

## SYSTEMATIC REVIEW

# Current use of factor concentrates in pediatric cardiac anesthesia

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**Summary**

Excessive bleeding following pediatric cardiopulmonary bypass is associated with increased morbidity and mortality, both from the effects of hemorrhage and the therapies employed to achieve hemostasis. Neonates and infants are especially at risk because their coagulation systems are immature, surgeries are often complex, and cardiopulmonary bypass technologies are inappropriately matched to patient size and physiology. Consequently, these young children receive substantial amounts of adult-derived blood products to restore adequate hemostasis. Adult and pediatric data demonstrate associations between blood product transfusions and adverse patient outcomes. Thus, efforts to limit bleeding after pediatric cardiopulmonary bypass and minimize allogeneic blood product exposure are warranted. The off-label use of factor concentrates, such as fibrinogen concentrate, recombinant activated factor VII, and prothrombin complex concentrates, is increasing as these hemostatic agents appear to offer several advantages over conventional blood products. However, recognizing that these agents have the potential for both benefit and harm, well-designed studies are needed to enhance our knowledge and to determine the optimal use of these agents. In this review, our primary objective was to examine the evidence regarding the use of factor concentrates to treat bleeding after pediatric CPB and identify where further research is required. PubMed, MEDLINE/OVID, The Cochrane Library and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched to identify existing studies.

**Introduction**

Bleeding after cardiopulmonary bypass (CPB) is a serious complication of pediatric cardiac surgery and often requires significant transfusion of blood products to achieve hemostasis (1–3). Neonates and small infants in particular are susceptible to the coagulopathic effects of CPB. Their immature coagulation system, massive hemodilution from large circuit primes relative to patient size and the extensive suture lines required for complex congenital cardiac repairs all potentiate the bleeding these children experience following CPB (4). To restore the hemostatic balance, transfusion of packed red blood cells (pRBCs), platelets, cryoprecipitate, and coagulation factors is the current standard of

care. Fresh frozen plasma (FFP) can be used to replenish coagulation factors; however, large volumes (up to 15 ml·kg<sup>-1</sup>) are required to increase coagulation factor levels by as little as 20% (5). Such a volume overload is often not tolerated immediately after CPB in small children with a limited cardiopulmonary reserve. In addition, large volume FFP transfusion results in significant hemodilution of hemoglobin and other coagulation proteins including platelets and fibrinogen (6,7). Overall, the administration of allogeneic blood products is associated with significant infectious and noninfectious risks that affect morbidity and mortality (2,8,9). Thus, the search for other effective options to treat coagulopathy after CPB in children remains an important challenge.

Pediatric cardiac anesthesiologists are ever searching for effective, and safe, therapies to augment hemostasis after CPB. Secondary to its success in hemophilia patients, recombinant activated factor VII (rFVIIa; NovoSeven® RT, Novo Nordisk, Bagsvaerd, Denmark) was one such therapy that became increasingly used adjunctively to control bleeding unresponsive to conventional therapy despite a paucity of supportive evidence (10). Today, the focus has shifted to other factor concentrates that offer promise as procoagulant agents, specifically fibrinogen concentrate (FC; RiaSTAP®, CSL Behring, Marburg, Germany) and prothrombin complex concentrates (PCCs). Unfortunately, similar to rFVIIa, these agents have not been adequately studied in pediatric patients undergoing CPB thus limiting their cogent use in this setting. In addition, the limited experience with them in adult open-heart surgery may not be relevant to pediatric practice.

The objective of this review was to assess the current use of factor concentrates for the treatment of bleeding after CPB in children and highlight areas where further research is indicated. To accomplish this, we performed a comprehensive literature search using the following electronic databases: PubMed (1946-October 2016), MEDLINE/OVID (1946-October 2016), The Cochrane Library and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy included a combination of the following medical subject headings (MeSH) terms and keywords: (factor concentrate or recombinant activated factor VII or fibrinogen concentrate or prothrombin complex concentrate) AND (cardiac surgery or cardiopulmonary bypass) AND (pediatric or children). Our final electronic search was performed on November 9, 2016; the results are shown in Table 1. In addition, the reference lists of included articles were manually examined.

