

**A is to 8, as B is to 9:  
Hemophilic  
Hemorrhage Treatments**

Nancy Balch, PharmD, BCCCP  
nbalch@mgh.harvard.edu

**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

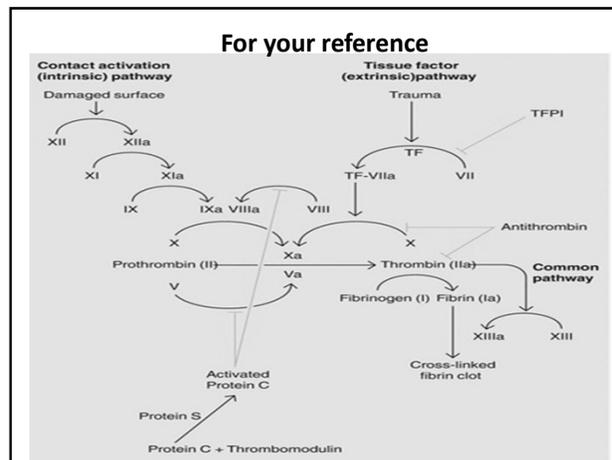
**Similar to Hemophilia**

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



**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, methylodopa, 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-borne infections
  - Exact mechanism of action not known
  - Increases VWF and Factor VIII
- Desmopressin + Factor VIII
  - Treat minor bleeding episodes

### Questions?

**Nancy Balch, PharmD, BCCCP**  
**[nbalch@mgh.harvard.edu](mailto:nbalch@mgh.harvard.edu)**

**References**

- Affaticati, A., Gerra, M.L., Amerio, A., Inglese, M., Antonioni, M.C., et al (2015, December). The Controversial Case of Biperiden From Prescription Drug to Drug of Abuse. *Journal of Clinical Psychopharmacology*, 35 (6), 749-750. Retrieved Aug 20, 2017, from OVID database.
- Baker, J.S., Graham, M., Davies, B. (2006, July). Gym users and abuse of prescription drugs. *Journal of the Royal Society of Medicine*, 99, 331-332. Retrieved Jul 30, 2017, from OVID database.
- Maier, L., Schaub, M.P. (2015). The Use of Prescription Drugs and Drugs of Abuse for Neuroenhancement in Europe Not Widespread But a Reality. *European Psychologist*, 20 (3), 155-166. Retrieved Feb 5, 2012, from OVID database.
- Jewell, C.E., Tomlinson, J., Weaver, M. (2011). Identification and Management of Prescription Opioid Abuse in Hospitalized Patients. *Journal of Addictions Nursing*, 22, 32-38. Retrieved Feb 5, 2012, from OVID database.
- Jena, A.B., Goldman, D.P., Foster, S.E., Califano, J.A. (2011). Prescription Medication Abuse and Illegitimate Internet-Based Pharmacies. *Annals of Internal Medicine*, 155, 848-850. Retrieved Feb 5, 2012, from OVID database.
- Cai, R., Crane, E., Poneleit, K., Paulozzi, L. (2010, June 10). Emergency Department Visits Involving Nonmedical Use of Selected Prescription Drugs – United States, 2004-2008. *Centers for Disease Control and Prevention MMWR Morbidity and Mortality Weekly Report*, 59 (23), 705-709. Retrieved Feb 5, 2012, from OVID database.

**References**

- <https://www.uspharmacist.com/article/hemophilia-review>
- <https://ashpublications.org/blood/article/133/5/389/272947/New-therapies-for-hemophilia>
- <https://globalrph.com/drugs/prothrombin-concentrates-complexes/>
- <https://www.cdc.gov/ncbddd/hemophilia/treatment.html>
- <https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a#:~:text=Hemophilia%20A%2C%20also%20called%20factor,have%20no%20previous%20family%20history.>
- <https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b#:~:text=Hemophilia%20B%2C%20also%20called%20factor,a%20change%20in%20a%20gene>
- <https://www.idelvion.com/powerful-bleed-protection>

**References**

- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-254-document-regarding-risks-of-gene-therapy-trials-for-hemophilia>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-247-recommendations-on-treatment-of-hepatitis-c-in-individuals-with-hemophilia-and-other-bleeding-disorders>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-243-recommendation-on-sippet-survey-of-inhibitors-in-plasma-product-exposed-toddlers-results-and-recommendations-for-treatment-products-for-previously-untreated-patients-with>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-242-recommendations-regarding-doses-of-clotting-factor-concentrate-in-the-home>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-241-recommendation-concerning-prophylaxis>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-233-recommendation-on-administration-of-inhibitor-bypassing-agents-in-the-home-for-patients-with-hemophilia-and-inhibitors>

**References**

- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-257-guidelines-for-emergency-department-management-of-individuals-with-hemophilia-and-other-bleeding-disorders>
- <https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a>
- <https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-263-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-other-bleeding-disorders>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-261-recommendations-for-bleeding-prophylaxis-in-bleeding-disorder-patients-undergoing-gi-endoscopy>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-258-recommendation-on-the-use-and-management-of-emicizumab-kxwh-hemlibra-for-hemophilia-a-with-and-without-inhibitors>
- <https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-256-recommendation-for-liver-biopsies-in-gene-therapy-trials-for-hemophilia>

**References**

- Smith-Martinez, L.A., Chatham, L.N., Muthukanagaraj, P. (2019, March) Intramuscular Ketamine Protocol as an Alternative to Physical Restraints for Electroconvulsive Therapy Administration in a Psychotic Patient. *The Journal of ECT*, 35 (1) e1-e2 doi: 10.1097/YCT.0000000000000522
- <http://dx.doi.org/10.1080/20961790.2017.1285219>
- [http://escholarship.org/uc/uciem\\_westjem](http://escholarship.org/uc/uciem_westjem) DOI: 10.5811/westjem.2019.10.43067