A is to 8, as B is to 9: Hemophiliac Hemorrhage Treatments

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Disclosure Statement

- I have no personal or financial conflicts of interest relating to this presentation

Objectives

- **Differentiation of the specific hemorrhagic treatments for each type of hemophilia**
- **Explain mechanism of action of hemophilia hemorrhagic treatments**
- **Tier hemorrhagic treatments for each type of hemophilia based on severity of bleeding and injury**

Basic Disease State Overview

- Primary focus will be treatments
- Hemophilia itself would require an entire discussion
- Treatments will cover which disease state may benefit from use

Hemophilia Types

A

- 'Classic' hemophilia
- Factor VIII deficiency

B

- 'Christmas disease'
- Factor IX deficiency

C

- 'Rosenthal syndrome', "PTA deficiency'
- Factor XI deficiency

More Rare

Parahemophilia	• 'Owren's Disease' • Factor V deficiency
Acquired	• 'AHA', 'AHB' • Autoimmune disorder
HAF deficiency	• 'F12 deficiency, 'Hagemen Trait' • Factor XII deficiency

Similar to Hemophilia

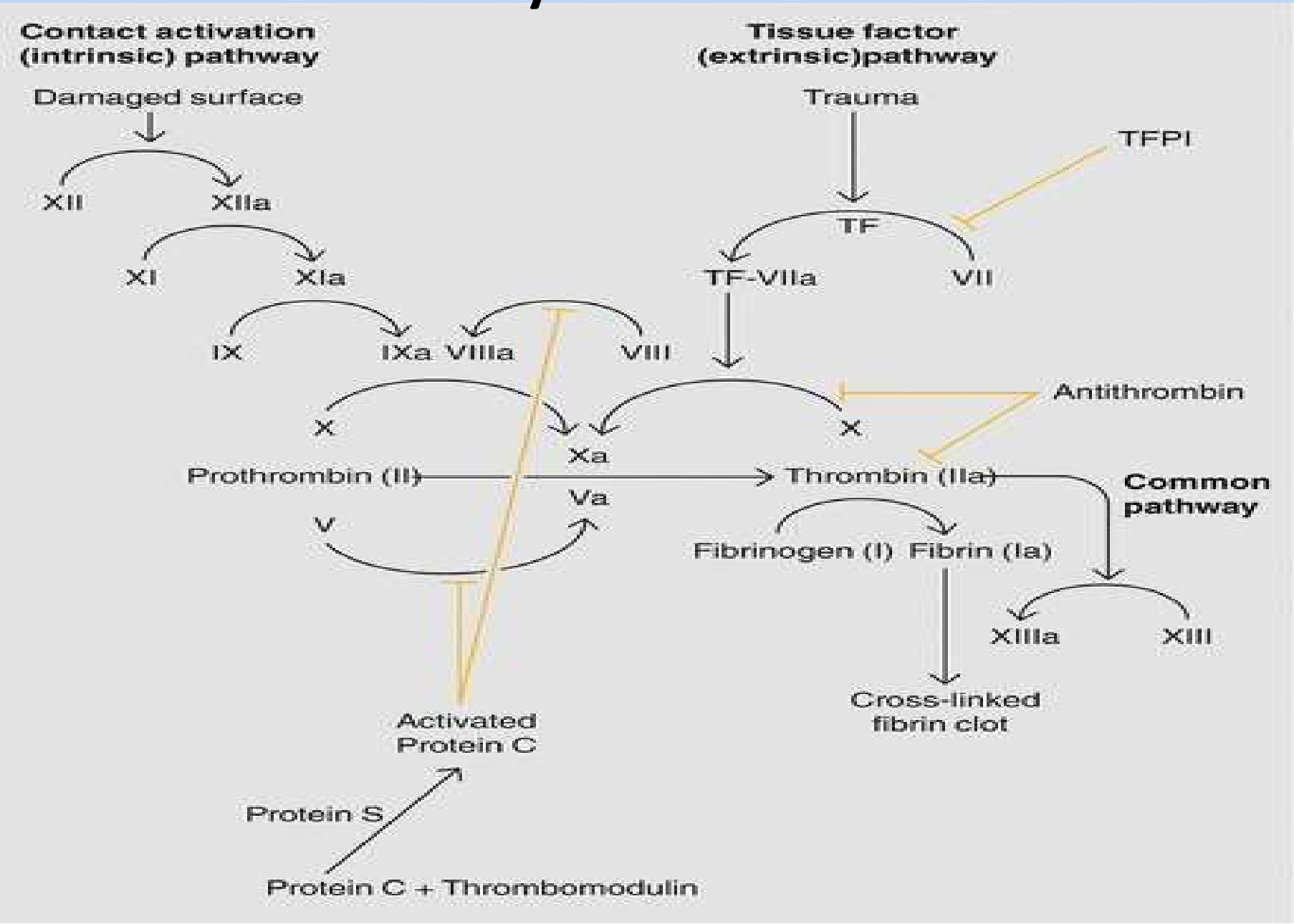
VWD

- 'Von Willebrand Disease'
- Deficiency of part of Factor VIII (VW factor, ristocetin cofactor)