### Hemostasis and its maturation

To begin, we describe several important maturational processes that occur in the hemostatic system and are pertinent to the context of this review. Although all the key components of the hemostatic system are present at birth, important quantitative and qualitative differences exist between neonates and adults (11,12). Procoagulant factors [e.g.,: prothrombin or factor (F) II, FVII, FIX, and FX] and anticoagulant factors (e.g.,: protein S, protein C, and antithrombin) are low at birth and do not reach adult ranges until approximately 6 months of age. As a result, the amount of thrombin that a neonate is able to generate is appropriately 50% of adult values (13). Nevertheless, neonatal coagulation is regarded

**Table 1** Results of search strategy

Database	MeSH Heading		
	Search 1: Factor concentrate or Recombinant activated factor VII or Prothrombin complex concentrate	Search 2: 1 AND Cardiac surgery or Cardiopulmonary bypass	Search 3: 2 AND Children or Pediatric
PubMed	4445	84	13
MEDLINE/OVID	5654	233	49
CDSR	26		
CENTRAL		24	

Search limited to human and English language only.  
CDSR, The Cochrane Database of Systematic Reviews.

adequate and in balance, but prone to perturbation because of limited factor reserves.

Fibrinogen plays a major role in clot formation, and recent work has increased our understanding of its maturational process. Although fibrinogen concentrations are comparable between neonates and adults, evidence suggests that fibrinogen exists in a fetal form that is qualitatively dysfunctional until approximately 1 year of age (14). The idea that a fetal form of fibrinogen might exist was based upon observations that thrombin and reptilase clotting times are prolonged in neonates when compared to adults (15). These tests measure the rate of conversion of fibrinogen to fibrin after the addition of an exogenous stimulus (either thrombin or reptilase) and suggest that polymerization of fibrin formed from cord fibrinogen is slower than that of fibrin formed from adult fibrinogen. Additionally, biochemical studies have shown that neonatal fibrinogen has a different electrical charge and higher phosphorus content than adult fibrinogen (16,17). An *in vitro* study utilizing the whole blood coagulation assay, thrombelastography (TEG®; Haemonetics Corporation, Braintree, MA), supported functional differences between fetal and adult fibrinogen (18). In adults, fibrinogen values showed excellent correlation with TEG maximum amplitude (MA) after modification with a glycoprotein IIb/IIIa receptor blocker that uncouples platelet–fibrinogen interactions. However, in children less than 1 year of age, this correlation was lost indicating a dysfunctional state of fibrinogen in these children.

Recent evidence supports that indeed there are significant age-related variations in fibrinogen structure and function (19). The ‘fetal’ fibrinogen present in neonates and young infants creates a fibrin network that is structurally different from that seen in adults. Polymerization of fibrin formed from neonatal fibrinogen favors

elongation rather than branching. The resultant clots lack significant three-dimensional structure, are more porous than adult clots and are composed of highly aligned fibers as opposed to highly branched fibers. Furthermore, neonatal and adult fibrinogen do not appear to integrate seamlessly during the process of fibrin formation so that neonatal clots are not fully restored despite the transfusion of adult fibrinogen (19). *In vitro* studies utilizing adult fibrinogen have shown that both the fibrinogen and thrombin concentration present at the time of clot formation profoundly influence fibrin network properties (20–22). Fibrin networks formed in the presence of low thrombin concentrations are composed of fibrin fibers that are thick, loosely assembled, and highly susceptible to degradation. Conversely, fibrin networks formed in the presence of high concentrations of thrombin are composed of fibers that are thin, densely packed, and relatively resistant to degradation (Figure 1). While the effect of thrombin concentration on fibrin network structures has been studied extensively in adults (23), no comparable thorough analysis has been performed in neonates and infants. Deeper insight into the molecular mechanisms of neonatal fibrin polymerization may enhance our understanding of the hemostatic dysfunction experienced by neonates and young infants after CPB.

