Hemophilia and Bleeding Disorders:
Diagnosis and Clinical Features

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Presentation Outline

1. Epidemiology and genetics
2. Clinical features of hemophilia
3. Inhibitors in congenital hemophilia
4. Acquired hemophilia

Q1: How often do you manage acute bleeding in patients with hemophilia?

a. Quite often, I am associated with a hemophilia treatment center
b. Once a year
c. Every few years
d. Never

What is Hemophilia?

- Congenital bleeding disorder
- Due to deficiency or absence of a coagulation cascade protein
- Hemophilia A = factor VIII deficiency
- Hemophilia B = factor IX deficiency
- Others . . .

Rare Bleeding Disorders

Protein	Prevalence	Genetics	Specific Rx
Fibrinogen	1 : 1,000,000	AR	Yes
Factor II	1 : 2,000,000	AR	No
Factor V	1 : 1,000,000	AR	No
Factor VII	1 : 500,000	AR	Yes
Factor X	1 : 1,000,000	AR	No
Factor XI	1 : 1,000,000	AD	Yes [#]
Factor XIII	1 : 2,000,000	AR	Yes

AR = autosomal recessive, AD = autosomal dominant [#] Not available in U.S.

- Account for 3 - 5% of all inherited coagulation disorders
- Higher prevalence in areas of geographic or social isolation

Hemophilia A

- Factor VIII deficiency
- Classical hemophilia
- 1 in 5,000 to 10,000 male births
- 80% of total cases
- Spontaneous mutations = 30%

Hemophilia B

- Factor IX deficiency
- Christmas disease
- 1 in 30,000 male births
- 20% of total cases
- Spontaneous mutations = 20%

Clinical phenotypes are indistinguishable

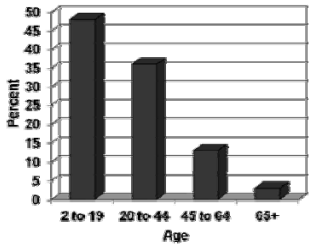





- Hemophilia affects all racial and socioeconomic groups equally
- There are ~ 20,000 hemophiliacs in the United States
- More than 500,000 hemophiliacs worldwide

Age Distribution of the U.S. Hemophilia Population

Age (yr)	Number	Percent
2 – 19	8584	48%
20 – 44	6418	36%
45 – 64	2274	13%
65+	524	3%



Centers for Disease Control and Prevention. Summary report of UDC Activity (National). Report date May 30, 2011.

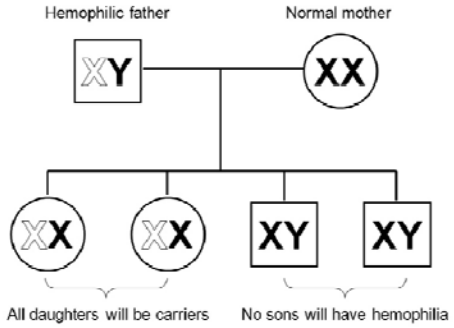
Genetics of Hemophilia

- Genes for factors VIII and IX are located on the X chromosome
- Females are carriers, males are affected

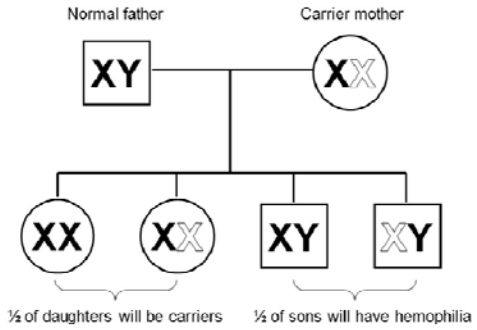
High rate of spontaneous mutations

- Unaware female carriers
- New mutation in baby boy
- ~30% have no family history of hemophilia

Genetics of Hemophilia



Genetics of Hemophilia



Diagnosis of Hemophilia

+ Family History

- Identify carriers
- Pre-conception counseling
- Cord blood testing of males
- Defer testing of females until sx or considering pregnancy

No Family History

- Bleeding with birth trauma, circumcision, immunizations
- Suspected child abuse
- Joint bleeds and hematomas start to occur when learning to walk

