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Educational Material*
First Quarter, 2020

Hemophilia

Summary:

Hemophilia is usually an inherited bleeding disorder in which the blood does not clot properly. This can lead to spontaneous bleeding as well as bleeding following injuries or surgery. The exact number of people living with hemophilia in the United States is not known. A CDC study conducted in six states in 1994 estimated that about 17,000 people had hemophilia at that time. Currently, the number of people with hemophilia in the United States is estimated to be about 20,000, based on expected births and deaths since 1994.

Objective(s):

1. Provide an overview of hemophilia A and B
2. Summarize the complications of hemophilia
3. Review current management/treatment strategies
4. Discuss the potential role of gene therapy and future target areas of therapy

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March 2020

*As required by Medicaid Mega Reg

Hemophilia

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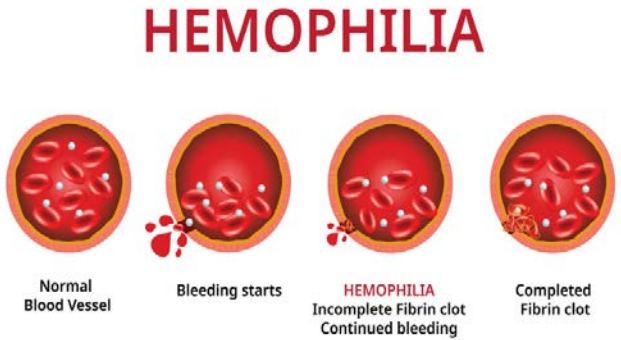
March 2, 2020

Objectives

- 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.

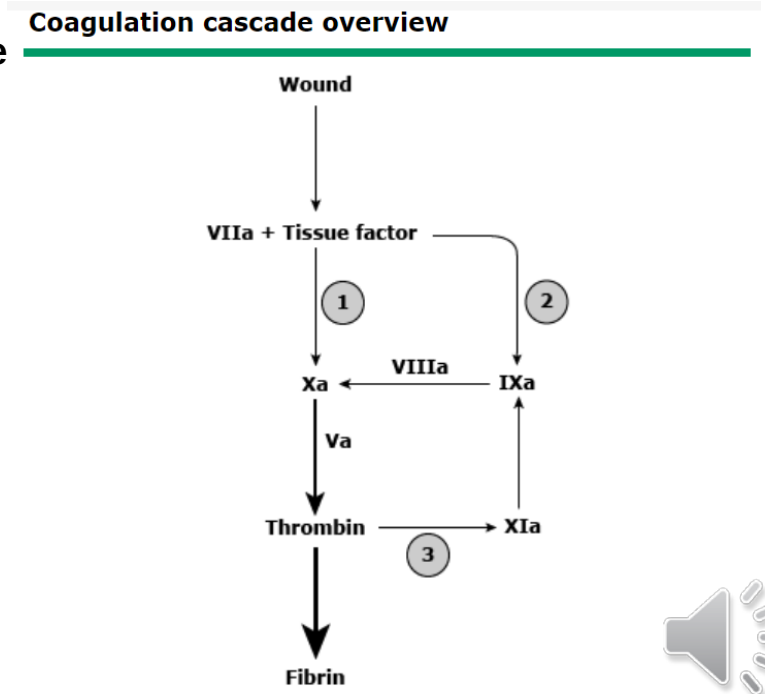
Cost

- 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.