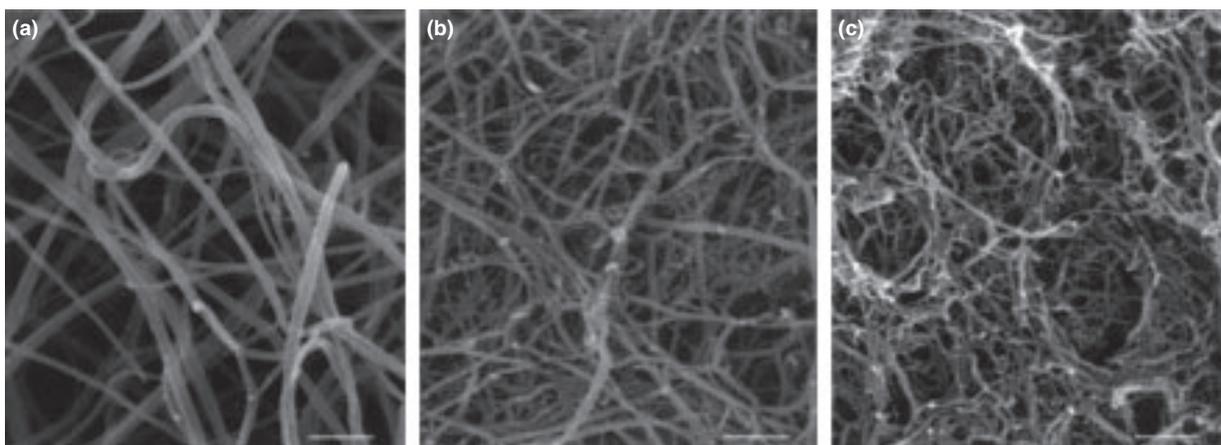
### Factor concentrates

The off-label use of factor concentrates, including rFVIIa, FC, and PCCs, as procoagulant adjuncts to limit exposure to allogeneic blood product transfusion has become increasingly common (24–26). Their use is

gaining in applicability as they do not require cross-matching, may be administered in a small volume and are readily available, less labor-intensive, and not associated with the same infectious and noninfectious risks as blood product transfusion. However, to establish their place in transfusion algorithms, factor concentrates must be better studied in terms of the timing of their administration, dosing (especially in children), risk of thrombotic complications and cost-effectiveness. Next, we will review our findings regarding the use of factor concentrates in pediatric cardiac surgery and highlight where further research is needed to confirm their clinical application and risk–benefit profile.

### Recombinant activated factor VII

rFVIIa is FDA approved for the treatment and prevention of uncontrolled bleeding in hemophiliac patients who have developed antibodies to clotting FVIII and FIX, factor VII deficiency, and Glanzmann thrombasthenia (27). It enhances the initiation phase of clot formation and, consequently, the amount of thrombin generated at the site of blood vessel injury (28). Because of its success as a procoagulant agent, rFVIIa was one of the first factor concentrates to be used off-label in adult and pediatric patients after CPB, and its usage became prolific despite a paucity of rigorous data. Although there is a substantial amount of literature documenting its off-label use in pediatric cardiac patients, the majority is in the form of case reports, small case series, and anecdotal experience (29). Only one study exists that is prospective in methodology. The investigators examined the prophylactic administration of  $40 \mu\text{g}\cdot\text{kg}^{-1}$



**Figure 1** Scanning electron micrograph of clot formed with increasing concentrations of thrombin. Reaction mixtures were comprised of fibrinogen  $3 \text{ mg}\cdot\text{ml}^{-1}$ , thrombin 0.05 (a), 1 (b), or 5 (c) NIHU per ml and FXIIIa inhibitor 1 mM. Bar =  $0.5 \mu\text{m}$ . Reprinted from Ryan et al. (22), with permission from Elsevier.

