Perioperative Hemostasis in Pediatric Surgery

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16.1 Pediatric Hemostasis

The development of hemostasis during childhood is a complex physiological process which aims to build a stable clot in situations of vascular injury, but which is also responsible for clot dissolution to maintain blood flow (Andrew et al. 1987, 1988, 1992). Although the most significant changes in this maturation process can be observed during the first 6 months of life, the hemostatic system continues to mature thereafter (Andrew et al. 1992; Miller et al. 1997). These changes include lower quantities of most of the coagulation factors (except for factor VIII and von Willebrand factor, vWF), decreased platelet activity, and a fetal dysfunctional fibrinogen (Guzzetta and Miller 2011). However, as the anticoagulant system (such as plasmin generation and fibrinolytic activity) is also diminished at birth, the overall hemostasis potential in neonates and young infants can be evaluated as good, with no increased risk of thrombosis or hemorrhage in the face of minor challenges (Kuhle et al. 2003). However, this maturation process is certainly not rigidly coupled to a child's age group, but rather it is highly individual. It is therefore essential that careful anamnesis, physical examination, and laboratory work-up should be adapted to actual age and underlying medical condition.

16.2 Perioperative Coagulation Testing in Children

16.2.1 Preoperative Screening of Hemostasis

At present, guidelines and recommendations for perioperative coagulation management do not support routine coagulation screening tests in otherwise healthy patients

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if their bleeding history shows negative results (Dzik 2004; Koscielny et al. 2004; Chee et al. 2008; Kozek-Langenecker 2010; Samkova et al. 2012). This approach is based on the fact that the prediction of perioperative bleeding could not be reliably determined by routine coagulation screening tests, while the combination of a clinical examination, together with a detailed (family) history, showed superior results in ensuring the detection of impaired hemostasis. For example, von Willebrand syndrome type I is the most common type of a clinically relevant congenital bleeding disorder, with an incidence of 1 in 500; because it cannot be detected by a prolonged activated partial thromboplastin time (aPTT), it will most likely come to light via a detailed bleeding history. Templates of standardized questionnaires can be downloaded from the Austrian Society of Anesthesiology (ÖGARI) (http://www.oegari.at/web_files/dateiarchiv/116/Recommendation%20questions%20bleeding%20symptoms%202009.pdf), the Canadian Pediatric Bleeding Questionnaire (http://www.ahcdc.ca/inheritedbleeds.html), and the International Society on Thrombosis and Haemostasis bleeding assessment tool (http://www.isth.org/default/assets/file/bleeding_type1_vwd.pdf).

If this preoperative approach reveals evidence of impaired hemostasis, or a child suffers from a congenital or known acquired coagulation disorder, an interdisciplinary work-up with a hematologist or another dedicated physician specialized in pediatric bleeding disorders is indicated.

16.2.2 Intraoperative Coagulation Testing

16.2.2.1 Standard Plasmatic Coagulation Testing

Intraoperative coagulation testing is a cornerstone of the identification of an underlying coagulation disorder, but is also an essential tool for guiding appropriate coagulation management. Unfortunately, routine plasmatic coagulation tests are of limited help for timely management of perioperative bleeding; this is due to long turnaround times, insufficient differential diagnosis of complex acquired intraoperative coagulopathy, and insensitivity to fibrinogen function, hyperfibrinolysis, and platelet dysfunction (Kozek-Langenecker 2010). Other important limitations are that the measurement of fibrinogen levels using the photometric Clauss assay can be considerably altered after massive fluid resuscitation, and that colloids may erroneously induce increased levels of fibrinogen (Fenger-Eriksen et al. 2010; Kozek-Langenecker 2010).

16.2.2.2 Thromboelastometry

Although data on the use of rotational thromboelastometry for intraoperative coagulation management in children were scarce (Haas et al. 2008, 2012c; Hayashi et al. 2011; Romlin et al. 2011), a recently published meta-analysis showed significant reduction in requirements of allogeneic blood products if thrombelastography/thromboelastometry was used to guide transfusion strategy (Afshari et al. 2011). In addition, the use of thromboelastometry for pediatric care is recommended by the European guidelines for perioperative bleeding management (Kozek-Langenecker et al. 2013). Thus it seems reasonable to also use this advanced coagulation test for coagulation management in children once it has been implemented as routine for adults.

