# Resuscitation and transfusion management in trauma patients: emerging concepts

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**Purpose of review**
Severe trauma is associated with hemorrhage, coagulopathy and transfusion of blood and blood products, all associated with considerable mortality and morbidity. The aim of this review is to focus on resuscitation, transfusion strategies and the management of bleeding in trauma as well as to emphasize on why coagulation has to be monitored closely and to discuss the rationale of modern and future transfusion strategies.

**Recent findings**
Coagulopathy and uncontrolled bleeding remain leading causes of death in trauma, lead to blood transfusions and increased mortality as it has been recently shown that blood transfusion per se results in an adverse outcome. In the last years, damage control resuscitation, a combination of permissive hypotension, hemostatic resuscitation and damage control surgery, has been introduced to treat severely traumatized patients in hemorrhagic shock. Goals of treatment in trauma patients remain avoiding metabolic acidosis, hypothermia, treating coagulopathy and stabilizing the patient as soon as possible. The place of colloids and crystalloids in trauma resuscitation as well as the role of massive transfusion protocols with a certain FFP : RBC ratio and even platelets have to be reevaluated.

**Summary**
Close monitoring of bleeding and coagulation in trauma patients allows goal-directed transfusions and thereby optimizes the patient's coagulation, reduces the exposure to blood products, reduces costs and may improve clinical outcome.

**Keywords**
goal-directed transfusions, ROTEM, thrombelastometry, transfusion management, traumatic coagulopathy

## INTRODUCTION

Although considerable progress has been made in the field of trauma resuscitation in the last few years, hemorrhage and coagulopathy remain one of the major causes of mortality in civilian trauma patients and combat casualties [1,2]. Some studies claim that up to 20% of deaths in trauma could be preventable as the majority is linked to uncontrolled bleeding [3–5]. One-third of patients arriving in the emergency rooms have already or will present coagulopathy further increasing the risk of uncontrolled bleeding [6–8]. Morbidity and mortality in trauma-induced coagulopathy is up to four times higher than in patients who do not present this state. It thus remains a crucial goal of resuscitation management to correct and prevent this type of coagulopathy by early aggressive treatment in order to increase the chances of survival [8,9,10▪,11]. This review will focus and discuss the ways of resuscitation, volume management, transfusion management, the use of point-of-care devices and the actual views and understandings of coagulopathy in trauma, the concept of damage control as well as related costs.

## COAGULOPATHY IN TRAUMA

Coagulopathy in trauma was classically described as being caused by hypothermia, metabolic acidosis,

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## KEY POINTS

- Close monitoring of bleeding and coagulation in trauma patients allows goal-directed transfusions and thereby optimizes the patient's coagulation, reduces the exposure to blood products, reduces costs and may improve clinical outcome.
- Damage control resuscitation, a combination of permissive hypotension, hemostatic resuscitation and damage control surgery, has been introduced to treat severely traumatized patients in hemorrhagic shock.
- Very recent studies confirm the fact that tranexamic acid is a useful tool in bleeding trauma patients.
- The liberal use of colloids thus cannot be generally advocated in trauma, except in situations in which the administration of crystalloids has proven ineffective; a negative effect on blood coagulation has to be expected.

dilution from excessive intravenous fluid and the consumption of coagulation factors [12]. This has been recently proven not to be the cause of early coagulation disorders and the term of acute traumatic coagulopathy was introduced.

Acute traumatic coagulopathy is an independent predictor of massive transfusions, death, protracted intensive care stay, multiorgan failure, especially renal failure and acute lung injury [7,8,13▪▪]. Hypothermia is induced by heat loss on the scene of the trauma and by treatment in hospital including resuscitation with fluids which are not prewarmed. An in-vitro study by Wolberg *et al.* showed that coagulation protease activity is reduced when temperatures decrease from 37.8 to 33.8°C [14,15]. Such a temperature decrease has an even greater impact on platelets reducing platelet activation, adhesion to vWF on endothelial surfaces and aggregation [16]. The additional effect of metabolic acidosis caused by hypoperfusion of tissues, tissue injury, hypoxia and the increased levels of lactate leads furthermore to malfunction of platelets and coagulation proteases [12]. The activity of factor Xa, factor Va and thrombin generation is reduced by 50% already at a pH of 7.2 [17]. In addition, pH seems to increase fibrinolysis [17,18▪▪].

In the preclinical and early clinical setting, hemodilution becomes a considerable cause of coagulopathy. Several studies have shown that the amount of volume administered is directly proportional to coagulopathy, regardless of the type of volume administered [19,20]. Colloids have been proven to lead to fibrinogen dysfunction, pathological fibrin polymerization and thus poor clot stability, whereas crystalloids lead to a reduction of factor VII inducing a prolongation of the prothrombin time [19,21,22▪▪].

Coagulopathy occurring within the first half–an-hour after trauma is not related to hemodilution but to hypoperfusion of tissues inducing an increase of tissue plasminogen activator (tPA) and thrombomodulin [11,23]. Thrombomodulin activates protein C which in combination with protein S inhibits factor Va and VIIIa on one side and leads to an inhibition of plasminogen activator inhibitor-1 (PAI-1) on the other side. The combination of high levels of tPA and low levels of PAI-1 leads to a hyperfibrinolytic state [6,11,23,24,25▪]. Another theory postulates that acute traumatic coagulopathy is not induced by activation of tissue factor but is the result of the consumption of coagulation proteases and the development of a disseminated intravascular coagulation syndrome with a significant fibrinolytic and hyperfibrinolytic component [26▪▪,27].

Up to 60% of the patients having major trauma will present acute traumatic coagulopathy regardless of the pathophysiology which is behind this phenomenon. Hyperfibrinolysis is of clinical importance as it results in increased transfusion requirements and increased mortality and morbidity [18▪▪,28–30]. Furthermore, coagulopathy leads to massive transfusion which is commonly defined as an administration of greater than 10 units of RBCs within the first 24 h. Different scores for predicting massive transfusions are found in the literature; variables used include blood pressure, injury mechanism, age, injury severity score (ISS), temperature, laboratory values (pH, PT, and base excess), point-of-care devices (ROTEM, TEM, International GmbH, Munich, Germany), sex and focused assessment with sonography for trauma (FAST), but none of these scores is able to correctly classify every patient. Nevertheless, the continuing interest in their use suggests that an early identification of patients in need for massive transfusion might be useful either to start early treatment to prevent it or to be aware of the risk [31–33,34▪▪,35–37].

