


# Interventional Algorithms for the Control of Coagulopathic Bleeding in Surgical, Trauma, and Postpartum Settings: Recommendations From the Share Network Group

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## Abstract

Several clinical settings are associated with specific coagulopathies that predispose to uncontrolled bleeding. With the growing concern about the need for optimizing transfusion practices and improving treatment of the bleeding patient, a group of 9 Portuguese specialists (Share Network Group) was created to discuss and develop algorithms for the clinical evaluation and control of coagulopathic bleeding in the following perioperative clinical settings: surgery, trauma, and postpartum hemorrhage. The 3 algorithms developed by the group were presented at the VIII National Congress of the Associação Portuguesa de Imuno-hemoterapia in October 2013. They aim to provide a structured approach for clinicians to rapidly diagnose the status of coagulopathy in order to achieve an earlier and more effective bleeding control, reduce transfusion requirements, and improve patient outcomes. The group highlights the importance of communication between different specialties involved in the care of bleeding patients in order to achieve better results.

## Keywords

bleeding, hemostasis, factor concentrates, algorithms, coagulopathy

## Introduction

Bleeding can be associated with specific coagulopathy related to several medical conditions. Occurrence of coagulopathy is itself a risk factor for the progression from initial bleeding to severe hemorrhage. With ongoing blood loss, with or without massive transfusion, major bleeding begins to show common pathological evolution, which consists of loss and consumption of coagulation factors, mainly and first fibrinogen, dilutional coagulopathy, and, in many cases, hyperfibrinolysis. For several years, allogeneic components, such as red blood cells (RBCs), fresh frozen plasma (FFP), cryoprecipitate, and platelets, have been the treatment of choice for restoring coagulation. However, several studies have shown that the transfusion of allogeneic blood products is linked to increased morbidity, mortality, and prolonged hospital stay in surgical patients.<sup>1-5</sup> More recently, transfusion was shown to be an independent risk factor for morbidity and composite mortality.<sup>6,7</sup> Additional adverse outcomes associated with transfusion include, for example, infection, delayed wound healing, transfusion-related acute lung injury (TRALI), multiple organ

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failure (MOF), cardiac arrest, stroke, volume overload, and bleeding requiring reoperation.<sup>8,9</sup> Moreover, allogeneic blood products have become scarcer, and current economic constraints require careful assessment of the cost-effectiveness of health interventions.

Current evidence suggests that targeted goal-directed therapy using coagulation factor concentrates guided by viscoelastic methods, such as thromboelastometry (ROTEM, Tem International GmbH, Munich, Germany) or thrombelastography (TEG, Haemoscope Inc., Niles, IL, USA), enables the effective correction of coagulopathy and is associated with a decreased incidence of allogeneic blood transfusion and thrombotic/thromboembolic events and with reduced costs.<sup>10-13</sup> Point-of-care (POC) testing using ROTEM or TEG is performed on whole blood samples and allows rapid identification of specific coagulation disorders and more accurate evaluation of coagulation. Conversely, the results of standard laboratory coagulation tests run in a central laboratory are not usually available until 45 to 60 minutes and are based on plasma samples, which, unlike whole blood samples, do not allow for a real evaluation of the patient's coagulation status. Furthermore, a recent publication emphasized that data supporting the usefulness of standard laboratory coagulation tests in the perioperative setting appear limited, and a number of investigations have challenged the reliability of these tests in assessing perioperative coagulopathy and guiding bleeding management.<sup>14</sup> As changes occurring during the coagulation process are time dependent, the group suggests that the administration of allogeneic blood products and factor concentrates should follow a logical, pathophysiology-determined sequence, guided either by POC viscoelastic test results and/or by clinical signs of coagulopathy, thus allowing treatment to be tailored to the patient's needs.<sup>15-18</sup> Prompt empirical therapy based on the most expected nature of coagulopathy for each individual clinical setting should be applied, and should be confirmed later on by laboratory results, if POC viscoelastic tests are not available.

The treatment algorithms presented here offer a structured approach and are intended as a guide for clinicians who deal with bleeding situations. Regardless of the specific clinical scenario, there are common approaches that should always be used, with the ultimate goal of bleeding control. Among them, the critical steps are the early recognition that clinically significant bleeding has occurred (physician assessment) and the effective communication between the clinical and blood transfusion team members. There are, however, specific approaches related to each clinical scenario that should be considered and these will be addressed here.

## Methods

### *Selection of the Working Group*

At a meeting on October 30, 2012, a group of experts in hematology, transfusion medicine, anesthesiology, obstetrics, perioperative bleeding, and trauma created a working group (Share Network Group). The group's primary aim was the development

of 3 interventional algorithms for the control of coagulopathic bleeding in the perioperative clinical settings of surgery, trauma, and postpartum hemorrhage (PPH).

The Share Network Group consists of a total of 9 specialists, namely, transfusion medicine specialists (Dra Anabela Rodrigues, Centro Hospitalar Lisboa Norte, Dr António Robalo Nunes, Centro Hospitalar Lisboa Norte, Dra Manuela Carvalho, Centro Hospitalar São João, Porto, and Dra Manuela Gomes, Centro Hospitalar Lisboa Ocidental), hematologists (Dr Manuel Campos, Centro Hospitalar do Porto), and anesthesiologists (Dr Alexandre Carrilho, Centro Hospitalar Lisboa Central, Dra Ângela Alves, Centro Hospitalar Lisboa Norte, Dr José Aguiar, Centro Hospitalar do Porto, Dra Rosário Orfão, Centro Hospitalar Universitário de Coimbra). The coordination of the group was attributed to Manuela Carvalho, transfusion medicine specialist of Centro Hospitalar São João, Porto. After several meetings and discussions, the developed algorithms were presented at the VIII National Congress of the Associação Portuguesa de Imuno-hemoterapia in October 2013.

### *The Search for Evidence*

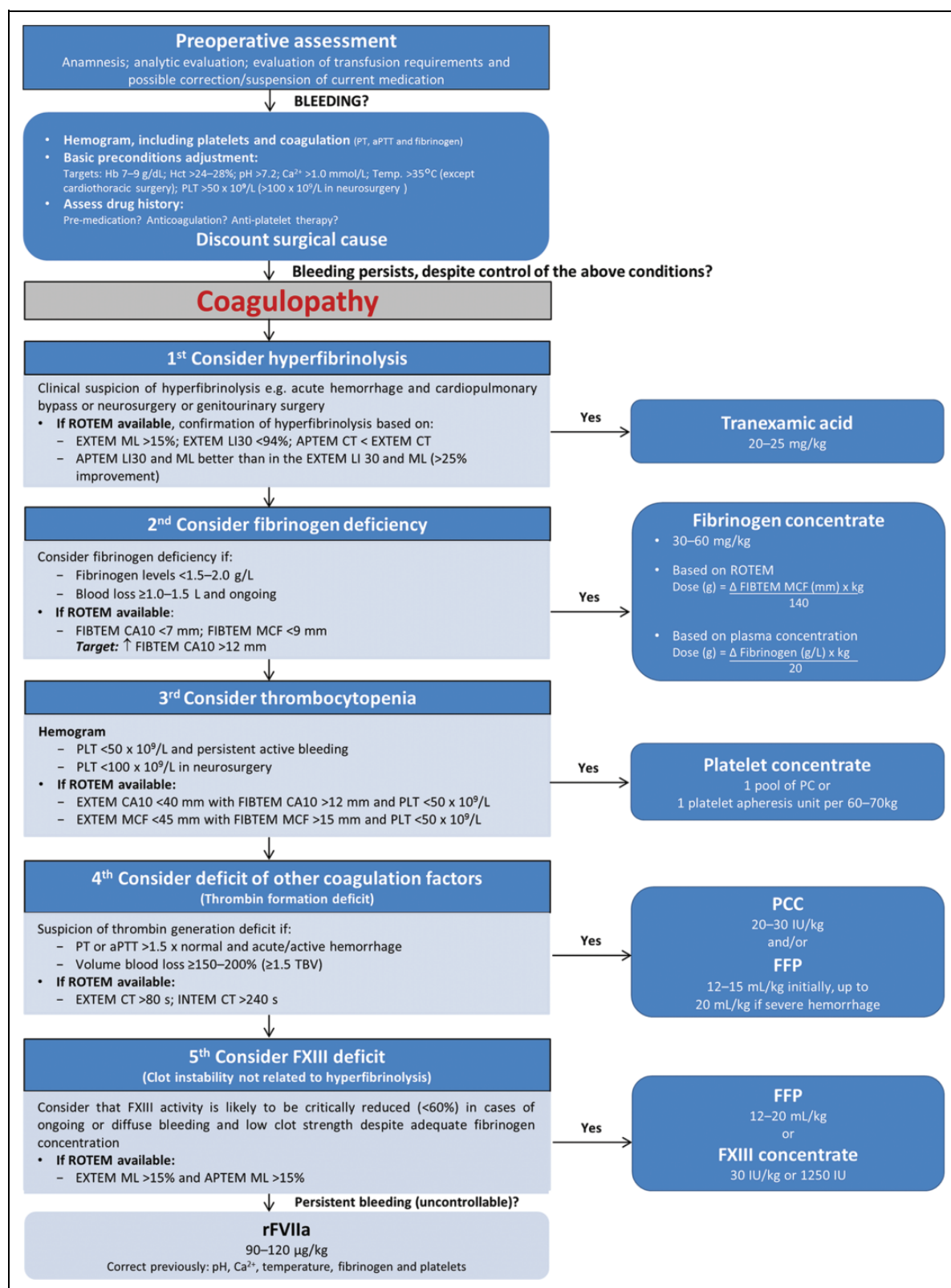
Initially, the group prepared and answered a questionnaire to better understand the specific features of each Portuguese Hospital Center and guarantee that the final consensus could be adapted to each one. An extensive literature search, using PubMed, was then undertaken in order to review the evidence and develop the final consensus. The bibliographic references used to develop the algorithms were obtained without a date limitation and using the following key words in conjunction: "perioperative bleeding", "trauma", "postpartum hemorrhage", "algorithm development", "blood management", "coagulation", "hemorrhage", "transfusion", "goal-directed therapy". This bibliographic search, together with the clinical experience of the experts, forms the basis of this consensus document.

