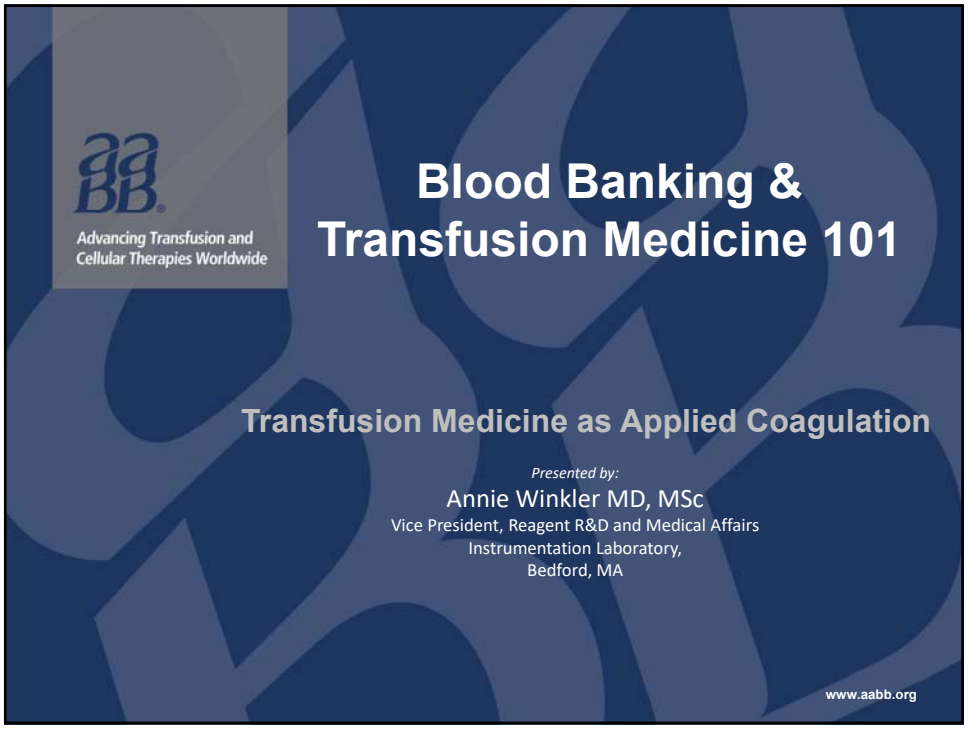

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Learning Objectives

After participating in this program you should be able to….

- Explain the role of blood components in coagulation.
- Discuss the use of transfusion medicine as a therapy for coagulopathies.
- Discuss the issues in the use of different blood components for coagulation.
- Introduce the most common factor concentrates that in many cases may be in the pharmacy and not the blood bank but part of the equation.

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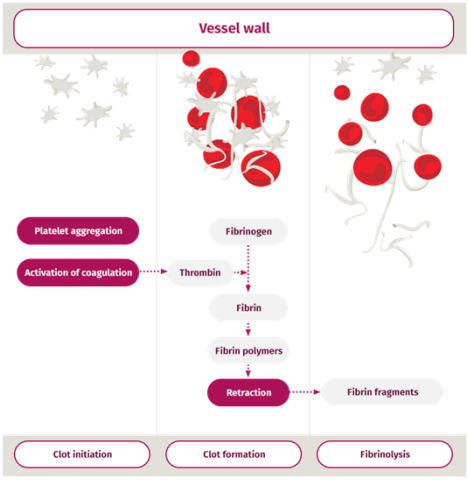
Introduction to Hemostasis

- Hemostasis is an orchestrated, balanced and tightly regulated process which is subdivided into three sequential processes
  - Primary hemostasis
  - Secondary hemostasis
  - Fibrinolysis



https://www.thrombosisadviser.com/haemostasis/

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Primary Hemostasis and Platelets