## CONCEPT OF DAMAGE CONTROL

New studies on the pathophysiology of acute coagulopathy in trauma and data published by the U.S. army lead to a shift in the treatment of trauma patients using multiple approaches to control tissue hypoperfusion, acidosis, trauma coagulopathy and hypothermia [38].

The first goal in this concept which aims at controlling hemorrhage is to stop the bleeding which mainly requires a surgical intervention. The second step of this concept is stopping

hypoperfusion, correcting acidosis, reversing hypothermia and getting coagulation under control. As severely injured trauma patients do not tolerate prolonged operative procedures, effective hemorrhage control is accomplished with the concept of damage control surgery by applying temporary, yet life-saving surgical procedures immediately after injury, with delayed definitive corrective surgery at a later date after the patient has been stabilized in the ICU.

So far, there is no evidence to support neither reversal of acidosis with bicarbonate nor repletion of calcium and magnesium, which could be desirable. Administration of fix packages of red blood cells, fresh frozen plasma and platelets has been discussed in the past years both in the civilian and military sector for patients suffering severe injury and needing massive transfusions. As this topic is discussed controversially, it will be mentioned under the section 'resuscitation concepts, volume and transfusion management' in this review.

At the present time, prospective trials supporting damage control resuscitation in case of major bleeding trauma are missing even if these concepts are widely accepted in practice and are mentioned in guidelines [39,40].

## LABORATORY RESULTS AND POINT-OF-CARE DEVICES

Diagnosis of coagulopathy in trauma remains a problem. Laboratory tests differ from one laboratory to another and not all tests are available 24 h a day in every hospital. Activated partial thromboplastin time and partial thromboplastin time are mainly used. However, the problem is that there is a lack of consensus on the definition of traumatic coagulopathy and on the cut-off values that should be used [10▪,41▪,42]. Another problem is that these laboratory tests are performed in plasma only, not revealing the entire reality of coagulation in whole blood *in vivo*, although some studies claim that activated partial thromboplastin time and partial thromboplastin time are independent predictors for mortality in trauma patients [7,43,44]. Furthermore, the time these results take to be available is usually in the range of 45–75 min which is far too long in a bleeding patient. In addition and importantly, acute hyperfibrinolysis cannot be detected [18▪▪].

In the last few years, rotation thrombelastometry (ROTEM), a viscoelastic test in whole blood, is increasingly used in trauma in both the civilian and combat setting, progressively replacing thromboelastography (TEG, Hemoscope Corportation, Niles, IL, USA) [45▪▪,46▪]. ROTEM provides within 5–10 min information on the initiation of coagulation, clot strength as well as coagulation factors, fibrinogen, platelets and hyperfibrinolysis as part of acute traumatic coagulopathy [18▪▪,47,48]. A recent study using ROTEM was even able to provide guiding information whether massive transfusion would be needed in patients or not [33]. Also mortality after trauma is independently associated with low clot strength values determined by ROTEM [49▪].

As it is possible to distinguish different hemostatic disorders following trauma, viscoelastic tests, particularly ROTEM, provide a means of individualizing coagulation management for patients and guiding transfusion resuscitation. However, in order to achieve this in a standardized way, algorithms are needed (detailed information is provided in the next section) [11,50,51].

## RESUSCITATION CONCEPTS, VOLUME AND TRANSFUSION MANAGEMENT AND ALGORITHMS

One major progress in trauma resuscitation was the introduction of permissive hypotension which limits fluid therapy, either by delaying the time of administration or minimizing the volume given [38]. The goal of this approach is to reduce fluid administration and thus to reduce dilutional coagulopathy as well as hypothermia induced by cold solutions by accepting a low systolic blood pressure until the bleeding source is surgically under control [52].

Data on permissive hypotension are unfortunately sparce and controversial. One older randomized controlled trial from 1994 reported a reduction of around 10% in mortality in patients with penetrating trauma who had a permissive hypotension until surgery [53]. Other studies were not able to reproduce these results and a systematic review in the Cochrane Database from 2003 could not confirm benefit or harm form permissive hypotension [54].

In the last year, three interesting studies on that subject were published, two in animals and one in humans. One study in rats showed that hypotension with a mean arterial pressure of 50–60 mmHg in uncontrolled hemorrhagic shock had the most benefit on survival provided that the hypotensive period was of less than 90 min [55▪]. In contrast, a pig model with blast injuries showed poorer outcome with permissive hypotension compared to normotensive resuscitation [56].

The third study, a randomized control trial in humans, in which 271 patients were recruited, where a mean arterial pressure of 50 versus 65 mmHg during initial surgery was compared showed already in the preliminary data with

90 patients that the group with the lower mean arterial pressure received less blood products, smaller volumes of intraoperative fluids, was less likely to develop postoperative coagulopathy and had a significantly lower all cause early mortality rate [57▪]. However, in the group with higher mean arterial pressure, the mean arterial pressure was higher than defined in the protocol and ISS was higher and blunt trauma more frequent compared to the low mean arterial pressure group. The final results once all patients are recruited will be available soon and may give future useful information.

Volume management with the longstanding crystalloids versus colloids debate is also being discussed controversially. Two large systematic reviews of 65 randomized controlled trials and with 90 trials of colloids compared to crystalloids in patients requiring volume replacement published in 2011 in the Cochrane Library by Perel and in 2012 by Benn showed that there is actually no evidence that resuscitation with colloids reduces the risk of death compared to resuscitation with crystalloids [58,59]. The first randomized, double-blind, controlled trial (called FIRST trial) recently published comparing saline with HES 130/0.4 in trauma resuscitation showed that lactate was lower in the HES group at day 1. Renal injury was only present in the saline group. Maximum sequential organ failure was lower in the HES group, but the HES group required significantly more blood and blood products. Outcomes were similar in terms of renal function and organ recovery, with no differences in mortality [60▪▪]. The liberal use of colloids thus cannot be generally advocated in trauma, except in situations in which the administration of crystalloids has proven ineffective; a negative effect on blood coagulation has to be expected.