Very Rare

- Factor deficiencies I, II, V, X, XIII
- Inherited platelet disorders

For your reference



Basic Genetics

- Male: X chromosome from mother and Y chromosome from father
- Female: X chromosome from mother and X chromosome from father
- Genetic disorder, on X chromosome
  - Male: XY chromosomes, if inherit, will have it
  - Female: XX chromosomes, carrier unless both parents have the disorder

Hemophilia A & B
Factor VIII & Factor IX Deficiency

- Severity depends on Factor VIII produced
  - Mild deficiency vs
  - Moderate deficiency vs
  - Severe deficiency

Hemophilia C: Factor XI deficiency

- Most cases due to genetics, but may also be acquired due to disease state: lupus
- Higher incidence: Ashkenazi (Eastern Europe) Jewish descent, Basque descent of Southern France

Acquired Hemophilia

- Not genetic, autoimmune disorder
  - Antibodies attack clotting factors
    - 50% idiopathic (unknown cause)
    - 50% known cause: lupus, rheumatoid arthritis, IBS, UC, Sjogrens, MS, infections, diabetes, hepatitis, postpartum, allergic medication reaction (penicillins, sulfamides, phenytoin, chloramphenicol, methyldopa, interferon alpha, fludarabine, BCG vaccination) , etc
- 2 types:
  - Acquired Hemophilia A (AHA): Factor VIII deficiency
  - Acquired Hemophilia B (AHB): Factor IX deficiency

Acquired Hemophilia

- May be initially missed
  - May be last consideration for patient symptoms
  - Invasive procedures, testing, often performed prior to consideration of acquired hemophilia
  - May never be diagnosed if no complications from it
- Genetic vs Acquired hemophilia
  - Acquired: bleed into skin, etc vs joint (genetic)
  - Acquired: compartment syndrome risk d/t bleeding
  - Both: at risk of life-threatening bleeds

Acquired Hemophilia A (AHA)

- Some never require treatment
  - May self resolve in months (postpartum)
  - May self resolve if offending medication d/c'd
- If possible:
  - Cure the disease, cure AHA
  - If unable to cure the disease, symptomatic treatment

HAF deficiency: Factor XII deficiency

- Both parents must carry the gene: women and men affected equally
- Higher incidence: Asian ethnicity

Hemophilia Complications

- May develop antibodies to clotting factors administered as prophylaxis or treatment
- Often require surgery later in life, due to chronic joint bleeding
  - Prophylaxis may decrease chronic bleeding, decreasing potential for surgery

Religious Restrictions

- Patients may decline blood products
- Synthetic options for treatment
- Some patients may decline if they are:
  - Jehovah's Witness
  - The Church of Christ, Scientist
  - The Followers of Christ
  - End Time Ministries

Minor vs Major Bleeding

- Minor: oral
- Major: compartment syndrome due to bleed, intracranial, large muscles, joints, trauma

Minor: Topical Treatments

- Non- Pharmacologic
  - Firm pressure to site of injury
  - Elevate if able
  - Ice packs, if able

Minor: Topical Dressings

- Kaltostat (Calcium Sodium Alginate)
- HemCon Bandage (chitosan)
- AllaQuix (chitosan)

- NOT beneficial in hemophilia:
  - QuickClot

Minor: Topical Treatments

- Topicals often not sufficient as monotherapy
- Lysteda (txa, tranexamic acid)
  - IV formulation may be used topically
  - Draw up, soak gauze, apply

Minor: Topical Fibrin Sealants

- Evicel: human fibrinogen and thrombin
- Raplixa: human fibrinogen and thrombin
- Tisseel: human fibrinogen and thrombin
- Vistaseal: human fibrinogen and thrombin

Prophylaxis

- History of thrombosis: risk vs benefit
- Factor deficiency: administer that factor
- Some patients not treated if have not had serious bleeding incident, chronic bleeding, etc

