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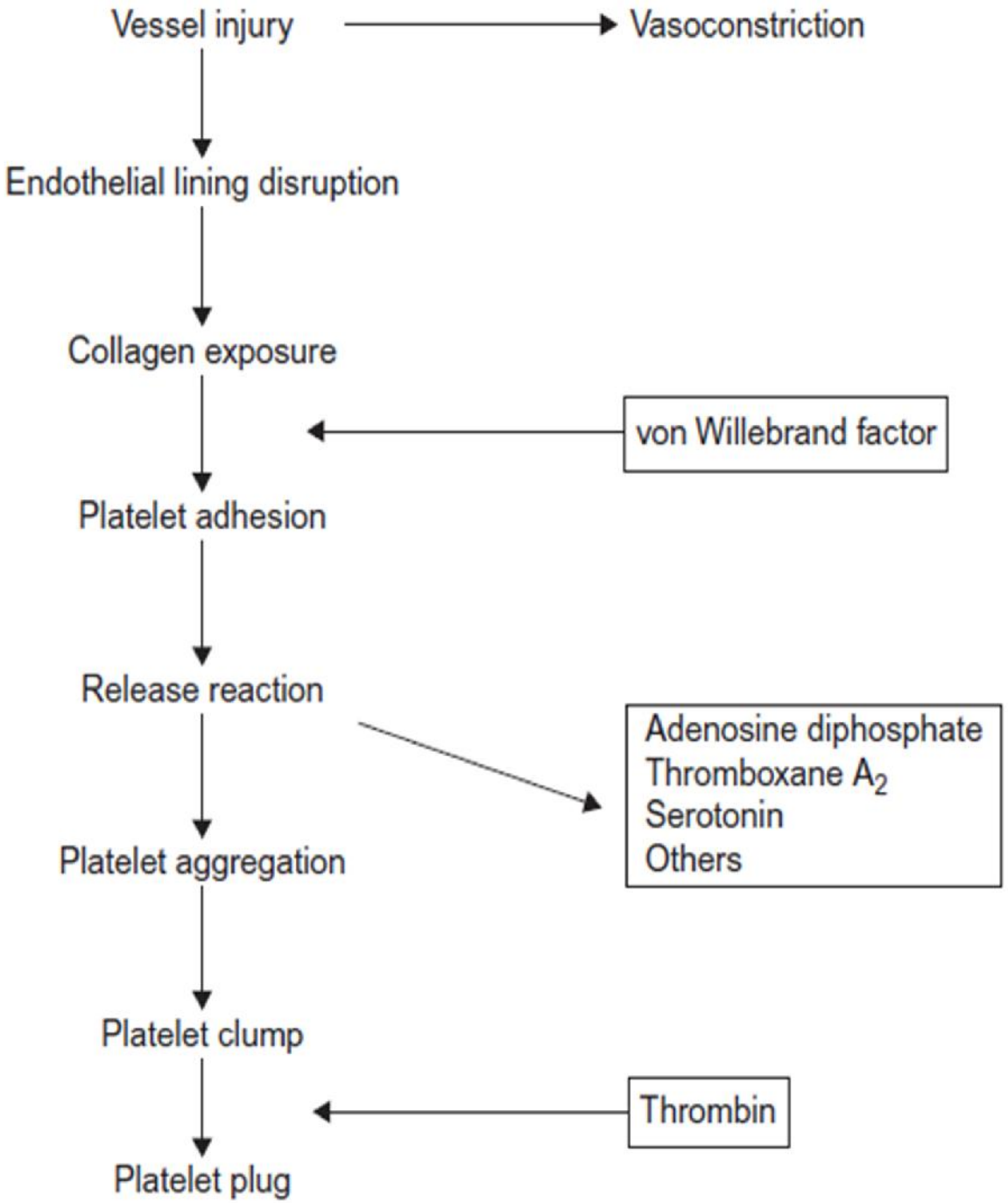
مرکزتحقیقات بیماری های خونی مادرزادی کودکان

Coagulation disorder

Dr Goudarzipour


Vessel injury
Vasoconstriction
Endothelial lining disruption
Collagen exposure
von Willebrand factor
Platelet adhesion
Release reaction
Adenosine diphosphate
Thromboxane A_2
Serotonin
Others
Platelet aggregation
Platelet clump
Thrombin
Platelet plug