While keeping in mind the functional maturity of the coagulation system, age-dependent reference ranges for the ROTEM® (Oswald et al. 2010) or TEG® (Miller et al. 1997) should be taken into account. The most striking finding from the evaluation of these reference ranges is that children aged 0–3 months exhibited accelerated coagulation and strong clot firmness, despite showing prolonged standard plasma coagulation test results. Similarly to adults, fibrinogen concentrations, platelet count, and FXIII in children also contribute to clot firmness as measured using ROTEM® assays. Furthermore, it was demonstrated that children aged 4–24 months showed the lowest 2.5 % percentiles for clot strength, indicating low reserve when exposed to hemodilution and blood loss. However, as a rule of thumb, from the 6th month of life, adult reference ranges from ROTEM® can safely be used to guide intraoperative coagulation management.

16.2.2.3 Pre-analytical Considerations

Depending on local resources, the following coagulation tests could reasonably be used for baseline measurements, for regular check-ups, and in situations of increased bleeding tendency or severe bleeding:

- ROTEM® INTEM, EXTEM, FIBTEM, and APTEM
- Plasmatic coagulation testing (including FXIII, if possible)
- Blood count (platelet count, hemoglobin level, hematocrit)
- Blood gas analysis

This full panel of coagulation tests can be performed with a total withdrawal of only 3.6 ml blood.

Thought must be given to the possibility of pre-analytical errors that can have considerable impact on the interpretation of laboratory results. These can include important but avoidable errors, such as an artificial activation of the blood sample by forced aspiration through the small diameters of pediatric cannulas, temperature effects, and an alteration of the correct whole blood/citrate ratio. Although laboratory tests should be repeatedly analyzed during any surgical procedure with massive or expected bleeding, only the minimum volume necessary should be withdrawn in order to prevent artificial anemia.

16.3 Perioperative Coagulation Management

16.3.1 Preoperative Considerations

Several publications have investigated coagulopathies in the clinical setting of cardiac surgery. However, if a cardiac bypass were used, additional disturbance to the coagulation system, such as platelet dysfunction, excessive fibrinolysis, or consumption of coagulation factors might aggravate dilution following administration of the priming volume (Friesen et al. 2006). Thus, coagulation testing and management should be adapted to the type of surgery.

There are some important prerequisites for adequate hemostasis that need to be carefully checked and treated throughout the entire perioperative phase. Anesthetized children are particularly prone to becoming hypothermic which, like

acidosis, inevitably leads to impairment of the coagulation process and may worsen bleeding (Dirkmann et al. 2008). Thus, forced-air warming should be rigorously performed, and temperature, as well as pH values, continuously measured during pediatric surgery.

Meta-analyses of major pediatric surgery (Sethna et al. 2005; Tzortzopoulou et al. 2008; Schouten et al. 2009; Goobie et al. 2011) and scoliosis surgery in children (Tzortzopoulou et al. 2008) have nicely demonstrated that the prophylactic administration of antifibrinolytic agents (e.g. tranexamic acid or TXA) may decrease blood loss and reduce allogeneic blood transfusion significantly. Therefore, the prophylactic use of TXA can generally be recommended for major pediatric surgery with estimated high blood loss or need for transfusion. Optimum doses are still debated; reported dosing ranges from 10 to 100 mg/kg bolus, while high doses might provoke seizures. Recent studies favored an initial bolus followed by continuous infusion due to TXA's relatively short half-live of about 120 min. Based on recently published data it seems reasonable to use an initial dose of 10–15 mg/kg infused over 15 min, followed by continuous infusion of up to 5 mg/kg/h throughout the entire surgical phase and upon transfer to the postoperative ward (Goobie et al. 2013).

Alternative means to minimize blood transfusion in major pediatric surgery were recently reviewed (Lavoie 2011). Results showed that acute normovolemic hemodilution (mostly in adolescents) showed modest benefits. Other strategies such as preoperative autologous donations (partly in combination with administration of erythropoietin), intraoperative cell salvage (may be feasible if child's body weight is >10 kg), or deliberate hypotension (in the absence of a hypovolemic state), or a combination of them, might be helpful in reducing allogeneic blood transfusion. However, approaches must largely depend on individual expertise and local facilities.

