012	Prospective
Peiniger et al. 2011	Retrospective			Chambers et al. 2011	Before/after
Holcomb et al. 2013	Prospective			Kahn et al. 2014	Prospective

Table 3. Mortality in trauma - 1:1:1(2) vs POCT-directed individualised therapy

Country	Author	Mortality	ISS
USA	Holcomb 2013	21.4-25.0%	25-26
USA	Nascimento 2013	24%	35 ± 13
USA	Holcomb 2015	24.3%	25
USA	Gonzalez 2016	27%	33 (25;43)
UK	Khan 2014	35%	34 (25;41)
Austria	Tauber 2011	12.8%	35 (25;50)
Austria	Innerhofer 2013	7.6%	37 (29;50)
Austria	Schöchl 2011	7.5-10%	35.5 ± 10.5
Austria	Innerhofer 2017	7.4%	34 (26;43)

trauma (Innerhofer 2017). The study was terminated early following interim analysis after inclusion of 100 patients, because predefined stopping was met, showing disadvantages with use of plasma. Correction of coagulopathy was feasible in 96% of patients in the CFC group; only 2 patients had treatment failure and also received plasma (**Table 4**).

In the plasma group more than 50% of patients had no stop of bleeding and no correction of coagulation. These patients received additionally fibrinogen concentrate, some also PCC and factor XIII. Transfusion requirements were increased and patients received more frequently platelet concentrates. Importantly, the rate of massive transfusion at comparable ISS was increased tremendously.

Our primary endpoint was difference in MOF. However, to answer this question, we would have needed to include at least 200 patients. Therefore the difference of 16% between groups with a higher rate of MOF in the plasma group was not significant. However, ISS and brain injury are confounders, which should be considered when analysing the likelihood of MOF. These confounders were used for stratification and considered in regression analysis. Results showed a significant increased risk of MOF with plasma even in this limited population of 94 patients.

What stops the bleeding–the concentration or the clot?

In the RETIC study the blue boxes refer to the CFC group that mainly received fibrinogen concentrate. The yellow boxes refer to the plasma group (**Figure 2**). Prothrombin is indexed as a percentage of normal, and at baseline they are comparable. After administration of plasma this improved, but decreased further in the CFC group. The patients in the plasma group received more RBC and platelets concentrates and, despite this, had a dramatic drop in platelet count. Also the haemoglobin levels were lower than in the CFC group that received fewer RBCS and platelets. Therefore improved INR or prothrombin time does not limit blood loss. What about fibrinogen and clot firmness? Fibrinogen increased to its normal levels immediately with the factor-based concept, but changed little and marginally and remained below normal in the plasma group. Consequently clot strength improved rapidly with CFC but remained unchanged or decreased in the plasma group. ■

Table 4. RETIC trial main findings

	CFC (n=50)	FFP (n=44)	OR	*P* value
Treatment failure (n)	2 (4%)	23 (52.3%)	25.34	<0.001
RBC/24h	4 (2.7)	6 (4,11)		.028
PC yes	20%	47.7%	3.599	.008
MT%	12%	29.5%	3.038	.042
MOF%	50%	65.9%		.1457

Logistic regression adjusted for confounders ISS/TBI
Significantly increased risk for MOF with FFP OR 3.1264 (CI 1.1906 - 9.8756), P = .0250

