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Hemophilia

Jamie Kawamata, Pharm.D.
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Objectives

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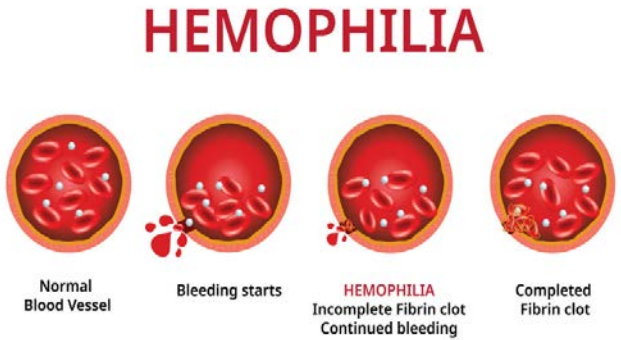
- Overview of hemophilia A and B
- Summarize the complications of hemophilia
- Review of current management/treatment strategies
- Discuss the potential role of gene therapy and future target areas of therapy

What is hemophilia type A and B?

- An inherited bleeding disorder caused by a deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B).
- The deficiency is the result of mutations of the clotting factor genes: F8 and F9.



Epidemiology

- Worldwide incidence of hemophilia: ~ **400,000** up to 1.2 million
  - **Hemophilia A: ~**1 in 5000 male births
    - half to two-thirds having severe disease
    - four times more common as **hemophilia B**
  - **Hemophilia B:** ~1 in 30,000 male births
    - one-third to half having severe disease

- Number of people with hemophilia in the United States is ~20,000 individuals.

Complications and Severity

- **Arthropathy -** repeated hemarthrosis and synovitis lead to pain and joint destruction.
- **ICH –** intracranial hemorrhage and central nervous system bleeding. Far less common but potentially more devastating.
- **Inhibitor development –** production of antibodies against the infused factor that inhibits the function of the factor.
- **HIV/HCV infection –** Improvements in donor screening and current viral inactivation measures in the commercial manufacturing process have made clotting factor products very safe since approximately 1993**;** increased prevalence of liver disease and risk of hepatocellular carcinoma development.
- **Disease severity** – difference in severity impacts treatment and costs.

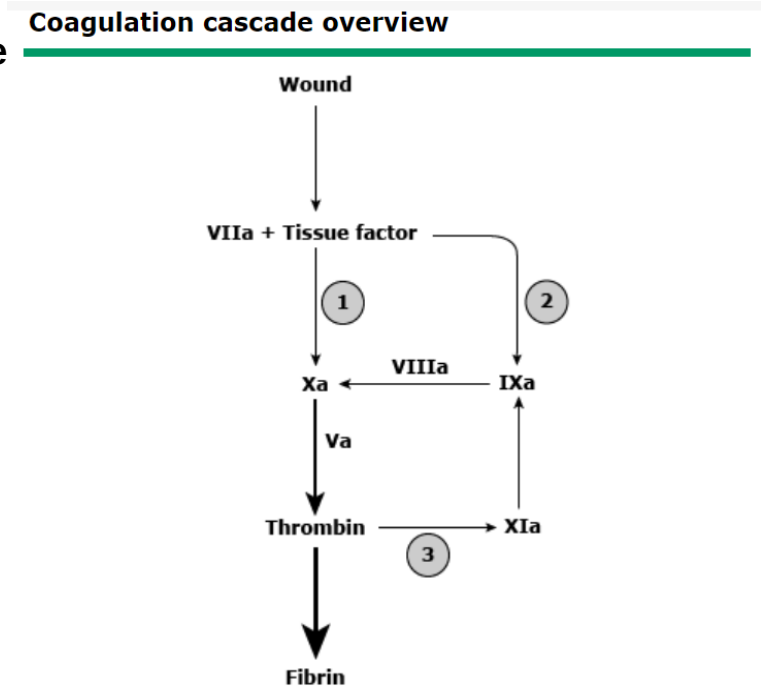
Cost

- Medications to treat hemophilia cost an average of more than $270,000 annually per patient, according to a 2015 Express Scripts report.
- Average cost of care for patients with hemophilia across different severity levels in the United States reported at almost $200,000 (World Federation of Hemophilia (WFH) 2012 guideline).
- Treatment cost for patients with inhibitors is even higher, with annual costs exceeding $400,000.
- Annual cost can soar above $1 million when complications arise.

