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Coagulation disturbances during major perioperative or traumatic bleeding

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1. Introduction

The coagulation system balances between bleeding and thrombosis through a highly regulated system of pro- and anticoagulant proteins and cells. During a bleeding situation, this very delicate balance is easily interfered with, and haemostatic abnormalities are common in patients with major bleeding, leading to a further increase in blood loss. Depletion, consumption and dilution of clotting factors and thrombocytes may cause a significant reduction in the haemostatic potential of the bleeding patient. Activation of the coagulation system, acidosis, hypothermia and excessive fibrinolysis in addition to iatrogenic measures such as fluid therapy can further deteriorate haemostasis. Inherited coagulation disorders and pre-existing treatment with anticoagulant medication can further aggravate the clinical management of these patients. As a consequence, all these changes can lead to isolated or various combinations of hyperfibrinolysis, lack of sufficient thrombin generation, inappropriate clot strength and altered platelet function.

Results from more recent epidemiologic studies and analyses from registry databases are consistently reporting that coagulopathy is present in approximately one-third of trauma patients upon arrival. Notably, it has been demonstrated that mortality is much higher in patients arriving with a coagulopathy defined as an abnormal prothrombin time (PT) and activated partial thromboplastin time (APTT), even when controlling for known prognostic factors such as injury severity score and head injury [1–3]. Additionally, in non-trauma patients, coagulopathy defined as INR $\geq$1.5 and/or platelet count $\leq$50 ^{x10} in cirrhotic patients were associated with bleeding after invasive procedures [4]. Many studies on coagulopathy during bleeding have focused on one pathology. Shenkman et al. evaluated the role of different coagulopathy constituents, such as dilution, fibrinolysis, acidosis and hypothermia, on clot formation and platelet function. In conclusion, the researchers found a differential effect on haemostasis and that one factor may influence the other [5].

Timely and adequate management of bleeding-associated coagulopathy calls for a thorough understanding of all the previously mentioned interactions and influencing factors. This review article summaries the key issues and pathophysiological changes that affect the haemostatic system in patients with major bleeding.

2. Acidosis

Trauma-induced or associated coagulopathy (TIC) is an important predictor of death in trauma patients; TIC was interpreted in the past in a very simplified manner as a combination of depletion, consumption and dilution of procoagulant factors. However, one of the main contributors to trauma-induced or associated coagulopathy is acidosis, which is part of the deadly triad (acidosis, hypothermia and coagulopathy) [6].

The detrimental effects of acidosis on coagulation include impaired enzyme activity and the depletion of fibrinogen and platelets, thus leading to a prolonged clotting time in the point-of-care devices and increased aPTT and PT values. For a few years, a further mechanism of acidosis-associated or induced coagulopathy has been reported. In cases of hypovolaemia and shock with accompanying acidosis, thrombomodulin expression is increased, resulting in the activation of Protein C (APC). It has profound anticoagulant effects, such as cleavage of Factor V and VIII, inactivation of Factor V and VIII and inhibition of Plasminogen Activator Inhibitor [7,8]. In a recently published study, tissue hypoperfusion and APC levels were shown to be strongly related to the presence of

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coagulopathy [9]. Furthermore, Cohen et al. observed in a study of 203 trauma patients that an increase in the APC levels at admission to the emergency department is associated with increased mortality, allogenic transfusion requirements, and the presence and extent of multi-organ failure and infections. The data by Cohen showed that coagulopathy occurred immediately after injury as a consequence of shock and acidosis and not delayed as a result of fluid administration/dilution since the transport time to the hospital was short and the amount of fluids administered was small [8].

In this context, the actual recommended strategy for permissive hypotension and the proposed strategy of the general avoidance of fluid or volume therapy to prevent from dilutional coagulopathy and thus prevent further blood loss because of elevated blood pressure may be misleading. The application of permissive hypotension should not tolerate shock-related acidosis. In fact, the prehospital administration of fluid has been shown to be associated with decreased hospital mortality but not with increased systolic blood pressure [10]. The avoidance of unnecessary dilution and high blood pressure should not be in conflict with an appropriate volume and pain management to stabilize the patient condition.

Avoidance and treatment of shock is also a serious part of "coagulation management" in TIC.

