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NARRATIVE REVIEW ARTICLE

Early Goal-Directed Hemostatic Therapy for Severe Acute Bleeding Management in the Intensive Care Unit: A Narrative Review

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This is a narrative review of the published evidence for bleeding management in critically ill patients in different clinical settings in the intensive care unit (ICU). We aimed to describe "The Ten Steps" approach to early goal-directed hemostatic therapy (EGDHT) using point-of-care testing (POCT), coagulation factor concentrates, and hemostatic drugs, according to the individual needs of each patient. We searched National Library of Medicine, MEDLINE for publications relevant to management of critical ill bleeding patients in different settings in the ICU. Bibliographies of included articles were also searched to identify additional relevant studies. English-language systematic reviews, meta-analyses, randomized trials, observational studies, and case reports were reviewed. Data related to study methodology, patient population, bleeding management strategy, and clinical outcomes were qualitatively evaluated. According to systematic reviews and meta-analyses, EGDHT guided by viscoelastic testing (VET) has been associated with a reduction in transfusion utilization, improved morbidity and outcome in patients with active bleeding. Furthermore, literature data showed an increased risk of severe adverse events and poor clinical outcomes with inappropriate prophylactic uses of blood components to correct altered conventional coagulation tests (CCTs). Finally, prospective, randomized, controlled trials point to the role of goal-directed fibrinogen substitution to reduce bleeding and the amount of red blood cell (RBC) transfusion with the potential to decrease mortality. In conclusion, severe acute bleeding management in the ICU is still a major challenge for intensive care physicians. The organized and sequential approach to the bleeding patient, guided by POCT allows for rapid and effective bleeding control, through the rational use of blood components and hemostatic drugs, since VET can identify specific coagulation disorders in real time, guiding hemostatic therapy with coagulation factor concentrates and hemostatic drugs with individual goals. (Anesth Analg 2023;XXX:00–00)

GLOSSARY

4f-PCC = Four-Factor Prothrombin Complex Concentrate; **A5 and A10** = amplitude 5 or 10 minutes after CT; **ABC** = Ensure patient's Airway, Breathing, and Circulation; **ADPTEM** = adenosine diphosphate; **APA** = antiplatelet agents; **aPCC** = activated prothrombin complex concentrate; **APTEM** = aprotinin; **AP-test** = aprotinin-test; **aPTT** = activated partial thromboplastin time; **ARATEM** = arachidonic acid; **ARU** = aspirin reaction units; **AT** = antithrombin; **ATLS** = advanced trauma life support; **CBC** = complete blood count; **CCTs** = coagulation conventional tests; **CT** = clotting time; **DDAVP** = desmopressin; **DIC** = disseminated intravascular coagulation; **DOACs** = direct oral anticoagulants; **DTIs** = direct thrombin inhibitors; **dTT** = diluted thrombin time; **ECA-test** = and the ecarin test; **ECT** = ecarin clotting time; **EGDHT** = early goal-directed hemostatic therapy; **EXTEM** = extrinsic pathway, **EX-test** = extrinsic test; **FDA** = Food and Drug Administration; **FDP** = fibrin degradation products; **FFP** = fresh frozen plasma; **FIBTEM** = fibrinogen test, **FIB-test** = fibrinogen test; **FVII** = factor VII; **FXIII** = factor XIII; **Hb** = hemoglobin; **HEPTEM** = heparinase; **HEP-test** = heparinase test; **ICU** = intensive care unit; **INR** = international normalized ratio; **INTEM** = intrinsic pathway, **IN-test** = intrinsic test; **IV** = intravenous; **LI30,45 and 60** = lysis index at 30, 45 and 60 min after CT; **LMWH** = low molecular weight heparin; **LOT** = lysis onset time; **MAP** = mean arterial pressure; **MCF** = maximum clot

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firmness; **ML** = maximum lysis; **MODS** = multiple organ dysfunction syndrome; **NSAID** = nonsteroidal anti-inflammatory drugs; **NA-test** = native test; **PAI-1** = plasminogen activator inhibitor type 1; **PBM** = patient blood management; **PCC** = prothrombin complex concentrate; **PFT** = platelet function test; **POCT** = point-of-care testing; **POB** = perioperative bleeding; **PPH** = postpartum hemorrhage; **PRU** = P2Y12 reaction units; **PT** = prothrombin time; **RBC** = red blood cell; **RCTs** = randomized controlled trials; **ROTEM** = rotational thromboelastometry; **RR** = relative risk; **RVV-test** = Russell's viper venom test; **t-PA** = tissue plasminogen activator; **TACO** = transfusion-associated circulatory overload; **TAFI** = thrombin activatable fibrinolysis inhibitor; **TBI** = traumatic brain injury; **TEG** = thromboelastography; **TEM** = thromboelastometry; **TF** = tissue factor; **TFPI** = tissue factor pathway inhibitor; **TIC** = trauma-induced coagulopathy; **TRALI** = transfusion-related acute lung injury; **TRAPTEM** = thrombin-activating peptide test; **TRIM** = transfusion-related immunomodulation; **TXA** = tranexamic acid; **VET** = viscoelatic testing; **VKA** = vitamin K- antagonists; **vWD** = von Willebrand disease; **vWF** = von Willebrand factor; **xabans** = direct factor Xa inhibitors

Hemorrhage and thrombosis are frequent complications in the intensive care unit (ICU), compromising the clinical outcome of patients.[1] Among them, the main cause of death in the world is thrombosis. However, there is concern about the risk of bleeding in patients who have pathological results from conventional coagulation tests (CCTs).[2] For this reason, prophylactic transfusion of allogeneic blood components is still very frequent, even in the absence of bleeding. However, transfusion is associated with life-threatening adverse events.[3] In this literature review, we aimed to describe critical aspects of the approach to patients with severe acute bleeding in the ICU, focusing on the importance of point-of-care testing (POCT) for early identification of coagulopathy to guide early goal-directed hemostatic therapy (EGDHT) using coagulation factor concentrates and hemostatic drugs.