16.3.2 Intraoperative Fluid Management

Prevention and treatment of hypovolemia during major pediatric surgery is essential and may be carried out by appropriate fluid management using crystalloids or colloids. Besides the 'traditional' usage of albumin for pediatric fluid resuscitation, modern synthetic colloids, e.g. gelatin solutions or hydroxyethyl starches, can be safely used even in neonates and small children (Standl et al. 2008; Sumpelmann et al. 2012). As with adults, the use of any synthetic or natural colloids may lead to volume-dependent changes in the hemostatic profile and eventually to dilutional coagulopathy and occurrences of generalized microvascular oozing (Osthaus et al. 2009; Haas et al. 2012b). One can only speculate as to whether early vasopressor therapy might have a beneficial impact on perioperative bleeding by reducing the amount of fluids administered during major surgery. However, to date, no conclusive statement can be made about which type of fluid should be used to stabilize hemodynamics in children, but caution should be exercised in clinical scenarios were colloids are administered to children with an increased risk of bleeding.

16.3.3 Intraoperative Laboratory Findings and Therapy

It is important to note that the reported triggers of standard plasmatic coagulation tests for assessment of coagulopathy or initiation of bleeding therapy are based on empirical rather than evidence based data. In addition, the results of standard laboratory tests and ROTEM® data cannot be used interchangeably for the detection of hemostatic disorders. As an example, the results of standard laboratory tests (prothrombin time, PT, or aPTT) alter frequently during early stages of surgery, thus indicating transfusion of fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC), while abnormal ROTEM® clotting time is a late phenomenon that may be observed after severe disturbances of hemostasis (Haas et al. 2012c). Thus, transfusion requirements will be completely different according to the underlying laboratory methods and transfusion triggers. The European guidelines for perioperative bleeding recommend the use of thromboelastometry in this setting (Kozek-Langenecker et al. 2013) (Table 16.1).

16.3.3.1 Impaired Clot Firmness

16.3.3.1.1 Fibrinogen Deficiency: Diagnostic and Therapy

Functional fibrinogen/fibrin activity can be quickly and reliably assessed using the ROTEM® FIBTEM assay. If the maximum clot firmness (MCF) at 10 min (A10) showed values <7 mm (which is approximate to a Clauss assay of ≤150 mg/dl) in a scenario of significant bleeding, fibrinogen should be administered (Fries et al. 2010; Kozek-Langenecker et al. 2013). It should be noticed that besides of fibrinogen deficiency, a low FIBTEM MCF may be also caused by inadequate amounts of FXIII necessary to stabilize the clot.

Table 16.1 Intraoperative laboratory findings and therapy

Hemostatic disorder	ROTEM®	Standard laboratory test	Therapy
Fibrinogen deficiency	FIBTEM A10 <7 mm	Clauss assay 150–200 mg/dl *(Cave: overestimation in presence of colloids)*	Fibrinogen concentrate: 30–50 mg/kg Cryoprecipitate: 5 ml/kg (or 15–30 kg bodyweight = 5 Units; >30 kg = 10 Units) FFP: 20 (–30) ml/kg
FXIII deficiency	FIBTEM MCF remains low despite adequate substitution with fibrinogen	FXIII activity <60 %	FXIII concentrate: 20 IU/kg FFP: 20 (–30) ml/kg
Low platelet count	EXTEM MCF <40 mm with normal FIBTEM MCF	Platelet count <50,000–100,000/µl	10 (–20) ml/kg of apheresis platelet concentrate (to a maximum of 1 Unit)
Inadequate thrombin generation	EXTEM or INTEM CT prolonged	Needs to be determined	FFP: 20 (–30) ml/kg PCC: about 20 IU/kg (Cave: thromboembolic risk)

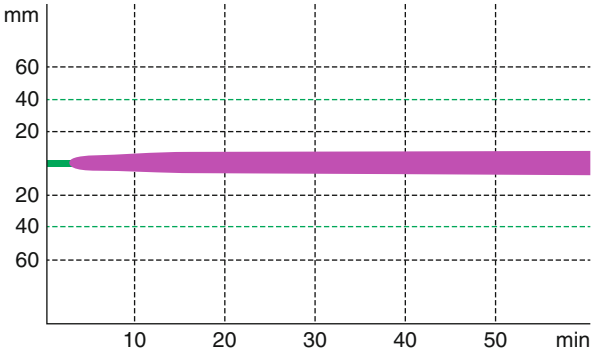

Fig. 16.1 ROTEM® trace of fibrinogen deficiency. FIBTEM MCF weak (6 mm)

Using the conventional Clauss assay, current recommendations (for adult patients) emphasize a trigger level of 150–200 mg/dl for initiating fibrinogen substitution therapy. However, if colloids were administered, fibrinogen levels analyzed using the Clauss assay may be erroneously high (Fenger-Eriksen et al. 2010).