Reduction of intracranial brain pressure, by improving cardiovascular output, cerebral oxygenation and reducing cerebral edema by administering small volumes of hypertonic saline in traumatic brain injury is reported [61]. There are no trials providing compelling evidence to support the use of hypertonic saline, neither for traumatic brain injury nor for hemorrhagic shock. The study by Bulger *et al.* [62] published in 2011 showed no significant difference in mortality at 28 days, but this study was terminated early because of concerns of a potential increase in mortality observed with a subgroup of patients receiving hypertonic saline but no blood transfusions within the first day.

As the use of blood products in trauma resuscitation often cannot be avoided, there were discussions coming up in the last few years on the optimal ratio of fresh frozen plasma and red blood cells to be delivered tending to a 1 : 1 ratio to control coagulopathy [38].

The problem is that a high percentage of data are from the military setting, in which the type of trauma is not comparable to the civilian sector and where the availability of bedside monitoring and factor concentrates is scarce. Results to be found in the literature confer: some report a reduction of up to 50% in patients receiving high ratios of FFR : RBC; some that FFP is beneficial in massive transfusions; others that FFP is of little benefit and leads to higher complications especially ARDS and multiorgan failure; and that coagulation is still not better or that there was no improvement in survival [63–76]; in addition, these retrospective studies on FFP : RBC ratio have to be interpreted with caution. The main criticism does not so much relate to the fact that cause and effect are difficult to establish with retrospective data, but rather to the danger of a so-called 'survivor bias'. This means that those patients who survived longer were more likely to receive FFPs in contrast to patients who died early after admission. A recent work by Ho and colleagues addressed this problem. Searching the MEDLINE database (from 1966 to 2011), they identified a total 26 studies from 2007 to 2011 comparing high and low FFP : RBC ratios for bleeding trauma patients. Fifteen of these 26 studies were classified as survivor bias-unlikely. Importantly, 10 of these 15 studies showed an association between higher FFP : RBC ratio and improved survival, whereas five did not [77▪▪]. Therefore, the argument of a potential survivor bias is not valid to reject all observational studies. Only well designed, randomized controlled trials can give a conclusive answer to this question. To date, there is one multicenter, prospective, randomized trial on the way, the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial (http://cetir-tmc.org/research/proppr) comparing a 1 : 1 : 1 ratio with a 1 : 1 : 2 ratio of FFP : platelets : RBC in patients who are predicted to require massive transfusion. However, at the time of submission of this manuscript, no patients have been enrolled yet (http://www.clinicaltrials.gov/ct2/show/NCT01545232?term=PROPPR&rank=1).

There is overwhelming evidence that blood and its products like FFP and platelets are associated with mortality, morbidity, increased length of stay, multiorgan failure, infections, transfusion overload, sepsis and TRALI [78]. Thus, the balance between risk and benefit of blood and its products has to be weighted carefully. Increased use of platelets and red blood cells was also discussed in addition with fibrinogen, showing no strong evidence for better outcome [76,79,80]. One major problem of all

those retrospective observational trials is that not all patients surviving have the same type of injuries [70,81▪].

According to the guidelines of the American Society of Anesthesiologists, red blood cell transfusion is recommended if the hemoglobin concentration drops below 6–10 g/dl. Transfusions over 10 g/dl are rarely indicated and transfusions seem almost always to be indicated if hemoglobin falls below 6 g/dl [82]. In Europe, a hemoglobin target of 7–9 g/dl is largely accepted in major trauma [39,83]. Physiological transfusion triggers on the contrary are tachycardia, hypotension, oxygen extraction higher than 50%, mixed venous oxygen partial pressure of less than 32 mmHg (4.3 kPa), increase of lactate and ECG changes [11,84,85]. The grade of shock, hemodynamic response to resuscitation and the rate of actual blood loss in the bleeding and hemodynamically unstable patient have also to be integrated into the indication for red blood cells transfusion; however, blood transfusions should be used restrictively and the risk versus the benefit has to be evaluated carefully [86].

In Europe and partially in other countries, several coagulation factor concentrates are available and can be substituted selectively. Fibrinogen is an essential substrate for clot formation. Several in-vitro and animal studies [87,88] have shown that fibrinogen substitution is capable of reversing dilutional coagulopathy. Furthermore, several human studies (civilian and noncivilian) confirmed these data, showing that early and aggressive replacement of fibrinogen in patients with severe hemorrhage and dilutional coagulopathy improves clot strength significantly and leads to better survival [19,89,90]. As hyperfibrinolysis might be a major problem in trauma, the use of tranexamic acid is essential [18▪▪]. The CRASH-2 trial with over 20 000 patients included examined the effect of tranexamic acid versus placebo on mortality and transfusion requirement in adults with traumatic injury and hemorrhagic shock. All-cause mortality was reduced following tranexamic acid administration as was mortality from bleeding [91]. The maximal beneficial effects of tranexamic acid were achieved when tranexamic acid was administered within the first 3 h after trauma [92▪▪]. Very recent studies confirm the fact that tranexamic acid is a useful tool in bleeding trauma patients [93▪▪,94▪▪].

Factor XIII is the key coagulation factor to stabilize the clot and additionally seems to have a certain influence on hyperfibrinolysis [95▪,96]. Trauma and major hemorrhage are known to be a cause of acquired factor XIII deficiency [97]. It seems reasonable to substitute factor XIII early, thereby improving clot firmness, reducing bleeding and minimizing the use of blood products [98]. The effect of factor XIII on coagulation has been shown in a trial by spiking blood with factor XIII. This trial also showed that low concentrations of fibrinogen can be compensated by higher concentrations of factor XIII [47,96].