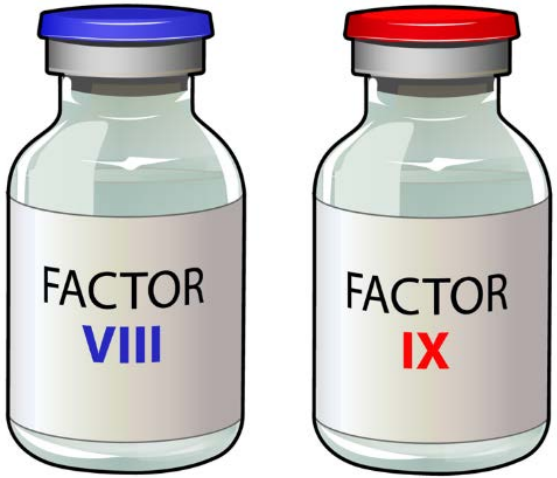
- Activation of factor X (Xa) occurs through 2 pathways which ultimately results in thrombin production which leads to fibrin production.
  - Thrombin: platelet activation/adhesion and stimulates fibrin production.
  - Fibrin: enmeshes and reinforces the platelet plug.
- Activated factor VIII (VIIIa) 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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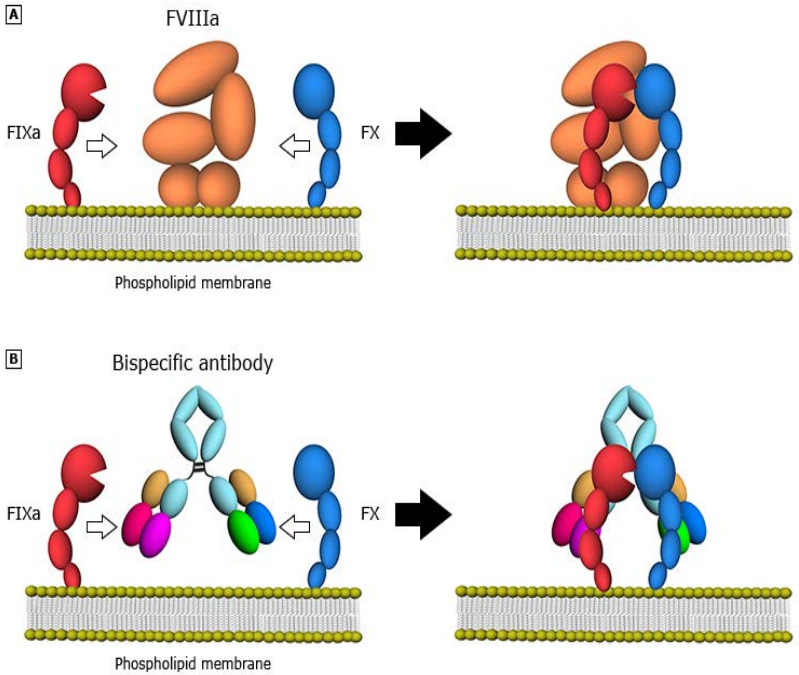
- **Hemophilia A** – Factor VIII, 25 to 40 units/kg given three times per week or 15 to 30 units/kg three times per week.

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

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- **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

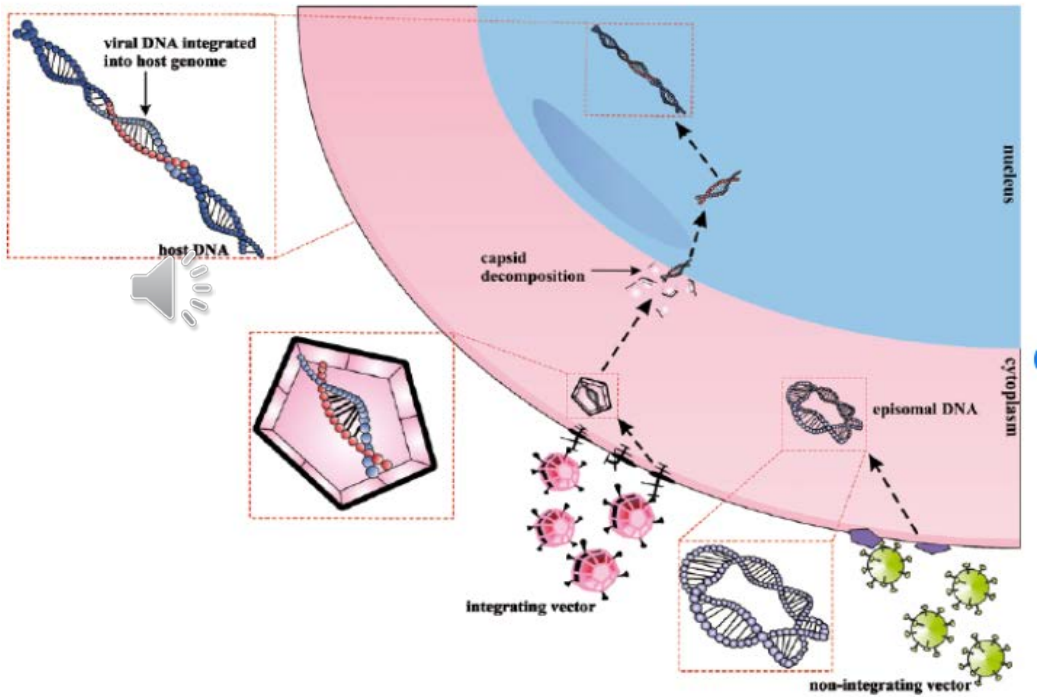
Journal of Managed Care & Specialty Pharmacy: **Hemophilia Burden of Disease: A Systematic Review of the Cost-Utility Literature for Hemophilia**