Treatment of acquired fibrinogen deficiency consists of the administration of purified fibrinogen concentrate, transfusion of cryoprecipitate, or FFP (Fig. 16.1).

16.3.3.1.2 Fibrinogen Deficiency: Rationale

Fibrinogen plays several key roles in the maintenance of hemostasis (Levy et al. 2012; Sorensen et al. 2012). Fibrinogen acts by bridging activated platelets and is the key substrate by which thrombin forms a mechanically stable clot. Accumulating data suggest that acquired fibrinogen deficiency seems to be the leading determinant in dilutional coagulopathy in adults and children (Fries 2006; Levy 2006; Kozek-Langenecker 2007; Fenger-Eriksen et al. 2009; Innerhofer and Kienast 2010; Haas et al. 2012b). Clinical trials and observations indicated a beneficial role for intraoperative substitution with human fibrinogen concentrate to treat fibrinogen deficiency (Danes et al. 2008; Fenger-Eriksen et al. 2008; Haas et al. 2008; Weinkove and Rangarajan 2008; Fenger-Eriksen et al. 2009a; Rahe-Meyer et al. 2009) with a very good safety profile (Dickneite et al. 2009; Manco-Johnson et al. 2009).

FFP and cryoprecipitate may also serve as alternative sources of fibrinogen, although this is not supported by evidence from good-quality randomized trials (Stanworth et al. 2004). Cryoprecipitate contains higher concentrations of fibrinogen than FFP, but was withdrawn from several European countries because of the risk of immunologic reactions and potential transmission of infectious agents. Recommended dosages for FFP of 10–15 ml/kg may not be adequate to achieve a clinically meaningful improvement in hemostatic potential, but the considerable necessary volume load often limits higher doses.

16.3.3.1.3 FXIII Deficiency: Diagnostic and Therapy

For clinical purposes, weak factor activity of FXIII can be either accurately analyzed in a laboratory (FXIII <60 % and severe bleeding indicative for therapy), or can be estimated in a clinical case, when clot firmness in the ROTEM® FIBTEM

assay remains relatively low despite adequate substitution with fibrinogen. Although it was shown that the FXIII-dependent increase in clot firmness can be displayed using the ROTEM®/TEG® (Nielsen et al. 2004; Theusinger et al. 2010), to date no commercially available point-of-care test for measuring FXIII activity is available. Recommended means of substitution for FXIII include administration of a purified factor concentrate, or FFP.

16.3.3.1.4 FXIII Deficiency: Rationale

Factor XIII is a significant ingredient in achieving clot stability by cross-linking fibrin monomers, and preventing clot lysis by covalent binding of α2-plasmin inhibitor to fibrin molecules. Although congenital FXIII deficiency is a very rare bleeding disorder, there is growing evidence that acquired FXIII deficiency can also be frequently observed in perioperative settings in the pediatric age group (Korte 2006; Haas et al. 2012a). More recent data point towards the importance of FXIII in clot stabilization during major surgery and consequent blood loss (Gerlach et al. 2002; Korte et al. 2009; Korte 2010). However, improvement of clot firmness and the concomitant decreased bleeding tendency following substitution of FXIII in pediatric surgery is currently based on clinical observation, not on evidence based data.

16.3.3.1.5 Low Platelet Count: Diagnostic and Therapy

Platelet transfusion should be considered if platelet counts fall to levels between 50,000–100,000/μl during major surgery with the presence of severe bleeding. To distinguish a platelet-based weakening of clots from a deficiency in fibrinogen and/or FXIII, results of EXTEM MCF and FIBTEM MCF were gathered and analyzed. An MCF <40 mm in the EXTEM test, in combination with a normal FIBTEM MCF, will be indicative of a low platelet count. Transfusion of 10–20 ml/kg of apheresis platelet concentrate (to a maximum of 1 Unit) should raise the platelet count by 50,000/μl (Fig. 16.2).

