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Facing coagulation disorders after acute trauma

F. Mullier[1], S. Lessire[2], J.-C. de Schoutheete[3], B. Chatelain[1], V. Deneys[4], V. Mathieux[5], S. Hachimi Idrissi[6], J.-M. Dogné[7], J.-B. Watelet[8], M. Gourdin[2], A.-S. Dincq[2*]*

[1]Université catholique de Louvain, CHU UCL Namur, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for Life Sciences (NARILIS), Namur, Hematology Laboratory, Belgium; [2]Université catholique de Louvain, CHU UCL Namur, Department of Anesthesiology, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for Life Sciences (NARILIS), Namur, Belgium; [3]Queen Astrid Military Hospital, Department of Surgery, Bruynstraat 1, 1120 Brussels, Belgium; [4]Université catholique de Louvain, CHU UCL Namur, Blood Transfusion Center, Namur, Belgium; [5]Université catholique de Louvain, CHU UCL Namur, Department of Hematology, Namur, Belgium; [6]Ghent University Hospital, Department of Emergency Medicine, De Pintelaan 185, 9000 Ghent, Belgium; [7]University of Namur, Department of Pharmacy, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for Life Sciences (NARILIS), Namur, Belgium; [8]Department of Otorhinolaryngology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium; *Contributed equally

Key-words. Trauma; coagulopathy; tranexamic acid; mechanisms; treatment; *(according to the MeSH®* (Medical Subject Headings-Annotated Alphabetic List), National Library of Medicine, Bethesda, Maryland)

Abstract. *Facing coagulation disorders after acute trauma. Problems/objectives:* Trauma is the leading cause of mortality for persons between one and 44 years of age, essentially due to bleeding complications.
Methodology: We screened the PubMed, Scopus and Cochrane Library databases, using specific keywords. Only publications in English were considered.
Main results: The pathophysiology of trauma-induced coagulopathy (TIC) is complex and includes the classic "lethal triad" (i.e., haemodilution, acidosis, hypothermia) but may also include activation of protein C, endothelial and platelet dysfunction, and fibrinogen depletion.
The time between trauma and treatment of the resultant massive bleeding should be as short as possible using techniques for rapid control of bleeding and avoiding aggravating factors (hypothermia, metabolic acidosis and hypocalcaemia). If given within three hours of injury, tranexamic acid (TXA) reduces all causes of mortality in trauma patients and reduces transfusion requirements. In a bleeding patient, crystalloids are preferred to colloids and the ratio of fresh frozen plasma to packed red blood cells should be at least 1:2. Damage control surgery (DCS) should be considered for patients who present with, or are at risk for developing, the "lethal triad", multiple life-threatening injuries or shock, and in mass casualty situations. DCS can also aid in the evaluation of the extent of tissue injuries and the control of haemorrhage and infection. Finally, there is currently no evidence of the added value of laboratory assays in the management of TIC.
Conclusions: TIC appears quickly after trauma and should be anticipated and detected as soon as possible. TXA plays a central role in the management of such patients. Each institution should establish a local algorithm for the management of bleeding patients.

Introduction and epidemiology

Trauma is the leading cause of mortality for persons between one and 44 years of age. Despite advances in transfusion practices and improvements in the prehospital management of trauma patients, bleeding remains the leading cause of death.[1,2] Twenty-five percent of severe trauma cases involve a major bleed associated with impaired blood clotting following trauma-induced coagulopathy (TIC). Such TIC contributes significantly to bleeding and is an independent factor of poor prognosis. It may occur very early after injury[6] and is associated with increases in: the risk of death during the first 24 hours, transfusion requirements, hospital stays and other complications.[3-5]

This chapter aims to review the mechanisms and treatment of TIC, as well as the practical implications of TIC for surgical management. The role of laboratory testing in the management of TIC is also addressed.

Methodology

We reviewed the literature by screening the PubMed, Scopus and Cochrane Library databases using a literature search strategy employing the following specific keywords: trauma, trauma-induced coagulopathy, coagulopathy, bleeding, mortality, mechanisms, treatment, tranexamic acid, damage control surgery, extracorporeal membrane oxygenation. Only publications in English were considered.

Part I: Molecular and clinical mechanisms of traumatic coagulopathy

In the past, TIC was explained by reference to a "lethal triad": haemodilution, acidosis and hypothermia. However, it appears that the pathophysiology of TIC is more complex than this account permits. In addition to the "lethal triad", TIC also involves activation of protein C, endothelial dysfunction, platelet dysfunction and fibrinogen depletion.

1. The classic lethal triad

For many years, haemodilution, hypothermia and acidosis were considered to be the primary aetiology of TIC. It now seems that these conditions should rather be considered as precipitating factors of TIC.

In the past, administration of high volumes of crystalloid solutions was considered a crucial step in trauma resuscitation to stabilize patients' haemodynamic parameters. However, it now appears that prehospital crystalloid administration worsens coagulopathy, acidaemia and hypothermia, affecting thrombin production, a central factor for clot formation. The induced dilution coagulopathy is directly correlated with the volume of fluid administered.[7-9] Crystalloid administration acts only through this dilution effect. It does not affect fibrinogen metabolism.[10] Gelatin derivatives also act through dilution but have some effects on the clot characteristics: decreasing clot weight and clot elasticity.[11] Solutions derived from hydroxyethyl starches cause coagulation factor dilution, a von Willebrand-like syndrome, hypocalcaemia, platelet coating, an antagonistic effect on the platelet fibrinogen receptor GIIb/IIIa and impairment of fibrin polymerization.[12] However, unlike the use of crystalloids, colloid administration in trauma patients is not associated with increased mortality.[13]

Nevertheless, it appears that haemodilution is a contributor to TIC, rather than its primary cause.