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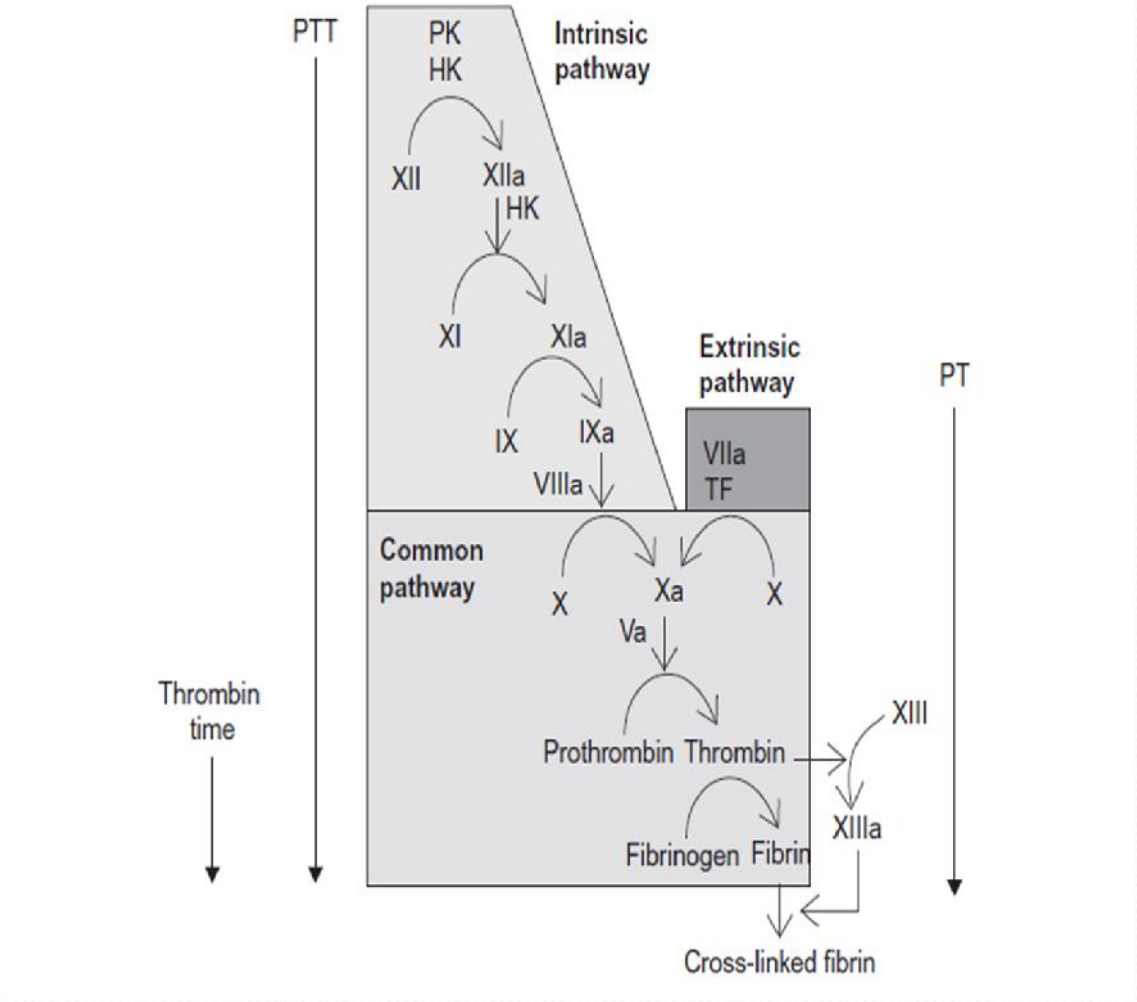