HEMOSTASIS

Hemostasis considers the interrelation of physical, cellular, and biochemical processes and involves an activation of coagulation proteins, inhibitors, platelets, and components of the vascular wall to form a clot at the site of vessel injury, preventing or stopping bleeding.[4] Hemostasis is an interplay between the endothelium, primary hemostasis, procoagulant system, natural inhibitors as well as fibrinolytic and antifibrinolytic systems (Figure 1).[5] In the current understanding, the cell-based model of coagulation replaces the traditional "cascade" or "waterfall model" and proposes that coagulation takes place on cell surfaces in 4 subsequent steps (initiation, amplification, propagation, and stabilization).[6] The recognition of the role of cell surface in clot formation allows an integrated understanding of the dynamic mechanisms of hemostasis in the vascular system.[7] The biochemical environment determined by pH, temperature, and Ca^{2+}, is critical for thrombin generation and clot formation. The coagulation cascade is also downregulated by physiological inactivation of coagulation factors.[8] The natural inhibitors composed of antithrombin (AT), protein C and its cofactor protein S, as well as tissue factor pathway inhibitor (TFPI) play a regulatory role in the procoagulant activity, thus limiting the formation of the thrombus (Supplemental Digital Content, Supplemental Figures 1 and 2, http://links.lww.com/AA/E583).[8–11] Fibrinolysis is an enzymatic process that dissolves the fibrin clot into fibrin degradation products (FDP and D-dimers) by plasmin during the activation of the coagulation cascade limiting the size and extent of clots (Supplemental Digital Content, Supplemental Figure 3, http://links.lww.com/AA/E583).[5]

A severe deficiency of only 1 procoagulant factor (<10%), for example, factor VII (FVII), can be associated with bleeding.[9] Hence, bleeding in critically ill patients has most often a multifactorial etiology.[10,11] In fact, the presence of bleeding will occur as a result of the imbalance of different pathways that comprise hemostasis, including coagulation factors, natural inhibitors, fibrinolysis, and endothelium. For a proper approach to patients with coagulopathy, it is essential to use a diagnostic tool that allows assessing in real time, the cellular component, biochemical phenomenon, and the whole process of clot formation, as well as platelet function.[12]

LABORATORY TESTS

Conventional Coagulation Tests

Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are important tests for the monitoring of anticoagulant drugs such as warfarin and heparin.[13] In contrast, CCTs are poor predictors of bleeding in the setting of critically ill patients.[14] CCTs are performed in plasma at a standardized temperature of 37°C. Due to removal of the cellular fraction, these tests do not consider the role of blood cells and the platelet component.[15] Further, do they only access the first 5% of the process of thrombin generation,[16] and fibrinolysis cannot be determined.

Viscoelastic Testing

Viscoelastic testing (VET) provides a quick and comprehensive graphical representation of the dynamics of the entire clot formation and lysis process that can

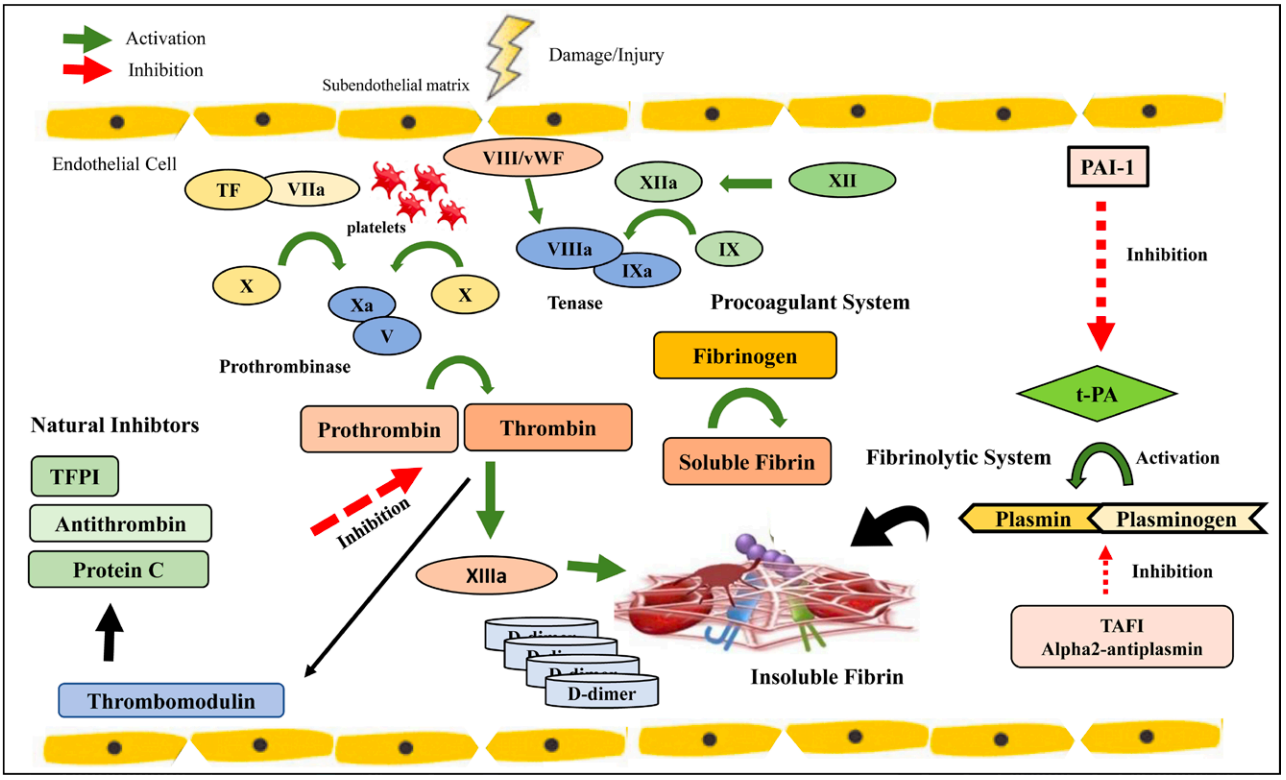


Figure 1. Hemostasis. PAI-1 indicates plasminogen activator inhibitor type 1; TAFI, thrombin activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.

be evaluated and reviewed at the point of care. This technology is over 70 years old; however, in recent years there has been a significant increase in research examining the use of VET in acute critical bleeding settings. Currently, best practice guidelines for implementing the use of VET-guided algorithms are an essential part of the patient blood management (PBM) concept, and recommend the use of VET in the diagnosis of trauma-induced coagulopathy (TIC), as well as to guide hemostatic interventions in perioperative bleeding (POB). The main technologies studied include rotational thromboelastometry (TEM, Tem Innovation GmbH), and thromboelastography (TEG, Haemonetics Corporation). However, more recently, the Quantra analyzer (HemoSonics LLC) is based on sonorheometry, and the ClotPro system (enicor GmbH; Haemonetics Corporation) based on thromboelastometry has been introduced into the market, too.[20,21]