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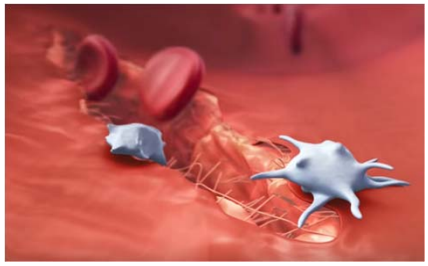
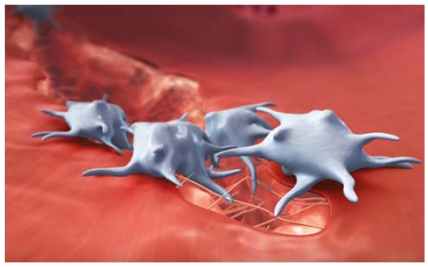
Primary Hemostasis I

- Following injury or damage to a blood vessel, the first response is vasoconstriction, leading to activation of endothelial cells
- Activated endothelial cells secrete von Willebrand factor (VWF) to recruit platelets to the injured endothelium
- VWF binds to exposed collagen and recruits circulating platelets by recognizing GPIb





https://www.thrombosisadviser.com/the-coagulation-cascade/

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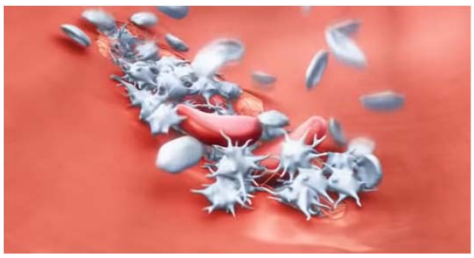
Primary Hemostasis II

- Signaling via glycoproteins, adhesion proteins, and soluble ligands induces platelet activation and aggregation via GPIIb/IIIa receptors
- Once a platelet plug has formed, activation of coagulation on the surface of platelets is necessary to form a stable, fibrin clot



Platelets are essential for normal hemostasis

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https://www.thrombosisadviser.com/the-coagulation-cascade/

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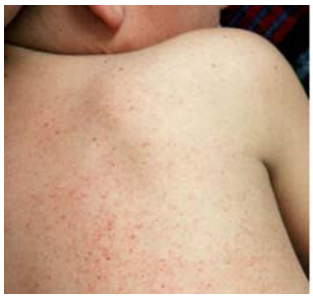
Disorders of Primary Hemostasis

- Deficiencies in platelet number or function can result in bleeding
- Thrombocytopenia and/or platelet dysfunction may result from:
  - Congenital diseases
  - Medications
  - Liver or kidney diseases
  - Sepsis
  - Disseminated intravascular coagulation (DIC)
  - Hematologic diseases
  - Massive transfusion
  - Cardiopulmonary bypass
  - Extracorporeal membrane oxygenation
- Clinical signs of platelet dysfunction include petechia, easy bruising, or mucosal bleeding



https://learn.pediatrics.ubc.ca/body-systems/hematology-oncology/approach-to-thrombocytopenia/

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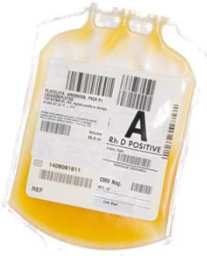
Platelet Products



- Whole blood-derived platelet units: $\geq 5.5 \times 10^{10}$ platelets in 90% of units tested
  - As a dose of platelets usually approximates $3\text{-}4 \times 10^{11}$ platelets for an adult, units must be "pooled" to make a single dose
    - 4-6 units may be pooled to yield a dose of $2.2\text{-}5.8 \times 10^{11}$ platelets
- In comparison, apheresis platelets contain 2-3 times the required minimum of 3×10^{11} platelets and may be split into multiple units
  - It is estimated that 93% of platelets transfused in the US are apheresis platelets

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Secondary Hemostasis and Coagulation Factors

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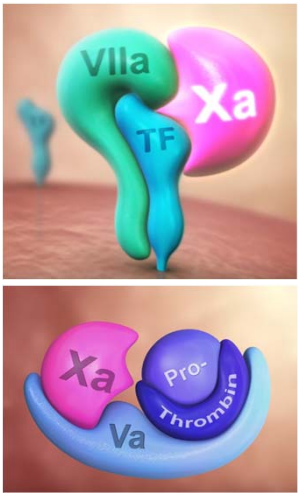
Secondary Hemostasis: Initiation