## Results and Discussion

### *Coagulopathic Bleeding in Surgical Settings*

The management of coagulopathic bleeding in the setting of surgery depends on the underlying cause and contributing factors. Surgical causes of bleeding always have to be discounted and managed accordingly. During the course of a surgical procedure, many patients develop coagulation and bleeding disorders, and most patients show multifactorial disorders in their hemostatic balance. The aim of coagulopathic bleeding management in surgical settings is to stabilize the coagulation system in order to stop the hemorrhage. The proposed algorithm is presented in Figure 1 and is described subsequently.

**Preoperative assessment.** Preoperative assessment is of great importance in identifying patients for whom perioperative bleeding risk may be increased and plays a critical role in patient blood management. This assessment should include the anamnesis (clinical history with evaluation of patient's



**Figure 1.** Proposed algorithm for the management of coagulopathic bleeding in surgical settings. aPTT indicates activated partial thromboplastin time; CA10, clot amplitude after 10 minutes; CFT, clot formation time; CT, clotting time; FFP, fresh frozen plasma; Hb, hemoglobin; Hct, hematocrit; LI30, lysis index after 30 minutes; MCF, maximum clot firmness; ML, maximum lysis; PC, platelet concentrate; PCC, prothrombin complex concentrate; PLT, platelet count; PT, prothrombin time; TBV, total blood volume.

hemorrhagic score and family bleeding history)<sup>19</sup>; standard laboratory testing, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, and platelet count; evaluation and planning of hemostatic therapy requirements for each specific surgery; and possible correction/suspension of current medication such as antiplatelet or anticoagulant therapy (heparin, warfarin, and new oral anticoagulant drugs).

**Early management of bleeding.** The critical first steps when clinically significant bleeding occurs are the rapid identification of a surgical cause and its effective control. Standard coagulation screens, including PT, aPTT, fibrinogen levels, and platelet count, should be performed as soon as the patient starts bleeding. At the same time, stabilization of basic conditions (eg, hypothermia, acidosis, hypocalcemia, and anemia) is essential, since these have an important influence on hemostasis and can lead to clinically relevant dysfunction of the coagulation system.<sup>19–21</sup> Hypothermia reduces hemostatic performance because it impairs fibrinogen synthesis; therefore, a temperature below 35°C should be avoided (except in cardiac surgery). Acidosis leads to a significant reduction in thrombin generation and to an important increase in fibrinogen breakdown; thus, the pH should be maintained above 7.2. Hemoglobin (Hb) level should be within the range 7 to 9 g/dL (grade 1C—European Society of Anaesthesiology [ESA] guidelines)<sup>19</sup> and hematocrit (Hct) >24% to 28%, as anemia with a low Hb concentration can significantly influence primary hemostasis. Moreover, hypocalcemia has an anticoagulation effect and can impact negatively on the cardiovascular system,<sup>19–22</sup> therefore,  $\text{Ca}^{2+}$  must be >1.0 mmol/L. Low platelet count is generally associated with bleeding and coagulation disorders, and it is recommended that the platelet count be kept above  $50 \times 10^9/\text{L}$  (or  $100 \times 10^9/\text{L}$  during neurosurgery).<sup>23,24</sup>

Finally, it is essential to reevaluate the patient's therapeutic history, as a full preoperative assessment may not be possible in some clinical situations, mainly during emergency surgery, where there is no time to preoperatively assess the patient's usual medication. If bleeding persists after controlling for all the above-mentioned conditions, it is very likely that the patient has developed coagulopathy and this should be treated immediately. In this situation, the group recommends to contact a transfusion medicine specialist to better manage hemostasis and to run ROTEM, if available.

**Hyperfibrinolysis.** The group recommends treatment with tranexamic acid (TXA, 20–25 mg/kg) if significant bleeding is accompanied by clinical suspicion of hyperfibrinolysis.

Hemostasis requires an appropriate balance between the coagulation cascade that produces a fibrin clot and the fibrinolytic system that dissolves the fibrin clot. Acquired hyperfibrinolysis results in acute excessive blood loss and is known to be associated with a number of clinical settings, for example, cardiac surgical procedures performed using cardiopulmonary bypass, neurosurgery, orthopedic, and genitourinary surgeries.<sup>25,26</sup> Standard laboratory tests are unsuitable for detecting hyperfibrinolysis; however, ROTEM may be used instead

to confirm the diagnosis (Figure 1) and guide hemostatic therapy.<sup>27,28</sup> Hyperfibrinolysis is treated with antifibrinolytic drugs in order to stabilize the fibrin clot. Tranexamic acid (TXA), as most commonly used, is a lysine synthetic derivative, which binds to plasminogen thereby blocking the interaction of plasmin or plasminogen with fibrin, preventing dissolution of the fibrin clot.<sup>25</sup> The group endorses the ESA guidelines' recommendation of treatment with TXA (20–25 mg/kg) if significant bleeding is accompanied by at least suspected hyperfibrinolysis (grade 1A).<sup>20</sup>

**Fibrinogen deficiency.** The group considers that fibrinogen concentration <1.5 to 2.0 g/L with active bleeding as an indication for fibrinogen supplementation with an initial fibrinogen concentrate dose of 30 to 60 mg/kg, depending on the clinical setting. If possible, the group also recommends the fibrinogen concentrate dose to be calculated according to plasma fibrinogen concentration or ROTEM parameters.

Functionally, fibrinogen is cleaved by thrombin to produce fibrin monomers that polymerize to form the basis of the clot. In addition, fibrinogen molecules facilitate the aggregation of platelets via binding of glycoprotein IIb/IIIa receptors on platelet surfaces. Fibrinogen plays other important roles, since it functions in vivo as an acute-phase reactant and helps modulate inflammatory cellular reactions. Bleeding leads to loss and consumption of coagulation factors with fibrinogen known to be the first coagulation factor to reach critical levels when acute bleeding occurs.<sup>15</sup> Low fibrinogen concentration, which can be caused by increased consumption, volume resuscitation-related hemodilution, or increased fibrinogen breakdown related to acidosis, has been described as a risk factor for perioperative bleeding.<sup>29</sup> Normal plasma levels of fibrinogen range between 1.5 and 4.0 g/L but can be higher in certain situations, as it is an acute phase protein, for example, after injury.<sup>30</sup> Plasma fibrinogen concentration is typically assessed using the Clauss method; however, the measurements may be falsely increased in the presence of colloids (such as hydroxyethyl starch [HES] or gelatin), which are commonly used during fluid replacement therapy.<sup>30</sup> Furthermore, the long turnaround time of the Clauss method-based fibrinogen concentration measurement is also a limitation.

Therapeutic options to supplement fibrinogen include fibrinogen concentrate, FFP, and cryoprecipitate. The low fibrinogen concentration found in FFP limits its utility as a source of fibrinogen, as it requires the administration of large volumes to raise fibrinogen levels.<sup>31</sup> Compared with FFP, cryoprecipitate has a higher concentration of fibrinogen, but its production does not include pathogen reduction steps, which increases the potential risk of patient exposure to blood-borne pathogens.<sup>32</sup> Cryoprecipitate can be produced from plasma that has undergone treatment with methylene blue or psoralen/ultraviolet light. However, these methods can reduce functional fibrinogen content.<sup>30,33</sup> Similar to FFP, cryoprecipitate also has disadvantages related to the thawing time required, variation in fibrinogen concentration, and ABO incompatibility problems.



The ESA guidelines recommend “treatment with fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen concentrations or function (grade 1C)” and “that a plasma fibrinogen concentration  $<1.5$  to  $2.0$  g/L or ROTEM/TEG signs of functional fibrinogen deficit should be triggers for fibrinogen substitution (grade 1C).”<sup>20(p275, p303)</sup> Alternatively, based on the model of Singbartl et al, the decision can be based on clinical suspicion of a fibrinogen concentration  $<1.5$  to  $2.0$  g/L after a blood loss of  $\geq 1.0$  to  $1.5$  L and ongoing bleeding.<sup>34</sup> When locally available, the diagnosis can also be confirmed by ROTEM-based analyses (Figure 1). Depending on bleeding severity, an initial fibrinogen concentrate dose of  $30$  to  $60$  mg/kg is suggested. The dose can also be calculated by specific formulas, based on ROTEM results (using the FIBTEM test to assess the fibrin-based maximum clot amplitude) or standard laboratory tests (using the Clauss method to determine plasma fibrinogen concentration). As a guide, approximately  $3$  g of fibrinogen concentrate are required to raise plasma concentration by  $1$  g/L in a  $70$ -kg patient.<sup>35</sup>

**Thrombocytopenia.** Upon persistent bleeding accompanied by a platelet count  $<50 \times 10^9/L$  (or  $<100 \times 10^9/L$  in a neurosurgical setting), confirmed by POC testing if available, the group recommends the administration of platelet concentrate (PC),  $1$  unit per  $10$  kg body weight or  $1$  pool of PC, or  $1$  platelet apheresis unit per  $60$  to  $70$  kg, or higher doses according to the clinical situation.

Platelet count is commonly measured in the perioperative setting; however, despite providing a measure of platelet concentration, platelet count does not assess the functional activity of platelets. Although ROTEM provides rapid information on the quality and stability of the clot, this method also fails to assess platelet function, due to the high amount of thrombin generated during the coagulation process activated with the standard reagents.<sup>36</sup> Multiple electrode aggregometry (Multiplate; Roche Diagnostics, Basel, Switzerland) is a new whole-blood method of assessing platelet function<sup>36</sup> but unfortunately is not available in many hospitals.

As recommended by a few guidelines, persistent active bleeding and a platelet count below  $50 \times 10^9/L$  (or below  $100 \times 10^9/L$  in a neurosurgical setting) is suggested as a threshold for platelet transfusion.<sup>20,23,24,28</sup> If available, ROTEM parameters can also be used as a trigger for platelet transfusion, as described in Figure 1.<sup>27,28</sup>

**Deficiency of other coagulation factors (insufficient thrombin generation).** In case of elevated bleeding tendency and prolonged clotting time, despite adequate substitution of fibrinogen, the group suggests the administration of PCC ( $20$ - $30$  IU/kg) and/or FFP ( $12$ - $15$  mL/kg, up to  $20$  mL/kg for severe hemorrhage).