Acidosis and hypothermia are two other independent contributors to the coagulopathy observed in trauma patients. They impair thrombin generation via distinct mechanisms.[14]

A body temperature below 34 ºC directly affects blood coagulation. In trauma patients, hypothermia increases the risk of severe bleeding and represents an independent risk factor for mortality.[15,16] The major adverse effects of hypothermia on coagulation are prolonged prothrombin and activated partial thromboplastin times.[16,17] It leads to platelet dysfunction, impairs or inhibits coagulation factor activities and increases fibrinolysis.[17,18] In models of severe hypothermia (< 32 °C), fibrinogen synthesis is decreased but fibrinolysis is not increased.[14]

Acidosis, induced by tissue hypoperfusion followed by a shift to anaerobic metabolism, can be worsened by the administration of large amounts of Ringer's lactate solution during early resuscitation. It represents an independent predictive factor of bleeding and death. Acidosis leads to the impaired activity of protease coagulation factors and a depletion in fibrinogen storage and platelet count, thus compromising clot formation. The rate of maximal clot strength on thromboelastography is slower, showing a delay in competent clot formation.[19] Moreover, acidosis leads to prolonged clotting times and increased bleeding time.[14,20]

Acidosis is also associated with accelerated fibrinogen consumption and, while it does not affect fibrin formation, it is associated with accelerated fibrinolysis.[21]

Taken together, acidosis and hypothermia have a synergistic effect on the impairment of blood coagulation.[15]

1.1. Platelet dysfunction in TIC

Platelets play two critical roles in the haemostasis process: adhesion and aggregation. At the site of endothelial injury, platelets form a haemostatic plug and platelets enhance activation of coagulation proteases, leading to thrombus formation. Despite their pivotal role in early coagulation, assessments of platelet function are rarely available in routine practice for the early management of trauma.

The following considerations are important to the understanding of the role of platelets in trauma.

1.1.1. Platelet count

On admission, platelet counts in critically injured trauma patients are often normal. However, they can quickly decrease after admission. Low platelet counts at admission and during the course of trauma care are associated with increased mortality and morbidity.[22-24]

1.1.2. Platelet dysfunction

Persistent bleeding despite a platelet count greater than $100x10^9$/L without clotting factor deficiency indicates the presence of a trauma-induced platelet dysfunction. A deficiency of platelet aggregation in response to adenosine diphosphate (ADP), arachidonic acid, collagen or thrombin receptor-activating peptide is often seen in trauma patients.[23,25-27] The most severe impairments of platelet function are observed in brain-injured patients.[28]

Platelet hypofunction on admission of a trauma patient to an intensive care unit (ICU) is associated with a 10-fold increase in risk of mechanical ventilation requirements, lower admission Glasgow Coma Scale and a higher level of early mortality.[27]

A leading cause of trauma-induced platelet dysfunction is exposure to high concentrations of the platelet activators tissue factor (TF) and platelet activating factor (PAF).[29] These two mediators can activate platelets and subsequently render them atomic. The atomic platelets limit thrombin production and clot stabilization. Platelet receptor inhibition prevents cellular initiation and amplification of the clotting cascade, limiting thrombin incorporation and clot stabilization, which usually stops haemorrhaging.[30,31]

1.1.3. Hypothermia

The effect of hypothermia on platelet function is not fully understood and published studies show conflicting results.[32] Hypothermia is frequent in trauma patients. It decreases platelet adhesion, coagulation factor activities and platelet activation.[33,34] In a study on pigs, animals with mild hypothermia (34 °C) displayed significantly longer clotting times and clot formation times, but the maximum clot firmness was not significantly different from that in normothermia. In this study, mild hypothermia affected the coagulation system but did not aggravate TIC.[35] However, a recent review shows that hypothermia-associated coagulopathy is to a greater extent related to a reduced availability of platelet activators than to an intrinsic platelet dysfunction.[36]

1.2. Endothelial dysfunction in TIC

During trauma, inflammation, cytokine production, hypoperfusion, hypoxia-reperfusion injuries or sympathoadrenal activation can upset endothelial homeostasis. These factors also promote shedding of the glycocalyx layer, inducing an auto-heparinization of the patient that occurs while large amounts of anticoagulant glycocalyx components, such as syndecan-1 and heparan sulphate, appear in the patient's blood circulation.[37-40] High circulating levels of syndecan-1 are associated with increased mortality.[40] Moreover, patients with high levels of syndecan-1 show a progressive depletion of protein C, increased soluble thrombomodulin expression and hyperfibrinolysis.[40] The trauma-induced degranulation of Weibel-Palade bodies enhances endothelial dysfunction and coagulopathy. Weibel-Palade bodies contain tissue plasminogen activator (TPA), von Willebrand factor antigen, thrombomodulin and angiopoietin-2. These compounds promote inflammation, fibrinolysis and vascular permeability, leading to interstitial oedema.

1.3. Activated protein c in TIC

Under normal physiological conditions, activated protein C (APC) has both cytoprotective and anticoagulant effects. It exerts these protective effects through activation by the thrombin-thrombomodulin complex in the presence of the endothelial protein C receptor. APC prevents thrombin generation by inhibiting factor Va and factor VIIIa. It also demonstrates profibrinolytic activity via inhibition of tPA-1. However, in trauma, the glycocalyx shedding and the damaged endothelium enhance the release of thrombomodulin and endothelial protein C receptor in the systemic circulation. This crucial step allows for a "thrombin switch" to occur, whereby thrombin acts as an anticoagulant. Indeed, the formation of the thrombin-thrombomodulin complex (thrombomodulin-thrombin-activated protein C receptor) in the systemic circulation leads to the formation of a large amount of APC, which can realize the following anticoagulant and profibrinolytic activities:[41]

- Cleavage of factor Va and factor VIIIa, preventing thrombin formation and clot stabilization.
- Activation of APC-related pathways associated with the depletion of factors I, II, V, VII, VIII, IX and X.
- Inhibition of the physiological inhibitor of tissue-derived and urokinase plasminogen activators.

These findings are supported by clinical studies showing that an increased production of APC in patients in the early phase of trauma resuscitation is a predictor of coagulopathy and higher mortality.[9,42-44]

1.4. Fibrinogen depletion in TIC

Recent studies suggest that a low fibrinogen level at admission is correlated with higher mortality in trauma patients.[41,45]

During acute traumatic coagulopathy, fibrinogen levels fall quickly after the beginning of major and severe bleeding events.[45] This is probably the first haemostatic abnormality observed in trauma. Loss of fibrinogen results from the operation of several mechanisms. Firstly, potent and rapid fibrinogen consumption is associated with uncontrolled bleeding. Secondly, fibrinogen synthesis is impaired. Fluid administration leads to a dilution of coagulation factors and consequently to fibrinogen concentration. Colloids (hydroxyethyl starches and gelatins) and hypothermia directly impair fibrin polymerization.[10,12] Thirdly, the hyperfibrinolysis state may cause loss of fibrinogen. The simultaneous release of tissue plasminogen activator (TPA) and its antagonist, plasminogen activator inhibitor type 1 (PAI-1), accompany activation of the coagulation cascade by exposure of the sub-endothelial surfaces and the presence of TF in the systemic circulation. During the early phase of trauma, it seems that the TPA level outstrips levels of PAI-1, inducing a profibrinolytic state.[46] These observations support the use of antifibrinolytic drugs in trauma resuscitation.[47] Moreover, APC mediates enhanced fibrinolysis through its actions on PAI-1 and TPA.[41]

Part II: Medical treatment of trauma-induced coagulopathy

This material is summarized in Figure 1.