of rFVIIa or placebo, in lieu of conventional blood products, to prevent bleeding in children less than 1 year of age after CPB (30). They reported no significant differences in any of the measured endpoints between the rFVIIa and placebo groups. There were two distinct criticisms of their negative findings. One was that the dose was ineffective. Data suggest that children require a higher initial dose and more frequent dosing to achieve and maintain an effective plasma concentration in comparison to adults (31). This has been supported by clinical data. In a review analyzing the dosing regimens of 47 pediatric cardiac surgery patients receiving rFVIIa, the mean bolus dose associated with efficacy (defined as a reduction in chest tube drainage or need for blood product transfusion) was  $93.2 \mu\text{g}\cdot\text{kg}^{-1}$  (32). The second criticism was that rFVIIa is not intended to act as a “universal hemostatic agent” (33) but requires contributions from other coagulation system components. In a large retrospective cohort of adult cardiac surgical patients, identified predictors of treatment failure included an INR  $>2.0$ , platelet count  $80 \times 10^6$  and fibrinogen  $<100 \text{ mg}\cdot\text{dl}^{-1}$ , thus reinforcing the concept that platelets, fibrinogen, and coagulation factors should be replaced prior to the administration of rFVIIa in order to optimize its effectiveness (34).

Studies in the adult cardiac literature have raised safety concerns regarding the potential thrombotic risk of rFVIIa without providing a clear indication of its benefit. Yank *et al.* (35) evaluated 16 randomized, controlled trials (RCTs), 26 comparative observational studies, and 22 noncomparative observational studies to assess the benefits and harms of rFVIIa for off-label indications. For the adult cardiac surgery group, they concluded that rFVIIa administration after CPB did not reduce mortality but did increase the rate of thromboembolic events [risk difference, 0.05 (CI, 0.01–0.10)]. Levi *et al.* (36) also analyzed pooled data from 35 RCTs, three of which involved adult cardiac surgery, in order to determine thromboembolic rates associated with rFVIIa administration. The authors found an overall rate of 10.2% in patients who received rFVIIa compared to 8.7% in patients who received placebo (odds ratio, 1.17; 95% CI, 0.94–1.47;  $P = 0.16$ ). This rate is similar to the 10.9% thromboembolic rate reported with its off-label administration in children (37). A Cochrane review assessing the off-label use of rFVIIa found that none of the examined outcomes showed a reliable advantage of rFVIIa over placebo, but there was a statistically significant increase in arterial thrombotic events (relative risk 1.45; 95% CI 1.02–2.05). The authors concluded that the off-label effectiveness of rFVIIa as a general hemostatic drug was not justified and that its use should be restricted to clinical trials (38).

In 2012, the Congenital Cardiac Anesthesia Society (CCAS) convened a special task force to review the off-label use of rFVIIa during pediatric cardiac surgery. They concluded that there was insufficient data to make evidence-based recommendations although there was observational evidence of benefit as rescue therapy for post-CPB hemorrhage refractory to maximal standard hemostatic therapy (10). The task force encouraged the development of future clinical trials to assess rFVIIa efficacy as prophylactic, routine, or rescue therapy and to determine the drug’s safety profile particularly with regard to thrombosis. However, since that publication, there have been no further prospective studies comparing rFVIIa to either standard hemostatic therapy or other procoagulant agents in pediatric cardiac surgery patients after CPB. Such studies are critical to provide evidence supportive of its use.

### Fibrinogen concentrate

Fibrinogen concentrate is manufactured from adult human plasma and contains purified fibrinogen as a pasteurized, lyophilized powder without other coagulation factors. This is in contrast to the blood product, cryoprecipitate, which contains FVIII, von Willebrand factor, FXIII, and fibronectin in addition to fibrinogen. During the manufacturing process of FC, viral inactivation steps are performed thereby minimizing the risk of viral transmission. The viral inactivation processes also remove antibodies and antigens, thus reducing the risk of immunological and allergic reactions (39). The administration volume is small and the preparation time is short since there is no requirement for thawing. The concentration of fibrinogen contained in each vial varies between 900 and 1300 mg of fibrinogen (40). In patients with congenital afibrinogenemia, a prophylactic dose of  $70 \text{ mg}\cdot\text{kg}^{-1}$  of FC raises fibrinogen levels by a mean of  $100 \text{ mg}\cdot\text{dl}^{-1}$  (41). A recent study assessing the pharmacokinetic profile of FC showed that, after the administration of  $70 \text{ mg}\cdot\text{kg}^{-1}$ , median fibrinogen plasma activity reached the targeted range of  $100\text{--}150 \text{ mg}\cdot\text{dl}^{-1}$  within 1 h (42). Plasma recovery was similar in both children (age range: 8–14 years;  $n = 4$ ) and adults (age range: 16–65 years;  $n = 10$ ). However, in children the terminal elimination half-life was shorter with an increased clearance suggesting more frequent dosing may be required. Similar data for younger children, infants, and neonates do not exist.

