The Relevance of Developmental Hemostasis to Hemorrhagic Disorders of Newborns

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The hemostatic system is a dynamic evolving process that is age-dependent. Components of the hemostatic system are synthesized in early fetal life and do not cross the placenta from mother to fetus. However, plasma concentrations of proteins involved in hemostasis significantly differ from adults. Physiological reference ranges are available for premature infants, full-term infants and children from ages 1 to 16 years. In the coagulation system, plasma concentrations of the vitamin K-dependent and contact factors are decreased at birth, whereas other factors such as fibrinogen, FV, FVIII, and FXIII are similar or increased compared with adults at birth. In the fibrinolytic system, plasma concentrations of plasminogen are decreased at birth, whereas tissue plasminogen activator and plasminogen activator inhibitor are increased. Clinically, the hemostatic system of the young is effective and healthy infants do not suffer from spontaneous hemorrhagic complications. However, infants are more vulnerable, compared with older patients, for bleeding in the presence of either congenital or acquired haemostatic defects. Severe congenital bleeding disorders, although rare, frequently present in the newborn period. The most common acquired causes of bleeding newborns include disseminated intravascular coagulation, vitamin K deficiency, and liver disease. A description of these disorders and treatment guidelines are provided.

The hemostatic system is a dynamic evolving process that is age-dependent. Components of hemostasis are synthesized in early fetal life and do not cross the placenta from mother to fetus. The hemostatic system of the young is effective, and healthy infants do not experience spontaneous hemorrhagic complications. However, infants are more vulnerable to serious hemostatic complications from either congenital or acquired hemostatic defects compared with older children and adults.

The accurate diagnosis of hemostatic disorders in newborns presents unique challenges that reflect the profound influence of gestational and postnatal age on physiologic concentrations of components of hemostasis. Reference ranges for the population in question provide a guide upon which the correct diagnosis and optimal treatment of hemostatic complications rely. However, difficulties in obtaining blood samples, wide physiologic variability in concentrations of many hemostatic components, and reduced plasma volume available for assay all contributed to a delay in our understanding of developmental hemostasis. For many years, studies of cord plasma provided the only available reference ranges for newborns. The development of micro techniques permitted the assessment of hemostatic components in small volumes of plasma[1] and led to studies that defined reference ranges for components of hemostasis in the young. Not surprisingly, more recent studies show that cord plasma does not accurately reflect the hemostatic system during the first days and weeks of life.

All diagnoses must be made in the context of age-dependent physiologic ranges for hemostatic components. The clinician's index of suspicion for severe congenital deficiencies must be heightened because many patients with severe congenital deficiencies of hemostatic components present with clinical symptoms during early infancy. The following review summarizes our current understanding of developmental hemostasis in the fetus and newborn. The relevance of some of the more striking features to inherited and acquired hemorrhagic disorders is provided.

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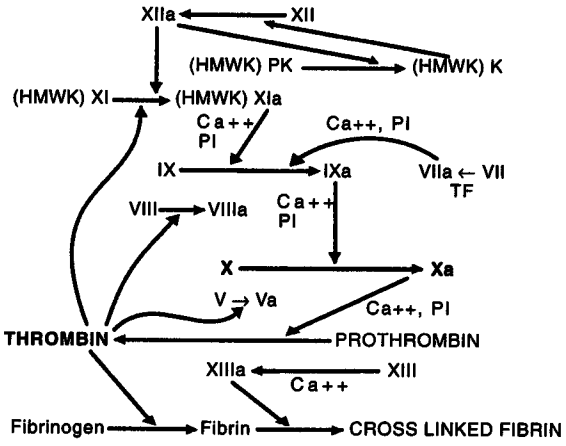

Figure 1. A schema of the coagulation system. (Reprinted with permission.[17])

Developmental Hemostasis

The Coagulation System

Physiology. The physiology of the coagulation system is depicted in Fig 1. Factor (F) VIIa binding to tissue factor (TF), in the presence of Ca++ and a phospholipid surface, initiates coagulation as FVIIa-TF activates both FX and FIX. FVII is cleaved to a two chain serine protease by several coagulation enzymes including FXa, FXIIa, FIXa, and thrombin. Although FXI can be activated by FXIIa, the physiological activator of FXI is likely small amounts of thrombin generated by the TF pathway. FXIa, in the presence of Ca++ and a phospholipid surface, activates FIX to FIXa by limited proteolytic cleavage by either FVIIa or FXIa. FIXa, in the presence of FVIIIa, Ca++, and a phospholipid surface activates FX to FXa. FVIII is converted to FVIIIa by limited cleavage by thrombin and to a lesser extent by FXa. FVIIIa functions as the cofactor when FIXa activates FX. The final reaction of the coagulation pathway is catalyzed by the prothrombinase complex which consists of FVa (cofactor), Fa (enzyme), Ca++ and a phopholipid surface. The prothrombinase complex converts prothrombin to thrombin by two peptide bond cleavages in the zymogen giving rise to pro-

Table 1. Reference Values for Components of the Coagulation System in Healthy Fetuses (19 to 27 Weeks GA) and Premature Infants at Birth (28 to 31 weeks GA)

	Gestational Age (Weeks)			
	19-27		*28-31*	
Coagulation Tests	*M*	*B*	*M*	*B*
PT (s)	—		15.4	(14.6-16.9)[148]
APTT (s)	—		108	(80.0-168)[148]
Fibrinogen (g/L)	1.0	(±0.43)[149]	2.56	(1.60-5.50)[148]
II (U/mL)	0.12	(±0.02)[146]	0.31	(0.19-0.54)[148]
V (U/mL)	0.41	(±0.10)[145]	0.65	(0.43-0.80)[148]
VII (U/mL)	0.28	(±0.04)[146]	0.37	(0.24-0.76)[148]
VIII (U/mL)	0.39	(±0.14)[145]	0.79	(0.37-1.26)[148]
vWF (U/mL)	0.64	(±0.13)[145]	1.41	(0.83-2.23)[148]
IX (U/mL)	0.10	(±0.01)[146]	0.18	(0.17-0.20)[148]
X (U/mL)	0.21	(±0.03)[146]	0.36	(0.25-0.64)[148]
XI (U/mL)	—		0.23	(0.11-0.33)[148]
XII (U/mL)	0.22	(±0.03)	0.25	(0.05-0.35)[148]
PK (U/mL)	—		0.26	(0.15-0.32)[148]
HMWK (U/mL)	—		0.32	(0.19-0.52)[148]
AT (U/mL)	0.24	(±0.03)[147]	0.28	(0.20-0.38)[148]
HCII (U/mL)	0.27	(±0.05)[147]	—	
Protein C (U/mL)	0.11	(±0.03)[146]	—	

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; VIII, factor VIII procoagulant; vWF, von Willebrand factor; PK, prekallikrein; HMWK, high molecular weight kininogen; AT, antithrombin; HCII, heparin cofactor II.

