# Point of care and factor concentrate-based coagulation algorithms

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# Point of Care and Factor Concentrate-Based Coagulation Algorithms

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## Summary

In the last years it has become evident that the use of blood products should be reduced whenever possible. There is increasing evidence regarding serious adverse events, including higher mortality and morbidity, related to transfusions. The use of point of care (POC) devices integrated in algorithms is one of the important mechanisms to limit blood product exposure. Any type of algorithm, especially the POC-based ones, allows goal-directed transfusions of blood products and even better targeted factor concentrate substitutions. Different types of algorithms in different surgical settings (cardiac surgery, trauma, liver surgery etc.) have been established with growing interest in their use as they offer objective therapy for management and reduction of blood product use. The use of POC devices with evidence-based algorithms is important in the bleeding patient independent of its origin (traumatic vs. surgical). The use of factor concentrates compared to the classical blood products can be cost-saving, beneficial for the patient, and in agreement with the WHO-requested standard of care. The empiric and uncontrolled use of blood products such as fresh frozen plasma, red blood cells, and platelets without POC monitoring should no longer be followed with regard to actual evidence in literature. Furthermore, the use of factor concentrates may provide better outcomes and potential for cost saving.

## Introduction

Uncontrolled bleeding in trauma or major surgery (e.g. cardiac, liver, orthopedic) leads to a loss of coagulation factors and bears an additional risk for further dilution of coagulation factors by volume replacement. Dilutional coagulopathy impairs coagulation and, if not recognized and promptly and adequately treated by rapid hemostatic interventions, will lead to exsanguination. In 2010 the World Health Organization (WHO) recommended to start using transfusion alternatives and to develop individualized patient blood management programs to reduce transfusion requirements. The patient blood management program consists of three main considerations for management: i) detection and treatment of preoperative anemia, ii) reduction in perioperative RBC loss, and iii) optimizing the patient-specific physiological reserve of anemia (including restrictive hemoglobin transfusion triggers) [1–5].

The purpose of this review is to review the optimal bleeding management by using point of care (POC) devices and transfusion algorithms. This aspect is of major importance as adverse outcome related to blood products (red blood cells (RBCs), fresh frozen plasma (FFP), and platelets) has been proven. The costs can be significantly reduced by lowering blood product administration which may also have the potential to decrease length of hospital stay and to prevent serious adverse events such as infections. Although standard laboratory coagulation tests are widely used to determine coagulopathy in the operating room and for trauma patients in the emergency department, their diagnostic value in the acutely bleeding patient is limited based on turnaround time. Moreover, they have limited predictive value for bleeding and were not developed for the use in actively bleeding patients [6].

The use of POC devices includes whole blood assays such as rotational thromboelastometry or thromboelastography, platelet mapping or platelet aggregometry, and international normalized ratio (INR) / prothrombin time (PT) that will be briefly highlighted in this review [7–9].

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**Table 1.** Differences in terms between ROTEM and TEG from Theusinger et al., 2013 [65]

| Parameter | ROTEM | TEG |
|---|---|---|
| Clot time period to 2 mm amplitude | clotting time (CT) | retraction time (R) |
| Clot kinetics period from 2 to 20 mm amplitude | clot formation time (CFT) | kinetics (K) |
| α-angle | slope of tangent at 2 mm amplitude (α) | slope between R and K (α) |
| Maximum clot strength | maximum clot firmness (MCF) | maximum amplitude (MA) |
| Clot elasticity | maximum clot elasticity (MCE) | G |
| Lysis at certain points of time | amplitude reduction after 30 or 60 min after MCF (CL30, CL60) | amplitude reduction after 30 or 60 min after MA (Ly30, Ly60) |
| Clot lysis | maximum lysis (ML) | estimated percent lysis (EPL) |