Diagnosis of Hemophilia

Laboratory testing

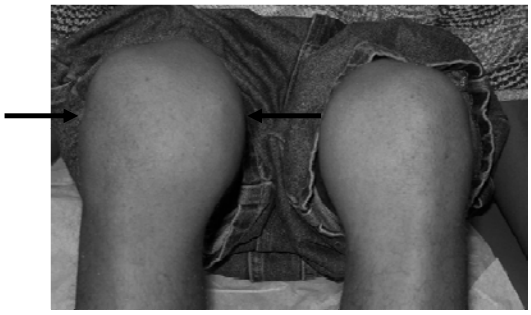
- Normal CBC
- Normal platelet function
- Normal PT / INR
- Prolonged aPTT
- Measure factor VIII and IX levels

Clinical Features of Hemophilia

Severity of bleeding tendency depends on the factor level

Mild (> 5%)	Moderate (1-5%)	Severe (< 1 %)
• Bleed only after severe injury, trauma, or surgery • May not be diagnosed until adulthood	• Bleed after injury, surgery • May have occasional spontaneous bleeding	• Frequent spontaneous bleeding • Diagnosis made in early childhood

Clinical Features of Hemophilia: *Joint bleed (hemarthrosis)*

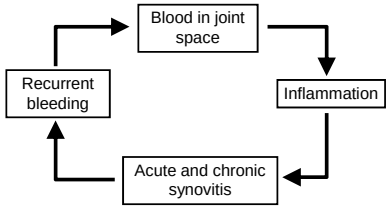


The Clinical Problem of Joint Bleeding

- Hemarthrosis, primarily involving the ankles, knees, and elbows, is the most common complication of hemophilia
- 45% experience first joint bleed within first year of life
- Median age at first joint bleed: 17 – 26 months
- 90% have at least one joint bleed by 4 years of age
- 90% of those with severe hemophilia have chronic degenerative changes involving at least 1 joint by age 25
- 40% report restricted physical activities due to arthropathy

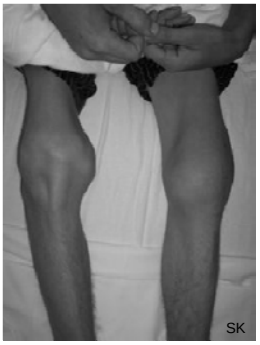
Lafeber et al. *Haemophilia*. 2008; 14(Suppl 4):3-9.
Valentino et al. *Semin Hematol*. 2008; 45(Suppl 1):S50-S57.

The Clinical Problem of Joint Bleeding



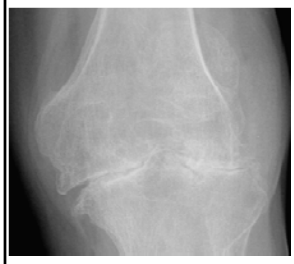
- Hemophilic arthropathy is characterized by cartilage and bone destruction, bone remodeling, and progressive loss of function
- Prophylactic administration of clotting factor concentrates is essential for preventing hemophilic arthropathy

Clinical Features of Hemophilia: *Joint bleed (hemarthrosis)*

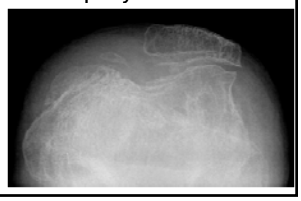


- 26 yo with severe hemophilia A and fVIII inhibitor
- Recurrent traumatic and spontaneous knee bleeds
- Left side surgically replaced
- Note severe muscular atrophy

Clinical Features of Hemophilia:
Joint bleed (hemarthrosis)



- 36 year old
- Severe hemophilia A
- Recurrent left knee bleeds
- Severe hemophilic arthropathy



TS

Clinical Features of Hemophilia:
Joint bleed (hemarthrosis)

- 36 year old
- Severe hemophilia A
- Recurrent left knee bleeds
- Severe hemophilic arthropathy
- Underwent total knee arthroplasty
- Infected prosthesis had to be removed 3 months later

