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Use and Future Investigations of Recombinant and Plasma-Derived Coagulation and Anticoagulant Products in the Neonate

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ABSTRACT

Although congenital bleeding disorders can manifest in the newborn period, the most common causes of bleeding and thrombosis in neonates are acquired conditions. Factor concentrates are used for specific diagnoses (hemophilia with inhibitors, specific factor deficiency, von Willebrand disease) and approved indications, and increasingly for off-label indications (bleeding in surgery cardiopulmonary bypass, extracorporeal membrane oxygenation). We will review the approved indications for factor products in the neonate and discuss the evidence and rationale for off-label use of factor products in management of bleeding and thrombosis in the neonate.

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Although congenital bleeding and thrombotic disorders can manifest in the newborn period, the most common causes of bleeding and thrombosis in neonates are acquired conditions. In this population, replacement of both coagulant and anticoagulant factor is achieved most commonly with blood product transfusion. However, factor concentrates are used for specific diagnoses and approved indications, and increasingly for off-label indications. We will review the approved indications for factor products in the neonate and discuss the evidence and rationale for off-label use of factor products in management of bleeding and thrombosis in the neonate.

Any assessment of the need for replacement of coagulation and anticoagulation factors in neonates needs to account for the differences in hemostasis and thrombosis between the developing fetus and neonate and older children and adults. In neonates, most coagulation

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factors are decreased, with the exception of factor VIII (FVIII), von Willebrand factor (vWF), and fibrinogen (Table 1) [1-3]. On the other hand, anticoagulant and fibrinolytic proteins (Table 1) are also decreased [1,2]. These decreases can be more pronounced in the preterm neonate [3,4].

Inherited Bleeding Disorders in the Neonate

Hemophilia

Neonates with severe hemophilia (FVIII or factor IX [FIX] levels <0.01 IU/mL) bleed at sites different from those in older children and adults. In a recent US national hemophilia database survey, about 44% of children with hemophilia developed bleeding before age <1 month. The most common sites of bleeding were circumcision, heel stick, soft tissue, oral, organ bleeding, extracranial hemorrhage, and intracranial hemorrhage (ICH) [5]. Most ICHs were silent [6]. About 9.5% of children with hemophilia received factor concentrate within 24 hours of birth (48% for prophylaxis) [5].

First-line treatment of bleeding and prophylaxis for patients with hemophilia A is recombinant FVIII (rFVIII), and for with hemophilia B is recombinant FIX (Table 2). Little is known about the pharmacokinetics of these products in neonates so dosing is derived from data in older children [7]. Close monitoring is necessary because the recovery and half-life may be decreased during acute bleeding [8]. Also, there is known decreased factor recovery after recombinant FIX administration in children [9] and differences in half-life in children and adults (Table 2). The goal of dosing should be 100% factor correction for severe bleeding and 50% correction for non–major bleeding. There are recently approved extended half-life products that have been studied in patients 1 to 18 years old (Table 2) but not in neonates [10-12].

Inhibitors develop in about 20% to 35% of patients with hemophilia A [13]. Although rare, inhibitors to FVIII have developed during the newborn period, some high titer and requiring immune tolerance therapy [14]. Despite the rarity of inhibitors in neonates, prevention of inhibitors in neonates with hemophilia A (which could include choice of factor product for treatment) is important because inhibitors can develop early (median, 22 days; range, 1-50 days) [15] and during acute bleeding, which is common in neonates.

Risk factors for inhibitor development include treatment with rFVIII instead of plasma-derived FVIII (pdFVIII) [16,17]. In a recent meta-analysis of 28 prospective studies, there was no difference in inhibitor development between patients who received pdFVIII vs rFVIII [18]. However, in a recently published multinational randomized control study of previously untreated children with severe hemophilia A, inhibitors developed less in patients who received only pdFVIII (29/125 children), compared with those who received only rFVIII (47/126) [19]. These conflicting findings likely indicate that more studies are needed before definitive recommendations can be made.

Patients with hemophilia A or B and inhibitors are treated with immune tolerance therapy, but management of bleeding is achieved with bypassing agents. Recombinant factor VIIa (rFVIIa; Novoseven, Novo Nordisk, Bagsvaerd, Denmark) is a genetically engineered protein that is approved for use in management and prevention of bleeding in patients with hemophilia and inhibitors and FVII deficiency. Activated prothrombin complex concentrate (PCC; FEIBA, Baxalta, Westlake Village, California) is purified from pooled human plasma and contains mostly nonactivated factors II, IX, and X and mostly activated FVII. Both have been studied in several bleeding and prophylaxis situations in patients (including neonates) with hemophilia A or B and inhibitors, with an overall efficacy rate of about 80% [20,21] and overall no difference in efficacy or safety [22].

