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CASE REPORT

Thromboelastometry-guided blood transfusion in septic shock complicated with disseminated intravascular coagulation: a case report

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Key Clinical Message

Approximately 25–50% of septic patients develop disseminated intravascular coagulation. The thromboelastometry evaluates whole blood clot formation and dissolution in real time and has been considered for management of bleeding in diverse clinical conditions. We present a case of thromboelastometry-guided bleeding management of a septic shock patient with overt disseminated intravascular coagulation (DIC).

Keywords

Blood coagulation disorders, blood transfusion, disseminated intravascular coagulation, septic shock, thrombelastography.

Introduction

Septic shock is a critical clinical condition with a high mortality rate [1]. Approximately 25–50% of septic patients develop disseminated intravascular coagulation (DIC) [2]. Disseminated intravascular coagulation is an acquired disease characterized by diffuse activation of coagulation, leading to intravascular fibrin deposition and widespread thrombotic microvascular occlusion, compromising blood supply to tissue cells [3]. Along with derangements on systemic and regional hemodynamics, DIC has been implicated to the development of organ dysfunction, failure, and death in septic patients [4].

The pathogenesis of sepsis-related DIC is complex and multifactorial, including increased thrombin generation mediated by tissue factor and activated factor VII, impaired anticoagulant system (decreased antithrombin III, protein C, and tissue factor inhibitor), impaired fibrinolysis, and systemic inflammation [5]. This continuous activation of coagulation system leads to depletion of platelets and coagulation factors, leading to a severe and potentially life-threatening bleeding [5].

The clinical picture of DIC is nonspecific and can manifest through bleeding or thrombosis [3]. Therefore, the diagnosis of DIC remains a challenge. Currently, it is based on the combination of laboratory tests, clinical signs, and medical history [6]. Hemorrhagic symptoms, from mild to life-threatening, may occur in the early phases of disease, while thrombotic manifestations are more commonly observed in the late phases [6].

Classical findings observed in conventional coagulation tests (CCT) are prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low platelet count and fibrinogen levels, increased d-dimer levels, low plasma coagulation factor levels, low protein C, and antithrombin [6]. Moreover, decreased plasma fibrinogen level represents a marker of poor outcome [4].

Rotational thromboelastometry (ROTEM) is a point-of-care test that has been considered an useful tool to manage coagulation disorders in critically ill patients [7,

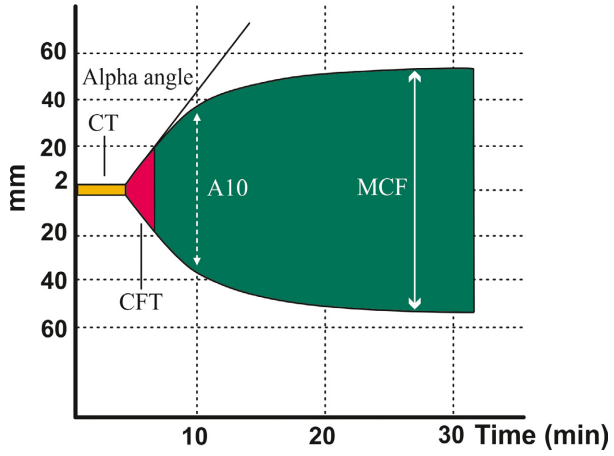

Figure 1. Graphical representation of a rotational thromboelastometry (ROTEM) analysis. Clotting time (CT; sec) represents the beginning of the test until a clot firmness of 2 mm, clot formation time (CFT; sec) represents a clot firmness of 20 mm, alpha angle (degrees) represents the slope (tangent) between a CT of 2 mm and CFT of 20 mm, amplitude 10 mm represents the clot amplitude 10 min after the beginning of clotting, and maximum clot firmness (MCF; mm) represents the greatest amplitude of the thromboelastometric trace and reflects the "strength" of the clot [9].

8]. The ROTEM uses the viscoelastic properties of blood to assess initiation, formation, quality, and stability of clot, displayed in a graphical manner [9]. A schematic illustration of a ROTEM analysis along with its main parameters is shown in Figure 1. The ROTEM has been used in early coagulopathy detection, prediction of bleeding complications, and in guiding hemostatic therapy in perioperative and critically ill patients, including complex cases of DIC [7, 10].

Our objective was to describe a case of a septic shock patient complicated with DIC in which the thromboelastometry was successfully applied to identify the underlining coagulopathy and guide blood transfusion during the ICU stay.