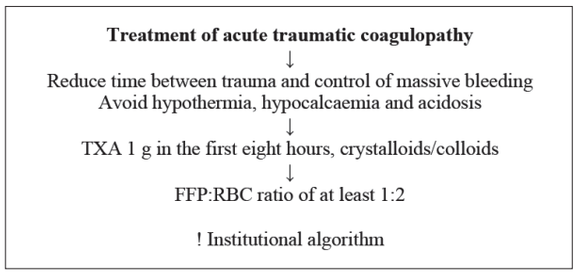

Figure 1
Treatment of acute traumatic coagulopathy

1. Minimize elapsed time

The earlier and more targeted the treatment of TIC, the better the results. It is very important to reduce the time between admission and control of haemorrhagic shock. An initial assessment – comprising evaluation of severity, localization and the mechanism of trauma, and assessment of the patient's physiological presentation and response to resuscitation – facilitates early surgical bleeding control. If the source of bleeding is unidentified, imaging such as focused assessment with sonography for trauma (FAST) or a computed tomography (CT) scan should be performed. Various tools can assist clinicians' decision-making, such as the Advanced Trauma Life Support classification (ATLS) and the Shock Index (heart rate divided by systolic blood pressure).[48]

Reduce the time between trauma and the treatment of massive bleeding, consider urgent surgical bleeding control (Grade 1A)[49]

2. Rapid bleeding control techniques

Use of techniques for rapid control of bleeding, such as tourniquets on arrival for open extremity injuries, may decrease transfusion requirements. However, such techniques may themselves cause complications (e.g., nerve paralysis or limb ischaemia). Damage control surgery (see part III) should be initiated as quickly as possible. Topical haemostatic agents can be used as adjuncts to surgery to obtain haemorrhagic control.

Use rapid bleeding control techniques: tourniquets, damage control surgery (Grade 1B)[49]

3. Avoid aggravating factors

Three factors aggravate coagulation disorders: hypothermia (temperature < 35 °C), metabolic acidosis (pH < 7.2) and hypocalcaemia (< 1 mmol/L); they must be avoided to decrease the risk of TIC.

3.1. Hypothermia

Upon arrival at the incident, since clinical evaluation is of the utmost importance, undressing the victim is a priority. However, this should be accompanied by the use of blankets or fluid heaters to maintain normal body temperature. Maintaining a lower temperature of 33-35 °C should be considered in patients with isolated traumatic brain injury (TBI) once haemorrhaging is controlled. Hypothermia reduces platelet and coagulation factor function – for example, a drop of 1 °C in body temperature leads to a 10% drop in function, enzyme inhibition and fibrinolysis.[49]

Avoid potential heat loss and warm the patient (Grade 1C) except in cases of isolated TBI (Grade 2C)[49]

3.2. Metabolic acidosis

Metabolic acidosis is often seen in trauma patients subjected to massive blood transfusions. There are two origins of this condition: lactate production from hypoperfused tissues or excessive chloride administration through the saline drip. At a pH < 7.4, various coagulation abnormalities are encountered, such as inhibition of thrombin generation and increase of degradation of fibrinogen.[50] High concentrations of lactate in the venous or arterial systems constitute an independent predictor of mortality in haemorrhagic trauma.[51] However, this measure is less reliable in alcohol-associated trauma because alcohol itself increases a patient's blood lactate level.[52] A base deficit derived from arterial blood is an alternative measure for such patients and is also correlated with mortality.[53]

Avoid acidosis, measure serum lactate as a predictor of poor prognosis in severely injured patient (Grade 1B)[49]

3.3. Hypocalcaemia

Low ionized calcium concentrations at admission are associated with an increase in mortality as well as a need for massive transfusion. The normal range for ionized calcium is between 1.1 and 1.3 mmol/L and is inversely correlated with blood pH. Citrate used in blood products (fresh frozen plasma and platelets) exerts its anticoagulant effect by binding ionized calcium.

Calcium levels should be monitored and maintained in the normal range during massive transfusions (Grade 1C)[49]

4. Antifibrinolytics

Tranexamic acid (TXA) reduces all causes of mortality in trauma patients and reduces transfusion requirements (CRASH-2 trial).[47] The risk of death due to bleeding is significantly decreased if TXA is given within one hour of trauma injury and this beneficial effect persists for administration up to three hours after injury. However, TXA administration more than three hours after trauma leads to an increased risk of death due to bleeding.[54] The ongoing CRASH-3 trial will evaluate TXA for the treatment of significant TBI in term of death and disability.[55] In addition, TXA does not increase the risk of vascular occlusive events.[56]

Give TXA as a 1g bolus over 10 minutes as early as possible, followed by another 1g given continuously over the next eight hours[49] (Grade 1A)

5. Fluids

The use of fluids as volume replacement therapy in hypotensive patients should be undertaken carefully, taking into account the type and amount of fluid given to the patient. The goal of fluid replacement therapy is to restore tissue perfusion to maintain aerobic cell function. The optimal type of fluid is still a matter of debate. It seems that administration of crystalloids during the initial treatment of a hypotensive bleeding patient is justified. Ringer's lactate solution should be avoided in TBI due to the risk of fluid shifting into the damaged cerebral tissue. After this initial infusion, colloids might be considered to replace fluid loss. Older hydroxyethyl starch (HES) solutions with higher molecular weight

and degree of substitution, as compared to more recent HES solutions, accumulate faster and may cause renal dysfunction.[57] Only 6% HES 130/0.4 infusion should be used. However, the appropriate dosage of these products is as yet unclear. A patient's renal function must be monitored following HES infusion.[58]

These infusions are safe but do not appear to improve survival or neurological outcome. If target arterial pressure is not achieved with fluid replacement therapy, vasopressors should be considered. A targeted systolic blood pressure of 80 to 90 mmHg, or ≥ 80 mmHg in the case of associated TBI, is recommended until major bleeding is controlled. The patient must have a large bore intravenous catheter (peripheral or central) inserted to transfuse large volumes of fluid as quickly as possible. If vascular access is difficult an intraosseous infusion should be considered.