3. Hypothermia

Hypothermia is also part of the lethal triad and is associated with a worsened outcome in severely injured patients and known to contribute to the presence of TIC [7]. This is of particular importance as a body core temperature of $\leq$34 °C is commonly observed in severely injured patients. Notably, isolated hypothermia below 33 °C is associated with a 23% mortality rate, whereas trauma-induced hypothermia below 32 °C has been shown to result in a 100% mortality rate.

Prolonged PT and aPTT is a frequent finding in hypothermic trauma patients. A body core temperature of below 34 °C is judged to be the critical point at which coagulation factor enzyme activity is significantly slowed and at which a significant alteration in platelet activity is to be expected [11]. In mild hypothermia (35 °C–32 °C), bleeding results primarily from a platelet adhesion defect, whereas this condition does not seem to influence the clotting onset. The in vivo effects of temperature on thrombin generation kinetics were investigated in a swine model. Hypothermia at 32 °C primarily inhibited the initiation phase of thrombin generation, involving the formation of the factor VIIa/tissue factor complex, while the propagation phase was not affected [12]. At temperatures <33 °C, reduced platelet function and weakened enzyme activity contribute to coagulopathy. Hypothermia at 32 °C also decreases fibrinogen synthesis by 50% but shows no effects on fibrinogen degradation. Fibrinogen synthesis and degradation are regulated via different mechanisms, and in general, there is a potential deficit in fibrinogen availability after hypothermia [13].

4. Dilutional coagulopathy (crystalloids, colloids)

The question of the optimal volume replacement fluid for compensating intravascular blood loss is still subject to ongoing controversy. Because of conflicting results, particularly in critically ill patients, there are major concerns with the use of synthetic colloids in trauma or acute bleeding, although there is no new evidence for these doubts. The current European trauma guideline recommends fluid resuscitation as first-line therapy with balanced electrolyte solutions, the avoidance of saline and hypotonic solutions such as Ringer's lactate but also approves the use of colloids with restrictions because of adverse effects on coagulation [14]. The most recent meta-analysis comparing colloids and crystalloids failed to demonstrate any positive effect of colloids in critically ill or elective surgical patients [15]. Nevertheless, it seems questionable to draw any conclusions from these studies, which were performed under different conditions compared to the setting of acute hypovolemic trauma management. It should be noted that published meta-analyses involve US American studies and thus employ dextrans and hetastarches (high molecular hydroxyethyl starch preparations with a high substitution degree), which have not been used for a long time in Central Europe and most Asian countries because of their high potential for side effects, particularly involving the coagulation system [16]. As such, it needs to be carefully reconsidered if these results can be applied to the European market.

Fluid resuscitation in haemorrhagic shock is almost always associated with dilutional coagulopathy. However, the degree of severity of the dilutional coagulopathy depends on the amount and type of resuscitation fluid [17]. Crystalloids are not very effective in restoring intravascular blood loss, which is shifted by more than 80% into the interstitium, thus causing edema and impairing microcirculation [18]. In contrast to colloid solutions, crystalloids interfere with the coagulation system primarily by means of their dilutional effect. Gelatine solutions are available in most European and Asian countries. From clinical aspects, modified succinylated gelatine solutions have the same volume effect as starches or albumin. In addition to their dilutional effect, gelatine preparations also exert some specific effects on the coagulation system. Above all, they impair fibrin polymerization and disturb the network of the fibrin monomers.

Since 2013 the use of Hydroxyethyl starch (HES) solutions has been restricted and not allowed anymore in critically ill patients, in patients with burn injury, in patients with kidney injury and not for longer than 24 h. However, the critical illness was never defined. Furthermore, since 2018 the EMEA requires product training for the administration of HES solutions because a drug utility study detected a high non-adherence of the correct use of HES. It should be mentioned that the questionnaire used in that study had severe problems. Nevertheless, in critically ill patients, Perner et al. showed an increased mortality in patients who received hydroxyethylstarches in contrast to crystalloids, this study had also several methodological flaws [19]. Annane et al. detected conflicting results [20]. Within the CRISTAL study, patients who received colloids showed an improved 90 day survival. Summarizing the findings of the actual clinical studies, the answer of the optimal fluid for volume resuscitation in septic critical ill patients remains unclear. Nevertheless, it should be kept in mind that crystalloids are not very effective to restore intravascular blood loss while it disappears into the interstitium and cause edema, which decreases microcirculation. In terms of coagulation and bleeding. Additionally, (HES) is associated with an increased tendency to bleed, kidney injury and accumulation in the RES with unknown effects on the immune system, especially when using solutions with a high molecular weight and a high replacement degree. HES solutions cause a von Willebrand type 1-like syndrome characterized by diminished FVIII activity and diminished vWF plasma levels. In addition, HES also impairs fibrin polymerization to an even higher degree than gelatine [21].