Case Report with Results

A 34-year-old Caucasian woman (weight 60 kg) presented to the emergency department (ED) with 3 days of lower back pain and 1 day of fever. She was taking nitrofurantoin (100 mg/day) for the last 4 days at home for a urinary tract infection. At the ED, her arterial blood pressure was 70/35 mm Hg, and heart rate was 135 bpm, with decreased level of consciousness (Glasgow Coma Scale of three). She presented hematemesis, petechiae in the cervical region, and left conjunctival hemorrhage. Blood and urine cultures were collected, and ceftriaxone was started (2.0 g intravenous BID). Endotracheal intubation and fluid load with crystalloids (3500 mL of 0.9% saline) were carried out, followed by norepinephrine administration. Then, the patient was referred to the ICU. Her APACHE II (Acute Physiology and Chronic Health Evaluation) score [11] was 24. Scores on the APACHE II range from 0 to 71, with higher values denoting more severe disease [11].

Table 1. Laboratory and conventional coagulation test results.

Characteristics	ICU admission	16 h after ICU admission
Arterial pH	7.35	7.40
Ionic calcium (mmol/L)	0.96	1.06
Peripheral temperature (°C)	36.4	36.5
Hemoglobin (g/dL)	12.6	8.3
Hematocrit (%)	36.7	23.5
White blood cells (x$10^3/\mu$L)	5470	15.540
Bands (%)	0	21
Platelets (x10^3/mm^3)	24	38
Prothrombin time (%)	10	47
INR	7.94	1.74
aPTT (sec)	132.1	45.8
Fibrinogen (g/dL)	70	334
D-dimer (ng/mL)	>100,000	

INR, international normalized ratio; aPTT, activated partial thromboplastin time.

The laboratory workup revealed hemoglobin 12.6 g/dL, platelets 24 × 10^3/mm^3, INR 7.94, aPTT 132 sec, fibrinogen 70 mg/dL, and procalcitonin 42 ng/mL (Table 1). Her DIC score (Scoring system for overt DIC of the International Society on Thrombosis and Haemostasis [12]) was 8. For overt DIC, a cumulative score of five has been proposed [12]. The diagnosis was septic shock associated with multiple organ dysfunction and overt DIC.

A thromboelastometry (ROTEM®, Pentapharm Co., Munich, Germany) was performed at the ICU admission (Table 2 and Fig. 2A and B). ROTEM depicted an intense kinetics and structural hypocoagulate state (Table 2 and Fig. 2A and B). The FIBTEM revealed impaired fibrinogen function, while INTEM showed coagulation factor deficiency. Based on these findings, the patient received 6.0 g of fibrinogen concentrate (Haemocomplettan® P, CSL Behring, Marburg, Germany), 1.500 IU (25 IU/Kg) of prothrombin complex concentrate (Beriplex® P/N 500 UI, CSL Behring, Marburg, Germany), and one unit of apheresis platelets. Six hours later, a second ROTEM was performed (Table 2 and Fig. 2C and D) and showed persistent fibrinogen dysfunction. Thus, another 6.0 g of fibrinogen concentrate (Haemocomplettan® P, CSL Behring, Marburg, Germany) was administered. A third ROTEM was performed approximately 9 h after ICU admission, in the presence of active bleeding, showing a

Table 2. Sequential rotational thromboelastometry (ROTEM) analysis.

Time points	Assays	CT (sec)	CFT (sec)	α angle (°)	A10 (mm)	MCF (mm)
ICU admission	INTEM	468	2144	14	10	23
	FIBTEM					0
6 h after ICU admission	INTEM	300	783	29	17	30
	FIBTEM					6
9 h after ICU admission	EXTEM	142	711	27	18	34
	INTEM	414	726	29	17	30
	FIBTEM					7
16 h after ICU admission	EXTEM	78	137	80	41	54
	INTEM	189	153	77	39	51
	FIBTEM				21	24

CT, clotting time; CFT, clot formation time; A10, amplitude 10 min; MCF, maximum clot firmness.

serious state of hypocoagulability associated to coagulation factor deficiency on INTEM CT and persistent reduced FIBTEM MCF after replacement of 12 g of fibrinogen. Therefore, two units of fresh-frozen plasma (FFP), eight units of cryoprecipitate, and one unit of apheresis platelets were administered (Table 2 and Fig. 2E and F). Finally, 16 h after ICU admission, a fourth ROTEM was performed showing no coagulation abnormality (Table 2 and Fig. 2G and H). Her laboratory workup revealed platelets count $38 \times 10^3/mm^3$, fibrinogen 334 mg/dL, INR 1.74, and aTTP 45.8 sec. There was no active bleeding at this time. The patient remained stable, with no bleeding during the recovery phase. She was discharged to a step-down unit 3 days after ICU admission. Six days later, she was discharged from the hospital.