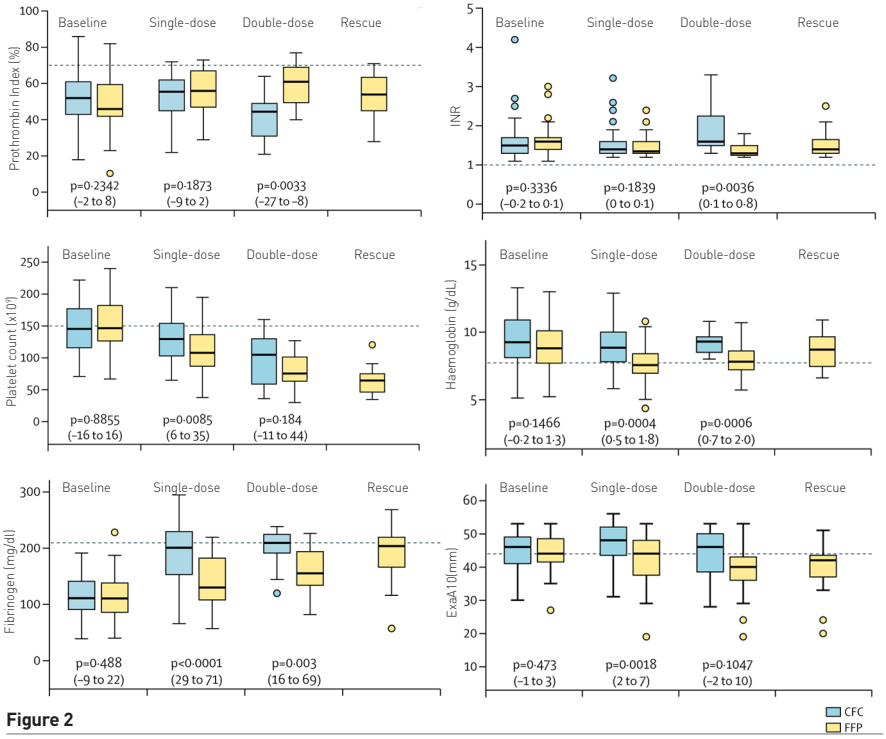

Figure 2

Abbreviations

ISS injury severity score
MOF multi-organ failure
TACO transfusion-associated circulatory overload
TRALI transfusion-associated lung injury
TRIM transfusion-associated immunomodulation

References

For full references, please email editorial@icu-management.org or visit https://iii.

Conclusion/ Key points

- Early and effective fibrinogen supplementation is really important to limit blood loss and minimise risk of MOF
- Fibrinogen improves clot strength and also exhibits a platelet-saving effect. This is very important because platelets are one of the transfusion components that are sometimes dangerous and have many side effects
- Fibrinogen limits coagulopathy and massive bleeding and has less transfusion requirements especially massive transfusion and thereby it also decreases the risk of MOF
- An effective rise of fibrinogen concentration is not feasible with plasma
- The lower, better INR after plasma does not reduce the bleeding, therefore we should not focus on the INR
- Fibrinogen is of interest, should be monitored and should be supplemented early

Dietmar Fries
Professor
Department of Surgical and General Care Medicine
Medical University Innsbruck
Innsbruck, Austria

dietmar.fries@i-med.ac.at

Implementation of a revised trauma management protocol

Goal-directed therapy of coagulopathy is recommended for trauma patients.

Can guidelines direct our strategy?

When presented with bleeding trauma patients, our management strategy may be directed by guidelines, e.g. the European trauma guideline (Rossaint et al. 2016). This recommends treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5–2.0 g/L. An initial fibrinogen supplementation of 3–4 g is suggested, and repeat doses must be guided by viscoelastic monitoring and laboratory assessment (Rossaint et al. 2016).

Guidelines are developed on a scientific empirical basis, but in clinical practice it can be hard to define which patient will bleed in the next 30 minutes with a clinically substantial bleed. The U.S. guidelines recommend 1:1:1 massive transfusion packages (American Society of Anesthesiologists Task Force on Perioperative Blood Management 2015), which have the advantage of additional volume effect, but the disadvantages of side effects of fresh frozen plasma (FFP), time delay, prophylactic transfusion and lower efficacy. The European guideline recommends individualised targeted controlled coagulation management and transfusion, which requires point-of-care monitoring and administration of colloids/crystalloids to give additional volume. The advantages are that no prophylactic transfusion is required, there are fewer side effects of transfusion-related complications and it is efficacious.

Massive transfusion protocols: fixed ratios (1:1:1)

The evidence for a 1:1:1 (platelets:FFP:red blood cells [RBC]) ratio in transfusion is that it is not beneficial. Abdel-Wahab and colleagues showed in an audit of patients transfused FFP for mild coagulation values that prothrombin time (PT) was partially normalised in a minority of patients and did not correct the PT in 99 percent of patients, regardless of the number of units of FFP transfused (Abdel-Wahab et al. 2006). Concentration is not increased by transfusing FFP, which has a low concentration of coagulation factor.