## Point of Care Testing

*PT POC Testing – e.g. CoaguChek®*

Besides the CoaguChek® (Roche Diagnostics, Mannheim, Germany), there are various other INR POC devices on the market but because of its use in our institution we stuck to this one. CoaguChek measures the INR and Quick value (In many countries, blood coagulability is expressed in a unit named Quick value. The measured PT is expressed in relation to the coagulation time of a healthy person. The value obtained is the 'percentage of the standard value'. In a person not receiving oral anticoagulation the 'normal' Quick value is between 70 and 100%, but might be different depending on the reagent used according to the calibration against the WHO 'standard') in whole blood within 1 min after the addition of 8 µl of blood to the device. These two values are calculated back by the device from a programmed calibrator result. Normally, these results would take 30 to 60 min to be available from the standard laboratory and are obtained by using citrated cell-free plasma. The PT represents the coagulation time in a system that was 'extrinsically' activated via factors VII, V and X and the activation of prothrombin to thrombin, which converts fibrinogen to fibrin. This device is ideal to monitor patients taking vitamin K antagonists (e.g. warfarin) in the emergency department, in cardiovascular surgery, in acutely bleeding patients, or in patients with traumatic brain injury; the test can be used for rapid diagnosis and therapy with factor concentrates to rapidly reverse the anticoagulation. The device is also validated to guide outpatient oral anticoagulation (vitamin K antagonists). In the perioperative setting and the emergency department, however, evidence supporting its use is limited to case series. In 17 patients needing emergency surgery (burr hole, craniotomy, or laminectomy), the anticoagulation was assessed and reversed before the intervention using this assay. The measurements on the CoaguChek correlated well with the laboratory values, and the mean time gained using the POC assay was 47 min [10]. In other settings like war casualties the time gained using this assay was approximately 26 min compared to the laboratory [11]. In ischemic strokes, time to lysis and detection of oral anticoagulants was reduced [12], and in patients after cardiopulmonary bypass PT was determined much earlier than by the laboratory by using this type of POC device [13].

*Clot Formation in Whole Blood Thromboelastography and Rotational Thromboelastometry*

The preliminary and most important statement regarding the use of these devices is that, regardless of which results are obtained – even if they are pathological –, a non-bleeding patient needs no therapeutic intervention. All standard coagulation tests in the laboratory are measured in plasma and assess usually extrinsic and an intrinsic pathways using PT and partial thromboplastin time, respectively. Only the clotting time is measured, giving no information about the following development or stability of the blood clot.

In 1948 Hartert [14] first presented a method to measure the formation of a clot from whole blood. Almost 50 years passed until thromboelastography (TEG® by Hemoscope Corporation, Niles, IL, USA) and rotational thromboelastometry (ROTEM®; initially by Pentapharm, now TEM International GmbH, Munich, Germany) were developed and made registered trademarks in 1996 and 2000, respectively. Today, these two systems are the most commonly used POC devices for whole blood coagulation diagnostic testing in trauma, liver surgery, cardiac surgery, post-partum hemorrhage, and many other settings. They provide valuable information about clot initiation, formation, and lysis corresponding to platelet number and function, fibrinogen quantity and function as well as pro- and anticoagulation enzymes. Measurements are usually made using citrated whole blood. Reagents and whole blood are pipetted and incubated in heated (37 °C) small cups. A pin is introduced into the sample measuring the changes of the viscoelastic properties of the forming blood clot. In TEG, the cup oscillates with an angle of 4.45°, and the consecutive movement of the pin is translated into an electric signal by a torsion wire. In ROTEM, the cup is stationary and the pin moves 4.75°; the impedance of pin rotation is measured by an optical detector [15]. Information is gained by the initiation of clot formation, clot formation itself, maximum clot firmness, and clot lysis. Terminology in TEG and ROTEM is different and summarized in table 1.

The ROTEM device can measure 4 channels in parallel. Five commonly used different tests can be started, and the clot formation can be visualized. With EXTEM, coagulation is started by the addition of tissue factor, representing the classical extrinsic pathway activation. With INTEM, coagulation is initiated by contact

activator leading to intrinsic pathway activation. The inhibition of the platelets by cytochalasin D in the FIBTEM test shows the fibrinogen clotting which corresponds to fibrinogen plasma levels and can be visualized [16, 17]. Furthermore the amount of factor XIII plays a role regarding the maximal amplitude of this test [18]. No effect of platelets should be present anymore as they were completely inhibited by cytochalasin D.

The addition of aprotinin, which is called APTEM test, inhibits fibrinolysis, and addition of heparinase before contact activation visualizes a heparin effect in the HEPTEM test.

