

An Approach to the Diagnosis and Treatment of Bleeding Disorders in Infants

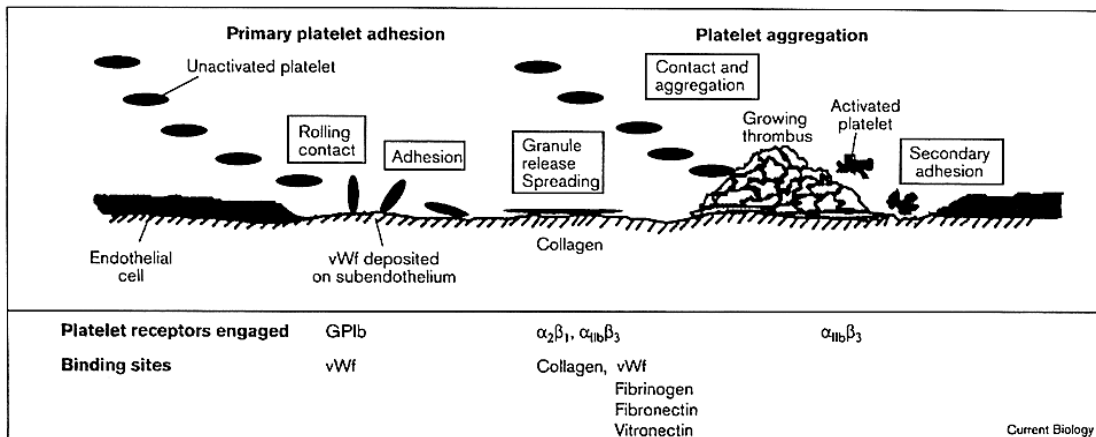
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Abstract

The approach to a newborn or infant who is bleeding can be troublesome for the physician. This lecture will focus upon utilizing the history and screening laboratory to narrow the differential diagnosis in order to provide the most appropriate treatment for this potentially challenging patient population. First, a new approach to understanding the mechanism of coagulation and fibrin deposition will be presented followed by a discussion of the unique aspects of the coagulation system in the infant as well the importance of properly interpreting these laboratory values within the context of the medical history will be reviewed. Next, an overview of possible diagnoses for the bleeding infant will be surveyed with focus upon five specific bleeding conditions commonly encountered in infancy. Finally, general treatment considerations will be explored, followed by a brief offering of case studies when diagnosed based upon the screening laboratory.

- I) General Considerations of Hemostasis
 - 1) Platelet-vessel interaction (Figure 1)
 - 2) Coagulation and fibrin deposition (Figure 2)
- II) Unique aspects of Hemostasis in the Neonate
 - 1) The importance of the family and obstetrical history
 - 2) Clues to a bleeding disorder on physical examination
 - 3) Screening laboratory and their use (Figure 3)
 - 4) Normal values in the newborn (Figure 4)
- III) Differential Diagnosis of the Bleeding Infant (Figure 5)
- IV) Specific Bleeding Conditions Unique in Infancy
 - 1) Thrombocytopenias: Neonatal alloimmune thrombocytopenia (Figure 6)
 - 2) Hemorrhagic disease of the newborn: Vitamin K deficiency
 - 3) Hereditary factor deficiency: FXIII deficiency
 - 4) Disseminated Intravascular Coagulation (DIC): Hypoxia-acidosis
 - 5) Severe liver disease: Neonatal hepatitis
- V) General Treatment Considerations (Figure 7)
- VI) Using the Screening Laboratory to Establish a Diagnosis (Figure 8)



Platelet adhesion, activation and aggregation on exposed subendothelium at a wound site. See text for details. Used with permission from Clemetson KJ: Primary haemostasis: sticky fingers cement the relationship. Current Biology 9:R110, 1999.

Figure 1. Platelet-Vessel Interaction.

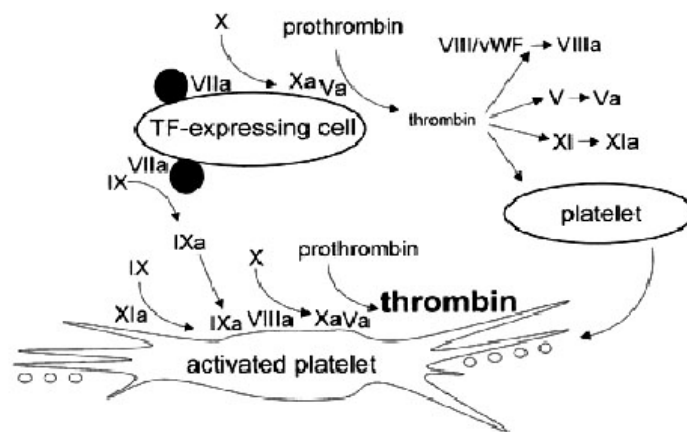


Figure 2. Coagulation and Fibrin Deposition.