Thromboelastography and Thromboelastometry

The TEG method was first described by Helmut Hartert in 1948, a VET to evaluate the function of the coagulation system.[17] The first commercial generation of modern VET-devices, the TEG5000, was very sensitive to agitation and therefore required a specific environment in the laboratory to avoid artifacts.[18] Furthermore, assays with tissue factor (TF) as an activator and additional additives (such as platelet inhibitors or aprotinin) for more specific diagnostic tests were developed later.[19]

Rotational thromboelastometry including rotational thromboelastometry (ROTEM) 05, *gamma,* and *delta*, came up in the mid-1990s to assess the viscoelastic changes of blood during the whole period of clot formation. ROTEM 05, *gamma,* and *delta* are semiautomated devices using modern software, composed of 4 integrated channels, an electronic pipette, and color-coded reagents and graphics (temograms).[20] Currently, ROTEM *sigma* is a fully automated device with 2 different cartridges allowing closed-tube sampling, without pipetting or manual reagent handling. The automatization of testing reduces technical and avoids pipetting errors. Five reagents are used in clinical practice to allow rapid identification of specific coagulation disorders: EXTEM (activation of the extrinsic pathway by TF and heparin neutralization by polybrene), INTEM (activation of the intrinsic pathway by ellagic acid), FIBTEM (elimination of platelet contribution to clot firmness by cytochalasin D), HEPTEM (elimination of heparin effects by heparinase), and APTEM (elimination of hyperfibrinolysis by aprotinin). Coagulation factor deficiencies, hypofibrinogenemia, decreased platelet contribution to clot firmness, hyperfibrinolysis, fibrinolysis shutdown, heparin-like effects, protamine overdose, and oral anticoagulants may be quickly identified at the bedside.[12,21–24]

Like other VET devices, ROTEM does not provide a comprehensive or sensitive reflection of von Willebrand disease (vWD) or impaired platelet aggregation.[25,26] Limitations of VETs include the absence of endothelium and blood flow, as the tests are performed on whole blood with low shear stress.[20] VET is a cornerstone of the EGDHT concept, since it globally accesses the entire clot formation process in real time, from clot initiation, clot formation to its lysis. ROTEM not only allows for a shorter turnaround time compared to CCTs, hence earlier identification of coagulopathy within 5 minutes, but ROTEM assays, such as FIBTEM, have also been shown to be superior to CCTs, such as plasma fibrinogen concentration, for predicting bleeding and transfusion in multiple clinical settings.[31]Several institutions moved during the last years to fully-automated VET devices such as ROTEM sigma, TEG6s, or Quantra, particularly if used at the point-of-care.[32]

Notably, TEG and -metry algorithms follow different concepts of result interpretation and clinical strategies in bleeding management, besides technical differences and different assay compositions. In this review paper, we focus on the concept of EGDHT for severe acute bleeding management based on thromboelastometry algorithms.[15,24,33,34]

VET has been shown to be effective in reducing bleeding, transfusion requirements, complication rates, and health care costs in perioperative settings.[12] Systematic reviews and meta-analyzes demonstrated growing evidence, particularly in cardiac surgery, liver transplantation, trauma, and more recently in postpartum hemorrhage (PPH), as a useful tool for the management of severe acute bleeding, allowing the rationalization in the use of blood components.[27,28] Therapeutic alternatives to transfusion, such as hemostatic drugs, antifibrinolytics, and coagulation factor concentrates, reduced the incidence of adverse effects related to allogeneic blood components, such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion-related immunomodulation (TRIM) with nosocomial infections.[38,39] A retrospective cohort study observed reduced blood product use, and less infections in severely burned patients with treatment guided by a goal-directed coagulation algorithm.[29] A systematic review with meta-analysis published in 2017 by Wikkelsø et al showed a significant reduction in mortality using TEG or ROTEM-guided algorithms versus any comparison in longer follow-up mortality (3.9% vs 7.4%).[30] This corresponds to a relative risk reduction of 48% favoring a TEG- or ROTEM-guided transfusion. These results were confirmed by the last meta-analysis published by Santos et al[36] based on 21 randomized controlled trials (RCTs) including 8900 participants: relative risk (RR) for mortality in ROTEM studies 0.48 (P = .09), in TEG studies 0.71 (P = .15) and for ROTEM and TEG together 0.64 (P = .03).[31]

Other VET Devices

The Quantra platform is a cartridge-based VET device that uses ultrasound to characterize dynamic changes in the viscoelastic properties of blood during clot formation.[20] There are currently limited studies addressing the interchangeability of VET parameters.[32]

ClotPro is a recent device that uses a modified viscoelastic clotting test based on the established cup-and-pin technology principle of ROTEM.[21] This technology features a dual-bearing guidance system, 6 multitest channels, and 8 different assays. Some assays are comparable to commonly used ROTEM assays (eg, extrinsic test [EX-test], fibrinogen test [FIB-test], aprotinin-test [AP-test], intrinsic test [IN-test], heparinase test [HEP-test], and native test [NA-test]). Additional assays have been developed specifically for the detection and differentiation of direct oral anticoagulants (DOACs): the Russell's viper venom test (RVV-test) and the ecarin test (ECA-test). The tissue plasminogen activator assay contains a recombinant tissue plasminogen activator and may be used to identify impaired fibrinolysis and fibrinolytic resistance.[43,44] As ROTEM *delta*, ClotPro is a semiautomatic VET analyzer that requires pipetting. Its clinical application has been based on studies using well-established ROTEM cutoff values which may have to be adapted to ClotPro.[33–35]

FUNCTIONAL CLASSIFICATION OF THE COAGULATION SYSTEM

For a better interpretation of hemostasis at the bedside and to support decision-making for optimum hemostatic therapy, we propose a functional classification of coagulation based on the physiology in 3 phases: thrombin generation, clot firmness, and clot stabilization (Figure 2). Thrombin generation is determined by enzymatic coagulation factors and can be modified by the biochemical environment, anticoagulants, inhibitors, and coagulation factor deficiencies. This phase is represented by CT (clotting time) in ROTEM.[12] Clot firmness is determined by fibrin polymerization, platelet aggregation, and platelet-fibrin-interaction. This can be modified by factor XIII (FXIII) and colloids.[12,36–40] This phase can be altered by deficiency of any of these components and corresponds to early (amplitude 5 or 10 minutes after CT: A5 and A10) and late clot firmness parameters (maximum clot firmness: MCF) in ROTEM.[12] Clot stabilization is determined by fibrinolysis, FXIII, and platelet-mediated clot retraction, and is represented by maximum lysis (ML), lysis onset time (LOT), and lysis index at 30, 45, and 60 minutes after CT (LI30, LI45, and LI60).[12,41–44] FIBTEM is the most sensitive and specific assay for the detection of hyperfibrinolysis.[45–47] The combination of EXTEM (sensitive to fibrinolysis and platelet-mediated clot retraction), FIBTEM (not sensitive to platelet-mediated