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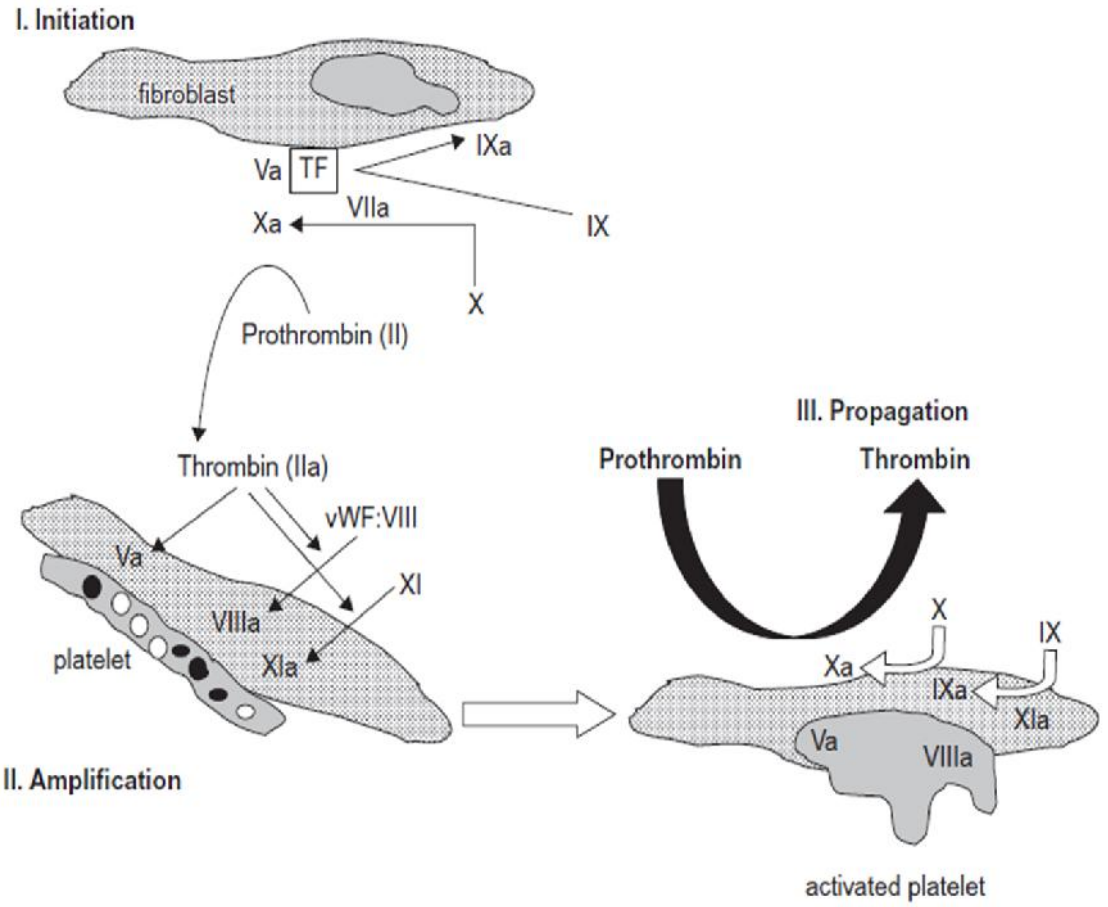

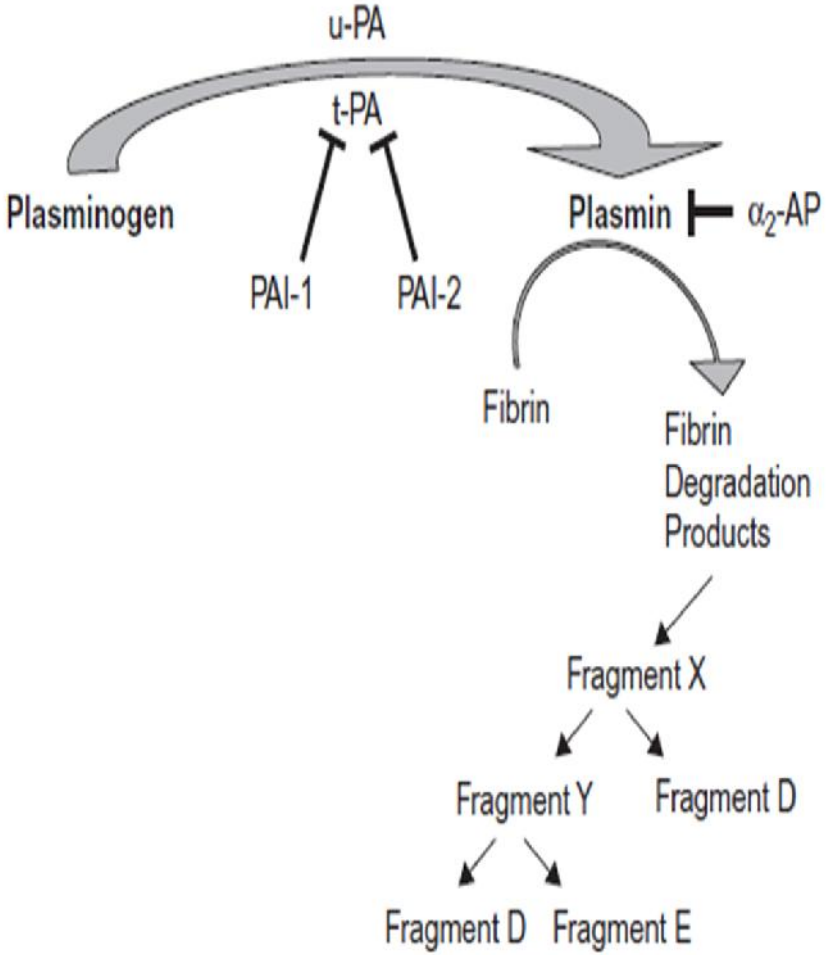
u-PA
t-PA
Plasminogen
Plasmin
α_2-AP
PAI-1
PAI-2
Fibrin
Fibrin
Degradation
Products
Fragment X
Fragment Y
Fragment D
Fragment D
Fragment E