Discussion

Disseminated intravascular coagulation is a serious complication with a high mortality rate, reaching up to 80% in sepsis [13]. DIC represents an acquired syndrome, secondary to a systemic inflammatory disease, characterized by diffuse activation of coagulation, with fibrin production and microvascular thrombosis, leading to tissue hypoperfusion and progressive organ dysfunction [4]. Initially, there is an increased activation of the fibrinolytic system. Lastly, a consumption of coagulation factors and platelet depletion result in massive hemorrhage [3].

Conventional coagulation tests are neither sensitive nor specific enough to allow a definitive diagnosis of DIC [3]. Thromboelastography, originally described in 1948 by Hartert [14], addresses the viscoelastic blood properties through graphical representation. The ROTEM came up in the 1990s as a technological improvement of thromboelastography, providing an automated pipetting and four channels for simultaneous measurement [15]. It allows a quick detection of hemostatic disorders in up to 5–15 min, and it is performed with the patient's temperature and with whole blood, which allows a dynamic evaluation of the coagulation kinetics [16]. Furthermore, CCT only detect 3–5% of the thrombin generation process [17]. It is well defined that septic patients may exhibit hypocoagulability, hypercoagulability, and hyperfibrinolysis, which can only be accessed by ROTEM [18].

Rotational thromboelastometry has been used in different populations of critically ill patients to guide therapy with specific hemostatic drugs, such as coagulation factor concentrates and blood products [7]. As a result, its use reduced blood transfusion in many clinical scenarios, that is, cardiac surgery, hepatic transplantation, trauma, and obstetrics. The relationship between CCT and thromboelastometry was addressed in observational studies involving septic patients.

Andersen et al. demonstrated that ROTEM analysis of nonbleeding septic shock patients was within the normal reference range, while CCT showed conflicting results, varying from a hypercoagulable state and hypocoagulation [19]. Sivula et al. showed that EXTEM and FIBTEM of patients with DIC indicated hypocoagulation compared to healthy controls and patients without DIC, while patients without DIC exhibited a trend toward a hypercoagulability [20]. They also demonstrated that thromboelastometry alterations correlated well with CCT [20]. The authors suggest EXTEM CT >80 sec, CFT >160 sec, and MCF ≤52 mm [20] as cutoff for differentiating nonovert from overt DIC.

The current management of DIC is based on the treatment of the underlying disease in association with supportive care and treatment of bleeding manifestations [3]. According to the international guidelines for the diagnosis and management of DIC, patients with active bleeding should receive platelets when their count is lower than $50 \times 10^3/mm^3$, and FFP when INR >1.5, aPTT >32 sec, and cryoprecipitate or fibrinogen concentrate when fibrinogen is <150 to 200 mg/dL [21].

We reported a case of septic shock complicated with DIC, presenting with active bleeding at different sites. The initial CCT showed prolonged PT and aTTP, low platelet count, severe hypofibrinogenemia, and high level of d-dimer. The ROTEM analysis demonstrated a severe hypocoagulable state, compromising initiation, strength, and stabilization of clot in the presence of active bleeding. Fibrinogen concentrate, prothrombin complex concentrate, platelets, cryoprecipitate, and FFP were needed to control bleeding and correct the underlying coagulopathy. FFP contains low amounts of fibrinogen, approximately 250 mg per unit, while each unit of cryoprecipitate contains approximately 200 mg of fibrinogen. Therefore,