- Cell based model of coagulation is divided into three phases:
  - Initiation
  - Amplification
  - Propagation
- During initiation, tissue factor (TF) binds to FVIIa. TF-FVIIa complex cleaves small amounts of FIX and FX, activating the common pathway
- The newly formed FXa complexes with FVa to form the prothrombinase complex



https://www.thrombosisadviser.com/the-coagulation-cascade/

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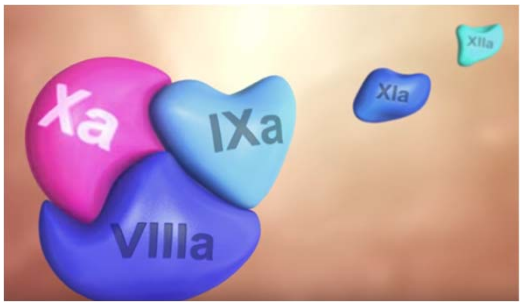
Secondary Hemostasis: Amplification

- The small amount of thrombin generated during initiation can amplify key coagulation reactions
  - FXI, FVIII, and FV



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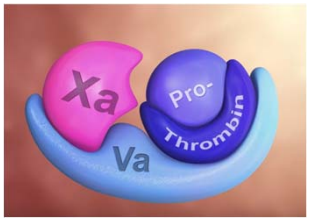
Secondary Hemostasis: Propagation

- In the propagation phase, a large amount of thrombin is formed through actions of the tenase and prothrombinase complexes
- Once a large amount of thrombin is generated, thrombin activates FXIII to cross-link fibrin and stabilize the clot



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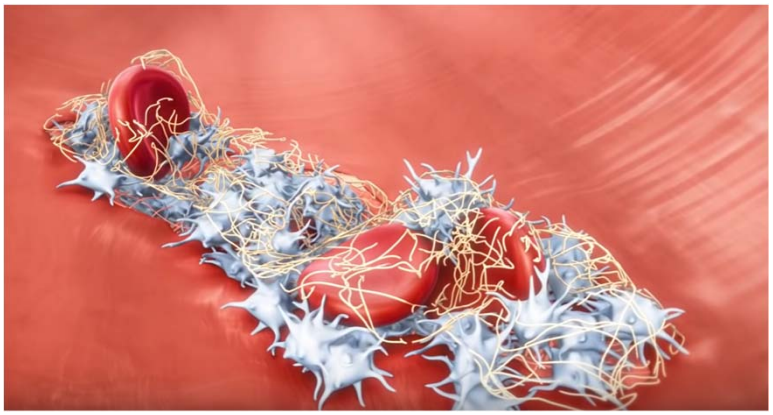
Secondary Hemostasis



Coagulation factors are essential for normal hemostasis

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Disorders of Secondary Hemostasis

- Quantitative or qualitative abnormalities in coagulation factors can result in bleeding
- Coagulation factor deficiencies include:
  - Associated with bleeding:
    - Factor VIII deficiency / Hemophilia A
    - Factor IX deficiency / Hemophilia B
    - Factor XI deficiency / Hemophilia C
    - Factor VII, II, V, and X deficiencies
  - Not associated with bleeding:
    - Factor XII deficiency
    - Prekallikrein and high molecular weight kininogen deficiencies
- Unlike disorders of primary hemostasis, clinical signs of coagulation factor abnormalities include deep tissue bleeding (*e.g.* joint or muscle bleed) and post-procedural related bleeding

https://www.ihtc.org/userfiles/File/5-PT-Hemophilia-Care-Manual.pdf

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Plasma Products

- Plasma products include:
  - Fresh frozen plasma (FFP)
  - Plasma frozen within 24 hours after phlebotomy (PF24, FP24)
  - Plasma frozen within 24 hours after phlebotomy held at room temperature up to 24 hours after phlebotomy (PF24RT24)
  - Thawed plasma (TP)
  - Liquid plasma (LP)
  - Solvent detergent plasma
  - Pathogen inactivated plasma
  - *Cryoprecipitate reduced plasma*
- Contain all soluble clotting factors including fibrinogen, FII, FVII, FVIII, FIX, FX, FXIII, and VWF