Crystalloids are recommended to treat hypotensive bleeding trauma patients (Grade 1B). If colloids are used, dosage should be within the prescribed limits (Grade 1B)[49]

6. Blood components and plasma-derived products

Clinicians must decide when to infuse blood products. In Belgium in 2015, available blood component products approved by the National Institute for Public Sickness Insurance and Disability (INAMI/RIZIV) included: packed red blood cell (RBC) concentrates: €117.1; platelets: €430.4 for a minimum of $4x10^{11}$ platelets; fresh frozen plasma (FFP): €91.0. Prothrombin complex concentrates (PCC), such as PPSB® (€274) or fibrinogen (€419), are approved by INAMI/RIZIV only for specific clinical situations, such as treatment of vitamin K antagonist overdose or congenital hypofibrinogenaemia, respectively, but not in the context of TIC, except for patients taking an oral anticoagulant and requiring emergency surgery. Activated coagulation factors, such as Novoseven®, is reimbursed (50000 UI: €592) in patients with congenital deficiencies (haemophilia A with FVIIIC inhibitors, congenital deficiency in FVII or Glanzmann thrombasthaenia) but not in acute trauma. rFVIIa is not a first-line treatment for bleeding. We suggest that the use of rFVIIa should be considered if major bleeding and traumatic coagulopathy persist despite standard attempts to control bleeding and best practice use of conventional haemostatic measures (Grade 2C).

6.1. Packed red blood cells

A preliminary question must be answered before considering a transfusion of RBC: what haemoglobin (Hb) concentration is needed to ensure adequate oxygen delivery to tissues? Since oxygen delivery is directly related to Hb concentration, a fall in Hb concentration could be responsible for tissue hypoxia. Therefore, a transfusion is recommended if Hb concentration is < 7g/dl and is probably not useful if Hb > 10 g/dl.[59] Note that, for severe TBI, transfusion thresholds are the same. Regarding the haematocrit (Hct), this may be influenced by administration of intravenous fluid and RBC, acting as confounding factors. Therefore, a patient with massive blood loss may have a stable Hct due to simultaneous loss of plasma and red blood cells, while decreasing serial Hct measurements may reflect ongoing bleeding.

A target Hb concentration between 7 to 9 g/dl is recommended (Grade 1 C). A single Hct is not recommended as an isolated laboratory marker of bleeding (Grade 1B)[49]

6.2. Fresh frozen plasma

An FFP plasma unit contains about 70% of the level of all normal clotting factors, including fibrinogen. One unit of FFP contains, on average, 0.4 to 0.5 g of fibrinogen. In Belgium, plasma only exists in the thawed form. As with other blood components, transfusion of plasma is not free from risk of worsening post-injury multiple organ failure, acute respiratory distress syndrome or infections. Data from war zones have demonstrated that a plasma to RBC ratio of at least 1:1 decreases the number of deaths from haemorrhaging and improves rates of survival to hospital discharge.[60-62] This positive effect of FFP:RBC ≥ 1:1 is not observed among survivors after 24 hours.[63] This trend combines with data from Holcomb et al. (the PROPPR randomized clinical trial), which compared a ratio of plasma to platelets (1 pool of 6U, on average) to RBC of 1:1:1 and 1:1:2, in patients with severe trauma and major bleeding. They found that, whatever the ratio, there was no difference in mortality at either 24 hours or 30 days. More patients from the 1:1:1 ratio

group reached haemostasis and fewer died from exsanguination by 24 hours.[64] The aim is to reflect, as far as possible, the constitution of whole blood. Unavailability of sufficient universal donor (AB) plasma may be a clinical challenge when treating massively bleeding trauma patients. Male blood group A low-titer B has been used as universal donor plasma in the early phases of trauma resuscitation without evidence of haemolysis or other reactions.[65]

In cases of massive bleeding, an FFP:RBC ratio of at least 1:2 is recommended (Grade 2C)[49]

6.3. Fibrinogen

This is the first blood component that reaches a critical level during blood loss replacement by plasma-poor red cell concentrates.[66] The decrease in fibrinogen plasma concentration quantified by thromboelastography (TEG) or rotational thromboelastometry (ROTEM, TEM International GmBH, Munich, Germany) measurements provides predictive values for massive transfusions in trauma patients.[67] However, there have not yet been enough prospective clinical trials to assess the necessity of using a source of additional fibrinogen in the management of bleeding trauma patients.[68,69]

We recommend fibrinogen supplementation if significant bleeding is accompanied by thrombo-elastometric signs of deficit or a plasma level < 1.5 to 2g/l (Grade 1C): the initial dose is 3 to 4 g (Grade 2C)[49]

6.4. Platelets

The place of platelets in TIC has not been clearly shown and is controversial. The threshold for transfusion is also a matter for debate, ranging from 50,000 to 75,000/μl. A target platelet count above 100,000/μl should be considered in patients with ongoing bleeding and/or with a TBI. A dose of between four and eight platelet units increases the platelet count by 30,000 to 50,000/μl.

Platelet count should be maintained > 50,000/µl (Grade 1C) or > 100,000/µl in patients with ongoing bleeding and/or TBI[49]

As with all blood products, transfusion carries risks of circulatory overload, ABO incompatibility (usually resulting from human error), transmission of infectious diseases (including prions) and allergic reactions.[70] Finally, it should be noted that, in Belgium, the use of pathogen inactivation methods to decrease the risk of infectious disease transmission is mandatory for all plasma use (blood components and drugs and platelet concentrates).

7. Special populations: patients taking antithrombotic drugs

Given the ageing population, growing numbers of patients are taking antithrombotic drugs (antiplatelet agents, vitamin K-dependent and direct oral anticoagulants: DOAC). When a medical history cannot be taken (e.g., for an intubated or unconscious patient), the presence of antithrombotic agents cannot be assessed from routine laboratory data, especially in the case of antiplatelet agents and apixaban.

7.1. Antiplatelet agents

In patients with massive bleeds, platelet transfusion is indicated even at high platelet counts.[71] Ticagrelor (Brilique®, AstraZeneca) binds reversibly and selectively to the P_2Y12 receptor. Circulating ticagrelor and its active metabolite are likely to inhibit transfused platelets. Case reports have demonstrated the ineffectiveness of platelet transfusion in the presence of ticagrelor.[72] For patients taking acetylsalicylic acid, desmopressin (0.3 μg/kg) is indicated; for all other patients, there is no indication for routine administration of desmopressin in massive bleeding due to trauma.[50]

Administration of platelets is indicated for patients with massive bleeding or TBI who have received antiplatelet agents (Grade 2C)[49]

7.2. Vitamin k-dependent oral anticoagulants

For patients treated with a *vitamin K-dependent oral anticoagulant*, PCC is used if a rapid reversal is indicated. This indication must be weighed against the risk of thrombosis. The dosage should be determined according to the manufacturer's instructions, but is usually around 50 U/kg of body weight.