Studies on 1:1:1 transfusions have a clear survivor/publication bias, as most studies in support came from war situations, when RBCs were available in 20 minutes and plasma within 90 minutes. The result was not that FFP saved the patient, but that the patients who survived at least the first 60-90 minutes were able to receive the plasma. For example, Snyder and colleagues (2009) found an association between higher FFP:packed red blood cells [PRBC] ratios at 24 hours and improved survival, which after adjustment for survival bias was no longer statistically significant. Manotti and colleagues (2011) analysed outcomes for trauma patients who received massive blood transfusion. Patients who received a higher plasma ratio during the first 24 hours had an improved survival rate, but were in less shock. The authors note: "The proposed survival advantage of a high-ratio may be because of selection of those not likely to die in the first place; that is, patients die with a low-ratio not because of a low-ratio."

A prospective cohort study of 517 trauma patients in whom FFP and RBCs were administered in fixed ratios found that fibrinogen was always low at admission, and they needed to administer cryoprecipitate to increase fibrinogen levels (Rourke et al. 2012). In patients with low fibrinogen at admission mortality was increased, while patients who received cryoprecipitate had improved survival.

Frith and colleagues (2015) analysed thrombin generation parameters in 440 trauma patients following FFP transfusion in a RBC:FFP:platelets ratio of 1:1:5. Both patients with and without acute traumatic coagulopathy had low thrombin generation after receiving four units. Both groups had a further 25% decline in thrombin generation during the next four units, so conventional haemostatic resuscitation failed to support the thrombin generation required for fibrinogen conversion.

Khan and colleagues, in an international prospective cohort study, drew a blood sample when trauma patients arrived at the hospital, and after 4, 8 and 12 PRBC transfusions in 160 patients. The percentage of coagulopathic patients went up the more transfusions were received (58% after 4 PRBC, 81% after 8) (Khan et al. 2015).

Nascimento and colleagues compared the effect of a fixed-ratio (1:1:1) transfusion protocol vs laboratory-results-guided transfusion in 78 patients with severe trauma (Nascimento et al. 2013). They concluded that the 1:1:1 protocol could be exposing patients not only to unnecessary blood transfusion but also to increased risk of acute respiratory distress syndrome, sepsis and multiple organ dysfunction.

The *Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study* compared the effectiveness of early transfusion of plasma and/or platelets to time-varying plasma:RBC and platelet:RBC ratios, with the primary outcome of in-hospital mortality. Higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who received at least three units of blood products over the first

24 hours after admission. In patients who survived 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios, however (Holcomb et al. 2013).

The *Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)* trial compared transfusion of plasma, platelets and red blood cells in a 1:1:1 vs 1:1:2 ratio and found no difference in mortality at 24 hours or at 30 days (Holcomb et al. 2015). More patients in the 1:1:1 group achieved haemostasis and fewer experienced death due to exsanguination by 24 hours.

Formula-driven protocols are not effective to reverse coagulopathy, and result in high complications. FFP transfusion increases the risk of hospital-acquired infection by three (Sarani et al. 2008). Dara and colleagues (2005) found no difference in new bleeding episodes, but new-onset acute lung injury was more frequent in the transfused group (18% vs 4%, p = 0.21). The more plasma used, the more complications. Watson and colleagues (2009) showed that each unit of FFP transfused was associated with a 2.1% higher risk of multi-organ failure (MOF) and 2.5% higher risk of ARDS.

Massive transfusion protocols: plasma first followed by factor concentrates

The alternative to 1:1:1 transfusion is to give plasma first in hypovolaemic situations and then on top factor concentrates. Innerhofer and colleagues investigated exclusive use of CFCs in 144 trauma patients with similar ISS (37-38). One group received coagulation factor (CF) only and the other group was treated with CF+FFP in the emergency room (ER). The primary outcome was the response profile for coagulation parameters and secondary transfusion rates and outcome. **Table 1** shows the transfusion requirements in the first 24 hours. **Table 2** shows the outcomes.

Outcome was worse in the group that received FFP additionally, and there was more ARDS, more MOF, more sepsis, and by day 30 increased mortality. The use of CF alone effectively corrected coagulopathy in patients with severe blunt trauma.

In the RETIC single-centre open label parallel-group crossover study (Innerhofer et al. 2017), patients who were coagulopathic in the ER were randomised to receive FFP or CFC and were monitored for incidence of MOF. Patients who received initially coagulation factors had 50% less massive transfusions. Bleeding was increased in coagulation factor-treated patients, especially those patients who received some kind of rescue therapy. The group treated with plasma and then with coagulation factor had a higher MOF score.