Prothrombin complex concentrates (PCCs) provide a source of vitamin K-dependent coagulation factors. Depending on different production techniques, there exist both three-factor (USA) and four-factor (Europe) PCCs that are recommended for emergent reversal of oral anticoagulants [99▪, 100,101▪▪]. Furthermore, studies demonstrated that the use of PCCs in trauma patients leads to a considerable reduction in the use of blood products (FFP, RBCs and cryoprecipitate) and that survival improved and bleeding stopped earlier. Therefore, PCCs might have a place in control of trauma-related bleeding, although this indication is currently off label and one should be aware of a possible thrombotic risk [102–110,111▪▪].

Recombinant activated factor VII (rFVIIa) transforms fibrinogen to fibrin by inducing a thrombin burst. Risks and benefits of a treatment with rFVIIa have to be carefully evaluated and economic aspects taken into consideration, as the consensus view remains that there is no strong evidence to support rFVIIa use in the standard treatment for traumatic bleeding [112].

## COSTS

As bleeding management is a highly complex process, algorithms are needed to get a standardized, logical and clearly structured pathway to treat this complex pathology [11,113]. Goal-directed transfusion algorithms have the potential of reducing blood components and leading to a favorable outcome by controlling the nonsurgical bleeding in trauma. At our institution, we recently implemented the second version of the transfusion algorithm for massively bleeding patients (Fig. 1). This algorithm incorporates information obtained from the patient's history, clinical presentation, coagulation laboratory tests and bedside viscoelastic coagulation tests. Despite an increase in costs for point-of-care coagulation monitoring and more frequent administration of specific coagulation factor concentrates, algorithms may be cost saving and the future in treating traumatic bleeding. Interestingly, similar algorithms have shown to result in a lower than expected mortality and a shorter length of hospital stay in severely injured patients [30,51].

| Diagnostic | Intervention |
|---|---|
| **Preoperative history**<br>1. Coagulation-effecting drugs<br>- Antiplatelet drugs<br>- Heparin<br>- Oral anticoagulation<br>2. Coagulation status?<br>3. HIT II? | **ROTEM after anesthesia induction**<br>- Transplant surgery<br>- Cardiac and vascular surgery<br>- Difficult cancer surgery<br>- Liver insufficiency<br>- Intra-abdominal sepsis<br>- Trauma room entry |
| Blood loss >50% with diffuse bleeding | |
| **ROTEM analysis**<br>- EXTEM, INTEM, FIBTEM, APTEM<br>- HEPTEM in heart and vascular surgery | **Target values**<br>- Hypothermia (temperature >35°C)<br>- Hypocalcemia (Ca >1.15 mmol/l)<br>- Acidosis<br>- Anemia (haematocrit >0.21)<br>- Hypertension (MAP 55–60 mmHg)<br>**Crystalloid and/or colloid volume substitution** |
| **FIBTEM** <7 mm | Fibrinogen 2–4 g i.v.(maximal 3x2g), after a total of 6 g give FXIII |
| **INTEM** (CT and CFT prolonged)<br>**HEPTEM** normal, and/or ACT pathological or heparinase ACT normal | Protamine sulphate 1 : 1 to heparin<br>**Crystalloid and colloid volume substitution** |
| **EXTEM/INTEM** :<br>Decrease of MCF after maximum was reached<br>**APTEM:** normal<br>⇨ Hyperfibrinolysis | Tranexamic acid<br>- 15 mg/kg bodyweight as bolus i.v.<br>- 1–2 mg/kg/h during surgery i.v. as perfusion |
| Ongoing diffuse bleeding | |
| **EXTEM/INTEM MCF <40 mm**<br>CT EXTEM/INTEM normal<br>MCF FIBTEM <7 mm<br>Hct >0.21<br>MCF FIBTEM >7 mm<br>Platelets <50 000/µl (<100 000/µl in cardiac surgery or in patients suffering from traumatic brain injury)<br>**Coagulation test including F XIII, F V, INR, PT, aPTT** | Fibrinogen up to 6 g, followed by **factor XIII** 15 U/kg bodyweight<br>**Crystalloid and colloid volume substitution**<br>**Platelet concentrates**<br>**Target area of factor XIII: > 60%**<br>**Target area of factor V: > 20% (in particular in liver insufficiency or intra-abdominal sepsis 2–4 U FFP)** |
| Ongoing diffuse bleeding | |
| Quick's value < 30% and<br>Factor V > 20%<br>OR<br>EXTEM/INTEM: CT, CFT prolonged | **4 factor prothrombin complex concentrate** 1000–2000 IU<br>- Factor II, VII, IX and X<br>Depending on the patients' bodyweight |
| In case of massive transfusion | Target haematocrit >0.21–0.24 |
| | |
| If massive diffuse bleeding continues and | |
| Treated acidosis<br>Treated hypothermia<br>Excluding hypocalcemia<br>Hematocrit > 0.21–0.24 | Recombinant factor VIIa<br>60 µg/kg body weight i.v.<br>A second dose of 60 µg/kg bodyweight i.v. can be given again after 2–4 h, if bleeding is not completely stopped |
| Excluding DIC<br>Fibrinogen was substituted<br>Platelets <50 000/µl (<100 000/µl in cardiac surgery or in patients suffering from traumatic brain injury) | |

**FIGURE 1.** Second version of the transfusion algorithm of the University Hospital of Zürich – copyright 2012, Switzerland.

## CONCLUSION

Tissue hypoperfusion and ischemia seem to be the major causes of coagulopathy of trauma characterized by hypocoagulopathy and hyperfibrinolysis. Close monitoring of bleeding and coagulation allows individualized and goal-directed treatment algorithms to optimize patients' coagulation and to reduce the need and exposure to blood products resulting in improved clinical outcome.

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### Conflicts of interest

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## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 726–727).

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This review collated and summarized all the systematic review evidence relating to the diagnosis and management of trauma-related coagulopathy and transfusion, thereby covering the widest possible body of literature. There is a need for randomized controlled trials to answer these questions. The approach described in this report provides a framework for incorporating new evidence.