PCCs are used for emergency reversal of vitamin K-dependent oral anticoagulants (Grade 1B)[49]

7.3. Direct oral anticoagulants

For patients treated with direct oral anticoagulants (dabigatran: anti-IIa/rivaroxaban, apixaban and edoxaban: anti-Xa), in cases of life-threatening bleeding, PCC of 25 to 50 U/kg can be used.[73] Haemodialysis may be a suitable approach for dabigatran due to its renal elimination and low protein binding. Nevertheless, the most important advance in this field is the availability of specific antidotes. Andexanet and ciraparantag are being studied as antidotes for anti-Xa. However, it is not yet known if these antidotes improve outcomes in patients with massive bleeding. For dabigatran, a humanized monoclonal antibody antigen-binding fragment, idarucizumab (Praxbind®), was approved by the US Food and Drug Administration (FDA) in October 2015[74] and the European Medicines Agency (EMA) in November 2015.

For DOACs, PCC (25-50 U/kg) can be used (Grade 2C), antidotes are under evaluation for FXa inhibitors and Praxbind® is authorized for dabigatran.[49]

8. Special situation: extracorporeal membrane oxygenation (ECMO) and trauma

Thoracic injuries occur in about 50% of patients with multiple trauma.[75] These may cause acute lung failure (ALF), which can rapidly lead to death due to life-threatening impairment in gas exchange (hypoxia, hypercapnia and respiratory acidosis). If conventional mechanical ventilation strategies fail, ECMO can be considered to support tissue oxygenation.[76] Apart from ALF – and if anatomical sites of bleeding are controlled – another indication for ECMO in trauma patients is tracheobronchial injury.[77] The type of ECMO used should be dictated by the affected organ:

- Venovenous (VV) ECMO can be used as lung support in trauma patients with chest injuries without cardiac dysfunction. For example, the following situations may justify a VV-ECMO: pulmonary contusions after blunt trauma leading to alveolar haemorrhage and parenchymal destruction,[78] air leak in the tracheobronchial tree or compromised airway patency and secondary pneumonia. A VV-ECMO circuit is composed of an inflow cannula placed in the mid inferior vena cava via a femoral vein, and connected to a pump and an oxygenator. The return is provided by an outflow cannula placed in the superior vena cava or pushed from the other femoral vein into the right atrium. Cannulas can be inserted using surgical or percutaneous approaches.[79]

- Arteriovenous (AV) ECMO is preferred if the heart must be supported (e.g., cardiopulmonary failure in a drowned person with hypothermia or cardiac contusion) regardless of any lung damage. In this configuration, AV-ECMO also provides blood flow in place of the heart. The inflow system is the same as for VV-ECMO, but the outflow system is provided by a cannula placed in the ascending aorta, from a femoral or subclavian artery.

ECMO circuits are supplied with blood, colloids or crystalloids. The main potential limit regarding their use for trauma patients is the requirement for heparinization. Moreover, such systems require a dedicated perfusion team which may not be available in all settings.

Part III: Practical implications of traumatic coagulopathy on surgical management

1. Introduction

Post-traumatic or hazard-induced coagulopathy must be aggressively corrected in all patients and especially in those with severe head or neck injuries. Trauma resuscitation for severely injured patients has undergone a paradigm shift in the last decade, with many centres switching from crystalloid-based to blood product-based resuscitation. Damage control resuscitation (DCR)[80] includes early blood product transfusion, immediate arrest and/or temporization of ongoing haemorrhage (i.e., temporary intravascular shunts and/or balloon tamponades), permissive hypotension, restoration of blood volume and physiological/haematological stability,[81] and coagulopathy correction. DCR is strongly recommended if available on-site or at the first tactical care level.[82]

Some essential lessons can be learned from military medicine, where polytrauma is the predominant form of battlefield injury and where catastrophic blood loss often leads to death. Neck wounds commonly cause life-threatening blood loss. Exsanguinating haemorrhage accounts for 33-40% of all trauma-associated deaths, approximately half of which occur before the patient reaches the

hospital.[83-86] However, another major cause of death in head and face injuries is airway compromise.[87,88]

Although the head and neck region accounts for only 12% of total body surface area, head and neck injuries are seen in over 20% of battlefield casualties in 21st century conflicts.[89,90] By comparison, in the 20th century approximately 16% of battlefield injuries involved the head and neck regions.[91] This is most likely due to a reduction in thoracoabdominal injuries due to the effectiveness of modern body armour, combined with the increased incidence of improvised explosive devices.[92]

For these reasons, the concepts of DCR and damage control surgery (DCS)[93-95] have been developed and applied to all severely injured oral and maxillofacial surgical patients.[96]

2. Surgery to control haemorrhage

2.1. Introducing DCS

In 2007, the multidisciplinary Task Force for Advanced Bleeding Care in Trauma published evidence-based recommendations and flow charts covering many aspects of the acute management of bleeding trauma patients. Massive bleeding in trauma patients was defined as the loss of total blood volume within 24 hours or the loss of 50% of blood volume within three hours.[97] It recommends that the time between injury and operation should be minimized for patients in need of urgent surgical bleeding control and that patients presenting with haemorrhagic shock and an identified source of bleeding should undergo immediate surgical bleeding control if initial resuscitation measures are not successful. Finally, adopting a DCS approach is considered essential for severely injured patients (Figure 2).[98-100]

DCS is the most technically demanding and challenging surgery a trauma surgeon can perform.[101] Such techniques are used to manage critically ill patients. The emphasis is on restoring normal physiology to prevent the "lethal triad" (metabolic acidosis, hypothermia and coagulopathy) rather than correcting anatomy.[102,103]

DCS is indicated when a person sustains a severe injury that impairs their ability to maintain homeostasis due to severe haemorrhage.[104] As with DCR, the principles of DCS are control of