Hiippala et al observed that prothrombin activity reaches a critical level when blood loss exceeds  $200\%$ .<sup>15</sup> Based on this study and other previous publications, the group considered an approximate value of blood loss exceeding  $150\%$  to  $200\%$  ( $\geq 1.5$  total blood volume) or when PT or aPTT  $>1.5$  times

normal with acute/active hemorrhage to suspect poor thrombin generation.<sup>20,37</sup> The ROTEM-based analyses using the EXTEM and APTM tests can also be used, if available, to diagnose a suspected thrombin generation deficit (Figure 1).<sup>27</sup> Besides recombinant activated factor VII (rFVIIa), further options for increasing thrombin generation include FFP or prothrombin complex concentrate (PCC). The group accepts both therapies, depending on individual clinical judgment. However, to guarantee effective treatment the following should be considered.

First, the initial recommended dose of  $12$  to  $15$  mL/kg FFP, recommended by the British guidelines on the management of massive blood loss,<sup>38</sup> may be insufficient, and depending on the clinical situation and the severity of the hemorrhage, higher doses might have to be administered to allow for a satisfactory correction of coagulation factors. This can have a negative impact on patient outcomes because of the high plasma volume needed to correct coagulopathy which, in turn, may cause fluid overload, TRALI, and associated problems. Furthermore, there is no consensus on a fixed ratio of FFP/RBC/platelet concentrate (PC).<sup>37</sup>

Second, because of the potential thromboembolic risks associated with PCC administration, the group suggests that if available, ROTEM analysis should be performed to guide PCC administration. In fact, it is documented that targeted therapy with fibrinogen and/or PCC guided by ROTEM/TEG is not associated with an increased incidence of thromboembolic events.<sup>20</sup> Prolonged PT or aPTT alone is not an indication for PCC, especially in critically ill patients (grade 2C), and the ESA guidelines suggest administering PCC ( $20$ - $30$  IU/kg), even in the absence of oral anticoagulant therapy, if elevated bleeding tendency and prolonged clotting time persist even with adequate substitution of fibrinogen (grade 2C).<sup>20</sup> Despite the data being limited, some centers do administer PCC for perioperative bleeding in cases of massive bleeding and prolonged clotting times,<sup>39</sup> avoiding the problems related to excessive FFP transfusion (TRALI and fluid overload).

**Factor XIII deficiency.** The group suggests factor XIII (FXIII) substitution in case of ongoing or diffuse bleeding and low clot strength, despite adequate fibrinogen concentration. The empiric administration of  $12$  to  $20$  mL/kg FFP is suggested or, if available, FXIII concentrate at a dose of  $30$  IU/kg or  $1250$  IU.

If bleeding continues despite correction of all the previous factors/conditions, a deficiency in other coagulation factors may be considered. It is reasonable to focus on FXIII, as it determines the maintenance or restoration of clot strength along with fibrinogen and activated platelets.<sup>27,28</sup> A deficiency in FXIII leads to clot instability not related to hyperfibrinolysis.<sup>28</sup> Indeed, fibrin clot strength depends on FXIII, which is known to promote the cross-linking of fibrin monomers and to enhance clot resistance against fibrinolysis, thereby playing an important role in the hemostatic balance.

According to the Austrian guidelines, FXIII concentrates and rFVIIa are additional options for the treatment of persistent

bleeding.<sup>37</sup> The ESA guidelines state that “In cases of ongoing or diffuse bleeding and low clot strength despite adequate fibrinogen concentration, it is likely that FXIII activity is critically reduced” and “In cases of significant FXIII deficiency (ie, <60% activity), we suggest that FXIII concentrate (30 IU kg<sup>-1</sup>) can be administered (grade 2C).”<sup>20(p275, p304)</sup> The group suggests replacing FXIII with FFP if FXIII concentrate is not available, because in almost all hospitals in Portugal, FXIII is only available for treatment of congenital deficiency, with a special request authorization of use; furthermore, there is a scarce experience of its use in this setting.

Few clinical studies have demonstrated an increased bleeding tendency in patients with decreased FXIII activity. An association between decreased perioperative FXIII and increased risk of postoperative hemorrhage has been shown in neurosurgical patients.<sup>40,41</sup> An observational study to determine the activity of individual coagulation factors after coronary artery bypass graft demonstrated that both FXIII activity and plasma fibrinogen concentration correlate inversely with postoperative blood loss.<sup>42</sup> Wettstein et al have suggested that preexisting hemostatic disorders in surgical patients (increased preoperative coagulation activation with decreased FXIII activity and impaired clot firmness) is not a rare condition and may result in clinically relevant perioperative bleeding.<sup>43</sup> The authors proposed that early substitution of FXIII might reduce the loss of clot firmness and reduce bleeding in patients at risk. This hypothesis has been evaluated in a prospective, randomized controlled trial, including patients undergoing elective gastrointestinal cancer surgery, randomized to receive FXIII (30 U/kg) or placebo.<sup>44</sup> In this study, patients at high risk of intraoperative bleeding showed reduced loss of clot firmness when FXIII was administered early during surgery.

**Administration of rFVIIa.** The group recommends considering the administration of rFVIIa (90–120 µg/kg) only as last-line therapy in case of uncontrolled persistent bleeding but advises that this is an off-label use with its administration being at the discretion of the treating physician and only after correction of fibrinogen levels, acidosis, hypocalcemia, hypothermia, thrombocytopenia, and hyperfibrinolysis.

If diffuse bleeding does not stop after optimization of coagulation by the standard therapy recommended previously, an additional option is rFVIIa. The ESA guidelines suggest that the off-label administration of rFVIIa should only be considered if bleeding cannot be stopped by conventional, surgical, or interventional radiological means and/or when comprehensive coagulation therapy fails (grade 2C, grade 2B in cardiac surgery, and grade 1C in orthopedic and neurosurgery).<sup>20</sup> Before the administration of rFVIIa, it has been suggested that fibrinogen concentration, platelet count, temperature, pH, and hyperfibrinolysis should be optimized to improve clot formation.<sup>19,20,37,45</sup> Administration of rFVIIa has been limited because of its potential thromboembolic risk, its controversial effectiveness in reducing transfusion requirements and mortality, and the high costs of this treatment.<sup>20,46–48</sup> In different clinical indications, rFVIIa might increase the risk of venous

thromboembolism, without improving mortality.<sup>49</sup> However, high response rates and reduced blood product usage and blood loss have been reported.<sup>50,51</sup> In a double-blind, randomized controlled trial, treatment with rFVIIa significantly reduced the incidence of reoperation and transfusion requirements in patients experiencing bleeding after cardiac surgery. Nevertheless, there was an increase in the number of serious adverse events, including stroke, in those patients randomized to receive rFVIIa.<sup>46</sup> This suggests the need for large randomized controlled trials (RCTs) to assess the safety of rFVIIa in this setting.

### Management of Traumatic Acute Hemorrhage

Coagulopathy is an important contributor to morbidity and mortality in patients with trauma, and its incidence increases with severity of injury. Approximately 25% of patients with trauma present at emergency departments with acute coagulopathy, and these patients have a 4-fold higher risk of mortality than those without coagulopathy.<sup>52–54</sup> The pathophysiology of trauma-induced coagulopathy (TIC) has to be considered for the coagulation management of patients with trauma and bleeding patients. Areas of tissue injury can become severely hypoperfused, which can lead to acidosis.<sup>53</sup> Hypoperfusion acidosis causes the release of tissue-type plasminogen activator by endothelial cells, which in turn leads to hyperfibrinolysis.<sup>55</sup> Additionally, tissue perfusion deficits may lead to increased concentrations of activated protein C. The activation of this pathway can cause an inappropriate reduction in thrombin generation,<sup>53,56</sup> enhanced hyperfibrinolysis, and reduced plasma protein C level.<sup>57</sup>

Volume resuscitation, which can lead to dilutional coagulopathy, is another important source of TIC. Crystalloids compromise the coagulation system mainly through their dilution effect, while the use of synthetic colloid plasma expanders (such as HES, gelatin, or dextran) can further impair coagulation beyond that expected from dilution alone.<sup>58,59</sup> A study conducted by Fenger-Eriksen et al showed that volume substitution with isotonic saline, HES, or dextran reduces clot firmness (or clot strength) and compromises the propagation phase of clot formation.<sup>58</sup> The impact of volume substitution on coagulation is more complex than a simple dilution of coagulation factors. Fenger-Eriksen et al<sup>60</sup> have shown that hemodilution produces a specific pattern of hemostatic disturbances affecting some (but not all) coagulation factors. Indeed, fibrinogen, FII, FX, and FXIII decrease significantly below the levels expected from the dilutional effect, while no significant change is seen in Hct, platelet count, FVII, FVIII, or thrombin generation. Similarly, another study reported an uncompromised thrombin generation after dilution with HES.<sup>61</sup>

Retrospective evidence, derived initially from military practice, suggests that the administration of a ratio of FFP, PC, and RBC close to 1:1:1 reduces mortality in patients with trauma having major bleeding.<sup>62,63</sup> However, the evidence supporting this approach is not conclusive, and an optimal ratio of

plasma–RBC is yet to be found, mainly because of the possible survival bias found in most of the studies.<sup>64,65</sup>

There are several limitations to the use of plasma to prevent and treat TIC. Besides the increased risk of TRALI, volume overload, acute respiratory distress syndrome, and the transmission of infectious diseases, FFP needs to be group matched, thawed, and warmed before administration. As a result, plasma administration cannot be started at the same time as RBC.<sup>66</sup> This might explain why the targeted plasma–RBC ratio is reached only a few hours after the beginning of treatment. It seems reasonable that strategies aimed at limiting the use of plasma in patients who are not likely to need it and should be implemented in order to reduce plasma-related adverse effects.

After the emergence of viscoelastic POC coagulation-monitoring tools, such as ROTEM, the use of coagulation factor concentrates has been proposed for the treatment of TIC.<sup>67,68</sup> These rapid POC assessment techniques are used to guide hemostatic therapy with coagulation factor concentrates as the hemostatic therapy of choice.<sup>69–71</sup> The POC tests have also provided valuable information about the hemostatic abnormalities that occur after injury and the sequence of these alterations over time. The learning acquired by this technology may help to develop treatment algorithms/protocols even when these rapid diagnostic tools are not available. The proposed algorithm for the management of bleeding patients with trauma is shown in Figure 2.