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A retrospective review of data over a 5-year period was performed to determine the associations between variables considered to contribute to mortality for adult major trauma patients receiving blood transfusions as part of their initial resuscitation. There were 772 patients included in this study. Acute traumatic coagulopathy, independent of injury severity, transfusion practice or other physiological markers for hemorrhage, was associated with early death in major trauma patients requiring a blood transfusion. Early recognition and management of coagulopathy, independent of massive transfusion guidelines, may improve outcome from trauma resuscitation.

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Over 2 years, all emergency patients with hyperfibrinolysis were enrolled in this study. Hyperfibrinolysis patients were divided into traumatized and nontraumatized. The trauma hyperfibrinolysis group was matched with 24 polytrauma patients without hyperfibrinolysis. Thirty-five patients with hyperfibrinolysis were identified. Overall mortality for hyperfibrinolysis was 54%. Hyperfibrinolysis is significantly ($P = 0.017$) associated with mortality in trauma patients. Mortality from hyperfibrinolysis is significantly higher in trauma compared with nontrauma patients, and hyperfibrinolysis is an independent factor predicting mortality in trauma patients. Rotational thromboelastometry provides real-time recognition of hyperfibrinolysis allowing early treatment.

19. Haas T, Fries D, Velik-Salchner C, *et al.* The in vitro effects of fibrinogen concentrate, factor XIII and fresh frozen plasma on impaired clot formation after 60% dilution. Anesth Analg 2008; 106:1360–1365; table of contents.
20. Bolliger D, Szlam F, Molinaro RJ, *et al.* Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. Br J Anaesth 2009; 102:793–799.
21. Fenger-Eriksen C, Tonnesen E, Ingerslev J, Sorensen B. Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy. J Thromb Haemost 2009; 7:1099–1105.
22. ■■ Shaz BH, Winkler AM, James AB, *et al.* Pathophysiology of early trauma-induced coagulopathy: emerging evidence for hemodilution and coagulation factor depletion. J Trauma 2011; 70:1401–1407.

This study showed that early induced trauma coagulopathy following injury is associated with decreased factor activities without significant differences in thrombin and fibrin generation, suggesting that despite these perturbations in the coagulation cascade, patients displayed a balanced hemostatic response to injury. The lower factor activities are likely secondary to increased hemodilution and coagulation factor depletion. Thus, decreasing the amount of crystalloid infused in the early phases following trauma and administration of coagulation factors may prevent the development.

23. Brohi K, Cohen MJ, Ganter MT, *et al.* Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma 2008; 64:1211–1217; discussion 7.
24. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003; 54:1127–1130.
25. ■ Hayakawa M, Sawamura A, Gando S, *et al.* Disseminated intravascular coagulation at an early phase of trauma is associated with consumption coagulopathy and excessive fibrinolysis both by plasmin and neutrophil elastase. Surgery 2011; 149:221–230.

This study showed that disseminated intravascular coagulation at an early phase of trauma is associated with consumption coagulopathy and excessive fibrinolysis both by plasmin and neutrophil elastase independent of hypoperfusion and continues to disseminated intravascular coagulation at a late phase of trauma. Increased fibrinolysis requires more blood transfusions, contributing to a poor patient outcome.

26. ■■ Floccard B, Rugeri L, Faure A, *et al.* Early coagulopathy in trauma patients: an on-scene and hospital admission study. Injury 2012; 43:26–32.

This study compares on scene coagulation and hospital admission coagulation showing that coagulopathy occurs very early after injury, before fluid administration, at the site of accident. Coagulation and fibrinolytic systems are activated early. The incidence of coagulopathy is high and its severity is related to the injury and not to hypoperfusion.

27. Gando S, Nanzaki S, Morimoto Y, *et al.* Tissue factor pathway inhibitor response does not correlate with tissue factor-induced disseminated intravascular coagulation and multiple organ dysfunction syndrome in trauma patients. Crit Care Med 2001; 29:262–266.
28. Kashuk JL, Moore EE, Sawyer M, *et al.* Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. Ann Surg 2010; 252:434–442; discussion 43–44.
29. Schochl H, Frietsch T, Pavelka M, Jambor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. J Trauma 2009; 67:125–131.
30. Schochl H, Nienaber U, Hofer G, *et al.* Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010; 14:R55.
31. Cosgriff N, Moore EE, Sauaia A, *et al.* Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. J Trauma 1997; 42:857–861; discussion 61–62.
32. Cancio LC, Wade CE, West SA, Holcomb JB. Prediction of mortality and of the need for massive transfusion in casualties arriving at combat support hospitals in Iraq. J Trauma 2008; 64:S51–S55; discussion S5–S6.
33. Leemann H, Lustenberger T, Talving P, *et al.* The role of rotation thromboelastometry in early prediction of massive transfusion. J Trauma 2010; 69:1403–1408; discussion 8–9.
34. ■■ Levi M, Fries D, Gombotz H, *et al.* Prevention and treatment of coagulopathy in patients receiving massive transfusions. Vox Sang 2011; 101:154–174.

This study summarizes the opinion of international experts on coagulation in trauma and its treatment in different countries.

35. Maegele M, Lefering R, Wafaisade A, *et al.* Revalidation and update of the TASH-Score: a scoring system to predict the probability for massive transfusion as a surrogate for life-threatening haemorrhage after severe injury. Vox Sang 2011; 100:231–238.
36. Stanworth SJ, Morris TP, Gaarder C, *et al.* Reappraising the concept of massive transfusion in trauma. Crit Care 2010; 14:R239.
37. Ruchholtz S, Pehle B, Lewan U, *et al.* The emergency room transfusion score (ETS): prediction of blood transfusion requirement in initial resuscitation after severe trauma. Transfus Med 2006; 16:49–56.
38. Jansen JO, Thomas R, Loudon MA, Brooks A. Damage control resuscitation for patients with major trauma. BMJ 2009; 338:b1778.
39. Rossaint R, Bouillon B, Cerny V, *et al.* Management of bleeding following major trauma: an updated European guideline. Crit Care 2010; 14:R52.
40. Thomas D, Wee M, Clyburn P, *et al.* Blood transfusion and the anaesthetist: management of massive haemorrhage. Anaesthesia 2010; 65:1153–1161.
41. ■ Curry N, Hopewell S, Doree C, *et al.* The acute management of trauma hemorrhage: a systematic review of randomized controlled trials. Crit Care 2011; 15:R92.