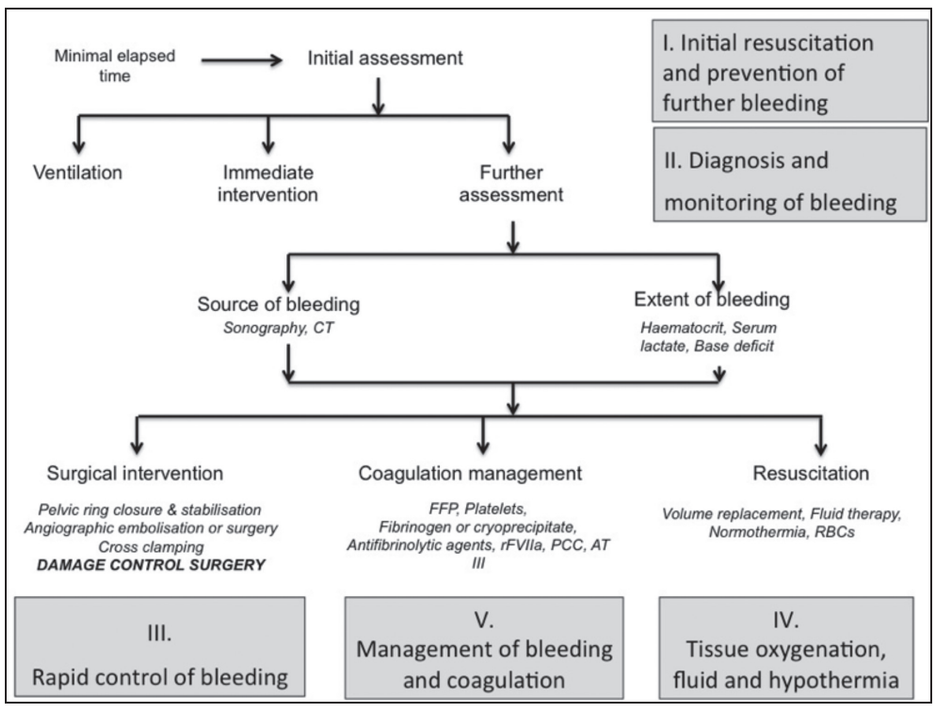

Figure 2
Medical treatment of traumatic coagulopathy. Adapted from Spahn DR et al.[49]

haemorrhage, prevention of contamination and protection from further injury.[105] The physiological impact of surgery is limited by carrying out the minimum amount of surgery in the shortest time necessary to stabilize the patient, prevent infection and avoid the "lethal triad".

While it may be tempting to combine DCS with a definitive, corrective operation, this should be avoided as patients may yet succumb to the physiopathological effects of the injury, despite anatomical correction.

2.2. Indications for DCS (Table 1)

The earlier DCS is applied in at-risk patients,[106] the better the outcomes.[107-109] Patients who died in hospital during the DCR period were more likely to be severely injured and to have had severe brain injury, consistent with a decrease in deaths among potentially salvageable patients.[110]

Another complementary consideration could be added to the DCS paradigm:

the requirement to take into account the ability to control haemorrhage – for example, in cases of severe abdominal compartment syndrome,[111] liver injury[112] or associated injuries.[113,114]

2.3. Phases of DCS (Figure 3)

Tactical Combat Casualty Care for Medical Personnel (TCCC) guidelines are designed to direct basic management of care under fire or in hostile environments. The phases of TCCC are: (1) Care Under Fire (or in an unstable environment), (2) Tactical Field Care and (3) Tactical Evacuation Care, mainly determined according to distinct hazard zones (hot, warm or cold) (cfr. chapter on prehospital interventions).

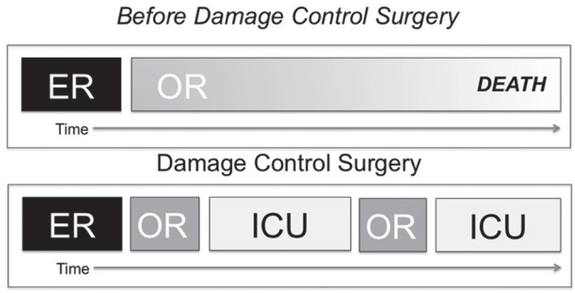

Figure 3

Damage control surgery paradigm. In contrast with previous views regarding trauma management, DCS is characterized by sequences of abbreviated surgery followed by resuscitation in an ICU with subsequent revision or repair until restoration of a normal physiology is achieved.
(ER): Emergency Room; (OR): Operating Room; (ICU): Intensive Care Unit

2.3.1. Phase 0 (Ground 0): prehospital and early resuscitation

The emphasis of phase 0 is the early recognition of patients who are at risk of developing the "lethal triad" and those for whom damage control techniques may be indicated.

The management steps of phase 0 are the following: stop bleeding using tourniquets or direct pressure (if the patient has noncompressible bleeding, practice permissive hypotension),[115] stabilize following the ABCDE (Airways, Breathing, Circulation, Disability and Exposure) sequence, rapidly transfer to the medical treatment facility with initiation of DCR, prevent the "lethal triad" and, finally, rapidly transfer to the operating room.

Table 1
Indications for damage control surgery

Patient	Symptoms	Severity stage
Is presenting with or is at risk for developing	Multiple life-threatening injuries	
	Acidosis	pH < 7.25
	Hypothermia	Temperature < 34 °C
	Shock[45] on presentation	
	Combined hollow viscous and vascular or vascularized organ injury	
	Coagulopathy	INR > 1.4
	Mass casualty situation	

2.3.2. Phase 1: primary DCS

Primary DCS aims to control haemorrhage and contamination, determine the extent of injury, apply therapeutic packing and, if necessary, perform temporary abdominal closure.

2.3.3. Phase 2: critical care

Physiological support of the post-operative DCS patient is paramount to survival. This phase includes: core rewarming (by means of warmed resuscitative fluids, blankets, ventilator air and environment), reversal of coagulopathy using coagulation factor replacement, ventilation support (preferring ARDSNet[116] low tidal volume to avoid barotrauma) and, finally, injury identification.

2.3.4. Phase 3: planned re-operation

Packing should generally be left in place until the patient's haemodynamic profile is stabilized and all major sites of haemorrhage have had time to clot. When removed, packing should be taken out slowly with plans for vascular control. Re-operation should be scheduled when the probability of achieving definitive organ repair and complete fascia closure is highest, although an estimation that the fascia cannot be closed should not preclude initial re-exploration(s). Re-exploration must occur after correction of hypotension, acidosis, hypothermia and coagulopathy. It typically occurs 24-48 hours following the initial operation. Timing can, however, be dictated by other pressing clinical concerns, such as cardiac failure, limb ischaemia and suboptimal control of spillage at primary operation.