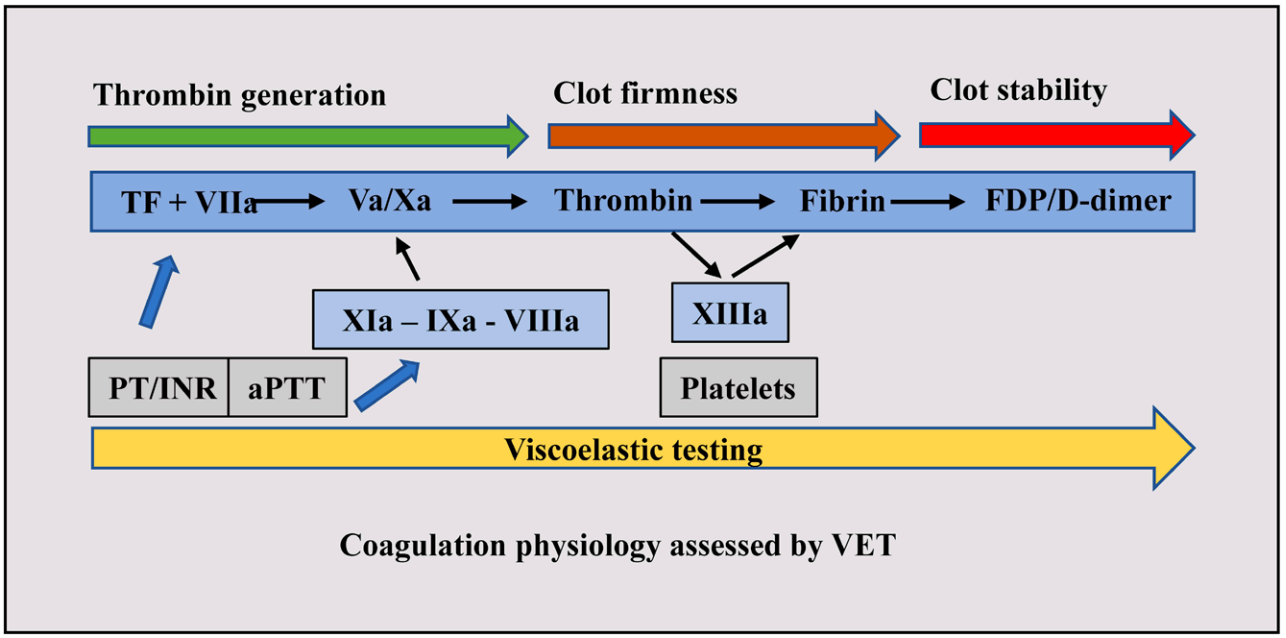


Figure 2. Functional classification of the coagulation. aPTT indicates activated partial thromboplastin time; FDP, fibrin degradation products; INR, international normalized ratio; PT, prothrombin time; TF, tissue factor; VET, viscoelatic testing.

clot retraction but very sensitive to fibrinolysis), and APTEM (not sensitive to fibrinolysis but to platelet-mediated clot retraction) can be used to differentiate between hyperfibrinolysis and platelet-mediated clot retraction.[25,26,55,56] Fortunately, the latter is not associated with bleeding and does not require therapy with antifibrinolytics.[57,58]

BLEEDING MANAGEMENT IN THE ICU

Based on physiology of hemostasis, pathophysiology of different diseases, as well as the use of VET to monitor hemostasis and guide hemostatic therapy in face of a severe acute bleeding, we suggest the concept of "The Ten Steps" for severe acute bleeding management in the ICU, including an EGDHT algorithm to support clinicians in decision-making (Figure 3).

The Ten Steps

We propose the following "ten steps" approach (Figure 4):

1. ABC: Ensure patient's Airway, Breathing, and Circulation (oxygen supply, vascular access, and restrictive volume resuscitation).
2. Tissue perfusion and oxygenation: Optimize perfusion parameters and intravascular volume resuscitation with crystalloids and RBC. Target mean arterial pressure (MAP) > 65 mm Hg, lactate <2 to 4 mmol/L, diuresis >0.5 mL/kg/h. Blood lactate is considered as a sensitive test to estimate the extent of tissue hypoperfusion: If lactate results are not available, base deficit can be used in this context. Permissive hypotension may be necessary in some cases such as variceal bleeding or active arterial bleeding until surgical or interventional hemostasis. Administration of large volumes of crystalloids and colloids should be avoided since this is associated with dilutional coagulopathy, which may lead to transfusion- and tissue edema-related adverse outcomes.[59] Ideally, balanced crystalloid solutions are recommended by the European guideline for volume therapy in hypotensive patients due to trauma-induced bleeding.
3. Anemia management: A restrictive transfusion strategy (RBC transfusion trigger of hemoglobin [Hb] < 7 g/dL) for most stable patients is recommended. RBC transfusion should be performed based on the estimated volume of blood loss during active bleeding.[48,49] In hemorrhagic shock with hemodynamic instability, one should consider that RBC are fundamental for the hemostasis mechanism of platelet marginalization to the vessel wall.[50–52] Two units of RBC (4 units in case of massive bleeding) and blood typing should be requested.
4. A recent Cochrane review published in 2021 on transfusion thresholds to guide RBC transfusion suggests that allogeneic RBC transfusion can be avoided in most patients with Hb thresholds between 7.0 and 8.0 g/dL, even if the evidence for a reduction in mortality by a restrictive compared to a liberal transfusion