All factors except fibrinogen are expressed as units per milliliter (U/mL) where pooled plasma contains 1.0 U/mL. All values are extrapolated from designated references 145 through 149 and expressed as a mean (M) followed by the lower and upper boundary (B).

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Table 2. Reference Values for Coagulation Tests in the Healthy Premature Infant (30 to 36 Weeks of Gestation) During the First 6 Months of Life

Coagulation Tests	*Day 1*		*Day 5*		*Day 30*		*Day 90*		*Day 180*		*Adult*	
	M	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*
PT (s)	13.0	(10.6-16.2)*	12.5	(10.0-15.3)*	11.8	(10.0-13.6)*	12.3	(10.0-14.6)	12.5	(10.0-15.0)*	12.4	(10.8-13.9)
INR	1.0	(0.61-1.70)	0.91	(0.53-1.48)	0.79	(0.53-1.11)	0.88	(0.53-1.32)	0.91	(0.53-1.48)	0.89	(0.64-1.17)
APTT (s)	53.6	(27.5-79.4)†	50.5	(26.9-74.1)	44.7	(26.9-62.5)	39.5	(28.3-50.7)	37.5	(27.2-53.3)	33.5	(26.6-40.3)
TCT (s)	24.8	(19.2-30.4)	24.1	(18.8-29.4)*	24.4	(18.8-29.9)	25.1	(19.4-30.8)	25.2	(18.9-31.5)	25.0	(19.7-30.3)
Fibrinogen (g/L)	2.43	(1.50-3.73)*†	2.80	(1.60-4.18)*†	2.54	(1.50-4.14)	2.46	(1.50-3.52)	2.28	(1.50-3.60)	2.78	(1.56-4.00)
II (U/mL)	0.45	(0.20-0.77)	0.57	(0.29-0.85)†	0.57	(0.36-0.95)	0.68	(0.30-1.06)	0.87	(0.51-1.23)	1.08	(0.70-1.46)
V (U/mL)	0.88	(0.41-1.44)*†	1.00	(0.46-1.54)*	1.02	(0.48-1.56)*	0.99	(0.59-1.39)	1.02	(0.58-1.46)*	1.06	(0.62-1.50)
VII (U/mL)	0.67	(0.21-1.13)	0.84	(0.30-1.38)	0.83	(0.21-1.45)	0.87	(0.31-1.43)	0.99	(0.47-1.51)*	1.05	(0.67-1.43)
VIII (U/mL)	1.11	(0.50-2.13)	1.15	(0.53-2.05)*†	1.11	(0.50-1.99)	1.06	(0.58-1.88)*†	0.99	(0.50-1.87)*†	0.99	(0.50-1.49)
vWF (U/mL)	1.36	(0.78-2.10)	1.33	(0.72-2.19)	1.36	(0.66-2.16)	1.12	(0.75-1.84)*†	0.98	(0.54-1.58)*	0.92	(0.50-1.58)
IX (U/mL)	0.35	(0.19-0.65)†	0.42	(0.14-0.74)†	0.44	(0.13-0.80)	0.59	(0.25-0.93)	0.81	(0.50-1.20)	1.09	(0.55-1.63)
X (U/mL)	0.41	(0.11-0.71)	0.51	(0.19-0.83)	0.56	(0.20-0.92)	0.67	(0.35-0.99)	0.77	(0.35-1.19)	1.06	(0.70-1.52)
XI (U/mL)	0.30	(0.08-0.52)†	0.41	(0.13-0.69)†	0.43	(0.15-0.71)†	0.59	(0.25-0.93)*	0.78	(0.46-1.10)	0.97	(0.67-1.27)
XII (U/mL)	0.38	(0.10-0.66)†	0.39	(0.09-0.69)†	0.43	(0.11-0.75)	0.61	(0.15-1.07)	0.82	(0.22-1.42)	1.08	(0.52-1.64)
PK (U/mL)	0.33	(0.09-0.57)	0.45	(0.25-0.75)	0.59	(0.31-0.87)	0.79	(0.37-1.21)	0.78	(0.40-1.16)	1.12	(0.62-1.62)
HK (U/mL)	0.49	(0.09-0.89)	0.62	(0.24-1.00)†	0.64	(0.16-1.12)†	0.78	(0.32-1.24)	0.83	(0.41-1.25)*	0.92	(0.50-1.36)
$XIII_a$ (U/mL)	0.70	(0.32-1.08)	1.01	(0.57-1.45)*	0.99	(0.51-1.47)*	1.13	(0.71-1.55)*	1.13	(0.65-1.61)*	1.05	(0.55-1.55)
$XIII_b$ (U/mL)	0.81	(0.35-1.27)	1.10	(0.68-1.58)*	1.07	(0.57-1.57)*	1.21	(0.75-1.67)	1.15	(0.67-1.63)	0.97	(0.57-1.37)

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; TCT, thrombin clotting time; VIII, Factor VIII procoagulant; WF, von Willebrand factor; PK, prekallikrein; HK, high molecular weight kininogen; INR, international normalized ratio.

All factors except fibrinogen are expressed as units per milliliter (U/mL) where pooled plasma contains 1.0 U/mL. All values are given as a mean (M) followed by the lower and upper boundary encompassing 95% of the population (B). Between 40 to 96 samples were assayed for each value for the newborn. Some measurements were skewed due to a disproportionate number of high values. The lower limit, which excludes the lower 2.5% of the population, has been given (B).

* Values that are indistinguishable from the adult.

† Values different from those of the full-term infants.