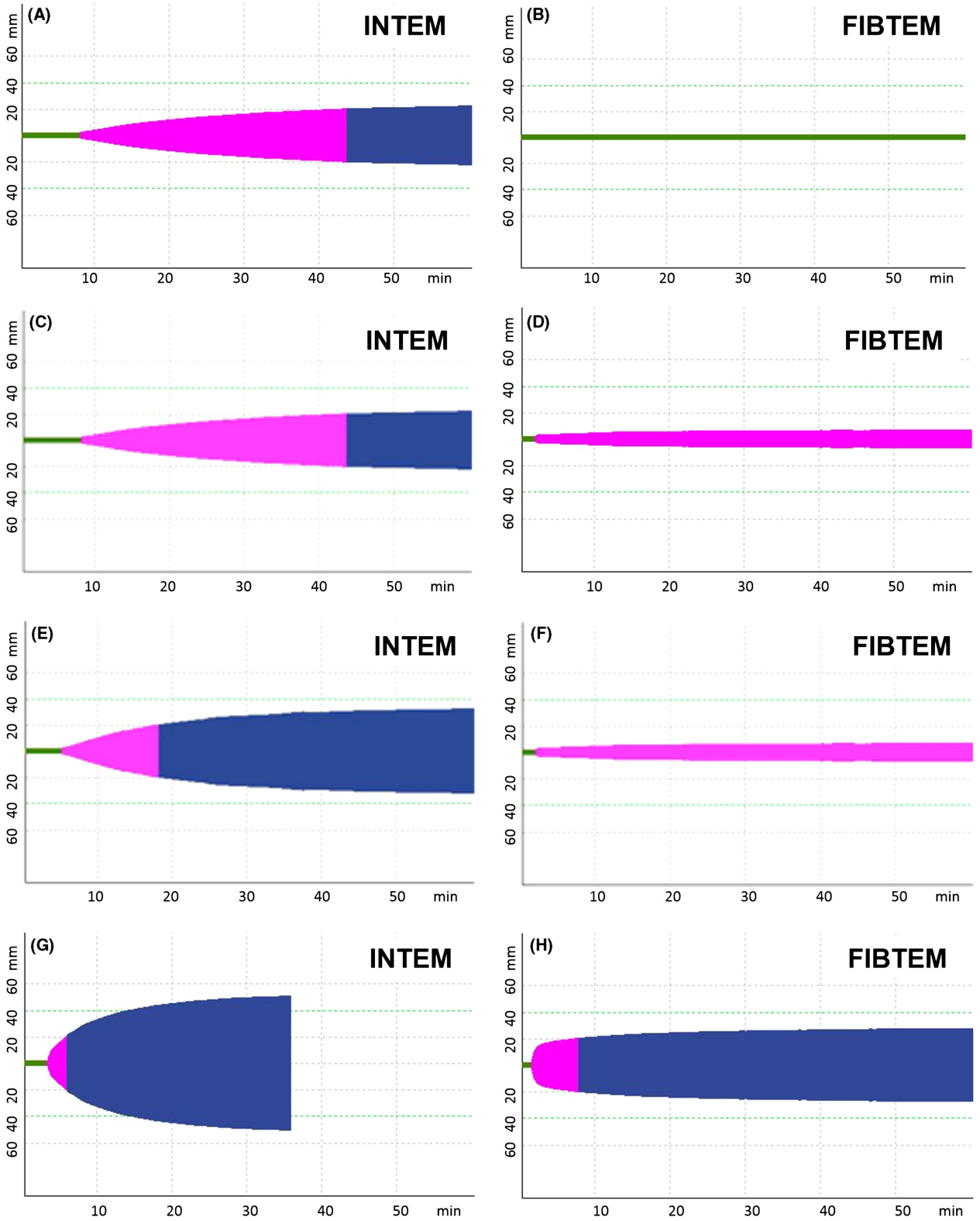

Figure 2. Sequential rotational thromboelastometry (ROTEM) analysis. Panels A and B represent ROTEM at ICU admission; panels C and D represent ROTEM at 6 h after ICU admission; panels E and F represent ROTEM at 9 h after ICU admission, and panels G and H represent ROTEM at 16 h after ICU admission.

approximately 48 bags of FFP or 60 units of cryoprecipitate would be necessary to replace 12 g of fibrinogen in the presented case. The transfusion of blood components based on CCT might have exposed the patient to an increased risk of serious transfusion-related adverse events such as transfusion-related lung injury, transfusion-associated circulatory overload, and transfusion-related immunomodulation, with potential to adverse outcomes [22].

Conclusion

The management of septic shock patients complicated with DIC is challenging. Thromboelastometry allowed us to perform an early diagnosis and apply an individualized transfusion therapy in a patient presenting with overt DIC. As a result, the need of blood components was minimized, as well as the risk of deleterious side effects related to blood transfusion. Nevertheless, additional studies are needed to define the actual benefit of thromboelastometry for identification as well as to guide transfusion of blood products and hemostatic therapy in patients with DIC.

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Authorship

TC: devised the case report. TC and PP: collected the data. TC, TDC, FNDC, CM, LLR: wrote the first manuscript draft. TC, LLR, and TDC: critically revised the manuscript. All authors approved the final manuscript.

Conflict of Interest

The authors report no conflict of interests. The authors alone are responsible for the content and writing of the manuscript.