In critically ill patients as well as in patients exhibiting severe haemorrhagic shock and needing intravascular volume replacement, the use of gelatine solutions may be employed as a possible alternative because of fewer side effects involving coagulation system/fibrinogen polymerization, less accumulation in the RES, fewer effects on kidney function and the lack of missing dose limitations compared to starch solutions [22].

A prospective controlled randomized double-blinded study compared the effect of saline with 130/0.4 HES in severely injured patients with blunt or penetrating trauma. The authors noted that patients who received HES showed improved microcirculation and organ perfusion, resulting in increased lactate clearance. In addition, the incidence of acute renal failure was reduced in patients with penetrating injuries receiving HES compared to saline [23]. In a matched case control study of trauma patients who received ≥ four red blood cell concentrates during damage-control surgery, the administration of crystalloids was associated with increased mortality, whereas the use of low volumes of colloids was associated with increased survival [24].

In summary, crystalloids are not effective in volume replacement following major blood loss or as a treatment option for severe intravascular volume depletion. Administration of large amounts of crystalloids causes edema, which may decrease microcirculation. On the other hand, the use of colloids is associated with adverse effects on haemostasis, especially on fibrinogen polymerization [25]. In a pig model of uncontrolled haemorrhagic shock, the combination of colloid with fibrinogen concentrate was superior to fluid resuscitation solely or no fluid resuscitation [26]. It is of great importance that gelatine-induced fibrin polymerization disorder can be successfully compensated by the substitution of fibrinogen, while this treatment is not effective following HES-induced coagulopathy [27].

5. Hyperfibrinolysis

Fibrinolysis encompasses a complex self-regulating system that is activated in parallel to the coagulation process, with the ultimate goal of generating plasmin and breaking down fibrin clots [28]. Fibrinolysis is inhibited by plasminogen activator inhibitor 1 (PAI-1), by α-2-plasmin inhibitor (α_2-PI), and by thrombin activatable fibrinolysis inhibitor (TAFI), resulting in limited fibrin digestion. Under physiological conditions, the fibrinolytic system is well balanced with the coagulation cascade; however, many clinical conditions can trigger a qualitative or quantitative abnormality of proteins involved in the fibrinolytic process (primary hyperfibrinolysis) or an imbalance between pro- and anticoagulant pathways (secondary hyperfibrinolysis) [29].

Excessive clot breakdown (hyperfibrinolysis), as observed in trauma patients, is associated with exacerbation of bleeding, massively increased mortality, and multi-organ failure [30]. Hyperfibrinolysis is a contributing factor for the development of acute traumatic coagulopathy and accounts for up to 40% of deaths following major trauma [31]. Current understanding of the mechanisms responsible for the development of hyperfibrinolysis encompasses a hypoxia-driven release of t-PA from endothelial cells as well as the activation of protein C promoted by thrombin-thrombomodulin complexes that are built detached from damaged endothelium, eventually neutralizing PAI-1 [28,32]. A recent review by Gando et al. included 17 clinical trials and showed no relationship between activated protein C and increased fibrinolysis. Thus, the clinical consequences of ATC have not yet been clarified [33]. The occurrence of hyperfibrinolysis is not exclusively linked to trauma patients but can also be observed in many other settings, such as liver transplantation [34], cardiopulmonary bypass surgery [35], and post-partum haemorrhage [36].

The complexity of the fibrinolytic system calls for a global whole blood assay to show a complete picture of the haemostatic process to detect abnormalities [28]. The euglobulin clot lysis test (ECLT) is a validated assay for in vivo fibrinolysis, but it is performed on diluted platelet poor plasma, has a prolonged assay time and, as such, has little clinical utility for its use in acutely bleeding patients [36]. Viscoelastic techniques may be advantageous for detecting hyperfibrinolysis as they are measured in whole blood and generate rapid results [37,38]. However, both those tools appear to be relatively insensitive for detecting a lower degree of fibrinolytic activation. Hyperfibrinolysis can be defined by thrombelastography (TEG) as a reduction of the amplitude ≥ 3%, 30 min after the maximum amplitude (Lysis Index; LY30), or by rotational thromboelastometry (ROTEM) as reduction of maximum clot firmness > 15% at 60 min (Maximum Lysis; ML) [39]. Depending on the severity and onset of hyperfibrinolysis, it is described as fulminant, intermediate, or late lysis [40].