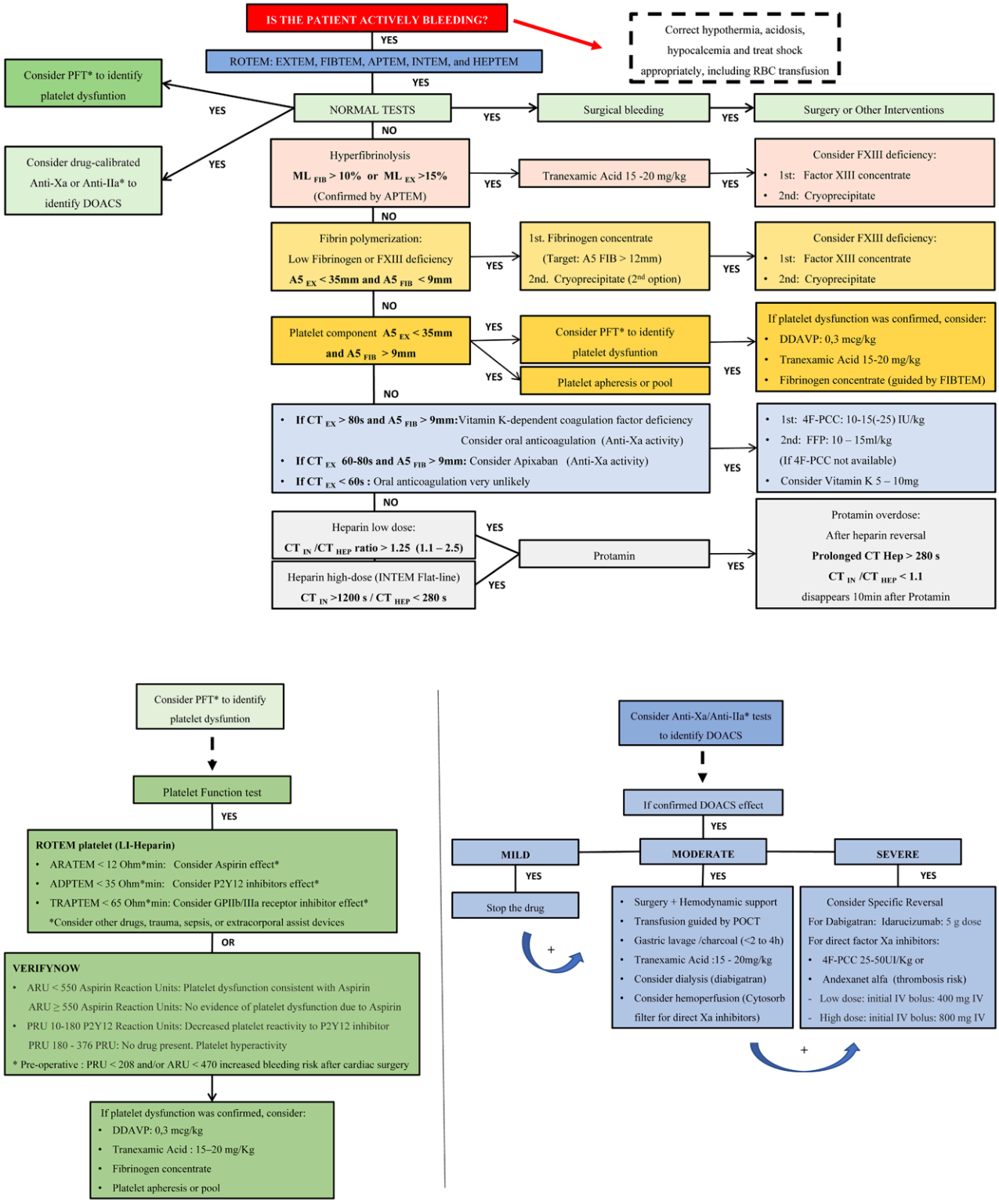


Figure 3. EGDHT algorithm. 4F-PCC indicates four-factor prothrombin complex concentrate; ADPTEM, adenosine diphosphate; APTEM, aprotinin; ARATEM, arachidonic acid; ARU, aspirin reaction units; CT, clotting time; DDAVP, desmopressin; DOACS, direct oral anticoagulants; EGDHT, early goal-directed hemostatic therapy; EXTEM, extrinsic pathway; FIBTEM, fibrinogen test; HEPTEM, heparinase; INTEM, intrinsic pathway; IV, intravenous; ML, maximum lysis; PCC, prothrombin complex concentrate; PFT, platelet function test; POCT, point-of-care testing; PRU, P2Y12 reaction units; RBC, red blood cell; ROTEM, rotational thromboelastometry; TRAPTEM, thrombin-activating peptide.

strategy is limited.[64] Notably, a meta-analysis published in 2017 comparing restrictive versus liberal blood transfusion in gastrointestinal bleeding demonstrated that restrictive transfusion was associated with a lower risk of all-cause mortality.[65]

5. Biochemical environment. Once clinically relevant bleeding has been identified, a "clot friendly" environment is mandatory for proper thrombin generation and clot formation. Hypothermia causes coagulopathy due to impaired platelet aggregation and reduced activity of enzymes in the coagulation cascade. Anemia, acidemia, hypocalcemia should also be promptly corrected.[66] Hypocalcemia can be corrected by the administration of Ca^{2+} gluconate or Ca^{2+} chloride with a ionized Ca^{2+} concentration of 4.7 to 5.2 mg/dL (1.17–1.30 mmol/L) as a target. Cornerstone of acidemia management is shock therapy by correcting hypovolemia with crystalloids and RBC, and the correct acidosis before hemostatic interventions with 8.4% sodium bicarbonate (target pH > 7.35). To avoid or correct hypothermia, (re)warm the patient by using warm infusions and transfusions, thermal blankets, convective warming therapy, and increased room temperature.
6. Bleeding source: VET allows to differentiate between coagulopathy or surgical reasons for the bleeding.[67] If there is an "open vessel," surgical hemostasis is mandatory, including manual compression, clips, sutures, or interventional radiology.[53,68] In case of microvascular bleeding, VET may help to identify specific coagulation disorders and may be complemented by platelet function testing (PFT).[69]
7. EGDHT: consider the use of coagulation factor concentrates and/or hemostatic drugs instead of allogeneic blood components since liberal transfusion has been associated with severe adverse events.[70–73]
8. Early administration of tranexamic acid (TXA) within the first 3 hours after injury or delivery in TIC and PPH.[74,75] Fibrinogen concentration should be monitored early, and in the presence of hypofibrinogenemia, supplementation should be performed with fibrinogen concentrate or cryoprecipitate.[67,69]
9. CCTs: Complete blood count (CBC) should be performed to assess platelet count, PT/INR, and aPTT to monitor the anticoagulant effects, anti-Xa activity for low-molecular-weight heparin (LMWH). D-dimer is helpful for differentiating disseminated intravascular coagulation (DIC) from other conditions potentially associated with a low platelet count, low fibrinogen, and prolonged clotting times, such as in liver disease. The role of CCTs in the assessment of DOAC effects is described below.
10. PFT: PFT can be helpful to detect the effects of antiplatelet agents (APAs), antiplatelet effects of other drugs used in critically ill patients (eg, beta-blockers, Ca^{2+} antagonists, antibiotics, antidepressants, and analgetic drugs), and the effects of trauma, sepsis, and extracorporeal assist devices on platelet function.[76–81] Some studies suggest that VET and PFT better predict bleeding than platelet count.[82–85]
11. DOACs: Specific assays can assess the effects of DOACs and IV direct thrombin inhibitors (DTIs), such as anti-Xa activity (calibrated for rivaroxaban, apixaban, and edoxaban), and diluted thrombin time (dTT; DTI assay), or ecarin clotting time (ECT; chromogenic anti-IIa assay) for dabigatran, argatroban, and bivalirudin.[23,24,54–57] Standard and modified thromboelastometric assays can be helpful, too.[23,56–59,86–91]