Prophylaxis

- Primary
  - Usually start as child, prior to severe bleeds
  - Decreased episodes of bleeding
  - Decreased chronic joint disease, due to less bleeding in joints
- Secondary
  - After multiple bleeds to a single joint
  - Prevent further joint bleeding
  - Decreased chronic joint disease

Amicar (aminocaproic acid)

- Synthetic antifibrinolytic:

Cryoprecipitate + FFP

- Both contain low amounts of factors
- Rarely useful as monotherapy

DDAVP (Desmopressin, ADH)

- Synthetic: 8-arginine vasopressin
- Intranasal, subcutaneous, intravenous
- Mechanism of Action not completely understood
- Vasopressin binds to V2 receptors
  - Von Willebrand Factor released
  - Increase in Factor VIII
  - Response is not the same in all patients

DDAVP (Desmopressin, ADH)

- Von Willebrand disease treatment
- Mild Hemophilia A

Hemlibra (emicizumab-kxwh)

- Factor VIII deficiency
- Effective for patients with or without inhibitors
  - Prophylaxis
  - Must discontinue any bypassing agents
- Humanized monoclonal modified immunoglobulin
- Genetically modified hamster ovary

Factors

- Administer factor that is deficient
- Replenish to normal levels
- Prophylaxis and Treatment of bleeding
- Prophylactic use
  - May decrease or prevent localized bleeding (joints, under skin, etc), eventually causes chronic pain
  - May decrease or prevent irreversible damage
  - May decrease or prevent chronic pain
  - Compliance: adults better than adolescents
  - Less effective when involved in sports

Factors

- May be administered at home
  - Patients often bring for acute incidents
  - Patients may administer for chronic pain, thinking they are having pain from an acute bleed
- Hospital for surgery, bleeds, etc

Factor VIII

- Alphanate (antihemophilic factor/ Von Willebrand Factor Complex): plasma derived factor VIII, VWF
- Jivi (antihemophilic factor, recombinant, PEGylated-aucl): recombinant factor VIII , genetically modified baby hamster kidney cells
- Nuwik (recombinant antihemophilic factor): recombinant glycoprotein, genetically modified human embryonic kidney
- Obizur (antihemophilic factor, recombinant, porcine sequence): genetically modified baby hamster kidney cells

Factor IX

- AlphaNine (Coagulation Factor IX): plasma derived, factors II, VII, IX, X. Factor IX only: therapeutic levels.
- Benefix (Coagulation Factor IX, Recombinant): genetically modified hamster ovary
- Idelvion (Coagulation Factor IX, Recombinant): genetically fused recombinant albumin and recombinant Factor IX
- Ixinity (Coagulation Factor IX Recombinant): genetically modified hamster ovary

Factor IX

- Mononine (Factor IX complex): plasma derived
- Profilnine (Factor IX complex): plasma derived, factors II, IX, X
- Rixubis (coagulation Factor IX complex, recombinant): genetically engineered hamster ovary

Inhibitors to Factors

- Antibodies = Inhibitors
- Inhibit (prevent) factor therapy from working
- Inhibitors prevent treatment of bleeds
- Must administer enough factor therapy to overcome inhibitor vs treatment against the inhibitor

Hemophilia A & B Inhibitor Treatment

- Feiba (anti-inhibitor coagulant complex): derived from human plasma
- NovoSeven RT (Coagulation factor VIIa, recombinant): genetically engineered baby hamster kidney

Factor VIII Inhibitor Treatment

- AutoPlex T (Anti-Inhibitor Coagulant Complex Heat Treated): derived from human plasma

Kcentra (Prothrombin Complex Concentrate, Human)

- Factors II, VII, IX, X, Proteins C + S, antithrombin III, albumin, heparin (to prevent clotting while stored)
- Dosed by the Factor IX content
- Factor IX, sole agent, preferred over Kcentra
- Made from human blood products

Tranexamic Acid

- Synthetic lysine derivative: blocks lysine binding sites on plasminogen
- With factors (PCC) increases thrombosis risk
  - Separate dosing by 12+ hours

Gene Therapy

- Difficulties with all research
- Unclear which may make it to market first
- Multiple experimental gene therapies
- Human trials underway
- May not be beneficial if immune bodies already formed

Acquired Hemophilia A (AHA) Potential Treatments

- Factor VIII
- Desmopressin
  - Usually well tolerated
  - No risk of blood-born infections
  - Exact mechanism of action not known
  - Increases VWF and Factor VIII
- Desmopression + Factor VIII
  - Treat minor bleeding episodes

Questions?

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