Pathophysiology

Blood clot formation: formation of the platelet plug, followed by activation of the clotting cascade and propagation of the clot.

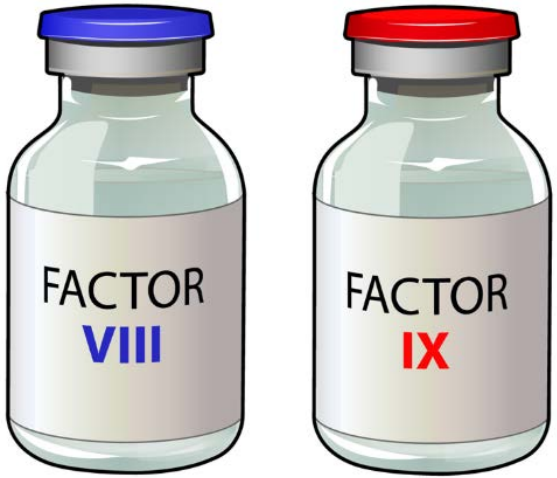
- Activation of factor X (Xa) occurs through 2 pathways which ultimately results in thrombin production which leads to fibrin production.
  - Thrombin: platelet activation/adhesion and stimulates fibrin production.
  - Fibrin: enmeshes and reinforces the platelet plug.
- Activated factor VIII (VIIIa) and factor IX (IXa) are involved in activation of factor X through one pathway (intrinsic pathway)
- Sustained generation of thrombin depends upon the activation of factor VIII and factor IX.



Management/Treatment

Management

- Prevent bleeding from occurring and treat episodes of active bleeding that do occur early on with replacement of deficient clotting factor.



Prophylaxis Therapy

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- Prophylactic therapy for hemophilia has been shown to be cost-effective compared with on-demand therapy
- Start at as young of an age as possible considering the burdens of regular IV therapy and severity of disease
- Focus: Convert from a severe hemophilia phenotype (i.e factor activity level (FAL) <1% with significant bleeding of the joint(s) and muscle(s) excluding mucosal bleeds (nose and mouth)) → moderate hemophilia (FAL >2%)
  - Bleeding frequency: 1% increase of FAL = 18% reduction

Prophylaxis Therapy

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Types:

- **Primary prophylaxis** – Used in individuals with no prior bleeding episode(s) but are at high risk of bleeding based on severe factor deficiency (i.e. FAL <1%)
- **Secondary prophylaxis**
  - Individuals with more than one bleeding episode (i.e. two or more bleeds into a target joint, evidence of joint disease by physical examination or radiography) regardless of factor activity level
  - Individuals with severe deficiency (FAL <1%) and more than one bleeding episode
- **Intermittent prophylaxis**
  - Factor level (moderate or mild factor deficiency (i.e. FAL >5%) and no prior bleeding)
  - Deficient factor (factor VIII or factor IX)
  - Physical activity level: high-impact physical activities, sports
  - Joint bleeding
  - Surgical procedures

Prophylaxis Therapy – Hemophilia A

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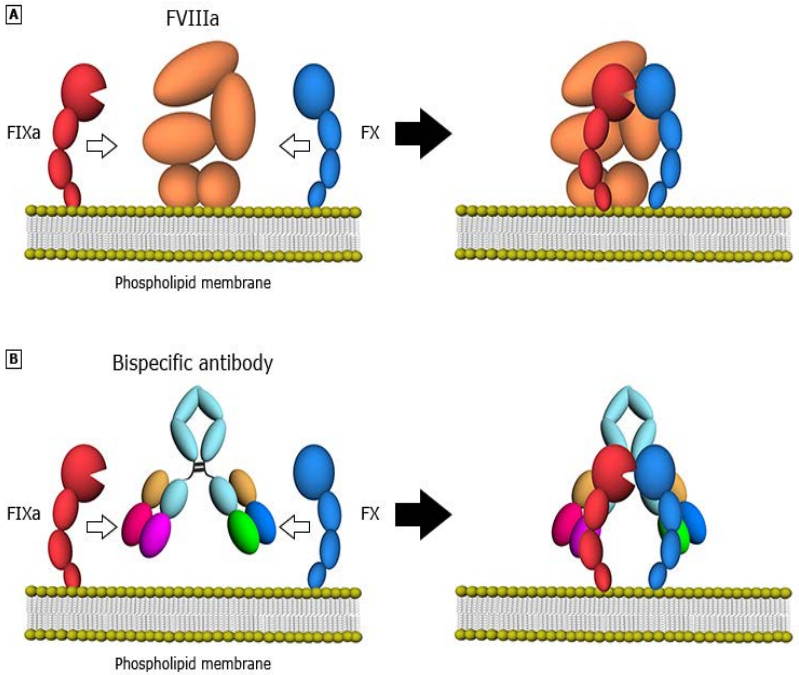
- **Hemophilia A** – Factor VIII, 25 to 40 units/kg given three times per week or 15 to 30 units/kg three times per week.