Unlike the occurrence of hyperfibrinolysis-induced excessive bleeding following major trauma, recently published concepts have demonstrated a state of fibrinolytic shutdown, resulting in fibrin deposition, lung injury and systemic coagulation, which represents a distinct entity within the spectrum of severely injured patients [41]. Fibrinolytic shutdown is presently defined by LY30 < 0.8% using TEG [14] or ML < 3.5% using ROTEM [41]. Both hyperfibrinolysis and fibrinolytic shutdown are associated with high mortality of up to 34% [30]. However, this concept was recently challenged as no increase in mortality, massive transfusion or thrombotic events if fibrinolytic shutdown was detected among 550 trauma patients [42]. Authors of that study have suggested that fibrinolytic shutdown is a physiologic response to life-threatening trauma. This discrepancy may be explained by the different sensitivity of TEG and ROTEM in detecting hyperfibrinolysis and by marked differences in the methodology of published data (e.g., inclusion of patients pre-treated with an antifibrinolytic, assessment of other laboratory parameters for the characterization of hyperfibrinolysis, and timing of first blood withdrawal). As such, further studies are urgently needed to interpret findings of decreased clot degradation.

The treatment of hyperfibrinolysis using an antifibrinolytic drug is undeniably evidence-based. Tranexamic acid (TXA) is a lysine analogue that prevents the interaction between plasmin(ogen) and fibrin. TXA can effectively lower mortality in adult and paediatric trauma patients [43–45], reduce bleeding and mortality in women suffering from post-partum haemorrhage [46,47], and reduce bleeding/transfusion requirements during and after major/cardiac surgery [48–50]. A variety of dose regimens exists. A recent systematic review of pharmacodynamics studies revealed that TXA concentrations of 10–15 mg/l caused substantial inhibition of fibrinolysis [51]. Among a cohort of 73 trauma patients all receiving pre-hospital 1000 mg TXA had TXA concentrations at mean 28.7 mg/l, (SD; 21.5–38.5) upon hospital arrival, with 21% of the patients below 20 mg/l, indicating that re-dosing is mandatory to achieve decent plasma concentrations [52]. A pooled analysis does not report an increased risk of thromboembolic events, leaving an increased risk of seizures as the main side effect [48]. TXA is effective not only in treating hyperfibrinolysis but also in achieving clinically relevant clot stabilization. This is another excellent feature of TXA, as it can be administered preemptively before procedures with a high likelihood of bleeding, thereby demonstrating significantly reduced perioperative bleeding and transfusion requirements [53].

One thing has proven to be crucial: the timing of TXA administration. Analysis of results from trauma patients has shown that the survival benefit is greatest when TXA is administered within the first hour after trauma, while delayed administration beyond 3 h after trauma is linked to a negative effect on outcome [43]. Similar but not significant findings were observed in a large trial for the treatment of post-partum haemorrhage [46]. This finding leads to the assumption that the presence and severity of (hyper)fibrinolysis is likely to undergo marked temporal changes and can be further affected by contributing factors such as dilution, acidosis, or the presence of shock. Despite these temporal changes and the

given inaccuracy of available assays to detect all stages of hyperfibrinolysis, there is published data to support the empiric administration of TXA in suspected traumatic haemorrhage [43] and in the prevention and treatment of perioperative bleeding [53]. In addition, it needs to be mentioned that the too liberal usage of TXA especially in non-severely bleeding may increase the preventable risk for thromboembolic complications. In summary, more evidence is urgently needed before strong recommendations can be made.