It is widely acknowledged that, when acute hemorrhage does occur, fibrinogen is the first clotting factor to reach critically low levels (43). Despite its importance in achieving adequate hemostasis, there is no concrete agreement upon the minimal plasma concentration

required for optimal fibrinogen function. The revised European trauma guidelines published in 2010 recommend a threshold fibrinogen concentration of 150–200 mg-dl<sup>-1</sup> to promote effective clot formation, an increase from the previous recommendation of 100 mg-dl<sup>-1</sup> (44). This target is corroborated by several *in vitro* studies. In a hemodilution model simulating massive transfusion, a plasma fibrinogen concentration of 200 mg-dl<sup>-1</sup> was necessary to improve the rate of fibrin polymerization as measured by thromboelastometry (ROTEM™; Pentapharm, Munich, Germany) (45). Similarly, using thrombelastography, overall clot strength increased significantly as fibrinogen concentrations rose from 75 to 300 mg-dl<sup>-1</sup> (46).

During CPB, fibrinogen levels decrease up to 40% below baseline levels even in adults and fibrin formation is significantly impaired, greater than platelet function or total thrombin generation (47,48). Several studies in adult cardiac surgery patients undergoing CPB suggest that preoperative or postoperative fibrinogen levels correlate with or predict postoperative bleeding. A meta-analysis of 20 individual studies identified a weak to moderate correlation between pre- and postoperative fibrinogen levels and excessive postoperative chest tube drainage, with a greater correlation in patients with a lower preoperative fibrinogen (49). A large prospective, observational study of 1956 consecutive adult cardiac patients requiring CPB analyzed the association between preoperative and postoperative fibrinogen levels and the perioperative variation in fibrinogen level with 24-h postoperative chest tube output (50). The authors found that the postoperative fibrinogen level at the time of ICU admission was an independent risk factor for excessive bleeding. However, the results of a phase III, multicenter, and randomized, controlled study did not support the use of FC after CPB in adults undergoing elective aortic surgery (51). When administered according to a bleeding calculation 5 min after CPB, FC was associated with an increase in the administration of blood products during the first 24 postoperative hours. The authors speculate that low bleeding rates, normal-range fibrinogen values before the administration of FC and a low adherence rate to the study protocol may have contributed to their negative results.

In pediatric patients undergoing CPB, the relationship between pre- and/or postoperative plasma fibrinogen concentration and postoperative bleeding has not been thoroughly studied. In a retrospective review of 156 children undergoing CPB, Faraoni *et al.* (52) demonstrated that plasma fibrinogen concentration and maximal clot firmness (MCF) on FIBTEM measured 10 min after protamine administration were significantly associated with postoperative blood loss. A plasma fibrinogen

concentration of less than 150 mg-dl<sup>-1</sup> predicted postoperative bleeding with a sensitivity of 68.9% and specificity of 83.8%. Similarly, a cutoff of 3 mm for MCF on FIBTEM predicted postoperative bleeding with a sensitivity of 78.6% and specificity of 70%. In a small pilot study, Galas *et al.* (53) investigated the efficacy and safety of FC. Sixty-three children with a median age of 3.5 (interquartile range: 1–51.6) months undergoing cardiac surgery were randomized to receive either FC (60 mg·kg<sup>-1</sup>) or cryoprecipitate (10 ml·kg<sup>-1</sup>) after weaning from CPB if bleeding was associated with a fibrinogen level less than 100 mg-dl<sup>-1</sup>. The primary outcome was postoperative blood loss during the first 48 h after surgery. After treatment, plasma fibrinogen concentration increased similarly following the administration of both products. The median amount of blood loss in the first 48 h after surgery was not significantly different between the two groups, and there was no significant difference in the amount of allogeneic blood product transfusion received by the two groups.