References

1. Angus, D. C., A. E. Barnato, D. Bell, R. Bellomo, C. R. Chong, T. J. Coats, et al. 2015. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. 41:1549–1560.
2. Zeerleder, S., C. E. Hack, and W. A. Wuillemin. 2005. Disseminated intravascular coagulation in sepsis. Chest 128:2864–2875.
3. Franchini, M., G. Lippi, and F. Manzato. 2006. Recent acquisitions in the pathophysiology, diagnosis and treatment of disseminated intravascular coagulation. Thromb. J. 4:4.
4. Levi, M., E. de Jonge, T. van der Poll, and H. ten Cate. 1999. Disseminated intravascular coagulation. Thromb. Haemost. 82:695–705.
5. Nimah, M., and R. J. Brilli. 2003. Coagulation dysfunction in sepsis and multiple organ system failure. Crit. Care Clin. 19:441–458.
6. Siegal, T., U. Seligsohn, E. Aghai, and M. Modan. 1978. Clinical and laboratory aspects of disseminated intravascular coagulation (DIC): a study of 118 cases. Thromb. Haemost. 39:122–134.
7. Haas, T., K. Gorlinger, A. Grassetto, V. Agostini, P. Simioni, G. Nardi, et al. 2014. Thromboelastometry for guiding bleeding management of the critically ill patient: a systematic review of the literature. Minerva Anestesiol. 80:1320–1335.
8. Kander, T., A. Larsson, V. Taune, U. Schott, and N. Tynngard. 2016. Assessment of haemostasis in disseminated intravascular coagulation by use of point-of-care assays and routine coagulation tests, in critically Ill patients; a prospective observational study. PLoS One 11: e0151202.
9. Whiting, D., and J. A. DiNardo. 2014. TEG and ROTEM: technology and clinical applications. Am. J. Hematol. 89:228–232.
10. Kilic, Y., I. Topcu, H. Bambal, and M. Civi. 2014. Thromboelastography in the evaluation of coagulation disorders in patients with sepsis. Turk. J. Med. Sci. 44:267–272.
11. Knaus, W. A., E. A. Draper, D. P. Wagner, and J. E. Zimmerman. 1985. APACHE II: a severity of disease classification system. Crit. Care Med. 13:818–829.
12. Taylor, F. B. Jr, C. H. Toh, W. K. Hoots, H. Wada, and M. Levi. 2001. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb. Haemost. 86:1327–1330.
13. Smith, O. P., B. White, D. Vaughan, M. Rafferty, L. Claffey, B. Lyons, et al. 1997. Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. Lancet 350:1590–1593.
14. Hartert, H. 1948. Blutgerinnungsstudien mit der Thrombelastographie, einem neuen Untersuchungsverfahren. Klin Wochenschr. 26:577–583.
15. Jackson, G. N., K. J. Ashpole, and S. M. Yentis. 2009. The TEG vs the ROTEM thromboelastography/ thromboelastometry systems. Anaesthesia 64:212–215.
16. Song, J. G., S. M. Jeong, I. G. Jun, H. M. Lee, and G. S. Hwang. 2014. Five-minute parameter of thromboelastometry is sufficient to detect

thrombocytopenia and hypofibrinogenaemia in patients undergoing liver transplantation. Br. J. Anaesth. 112:290–297.
17. Nakashima, M. O., and H. J. Rogers. 2014. Hypercoagulable states: an algorithmic approach to laboratory testing and update on monitoring of direct oral anticoagulants. Blood Res. 49:85–94.
18. Muller, M. C., J. C. Meijers, M. B. Vroom, and N. P. Juffermans. 2014. Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. Crit. Care 18:R30.
19. Andersen, M. G., C. L. Hvas, E. Tonnesen, and A. M. Hvas. 2014. Thromboelastometry as a supplementary tool for evaluation of hemostasis in severe sepsis and septic shock. Acta Anaesthesiol. Scand. 58:525–533.
20. Sivula, M., V. Pettila, T. T. Niemi, M. Varpula, and A. H. Kuitunen. 2009. Thromboelastometry in patients with severe sepsis and disseminated intravascular coagulation. Blood Coagul. Fibrinolysis 20:419–426.
21. Levi, M., C. H. Toh, J. Thachil, and H. G. Watson. 2009. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br. J. Haematol. 145:24–33.
22. Lier, H., M. Vorweg, A. Hanke, and K. Gorlinger. 2013. Thromboelastometry guided therapy of severe bleeding. Essener Runde algorithm. Hamostaseologie 33:51–61.