6. Massive transfusion induced coagulopathy

Massive transfusion of red blood cell concentrates (RBCs) can lead to dilutional coagulopathy due to a lack of platelets and coagulation factors. RBCs contain small amounts of citrate, while the concentration is much higher in fresh frozen plasma (FFP) and platelet concentrates. As citrate binds calcium patients who receive many transfusions and/or have a reduced capability of hepatic clearance (i.e., hypotension/hypovolaemia), hypocalcaemia may reach significant levels that require substitution therapy. Approximately 55% of total calcium is protein bound while the remaining 45% is free ionized and physiological important for the timely formation and stabilization of fibrin polymerization sites as well as platelet aggregation. The acid load from RBC transfusion can be significant as the pH levels of RBCs range from 6.3 to 7.0, depending on the storage time. All products, especially RBCs, stored at 4 °C may result in hypothermia-related coagulopathy. Hypothermia itself reduces the enzymatic processes of coagulation and further reduces the metabolism of citrate and lactate [54]. To counteract the negative effect of blood product transfusion on the coagulation profile, a balanced approach has been increasingly used. The rationale behind this approach would be to mix RBCs, FFP and single-donor-platelets in a 1:1:1 model mimicking the content of whole blood. However, reconstituting whole blood in a 1:1:1 ratio still causes significantly lower coagulation factor, platelet and haemoglobin and fibrinogen levels, resulting in decreased thrombin generation and prolonged standard laboratory tests compared with native whole blood [55]. This may be explained by dilution due to the presence of anticoagulants in transfusion bags, lactate production during storage, loss of coagulation factor activity due to the freezing-thawing process and storage-induced loss of functional platelet function [56].

7. Endotheliopathy

Endothelial cells line the inside of every blood vessel in the body and are an important part in balancing haemostasis and homeostasis between the circulating blood and the extravascular space. The luminal part is covered by the endothelial glycocalyx (thickness of 0.2–2 μm). Following trauma and bleeding, a number of prospective studies consistently report endothelial damage, with glycocalyx shedding and endothelial cell injury estimated to occur at approximately 5 and 8 min after injury, respectively [57,58]. However, in most studies, syndecan-1, thrombomodulin, and sE-selectin are used as surrogate markers for endothelium cell damage and glycocalyx shedding. Although the findings are closely correlated with increased mortality, the exact mechanism and therapeutic options remain unclear, as evidenced by the observations that a number of clinical pathological processes, i.e., sepsis and ischaemia-reperfusion conditions, change the functional composition of the glycocalyx layer [59]. As proposed by Johansson et al., the initial driver of endotheliopathy seems to be shock and high levels of circulating catecholamines [60]. A possible clinical consequence is autoheparinisation, in which heparan sulfate, a prominent glycosaminoglycan, is released into the circulation and can lead to systemic anticoagulation. Among a trauma population, Ostrowski et al. found acute endogenous coagulopathy with autoheparinisation as evaluated by TEG in approximately 5% [61]. Recently, very different treatment options, such as plasma, albumin, and hydrocortisone, have proven effective at restoring a biomarker-damaged endothelium [62]. A recent study by Pati et al. found in a mice model that prothrombin complex concentrate and FFP, but not albumin, vascular permeability [63]. Nevertheless, none of these strategies so far have shown beneficial results in any outcome-related parameter. The avoidance of shock and timely treatment are areas of future interest as endothelium damage and glycocalyx shedding can stimulate thrombin formation and activation of protein C pathway/hyperfibrinolysis and interrupt fluid homeostasis [64].

8. Pre-existing coagulopathies

Congenital deficiencies of coagulation factors are rare but can cause lifelong bleeding disorders, including significant challenges during surgery. The prevalence of haemophilia (A and B) is 1:12.000 and 0.1%–1% of the general population suffering from von Willebrand disease, although the prevalence of symptomatic vWD requiring treatment is much lower. The estimated prevalence of the remaining rare coagulation disorders is 1:500.000 to 1:2 million, with FVII and FXI being the most prevalent (38% and 22%, respectively), followed by fibrinogen (8%), FX (8%) and FXIII (7%) [65]. For most deficiencies, there is a close relationship between the severity of bleeding complications and residual factor activity, with the strongest association for fibrinogen, FV, FX, FXIII and combined FV + FVII. In haemophilia patients, FVIII and FIX levels <1 U/dL are associated with spontaneous bleeding, whereas factor levels above 5% remain largely asymptomatic. VWD patients with VWF levels <20 U/dL are likely to have bleeding problems [66].

PT and APTT, together with the Clauss assay for fibrinogen activity, are the most widely used screening tools. The distinction between low levels and qualitative deficiency is important in some cases, i.e., dysfibrinogenaemia/vWD, and may require antigen or other specific measurements.