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Table 3. Reference Values for Coagulation Tests in Healthy Full-Term Infants During the First Six Months of Life

Coagulation Tests	*Day 1*		*Day 5*		*Day 30*		*Day 90*		*Day 180*		*Adult*	
	M	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*
PT (s)	13.0	(10.1-15.9)*	12.4	(10.0-15.3)*	11.8	(10.0-14.3)*	11.9	(10.0-14.2)*	12.3	(10.7-13.9)*	12.4	(10.8-13.9)
INR	1.00	(0.53-1.62)	0.89	(0.53-1.48)	0.79	(0.53-1.26)	0.81	(0.53-1.26)	0.88	(0.61-1.17)	0.89	(0.64-1.17)
APTT (s)	42.9	(31.3-54.5)	42.6	(25.4-59.8)	40.4	(32.0-55.2)	37.1	(29.0-50.1)*	35.5	(28.1-42.9)*	33.5	(26.6-40.3)
TCT (s)	23.5	(19.0-28.3)*	23.1	(18.0-29.2)	24.3	(19.4-29.2)	25.1	(20.5-29.7)*	25.5	(19.8-31.2)*	25.0	(19.7-30.3)
Fibrinogen (g/L)	2.83	(1.67-3.99)*	3.12	(1.62-4.62)*	2.70	(1.62-3.78)*	2.43	(1.50-3.79)*	2.51	(1.50-3.87)*	2.78	(1.56-4.00)
II (U/mL)	0.48	(0.26-0.70)	0.63	(0.33-0.93)	0.68	(0.34-1.02)	0.75	(0.45-1.05)	0.88	(0.60-1.16)	1.08	(0.70-1.46)
V (U/mL)	0.72	(0.34-1.08)	0.95	(0.45-1.45)	0.98	(0.62-1.34)	0.90	(0.45-1.32)	0.91	(0.55-1.27)	1.06	(0.62-1.50)
VII (U/mL)	0.66	(0.28-1.04)	0.89	(0.35-1.43)	0.90	(0.42-1.38)	0.91	(0.39-1.43)	0.87	(0.47-1.27)	1.05	(0.67-1.43)
VIII (U/mL)	1.00	(0.50-1.78)*	0.88	(0.50-1.54)*	0.91	(0.50-1.57)	0.79	(0.50-1.25)*	0.73	(0.50-1.09)	0.99	(0.50-1.49)
vWF (U/mL)	1.53	(0.50-2.87)	1.40	(0.50-2.54)	1.28	(0.50-2.46)	1.18	(0.50-2.06)	1.07	(0.50-1.97)	0.92	(0.50-1.58)
IX (U/mL)	0.53	(0.15-0.91)	0.53	(0.15-0.91)	0.51	(0.21-0.81)	0.67	(0.21-1.13)	0.86	(0.36-1.36)	1.09	(0.55-1.63)
X (U/mL)	0.40	(0.12-0.68)	0.49	(0.19-0.79)	0.59	(0.31-0.87)	0.71	(0.35-1.07)	0.78	(0.38-1.18)	1.06	(0.70-1.52)
XI (U/mL)	0.38	(0.10-0.66)	0.55	(0.23-0.87)	0.53	(0.27-0.79)	0.69	(0.41-0.97)	0.86	(0.49-1.34)	0.97	(0.67-1.27)
XII (U/mL)	0.53	(0.13-0.93)	0.47	(0.11-0.83)	0.49	(0.17-0.81)	0.67	(0.25-1.09)	0.77	(0.39-1.15)	1.08	(0.52-1.64)
PK (U/mL)	0.37	(0.18-0.69)	0.48	(0.20-0.76)	0.57	(0.23-0.91)	0.73	(0.41-1.05)	0.86	(0.56-1.16)	1.12	(0.62-1.62)
HK (U/mL)	0.54	(0.06-1.02)	0.74	(0.16-1.32)	0.77	(0.33-1.21)	0.82	(0.30-1.46)*	0.82	(0.36-1.28)*	0.92	(0.50-1.36)
$XIII_a$ (U/mL)	0.79	(0.27-1.31)	0.94	(0.44-1.44)*	0.93	(0.39-1.47)*	1.04	(0.36-1.72)*	1.04	(0.46-1.62)*	1.05	(0.55-1.55)
$XIII_b$ (U/mL)	0.76	(0.30-1.22)	1.06	(0.32-1.80)	1.11	(0.39-1.73)*	1.16	(0.48-1.84)*	1.10	(0.50-1.70)	0.97	(0.57-1.37)

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; TCT, thrombin clotting time; VIII, factor VIII procoagulant; vWF, von Willebrand factor; PK, prekallikrein; HK, high molecular weight kininogen; INR, international normalized ratio.

All factors except fibrinogen are expressed as units per milliliter (U/mL) where pooled plasma contains 1.0 U/mL. All values are expressed as mean (M) followed by the lower and upper boundary encompassing 95% of the population (B). Between 40 and 77 samples were assayed for each value in each population.

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Table 4. Reference Values for the Inhibitors of Coagulation in the Healthy Full-Term Infant and the Premature Infant (30 to 36 Weeks Gestation) During the First 6 Months of Life