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	Normal Adults/Children	Preterm Infant (28–32 Weeks)	Preterm Infant (33–36 Weeks)	Term Infant
PT (s)	10.8–13.9	14.6–16.9	10.6–16.2	10.1–15.9
APTT (s)	26.6–40.3	80–168	27.5–79.4	31.3–54.3
Fibrinogen (mg/dl)	95–425	160–346	150–310	150–280
II (%)	100[a]	16–46	20–47	30–60
V (%)	100[a]	45–118	50–120	56–138
VII (%)	100[a]	24–50	26–55	40–73
VIII(%)	100[a]	75–105	130–150	154–180
vWF Ag (%)	100[a]	82–224	147–224	67–178
vWF (%)	100[a]	83–223	78–210	50–200
IX (%)	100[a]	17–27	10–30	20–38
X (%)	100[a]	20–56	24–60	30–54
XI (%)	100[a]	12–28	20–36	20–64
XII (%)	100[a]	9–35	10–36	16–72
XIII (%)	100[a]	–	35–127	30–122
PK (%)	100[a]	14–38	20–46	16–56
HMW-K (%)	100[a]	20–36	40–62	50–78

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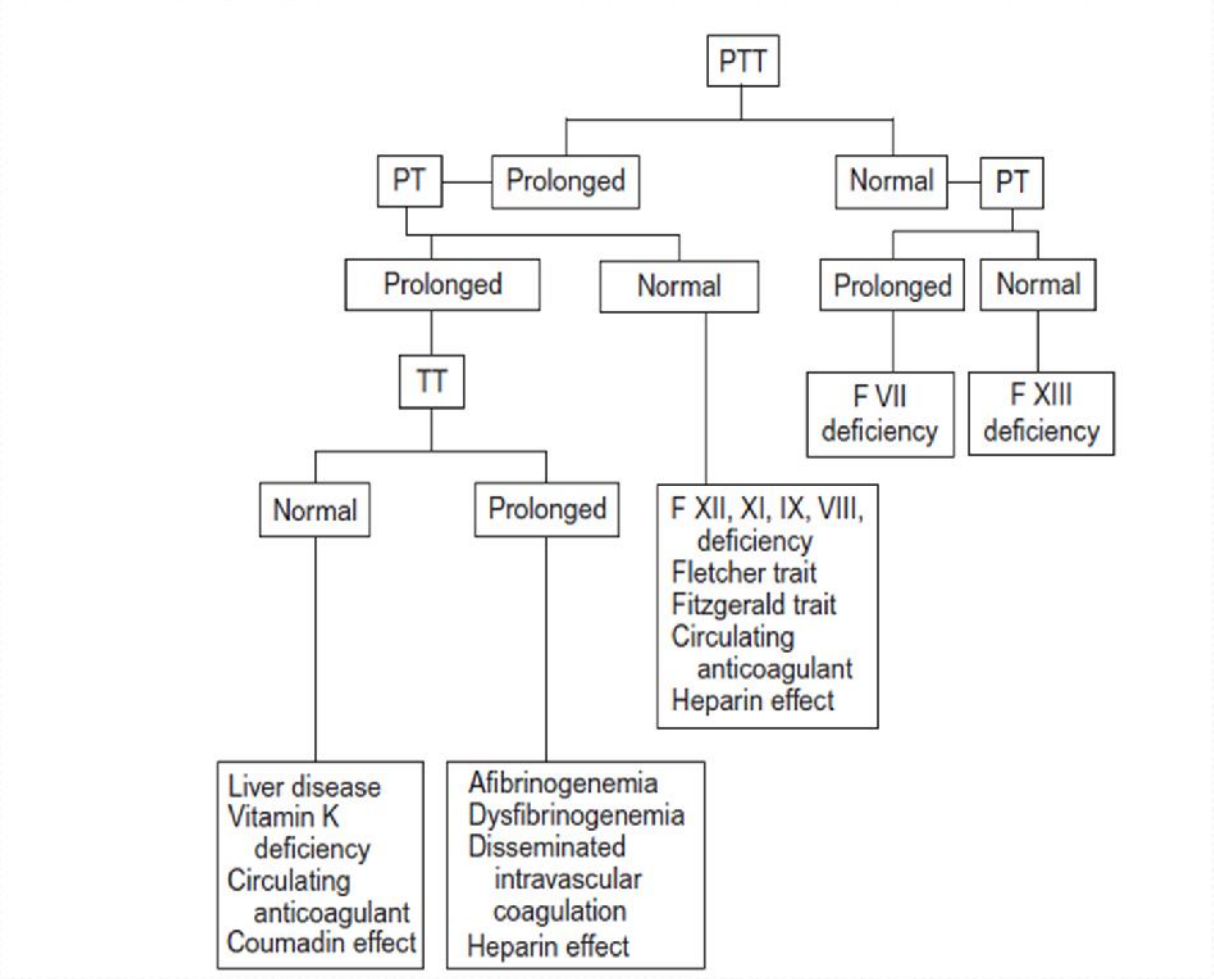
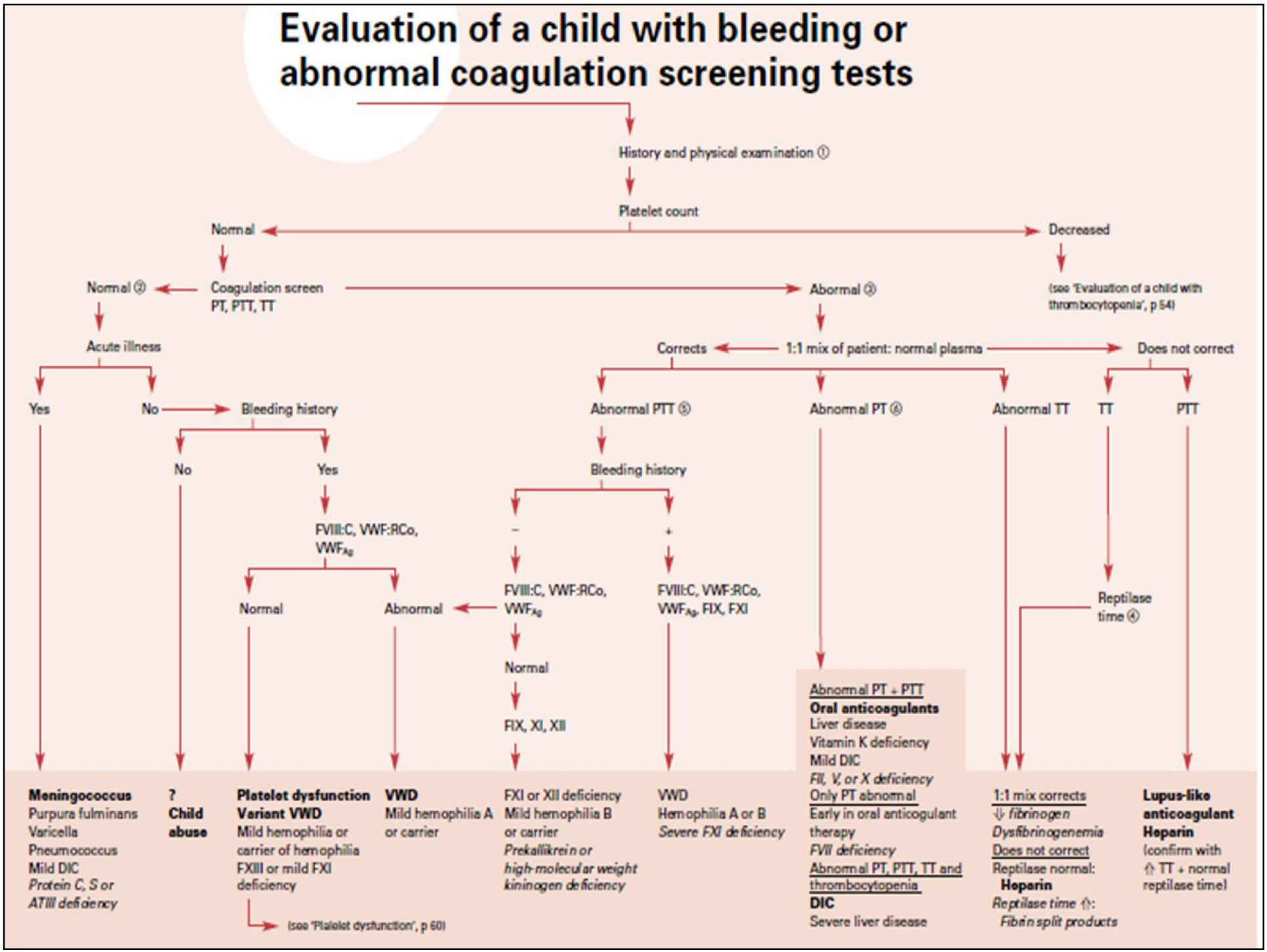