In general, laboratory tests such as PT and APTT fail to predict bleeding problems. In a systematic review by Liontos et al., 54 studies were included to test if unselected preoperative PT and aPTT could predict bleeding outcomes. Only 5 showed an association between coagulation test results and perioperative bleeding [67]. The most reliable method to predict peri-operative bleeding is the use of a clinical questionnaire whereby a number of detailed bleeding scores are available to identify i.e., VWD. However, even simple questions such as family history of bleeding and history of profuse bleeding from simple wounds increase the likelihood of a bleeding disorder [68]. Commercially coagulation factor concentrates are available for the treatment of VWD, FI, FII, FVII, FVIII, FXI, FX and FXIII deficiency. The specific dose is dependent on residual activity and the surgical procedure. Only FV concentrate is not available; thus, plasma transfusion or even total plasma exchange represents the main therapy. For vWD patients, desmopressin is indicated in mild cases of type 1 and 2A, whereas VWF/FVIII concentrates are indicated in more severe cases or some types [69].

9. Thrombocytopathia/penia

Platelet count and function are key elements in haemostasis, as many steps in clot formation occur on the surface of activated platelets. In addition, platelets are involved in inflammatory and immune responses and can contribute to organ damage, such as acute kidney or lung injury [70]. In theory, any change in platelet count or function can lead to substantial changes in physiology.

Thrombocytopenia is not a rare event; in critically ill patients, the incidence is reported to be 35–40% [71]. If dilutional coagulopathy occurs during bleeding, the platelet count is usually maintained much longer than the levels of other coagulation factors because of compensating release of platelets from the spleen, lungs and bone marrow [72].

Results from a large observational trial have shown that only a mild decrease in the preoperative platelet count of 100-150 $\times 10^9\,L^{-1}$ is associated with a higher 30-day mortality and a higher likelihood of being transfused [73]. Unfortunately, in that study, the analysis did not include information on platelet transfusion; therefore, no conclusive association between platelet transfusion and worse outcome can be made. In addition, there is no proven linearity between platelet count and bleeding risk, as platelet function or other patient-specific factors may be able to compensate for a low platelet count [74]. In a trial including 1077 adult haematology/oncology patients, platelet counts ranging from 6 to 80 $\times 10^9\,L^{-1}$ did not show any differences in attributable risk of spontaneous bleeding [75].

Based on current clinical practice guidelines, prophylactic platelet transfusion is recommended in adult patients if the platelet count is $\leq 10 \times 10^9\,L^{-1}$ [76]. In the perioperative setting, platelet transfusion is suggested in a bleeding patient if the platelet count is $\leq 50 \times 10^9\,L^{-1}$ or if there is bleeding related to the antiplatelet drug effect [77]. However, this suggestion is challenged by a recently published trial showing an increased risk of further bleeding or occurrence of infections if patients suffering from antiplatelet drug-related intracerebral haemorrhage received platelet transfusion [78]. Platelet transfusion can cause febrile transfusion reactions, allergic reactions, infectious risk, immunomodulation and alloimmunization and contribute to volume overload. Summarizing recent guidelines, any indication for platelet transfusion should be based on clinical judgement, rather than following a sole specific platelet count threshold [76]. It seems wise to re-emphasise that platelet count does not equal platelet function. The use of platelet function testing may help to identify patients in need for platelet transfusion, but no clear recommendations for a timely, reliable platelet function test are published. The use of viscoelastic testing is not reliable to detect platelet dysfunction for antiplatelet agents.

In the current state, platelets are stored with agitation at room temperature for a maximum of 7 days, and as a consequence, platelet transfusion is associated with the highest risk of bacterial contamination of all blood products. Cold-stored platelets (stored at 2–6 °C without agitation) or even delayed-stored cold platelets (stored at 2–6 °C after 4 days of storage at room temperature) may offer viable options to preserve the haemostatic function of platelets and to maximize storage time but are not yet legally approved [79–81]. Strategies to improve primary haemostasis with antifibrinolytic agents (clot stabilization), desmopressin (release of large von Willebrand factor multimers), and the use of thrombopoietin receptor agonists (boost in platelet production by megakaryocytes) exists and may hold the potential to avoid or reduce platelet transfusion [74].