	Day 1		*Day 5*		*Day 30*		*Day 90*		*Day 180*		*Adult*	
Inhibitor Levels	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*
Healthy full-term infant												
AT (U/mL)	0.63	(0.39-0.87)	0.67	(0.41-0.93)	0.78	(0.48-1.08)	0.97	(0.73-1.21)*	1.04	(0.84-1.24)*	1.05	(0.79-1.31)
α_2M (U/mL)	1.39	(0.95-1.83)	1.48	(0.98-1.98)	1.50	(1.06-1.94)	1.76	(1.26-2.26)	1.91	(1.49-2.33)	0.86	(0.52-1.20)
C_1E-INH (U/mL)	0.72	(0.36-1.08)	0.90	(0.60-1.20)*	0.89	(0.47-1.31)	1.15	(0.71-1.59)	1.41	(0.89-1.93)	1.01	(0.71-1.31)
α_1AT (U/mL)	0.93	(0.49-1.37)*	0.89	(0.49-1.29)*	0.62	(0.36-0.88)	0.72	(0.42-1.02)	0.77	(0.47-1.07)	0.93	(0.55-1.31)
HCII (U/mL)	0.43	(0.10-0.93)	0.48	(0.00-0.96)	0.47	(0.10-0.87)	0.72	(0.10-1.46)	1.20	(0.50-1.90)	0.96	(0.66-1.26)
Protein C (U/mL)	0.35	(0.17-0.53)	0.42	(0.20-0.64)	0.43	(0.21-0.65)	0.54	(0.28-0.80)	0.59	(0.37-0.81)	0.96	(0.64-1.28)
Protein S (U/mL)	0.36	(0.12-0.60)	0.50	(0.22-0.78)	0.63	(0.33-0.93)	0.86	(0.54-1.18)*	0.87	(0.55-1.19)*	0.92	(0.60-1.24)
Healthy premature infant												
AT (U/mL)	0.38	(0.14-0.62)†	0.56	(0.30-0.82)	0.59	(0.37-0.81)†	0.83	(0.45-1.21)†	0.90	(0.52-1.28)†	1.05	(0.79-1.31)
α_2M (U/mL)	1.10	(0.56-1.82)†	1.25	(0.71-1.77)	1.38	(0.72-2.04)	1.80	(1.20-2.66)	2.09	(1.10-3.21)	0.86	(0.52-1.20)
C_1E-INH (U/mL)	0.65	(0.31-0.99)	0.83	(0.45-1.21)	0.74	(0.40-1.24)†	1.14	(0.60-1.68)*	1.40	(0.96-2.04)	1.01	(0.71-1.31)
α_1AT (U/mL)	0.90	(0.36-1.44)*	0.94	(0.42-1.46)*	0.76	(0.38-1.12)†	0.81	(0.49-1.13)*†	0.82	(0.48-1.16)*	0.93	(0.55-1.31)
HCII (U/mL)	0.32	(0.10-0.60)†	0.34	(0.10-0.69)	0.43	(0.15-0.71)	0.61	(0.20-1.11)	0.89	(0.45-1.40)*†	0.96	(0.66-1.26)
Protein C (U/mL)	0.28	(0.12-0.44)†	0.31	(0.11-0.51)	0.37	(0.15-0.59)†	0.45	(0.23-0.67)†	0.57	(0.31-0.83)	0.96	(0.64-1.28)
Protein S (U/mL)	0.26	(0.14-0.38)†	0.37	(0.13-0.61)	0.56	(0.22-0.90)	0.76	(0.40-1.12)†	0.82	(0.44-1.20)	0.92	(0.60-1.24)

Abbreviations: AT, antithrombin; α_2M, $\alpha_2$macroglobulin; C_1-INH, $c_1$esterase-inhibitor; α_1-AT, $\alpha_1$antitrypsin; HCII, heparin cofactor II.
All values are expressed in units per milliliter (U/mL) where pooled plasma contains 1.0 U/mL. All values are given as a mean (M) followed by the lower and upper boundary encompassing 95% of the population (B). Between 40 and 75 samples were assayed for each value for the newborn. Some measurements were skewed due to a disproportionate number of high values. The lower limits, which exclude the lower 2.5% of the population, have been given (B).
* Values that are indistinguishable from those of the adult.
† Values different from those of the full-term infant.
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thrombin fragment 1.2 and α-thrombin. FX and prothrombin bind to negatively charged phospholipids through their GLA residues. FVa functions as a receptor in platelet membranes binding both prothrombin and FX in close proximity. Cleavage of fibrinopeptide A and B from fibrinogen initiates fibrin assembly. In the presence of FXIIIa, assembled fibrin undergoes covalent cross-linking providing structural stability and integrity to an otherwise easily deformable fibrin clot.

Reference Ranges. Coagulation proteins are synthesized by the fetus and present in measurable quantities by approximately 10 weeks of gestational age (GA). Plasma concentrations of most coagulation proteins gradually increase postnatally, necessitating multiple age-dependent reference ranges. Tables 1 to 4 provide reference ranges for coagulation proteins for the fetus (19 to 27 weeks) and premature infants at birth (28 to 31 weeks); for healthy premature infants (30 to 36 weeks GA); and full-term infants from day 1 to 6 months of life.[2,3]

Screening Tests. There is considerable variability in published reference ranges for screening tests such as the prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin clotting time (TCT) in newborns. The inconsistencies between studies reflect the use of cord blood instead of samples from newborns, differing ethnic populations, and different reagents. Reagent-dependent variations in PT results can be minimized by reporting the PT as an international normalized ratio (INR) (Tables 2 and 3).[4,5] Variable results for the TCT reflect the sensitivity of the assay conditions for "fetal" fibrinogen.[2,3,6] The TCT values in Tables 2 and 3 were measured in the presence of calcium, which reduces the sensitivity to "fetal" fibrinogen but retains sensitivity to heparin and fibrinogen concentration.

Vitamin K (VK)-Dependent Coagulant Factors. The clinical importance of hemorrhagic disease of the newborn (HDN) led to studies early in the 20th century that focused on determining physiological concentrations of the VK-dependent coagulation proteins and their role in hemorrhagic disease of the newborn (HDN).[7-9] Plasma concentrations of all four VK-dependent coagulant proteins are decreased at birth and for many weeks postnatally (Tables 1 through 3). The diagnosis of homozygous FII, and FX deficiency at birth with functional assays may be problematic because the lower physiological limits overlap with values characteristic of these states. In contrast, newborns with homozygous FVII deficiency and the severe/moderate forms of FIX deficiency are easily diagnosed at birth because concentrations of these proteins are clearly less than the physiologically lower limit of normal for age.

Contact Factors. Plasma concentrations of the four contact factors (FXI, FXII, prekallikrein [PK], and high molecular weight kininogen [HMWK]) are similar to the VK-dependent proteins, decreased at birth and gradually increasing to values approaching those in adults by 6 months of age.[2] The prolonged APTT during the first months of life primarily reflects low levels of the contact factors.[2,10-16] The diagnoses of homozygous FXI deficiency in newborns with functional assays may be problematic because the lower physiological limit is 0.20 units/mL, which is similar to severe FXI deficiency.[17]

Other Coagulant Proteins. Concentrations of fibrinogen, FV, and FXIII are similar to adult values at birth (Tables 2 and 3).[2,3] In contrast, levels of FVIII and von Willebrand factor (vWF) are increased (Tables 2 and 3). The lower limit of normal for FVIII was adjusted to accommodate for very high levels that skewed the reference ranges (Table 3).[2] Both vWF levels and high molecular weight multimers are increased at birth and during the first 3 months of life.[2] Newborns with homozygous FV, FXIII, and fibrinogen deficiency are easily diagnosed at birth because concentrations of these proteins are clearly less than the physiological lower limit of normal for age. Similarly, the severe and moderate forms of FVIII (<0.01 and 0.01 to 0.10 units/mL, respectively) are easily distinguished from physiologic values. Most forms of vWD cannot be diagnosed at birth based on functional levels.[18] Only the most severe forms of vWD are characterized by very low plasma concentrations of FVIII and vWF.