2.3.5. Unplanned re-exploration

Emergent, unplanned re-exploration should be considered in any patient who remains unstable, persistently coagulopathic or acidotic despite continued resuscitation and full cardiopulmonary support.

2.4. Principles of management for head and neck surgery[117]

Surgical judgement is required to determine the amount of soft tissue and bone debridement that is initially required to adequately clean tissues and prevent infection, and which early definitive treatments can be performed to provide the best possible final form and function.

The principles of management include early tracheotomy (cfr. chapter on complex intubation, cricothyroidotomy and tracheotomy), vigorous replacement of blood loss and correction of coagulopathy, nasal packing, neck exploration and management of carotid injury, early generous decompressive craniotomy, intracranial haematoma evacuation, removal of accessible fragments and debridement of devitalized cerebral tissue, external ventricle drain, duraplasty and use of broad-spectrum antibiotics.

The neurosurgical procedures required for these injuries are generally more extensive and aggressive than those that have been described for penetrating brain injuries in the literature from previous wars. A CT scan (if available) is invaluable for planning the extent of neurosurgery and CT angiography is useful when cervical vascular injuries are suspected. The timing and extent of neurosurgery and maxillofacial surgery must be balanced against the relative priorities of other injuries and the state of physiological stabilization. Repair of ocular injury or eye removal is often deferred.[118]

2.5. Particular issues in generic DCS relevant for ent specialists

2.5.1. Thoracic injuries

The goal of abbreviated thoracotomy is to stop bleeding and restore a survivable physiology; contamination is usually not a problem. Tracheal injury can be temporized with airway control placed through the site of injury (mask or tube) (cfr. chapter on complex intubation, cricothyroidotomy and tracheotomy). When dealing with oesophageal injury, nasogastric tube diversion and wide drainage, without definitive organ repair, are the best initial courses of action.[119]

2.5.2. Specific DCS considerations in head and neck injuries

(For more detail, please consult the chapter on neck injuries.)

Maxillofacial DCS is restricted to tracheotomy, arrest of haemorrhage, initial wound debridement, reduction and immobilization of fractures and sight-saving procedures, such as lateral canthotomy.[120] Vascular injury is seen in 20% of cases involving penetrating neck trauma and exsanguination is the primary cause of death.

The neck is traditionally divided into three zones to aid decision-making and management (Figure 4). Zone 2 neck injuries involving hard signs of vascular injury require immediate exploration, eventually supported by angiography.[121] These hard signs include uncontrollable haemorrhage, rapidly expanding haematoma, pulsatile haemorrhage, palpable thrill or audible bruit, and signs of neurovascular compromise.

2.5.3. Example of bomb blasts

Bomb blasts cause combinations of blast injury,

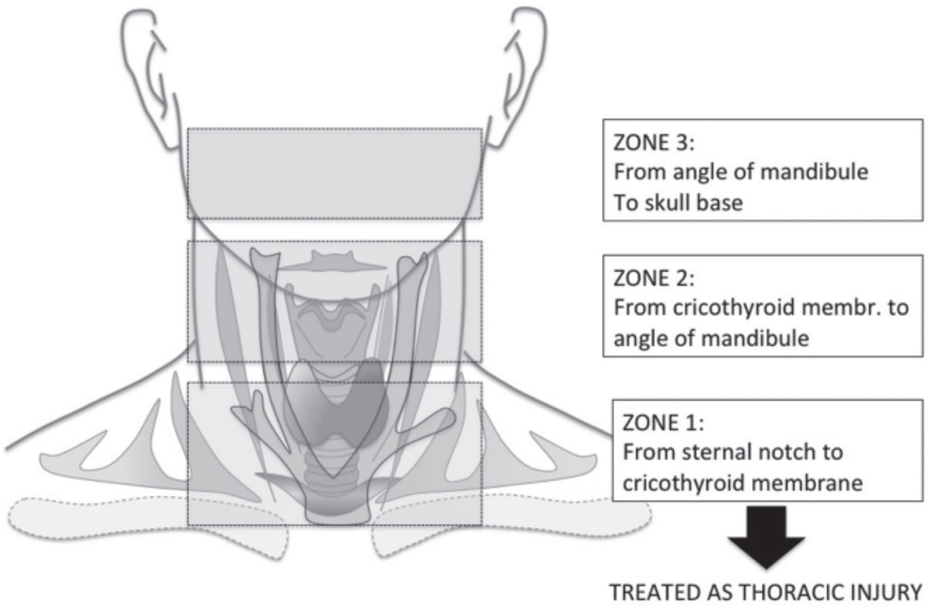

Figure 4
Neck zones as considered in DSC

Table 2
Factors capable of influencing peroperative and post-operative bleeding

Does not affect	Occasionally affects	Frequently affects
- Prophylactic dose of heparin, LMWH or fondaparinux - Osler-Weber-Rendu syndrome (hereditary haemorrhagic telangiectasia) - Mild thrombocytopaenia (e.g., > 60,000/ml)	- Aspirin or NSAID administration - Poor metabolic/nutrition states - Moderate thrombocytopaenia (30,000-60,000/ml)	- Platelet defects, especially with concomitant aspirin or NSAID administration - Factor VIII or IX < 30% of normal levels - Fibrinogen < 60 mg/dl - Severe thrombocytopaenia (< 30,000/ml) - Multiorgan failure

Table 3
Major causes of peroperative or post-operative haemorrhage

Peroperative haemorrhage	Early post-operative (days zero to three)	Delayed post-operative bleeding (days three to seven)
- Structural/technical defects - Disseminated intravascular coagulation - Anticoagulant overdosage - Hyperfibrinolysis	- Structural/technical defects - Thrombocytopaenia - Qualitative platelet disorders - Mild/moderate hereditary coagulation disorder	- Thrombocytopaenia - Aspirin or NSAID administration - Vitamin K deficiency - Multiorgan failure - Poor wound healing (often with dehiscence) from chronic liver disease

multiple penetrating injuries and burns. The pattern of injury to the head and neck includes intracranial haemorrhage, brain swelling with multiple intracranial metal and bone fragments, cervical and facial vascular injury, pharyngolaryngeal injury, acute airway compromise, facial and scalp burns, large scalp defects and extensive skull base fractures.