Evaluation of a child with bleeding or abnormal coagulation screening tests



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Factor Deficiency	Genetics	Est. Prevalence	BT	APTT	PT	Associated with Bleeding Episodes
Afibrinogenemia	AR	1:1 million	N	P	P	++
Dysfibrinogenemia	AR		N	N/P	P	+/− thrombosis
II	AR	1:2 million	N	P	P	++
V (parahemophilia)	AR	1:1 million	N	P	P	++
VII	AR	1:500,000	N	N	P	+
VIII (hemophilia A)	XLR	1:10,000	N	P	N	+++
von Willebrand's disease		1:1000				
Type 1	AD		N/P	N/P	N	+
Type 2	AD		P	N/P	N	++
Type 3	AR		P	P	N	++
IX (hemophilia B)	XLR	1:60,000	N	P	N	+++
X	AR	1:1 million	N	P	N	++
XI (hemophilia C)	AR	1:1 million	N[a]	P	N	+
XII	AD		N	P	N	−
XIII	AR	1:1 million	N	N	N	+[c]
Prekallikrein (Fletcher trait)	AD		N	P[b]	N	−
HMW kininogen (Fitzgerald trait)	AR		N	P	N	−
Passovoy (?)	AR		N	P	N	+/−

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Hemophilia A and B

- The most common coagulation disorders, following von Willebrand disease, are hemophilia A and B.
- Genetic:X linked
- Incidence:1/5000
- Type A:80-85%

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Table 13-17 Differences Between von Willebrand Disease and Hemophilia A

	von Willebrand Disease	Hemophilia A
Symptoms	Bruising and epistaxis Menorrhagia or mucosal bleeding	Joint bleeding Muscle bleeding
Sexual distribution	Males = females	Males
Frequency	1:200 to 1:500	1:6000 males
Abnormal protein	vWF	Factor VIII
Molecular weight	$0.6\text{-}20 \times 10^6$ Da	280 kDa
Function	Platelet adhesion	Clotting cofactor
Site of synthesis	Endothelial cell or megakaryocytes	??
Chromosome	Chromosome 12	X chromosome
Inhibitor frequency	Rare	14-25% of patients
Laboratory tests		
History	Abnormal	Abnormal
aPTT	Normal or prolonged	Prolonged
Factor VIII	Borderline or decreased	Decreased or absent
vWF Ag	Decreased or absent	Normal or increased
vWF R:Co	Decreased or absent	Normal or increased
vWF multimers	Normal or abnormal	Normal