Inhibitors of Coagulation

Direct Inhibitors of Thrombin. Plasma concentrations of two direct inhibitors of thrombin, antithrombin (AT, formerly antithrombin III) and heparin cofactor II (HCII), are decreased at birth and similar to heterozygote adults who develop spontaneous thrombotic complications (Table 4).[2,3,18] In contrast, plasma concentra-

tions of a third direct inhibitor of thrombin, $\alpha_2$macroglobulin (α_2M), are increased at birth and throughout childhood. α_2M inhibition of thrombin compensates, at least partly, for the reduced inhibition of thrombin by AT in newborns,[19-21] even in the presence of endothelial cell surfaces.[22]

Fetal Anticoagulant. There is a proteoglycan present in cord blood (0.29 μg/mL) with anticoagulant properties similar to dermatan sulphate,[23] not heparin.[23] The proteoglycan catalyzes thrombin inhibition by HCII, not AT, and has a molecular weight of 150,000 kDA. The dermatan sulphate-like proteoglycan seems to be produced by the placenta,[24] circulates in maternal blood, and disappears from the maternal circulation by approximately day 5 of life.[23]

Protein C/Protein S/Thrombomodulin System. When thrombin is generated in vivo, it binds to the endothelial cell receptor, thrombomodulin (TM). Thrombin bound to TM loses it procoagulant activities and cannot cleave fibrinogen, FV, FVIII, or activate platelets. However, thrombin bound to TM can activate the VK-dependent inhibitor protein C to its activated form, activated protein C (APC). APC inactivates FVa and FVIIIa by proteolytic degradation, a process enhanced by protein S, a second VK-dependent inhibitor.[25] Plasma concentrations of protein C are decreased at birth, with levels usually less than those reported for heterozygote-deficient adults. In addition, protein C exists in a "fetal" form at birth, characterized by a twofold increase in single chain protein C.[25] The physiological significance of fetal protein C remains unclear. Although total amounts of protein S are decreased at birth, the overall activity remains similar to adults because protein S only exists in the free, active form due to the absence of C4B-binding protein.[26,27] The influence of age on endothelial cell expression of TM has not been determined. However, plasma concentrations of TM are increased severalfold at birth and remain increased during early childhood.[28] Whether the overall activity of the protein C/protein S system varies with age is unknown.

Tissue Factor Pathway Inhibitor. A third mechanism for regulating the generation of thrombin is by tissue factor pathway inhibitor (TFPI). A TFPI/FXa complex binds to FVIIa/TF in a FXa calcium-dependent reaction, resulting in the inhibition of FVIIa. After the generation of small amounts of thrombin, TFPI prevents further generation of thrombin via TF/FVIIa. There is limited information on the influence of age on TFPI. Cord plasma concentrations of TFPI are decreased to 64% of adult values.[29,30]

Regulation of Thrombin by Fibrin. The capacity of newborn fibrin clots to bind thrombin has been assessed by measuring FPA production by fibrin clots prepared from adult and cord plasmas.[31] Cord plasma clots generate significantly less FPA compared with adult plasma clots. The responsible mechanism seems to be decreased plasma concentrations of prothrombin, resulting in decreased thrombin bound to fibrin.[31] Clot bound thrombin may be an important mediator of clot extension because it serves as a reservoir of thrombin that is protected from inactivation by plasma inhibitors. Because clot bound thrombin is enzymatically active, it can locally amplify coagulation by activating platelets, or FV and FVIII. This observation suggests that thrombi in newborns may not have the same propensity to propagate compared with thrombi in adults patients.

Physiological Mechanisms

Potential mechanisms explaining the physiologically different plasma concentrations of coagulation proteins at birth include decreased synthesis, accelerated clearance, and consumption at birth.

Production. mRNA levels have been measured for FVII, FVIII, FIX, FX, fibrinogen, AT, and protein C in hepatocytes from 5- to 10-week-old human embryos and fetuses, and from adults.[32] The embryonic-fetal transcripts and adult mRNAs were similar in size; and the nucleotide sequence of FIX and FX mRNA were identical.[33] However, the expression of mRNA was variable, with adult values for some coagulation proteins and decreased expression for others. Similar concentrations of prothrombin mRNA are found in newborn and adult rabbit livers[34]; and another study reported lower prothrombin mRNA concentrations in sheep.[32]

Clearance. Some coagulation proteins are cleared more rapidly in newborns than in adults.[35] Fibrinogen, whether of fetal or adult origin, is cleared more rapidly in newborn lambs compared with sheep.[35] Similarly, clearance of fibrinogen is accelerated in premature infants, with or without respiratory distress syndrome (RDS).[36,37] AT survival times are shorter in

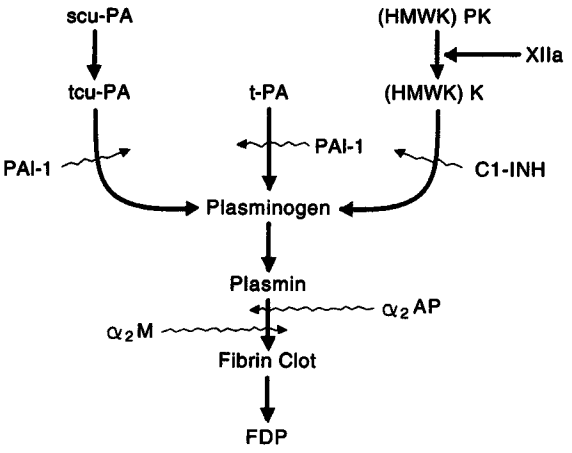

Figure 2. A schema of the fibrinolytic system. (Reprinted with permission.[17])

healthy infants, requiring an exchange transfusion for hyperbilirubinemia compared with adults.[38] An increased basal metabolic rate in the young probably contributes to the accelerated clearance of proteins.[39]