Disorder	Screening Test					
	Platelet Count	Bleeding Time	aPPT	PT	TCT	Fibrinogen
Thrombocytopenia	X					
Platelet dysfunction		X				
Hemophilia			X			
Factor VII deficiency				X		
Dysfibrinogenemia					X	
Hypofibrinogenemia						X

Figure 3. Abnormal Screening Tests in Various Hemorrhagic Disorders. Goodnight SH, Hathaway NE: Disorders of Hemostasis and Thrombosis, a Clinical Guide. New York, The Mc Graw-Hill Companies, 2001

Measurements	Normal Adults	Fetus (20 wk)	Preterm (25-32 wk)	Term Infant	Infant (6 mos)
Platelets					
Count $\mu\text{L}/10^3$	250	107-297	293	332	----
Procoagulant System					
PTT*	1	4.0	3	1.3	1.1
PT*	1.0	2.3	1.3	1.1	1
TCT*	1	2.4	1.3	1.1	1
Fibrinogen, mg/dL	278 (0.61)	96 (50)	250 (100)	240 (150)	251 (160)
II, U/mL	1 (0.7)	0.16 (0.10)	0.32 (0.18)	0.52 (0.25)	0.88 (0.6)
V, U/mL	1.0 (0.6)	0.32 (0.21)	0.80 (0.43)	1.00 (0.54)	0.91 (0.55)
VII, U/mL	1.0 (0.6)	0.27 (0.17)	0.37 (0.24)	0.57 (0.35)	0.87 (0.50)
VIIIc, U/mL	1.0 (0.6)	0.50 (0.23)	0.75 (0.40)	1.50 (0.55)	0.90 (0.50)
vWF, U/mL	1.0 (0.6)	0.65 (0.40)	1.50 (0.90)	1.60 (0.84)	1.07 (0.60)
IX, U/mL	1.0 (0.5)	0.10 (0.05)	0.22 (0.17)	0.35 (0.15)	0.86 (0.36)
X, U/mL	1.0 (0.6)	0.19 (0.15)	0.38 (0.20)	0.45 (0.3)	0.78 (0.38)
XI, U/MI	1 (0.6)	0.13 (0.08)	0.2 (0.12)	0.42 (0.20)	0.86 (0.38)
XII, U/mL	1.0 (0.6)	0.15 (0.08)	0.22 (0.09)	0.44 (0.16)	0.77 (0.39)
XIII, U/mL	1.04 (0.55)	0.30	0.4	0.61 (0.36)	1.04 (0.50)
PreK, U/mL	1.12 (0.06)	0.13 (0.08)	0.26 (0.14)	0.35 (0.16)	0.86 (0.56)
HK, U/mL	0.92 (0.48)	0.15 (0.10)	0.28 (0.20)	0.64 (0.50)	0.82 (0.36)

Figure 4. Development Changes in the Hemostatic System. Goodnight SH, Hathaway NE: Disorders of Hemostasis and Thrombosis, a Clinical Guide. New York, The Mc Graw-Hill Companies, 2001. *ratio of subject/ mean adult, () - 2SD of lower range