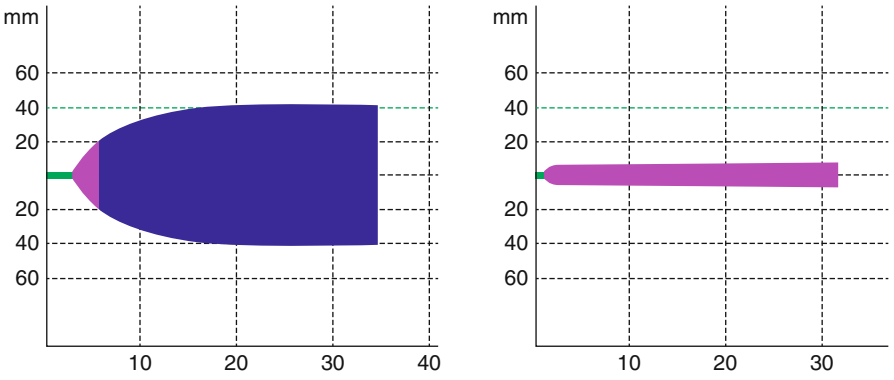

Fig. 16.2 ROTEM® trace of low platelet count. INTEM MCF decreased (40 mm); FIBTEM MCF normal (10 mm)

16.3.3.1.6 Low Platelet Count: Rationale

Recommendations for a safe lower platelet count threshold vary significantly in current literature. However, a significant decrease in platelet count seems to be a rather late phenomenon. In a retrospective analysis of 150 children who had undergone craniofacial surgery only 2 showed a platelet count ≤50,000/μl (Stricker et al. 2011). Note that the transfusion of platelet concentrate carries the highest risk of side-effects of all allogeneic blood products and should therefore be performed with caution.

16.3.3.2 Inadequate Thrombin Generation

16.3.3.2.1 Diagnostic and Therapy

Inadequate thrombin generation due to a deficiency of coagulation factors can be quite accurately estimated by prolonged clotting time (CT) in both the EXTEM and the INTEM assay, although no clear cut-off value was defined by now. Additionally, results from the ROTEM® HEPTEM assay may more usefully distinguish the impact of heparin, compared to the results of an INTEM test, if heparin was used during the procedure. It should be noticed that arbitrarily defined threshold for aPTT or PT prolonged >1.5–1.8 times are still used in the literature although no evidence based data exists to justify these values in this setting. Transfusion of FFP at a dose of about 20 ml/kg was routinely used if any signs of impaired hemostasis were observed, however, evidence based data to support its general use are weak. Administration of PCC (about 20 IU/kg) might offer an alternative approach, although no high quality data from pediatric trials are available (Fig. 16.3).

16.3.3.2.2 Rationale

Adequate thrombin generation is inevitably needed to induce the building of a stable clot. Notably, a perioperative decrease in thrombin generation, to levels that are unlikely to initiate clot building, is typically found late on in severe bleeding, even in neonates with lower vitamin K dependent coagulation factor levels. Unfortunately, neither aPTT nor PT correlates with clinically relevant coagulopathies or bleeding conditions (Johansson et al. 2010). Little evidence supports the use of standard coagulation tests for the guidance of perioperative coagulation therapy (Spahn et al. 2013). As viscoelastic tests are not used everywhere, empirical thresholds still exist to serve as rough estimates of disturbed hemostasis. In contrast, the prolonged coagulation times of thromboelastometry, in conjunction with increased bleeding tendency, might be interpreted as a relevant deficiency in coagulation factors and can

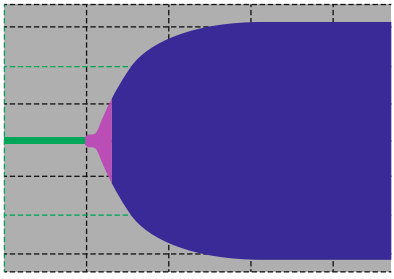

Fig. 16.3 ROTEM® trace of inadequate thrombin building

be treated with either an administration of PCC or a transfusion of FFP (Schochl et al. 2009, 2010). The accepted indication for administering PCC is reversal of the effects of vitamin K antagonists, but also for prophylaxis and treatment of factors of the prothrombin complex. Although numerous publications have shown the effective use of PCC in the latter indication, no evidence for its safe use in children exists to date. However, in severe bleeding episodes, where FFP is unavailable as a source of coagulation factors, or where there is a risk of hypervolemia due to large amounts of FFP, using PCC might offer a useful approach.