Product name	Half-life (hours)*	Characteristics
Standard half-life products¶		
Advate	9 to 12	Recombinant
Kogenate FS	11 to 15	Recombinant
Hemofil M	15	Plasma-derived; mAb-purified
Koate (previously called Koate DVI)	16	Plasma-derived; chromatography purified
Kovaltry	12 to 14	Recombinant
Novoeight	8 to 12	Recombinant
Nuwiq	12 to 17	Recombinant
Recombinate	15Δ	Recombinant
Xyntha	8 to 11	Recombinant
Longer-lasting products		
Adynovate	13 to 16	Recombinant; PEGylated
Afstyla	10 to 14	Recombinant; single chain
Eloctate	13 to 20	Recombinant; Fc fusion
Esperoct	17 to 22	Recombinant, glycoPEGylated

Prophylaxis Therapy-Hemophilia A

- Hemlibra® (emicizumab)
  - MOA: Recombinant humanized bispecific monoclonal antibody that acts like factor VIIIa to bind factors IXa and X in activating factor X.
  - DOSE: Loading dose 3mg/kg SC once weekly x 4 weeks, then a maintenance dose of either 1.5mg/kg once per week, 3mg/kg every 2 weeks, or 6mg/kg every 4 weeks.
  - Not to be used for acute bleeding
  - ROLE: Used for routine prophylaxis with or without factor VIII inhibitors in adults and children of all ages from newborn and older.
  - Flexible maintenance dosing frequency
  - Approximate cost (AWP):
    - $18,034.99 per injection 150mg/ML (0.4ML, 0.7ML, 1ML)
    - $3,607.00 per injection 30mg/ML



Prophylaxis Therapy-Hemophilia B

- **Hemophilia B** – Factor IX, 25 to 40 units/kg given two times per week or 15 to 30 units/kg two times per week. Longer lasting products allow for once per week or once every two week dosing.

Product name	Half-life (hours)*	Characteristics
Standard half-life products		
AlphaNine SD	18¶	Plasma-derived; solvent/detergent treated
BeneFIX	16 to 19	Recombinant
Ixinity	24Δ	Recombinant
Mononine	23¶	Plasma-derived; mAb purified
Rixubis	23 to 26	Recombinant
Longer-lasting products		
Alprolix	54 to 90	Recombinant; Fc fusion
Idelvion	104¶	Recombinant; albumin fusion