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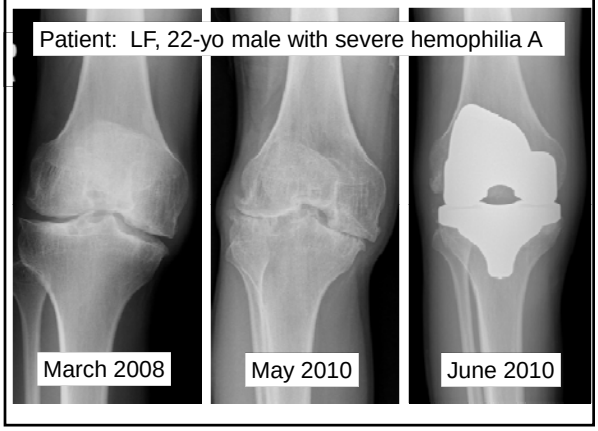
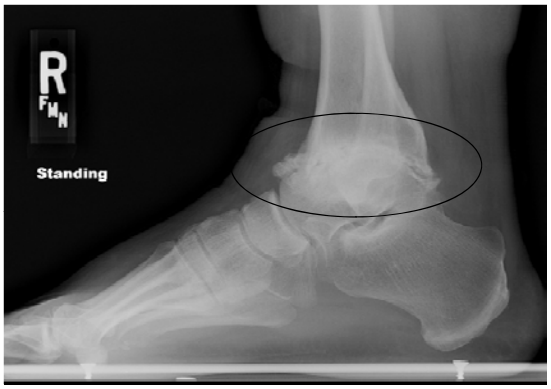
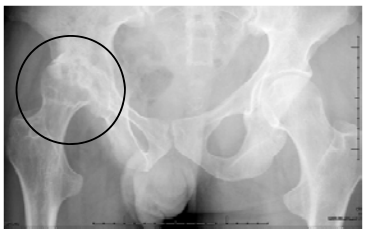




Severe hemophilia A, no inhibitor, morbidly obese

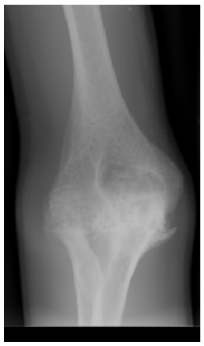
RS

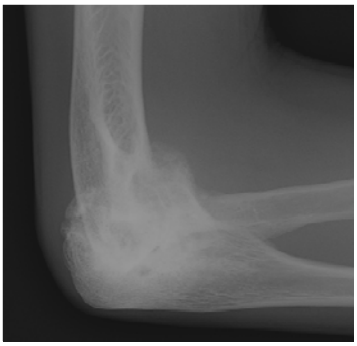
Clinical Features of Hemophilia:
Joint bleed (hemarthrosis)



- Severe hemophilia A with inhibitor and advanced arthropathy
- Required right total hip arthroplasty

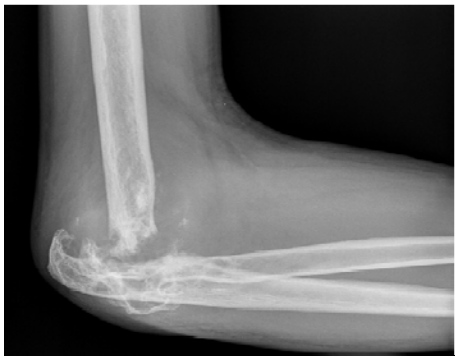
SK





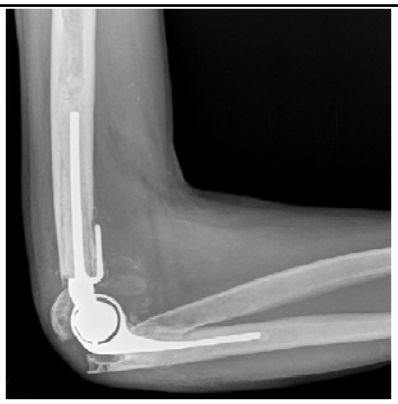
- 36 year old, severe hemophilia A, followed by hemophilia treatment center since birth. No history of fVIII inhibitor.
- Target joint in childhood, no longer bleeds (or moves).