This review looked at 35 randomized clinical trials and there has been little improvement in outcomes over the last few decades. No clear correlation has been demonstrated between transfusion requirements and mortality. The global trauma community should consider a coordinated and strategic approach to conduct well designed studies with pragmatic endpoints.

42. Frith D, Goslings JC, Gaarder C, *et al.* Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010; 8:1919–1925.
43. Niles SE, McLaughlin DF, Perkins JG, *et al.* Increased mortality associated with the early coagulopathy of trauma in combat casualties. J Trauma 2008; 64:1459–1463; discussion 63–65.
44. Hess JR, Lindell AL, Stansbury LG, *et al.* The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center. Transfusion 2009; 49:34–39.
45. ■■ Larsen OH, Fenger-Eriksen C, Christiansen K, *et al.* Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. Anesthesiology 2011; 115:294–302.

This is a very important study showing that monoanalysis with kaolin (TEG) was unable to distinguish coagulopathies caused by dilution from that of thrombocytopenia. Algorithms based on the use of kaolin may lead to unnecessary transfusion with platelets, whereas the application of TEM-reagents (ROTEM) may result in goal-directed fibrinogen substitution.

46. ■ Woolley T, Midwinter M, Spencer P, *et al.* Utility of interim ROTEM((R)) values of clot strength, A5 and A10, in predicting final assessment of coagulation status in severely injured battle patients. Injury 2012. [Epub ahead of print]

This study shows as previous did already that the maximum clot firmness after 10 min of ROTEM provides an early sensitive and specific assessment of coagulopathy after military trauma and may be of utility in guiding bespoke resuscitation.

47. Theusinger OM, Baulig W, Asmis LM, *et al.* In vitro factor XIII supplementation increases clot firmness in Rotation Thromboelastometry (ROTEM). Thromb Haemost 2010; 104:385–391.
48. Theusinger OM, Nurnberg J, Asmis LM, *et al.* Rotation thromboelastometry (ROTEM) stability and reproducibility over time. Eur J Cardiothorac Surg 2010; 37:677–683.
49. ■ Tauber H, Innerhofer P, Breitkopf R, *et al.* Prevalence and impact of abnormal ROTEM(R) assays in severe blunt trauma: results of the 'Diagnosis and Treatment of Trauma-Induced Coagulopathy (DIA-TRE-TIC) study'. Br J Anaesth 2011; 107:378–387.

This study provides additional evidence showing that ROTEM assays are useful in trauma patients. Treatment concepts should focus on maintaining fibrin polymerization and treating hyperfibrinolysis.

50. Afshari A, Wikkelso A, Brok J, *et al.* Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev 2011; CD007871.
51. Schochl H, Forster L, Woidke R, *et al.* Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. Anaesthesia 2010; 65:199–203.
52. Stern SA, Dronen SC, Wang X. Multiple resuscitation regimens in a near-fatal porcine aortic injury hemorrhage model. Acad Emerg Med 1995; 2:89–97.

**53.** Bickell WH, Wall MJ Jr, Pepe PE, *et al.* Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994; 331:1105–1109.

**54.** Kwan I, Bunn F, Roberts I. Timing and volume of fluid administration for patients with bleeding. Cochrane Database Syst Rev 2003; CD002245.

**55.** ■ Li T, Zhu Y, Hu Y, *et al.* Ideal permissive hypotension to resuscitate uncontrolled hemorrhagic shock and the tolerance time in rats. Anesthesiology 2011; 114:111–119.

This study shows that a target resuscitation pressure of 50–60 mmHg is the ideal blood pressure for uncontrolled hemorrhagic shock. Ninety minutes of permissive hypotension is the tolerance limit; 120 min of hypotensive resuscitation can cause severe organ damage and should be avoided.

**56.** Garner J, Watts S, Parry C, *et al.* Prolonged permissive hypotensive resuscitation is associated with poor outcome in primary blast injury with controlled hemorrhage. Ann Surg 2010; 251:1131–1139.

**57.** ■ Morrison CA, Carrick MM, Norman MA, *et al.* Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma 2011; 70:652–663.

This study shows that hypotensive resuscitation is a safe strategy for use in the trauma population and results in a significant reduction in blood product transfusions and overall IV fluid administration. Specifically, resuscitating patients with the intent of maintaining a target minimum MAP of 50 mmHg, rather than 65 mmHg, significantly decreases postoperative coagulopathy and lowers the risk of early postoperative death and coagulopathy. These preliminary results provide convincing evidence that support the continued investigation and use of hypotensive resuscitation in the trauma setting.

**58.** Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev 2012; 6:CD001319.

**59.** Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2011; CD000567.

**60.** ■■ James MF, Michell WL, Joubert IA, *et al.* Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011; 107: 693–702.

This study shows that in penetrating trauma, HES provided significantly better lactate clearance and less renal injury than saline. No firm conclusions could be drawn for blunt trauma.

**61.** Hashiguchi N, Lum L, Romeril E, *et al.* Hypertonic saline resuscitation: efficacy may require early treatment in severely injured patients. J Trauma 2007; 62:299–306.

**62.** Bulger EM, May S, Kerby JD, *et al.* Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. Ann Surg 2011; 253:431–441.

**63.** Borgman MA, Spinella PC, Perkins JG, *et al.* The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007; 63:805–813.

**64.** Gunter OL Jr, Au BK, Isbell JM, *et al.* Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma 2008; 65:527–534.

**65.** Holcomb JB, Zarzabal LA, Michalek JE, *et al.* Increased platelet:RBC ratios are associated with improved survival after massive transfusion. J Trauma 2011; 71:S318–S328.