- 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

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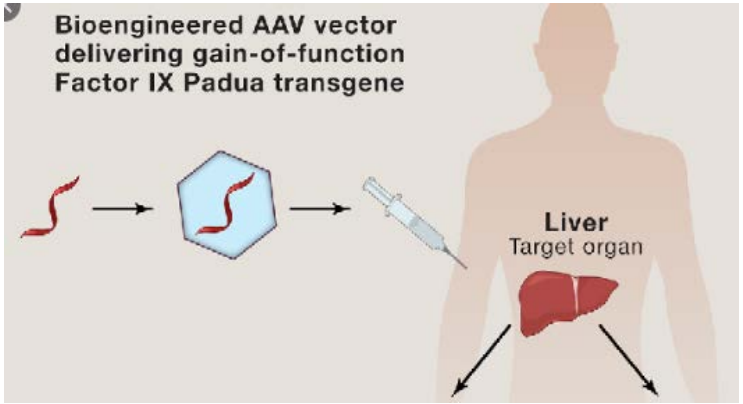
Hemophilia A

- 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

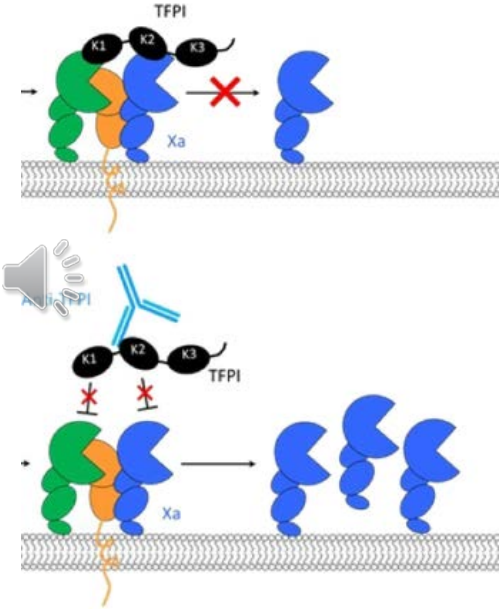
- Etranacogen dezaparvovec (AMT-061; UniQure)
  - Anticipated FDA approval projected for late 2020-early 2021
  - Currently in phase III trial
  - Barriers:
    - Inhibitors
    - Antibodies to AAV-5 viral capsid.

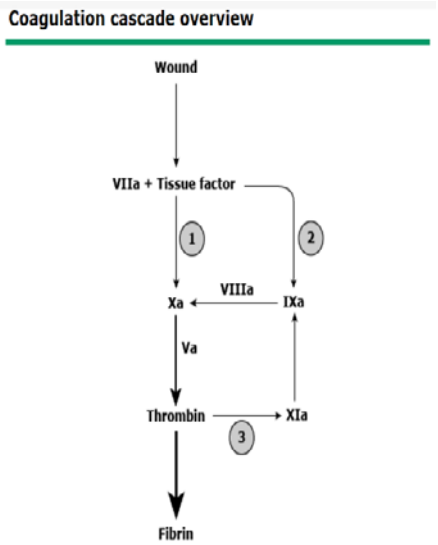
Gene Therapy – Hemophilia B

- 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 x 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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