1. ABC: ensure patient's Airway, Breathing, and Circulation
2. Tissue perfusion and oxygenation optimization
3. Anemia Management: target Hb < 7 g/dl – RBC 2 units (4 units in case of massive bleeding) and blood typing
4. Biochemical environment improvement: acidemia, hypothermia and hypocalcemia
5. Bleeding Source: identifying bleeding cause (coagulopathy x surgical bleeding) using VET
6. EGDHT: VET-guided coagulation factor concentrates and hemostatic drugs instead of allogeneic blood components
7. Early administration of TXA in trauma and PPH. In the presence of hypofibrinogenemia, supplementation should preferably be performed with fibrinogen concentrate or cryoprecipitate
8. Lab tests: CCTs, platelet count, Anti-Xa activity for LMWH. D-dimer for DIC
9. Platelet function: to access possible effect of antiplatelet drugs and platelet dysfunction due to trauma, sepsis, extracorporeal support devices, and other drugs
10. DOACS: Anti-Xa activity (calibrated for rivaroxaban, apixaban and edoxaban), Anti-IIa (dabigatran, argatroban, and bivalirudin)

Figure 4. The Ten Steps. ABC indicates Ensure patient's Airway, Breathing, and Circulation; CCTs, coagulation conventional tests; DIC, disseminated intravascular coagulation; DOACS, direct oral anticoagulants; EGDHT, early goal-directed hemostatic therapy; Hb, hemoglobin; LMWH, low-molecular-weight heparin; PPH, postpartum hemorrhage; RBC, red blood cell; TXA, tranexamic acid; VET, viscoelatic testing.

"REVERSE TREATMENT"

Once the coagulopathy is identified, an individualized treatment should be considered in a retrograde way following the advanced trauma life support (ATLS) concept of "treat first what kills first" (Figure 5).[92] Accordingly, we should firstly stabilize the clot by blocking hyperfibrinolysis, secondly improve clot firmness, and third improve thrombin generation. In this case, the order of factor replacement may compromise the result of bleeding control.

First Step: Clot Stabilization

(Supplemental Digital Content, Supplemental Figure 4.1, http://links.lww.com/AA/E583): The early use of antifibrinolytic drugs should be first line with an empirical approach within 3 hours after injury.[74,75,93,94] For bleeding trauma patients, TXA should be administered as soon as possible within 3 hours of injury without the need to wait for VET results, preferably on the route to the hospital. Recommended loading dose is 1 g infused over 10 minutes, followed by an IV infusion of 1 g over 8 hours.[67,74]

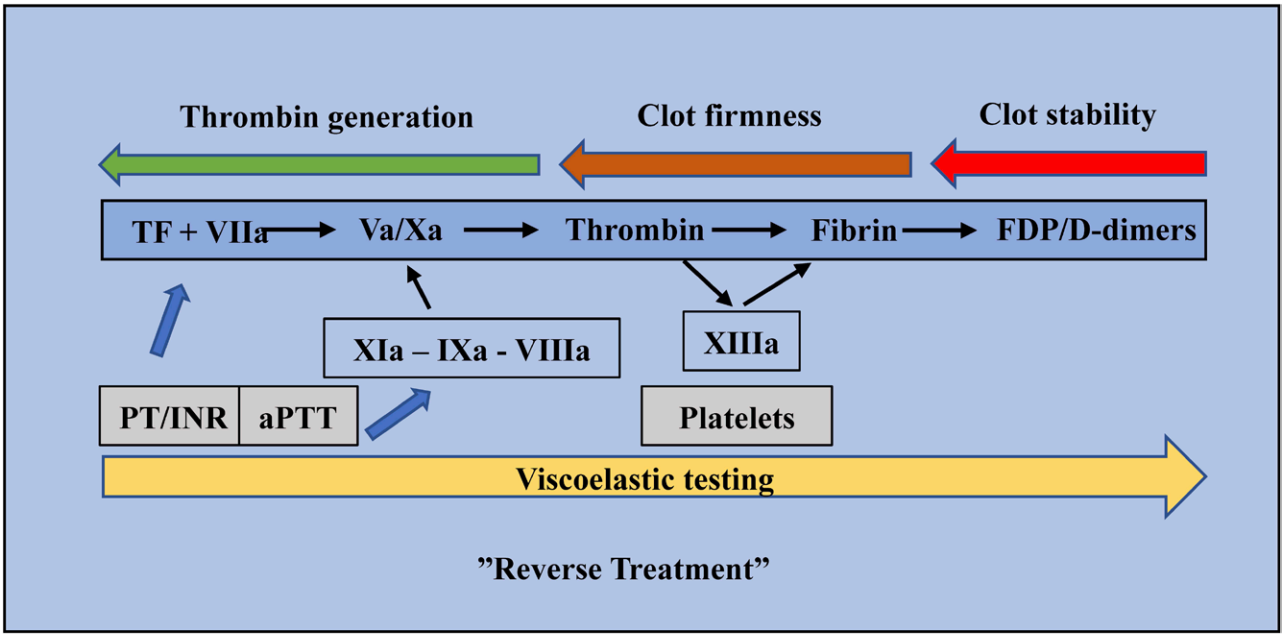
In massive bleeding, the replacement of FXIII, using factor XIII concentrate or cryoprecipitate may improve clot stabilization after antifibrinolytics.[95,96]