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Plasma Products Comparison

	Manufacturing Conditions	Storage Time after Thaw	Factor Activity (Change vs. FFP)
FFP	Frozen at ≤ 18°C within 8 hours of collection	24 hours	Normal factor activities (0.7-1 U/mL) and fibrinogen 1-2 mg/mL
PF24	Held at 1-6°C within 8 hours and ≤ 18°C within 24 hours of collection	24 hours	FII 0%, FV +1%, FVII -16%, FVIII -15%, FIX +6%, FX 0%, VWF +34%, Fib +29 mg/dL, PC -19%, PS -5%
PF24RT24	Held at 20-24°C before freezing at ≤ 18°C within 24 hours of collection	24 hours	Similar to FFP, except FV -1%, FVIII -9-13%, PS -11%
TP*	After thaw and 1-6°C storage for 24 hours	4 additional days at 1-6°C	FV -21%, FVII -33%, FVIII -37% at 5 days
LP	Prepared from whole blood, never frozen	N/A	At 14 days, FII -12%, FV -20%, FVII -37%, FVIII -34%, FXI -12%, FXII -2%, PC -4%, PS -45%

*FFP, PF24, or PF24RT24 may be relabeled as TP

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Plasma Transfusion

- Plasma transfusions are indicated for the treatment of bleeding in patients with congenital or acquired coagulation defects
  - However, plasma transfusion is contraindicated when a specific factor concentrate (*e.g.* recombinant FVIII or IX) is available
- Plasma dosage may be estimated as 10-15 mL/kg to increase clotting factor activities by ~30% in the absence of rapid and ongoing consumption

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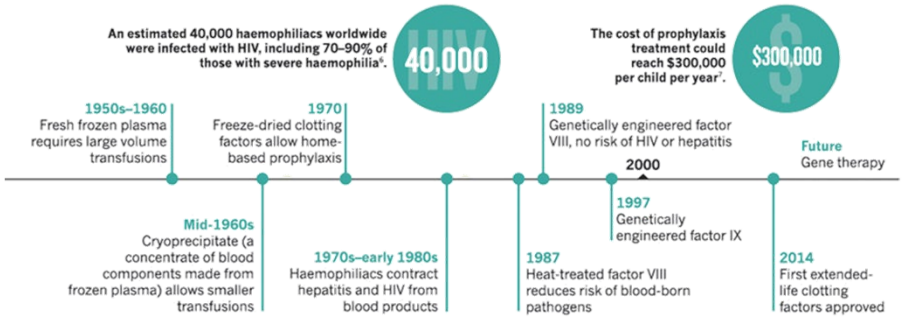
Coagulation Factor Products

- Historically, the major source of coagulation factors for treatment of congenital deficiencies was donated plasma or cryoprecipitate; however, use of plasma or cryoprecipitate is *contraindicated when a licensed concentrate is available*



https://www.scientificamerican.com/article/a-primer-on-haemophilia-graphic/

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FVIII and FIX Concentrates

- Plasma derived, recombinant, and modified recombinant FVIII and FIX concentrates are available
  - Modified recombinant factor concentrates increase the factor half-life and have recently become available
- Dosage and duration depend on the severity of FVIII or FIX deficiency, the location and extend of bleeding, and the clinical condition

Examples of FVIII and FIX Concentrates

	FVIII	FIX
Plasma Derived	Koate-DVI	AlphaNine Mononine
Recombinant	Advate Helixate FS Kogenate FS Novoeight Recombinant Xyntha	BeneFIX Ixinity Rixubis
Modified Recombinant	Adynovate Afstyla Eloctate Jivi	Alprolix Indelvion Rebinyn

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Hemophilia Bypassing Therapy

- A serious complication of congenital hemophilia is the development of inhibitors
  - Hemophilia A: 20-30%
  - Hemophilia B: 1-3%
- Bleeding in the setting of high-titer inhibitor often requires bypassing therapy with either:
  - High doses of NovoSeven RT
  - Activated prothrombin complex concentrate (aPCC), FEIBA
    - Contains factors II, VIIa, IX, X, and VIII

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VWF Concentrates

- Plasma derived and recombinant VWF concentrates are also available for patients with severe von Willebrand disease (VWD) or for mild to moderate VWD where the use of desmopressin is known or suspected to be inadequate