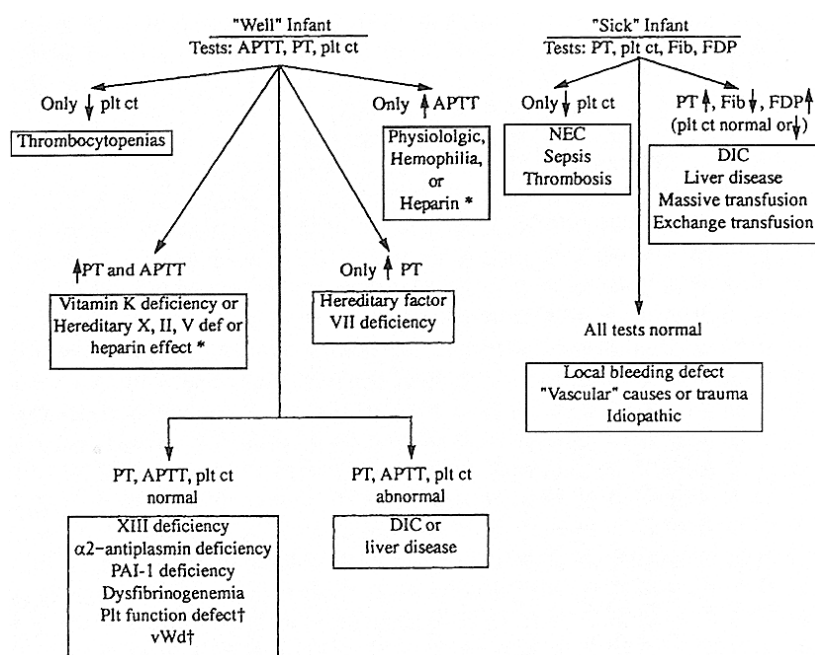


Figure 5. Differential Diagnosis of the Bleeding Infant. Goodnight SH, Hathaway NE: Disorders of Hemostasis and Thrombosis, a Clinical Guide. New York, The Mc Graw-Hill Companies, 2001

Infection	Bacterial: sepsis, congenital syphilis Viral: cytomegalovirus, herpes simplex virus, rubella syndrome, enterovirus, HTLV-III (HIV) Other: toxoplasmosis
Immune Disorders	Alloimmunization Maternal antibody induced: SLE, ITP
Bone marrow abnormality	Congenital megakaryocytic hypoplasia Absent radii (TAR) syndrome Phocomelia syndrome Fanconi's pancytopenia Aplastic anemia Trisomy syndromes Osteoporosis Congenital leukemia
Maternal Drugs	Tolbutamide, hydralazine, hydantoin, azathioprine
Infant Drugs	Intralipid, tolazoline
Intravascular coagulation syndromes	DIC Major vessel thrombosis (renal vein, aorta) Necrotizing enterocolitis Placental chorangioma Chronic vessel thrombosis
Excessive peripheral utilization	Giant hemangioma Hyperviscosity syndrome Erythroblastosis fetalis Congenital heart disease Hereditary Thrombocytopenia Sex-linked: Wiskott-Aldrich syndrome and variants Autosomal recessive: associated with renal disease and deafness Autosomal dominant: May-Hegglin anomaly
Other Causes:	Postexchange transfusion (syndrome) Maternal hyperthyroidism Metabolic disorders: hyperglycemia, cirrhosis, and mucopolidosis Thrombotic thrombocytopenia purpura Postmature and SGA infants (often with maternal toxemia) Neonatal neuroblastoma Neonatal cold injury Perinatal pulmonary syndromes

Figure 6. Causes: Neonatal Thrombocytopenia. (SLE, systemic lupus erythematosus; ITP, immune thrombocytopenic purpura; TAR, Thrombocytopenia with absent radius; DIC, disseminated intravascular coagulation; SGA, small for gestational age. Hathaway NE, Bonnar J: Hemostatic Disorders of the Pregnant Woman and Newborn Infant. New York, Elsevier Science, 1987)

Product	Dose	Indication
Platelet concentrate	10 cc/kg	Low pt; p1t dysfunction
Fresh frozen plasma	15-20 cc/kg	Multi-factor coagulopathy FII, V, X (XI, XIII) deficiency
Cryoprecipitate	1 bag/10 kg	Low fibrinogen, FXIII deficiency Platelet dysfunction
Prothrombin concentrate	75-100 U/kg	Multiple Vitamin K deficiency Liver Disease
Aminocaproic Acid	100 mg/kg	Excessive fibrinolysis
DDAVP	0.3µg/kg	Platelet dysfunction
Factor concentrate		
-rFVIIa	20-30µg/kg	FVII deficiency
-FVIII	40-50 U/kg	FVIII deficiency
-FIX	80-100 U/kg	FIX deficiency

Figure 7. General Treatment Considerations.

Diagnosis	Plt ct (uL/10 ³)	PFA (sec)	PT (sec)	aPTT (sec)	TCT (sec)	Fib mg/dL
Hemophilia	300	nl	10	75	12	300
FVII def	250	nl	27	30	11	250
VWD	200	Inc	11	42	12	260
FXIII def	350	nl	10	29	10	200
DIC (hypoxia)	160	-	20	43	17	40
DIC (severe)	10	-	28	>120	>60	10
Liver dis	90	Inc	25	40	19	85
Platelet dys	275	Inc	12	31	11	270
Vitamin K def	360	-	>60	>120	13	265
ITP	5	nl-Inc	11	29	12	255
Heparin	265	-	15	>120	>60	200

Figure 8. Case Studies Based upon Screening Laboratory.

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