**Early management of bleeding.** If bleeding persists, after the control of previous conditions, coagulopathy may be present and the blood transfusion specialist should be contacted and ROTEM analysis requested, if available. The critical first steps when treating severely bleeding patients with trauma are the rapid control of a mechanical cause and, similar to perioperative management, the early collection of samples to perform coagulation screens, stabilization of basic conditions (hypothermia, acidosis, hypocalcemia, anemia, and thrombocytopenia), and the evaluation of the therapeutic history of the patient.<sup>21,28</sup>

**Hyperfibrinolysis.** When hyperfibrinolysis is suspected, the group recommends the administration of TXA with a loading dose of 1 g infused over 10 minutes, followed by intravenous infusion of 1 g over 8 hours (or 15–20 mg/kg within the first 3 hours after injury). In order to ensure that TXA is given early, it is suggested to administer the first dose of TXA before hospital admission.

The Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) trial assessed the effects of early administration of TXA in patients with trauma who were bleeding or at risk of significant bleeding. The trial randomized 20 211 adult patients with trauma to either TXA or placebo within 8 hours of injury. This trial showed a significant reduction in all-cause mortality and risk of death due to bleeding in TXA-treated patients.<sup>72</sup> The risk of thrombosis with the use of antifibrinolytics such as TXA or  $\epsilon$ -aminocaproic acid has been a

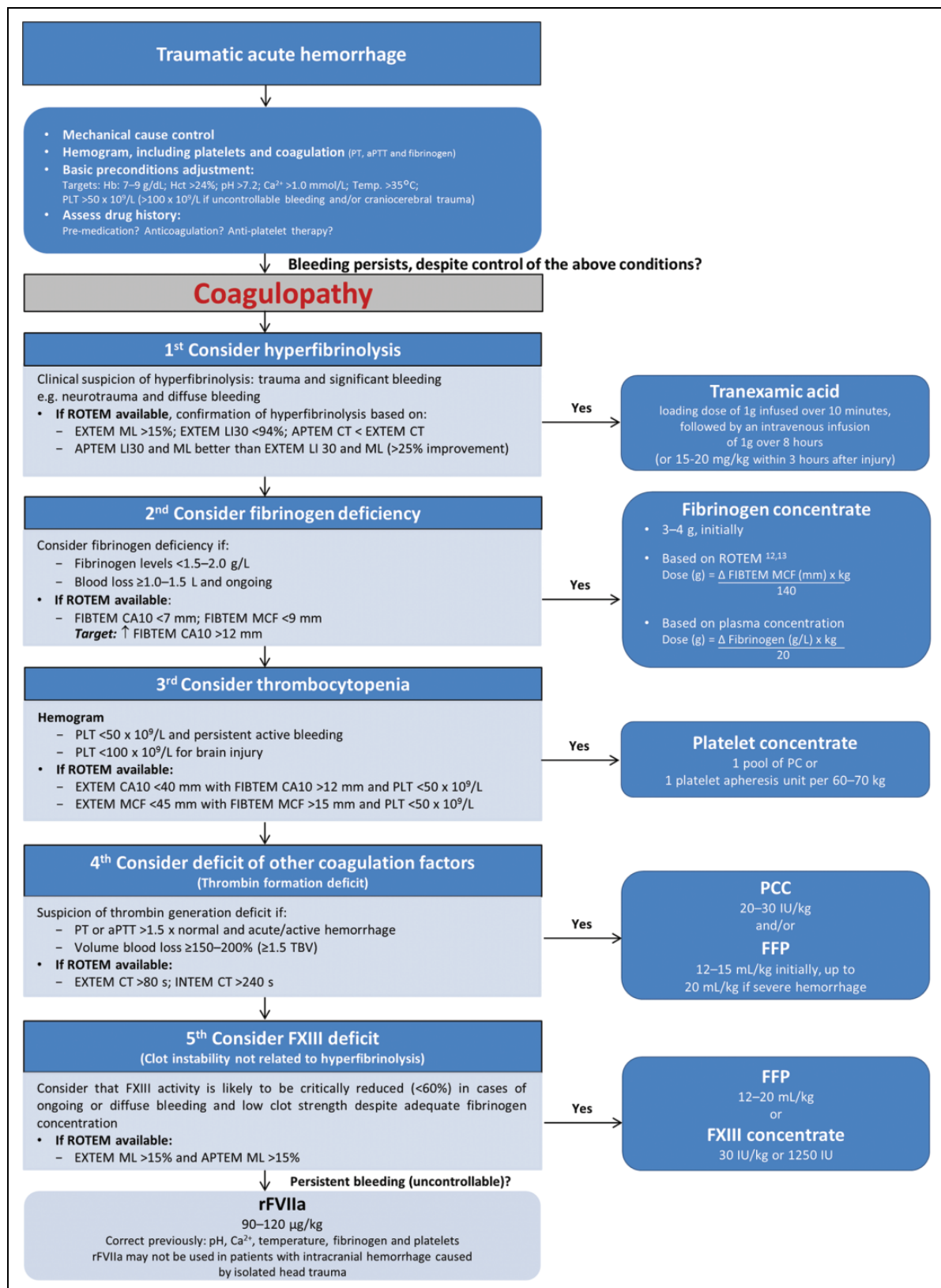
concern among clinicians. However, CRASH-2 showed that the rate of thrombosis was lower with the use of TXA. An exploratory analysis of the CRASH-2 trial showed that the effect of TXA on death due to bleeding varied according to the time from injury to treatment. Early treatment ( $\leq 1$  h from injury) significantly reduced the risk of death due to bleeding. Treatment given between 1 and 3 hours also reduced this risk and when given after 3 hours appeared to increase this risk.<sup>73</sup>

The CRASH-2 Intracranial Bleeding Study, nested within the CRASH-2 trial, aimed to quantify the effect of TXA on intracranial hemorrhage in patients with traumatic brain injury.<sup>74</sup> The results showed that TXA reduced intracranial hemorrhage after traumatic brain injury without increasing the risk of ischemic lesions. Although this trial has provided important findings, no trial has been conceived until now to evaluate the effect of TXA in these patient's outcomes. Based on the results of the CRASH-2 trial, the early administration of TXA is now the standard of care in most European trauma centers.<sup>72</sup> The European trauma guidelines recommend the administration of TXA “as early as possible to the trauma patient who is bleeding or at risk of significant hemorrhage”.<sup>21(p18, p30)</sup>

As described in the perioperative setting, hyperfibrinolysis can be detected using ROTEM.<sup>27,28</sup> If hyperfibrinolysis cannot be detected by standard coagulation tests or viscoelastic methods, the group suggests that a hyperfibrinolytic state can be suspected in all patients with trauma who present with diffuse hemorrhage.<sup>74,75</sup> When available, the diagnosis should be confirmed by viscoelastic methods such as ROTEM.

**Fibrinogen deficiency.** The group recommends treatment with fibrinogen concentrate (3–4 g initially, with repeated doses if necessary or calculated according to plasma fibrinogen concentration or ROTEM parameters) if plasma fibrinogen concentration is  $<1.5$  to  $2.0$  g/L or there is ongoing bleeding after blood loss  $\geq 1.0$  to  $1.5$  L.

Fibrinogen reaches critically low levels very soon after trauma.<sup>16,76</sup> An early observational study suggested that fibrinogen substitution (with an increased fibrinogen–RBC ratio) was independently associated with improved survival in combat-related trauma.<sup>77</sup> Moreover, the ex vivo addition of fibrinogen concentrate was shown to significantly improve clot firmness confirming the key role of fibrinogen in coagulopathy caused by in vivo hemodilution by HES.<sup>60</sup> As described for the perioperative setting, fibrinogen deficiency can be diagnosed using standard laboratory methods or viscoelastic tests.<sup>21,27,28,34</sup> With the methodological issues inherent in the standard laboratory tests, fibrinogen administration using viscoelastic methods as guidance may be preferable.<sup>21</sup> The ROTEM FIBTEM test provides an early indication of decreased fibrin clot quality, which is most likely due to low fibrinogen levels. Retrospective studies managing massive blood loss in patients with trauma have suggested that ROTEM-guided administration of fibrinogen concentrate results in a better survival rate when compared to expected mortality (as predicted by the trauma injury severity and revised injury severity classification



**Figure 2.** Proposed algorithm for the management of traumatic acute hemorrhage. aPTT indicates activated partial thromboplastin time; CA10, clot amplitude after 10 minutes; CFT, clot formation time; CT, clotting time; FFP, fresh frozen plasma; Hb, hemoglobin; Hct, hematocrit; LI30, lysis index after 30 minutes; MCF, maximum clot firmness; ML, maximum lysis; PC, platelet concentrate; PCC, prothrombin complex concentrate; PLT, platelet count; PT, prothrombin time; TBV, total blood volume.



scores)<sup>70</sup> and a reduced exposure to allogeneic blood products.<sup>78</sup> However, since this technique is not universally available, other diagnostic methods should also be considered. A recent study identified Hb levels, base excess (BE), and injury severity score (ISS) as good indicators of fibrinogen levels.<sup>79</sup> The Hb and BE are rapidly obtainable in routine laboratory tests and might provide an insightful and rapid tool to identify major patients with trauma at risk of acquired hypofibrinogenemia. The Hb <9 g/dL, BE <6 mmol/L, or ISS ≥30 were associated with fibrinogen levels below that recommended by the European trauma guidelines (1.5–2.0 g/L).<sup>21</sup> Consequently, the group recommends treatment with fibrinogen concentrate if plasma fibrinogen level is <1.5 to 2.0 g/L or after blood loss ≥1.0 to 1.5 L and ongoing bleeding (a clinical criteria that, according to the mathematical guide proposed by Singbartl et al,<sup>34</sup> may help to predict the presence of low fibrinogen level). The group suggests the initial administration of 3 to 4 g fibrinogen concentrate.<sup>21</sup> As described for the perioperative setting, the dose can be targeted using formulas based on either ROTEM parameters or plasma fibrinogen levels.<sup>35,80,81</sup>

**Thrombocytopenia.** The group suggests the initial administration of 1 pool of PC or 1 platelet apheresis unit per 60 to 70 kg, when a platelet count below  $50 \times 10^9/L$  is associated with persistent active bleeding or when the platelet count is below  $100 \times 10^9/L$  in patients with brain injury.