Therefore a 1:1:1 transfusion protocol is ineffective, but FFP initially and then coagulation factor concentrates also result in higher mortality and higher numbers of massively transfused patients.

Goal-directed treatment of trauma-induced coagulopathy

Gonzalez and colleagues (2016) found that using a goal-directed, thromboelastography-guided massive transfusion protocol (MTP) to resuscitate severely injured patients improved survival and used less plasma and platelet transfusions during the early phase of resuscitation, compared with an MTP guided by conventional coagulation assays. Kaserer and colleagues (2018) compared two different coagulation algorithms (a target haematocrit range vs a lower haematocrit limit only and goal-directed coagulation algorithm vs blind coagulation package) and effect on use of allogenic blood products and coagulation factors in a retrospective multicentre observational study of severely injured trauma patients (Kaserer et al. 2018). Factor XIII substitution was considered early. They found that a goal-directed coagulation algorithm led to

Table 1. Transfusion and coagulation factor requirements during the first 24 h in trauma patients treated with CF or CF+FFP

	CF n=66	CF + FFP n=78	p value
RBC (U)	2 (0, 4)	9 (5, 12)	< 0.001
FFP (U)	0 (0, 0)	10 (5, 13)	< 0.009
PC (U)	0 (0, 0)	1 (0, 2)	< 0.001
Fibrinogen concentrate (g) Patients treated (n)	4 (2, 4) 66 (100)	4 (2, 7) 70 (89.7)	0.0007 0.1252
PCC (IE) Patients treated (n)	0 (0, 1000) 23 (34.8)	750 (0, 1800) 40 (51.3)	0.0006 0.064

RBC red blood cell concentrate FFP fresh frozen plasma PC aphaeresis platelet concentrate PCC prothrombin complex concentrate (factors II, VII; IX, X) NT not tested.
Source: Innerhofer et al. 2013

Table 2. Outcome parameters of the full unmatched trauma population

	CF Group (*n* = 66)	FFP Group (*n* = 78)	*p*-Value
paO_2/FiO_2 24 h	317 (250, 377)	241 (201, 325)	0.002
Ventilator-free days	18 (8, 25)	16 (4, 23)	0.139
Sepsis (*n*)	11 (16.9)	28 (35.9)	0.014
MOF (*n*)	12 (18.2)	29 (37.2)	0.015
ICU stay (days)	12 (6, 24)	14 (7, 30)	0.217
LOS (days)	24 (12, 35)	29 (16, 50)	0.074
30-day mortality (*n*)	5 (7.6)	6 (7.7)	0.979
Thromboembolism (*n*)	6 (10.0)	6 (7.7)	0.772

Data are given as median (interquartile range) or numbers (%).
ICU intensive care unit LOS length of hospital stay MOF multi-organ failure
Source: Innerhofer et al. 2013