Second Step: Clot Firmness

(Supplemental Digital Content, Supplemental Figure 4.2, http://links.lww.com/AA/E583): Fibrinogen and platelets have been considered as the main determinants of clot firmness, as well as FXIII. Fibrinogen plays several key roles in the maintenance of hemostasis. It is the substrate for coagulation. Its transformation to fibrin monomers by thrombin and the subsequent polymerization to a crosslinked fibrin network by FXIII is essential to form a stable clot. Fibrinogen is the first coagulation factor to decline to a critical level of 1.5 to 2 g/L in massive hemorrhage.[97,98] In trauma, low fibrinogen levels are associated with increased transfusion requirements and mortality.[60] Therefore, fibrinogen supplementation should be performed early to improve clot firmness and to reduce transfusion requirements.[99–101]

The trigger for fibrinogen supplementation according to thromboelastometry may vary according to the underlying pathology. While in the cardiac surgery scenario FIBTEM A5 is considered <9 mm, some studies suggest FIBTEM A5 < 7mm in trauma and peripartum hemorrhage, and FIBTEM A5 < 8 mm in liver transplantation.[12,61,62]

Fresh frozen plasma (FFP) contains coagulation factors and inhibitors in a physiologic composition but unpredictable, low concentration.[102] Therefore, even high volumes of FFP (10–15 mL/kg body weight) are insufficient to reverse coagulopathy in bleeding patients.[103–105] This approach is associated with several complications such as TACO, TRALI, and TRIM, multiple-organ dysfunction syndrome (MODS), and nosocomial infection.[106–110] Current



"Reverse treatment": The sequential approach in the opposite direction to clot formation.

Figure 5. Reverse treatment. aPTT indicates activated partial thromboplastin time; FDP, fibrin degradation products; INR, international normalized ratio; PT, prothrombin time; TF, tissue factor.

guidelines recommend using lyophilized fibrinogen concentrate or cryoprecipitate to restore the fibrinogen concentration.[67,69]

Although cryoprecipitate contains a higher concentration of fibrinogen than FFP, it has some common disadvantages with FFP. The fibrinogen concentration is not standardized; transfusion should be compatible with type A, type B, type O, or type AB blood; and cryoprecipitate preparation requires more time for thawing and pooling.[111] In addition, it carries a risk of viral transmission similar to FFP.[112]

In contrast, fibrinogen concentrate is derived from human plasma, pasteurized, lyophilized, and stored at room temperature, and can be reconstituted quickly in low volume and high concentration. Since it does not require blood typing or thawing, it is immediately available for use, with lower risk of allergic reactions since antibodies are removed.[113] Literature data have demonstrated the role of fibrinogen concentrates in acquired hypofibrinogenemia in different settings of severe acute bleeding.[114,115]

Clot firmness can also be impaired by thrombocytopenia and/or severe platelet dysfunction (Supplemental Digital Content, Supplemental Figure 4.3, http://links.lww.com/AA/E583). To identify the latter, PFT may be performed to complement VET. Platelet concentrates should be considered (dose: 0.7 × 10^{11} per 10 kg body weight in adults) in bleeding situations associated with inherited or acquired dysfunction (eg Glanzmann's thrombasthenia or drug effects) or to thrombocytopenia of less than 50 × 10^9 L^{-1}.[63] As an attempt to improve platelet/vWF interaction, desmopressin (DDAVP; dose: 0.3–0.4 µg kg^{-1}) is an option to improve platelet function, for example, in uremic patients. DDAVP induces vWF release, improving platelet adhesion/aggregation, and has been shown to be effective for the treatment of POB.[116]

Platelet activity may be compromised by APAs such as aspirin, P2Y12 inhibitors, and glycoprotein IIb/IIIa inhibitors, other widely used drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, cardiovascular and lipid-lowering drugs, and selective serotonin reuptake inhibitors, as well as trauma, sepsis, and extracorporeal assist devices.[76–80] For further evaluation of platelet function, methods such as multiplate, ROTEM *platelet* or VerifyNow can be used. Considering low platelet counts, PFT should be interpreted with caution to identify a dysfunction correctly in the patient with active bleeding, and to assist in planning for the need for further intervention. Notably, platelet transfusions may cause more harm than benefits in patients with traumatic brain injury (TBI) or intracerebral hemorrhage on APA.[72,117] A meta-analysis published in 2017 evaluated the use of DDAVP for the treatment of platelet dysfunction and reversal of APA in patients undergoing cardiac surgery. Administration of DDAVP (0.3 µg/kg) resulted in a 25% reduction in RBC transfusion, a 23% reduction in blood loss compared to control, and a lower incidence of reoperation due to bleeding.[118] Furthermore, TXA results in improved platelet function in patients treated with APA.[119]

Factor XIII deficiency cannot be measured directly by VETs, but indirectly. In patients who present persistent low clot firmness in FIBTEM after the replacement of fibrinogen, FXIII deficiency could be considered.[48,49,120] Reduced levels of EXTEM and FIBTEM MCF but not high levels of EXTEM ML and APTEM ML are associated with factor XIII deficiency in patients with liver disease.[38]

FXIII is a plasma transglutaminase essential for normal hemostasis in the final stage of the coagulation cascade. It is responsible for crosslinking fibrin fibers and subsequent improvement of the mechanical stability of the fibrin clot as well as its protection against fibrinolysis.[121] In the presence of activatable platelets, FXIII protects the clot from premature degradation by crosslinking α2-antiplasmin to fibrin.[50,122,123] FXIII can be supplemented using cryoprecipitate or factor XIII concentrate. Schlimp et al[124] showed that the combination of fibrinogen concentrate and factor XIII concentrate to be highly effective in raising FIBTEM clot firmness after hemodilution.