Cost-Utility Analyses Review

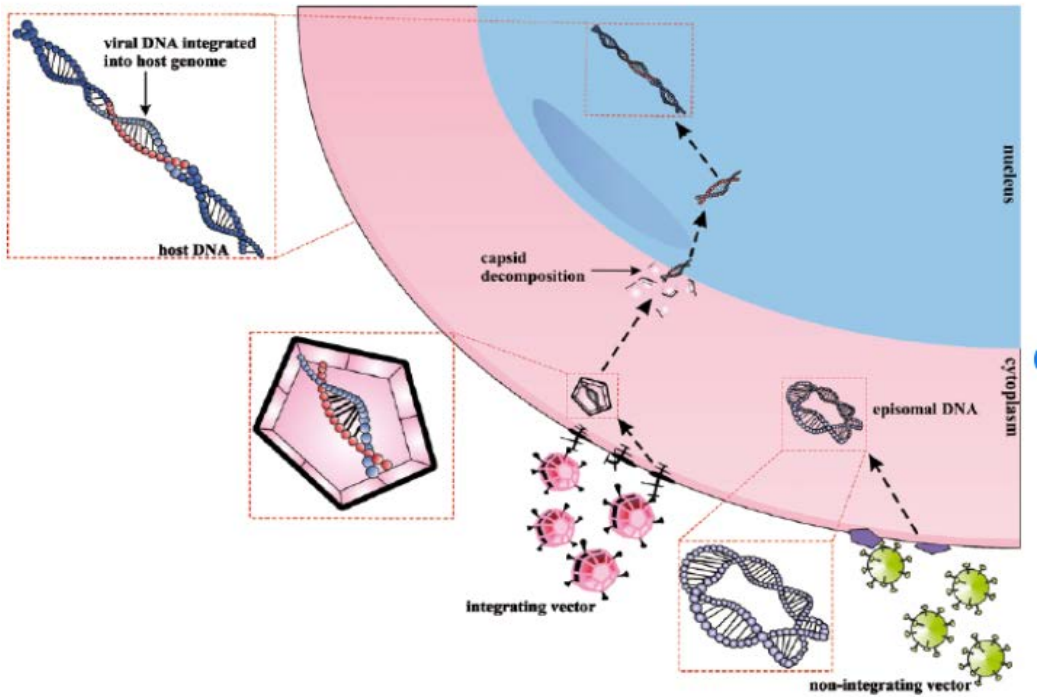
Journal of Managed Care & Specialty Pharmacy: **Hemophilia Burden of Disease: A Systematic Review of the Cost-Utility Literature for Hemophilia**

- Systematic literature review:
  - Reviewed the cost-utility analyses (CUA) of hemophilia treatments
  - 11 studies met inclusion criteria
  - Out of a total of 52 studies from Tufts Medical Center Cost-Effectiveness Analysis Registry and the National Health Service Economic Evaluation Database for English-language CUAs published from 2000 - 2015
  - Search terms: *hemophilia, haemophilia, factor VIII,* or *factor IX*
- Cost-utility of hemophilia treatments vary widely based on the following:
  - treatment approach
  - patient characteristics
  - disease severity
- Median cost-effectiveness ratios reported across the literature varied by hemophilia type:
  - $86,000 per quality-adjusted life-years (QALY) for hemophilia A treatments
  - $17,000 per QALY for hemophilia B treatments
  - $46,000 per QALY for patients with both hemophilia A and B
- Estimates of the cost-effectiveness of hemophilia treatments are comparable with those of other orphan drugs

Gene Therapy

- Vectors bind to specific receptors on the cell surface.
- Once bound to the cell surface receptors, the content of the viral capsid is released into the cytoplasm.
- Viral vector types:

1) Integrating - viral DNA translocates into the nucleus and integrates into the host genome.
2) Non-integrating - genetic material remains in the cytoplasm in an episomal form.



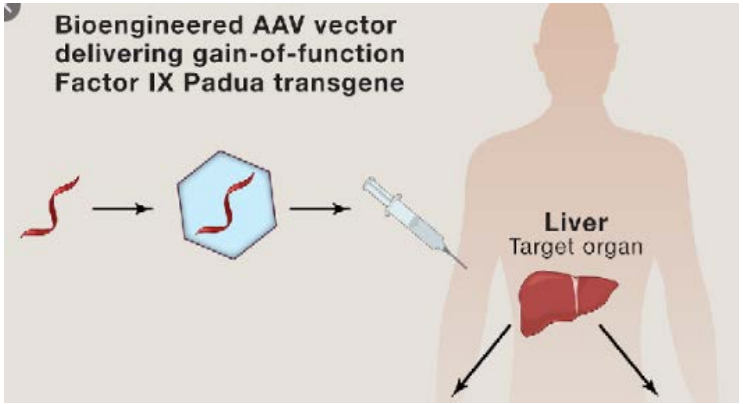
Gene Therapy – Hemophilia A

Hemophilia A

- Valoctocogene roxaparvovec (BMN 270; Biomarin)
  - Encodes human factor VIII through a gene via non-integrating vector.
  - Clinical improvements in bleeding rates due to sustained increases in factor VIII activity.
  - Dose: 6 x 10^3 vector genomes per kg showed a mean factor VIII activity level over 30% for 3 years.
  - Efficacy is dose-dependent
  - Mean annual bleeding rate decreased from 16.5 events per year to zero events per year.
  - Adverse effects: elevated hepatic transaminases, fever, myalgias, and headache.
  - Barriers:
    - Inhibitors
    - Antibodies to AAV-5 viral capsid
  - Estimated price: $3 million