The Influence of Age on Endogenous Regulation of Thrombin

Activation of coagulation in vivo, with the generation of thrombin, can be quantitated by specific activation peptides. Increased plasma concentrations of fibrinogen peptide A (FPA) and thrombin-antithrombin complexes (TATs) in cord plasma suggest that coagulation is activated at birth.[19,40-42] However, this process seems to be well controlled and self-limited. Indeed, activation of coagulation during the birth process does not result in significant consumption of circulating plasma coagulation proteins or clinical morbidity.[43,44]

The Fibrinolytic System

Age and Components of the Fibrinolytic System

During infancy and childhood, plasmin is generated and inhibited in a similar fashion as for adults (Fig 2). Once a fibrin clot has formed in vivo, it is modified by the fibrinolytic system. Analogous to thrombin, plasmin is the critical enzyme in fibrinolysis. Plasminogen circulates in two forms, one with an NH_2-terminal glutamic acid residue (glu-plasminogen) and a second form with NH_2-terminal lysine, valine, or methionine, residues (lys-plasminogen). Glu-plasminogen can be converted to lys-plasminogen by limited proteolytic degradation. Lys-plasminogen has both a higher affinity for fibrin and increased fibrinolytic acitivity compared to glu-plasminogen. Both forms of plasminogen bind to fibrin through specific lysine binding sites that also mediate the interaction of plasminogen with its inhibitor, α_2 antiplasmin (α_2AP). Plasminogen is converted to its enzymatically active form, plasmin, by several activators. Tissue plasminogen activator (TPA) is the most important physiological activator of plasminogen. TPA is a serine protease that also binds to fibrin through lysine-binding sites. TPA is a relatively poor enzyme in the absence of fibrin; however, fibrin greatly enhances the rate of plasminogen activation by TPA. Urokinase (UK) is a second physiological activator of plasminogen. Single-chain UK has relatively low thrombolytic activity until it is activated to its two-chain form by limited cleavage by plasmin or kallikrein. Once formed on the fibrin clot, plasmin cleaves fibrin in sequential steps, resulting in fibrin degradation products (Fig 2). As with thrombin regulation, there are important age-dependent differences in the fibrinolytic system (Table 5).[2,3] Plasminogen levels at birth are only 50% of adult values, and $\alpha_2$antiplasmin (α_2AP) levels 80% of adult values, whereas plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (t-PA) levels are significantly increased over adult values.[3,45,46] The increased plasma levels of t-PA and PAI-1 in newborns on day 1 of life are in marked contrast to values from cord blood, in which concentrations of these two proteins are significantly lower than in adults.[3,45,46] The discrepancy between newborn and cord plasma concentrations of t-PA, and PAI-1 can be explained by enhanced release of t-PA and PAI-1 from the endothelium shortly after birth. Plasminogen activator-2 (PAI-2) levels are detectable in cord blood but at significantly lower concentrations than for pregnant women.[47] Plasminogen, like fibrinogen, has a fetal form. Fetal plasminogen exists in two glycoforms with increased amounts of mannose and sialic acid.[48] There probably is decreased enzymatic activity of "fetal plasmin" as well as decreased binding to cellular receptors for fetal plasminogen.[48]

Table 5. Reference Values for the Components of the Fibrinolytic System in the Healthy Full-Term Infant and the Healthy Premature Infant During the First 6 Months of Life

	Day 1		*Day 5*		*Day 30*		*Day 90*		*Day 180*		*Adult*	
Fibrinolytic System	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*	*M*	*B*
Healthy full-term infant												
Plasminogen (U/mL)	1.95	(1.25-2.65)	2.17	(1.41-2.93)	1.98	(1.26-2.70)	2.48	(1.74-3.22)	3.01	(2.21-3.81)	3.36	(2.48-4.24)
TPA (ng/mL)	9.60	(5.00-18.9)	5.60	(4.00-10.0)*	4.10	(1.00-6.00)*	2.10	(1.00-5.00)*	2.80	(1.00-6.00)*	4.90	(1.40-8.40)
α_2AP (U/mL)	0.85	(0.55-1.15)	1.00	(0.70-1.30)*	1.00	(0.76-1.24)*	1.08	(0.76-1.40)*	1.11	(0.83-1.39)*	1.02	(0.68-1.36)
PAI (U/mL)	6.40	(2.00-15.1)	2.30	(0.00-8.10)*	3.4	(0.00-8.80)*	7.20	(1.00-15.3)	8.10	(6.00-13.0)	3.6	(0.00-11.0)
Healthy premature infant												
Plasminogen (U/mL)	1.70	(1.12-2.48)†	1.91	(1.21-2.61)†	1.81	(1.09-2.53)	2.38	(1.58-3.18)	2.75	(1.91-3.59)†	3.36	(2.48-4.24)
TPA (ng/mL)	8.48	(3.00-16.70)	3.97	(2.00-6.93)*	4.13	(2.00-7.79)*	3.31	(2.00-5.07)*	3.48	(2.00-5.85)*	4.96	(1.46-8.46)
α_2AP (U/mL)	0.78	(0.40-1.16)	0.81	(0.49-1.13)†	0.89	(0.55-1.23)†	1.06	(0.64-1.48)*	1.15	(0.77-1.53)	1.02	(0.68-1.36)
PAI (U/mL)	5.40	(0.00-12.2)*†	2.50	(0.00-7.10)*	4.30	(0.00-11.8)*	4.80	(1.00-10.2)*†	4.90	(1.00-10.2)*†	3.60	(0.00-11.0)

Abbreviations: TPA, tissue plasminogen activator; α_2AP, $\alpha_2$antiplasmin; PAI, plasminogen activator inhibitor.
For α_2AP, values are expressed as units per milliliter (U/mL) where pooled plasma contains 1.0 U/mL. Plasminogen units are those recommended by the Committee on Thrombolytic Agents. Values for TPA are given as nanograms per milliliter. Values for PAI are given as units per milliliter one unit of PAI-1 activity is defined as the amount of PAI-1 that inhibits one international unit of human single chain TA. All values are given as a mean (M) followed by the lower and upper boundary encompassing 95% of the population (B).
* Values that are indistinguishable from those of the adult.
† Values that are different from those of the full-term infant.
Reprinted with permission.[2,3]