To define the specific role of FC to treat bleeding after CPB in pediatric patients, there are several important clinical questions that need to be addressed: are the additional coagulation components found in cryoprecipitate necessary to optimally control bleeding or is fibrinogen alone sufficient; is the answer to the previous question dependent on the patient's age and/or clinical scenario; what is the optimal plasma fibrinogen concentration; which test best determines adequate fibrinogen restoration? Other equally important scientific questions regarding fibrinogen include: does adult fibrinogen, either from cryoprecipitate or FC, assimilate smoothly into the infant and neonatal coagulation system; if not, at what age does this change; is FC readily degraded by the neonatal fibrinolytic system? Research aimed at exploring the above questions would provide a more clear understanding of the hemostatic development of our youngest patients and how best to treat derangements in fibrin polymerization.

### Prothrombin complex concentrates

Prothrombin complex concentrates are plasma-derived coagulation factor concentrates that contain all the coagulation factors required to directly promote thrombin generation. The specific composition of PCC preparations varies depending on the manufacturer; however, most include FII, FVII, FIX, FX, and a few contain small amounts of the anticoagulant proteins C, S, and antithrombin. Three-factor (3F) PCCs contain low levels of FVII and therapeutic levels of FII, FIX, and FX in contrast to four factor (4F) PCCs which contain therapeutic amounts of all the vitamin K-dependent

factors. The majority of PCC formulations contain inactivated factors; Factor Eight Inhibitor Bypassing Activity (FEIBA; Baxter Healthcare Corporation, Westlake Village, CA) is the only activated PCC in the United States and contains FVIIa and small amounts of FXa. A list of the commercially available PCCs and their contents can be found in Tables 2 and 3.

Prothrombin complex concentrates enhance the amplification phase of coagulation by increasing the *in vivo* concentration of coagulation factors in the blood (54). They are most commonly administered for replacement therapy in patients with congenital or acquired coagulation factor deficiencies, and are also indicated to

reverse the anticoagulant effects of vitamin K antagonists. In the 2005 update on oral anticoagulation guidelines, the British Committee for Standards in Hematology recommended PCCs as preferential to FFP for reversing anticoagulation in patients with major bleeding (55). In the United States, in 2013, the FDA approved Kcentra (CSL Behring, King of Prussia, PA), a nonactivated 4F-PCC, for the urgent reversal of acute major bleeding due to vitamin K antagonists in adult patients.

Similar to other factor concentrates, PCCs are being used off-label for the treatment of acquired bleeding disorders. In animal models of uncontrolled hemorrhage and dilutional coagulopathy, the administration of PCC and fibrinogen concentrate restored clot formation, reduced blood loss and improved mortality (56,57). There are multiple publications reporting the success of 4F-PCCs to treat refractory bleeding in adult cardiac surgery patients after CPB (26,58–61). PCC administration was associated with reductions in transfusion requirements and the avoidance of re-exploration for bleeding. Unfortunately published data from pediatric patients are lacking. There is one prospective study in pediatric cardiac patients evaluating the prophylactic administration of a nonactivated 4F-PCC (Confidex<sup>®</sup>; CSL Behring, Milan, Italy) (62). Infants who received 0.1 mg·kg<sup>-1</sup> of Confidex<sup>®</sup> 30 min after weaning from CPB experienced less chest tube output and received fewer units of pRBCs in the first 24 postoperative hours than those infants who received nothing. However, FFP transfusion within the first 24 postoperative hours was the same between the two groups. An *ex vivo* study examined the effect of two different 4F-PCCs (one activated and one nonactivated) on thrombin generation

**Table 2** Commercially available prothrombin complex concentrates

Product	Manufacturer	Availability
Bebulin (Factor IX complex)	Baxalta	USA, Europe
Beriplex P/N, Confidex, or Kcentra	CSL Behring	USA, Canada, Europe, Australia
Cofact	Sanquin	Europe
FEIBA (Anti-inhibitor coagulant complex)	Baxalta	USA, Canada, Europe, Australia
Kaskadil	LFB Biomedicaments	France
Octaplex	Octapharma	Canada, Europe
PPSB-human sd/Nano	Octapharma	Germany
Profilnine sd	Grifols	USA
Prothromplex Total (Human Prothrombin Complex Concentrate)	Shire	Europe
Uman-Complex D.I.	Kedrion	Italy

Adapted with permission from Grottke and Levy (54). <http://anesesthesiology.pubs.asahq.org/article.aspx?articleid=2111046>.