As for the perioperative setting, thrombocytopenia can be indicated by a low platelet count and diagnosed through the means of ROTEM.<sup>27,28</sup> It is generally recommended to maintain the platelet count above  $50 \times 10^9/L$  in bleeding patients with trauma (or above  $100 \times 10^9/L$  in patients with multiple trauma, brain injury, and massive bleeding).<sup>21,23,24,28</sup> In most patients with trauma, platelet count is within the normal range at admission to the emergency department.<sup>82,83</sup> Furthermore, in patients presenting with traumatic coagulopathy, the platelet count does not decline to levels that might be expected to contribute significantly to coagulopathy.<sup>83</sup> Platelet count alone is a weak indicator of the need for platelet transfusion because it ignores platelet dysfunction. Therefore, platelet function tests should be performed to guide platelet transfusion in major patients with trauma, if platelet dysfunction is documented.<sup>69</sup>

The implementation of clinical practices supporting early and high platelet transfusion rates have not shown any improvement in the survival rate.<sup>84,85</sup> On the other hand, improved survival and decreased rates of hemorrhagic deaths were also reported in patients receiving a high ratio of PC–RBC; however, MOF increased as the PC–RBC ratio increased. Therefore, the value of platelet transfusion in a fixed, predefined ratio for the management of TIC is currently unclear and carries the potential for wasting valuable resources and the risk of complications. These studies may also be subject to serious confounding factors, such as survivorship bias, and routine early platelet transfusion, as part of a massive transfusion protocol appears unjustified.

**Deficiency of other coagulation factors (insufficient thrombin generation).** The group recommends the administration of PCC 20 to 30 IU/kg and/or FFP (12–15 mL/kg initially, up to 20 mL/kg in severe bleeding) when PT or aPTT >1.5 times normal in the presence of acute/active bleeding or after a blood loss exceeding 150%–200% (≥1.5 total blood volume).

Since thrombin generation is not considerably affected in the early stages of TIC, the concept of early, high-dose FFP transfusion with the aim of increasing thrombin generation has been recently reviewed.<sup>28</sup> If bleeding is ongoing after correction of all the previous conditions/factors, it is reasonable to think that there might be a deficiency in coagulation factors that may influence thrombin generation. Current options for increasing thrombin generation during trauma-related bleeding include FFP, PCC, and rFVIIa.<sup>28</sup>

Outside the indication of PCC for the emergency reversal of vitamin K-dependent oral anticoagulants, current available data on the use of PCC in the treatment of TIC are limited. Prothrombin complex concentrate is a procoagulant drug, and a possible risk of thrombosis must be considered alongside a patient's potential tendency to thrombosis events after trauma. Accurate monitoring of patients' coagulation status may allow thrombotic risk to be reduced, and POC testing appears to be a useful tool to guide PCC therapy in patients with traumatic coagulopathy.<sup>71,78,86,87</sup>

As described for the perioperative setting, poor thrombin generation is likely to be detected after a blood loss exceeding 150% to 200% (≥1.5 total blood volume) or when PT or aPTT >1.5 times normal with acute/active bleeding.<sup>15,20,37</sup> The approximate recommended dose of PCC is 20 to 30 IU/kg and of FFP is 12 to 15 mL/kg initially (up to 20 mL/kg in severe bleeding).<sup>28,38</sup> The ROTEM parameters indicating a need for treatment to improve thrombin generation are indicated in Figure 2.<sup>27,28</sup>

**FXIII deficiency.** The group suggests administering FFP (12–20 mL/kg) or FXIII (30 IU/kg or 1250 IU) if available, in cases of ongoing acute bleeding and low clot strength, despite adequate fibrinogen levels.

After correction of the previous factors/conditions, it is reasonable to consider that other coagulation factors may be depleted. Massive bleeding may cause an acquired deficiency in FXIII (significant if <60%), which has a central role in clot stabilization and clot firmness.<sup>20</sup> It has also been suggested that a decreased FV activity, as well as a deficit in FXIII concentration, might play a role in the pathogenesis of acute traumatic coagulopathy.<sup>88,89</sup> The AUVA Trauma Hospital algorithm for management of TIC proposed by Schöchl et al suggests the administration of FXIII concentrate in cases of clot instability not related to hyperfibrinolysis, which can be detected by ROTEM EXTEM maximum lysis (ML) >15% and APTM ML >15%.<sup>28</sup>

The group suggests administering FFP (12 to 20 mL/kg) or, if available, FXIII concentrate (30 IU/kg or 1250 IU), in cases of ongoing acute bleeding and low clot strength, despite adequate fibrinogen levels. If possible, ROTEM should be used

to confirm the diagnosis (Figure 2). As FXIII concentrates are not available in most hospitals in Portugal, FFP is usually the alternative.

**Recombinant activated factor VII.** The group recommends that rFVIIa (90–120 µg/kg) should only be considered if surgical approaches, combined with first-line hemostatic treatment with factor concentrates and correction of acidosis, hypothermia, hypocalcemia, thrombocytopenia and hyperfibrinolysis, fail to effectively control bleeding (uncontrolled bleeding) but advises that this is an off-label use and the administration is at the discretion of the treating physician.

Recombinant activated factor VII is a therapeutic option for increasing thrombin generation during trauma-related bleeding. Despite some studies reporting that treatment with rFVIIa can be beneficial for controlling bleeding in patients with trauma,<sup>90-92</sup> there are few high-quality studies. Two randomized, placebo-controlled, double-blind trials were simultaneously conducted (1 in blunt trauma,  $n = 143$ , and 1 in penetrating trauma,  $n = 134$ ) to evaluate the efficacy of rFVIIa and showed that there were no significant differences in survival rates between treatment groups (placebo or rFVIIa) in both populations with trauma. However, trends toward reductions in RBC transfusions and massive blood transfusions were observed, reaching statistical significance in the blunt trauma group.<sup>93</sup> Another randomized clinical trial showed that rFVIIa reduced blood product use but did not affect mortality when compared to placebo,<sup>94</sup> and follow-up analyses showed that rFVIIa administration was not associated with an increased risk of thromboembolic complications.<sup>95</sup>

The European trauma guidelines suggest that the use of rFVIIa be considered if major bleeding and traumatic coagulopathy persist, despite standard attempts to control bleeding and best-practice use of conventional hemostatic measures.<sup>21</sup> Conversely, a case-control study of patients with traumatic intracerebral hemorrhage showed that the use of rFVIIa in isolated head injury was harmful. As a result, the guidelines do not suggest the use of rFVIIa in these patients.<sup>21</sup>

## Management of PPH

Postpartum hemorrhage is the leading cause of severe maternal morbidity and mortality around the world.<sup>96</sup> Its rapid diagnosis and early treatment are critical. In general, PPH is defined as blood loss of more than 500 mL within 24 hours after vaginal delivery or 1000 mL after cesarean delivery.<sup>96</sup> Uterine atony is the major cause of PPH; other causes include surgical incisions and lacerations as well as the presence of coagulopathy. In some cases, coagulopathy precedes delivery and is a direct cause of PPH.<sup>97</sup> At the final stages of a normal pregnancy, the concentrations of a variety of coagulation factors are generally elevated in comparison with the nonpregnant state and antagonists of coagulation are decreased or remain unchanged. This pregnancy-induced hypercoagulable state may reduce the risk of hemorrhage naturally.<sup>98,99</sup> During the third trimester, maternal fibrinogen concentrations are above what is considered

normal for nonpregnant women (2–4 g/L) and can vary from 3 to 6 g/L.<sup>99,100</sup>

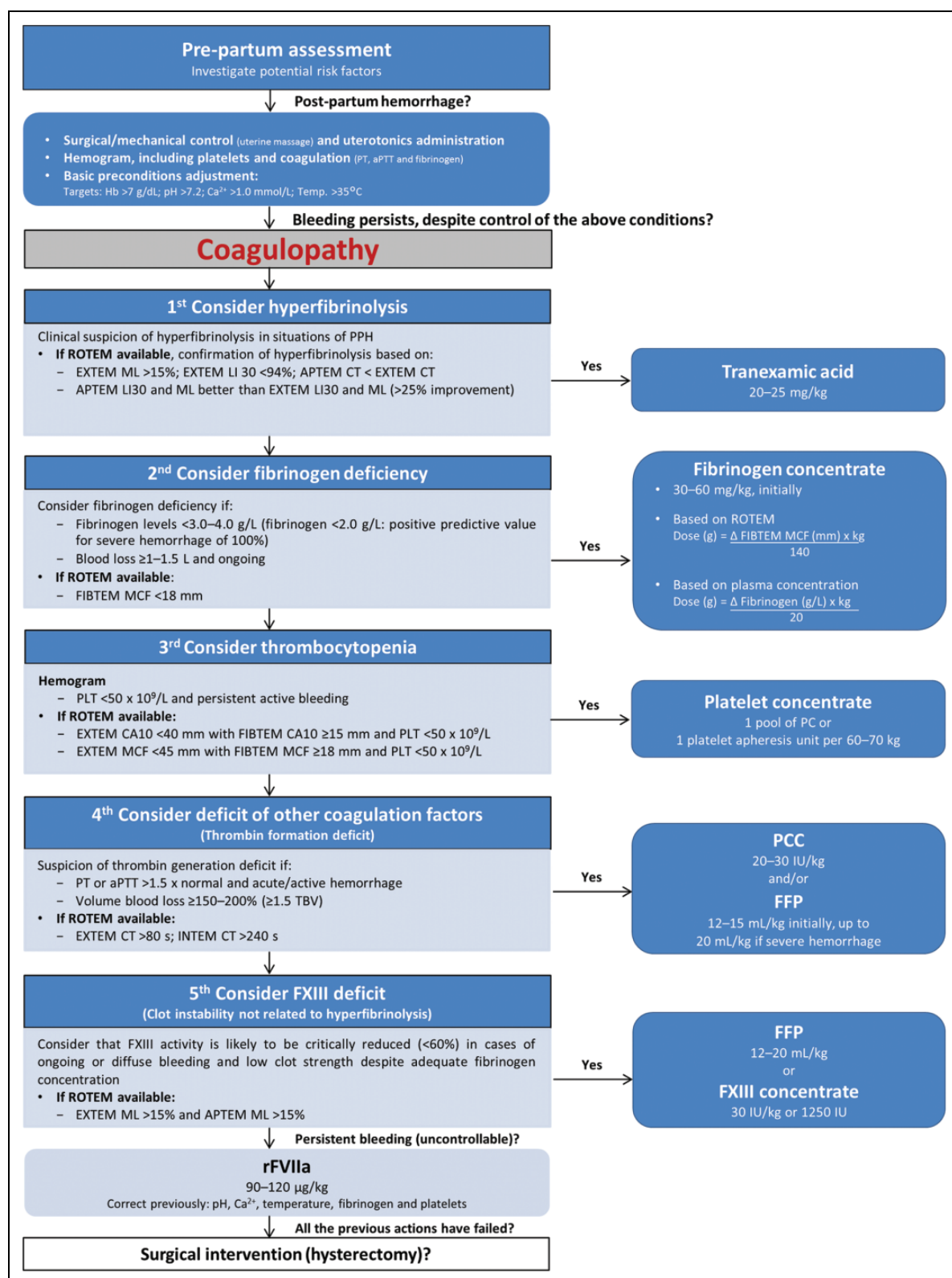
It has been shown in different clinical settings that, when bleeding occurs, the decrease in fibrinogen concentration is the most important change observed among markers of coagulation.<sup>15</sup> In obstetric bleeding, recent studies have shown that fibrinogen/fibrin deficiency, and not thrombin, is the major informative marker for the severity of hemorrhage.<sup>101-103</sup> In particular, a recent prospective observational study by Collins et al, performed in a cohort of 346 consecutive women experiencing 1000 to 1500 mL PPH, identified fibrin-based clot firmness (evaluated by the ROTEM FIBTEM test) as an early and rapidly available biomarker of PPH progression.<sup>104</sup> In the management of PPH, it should be taken into account that these specific pathophysiologic processes occur and that the values used to guide interventions might differ from nonpregnant levels.<sup>99</sup> As in other clinical settings, it has been shown that thromboelastometry can provide early identification of obstetric coagulopathy and guide hemostatic therapy with TXA, fibrinogen concentrate, PCC, FFP, and platelets.<sup>105</sup> The suggested algorithm is shown in Figure 3.