Third Step: Thrombin Generation Phase

After taking care of the clot stabilization and firmness, efforts will be aiming at improving thrombin generation – in case of ongoing bleeding.[15,125–127] The impairment in the thrombin generation can be the result of a coagulation factor deficiency, or the effect of anticoagulants, and can be accessed by ROTEM CT (Supplemental Digital Content, Supplemental Figure 4.4, http://links.lww.com/AA/E583).[28] Notably, ROTEM CT results can be prolonged by severe hypofibrinogenemia, too, and can be normalized by fibrinogen administration, only, in most cases.[15,128] Therefore, prolonged CT results should only be considered to trigger FFP or Four-Factor Prothrombin Complex Concentrate (4F-PCC) administration in bleeding patients with normal FIBTEM clot firmness. The supplementation of coagulation factors may improve thrombin generation and can be done by the administration of FFP or 4F-PCC.[69,126,129] 4F-PCC is a human plasma-derived coagulation factor concentrate, produced by ion-exchange chromatography with viral inactivation, and contains vitamin K-dependent coagulation factors and inhibitors: factor II, VII, IX, X as well as AT, protein C, S, Z, and heparin. Its Food and Drug Administration (FDA)-cleared indication is the reversal of the effect of vitamin K- antagonists (VKA), whereas in Europe it is approved for the prophylaxis and therapy of bleeding due to vitamin K-dependent factor deficiencies.[130,131] 4F-PCC has several advantages

over FFP in reversing VKA. It is a virus-inactivated, pasteurized, nanofiltrated, lyophilized powder, standardized to the factor IX activity, with factor activities 25 times higher compared to plasma. It can be reconstituted in small volumes. The reversal occurs within minutes after 4F-PCC administration.[132–134] While FFP must be thawed, even transfusion of large volumes is often inadequate to correct INR.[134,135]

Once heparin (exogenous unfractionated heparin or endogenous heparin-like effects) has been detected by an INTEM/HEPTEM CT-ratio above 1.25 in the presence of acute bleeding, protamine administration may be considered to reverse this effect (Supplemental Digital Content, Supplemental Figure 4.5, http://links.lww.com/AA/E583).[28,136]

Limitations of VET include a low sensitivity to platelet dysfunction.[25] Accordingly, PFT devices such as Multiplate, ROTEM *platelet* or VerifyNow can be used, complementarily. These tests make it possible to differentiate between the effects of different APA. Changes found in these tests may indicate the need for platelet concentrate transfusion, DDAVP, or TXA administration to improve platelet function.[67,69,118,119]

MANAGEMENT OF BLEEDING DUE TO DOACs

In the presence of ongoing bleeding, with normal ROTEM results (Supplemental Digital Content, Supplemental Figure 4.6, http://links.lww.com/AA/E583), normal PFT results, and exclusion of mechanical reasons for bleeding, a residual effect of DOACs should be considered measuring the activities of calibrated Anti-Xa (for Rivaroxaban, Apixaban and Edoxaban), anti-IIa or dTT (for Dabigatran).[27,28,137] Normal PT and aPTT exclude supratherapeutic concentrations of rivaroxaban and edoxaban but might not fully exclude clinically relevant drug concentrations.

On the other hand, in the presence of CT prolongation in EXTEM, this alteration is less pronounced for Apixaban than for rivoroxaban and edoxaban. Therefore, it is critical to measure calibrated anti-Xa activity in addition to ROTEM to detect an elevated apixaban plasma level.

Furthermore, coagulation screening using CCTs might be normal in patients taking apixaban. A normal TT excludes clinically relevant dabigatran concentrations; if the dTT assay is prolonged, a dabigatran effect might be present. ECT can be performed to detect dabigatran. Anti-Xa activity (calibrated for rivaroxaban, apixaban or edoxaban) should be performed to quantify direct factor Xa inhibitors (xabans).[138,139] Once clinically relevant bleeding has been detected, some points should be considered: last ingestion of the drug, chronic disorders like kidney or liver disease. As life-saving measures stopping the anticoagulant effect, hemodynamic support with fluid resuscitation and blood products, mechanical compression, or surgical or radiological intervention to identify and treat the cause of bleeding should be considered. Laboratory screening (CCTs, CBC, liver, and renal function) may help to estimate potential accumulation and the remaining duration of drug effects. If ingestion was within the past 2 hours, oral activated charcoal can be administered. Furthermore, intravenous TXA and specific reversal agents for different DOACs can be administered in life-threatening bleeding.

NONSPECIFIC REVERSAL THERAPIES

Two systematic reviews and meta-analyses demonstrated the efficacy and safety of the off-label use of 4F-PCC in major bleeding associated with xabans. 4F-PCC is considered an option for managing direct FXa-related major bleeding.[140,141] Dager et al[142] reported on the use of activated prothrombin complex concentrate (aPCC) to reverse the anticoagulation effects of DOACs, which appears to be safe and has the potential to restore hemostasis in critical bleeding situations. Both low dose with repeat option and moderate dose, depending on the urgency of the situation, can be an effective management strategy with a positive clinical benefit for major bleeding events of DOACs. aPCC doses of 25 units/kg or less could be a potential strategy for ICH or life-threatening massive bleeding events. Furthermore, dabigatran plasma concentrations can be decreased by hemodialysis and plasma concentrations of xabans by hemoperfusion with Cytosorb filters during cardiopulmonary bypass.[143–147]

SPECIFIC DRUGS FOR REVERSAL OF ANTICOAGULANTS

For dabigatran reversal, a specific antidot is available. Idarucizumab, a humanized antibody fragment that specifically binds dabigatran with high affinity and reverses its effects within minutes. The recommended dose is 5 g, given intravenously when rapid reversal is required in uncontrolled bleeding.[148] For reversal of xabans, Andexanet alfa is available, a recombinant modified human activated factor X protein, recently approved by the FDA, that specifically binds xabans. Andexanet alfa is indicated for reversal of either rivaroxaban or apixaban due to life-threatening bleeding.[149] However, thromboembolic events have been identified and considered to be of high frequency with Andexanet alfa.[150] Another potential disadvantage might be the need for a continuous infusion of the drug and very high costs.

CONCLUSIONS

Understanding the concept of the cell-based model of hemostasis, as well as the pathophysiology of specific

coagulopathies, allows for a better approach to bleeding management in critically ill patients. The dynamic and structured performance of the step-by-step approach for EGDHT using VET to guide hemostatic drugs and coagulation factor concentrates administration are key for the successful control of severe acute bleeding in the ICU. Patients' outcome will be determined by the diagnostic performance of POCT to differentiate between surgical and coagulopathic bleeding, the precision in differentiation between different coagulopathies guiding hemostatic therapy, the avoidance of inappropriate blood transfusion, and subsequent transfusion-related complications and costs.

DISCLOSURES

Name: Tomaz Crochemore, MD.
Contribution: This author helped perform this study through the literature review, the creation of the concept of "early goal-directed hemostatic therapy" and the proposal of "The 10 steps" for the bleeding management; creating figures and tables; writing and revising the article; and approving the final version.
Conflicts of Interest: T. Crochemore has worked as a medical manager of Werfen Latin America since 2022.
Name: Klaus Görlinger, MD.
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Conflicts of Interest: K. Görlinger has worked as the medical director of TEM Innovations since 2012.
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