**66.** Holcomb JB, Wade CE, Michalek JE, *et al.* Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008; 248:447–458.

**67.** Kashuk JL, Moore EE, Johnson JL, *et al.* Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? J Trauma 2008; 65:261–270; discussion 70–71.

**68.** Maegele M, Lefering R, Paffrath T, *et al.* Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. Vox Sang 2008; 95:112–119.

**69.** Scalea TM, Bochicchio KM, Lumpkins K, *et al.* Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. Ann Surg 2008; 248:578–584.

**70.** Snyder CW, Weinberg JA, McGwin G Jr, *et al.* The relationship of blood product ratio to mortality: survival benefit or survival bias? J Trauma 2009; 66:358–362; discussion 62–64.

**71.** Sperry JL, Ochoa JB, Gunn SR, *et al.* An FFP:PRBC transfusion ratio $\geq$1:1.5 is associated with a lower risk of mortality after massive transfusion. J Trauma 2008; 65:986–993.

**72.** Zink KA, Sambasivan CN, Holcomb JB, *et al.* A high ratio of plasma and platelets to packed red blood cells in the first 6 h of massive transfusion improves outcomes in a large multicenter study. Am J Surg 2009; 197:565–570; discussion 70.

**73.** Shaz BH, Dente CJ, Nicholas J, *et al.* Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion 2010; 50:493–500.

**74.** Murad MH, Stubbs JR, Gandhi MJ, *et al.* The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. Transfusion 2010; 50:1370–1383.

**75.** Phan HH, Wisner DH. Should we increase the ratio of plasma/platelets to red blood cells in massive transfusion: what is the evidence? Vox Sang 2010; 98:395–402.

**76.** Inaba K, Branco BC, Rhee P, *et al.* Impact of plasma transfusion in trauma patients who do not require massive transfusion. J Am Coll Surg 2010; 210:957–965.

**77.** ■■ Ho AM, Dion PW, Yeung JH, *et al.* Prevalence of survivor bias in observational studies on fresh frozen plasma:erythrocyte ratios in trauma requiring massive transfusion. Anesthesiology 2012; 116:716–728.

These observational studies on transfusion in trauma comparing high versus low plasma:erythrocyte ratio were prone to survivor bias because plasma administration typically started later than erythrocytes. When early deaths were excluded, however, a bias against higher ratio can be created. Survivor bias could be reduced by performing before-and-after studies or treating the plasma:erythrocyte ratio as a time-dependent covariate. Without randomized controlled trials controlling for survivor bias, the current available evidence supporting higher plasma:erythrocyte resuscitation is inconclusive.

**78.** Lelubre C, Piagnerelli M, Vincent JL. Association between duration of storage of transfused red blood cells and morbidity and mortality in adult patients: myth or reality? Transfusion 2009; 49:1384–1394.

**79.** Davenport R, Curry N, Manson J, *et al.* Hemostatic effects of fresh frozen plasma may be maximal at red cell ratios of 1:2. J Trauma 2011; 70:90–95; discussion 5–6.

**80.** Stinger HK, Spinella PC, Perkins JG, *et al.* The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma 2008; 64:S79–S85; discussion S85.

**81.** ■ Magnotti LJ, Zarzaur BL, Fischer PE, *et al.* Improved survival after hemostatic resuscitation: does the emperor have no clothes? J Trauma 2011; 70:97–102.

Improved survival was observed in patients receiving a higher plasma ratio over the first 24 h. However, temporal analysis of mortality using shorter time periods revealed those who achieve early high ratio are in less shock and less likely to die early from uncontrolled hemorrhage compared with those who never achieve a high ratio. Thus, 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.

**82.** Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 2006; 105:198–208.

**83.** Spahn DR, Ganter MT. Towards early individual goal-directed coagulation management in trauma patients. Br J Anaesth 2010; 105:103–105.

**84.** Spahn DR, Madjdpour C. Physiologic transfusion triggers: do we have to use (our) brain? Anesthesiology 2006; 104:905–906.

**85.** Madjdpour C, Spahn DR, Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. Crit Care Med 2006; 34:S102–S108.

**86.** Earley AS, Gracias VH, Haut E, *et al.* Anemia management program reduces transfusion volumes, incidence of ventilator-associated pneumonia, and cost in trauma patients. J Trauma 2006; 61:1–5; discussion -7.

**87.** Fries D, Streif W, Margreiter J, *et al.* The effects of perioperatively administered crystalloids and colloids on concentrations of molecular markers of activated coagulation and fibrinolysis. Blood Coagul Fibrinolysis 2004; 15:213–219.

**88.** Innerhofer P, Fries D, Margreiter J, *et al.* The effects of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation. Anesth Analg 2002; 95:858–865; table of contents.

**89.** Haas T, Fries D, Velik-Salchner C, *et al.* Fibrinogen in craniosynostosis surgery. Anesth Analg 2008; 106:725–731; table of contents.

**90.** Haas T, Fries D, Holz C, *et al.* Less impairment of hemostasis and reduced blood loss in pigs after resuscitation from hemorrhagic shock using the small-volume concept with hypertonic saline/hydroxyethyl starch as compared to administration of 4% gelatin or 6% hydroxyethyl starch solution. Anesth Analg 2008; 106:1078–1086; table of contents.

**91.** Shakur H, Roberts I, Bautista R, *et al.* 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 2010; 376:23–32.

**92.** ■■ Roberts I, Shakur H, Afolabi A, *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011; 377:1096–1101; 101 e1–101 e2.

This study shows that tranexamic acid should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, tranexamic acid is less effective and could be harmful.

**93.** ■■ Ker K, Kiriya J, Perel P, *et al.* Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. BMC Emerg Med 2012; 12:3.

This study shows that the use of tranexamic acid in the treatment of traumatic bleeding has the potential to prevent many premature deaths every year. A large proportion of the potential health gains are in low-income and middle-income countries.