The platelet count decreases during bleeding due to consumption and dilution, which can be easily detected. Measurement of platelet function is most often not a standard procedure during bleeding, although it can be seriously affected. Solomon et al. evaluated 163 trauma patients and found that the platelet function was significantly reduced in non-survivors compared to survivors, and up to 10% in both groups had a platelet function below the reference range [82].

In contrast to the more common observation of thrombocytopenia in the perioperative setting, the number of patients treated with an antiplatelet drug or with drugs affecting platelet function are increasing [83]. For the work-up of patients with a suggested platelet disorder or thrombocytopenia, a thorough medical and bleeding history should be obtained, and an artefactual thrombocytopenia should be ruled out [73]. The next steps may encompass an assessment of heparin-induced or associated thrombocytopenia and assessment of immune or non-immune aetiologies (e.g., immune thrombocytopenia, drug-induced platelet destruction, sepsis, dilutional coagulopathy, spleen or liver disease, etc.) [84]. Numerous tools and techniques are available to detect acquired or drug-induced platelet disorders [85]; therefore, a pragmatic strategy for the reversal of patient bleeding due to antiplatelet drugs [86] should be prepared based on local conditions and personal resources.

10. Conclusion

The present review points towards the many different aspects affecting the coagulation system during a clinical scenario with massive bleeding. Table 1 illustrates how the different parameters affects the coagulation system, although most of these influences are dose depended. The development of coagulopathy during major blood loss can significantly reduce the likelihood of proper haemostasis during and after surgery and worsen the outcome of the patient [3]. Coagulation management of perioperative and traumatic bleeding is quite similar although the some differences appear. Traumatic bleeding can be challenged by significant hyperfibrinolysis driven by hypoperfusion and release of fibrinolytic substances in addition of massive tissue damage and coagulation activation.

Table 1
Principle changes in parameters of coagulopathy and contribution to haemostatic dysfunction. NA: Not applicable.

	Thrombin generation	Clot Strength	Platelet function
Acidosis	↓	→	↓
Hypothermia	↓	→	↓
Hypofibrinogenaemia	→	↓↓	→
Hyperfibrinolysis	→	↓↓	→
Haemodilution	→ (↑)	↓↓↓	↓
Endotheliopathy	NA	NA	NA
Massive transfusion	↓	↓↓↓	↓

Often, the first coagulation factor to reach critical levels is fibrinogen, even before significant thrombocytopenia or lack of other coagulation factors appears. The explanations include consumption due to active bleeding, hyperfibrino- and fibrinogenolysis, colloid fluid expanders and acidosis, and fibrinogen supplementation holds the potential to reduce blood loss [87]. Point-of-care monitoring is a crucial part of haemostatic optimizing, which helps to differentiate between platelet, thrombin generation or fibrinogen deficiency as well as verify present hyperfibrinolysis.

An increasing proportion of patients are receiving anticoagulants such as platelet inhibitors, such as vitamin K antagonists, FX or direct thrombin inhibitors. These drugs may further challenge the management of the bleeding patient significantly, especially in situations where acute surgery is needed or there is ongoing traumatic or spontaneous bleeding. The present review also highlights the importance of the critical use of the transfusion 1:1:1 approach. Reconstituted whole blood remains anaemic, thrombocytopenic and coagulopathic due to dilution from anticoagulants and manufacturing and cooling processes. Again, this issue points towards the importance of point-of-care monitoring.

A majority of the influencing factors can be properly avoided or treated in order to ensure a proper basis for sufficient haemostasis. In conclusion, prophylactic and definitive haemostatic precautions are important to ensure a proper haemostatic capacity in bleeding patients. These precautions include the avoidance and treatment of acidosis and hypothermia. Optimizing fluid therapy not only to prevent shock but also to avoid dilutional coagulopathy involves the administration of tranexamic acid within a specific time limit, monitoring with thromboelastometry/graphy, and targeted treatment with coagulation factor concentrates.

Declaration of interest

CFE: Received speaker honoraria and/or research support from CSL Behring TEM International and LFB.

TH: Received travel support and lecturer's fee from Octapharma and Instrumentation Laboratory and is a consultant for Octapharma.

DF: Received study funding and honouraria for consultancy and board activity from BBraun, CSL Behring, LFB, Mitsubishi Pharma and IL.

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