VWF Concentrates

	VWF
Plasma Derived (also contain FVIII)	Humate-P Alphanate Wilate
Recombinant	Vonvendi

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Other Factor Concentrates for Congenital Disorders

- Factor concentrates are also available for other factor deficiencies, including:
  - FVII (NovoSeven RT)
  - FX (Coagadex)
  - FXIII (Corifact, Tretten)
  - Fibrinogen (RiaSTAP)
  - Antithrombin (Thrombate III, ATryn)
  - Protein C (Ceprotin)

- However, many of these products are used off-label for acquired bleeding (*e.g.* NovoSeven RT, RiaSTAP) or acquired heparin resistance (*e.g.* Thrombate III, ATryn)

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Prothrombin Complex Concentrates

- Plasma derived factor concentrates composed of non-activated vitamin K dependent factors, II (76-160%), VII (40-100%), IX (80-124%), X (100-204%), proteins C (84-164%) and S (48-136%)
  - 3 factor (insufficient FVII)
    - Profilnine (FVII 35%)
    - Bebulin (FVII 13%)
  - 4 factor: Kcentra
    - Indicated for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA, *e.g.*, warfarin) therapy in adult patients with:
      - Acute major bleeding
      - Need for an urgent surgery/invasive procedure

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Summary

- Platelets and coagulation factors are essential for normal hemostasis
- Platelets can be transfused to treat disorders of primary hemostasis
- Plasma products contain physiologic amounts of coagulation factors and are indicated for the treatment of bleeding in patients with congenital or acquired coagulation defects; however, plasma transfusion is contraindicated when a specific factor concentrate is available
- Specific factor concentrates are indicated for congenital deficiencies, but are commonly used off-label to treat acquired bleeding

Please also listen to Topic 3: Blood Products and Indications On Why You Would Transfuse Each by Dr. Kerry O'Brien for more information

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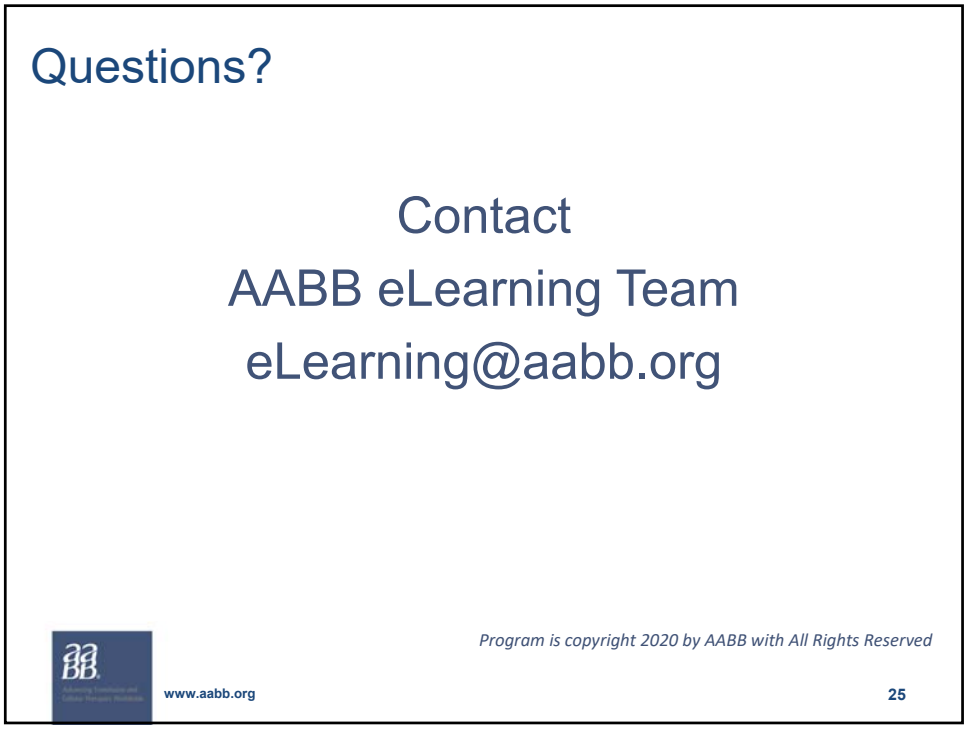

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