**Prepartum evaluation.** A prepartum evaluation should be performed to investigate potential risk factors for obstetric bleeding. Risk factors for PPH with coagulopathy include an underlying bleeding disorder, HELLP syndrome, massive bleeding due to uterine atony or lacerations, heart disease, or sociodemographic factors such as age and race/ethnicity.<sup>106,107</sup> Despite being able to identify risk factors for PPH in the antenatal period, the majority of women who develop PPH do not have any of these risk factors, and every pregnancy is at risk.<sup>106</sup>

**Early management of bleeding.** The critical steps in early assessment of bleeding are the rapid recognition that clinically significant bleeding has occurred, with effective mechanical/surgical control (such as uterine massage in situations of uterine atony), immediate resuscitation, and uterotonic administration. At the same time, the collection of blood samples for laboratory evaluation should be assured (hemogram with platelet count and coagulation assessment, PT, aPTT, and fibrinogen levels). It is also critical to simultaneously adjust the basic preconditions (pH, temperature,  $\text{Ca}^{2+}$ , and Hb).<sup>20</sup> If bleeding persists, after the control of previous conditions, coagulopathy may be present and the blood transfusion specialist should be contacted and ROTEM analyses requested, if available.

**Hyperfibrinolysis.** The group recommends that the administration of TXA (20–25 mg/kg) should be considered early in the treatment of women with severe PPH and prior to fibrinogen administration.

If bleeding persists despite the control of the previous conditions, we may suspect that coagulopathy has been established. Initially it is important to rule out the hypothesis of the presence of hyperfibrinolysis.<sup>20,25,108</sup> When available, POC testing can be used to confirm hyperfibrinolytic states.<sup>27,28</sup> The



**Figure 3.** Proposed algorithm for the management of postpartum hemorrhage. aPTT indicates activated partial thromboplastin time; CA10, clot amplitude after 10 minutes; CFT, clot formation time; CT, clotting time; FFP, fresh frozen plasma; Hb, hemoglobin; Hct, hematocrit; LI 30, lysis index after 30 minutes; MCF, maximum clot firmness; ML, maximum lysis; PC, platelet concentrate; PCC, prothrombin complex concentrate; PLT, platelet count; PT, prothrombin time; TBV, total blood volume.

ESA guidelines recommend the administration of TXA in obstetric bleeding to reduce blood loss, bleeding duration, and transfusion requirements (grade 1B).<sup>20</sup>

The procoagulant effects occur naturally during delivery, and to balance these effects, fibrinolysis is increased.<sup>109</sup> However, abnormal fibrinolysis is associated with complications, including placental abruption with antepartum bleeding, shock, and amniotic fluid embolism.<sup>110</sup>

A randomized, controlled, prospective, open-label, and multicenter study (n = 144) investigated the effect of TXA in women experiencing PPH (>800 mL following vaginal delivery) compared with no TXA administration.<sup>111</sup> The observed blood loss, bleeding duration, transfusion requirements, and progression to severe PPH were significantly lower in women who received TXA compared with the control group. A further, large, multinational, randomized, double-blind study—World Maternal Antifibrinolytic (WOMAN) trial—is currently underway and is designed to assess the efficacy of TXA administration (maximum dose 2 g) compared with placebo on patient outcomes, in women with PPH following vaginal or cesarean delivery.<sup>112</sup> Although some obstetricians are still worried about the risk of thrombosis with TXA, a very recent double-blind, placebo-controlled, randomized clinical trial showed that it is safe when administered 10 minutes before the start of a cesarean delivery in healthy women.<sup>113</sup>

**Fibrinogen deficiency.** If plasma fibrinogen concentration is <3.0–4.0 g/L in the presence of ongoing bleeding, the group recommends treatment with fibrinogen concentrate (initial dose of 30–60 mg/kg, to be repeated if necessary, or calculated according to plasma fibrinogen concentration or ROTEM<sup>®</sup> parameters).

The excessive activation of the coagulation system that occurs in PPH leads to a fast consumption of fibrinogen,<sup>99</sup> which is the first coagulation factor to reach critical levels during major bleeding.<sup>15</sup> Early fibrinogen supplementation is crucial for bleeding control. As referred to previously, the changes observed in hemostasis in pregnant and postpartum women may mean that transfusion strategies and trigger levels considered in other clinical settings are not applicable in the management of PPH. Consequently, higher levels of fibrinogen should be maintained to reduce the risk of severe PPH.<sup>99,110</sup>

The group recommends considering fibrinogen concentrate administration when fibrinogen levels are below 3.0 to 4.0 g/L in the presence of active bleeding; however, higher trigger levels (<4.0 g/L) were suggested by Charbit et al.<sup>101</sup> In fact, fibrinogen levels of 2 g/L or lower were reported to have a positive predictive value of 100% for the development of severe PPH and levels >4 g/L a negative predictive value of 79% for severe PPH development.<sup>101</sup>

Alternatively, when laboratory results are not available, a fibrinogen level <4.0 g/L can be suspected after a blood loss of 1.0 to 1.5 L (or higher) and ongoing bleeding.<sup>34,101</sup> The confirmation of fibrinogen deficiency can also be made using the results of ROTEM once this methodology is locally available (FIBTEM MCF <18 mm).<sup>99</sup> A dose of 30 to 60 mg/kg is

initially suggested, with additional doses if necessary.<sup>114</sup> The dose can also be calculated, based on ROTEM parameters or fibrinogen concentration measured by the Clauss method.<sup>35,80,81</sup> In severe situations, such as placental abruption, higher initial doses of fibrinogen concentrate might be required.

**Thrombocytopenia.** When thrombocytopenia is diagnosed (persistent bleeding accompanied by a platelet count <50 × 10<sup>9</sup>/L), the group recommends platelet transfusion (one pool of PC or one platelet apheresis unit per 60 to 70 kg) or higher doses according to the clinical situation.

A large retrospective analysis demonstrated an inverse association between the lowest platelet count and RBC transfusion requirements.<sup>103</sup> A subsequent prospective study showed that a decreasing platelet count during obstetric hemorrhage may be associated with progression to severe PPH. The most recent UK obstetric management guidelines recommend platelet transfusion only when the platelet count is below 50 × 10<sup>9</sup>/L, although different studies/guidelines suggest different trigger levels.<sup>20,103,115,116</sup>

The group suggests a trigger level of a platelet count below 50 × 10<sup>9</sup>/L with persistent active bleeding.<sup>115</sup> Despite the potential of platelet count as a target for hemostatic therapy, their utility in PPH management may be limited by long assay turnaround times (typically 30–60 minutes).<sup>117,118</sup> The rapid assessment of coagulation is of great importance to efficiently manage bleeding in PPH; delayed treatment is a strong predictor of poor outcomes.<sup>119</sup> Therefore, as an alternative, the group recommends inferring the platelet level from ROTEM analyses, using the results of a combination of different tests (eg, EXTEM, FIBTEM, INTEM, HEPTM; Figure 3).<sup>27,28</sup> The dose recommended by the group is 1 pool of PC or 1 platelet apheresis unit per 60 to 70 kg (or higher depending on clinical situation), with repeated doses if needed.

**Deficiency in other coagulation factors (insufficient thrombin generation).** If a deficiency in thrombin generation is suspected (when blood loss exceeds 150%–200% or when PT or aPTT >1.5 times normal in the presence of acute/active bleeding), the group recommends the administration of PCC (20–30 IU/kg) and/or FFP (12–15 mL initially, up to 20 mL/kg if severe hemorrhage)

Prothrombin activity is known to reach critical levels when blood loss exceeds 150% to 200%. Moreover, a thrombin generation deficit can be suspected when PT or aPTT is >1.5 times normal in the presence of active bleeding and bleeding loss above 150% to 200% of the total blood volume.<sup>15,20,37</sup> However, PT and aPTT can remain in the normal range even in severe PPH,<sup>103</sup> and the transfusion trigger of 1.5 times normal is mostly derived from trauma studies, which might not be appropriate in PPH. As a result, the ESA guidelines state that aPTT and PT are of little predictive value for PPH (grade C). In a case of amniotic fluid embolism following vaginal delivery, stable clotting was achieved by thromboelastometry-guided coagulation therapy comprising TXA, fibrinogen



concentrate, platelets, and PCC as well as RBC and FFP in a 1:1 ratio.<sup>105</sup> There are no further reports describing PCC or FXIII therapy in obstetric patients with noninherited coagulation deficiency.<sup>20</sup>

If a deficiency in thrombin generation is suspected, the group recommends the administration of FFP (12–15 mL initially, up to 20 mL/kg if severe hemorrhage) and/or PCC (20–30 IU/kg), the latter preferably guided by ROTEM.<sup>20,38,115</sup>

**FXIII deficiency.** The group suggests the administration of FFP (12–20 mL/kg) or, if available, FXIII concentrate (30 IU/kg or 1250 IU) in cases of ongoing or diffuse bleeding and low clot strength, despite adequate fibrinogen concentration.