In most active bleeding patient the first substrate to drop below critical levels will be fibrinogen. ROTEM is capable to determine indirectly fibrinogen concentration (as 7 mm correspond to 1.5 g/l, a curve regarding this correlation exists in the literature) within 10 min, which normally takes 30–60 min in the laboratory, and the efficacy of treatment can be readily determined [7, 19–22]. Hyperfibrinolysis can be readily detected by TEG and ROTEM. Reduction of clot strength or complete lysis after formation is the in vitro equivalent of pathological activation of fibrinolysis. Trauma patients with hyperfibrinolysis documented by ROTEM have a significantly higher mortality compared to those without [23]. Hyperfibrinolysis > 3% is associated with massive transfusion [24]. Fibrinogen substitution as a substrate and prothrombin complex concentrate as an enzyme, guided by rotational thrombelastometry, can be safely used to enhance thrombin generation in patients with severe multiple trauma [25–27]. Moreover the FIBTEM value can be used to predict massive transfusion in trauma [28]. ROTEM-guided coagulation management was associated with reduced transfusion rates of allogeneic blood products [21]. In pediatric cardiac surgery, thrombelastometry-guided coagulation management reduced bleeding and the use of allogeneic RBC transfusion and length of stay on the intensive care unit [29]. However, these tests are not readily suited for monitoring the oral anticoagulant agents. Also, vitamin K antagonists are not readily measured unless severely over-anticoagulated. Novel or directly acting oral anticoagulants alter viscoelastic tests. Their exact effect is difficult to quantify, although work is underway to develop specific tests [30].

*Qualification and Quantification of Platelet Function or Inhibition*

Different POC devices dealing with platelet function exist. The PFA-100® (Siemens Healthcare, Malvern, PA, USA) measures platelet adhesion, mimicking arterial high shear stress. Addition of whole blood measures a 'closure time' in collagen/epinephrine and collagen/ADP test cartridges. Information about inborn platelet function defects and von Willebrand disease can be obtained from this test [31]. However, its use in a bleeding and coagulopathic patient is not well characterized as many of these tests may not work with dilutional coagulopathy.

Multiplate® and TEG platelet mapping™ are POC devices to detect and quantify the effect of antiplatelet medication. Inhibition of the arachidonic acid pathway, the GPIIb/IIa pathway, and the ADP (P2Y12) receptor pathway can be measured.

Multiplate® (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) visualizes electrode coating by aggregated platelets leading to aggregation units (over time). Low volumes of whole blood in five channels (dual sensors) measure platelet inhibition by stimulation with arachidonic acid (ASPItest), adenosine diphosphate (ADPtest), collagen (COLtest), and thrombin receptor-activating peptide (TRAPtest).

The number of patients treated with antiplatelet drugs due to cardiovascular or cerebrovascular disease is continuously increasing [32]. New ADP receptor antagonists with specific pharmacokinetic and pharmacodynamic profiles like Ticagrelor® make a quantification of the clinical antiplatelet effect critical. Even for high-risk patients with drug-eluting stents needing emergency surgery, POC testing may be desired to guide a bridging protocol when one or two of the antiplatelet drugs are to be discontinued. Moreover, patients not responding to clopidogrel treatment can be identified [33]. Some institutions treat these patients without using these devices – the standard of care has to be determined yet.

After on-pump aorto-coronary bypass (CABG) surgery, TEG platelet mapping was able to predict excessive postoperative chest tube bleeding (CTB) and the need for platelet transfusion [34], but failed to correlate with 24-hour CTB [35]. Other platelet function testing failed to predict postoperative bleeding in patients with P2Y12 inhibitors [36, 37]. PFA-100 had a high negative predictive value of 98% to identify patients not needing platelet transfusions post cardiac bypass [38]. VerifyNow® (Accumetrics, San Diego, CA, USA) platelet function assay predicted the need for RBC transfusion, but not the need for platelet transfusion post CABG [39]. Platelet dysfunction measured by POC (collagen-activated platelet count) during rewarming was associated with high (>1,770 ml) blood loss in a cohort of 100 patients [40].

In neurosurgery, antiplatelet drugs were a risk factor for rebleeding after neurosurgical procedures [41]. Patients with impaired platelet function due to aspirin intake had higher mortality in the case of spontaneous intracranial hemorrhage [42]. Inability to normalize the VerifyNow aspirin assay value was associated with a trend towards higher mortality [43]. Of note, the use of platelet transfusions to normalize platelet function in patients with intracranial hemorrhage did not show a positive effect on patient outcome in retrospective analyses [44, 45].