The Influence of Age on Endogenous Regulation of Fibrinolysis

When fibrinogen is acted on by thrombin, an amino acid segment (Bβ1-15) is cleaved from fibrinogen. Plasmin cleaves the Bβ 42-43 bond in both fibrinogen and fibrin. Hence, the presence of Bβ 1-42 is an indication of fibrinogenolysis, and the presence of Bβ 15-42 is an indication of fibrin degradation. In newborns, increased plasma concentrations of the Bβ 15-42 fibrin-related peptides suggest that the fibrinolytic system is activated at birth.[3,45] Clot lysis times measure the action of plasminogen activators and plasmin in the blood. Abnormally short whole blood clotting times, short euglobulin lysis times, and increased plasma concentrations of the Bβ15-42 fibrin-related peptides all suggest that the fibrinolytic system is activated at birth.[3,45] At the same time, the capacity of the fetal fibrinolytic system to generate plasmin in response to stimulation with a thrombolytic agent is decreased compared with adults.[49] The latter reflects low plasma concentrations of plasminogen in newborns.[2,3,6,45,46,49-54]

The Diagnosis and Management of Some Hemorrhagic Disorders in Newborns

General Information

In the majority of newborns with a hemorrhagic disorder, the correct diagnosis can be made based on the history and physical examination alone with laboratory tests providing confirmation. One approach to making the correct diagnosis is to first distinguish whether the newborn is otherwise healthy or has serious underlying disorders. The causes of bleeding in otherwise healthy newborns are quite specific and include inherited, severe deficiencies of a hemostatic component FXI, FIX, FX, FVII, FVIII, FV, FII, FXIII, fibrinogen, vWF, α-2 antiplasmin deficiency, PAI, severe thrombocytopenia from transplacental transfer of antiplatelet antibodies, and VK deficiency. The majority of newborns with congenital coagulation factor deficiencies do not present with bleeding in the perinatal period, unless there is a hemostatic challenge. On the other hand, unexplained bleeding in an otherwise healthy newborn should be thoroughly investigated because it may be the presentation of a severe congenital factor deficiency. The most common acquired causes of bleeding in newborns include disseminated intravascular coagulation (DIC), liver disease, and VK deficiency.

Clinical Presentation

Congenital Factor Deficiencies. The clinical presentation of newborns with a congenital factor deficiency differs to some extent from newborns with acquired bleeding disorders. Common sites of bleeding include the umbilicus, peripheral blood sampling sites, scalp (cephalohematomas), at intramuscular injection sites (ie, for vitamin K) and after circumcision. A small but important proportion of infants initially present with an intracranial hemorrhage (ICH).[17] Full-term infants with unexplained ICH should be carefully evaluated for congenital bleeding disorders.[55-64] Although less common than ICH, subgaleal bleeding with concurrent shock and DIC may be the initial presentation of a congenital factor deficiency.[65] Joint bleeding, a typical site for bleeding in children and adults with congenital factor deficiencies, rarely occurs in newborns. The widespread use of ultrasound during pregnancy has resulted in the detection of ICH in utero and provided a safe modality for monitoring fetuses at risk. In utero factor replacement has also been accomplished in a few infants.[66]

DIC. DIC is a process that is always secondary to a serious primary disease such as impairment of the fetal-placental unit resulting in either acute or chronic asphyxia, shock, respiratory distress syndrome, infection, and others.[67-79] The clinical presentation ranges from no obvious symptoms to major hemorrhagic and thromboembolic complications.[80-83] The most common sites of bleeding in sick newborns with DIC are from the gastrointestinal tract, into the skin or scalp, at peripheral sampling sites, and from the lung.

Liver Disease. The coagulopathies of liver disease in newborns are similar to adults and reflect failure of hepatic synthetic functions superimposed on a physiologic immaturity, activation of the coagulation and fibrinolytic systems, poor clearance of activated coagulation factors, and the loss of hemostatic proteins into ascitic fluid.[84] The secondary effects of liver disease on platelet number and function also occur in newborns.[85-87] The most frequent causes

of liver failure in newborns are viral hepatitis, hypoxia, shock, fetal hydrops, and others.

Vitamin K Deficiency. The clinical presentation of VK deficiency can be considered according to the time at which the infants present: classical, early, and late. The classical form of VK deficiency presents on days 2 to 7 of life, in breastfed, healthy full-term infants.[7,50,88-91] Etiologies include poor placental transfer of VK,[92,93] marginal VK content in breast milk (less than 20 μg/L), inadequate milk intake, and a sterile gut.[94,95] VK deficiency rarely occurs in formula-fed infants because commercially available formulae are supplemented with VK (approximately 830 mg/L).[96] The early form of VK deficiency presents in the first 24 hours of life and is linked to maternal use of specific medications that interfere with VK stores or function.[18] The late form of VK deficiency presents between weeks 2 to 8 of life and is linked with disorders that compromise the supply of VK.[97-104]

Laboratory Evaluation

The correct diagnosis of a bleeding disorder is critically important to the selection of appropriate therapy. All laboratory tests must be considered in the context of age-dependent reference ranges. Initially, a bleeding newborn should be screened with a PT (INR), APTT, TCT, fibrinogen concentration, and platelet count. The results from these screening tests will direct further specific assays if necessary.

Congenital Factor Deficiencies. The majority of severe congenital factor deficiencies will result in the prolongation of either the PT or APTT. Subsequent functional factor assays determine which specific factor is affected. There are some congenital bleeding disorders that cannot be detected by screening tests and require direct measurement. These include homozygous deficiencies of FXIII,[105-108] α_2AP,[109] and PAI.[110-112] The diagnosis of heterozygote deficiencies of many congenital hemorrhagic disorders can be problematic because values may overlap with physiological levels. Molecular techniques are increasingly available for prenatal and postnatal diagnoses of most coagulation protein deficiencies.