16.3.3.3 Hyperfibrinolysis

Besides the recommendation to use antifibrinolytic agents as prophylactic treatment, there is no evidence based data published that hyperfibrinolysis is a common problem during major surgery in children. However, due to the fact that hyperfibrinolysis is significantly associated with higher morbidity and mortality (Schochl et al. 2009), and in light of current recommendations for adults, it seems adequate to treat signs of hyperfibrinolysis (ROTEM® maximum lysis >15 % and maintenance of MCF using the APTEM test) in children with 10–20 mg/kg tranexamic acid, if relevant bleeding occurs (Fig. 16.4).

16.3.3.4 Bleeding Without Abnormal ROTEM® Results

Anesthesiologists can be challenged by intraoperative diffuse bleeding which neither the results from standard laboratory tests nor ROTEM® can explain. The usual reasons are the presence of congenital or acquired von Willebrand disease, or platelet disorders. In both cases, a timely, reliable diagnosis can be hard to achieve. First, the patient's bleeding anamnesis should be checked, as should any possible hypothermic, acidotic, or hypocalcemic condition, and then surgical bleeding should be ruled out. Thereafter, a clear work-up procedure, preferably involving a hematologist or a physician specialized in pediatric hemostasis, should be put in place. For severe cases, an empirical administration of tranexamic acid (bolus of up to 20 mg/kg over 15 min) is reasonable. Depending on the effectiveness of the antifibrinolytic therapy, a supplementary desmopressin infusion of 0.3 µg/kg over 15–30 min can be administered if a mild von Willebrand syndrome or impaired platelet function is suspected. It is important to keep in mind that the highest levels FVIII and von

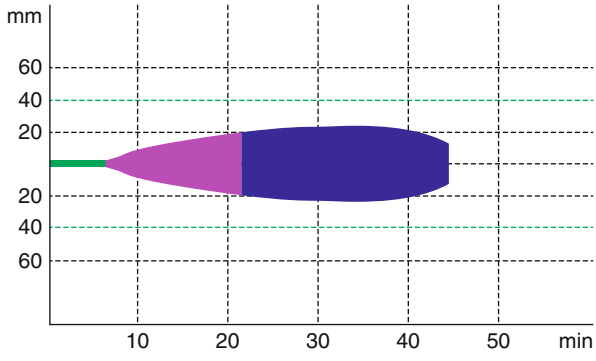

Fig. 16.4 ROTEM® trace of hyperfibrinolysis. Moderate lysis. Severe lysis

Willebrand factor (vWF) released from their storage sites within endothelial cells occur 30–60 min after desmopressin administration. If bleeding persists, administration of either vWF/FVIII concentrate (50 IU vWF:c/kg) or a platelet transfusion (20 ml/kg in children <15 kg; 1 apheresis unit platelets for children >15 kg) may be initiated, depending on the assumed underlying coagulation disorder.

16.3.3.5 Rescue Therapy

Final rescue therapy encompasses transfusion of at least FFP 20 ml/kg and/or administration of recombinant activated factor VII 90 μg/kg (rFVIIa). Final rescue therapy should only be considered after sufficient and timely treatment with standard therapy (as previously mentioned) has failed.

The licensed indications for rFVIIa are treatment of patients with hemophilia A or B with inhibitors, and patients with congenital FVII deficiency. In Europe, additional approval was granted for treatment of Glanzmann's thrombasthenia. Off-label treatment using rFVIIa to stop severe bleeding in children has been published concerning neurosurgical procedures (Heisel et al. 2004; Uhrig et al. 2007) and cardiac surgery (Ekert et al. 2006), but there is insufficient data to prove it is effective in off-label indications. It has been hypothesized that administration of rFVIIa for treatment of severe bleeding may only be efficacious if critical amounts of fibrinogen and platelets have been established or if extremely high doses of rFVIIa were administered (Spahn et al. 2013). Care should be taken to avoid excessive treatment with rFVIIa and PCC, as both substances may increase thromboembolic risk considerably. For this reason, rFVIIa is no longer recommended outside its licensed indications (Simpson et al. 2012).

This chapter reviewed acquired changes to hemostasis that may occur during major pediatric surgery. It also gave clinically useful trigger levels for ROTEM® as well as thresholds for standard laboratory tests for initiating structured and timely coagulation therapy. Further studies are urgently needed to elucidate optimal and safe thresholds for transfusion/coagulation management. As a general rule, treatment of laboratory findings without clinically relevant bleeding should be avoided, or considered very carefully, only if there is a high risk of bleeding.

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