3. Surgical issues due to coagulation impairments

3.1. Peri-operative risks

The direct consequence of post-traumatic or post-hazard coagulopathy is a higher risk of massive and ubiquitous peroperative haemorrhage. Some metabolic factors have been recognized as capable of affecting the peroperative or post-operative coagulation function (cfr. Table 2).[101] On the other hand, the delay of post-operative bleeding can be suggestive of underlying coagulation disorders (cfr. Table 3).[101]

Ligation, shunting or repair of injured vessels can control haemorrhage from visible blood vessels as they are encountered. The initial goal is control of the haemorrhage, rather than maintenance of blood flow. For patients in extremis, clamping or shunting of major vessels is recommended over repair. When necessary, fasciotomy should be performed. Additional methods of haemorrhage control can include balloon catheter tamponade of vascular or solid viscous injuries.

3.2. Post-operative risks

3.2.1. Early-onset complications

Considering that sometimes casualty evacuation is difficult, or that a surge of casualties to the tactical field care centre can occur, the risk of wound infection is substantial. TCCC procedures, described in the chapter dedicated to prehospital interventions, recommend systematic use of antibiotics for all open wounds on arrival at the tactical field care centre. If oral administration is possible, Moxifloxacin 400 mg PO once a day should be prescribed. In case of shock or unconsciousness, high doses of cephalosporins or beta-lactam antibiotics should be administered via IV or IM.[122] DCS consolidates the pharmacological effects of such interventions, controlling locally and systematically all wounds and tissue damage to avoid, as far as possible, all immediate or post-operative contamination. Contamination control also proceeds as injuries are encountered, utilizing clamps, primary repair or resection without reanastomosis.

3.2.2. Late-onset complications: wound healing

Wound healing is a highly coordinated process involving clot formation, inflammatory reaction, immune response and, finally, tissue remodelling and maturation. All interfering phenomena, such as coagulation disorders or locoregional infections, can lead to poor healing with extensive fibrotic fields inside the tissue parenchyma.[123,124]

4. Conclusions and take home messages for ent specialists

1) Consider DCS in patients who present with, or are at risk of developing, the "lethal triad", multiple life-threatening injuries, shock[125] or in mass casualty situations.

2) Injuries to zone 2 of the neck require emergency surgical haemorrhage control.

3) Besides haemorrhage control, DCS also aims to evaluate the extent of tissue injuries and to control haemorrhage and infection.

Part IV: Interest of laboratory tests

Point-of-care assays, such as thromboelastometry (ROTEM), are often used to guide administration of fibrinogen and prothrombin complex concentrates[126] in TIC.

However, there is currently no evidence of the added value of such approaches in the management of traumatic coagulopathy.[127,128] For example, fibrinolytic activation (FA) occurs in the majority of trauma patients and the magnitude of FA correlates with poor clinical outcomes. This is not detected by conventional ROTEM, which is an insensitive measure of endogenous fibrinolytic activity.[129]

In addition, the use of laboratory assays complicates patient management and prevents early treatment. There is no proof that peripheral blood reflects what is happening at the site of bleeding. Finally, a multicentre study showed very high variability between centres for ROTEM analysis, with a potential impact on patient management decisions. This illustrates the need for external

quality assessment.[130] In conclusion, in the context of traumatic coagulopathy, the use of ROTEM should be restricted to research protocols.[129]

In the future, results of Trans-Agency Consortium for Trauma-Induced Coagulopathy (TACTIC) studies will probably alter the management of TIC. This consortium aims to improve understanding of the mechanisms of TIC in connection to clinical trials. Functions anticipated at this early translational level include: (i) basic science groundwork for future therapeutic candidates; (ii) development of acute coagulopathy scoring systems; (iii) coagulation factor composition-based computational analysis; (iv) characterization of novel analytes including TF, polyphosphates, histones, meizothrombin and α-thrombin-antithrombin complexes, factor XIa, platelet and endothelial markers of activation, signatures of protein C activation and fibrinolysis markers; and (v) assessment of viscoelastic tests and new point-of-care methods.[131]

Conclusions

TIC appears quickly after trauma and should be detected and anticipated as soon as possible. Hypothermia, hypocalcaemia and acidosis should be combatted, and DCS should be considered early. Fluid resuscitation includes crystalloids and colloids (recommended doses must be respected). TXA (1 g as soon as possible) should be administered to any trauma patient. Desmopressin is not routinely indicated for trauma patients except those receiving acetylsalicylic acid. The target Hb should be between 7 and 9 g/dl, and an FFP:RBC ratio of at least 1:2 is recommended, along with a platelet count > 50000/μl, except for TBI or for patients treated with antiplatelet agents (> 100000/μl). PCC are considered in massive bleeding only for those patients receiving vitamin K-dependent oral anticoagulants or DOACs (20-50 U/Kg). A specific antidote is available for dabigatran (Pradaxa®) and is urgently needed for factor Xa inhibitors. Unfortunately, in Belgium, fibrinogen is not reimbursed except for congenital diseases. The only reimbursed source of fibrinogen is FFP. Each institution must establish a local algorithm for the management of bleeding patients.

Acknowledgements

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Abbreviations

ALF: acute lung failure
APC: activated protein C
AV: arteriovenous
CT: computed tomography
DCR: damage control resuscitation
DCS: damage control surgery
DOAC: direct oral anticoagulant
ECMO: extracorporeal membrane oxygenation
EMA: European Medicines Agency
FA: fibrinolytic activation
FAST: focused assessment with sonography for trauma
FDA: US Food and Drug Administration
FFP: fresh frozen plasma
Hb: haemoglobin
Hct: haematocrit
HES: hydroxyethyl starch
ICU:*f* intensive care unit
PAF: platelet activating factor
PAI-1: plasminogen activator inhibitor type 1
PCC: prothrombin complex concentrate
RBC: red blood cells
ROTEM: rotational thromboelastometry
TACTIC: Trans-Agency Consortium for Trauma-Induced Coagulopathy
TBI: traumatic brain injury
TCCC: Tactical Combat Casualty Care for Medical Personnel
TEG: thromboelastography
TF: tissue factor
TIC: trauma-induced coagulopathy
TPA: tissue plasminogen activator
TXA: tranexamic acid
VV: venovenous

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Francois Mullier
Université catholique de Louvain
CHU UCL Namur, Thrombosis and Hemostasis Center
Avenue Dr Gaston Therasse 1
5530 Mont-Godinne
Belgium
Tel.: 00 32 (0)81/424986
Fax: 00 32 (0)81/423204
E-mail: mullierfrancois@gmail.com