**Table 3** Content of available prothrombin complex concentrates

Product	FII	FVII	FIX	FX	Protein C	Protein S	AT	Heparin
Bebulin	24–38	<5	24–38	24–38	–	–	–	<0.15 <sup>a</sup>
Beriplex P/N, Confidex or Kcentra	20–48	10–25	20–31	22–60	15–45	12–38	0.2–1.5	0.4–2.0
Cofact	≥15	≥5	≥20	≥15	–	–	–	–
FEIBA <sup>b</sup>	1.3 <sup>c</sup>	0.9 <sup>c</sup>	1.4 <sup>c</sup>	1.1 <sup>c</sup>	1.1 <sup>c</sup>	–	–	None
Kaskadil	40	25	25	40	–	–	–	–
Octaplex	14–38	9–24	25	18–30	13–31	12–32	–	5–12.5
PPSB-human sd/Nano	25–55	7.5–20	24–37.5	25–55	20–50	5–25	0.5–3.0	0.5–6.0
Profilnine sd	1.5 <sup>a</sup>	0.35 <sup>a</sup>	100 <sup>d</sup>	1 <sup>a</sup>	–	–	–	None
Prothromplex Total	30	25	30	30	>20	–	0.75–1.5	<15
Uman-Complex D.I.	25	–	25	20	–	–	–	–

All units are IU·ml<sup>-1</sup> unless otherwise indicated.

<sup>a</sup>IU per IU factor IX.

<sup>b</sup>Contains activated FVII.

<sup>c</sup>U per 1U FEIBA.

<sup>d</sup>IU per dose.

Adapted with permission from Grottke and Levy (54). <http://anesesthesiology.pubs.asahq.org/article.aspx?articleid=2111046>.

**Table 4** Summary of critical research needs

	rFVIIa	FC	PCC
Therapy Goal: Prophylaxis	Efficacy <ul style="list-style-type: none"> <li>• Unknown—one study to support none (30)</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• Uncertain</li> </ul>	Efficacy <ul style="list-style-type: none"> <li>• Unknown</li> <li>• Risk/Benefit</li> <li>• Uncertain</li> </ul>	Efficacy <ul style="list-style-type: none"> <li>• Unknown—one study to support some (nonactivated 4F-PCC) (63)</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• Uncertain</li> </ul>
Therapy Goal: Replace blood products (Routine)	Efficacy <ul style="list-style-type: none"> <li>• Optimal trigger and target values</li> <li>• Compare to FFP</li> <li>• Compare to PCC</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• rFVIIa vs FFP vs PCC</li> </ul> Safety <ul style="list-style-type: none"> <li>• Compare to FFP</li> <li>• Compare to PCC</li> </ul>	Efficacy <ul style="list-style-type: none"> <li>• Optimal trigger and target values</li> <li>• One study to support similar to cryoprecipitate (54)</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• FC vs cryoprecipitate</li> </ul> Safety <ul style="list-style-type: none"> <li>• Compare to cryoprecipitate</li> </ul>	Efficacy <ul style="list-style-type: none"> <li>• Optimal trigger and target values</li> <li>• Comparison of various PCCs</li> <li>• Compare to FFP</li> <li>• Compare to rFVIIa</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• PCC vs FFP vs rFVIIa</li> </ul> Safety <ul style="list-style-type: none"> <li>• Compare to FFP</li> <li>• Compare to rFVIIa</li> </ul>
Therapy Goal: Augment blood products (Rescue)	Efficacy <ul style="list-style-type: none"> <li>• Optimal trigger and target values</li> <li>• Optimal timing of administration in transfusion algorithm</li> <li>• Compare to continued blood product therapy</li> <li>• Compare to PCC</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• rFVIIa vs no rFVIIa</li> </ul>	Efficacy <ul style="list-style-type: none"> <li>• Optimal trigger and target values</li> <li>• Compare to continued cryoprecipitate</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• FC vs no FC</li> </ul>	Efficacy <ul style="list-style-type: none"> <li>• Optimal trigger and target values</li> <li>• Optimal timing of administration in transfusion algorithm</li> <li>• Compare to continued blood product therapy</li> <li>• Compare to rFVIIa</li> </ul> Risk/Benefit <ul style="list-style-type: none"> <li>• PCC vs no PCC</li> </ul>
Risk Profile	<ul style="list-style-type: none"> <li>• Risk of thrombosis</li> <li>• Risk of multiple factor deficiencies</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of thrombosis</li> <li>• Risk of FXIII deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Prolonged risk of thrombosis</li> </ul>
Monitoring: Trigger to treat and target values	Coagulation tests <ul style="list-style-type: none"> <li>• INR</li> <li>• ROTEM</li> <li>• TEG</li> </ul>	Coagulation tests <ul style="list-style-type: none"> <li>• Quantitative (e.g., Clauss)</li> <li>• Functional (e.g., FIBTEM, TEG-FF)</li> </ul>	Coagulation tests <ul style="list-style-type: none"> <li>• INR</li> <li>• ROTEM</li> <li>• TEG</li> </ul>