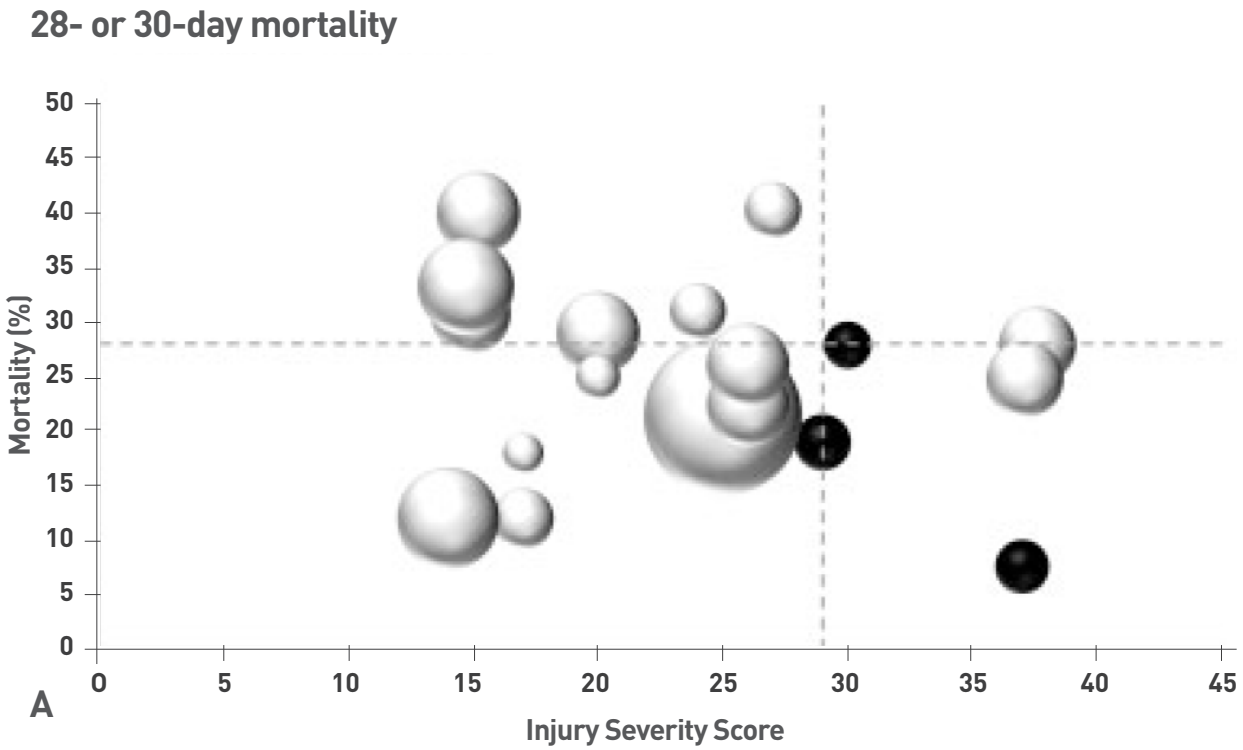

Figure 1

Source: Fries et al. 2017

less transfusion of RBC.

Stein and colleagues evaluated the results of changing the transfusion algorithm from 2007 when they introduced a coagulation trauma algorithm. They reduced ventilator days, mortality, FFP and RBC transfusion (Stein et al. 2017).

Figure 1 summarises the evidence for goal-directed therapy's effect on 28- or 30-day mortality.

The white spheres are larger as the number of patients included was larger, and mortality was higher (Fries et al. 2017). ■

Abbreviations

ARDS acute respiratory distress syndrome
ER emergency room
FFP fresh frozen plasma
ISS injury severity score
MOF multi-organ failure
PRBC packed red blood cells
PT prothrombin time
RBC red blood cells

Conclusion/ Key points

- Trauma is never standardised, patients are never standardised so a standard regime is not possible
- Do not start with massive transfusion algorithms for bleeding trauma patients
- Goal-directed therapy of coagulopathy is recommended for trauma patients

References

Abdel-Wahab OI, Healy B, Dzik WH (2006) Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion, 46(8): 1279-85.

American Society of Anesthesiologists Task Force on Perioperative Blood Management (2015) Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. Anesthesiology, 122(2): 241-75.

Dara SI, Rana R, Afessa B et al. (2005) Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Crit Care Med, 33(11): 2667-71.

Fries D, Innerhofer P, Spahn DR (2017) Transfusion approaches and mortality in trauma patients: a narrative review. Semin Thromb Hemost, 43(7): 759-71.

Frith D, Wall J, Baptista M et al. (2015) HEM-4 Thrombin generation potential declines during trauma haemorrhage despite haemostatic resuscitation. Shock, 44 Suppl 2: 1-2.

Gonzalez E, Moore EE, Moore HB et al. (2016) Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Ann Surg, 263(6): 1051-9.

Holcomb JB, del Junco DJ, Fox EE et al.; PROMMTT Study Group (2013) The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg, 148(2): 127-36.

Holcomb JB, Tilley BC, Baraniuk S et al.; 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. JAMA, 313(5): 471-82.

Innerhofer P, Westermann I, Tauber H et al. (2013) The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury, 44(2): 209-16.

Innerhofer P, Fries D, Mittermayr M et al. (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 Haematol, 4(6): e258-e271.

Kaserer A, Casutt M, Sprengel K et al. (2018) Comparison of two different coagulation algorithms on the use of allogenic blood products and coagulation factors in severely injured trauma patients: a retrospective, multicentre, observational study. Scand J Trauma Resusc Emerg Med, 26(1): 4.

For full references, please email editorial@icu-management.org or visit https://iii.