In severe brain trauma, platelet dysfunction was present due to a significantly increased inhibition of platelet ADP and arachidonic acid receptors [46]. In 46 trauma patients reported to be taking clopidogrel, the platelet inhibitory effect was measured with VerifyNow (P2Y12). Patients with low (<30%) platelet inhibition by clopidogrel did not die due to bleeding and had low rates of increased intracranial hemorrhage [47]. Using the multiple electrode aggregometry in 163 trauma patients, a retrospective analysis identified significant difference in the ADPtest between survivors and non-survivors [48]. The latest device, named TEM Platelet®, was developed by TEM International GmbH (Munich, Germany); this two-channel device measures platelet function by aggregometry and can be added to the ROTEM, allowing to meas-

**Table 2.** Cost / blood product savings by the first published algorithms using POC devices

| Publication | Type | Year | Field | Patients | Mortality | Savings of cost |
|---|---|---|---|---|---|---|
| O'Keeffe et al. [66] | retrospective | 2008 | trauma | 132 | 52.3% | 22% |
| Despotis et al.[67] | prospective | 1994 | cardiac | 66 | n.n. | reduction |
| Spiess et al. [68] | retrospective | 1995 | cardiac | 1,079 | n.n. | USD 50,000.00 in 6 months |
| Shore-Lesserson et al. [69] | prospective | 1999 | cardiac | 92 | n.n. | blood products –20% |
| Nuttall et al. [70] | prospective | 2001 | cardiac | 58 | n.n. | FFP and platelets –60% |
| Capraro et al. [71] | prospective | 2001 | cardiac | 58 | 3% | blood products –20% |
| Royston et al. [72] | prospective | 2001 | cardiac | 120 | n.n. | FPP and platelets –70% |
| Avidan et al. [73] | prospective | 2004 | cardiac | 220 | n.n. | RBCs, platelets –60%; FFP –90% |

ure in total 6 channels with complete coagulation assessment and platelet function. POC monitoring of blood coagulation at the bedside is not only desirable but also is becoming increasingly recommended [7].

## Factor Concentrates

The use of FFP leads to adverse effects, including increased mortality, multiple organ failure, risk of infection, lung injury, and immunomodulation [49, 50]. The effectiveness of FFP compared to fibrinogen concentrate regarding clinical endpoints as blood loss, transfusion requirements, hospital length of stay, survival and plasma fibrinogen concentration favors fibrinogen concentrates [49]. For this reason fibrinogen and potentially other factor concentrates should be considered in patients with substantial bleeding [7].

This consideration is based on target levels of fibrinogen for trauma patients that have been defined at 1.5–2.0 g/l in the European Trauma Treatment Guidelines [7]. Administration of fibrinogen concentrates is advantageous compared to FFP transfusion as fibrinogen concentration in FFP is variable (about 2 g/l on average), and large volumes of FFP would be necessary to effectively increase the fibrinogen concentration to achieve target fibrinogen concentrations of 1.5–2.0 g/l [51]. When replacing most FFP transfusions with fibrinogen concentrate, monitoring factor XIII levels is also advisable after the replacement of approximately 50% of the blood volume as this will be the moment when factor XIII reaches a critical level. A 60% factor XIII activity level is advised to be maintained by the administration of factor XIII concentrate [19, 52–54].

Besides single-factor concentrates, prothrombin complex concentrates (PCCs) are also part of factor-based algorithms [19, 21, 22, 32, 56, 55]. Individual PCCs differ regarding their factors contained, their relative composition, and their thrombotic potential. Although PCCs are approved for vitamin K antagonist reversal [57], their use is also suggested by the update of the European Trauma Guidelines in 2013 if the initiation of clot formation is prolonged in rotational thromboelastometry [7]. PCC should be used only within a strict algorithm, the dose should be small, and repeat doses should be given with caution to minimize thrombotic

risks [56]. Of note, studies indicate that significant reductions in RBCs, FFP and platelets transfusions can be facilitated by using a coagulation factor concentrate-based coagulopathy management in trauma patients [58]. Based upon data from four European countries (UK, Germany, Italy, and Switzerland), blood substitution levels and blood products were calculated and found to account for approximately 27% of all costs associated with trauma care on the intensive care unit [59]. Additional findings include a reduction in septic complications and organ failure which translated into trends towards reduced ventilator time and shorter overall inhospital length of stays. These important findings may also contribute to cost reduction in acute trauma care without increasing the risk for the individual patient.

## Algorithms Used

The first types of algorithm published used TEG/ROTEM to guide the administration of blood products such as platelets and FFP. They were all able to reduce blood product use and costs. Most studies were first performed in cardiac surgery in 1994. In table 2 a brief overview of the first publications is given regarding cost-savings.

