Factors and Associated Disorders

Clotting Factors: Nomenclature

I* Fibrinogen
Ia* Fibrin
II* Prothrombin
IIa * Thrombin
III* Thromboplastin
IV* Calcium
V Labile Factor; parahemophilia
VII Proconvertin; stable factor
VIII Anti-hemophilic factor (AHF); hemophilia A
IX Christmas Factor; hemophilia B
X Stuart-Prower Factor
XI Plasma Thromboplastin Antecendent (PTA); hemophilia C
XII Hageman Factor
XIII Fibrin Stabilizing Factor
* Indicates factors more commonly referred to as full name

Defects:

- FXIII (all by itself)
- Common Pathway: Fibrinogen (II), IIa, V, and X
- Extrinsic Pathway: VII
- Intrinsic Pathway: VIII, IX, XI, XII

Contact Factors: Prekallikrein, High-Molecular Weight Kininogen (HMWK)

	Prolonged PT	**Prolonged aPTT**	**Prolonged PT and aPTT**
Inherited			
	VII deficiency	vWF, VIII, IX, XI, or XII deficiency	Fibrinogen, Prothrombin, V, X or combined factor deficiency
Acquired			
	Vit. K deficiency	Heparin use	Liver Disease
	Liver Disease	Inhibitor of vWF, VIII, IX, XI, or XII	Supratherapuetic heparin or Warfarin therapy (or combined usage)
	Warfarin use	Lupus Anticoagulant	DIC
	FVII Inhibitor		Inhibitor of Prothrombin, fibrinogen, V, X or direct thrombin inhibitor (Dabigatran)

Factor Disorders

↑ PT / Normal aPTT / Normal TT

FACTOR VII Deficiency

- Rare autosomal recessive
- Deep muscle hematoma, joint hemorrhage, epistaxis menorrhagia
- DDx: DIC, Vit. K Deficiency
- Acquired with liver disease
    VII --shortest half-life of the Vit. K dependent factors (3-6 hours), so it is best used to detect early liver disease.
- Treat with FFP or Prothrombin complex
- Major surgery requires: >20% Factor VII level

↑ PT and ↑ aPTT: (Common Pathway)

1) Fibrinogen defects
    - Quantitative: hypofibrinogenemia and afibrinogenemia
    - Qualitative: dysfibrinogenemia

    - Afibrinogenemia

    ↑ PT, aPTT, Reptilase and TT, while fibrinogen levels are undetectable
    -Rare autosomal recessive with bleeding post trauma, cerebral hemorrhage, hemarthrosis, and poor wound healing
        - Can see umbilical cord stump bleeding
        - Since fibrinogen is a molecular bridge in platelet aggregation a long bleeding time and abnormal platelet aggregation may be seen
        - Treat with cryoprecipitate

    - Hypofibrinogenemia

    ↑ PT, aPTT, Reptilase and TT with fibrinogen levels <200 mg?dL
    - Heterozygous state of afibrinogenemia with bleeding rarely occurring unless fibrinogen levels <50 mg/dL
        -DDx: DIC and liver disease
        - Treat with cryoprecipitate

    - Dysfibrinogenemia

    ↑ PT, aPTT, Reptilase and TT with normal fibrinogen levels
    - Autosomal dominant with over 50% asymptomatic, and 25% with mild bleeding
        - remaining percentage can present with thrombosis

2) Prothrombin II defects

↑ PT / aPTT with normal TT, 1:1 mix corrects
- Autosomal recessive with heterozygotes asymptomatic and homozygotes showing severe spontaneous bleeding
- DDx: Acquired defects including warfarin therapy, Vitamin K deficiency, liver disorders
  - Treat with plasma or prothrombin complex

3) Factor V defects

↑ PT / aPTT with normal TT (low FV:C)
- Autosomal recessive has a short half-life and is heat labile
  "parahemophilia" – mucosal bleeding, ecchymoses, hemarthrosis

- Synthesized in the liver but stored in the alpha granules of platelets
- May have decrease in platelet alpha granule - associated FV
- DDx: acquired defect, especially when patient has been treated with bovine thrombin as well as liver disease, carcinoma, and TB

- Factor V Leiden effects seen when patient has 10% or less of factor V

4) Factor X -- Stuart-Prower defects

↑ PT/PTT, Russell Viper Venom Time (direct activator of FX)
(Stypven time): dependent on II, V, X
Normal TT, PLT, BT
- Vit. K dependent factor
- Very rare autosomal recessive with umbilical cord bleeding and more mucosal bleeding than hemophilia A
- DDx: Liver disease, DIC, acquired deficiency

Acquired: amyloidosis sequesters

Normal PT / ↑ aPTT / Normal BT / Normal TT

VIII, IX, XI, XII, PREKALLIKREIN [Fletcher], HMW KININOGEN [Fitzgerald]

1) Fletcher (prekallikrein) defects

- Autosomal dominant with NO risk of bleeding
  Very ↑ PTT/ normal PT, TT, BT, PLTs, and low FXII
  - single chain produced in the liver
  - 75% bound to HMW kininogen

2) Fitzgerald (HMW Kininogen) defects

- Autosomal recessive with NO risk of bleeding
  ↑ PTT/ normal PT, TT, BT, PLTs, and low FXII
  - Activation of XI and XII

3) Factor XII (Hageman factor) defects

- Autosomal recessive with NO risk of bleeding, may have inadequate fibrinolysis and increased risk of thrombosis
  Very ↑ PTT/ normal PT, TT, BT, PLTs, and low FXII

4) Hemophilia C- XI defects

- Incomplete autosomal recessive inheritance (high incidence in Ashkenazi Jews)
  ↑ PTT/ normal PT, BT, PLTS and low FXI
  - Circulates with HMW kininogen
  - Bleeding tendencies not similar to other hemophilia's

5) Hemophilia B – IX defects

- X-linked recessive- female carriers with spontaneous mutations occurring
  ↑ PTT/ normal PT, BT, PLTS and low FIX
  - Level of IX determines the severity, clinically identical to Hemophilia A
  - Homology to Vit K dependent serine proteases VII, X, protein C and S

6) Hemophilia A – VIII (classic hemophilia)

- X-linked recessive bleeding disorder with hemorrhage, deep tissue bleeding, hemarthrosis and intracranial bleeding
  - Hemophilia A male with normal female:
    Obligatory carrier in all daughters, normal in all sons
  - Hemophilia A carrier female with normal male:
    Hemophilia A in all sons, 50% chance of being carrier in all daughters
  - Female hemophilia A
    offspring from hemophilia A father and carrier mother

↑ PTT/ normal PT, BT, PLTS and low FVIII
- Anti-VIII antibody: severe hemophiliacs
- Detected with CAC and Bethesda assay

7) Familial Combined Factor Deficiencies

- V and VIII
  - Mutation causing abnormal protein trafficking issue of FV and FVIII with abnormal secretion
  - Disproportionally prolonged aPTT compared to PT
- II, VII, IX and X
  - Vitamin K carboxylase or reductase deficiency
- VII and X
  - Chromosome 13 deletion

Normal PT and aPTT

1) Factor XIII defects

- Autosomal recessive with severe bleeding in homozygotes
- Delayed umbilical stump healing
- Deep tissue hemorrhages
- Delayed post-traumatic or post-op bleeding
- Abnormal wound healing
- Pregnancy loss due to placental bleeding

Normal PT, aPTT, Platelets and BT
- Abnormal urea clot solubility test