The group extended the recommendation of the ESA guidelines on coagulation management in severe perioperative bleeding to situations of PPH: “In cases of ongoing or diffuse bleeding and low clot strength, despite adequate fibrinogen concentrations, it is likely that FXIII activity is critically reduced. In cases of significant FXIII deficiency (ie, <60% activity), we suggest that FXIII concentrate (30 IU kg<sup>-1</sup>) can be administered” (grade 2C).<sup>20(p275, p304)</sup>

**Recombinant activated factor VII.** The group recommends rFVIIa (90–120 µg/kg) as a last-line nonsurgical intervention if bleeding persists after correction of fibrinogen concentration and other physiological parameters (acidosis, hypocalcemia, hypothermia, thrombocytopenia, and hyperfibrinolysis) but advises that this is an off-label use and its administration is at the discretion of the treating physician.

As in other clinical scenarios, clinicians’ opinions about the off-label use of rFVIIa is still controversial in PPH. The ESA guidelines recommend that because of its thromboembolic risk, and rFVIIa should only be considered as a last-line therapy in obstetric bleeding (grade 1B).<sup>20</sup> Nevertheless, bleeding control has been reported in women with major hemorrhage.<sup>120,121</sup>

The group accepts the off-label administration of rFVIIa in PPH as the last-line, nonsurgical intervention but advises that this is an off-label use and decision is at the discretion of the treating physician, always based on the clinical judgment of each specific situation. It was previously demonstrated that in the case of severe PPH, adequate levels of platelets and fibrinogen levels are essential for rFVIIa to be effective.<sup>122</sup> Accordingly, the group also emphasizes that these parameters should be optimized before rFVIIa administration and also recommends the optimization of pH, Ca<sup>2+</sup>, and temperature. The administered dose of rFVIIa chosen by the group is 90 to 120 µg/kg, the dose most commonly used.<sup>120,121</sup> However, doses can vary between 16 and 228 µg/kg.<sup>120</sup>

**Last-line measures.** The group suggests hysterectomy as a last-line action and only if all previously recommended therapies have failed to correct PPH.

As a life-saving approach, when all the previous actions have failed, the final intervention for PPH is hysterectomy. The decision should be made by an experienced obstetrician and

should take into account the woman’s circumstances and expectations.

## Conclusion

The algorithms developed by the working group can be adapted for use in different hospitals and under different logistics settings. They can also be used even when rapid diagnostic tools are not available, by following a logical, pathophysiology-determined sequence of hemostatic therapy, considering clinical signs of coagulopathy. The group suggests that hemostatic therapy could consider the results of standard laboratory tests along with the clinical criteria indicating coagulation factor deficiencies. However, when available, POC testing using viscoelastic methods such as ROTEM or TEG should be performed to guide the early correction of deficient factors. The group recommends blood screening tests (Hb, Hct, and platelets), blood gases, and coagulation status assessments to be periodically repeated until bleeding is controlled and coagulopathy is corrected. Finally, the group highlighted the importance of communication between different specialties involved in the care of bleeding patients in order to achieve better results.

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## References

- Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med*. 2008;36(9):2667-2674.
- Aronson D, Dann EJ, Bonstein L, et al. Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. *Am J Cardiol*. 2008;102(2):115-119.
- Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation*. 2007;116(22):2544-2552.
- 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(4):578-584.
- Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma*. 2009;67(2):221-227.
- Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev*. 2012;4:Cd002042.
- Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11-21.
- Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. *Transfus Med Rev*. 2011;25(2):89-101.
- Hofmann A, Farmer S, Shander A. Five drivers shifting the paradigm from product-focused transfusion practice to patient blood management. *Oncologist*. 2011;16(suppl 3):3-11.
- Görlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology*. 2011;115(6):1179-1191.
- Weber CF, Görlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology*. 2012;117(3):531-547.
- Theusinger OM, Spahn DR, Ganter MT. Transfusion in trauma: why and how should we change our current practice? *Curr Opin Anaesthesiol*. 2009;22(2):305-312.
- Fries D, Innerhofer P, Schobersberger W. Time for changing coagulation management in trauma-related massive bleeding. *Curr Opin Anaesthesiol*. 2009;22(2):267-274.
- Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence [published online September 8, 2014]? *Br J Anaesth*. 2014.
- Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg*. 1995;81(2):360-365.
- Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med*. 2011;39(12):2652-2658.
- Solomon C, Rahe-Meyer N, Sorensen B. Fibrin formation is more impaired than thrombin generation and platelets immediately following cardiac surgery. *Thromb Res*. 2011;128(3):277-282.
- Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. *Br J Anaesth*. 2010;105(2):116-121.
- Görlinger K. Coagulation management during liver transplantation [in German]. *Hamostaseologie*. 2006;26(3 suppl 1):S64-S76.
- Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2013;30(6):270-382.
- Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*. 2013;17(2):R76.
- Martini WZ, Pusateri AE, Uscilowicz JM, Delgado AV, Holcomb JB. Independent contributions of hypothermia and acidosis to coagulopathy in swine. *J Trauma*. 2005;58(5):1002-1009.
- United Kingdom Blood Services. *Handbook of Transfusion*. 5th ed. London: TSO; 2013. <http://www.transfusionguidelines.org.uk/transfusion-handbook>. Accessed April 9, 2014.
- British Committee for Standards in Haematology and Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *Br J Haematol*. 2003;122(1):10-23.
- McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs*. 2012;72(5):585-617.
- Palmer JD, Francis DA, Roath OS, et al. Hyperfibrinolysis during intracranial surgery: effect of high dose aprotinin. *J Neurol Neurosurg Psychiatry*. 1995;58(1):104-106.
- Pérez ER, Ferrer AP, Diaz EG. Monitorización de la coagulación en quirófano. Tromboelastometría y tromboelastografía. In: Ferrer AP, Rodríguez FG, eds. *Medicina Transfusional: Ahorro de sangre en cirugía*. Madrid: Ed. Médica Panamericana; 2009:99-109.
- Schöchl H, Maegele M, Solomon C, Görlinger K, Voelckel W. Early and individualized goal-directed therapy for trauma-induced coagulopathy. *Scand J Trauma Resusc Emerg Med*. 2012;20:15.
- Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. *Transfusion*. 2014;54(5):1389-405; quiz 1388.
- Levy JH, Szlam F, Tanaka KA, Sniecinski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg*. 2012;114(2):261-274.
- Theusinger OM, Baulig W, Seifert B, Emmert MY, Spahn DR, Asmis LM. Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. *Br J Anaesth*. 2011;106:505-511.
- Yang L, Stanworth S, Baglin T. Cryoprecipitate: an outmoded treatment? *Transfus Med*. 2012;22(5):315-3120.
- Sørensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. *Br J Haematol*. 2010;149(6):834-843.
- Singbartl K, Innerhofer P, Radvan J, et al. Hemostasis and hemodilution: a quantitative mathematical guide for clinical practice. *Anesth Analg*. 2003;96(4):929-935.

35. Solomon C, Pichlmaier U, Schoechl H, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. *Br J Anaesth*. 2010;104(5):555-562.
36. Schöchl H, Posch A, Hanke A, Voelckel W, Solomon C. High-dose fibrinogen concentrate for haemostatic therapy of a major trauma patient with recent clopidogrel and aspirin intake. *Scand J Clin Lab Invest*. 2010;70(6):453-457.
37. Fries D, Innerhofer P, Perger P, et al. Coagulation management in trauma-related massive bleeding. Recommendations of the Task Force for Coagulation (AGPG) of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (OGARI) [in German]. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 2010;45(9):552-561.
38. Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. *Br J Haematol*. 2006;135(5):634-641.
39. Nienaber U, Innerhofer P, Westermann I, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. *Injury*. 2011;42(7):697-701.
40. Gerlach R, Tolle F, Raabe A, Zimmermann M, Siegemund A, Seifert V. Increased risk for postoperative hemorrhage after intracranial surgery in patients with decreased factor XIII activity: implications of a prospective study. *Stroke*. 2002;33(6):1618-1623.
41. Gerlach R, Raabe A, Zimmermann M, Siegemund A, Seifert V. Factor XIII deficiency and postoperative hemorrhage after neurosurgical procedures. *Surg Neurol*. 2000;54(3):260-264; discussion 4-5.
42. Ternstrom L, Radulovic V, Karlsson M, et al. Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery: a prospective observational study. *Thromb Res*. 2010;126(2):e128-e133.
43. Wettstein P, Haeblerli A, Stutz M, et al. Decreased factor XIII availability for thrombin and early loss of clot firmness in patients with unexplained intraoperative bleeding. *Anesth Analg*. 2004;99(5):1564-1569; table of contents.
44. Korte WC, Szadkowski C, Gahler A, et al. Factor XIII substitution in surgical cancer patients at high risk for intraoperative bleeding. *Anesthesiology*. 2009;110(2):239-245.
45. Tanaka KA, Taketomi T, Szlam F, Calatzis A, Levy JH. Improved clot formation by combined administration of activated factor VII (NovoSeven) and fibrinogen (Haemocomplettan P). *Anesth Analg*. 2008;106(3):732-738, table of contents.
46. Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation*. 2009;120(1):21-27.
47. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358(20):2127-2137.
48. Lodge JP, Jonas S, Oussoultzoglou E, et al. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology*. 2005;102(2):269-275.
49. Yank V, Tuohy CV, Logan AC, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med*. 2011;154(8):529-540.
50. Isbister J, Phillips L, Dunkley S, Jankelowitz G, McNeil J, Cameron P. Recombinant activated factor VII in critical bleeding: experience from the Australian and New Zealand Haemostasis Register. *Intern Med J*. 2008;38(3):156-165.
51. Dunkley S, Phillips L, McCall P, et al. Recombinant activated factor VII in cardiac surgery: experience from the Australian and New Zealand Haemostasis Registry. *Ann Thorac Surg*. 2008;85(3):836-844.
52. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54(6):1127-1130.
53. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. *Curr Opin Crit Care*. 2007;13(6):680-685.
54. Martini WZ, Dubick MA, Pusateri AE, Park MS, Ryan KL, Holcomb JB. Does bicarbonate correct coagulation function impaired by acidosis in swine? *J Trauma*. 2006;61(1):99-106.
55. 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.
56. Cohen MJ, Brohi K, Ganter MT, Manley GT, Mackersie RC, Pittet JF. Early coagulopathy after traumatic brain injury: the role of hypoperfusion and the protein C pathway. *J Trauma*. 2007;63(6):1254-1261; discussion 61-62.
57. Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann Surg*. 2012;255(2):379-385.
58. Fenger-Eriksen C, Anker-Moller E, Heslop J, Ingerslev J, Sørensen B. Thrombelastographic whole blood clot formation after ex vivo addition of plasma substitutes: improvements of the induced coagulopathy with fibrinogen concentrate. *Br J Anaesth*. 2005;94(3):324-329.
59. Sorensen B, Fries D. Emerging treatment strategies for trauma-induced coagulopathy. *Br J Surg*. 2012;99(suppl 1):40-50.
60. Fenger-Eriksen C, Tonnesen E, Ingerslev J, Sørensen B. Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy. *J Thromb Haemost*. 2009;7:1099-1105.
61. Nielsen VG. Hydroxyethyl starch does not decrease prothrombin to thrombin conversion. *Acta Anaesthesiol Scand*. 2008;52(1):163-164.
62. 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(4):805-813.
63. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma*. 2009;66(1):41-48; discussion 8-9.
64. Schöchl H, Schlimp CJ. Trauma bleeding management: the concept of goal-directed primary care. *Anesth Analg*. 2014;119(5):1064-1073.
65. Ho AM, Dion PW, Yeung JH, et al. Simulation of survivorship bias in observational studies on plasma to red blood cell ratios