However, depending on the country, different factor concentrates may not be available. The following examples show sophisticated algorithms which give clear instructions regarding the treatment of a bleeding patient depending on the results given by POC devices. Görlinger et al. [32] published in 2011 their 5-year experience in cardiac surgery in Essen, Germany. The used an algorithm in which ROTEM and Multiplate was integrated and which gave clearly structured therapeutical instructions. Thus they were able to significantly reduce the use of any allogeneic blood transfusion (52.5 vs. 42.2%; p < 0.0001), of packed RBCs (49.7 vs. 40.4%; p < 0.0001), and of FFP (19.4 vs. 1.1%; p < 0.0001). The amount of platelets transfused (10.1 vs. 13.0%; p = 0.0041) as well as the administration of fibrinogen concentrate (3.73 vs. 10.01%; p < 0.0001) and PCC (4.42 vs. 8.9%; p < 0.0001) increased significantly. During the course of the study, a switch from aprotinin to tranexamic acid occurred as well as an increase in the use of dual antiplatelet therapy (2.7 vs. 13.7%; p < 0.0001); as a consequence the incidence of massive (≥10 U packed RBCs) transfu-

sion (2.5 vs. 1.26%; p = 0.0057) and unplanned re-exploration (4.19 vs. 2.24%; p = 0.0007) decreased. Thrombotic and thromboembolic events also decreased significantly (3.19 vs. 1.77%; p = 0.0115), but inhospital mortality remained identical.

In another study by Schöchl et al. [21], a ROTEM-guided algorithm was used in trauma patients to compare patients receiving FFP versus those receiving fibrinogen concentrates and PPC instead. As hemostatic therapy in the emergency department and during surgery the FFP group (injury severity score 35.5 ± 10.5) received a median of 6 (range 2–51) units of FFP, while the fibrinogen-PCC group (injury severity score 35.2 ± 12.5) received a median of 6 (range 0–15) g of fibrinogen concentrate and 1,200 (range 0–6,600) U of PCC. RBC transfusion was avoided in 29% of patients in the fibrinogen-PCC group, compared with only 3% in the FFP group (p < 0.001). Transfusion of platelet concentrate was avoided in 91% of patients in the fibrinogen-PCC group, compared with 56% in the FFP group (p < 0.001). Mortality was comparable in both groups – 7.5% in the fibrinogen-PCC group and 10.0% in the FFP group (p = 0.69). This study also showed a clear benefit for using an algorithm guided by POC devices.

The third example to be mentioned is the algorithm published by Theusinger et al. [60, 61]. This algorithm also takes into consideration different laboratory and POC results, such as ROTEM, CoaguCheck and Multiplate, and gives clear treatment orders. Depending on the type of surgery – neurosurgery and cardiac surgery – versus trauma and others, the threshold values have been adapted to take into consideration different bleeding risks. A FIBTEM with a maximum clot firmness (MCF) of <7 mm, corresponding to approximatively 1.5 g/dl of fibrinogen, only needs substitution of fibrinogen if the patient is bleeding; in a non-bleeding patient no therapeutic intervention is needed. Platelets need to be above 100,000/µl in the bleeding patient during neurosurgery and cardiac surgery compared to 50,000/µl in all others. This algorithm aims to correct pathological values only in case of bleeding and to reach normal values at the lower range to avoid thromboembolic complications. This algorithm also include desmopressin which enhances platelet adherence and is the first choice in the treatment of bleeding patients with quantitative deficiency (type 1) and some of the qualitative defects (type 2) of von Willebrand factor (vWF) [62, 63]. Patients treated with aspirin and ADP receptor inhibitors such as clopidogrel could also benefit from POC testing to assess the individual efficacy of desmopressin treatment [64]. In case of insufficient treatment with desmopressin, transfusing platelets is the ultimate option.

## Conclusion

The use of POC devices with evidence-based algorithms seems mandatory in the bleeding patient independent of bleeding origin (traumatic vs. surgical) The use of factor concentrates, compared to the classical blood products, is cost-saving and beneficial for the patient and also in agreement with the WHO-requested standard of care. The uncontrolled use of blood products such as FFP, RBCs and platelets without POC control seems to be inadequate with regard to the actual evidence in literature. Furthermore, the use of factor concentrates seems to be in favor for better outcome and cost saving.

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