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Type	Percentage Factor VIII/IX	Type of Hemorrhage
Severe	<1	Spontaneous; hemarthroses and deep soft tissue hemorrhages
Moderate	1-5	Gross bleeding following mild to moderate trauma; some hemarthrosis; seldom spontaneous hemorrhage
Mild	5-25	Severe hemorrhage only following moderate to severe trauma or surgery
High-risk carrier females	variable	Gynecologic and obstetric hemorrhage common, other symptoms depend on plasma factor level

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- Hemarthrosis
- Intramuscular hematoma
- Hematuria
- Mucous membrane hemorrhage
  - Mouth
  - Dental
  - Epistaxis
  - Gastrointestinal
- High-risk hemorrhage
  - Central nervous system
    - Intracranial
    - Intraspinal
  - Retropharyngeal
  - Retroperitoneal
  - Hemorrhage causing compartment syndrome/nerve compression
    - Femoral (iliopsoas muscle)
    - Sciatic (buttock)
    - Tibial (calf muscle)
    - Perineal (anterior compartment of leg)
    - Median and ulnar nerve (flexor muscles of forearm)

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treatment

Treatment of bleeding in children with hemophilia ①

Collaborate with Hemophilia Treatment Center ② → Mild or moderate hemophilia ⑲

Severe hemophilia

Life-threatening

- Suspected CNS bleed ③ → Factor replacement prior to CNS imaging or LP
- Impending airway compromise, Tongue bleed, Neck trauma, Dental anesthesia without factor ④
- Surgery ⑤: Major trauma, GI hemorrhage, Retroperitoneal or large muscle hemorrhage

Non-life-threatening

Muscle bleed

50–100% level *via single i.v.* bolus q.d. or q.o.d. until improved, then q.o.d. until resolved
May need 30–50% doses with physical therapy to prevent rebleeding

- If neurovascular compromise, Rx as life-threatening bleed, Obtain neurology + surgical consult ⑥
- Fails to improve → Orthopedic evaluation, Consider X-ray, US, MRI

Hemarthrosis ⑦

40–80% bolus dose then 40% at 24 and 72 h, and q.o.d. until resolved
Initially rest + immobilize then physical therapy

- Recurrent bleeding → *Consider prophylaxis regimen for recurrent hemarthroses* ⑦ → Evaluate for radio-isotopic or surgical synovectomy ⑦

Mucosal bleed

- Epistaxis, oral mucosal oozing, or GI bleeding → *50–100% dose depending on severity Antifibrinolytics for 3–5 days* ⑱ → Persistent, recurrent bleeding → *30–50% dose q.o.d. up to 1 week Epistaxis: refer to otolaryngology for possible nasal packing or cautery*
- Hematuria → Bed rest ⑨ Hydration → *Persistent or recurrent bleeding 30-50% dose q.d. x 5* ***No antifibrinolytics*** ⑱ → Persistent, recurrent bleeding → *Redose to 100% Prednisone 1–2 mg/kg/day x 1–2 weeks GU evaluation*

Obtain inhibitor level (always prior to elective surgery)
Infuse factor to 100% level with i.v. bolus dose
Initiate continuous infusion to *maintain* 80–100% level **or** bolus therapy *maintaining* a trough level of >50%

Measure levels to ensure adequacy of Rx
Continuous or bolus therapy at minimum 50% level until wound healing begins and then ↓ to minimum 30% level for 7–14 days depending on type of bleeding

May need 30–50% level for physical therapy or other procedures in healing phase
May use prophylaxis for 6–12 weeks after CNS bleed to prevent early recurrence

(for any child failing Rx, see 'Evaluation of a child with hemophilia who fails infusion therapy', p 66)