Gene Therapy – Hemophilia B

- Hemophilia B
- Factor IX Padua variant transgene that enhances factor IX activity 8- to 12- fold.
- Non-integrating Vector Types:
  - Etranacogen dezaparvovec (AMT-061; UniQure)
  - Fidanacogene elaparvovec (SPK-9001/PF-06838435; Spark/Pfizer)



Gene Therapy – Hemophilia B

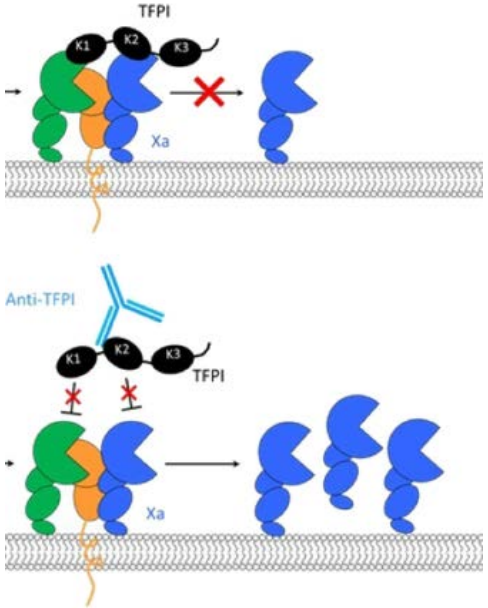
- Etranacogen dezaparvovec (AMT-061; UniQure)
  - Anticipated FDA approval projected for late 2020-early 2021
  - Currently in phase III trial
  - Barriers:
    - Inhibitors
    - Antibodies to AAV-5 viral capsid.

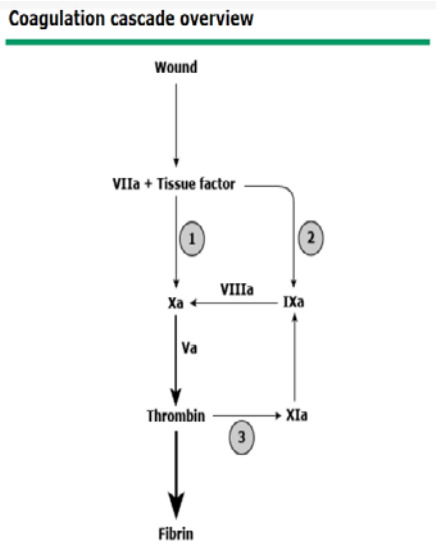
Gene Therapy – Hemophilia B

- Fidanacogene elaparvovec (SPK-9001/PF-06838435; Spark/Pfizer)
  - Investigational product not currently FDA approved.
  - Bioengineered viral capsid, liver-specific promoter and factor IX Padua transgene.
  - Annualized bleeding rate significantly decreased in all participants and amount of factor used was decreased. Some participants did not have any bleeding and did not use any factor.
  - Onset of action occurred within 1 week of vector infusion; factor IX expression reached steady state within 14 weeks after infusion; mean vector derived FAL was ~33.7±18.5%.
  - Dose: 5×10^{11} vector genomes/kg IV over 1 hour.
  - Adverse Events: elevated liver enzymes
  - Barriers:
    - Inhibitors
    - Antibodies to AAV-5 viral capsid

Other Potential Targets of Therapy

- **Concizumab** (mAb2021; Novo Nordisk) - monoclonal antibody directed against tissue factor pathway inhibitor (TFPI).
  - o TFPI: blocks the function of factor Xa by inhibiting the activity of the tissue factor-factor VIIa complex. Thrombin and fibrin will not be produced.
- Blocking TFPI allows generation of factor Xa and in turn thrombin and fibrin (even in the absence of factors VIII and IX).
- Can be administered subcutaneously or intravenously
- Considered for use in patients with hemophilia A and hemophilia A or B with inhibitors





Conclusion

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- The way in which hemophilia management and treatment is approached is rapidly changing with the development of gene therapy and agents that target other areas within the coagulation cascade
- The role of gene therapy has yet to be determined:
  - Usage of prophylaxis therapy and factor supplementation
  - Use in the presence of inhibitors
- Products that work at other targets of therapy within the coagulation cascade that can compensate for the presence of inhibitors and/or work in the absence of factor VIII and IX may have a promising role in the future.
- Efficacy and cost of these emerging agents are still to be determined

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