**94.** Perel P, Salman RA, Kawahara T, *et al.* CRASH-2 (Clinical Randomisation ■■ of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury – a nested randomised, placebo-controlled trial. Health Technol Assess 2012; 16:iii–xii, 1–54.

This was the first randomized controlled study to evaluate the effect of tranexamic acid in traumatic brain injury patients and it found that neither moderate benefits nor moderate harmful effects can be excluded. However, although uncertainty remains, this analysis suggests that tranexamic acid administration might improve outcome in traumatic brain injury patients and provides grounds for evaluating this hypothesis in future research.

**95.** Dirkmann D, Gorlinger K, Gisbertz C, *et al.* Factor XIII and tranexamic acid but ■ not recombinant factor VIIa attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood. Anesth Analg 2012; 114:1182–1188.

This study on hyperfibrinolysis showed that in thromboelastometric assays using whole blood, only tranexamic acid, factor XIII, and PCC significantly inhibited r-tPA-evoked hyperfibrinolysis, whereas rFVIIa had no effect. The effects of exogenous factor XIII were dependent on the presence of functional platelets.

**96.** Theusinger OM. The inhibiting effect of factor XIII on hyperfibrinolysis. Anesth Analg 2012; 114:1149–1150.

**97.** Egbring R, Kroniger A, Seitz R. Factor XIII deficiency: pathogenic mechanisms and clinical significance. Semin Thromb Hemostat 1996; 22:419–425.

**98.** Nielsen VG, Gurley WQ Jr, Burch TM. The impact of factor XIII on coagulation kinetics and clot strength determined by thrombelastography. Anesth Analg 2004; 99:120–123.

**99.** Baggs JH, Patanwala AE, Williams EM, Erstad BL. Dosing of 3-factor ■ prothrombin complex concentrate for international normalized ratio reversal. Ann Pharmacother 2012; 46:51–56.

This study showed that patients with a higher initial INR are less likely to achieve adequate INR reversal after receiving three-factor PCC and may require higher doses than were used in this study.

**100.** Sarode R, Matevosyan K, Bhagat R, *et al.* Rapid warfarin reversal: a 3-factor prothrombin complex concentrate and recombinant factor VIIa cocktail for intracerebral hemorrhage. J Neurosurg 2012; 116:491–497.

**101.** Honickel M, Rieg A, Rossaint R, *et al.* Prothrombin complex concentrate ■■ reduces blood loss and enhances thrombin generation in a pig model with blunt liver injury under severe hypothermia. Thromb Haemost 2011; 106:724–733.

In severely hypothermic pigs, the application of PCC corrected trauma-induced coagulopathy and reduced blood loss. Thus, the infusion of PCC might be a reasonable approach to reduce the need for blood cell transfusion in trauma. Furthermore, the impact and safety of PCC application can be monitored through thrombin generation and thromboelastometry under hypothermia.

**102.** McSwain N Jr, Barbeau J. Potential use of prothrombin complex concentrate in trauma resuscitation. J Trauma 2011; 70:S53–S56.

**103.** Marietta M, Pedrazzi P, Luppi M. Three- or four-factor prothrombin complex concentrate for emergency anticoagulation reversal: what are we really looking for? Blood Transfus 2011; 9:469; author's reply 470–471.

**104.** Chapman SA, Irwin ED, Beal AL, *et al.* Prothrombin complex concentrate versus standard therapies for INR reversal in trauma patients receiving warfarin. Ann Pharmacother 2011; 45:869–875.

**105.** Wong Y. Use of prothrombin complex concentrate for vitamin K antagonist reversal before surgical treatment of intracranial hemorrhage. Clin Med Insights Case Rep 2011; 4:1–6.

**106.** Patanwala AE, Acquisto NM, Erstad BL. Prothrombin complex concentrate for critical bleeding. Ann Pharmacother 2011; 45:990–999.

**107.** Makris M, Van Veen JJ. Three or four factor prothrombin complex concentrate for emergency anticoagulation reversal? Blood Transfus 2011; 9:117–119.

**108.** Imberti D, Barillari G, Biasioli C, *et al.* Emergency reversal of anticoagulation with a three-factor prothrombin complex concentrate in patients with intracranial haemorrhage. Blood Transfus 2011; 9:148–155.

**109.** Khorsand N, Veeger NJ, Muller M, *et al.* Fixed versus variable dose of prothrombin complex concentrate for counteracting vitamin K antagonist therapy. Transfus Med 2011; 21:116–123.

**110.** Godier A, Durand M, Emmerich J, *et al.* Efficacy of prothrombin complex concentrate to reverse the anticoagulant effect of the pentasaccharide fondaparinux in a rabbit model. Thromb Haemost 2011; 105:161–168.

**111.** Sorensen B, Spahn DR, Innerhofer P, *et al.* Clinical review: prothrombin ■■ complex concentrates – evaluation of safety and thrombogenicity. Crit Care 2011; 15:201.

PCCs are used mainly for emergency reversal of vitamin K antagonist therapy. The aims of the present review are to examine thrombotic complications reported with PCCs and to compare the safety of PCCs with human fresh frozen plasma. The risk of thrombotic complications may be increased by underlying disease, high or frequent PCC dosing and poorly balanced PCC constituents. The causes of PCC thrombogenicity remain uncertain, but accumulating evidence indicates the importance of factor II (prothrombin). With the inclusion of coagulation inhibitors and other manufacturing improvements, today's PCCs may be considered safer than earlier products. PCCs may be considered preferable to fresh frozen plasma for emergency anticoagulant reversal, and this is reflected in the latest British and American guidelines. Care should be taken to avoid excessive substitution with prothrombin, however, and accurate monitoring of patients' coagulation status may allow thrombotic risk to be reduced. The risk of a thrombotic complication because of treatment with PCCs should be weighed against the need for rapid and effective correction of coagulopathy.

**112.** Stanworth SJ, Birchall J, Doree CJ, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev 2007; CD005011.

**113.** Steiner ME, Despotis GJ. Transfusion algorithms and how they apply to blood conservation: the high-risk cardiac surgical patient. Hematol Oncol Clin North Am 2007; 21:177–184.