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Type of Hemorrhage	Hemostatic Factor Level	Hemophilia A	Hemophilia B	Comment/Adjuncts
Hemarthrosis	30–50% minimum	FVIII 20–40 U/kg q12–24 h as needed; if joint still painful after 24 h, treat for further 2 days	FIX 30–40 U/kg q24h as needed; if joint still painful after 24 h, treat for further 2 days	Rest, immobilization, cold compress, elevation
Muscle	40–50% minimum, for iliopsoas or compartment syndrome 100% then 50–100% × 2–4 days	20–40 U/kg q12–24h as needed for iliopsoas or compartment syndrome initial dose is 50 U/kg	40–60 U/kg q24h as needed for iliopsoas or compartment syndrome initial dose is 60–80 U/kg	Calf/forearm bleeds can be limb threatening. Significant blood loss can occur with femoral-retroperitoneal bleed
Oral mucosa	Initially 50%, then EACA at 50 mg/kg q6hr × 7 days usually suffices	25 U/kg	50 U/kg	Antifibrinolytic therapy is critical. Do not use with PCC or APCC
Epistaxis	Initially 30–40%, use of EACA 50 mg/kg q6h until healing occurs may be helpful	15–20 U/kg	30–40 U/kg	Local measures: pressure, packing
Gastrointestinal	Initially 100% then 50% until healing occurs	FVIII 50 U/kg, then 25 U/kg q12h	FIX 100 U/kg, then 50 U/kg q day	Lesion is usually found, endoscopy is recommended, antifibrinolytic may be helpful
Hematuria	Painless hematuria can be treated with complete bed rest & vigorous hydration for 48 h. For pain or persistent hematuria 100%	FVIII 50 units/kg, if not resolved 30–40 u/kg q day until resolved	FIX 80–100 units/kg, if not resolved then 30–40 U/kg q day until resolved	Evaluate for stones or urinary tract infection. Lesion may not be found. Prednisone 1–2 mg/kg/d × 5–7 days may be helpful. Avoid antifibrinolytics
Central Nervous system	Initially 100% then 50–100% for 14 days	50 U/kg; then 25 U/kg q12h	80–100 U/kg; then 50 U/kg q24h	Treat presumptively before evaluating, hospitalize. Lumbar puncture requires prophylactic factor coverage
Retroperitoneal or retropharyngeal	Initially 80–100% then 50–100% until complete resolution	FVIII 50 units/kg; then 25 U/kg q12h until resolved	FIX 100 U/kg; then 50 U/kg q24h until resolved	Hospitalize
Trauma or surgery	Initially 100%; then 50% until would healing is complete	50 U/kg; then 25 U/kg q12h	100 U/kg; then 50 U/kg q24h	Evaluate for inhibitor prior to elective surgery

- DDAVP:• Body weight ,50 kg: 150 µg (one metered dose), Body weight .50 kg: 300 µg (two metered doses).
- intravenously the dose is 0.3 µg/kg administered in 25–50 ml normal saline over 15–20 minutes. Its peak effect is observed in 30–60 minutes.

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Recommendations during the administration of DDAVP are:

- Mild fluid restriction to two-third maintenance fluids and drinking of electrolyte-containing fluids (avoiding free water) to satisfy thirst
- Monitoring urinary output and daily weights may be useful to track fluid retention.

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Side effects of DDAVP include:

- Asymptomatic facial flushing
- Thrombosis (a rarely reported complication)
- Hyponatremia is more common in very young patients, in patients receiving repeated doses of DDAVP or large volumes of oral or intravenous fluid; hyponatremic seizures have been reported in children under 2 years of age. DDAVP is contraindicated in children under 2 years of age.

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Antifibrinolytic Therapy

- Epsilon aminocaproic acid (EACA; Amicar): Orally; dose is 50–100 mg/kg every 6 hours (maximum, 24 grams total dose per day). Gastrointestinal symptoms may occur at higher doses; therefore, the preferred starting dose is 50 mg/kg. The drug is available as 500 mg, 1000 mg tabs or as a flavored syrup (250 mg/ml)
- Tranexamic acid (Cyklokapron): 20–25 mg/kg (maximum, 1.5 g) orally or 10 mg/kg (maximum, 1.0 g) intravenously every 8 hours. At the time of writing, this drug is not currently available in the United States.

Note:

- should not be utilized in patients with urinary tract bleeding.
- continued for up to 7 days.
- Avoid before 4-6 hours PCC or APCC

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1 case

- Case 1:the Pt is 2y/o,male.
- he was admitted in surgery ward due to inguinal hernia.
- CBC:WBC:6400

  Hb:12

  plt:265000, PT:12, PTT:53

No Hx of bleeding.

Family history:MI in his father

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Case 2

- 17 years old female
- Hx of bleeding due to plastic surgery.
- HX of surgery due to appendicitis without bleeding.
- PT,pTT,plt,BT,NL
- WHAT IS YOUR Dx?

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Case 3

- 8 years old,male
- HX of mild bleeding after urgent appendectomy
- PT:11,PTT:85,PLT,NL
- What is your Dx?