rFVIIa, recombinant activated factor VII; FC, fibrinogen concentrate; PCC, prothrombin complex concentrate; 4F, 4 factor; FFP, fresh frozen plasma; FXIII, factor XIII; INR, international normalized ratio; ROTEM, rotational thromboelastometry; TEG, thrombelastography; TEG-FF, TEG functional fibrinogen.

when added to neonatal plasma after CPB and after an initial transfusion of platelets and cryoprecipitate (63). Both PCCs enhanced the lag time, the peak amount, and the rate of thrombin generation; however, only the activated 4F-PCC, containing FVIIa, was capable of returning the lag time to its baseline value. The authors hypothesized that low-dose 4F-PCCs containing aFVII may prove to be an effective adjunct to the initial transfusion of platelets and cryoprecipitate to further augment coagulation and control bleeding in neonates after CPB.

Reports of thrombotic complications after the administration of PCCs are minimal but the studies citing these events are not appropriately powered to assess safety. Because PCCs are designed to promote thrombin

generation, the potential risk of unwanted thrombosis is ever present. In a study of trauma patients, treatment with a PCC resulted in an increase in thrombin potential for 3–4 days, a period of time consistent with the 60–72 h half-life of FII (64). Prothrombin (FII) has been identified as the key promotor of thrombogenicity in PCC formulations leading to the suggestion that PCCs should be labeled according to FII content instead of FIX (54). Although a few PCC formulations contain low doses of coagulation inhibitors, this does not negate the risk of adverse thrombotic complications as the amounts of these inhibitor proteins are much less than that of the coagulation factors contained in the concentrate. Similar to the other factor concentrates presented in this review, appropriately powered and well-designed

prospective studies are needed to determine when PCCs may serve as an appropriate alternative to FFP administration after pediatric CPB and to evaluate the potential thrombotic risk associated with their administration.

## Conclusion

Bleeding after CPB presents a unique challenge for pediatric cardiac anesthesiologists as the cause is often multifocal and unclear. The current standard of care in the United States to treat bleeding after CPB is the transfusion of adult blood products: pRBCs, platelets, fibrinogen (in the form of cryoprecipitate), and FFP. However, transfusion with any of these products carries significant risks that may affect morbidity and mortality. Procoagulant factor concentrates are increasingly being used off-label to reduce exposure to allogeneic blood products (24–26). Initially these agents were employed only for rescue after failed conventional therapy, but are now being incorporated into transfusion algorithms as first- or second-line treatment. However, because factor concentrates do not address all of the reasons that pediatric patients bleed after CPB, they must be integrated into a comprehensive strategy to achieve

hemostasis and limit blood product usage. In order to understand how they are best suited to accomplish these goals, data demonstrating their efficacy, safety, and cost-effectiveness are required. A summary of the research areas we find worthy of exploration is shown in Table 4. We believe such information is critical to the establishment of factor concentrates as treatment strategies for bleeding in pediatric patients after CPB. However, until such studies are performed, there are insufficient data to make evidence-based recommendations regarding their use.

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## Conflict of interests

The authors report no conflict of interest.

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