- in massive transfusion for trauma. *Br J Surg*. 2012;99(suppl 1):132-139.
66. 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(2):358-362.
  67. Innerhofer P, Westermann I, Tauber H, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. *Injury*. 2013;44(2):209-216.
  68. Schöchl H, Schlimp CJ, Voelckel W. Potential value of pharmacological protocols in trauma. *Curr Opin Anaesthesiol*. 2013;26(2):221-229.
  69. Nardi G, Agostini V, Maria BR, et al. Prevention and treatment of trauma induced coagulopathy (TIC). An intended protocol from the Italian trauma update research group. *J Anesthesiol Clin Sci*. 2013;2:22.
  70. Schöchl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM(R))-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010;14(2):R55.
  71. Grassetto A, De Nardin M, Ganzerla B, et al. ROTEM(R)-guided coagulation factor concentrate therapy in trauma: 2-year experience in Venice, Italy. *Crit Care*. 2012;16(3):428.
  72. CRASH-2 trial collaborators, Shakur H, Roberts I, 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(9734):23-32.
  73. CRASH-2 trial collaborators, Roberts I, Shakur H, 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(9771):1096-101, 101 e1-e2.
  74. CRASH-2 Collaborators and Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ*. 2011;343:d3795.
  75. Theusinger OM, Madjdipour C, Spahn DR. Resuscitation and transfusion management in trauma patients: emerging concepts. *Curr Opin Crit Care*. 2012;18(6):661-670.
  76. Chambers LA, Chow SJ, Shaffer LE. Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol. *Am J Clin Pathol*. 2011;136(3):364-370.
  77. 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(2 suppl):S79-S85.
  78. Schöchl H, Nienaber U, Maegele M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care*. 2011;15(2):R83.
  79. Schlimp CJ, Voelckel W, Inaba K, Maegele M, Ponschab M, Schöchl H. Estimation of plasma fibrinogen levels based on hemoglobin, base excess and Injury Severity Score upon emergency room admission. *Crit Care*. 2013;17(4):R137.
  80. Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. *J Thorac Cardiovasc Surg*. 2013;145(3 suppl):S178-S185.
  81. Rahe-Meyer N, Pichlmaier M, Haverich A, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. *Br J Anaesth*. 2009;102(6):785-792.
  82. Brown LM, Call MS, Margaret Knudson M, et al. A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients. *J Trauma*. 2011;71(2 suppl 3):S337-S342.
  83. Floccard B, Rugeri L, Faure A, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury*. 2012;43(1):26-32.
  84. Simmons JW, White CE, Eastridge BJ, Mace JE, Wade CE, Blackburne LH. Impact of policy change on US Army combat transfusion practices. *J Trauma*. 2010;69(suppl 1):S75-S80.
  85. Dirks J, Jorgensen H, Jensen CH, Ostrowski SR, Johansson PI. Blood product ratio in acute traumatic coagulopathy—effect on mortality in a Scandinavian level 1 trauma centre. *Scand J Trauma Resusc Emerg Med*. 2010;18:65.
  86. Sorensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R. Clinical review: prothrombin complex concentrates—evaluation of safety and thrombogenicity. *Crit Care*. 2011;15(1):201.
  87. Schöchl H, Forster L, Woidke R, Solomon C, Voelckel W. Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. *Anaesthesia*. 2010;65(2):199-203.
  88. Cohen MJ, West M. Acute traumatic coagulopathy: from endogenous acute coagulopathy to systemic acquired coagulopathy and back. *J Trauma*. 2011;70(5 suppl):S47-S479.
  89. Johansson PI, Sorensen AM, Perner A, et al. Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study. *Crit Care*. 2011;15(6):R272.
  90. Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma*. 2001;51:431-438; discussion 8-9.
  91. Harrison TD, Laskosky J, Jazaeri O, Pasquale MD, Cipolle M. “Low-dose” recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage. *J Trauma*. 2005;59(1):150-154.
  92. Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma*. 2004;57(4):709-718; discussion 18-19.
  93. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*. 2005;59(1):8-15; discussion 8.
  94. Hauser CJ, Boffard K, Dutton R, et al. Results of the CONTROL trial: efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. *J Trauma*. 2010;69(3):489-500.



95. Dutton RP, Parr M, Tortella BJ, et al. Recombinant activated factor VII safety in trauma patients: results from the CONTROL trial. *J Trauma*. 2011;71(1):12-19.
96. Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. *Clin Obstet Gynecol*. 2010;53(1):147-56.
97. Huissoud C, Carrabin N, Audibert F, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. *BJOG*. 2009;116(8):1097-102.
98. Bremme KA. Haemostatic changes in pregnancy. *Best Pract Res Clin Haematol*. 2003;16(2):153-168.
99. de Lange NM, Lance MD, de Groot R, Beckers EA, Henskens YM, Scheepers HC. Obstetric hemorrhage and coagulation: an update. Thromboelastography, thromboelastometry, and conventional coagulation tests in the diagnosis and prediction of postpartum hemorrhage. *Obstet Gynecol Surv*. 2012;67:426-435.
100. Peyvandi F, Biguzzi E, Franchi F, et al. Elevated prepartum fibrinogen levels are not associated with a reduced risk of postpartum hemorrhage. *J Thromb Haemost*. 2012;10(7):1451-1453.
101. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost*. 2007;5(2):266-273.
102. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth*. 2012;108(6):984-989.
103. de Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. *Int J Obstet Anesth*. 2011;20(2):135-141.
104. Collins PW, Lilley G, Bruynseels D, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. *Blood*. 2014;124(11):1727-1736.
105. Annecke T, Geisenberger T, Kurzl R, et al. Algorithm-based coagulation management of catastrophic amniotic fluid embolism. *Blood Coagul Fibrinolysis*. 2010;21(1):95-100.
106. James AH. More than menorrhagia: a review of the obstetric and gynaecological manifestations of bleeding disorders. *Haemophilia*. 2005;11(4):295-307.
107. Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. *BJOG*. 2008;115(10):1265-1272.
108. Ferrer P, Roberts I, Sydenham E, Blackhall K, Shakur H. Antifibrinolytic agents in post partum haemorrhage: a systematic review. *BMC Pregnancy Childbirth*. 2009;9:29.
109. Hellgren M. Hemostasis during normal pregnancy and puerperium. *Semin Thromb Hemost*. 2003;29(2):125-130.
110. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. *Br J Anaesth*. 2012;109(6):851-863.
111. Ducloy-Bouthors AS, Jude B, Duhamel A, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Crit Care*. 2011;15(2):R117.
112. Shakur H, Elbourne D, Gulmezoglu M, et al. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. *Trials*. 2010;11:40.
113. Senturk MB, Cakmak Y, Yildiz G, Yildiz P. Tranexamic acid for cesarean section: a double-blind, placebo-controlled, randomized clinical trial. *Arch Gynecol Obstet*. 2013;287(4):641-645.
114. Fenger-Eriksen C, Ingerslev J, Sorensen B. Fibrinogen concentrate—a potential universal hemostatic agent. *Expert Opin Biol Ther*. 2009;9(10):1325-1333.
115. Arulkumaran S, Mavrides E, Penney GC. Prevention and management of postpartum haemorrhage. London, United Kingdom: Royal College of Obstetricians and Gynaecologists; 2009: Green-top Guideline 52.
116. Thomas D, Wee M, Clyburn P, et al. Blood transfusion and the anaesthetist: management of massive haemorrhage. *Anaesthesia*. 2010;65(11):1153-1161.
117. Kozek-Langenecker SA. Perioperative coagulation monitoring. *Best Pract Res Clin Anaesthesiol*. 2010; 24: 27-40.
118. Huissoud C, Carrabin N, Benchaib M, et al. Coagulation assessment by rotation thrombelastometry in normal pregnancy. *Thromb Haemost*. 2009;101(4):755-761.
119. Bouvier-Colle MH, Ould El Joud D, Varnoux N, et al. Evaluation of the quality of care for severe obstetrical haemorrhage in three French regions. *BJOG*. 2001;108(9):898-903.
120. Alfrevic Z, Elbourne D, Pavord S, et al. Use of recombinant activated factor VII in primary postpartum hemorrhage: the Northern European registry 2000-2004. *Obstet Gynecol*. 2007;110(6):1270-1278.
121. Phillips LE, McLintock C, Pollock W, et al. Recombinant activated factor VII in obstetric hemorrhage: experiences from the Australian and New Zealand Haemostasis Registry. *Anesth Analg*. 2009;109(6):1908-1915.
122. Lewis NR, Bruner P, Lemire SJ, Kaufman RM. Failure of recombinant factor VIIa to correct the coagulopathy in a case of severe postpartum hemorrhage. *Transfusion*. 2009;49(4):689-695.