New approaches to treatment of hemophilia A, especially in patients with inhibitors, are being developed. Emicizumab, a humanized bispecific antibody acting as an FVIII mimetic, has been shown to be safe and decreased bleeding rates in adolescents and adults with severe hemophilia A (61% of whom had inhibitors to FVIII) [23]. Small interfering RNAs that deplete the production of antithrombin (AT) III has been shown to improve hemostasis and decrease bleeding in a mouse model of hemophilia A [24]; there is an ongoing phase 1 clinical trial of this agent [25]. In animal models of severe hemophilia A and B, the addition of tissue factor pathway inhibitor antagonist has been shown to increase thrombin generation to the levels observed in normal control, and several of these agents are currently in development [26].

Von Willebrand Disease

Severe von Willebrand disease (vWD) has been reported to present in the newborn period as ICH [27] and hemorrhagic edema [28]. First-line treatment of vWD in the neonate is vWF/FVIII concentrate, of which there are 3 formulations approved in the United States (Humate-P [CSL Behring, Kankaee, Illinois], Alphanate [Grifols, Los Angeles, California], Wilate [Octapharma USA, Hoboken, New Jersey]; see Table 2). These products have different ratios of FVIII/vWF. There

Table 1
Approximate coagulation reference range values in newborns compared with older children and adults[a] [1-4]

Test or level	Preterm infant, 30-36 GA, at day 1	Preterm infant, 30-36 GA, at day 30	Term infant, at day 1	Children 1-12 mo	Children 1-5 y	Children 6-10 y	Children 11-16 y	Adults
PT[a] (s)	10.6-16.2	10.0-13.6	14.4-16.4	11.5-15.3	12.1-14.5	11.7-15.1	12.7-15.1	11.5-14.5
aPTT[a] (s)	27.5-79.4	26.9-62.5	34.3-44.8	35.1-46.3	33.6-43.8	31.8-43.7	33.9-46.1	28.6-38.2
Fibrinogen (g/L)	1.5-3.25	1.50-4.14	1.92-3.74	0.82-3.83	1.62-4.01	1.99-4.09	2.12-4.33	1.9-4.3
PFA-100 collagen/ADP closure time (s)			40-92			89 ± 20		
Bleeding time (min)						2.5-13		1-7 [25]
vWF (U/mL)	0.78-2.10	0.66-2.16	0.50-2.87			0.44-1.44		0.50-1.58
Factor II (U/mL)	0.20-0.77	0.36-0.95	0.41-0.69	0.62-1.03	0.7-1.09	0.67-1.10	0.61-1.07	0.78-1.38
Factor V (U/mL)	0.41-1.44	0.48-1.56	0.64-1.03	0.94-1.41	0.67-1.27	0.56-1.41	0.67-1.41	0.78-1.52
Factor VII (U/mL)	0.21-1.13	0.21-1.45	0.52-0.88	0.83-1.6	0.72-1.5	0.7-1.56	0.69-2	0.61-1.99
FVIII (U/mL)	0.50-2.13	0.50-1.99	1.05-3.29	0.54-1.45	0.36-1.85	0.52-1.82	0.59-2	0.52-290
FIX (U/mL)	0.19-0.65	0.13-0.80	0.35-0.56	0.43-1.21	0.44-1.27	0.48-1.45	0.64-2.16	0.59-2.54
Factor X (U/mL)	0.11-0.71	0.20-0.92	0.46-0.67	0.77-1.22	0.72-1.25	0.68-1.25	0.53-1.22	0.96-1.71
Factor XI (U/mL)			0.07-0.41	0.62-1.25	0.65-1.62	0.65-1.62	0.65-1.39	0.67-1.96
Factor XII (U/mL)			0.43-0.8	0.2-1.35	0.36-1.35	0.26-1.37	0.14-1.77	0.35-2.07
AT (U/mL)	0.39-0.87	0.48-1.08	0.58-0.9	0.72-1.34	1.01-1.31	0.95-1.34	0.96-1.26	0.66-1.24
α_2-Macro-globulin (U/mL)	0.95-1.83	1.06-1.94	0.95-1.83			1.28-2.09		0.52-1.20
Protein C clotting (U/mL)	0.17-0.53	0.21-0.65	0.24-0.4	0.28-1.24	0.5-1.34	0.64-1.25	0.59-1.12	0.54-1.66
Protein S (clotting; U/mL)	0.12-0.60	0.33-0.93	0.28-0.47	0.29-1.62	0.67-1.36	0.64-1.54	0.65-1.4	0.54-1.03

Abbreviations: GA, gestational age in weeks; PT, prothrombin time; aPTT, activated partial thromboplastin time; PFA, platelet function analyzer; ADP, adenosine diphosphate.
[a] Actual reference ranges vary between laboratories and for different reagents and assays.