Disseminated Intravascular Deficiency. The classical laboratory diagnosis of DIC consisted of prolonged screening tests (PT, APTT); decreased levels of fibrinogen, FV, FVIII); increased fibrin degradation products (FDPs), thrombocytopenia and a microangiopathic hemolytic anaemia.[67-79] The availability of sensitive markers for endogenous thrombin and plasmin generation have complicated the diagnosis of DIC in newborns. Positive results for these sensitive paracoagulation tests do not necessarily indicate the presence of DIC or the need to intervene.

Liver Failure. The laboratory abnormalities induced by acute liver disease include a prolonged PT, and low plasma concentrations of several coagulation proteins including fibrinogen.[113,114] Chronic liver failure with cirrhosis is also characterized by a coagulopathy[115-118] and mild thrombocytopenia due to splenic sequestration.[119,120] Secondary VK deficiency due to impaired absorption from the small intestine may occur, particularly from intrahepatic and extrahepatic biliary atresia.[121]

Vitamin K Deficiency. Laboratory tests used to detect VK deficiency include screening tests, factor assays, detection of decarboxylated forms of VK-dependent factors (PIVKA), and direct measurements of VK.[122] The results of these tests must always be compared with values from age-matched, healthy, non–VK deficient infants to distinguish physiologic and pathological deficiencies. PIVKAs can be measured directly,[100,123-128] or as a discrepancy between coagulant activity and protein concentration measured immunologically or with an Echis assay.[127] Other tests have also been used to screen for VK deficiency.[129,130]

Treatment

General Information. In general, the approach to treatment in the presence of active bleeding or a planned hemostatic challenge, is to replace the missing hemostatic protein by transfusion of an appropriate blood product. The fundamental principle of treatment is to increase the plasma concentration of the deficient protein to a minimal hemostatic level. The definition of a minimal hemostatic level varies and is dependent on the protein and the nature of the hemostatic challenge. Table 6 provides an approximate lower limit that should be interpreted in the clinical situation. Blood products available for treatment include plasma, cryoprecipitate, and factor concentrates.

Treatment DIC. The successful treatment of DIC is dependent on the successful treatment of the underlying disease. In the absence of clinical manifestations, and with mild laboratory abnor-

Table 6. Coagulation Factor Proteins

Factor	*Plasma Concentration*	*Half-Life*	*Minimum Hemostatic Value*	*Replacement Therapy*
Fibrinogen	1.56-4.00 g/L	3-5 d	0.5-1.0 g/L	Plasma Cryo
II	0.10 mg/mL	72 h	0.40 u/mL	Plasma PCC FIIC
V	4.14 μg/mL	12-36 h	0.25 u/mL	FFP Cryo
VII	300-500 ng/mL	3-7 h	0.15 u/mL	Plasma PCC FVIIC
VIII	0.2 μg/mL	8-12 h	0.30 u/mL	FVIIIC
IX	4 μg/mL	24 h	0.10 u/mL	PCC FIXC
vWf	3-12 μg/mL	1-4 h	0.25-0.50 u/mL	Cryo FVIIIC
X	4-10 μg/mL	24-56 h	0.10 u/mL	Plasma PCC
XI	2-7 μg/mL	40-80 h	0.20 u/mL	Plasma
XIII	A: 15 μg/mL B: 21 μg/mL	4-14 days	0.10 u/mL	Plasma Cryo FXIIIC
ATIII	0.30 mg/mL	17-26 h	0.38-0.49	Plasma ATIIIC
Protein C	0.004 mg/mL	10 h	0.38-0.49	FFP PCC
Protein S	25 μg/mL	24 h	0.40-0.55	FFP

Abbreviations: cryo, cryoprecipitate; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; C, concentrate. Reprinted with permission.[17]

malities, treatment of the DIC itself may not be necessary. In the presence of clinically important bleeding, therapeutic intervention with blood products (ie, fresh frozen plasma, cryoprecipitate, platelet concentrates) is indicated and often improves hemostasis, at least temporarily. In the absence of definitive clinical trials, reasonable goals are to maintain platelet counts higher than 50×10^9/L, fibrinogen concentrations higher than 1.0 g/L, and PT values at normal levels for postnatal and gestational age.

Liver Failure. Patients with clinical bleeding may benefit temporarily from replacement of coagulation proteins with FFP, cryoprecipitate and/or exchange transfusion. However, without recovery of hepatic function, replacement therapy is futile. VK should be administered to infants suspected of cholestatic liver disease. Prothrombin complex concentrates containing FII, FVII, FIX, FX should in general be avoided in newborns due to the high risk of transmitting hepatitis and the risk of thrombotic disease.[131]

Prophylactic Vitamin K. Most of the controversy over the last century concerning the prophylactic use of VK can be explained by the design of the trials and subsequent interpretations. The evidence linking prophylactic VK to childhood cancer is weak and should not prevent prophylactic VK administration at birth. The current level of evidence permits a strong recommendation for prophylactic VK as either a single dose of 0.5 to 2 mg intramuscularly or an oral dose of 2 to 4 mg at birth. After oral VK administration, a variety of recommendations have been made, such as daily oral doses of 25 to 50 μg over a period of 3 months[132] or multiple oral doses of VK in the first weeks of life.[132-137] The repeated dosing of oral VK prophylaxis is necessary to prevent the late presentation of VK deficiency.[133]

In addition to general prophylaxis at birth, certain risk groups require additional VK prophylaxis (ie, infants with $\alpha_1$antitrypsin deficiency, chronic diarrhea, cystic fibrosis, or celiac disease). Pregnant women receiving oral anti-

convulsant therapy should receive about 5 mg of VK_1 daily during the third trimester to prevent overt VK deficiency in their infants at birth.

Treatment of Vitamin K Deficiency. An infant suspected of having VK deficiency should be treated immediately with VK while awaiting laboratory confirmation. All infants with bleeding should be given VK either subcutaneously or intravenously, depending on the clinical problem. VK should not be given intramuscularly to infants who are bleeding, because large hematomas may form at the site of the injection. The absorption of subcutaneous VK is rapid, and its effect is only slightly slower than systemically administered VK. Intravenous VK should be given slowly because it may induce an anaphylactic reaction. Infants with major bleeding secondary to VK deficiency should also be treated with plasma products to rapidly increase levels of VK-dependent proteins. Plasma is the product of choice for treatment of a non–life-threatening hemorrhagic event, whereas prothrombin complex concentrates should be considered for life-threatening bleeding.

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