NJ

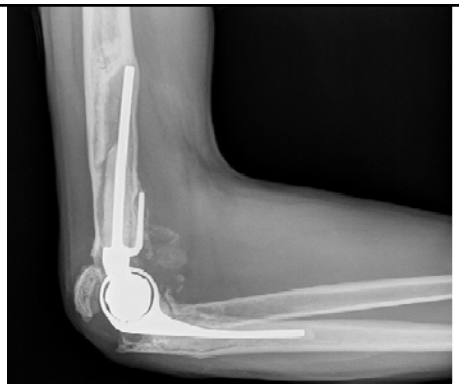


44-yo male with severe hemophilia A,
right elbow fracture after fall (July 2010)

DK

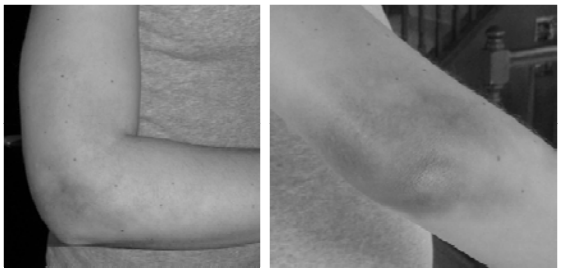


December 2010 – 4 months s/p arthroplasty, doing well



February 2012 – Resumed truck driving and heavy lifting.
Not doing so well.

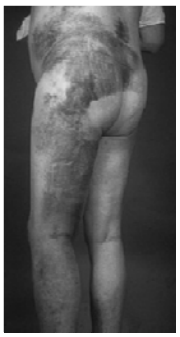
Clinical Features of Hemophilia:
Soft tissue bleeding



Acquired hemophilia, non-traumatic elbow bleed

DT

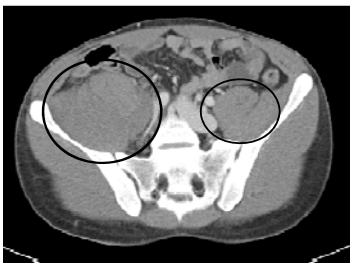
Clinical Features of Hemophilia:
Soft tissue bleeding



- 56 year old with severe hemophilia A and inhibitor
- Fell on icy sidewalk
- Did not treat aggressively enough
- Required transfusion of 6 units RBCs

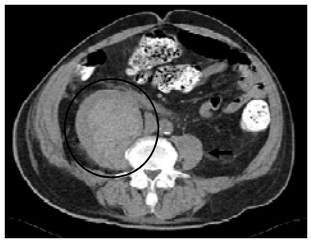
GR

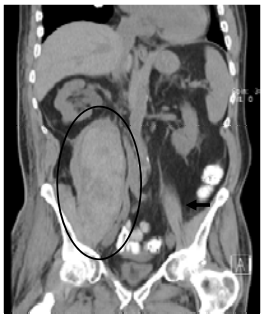
Clinical Features of Hemophilia:
Deep muscle bleeds



- 20 year old with mild hemophilia A
- No trauma
- Bled after light jogging

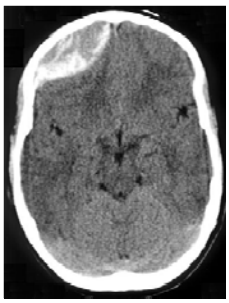
Clinical Features of Hemophilia:
Deep muscle bleeds





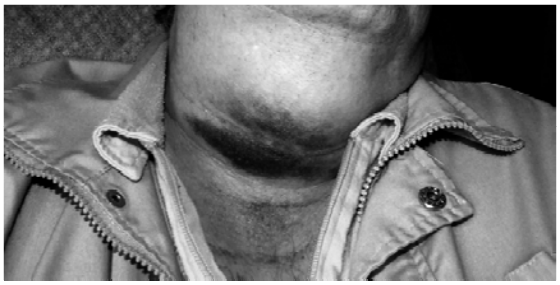
- 52 year old with severe hemophilia B
- Spontaneous bleed

Clinical Features of Hemophilia:
Intracranial bleeds



- 6 year old with severe hemophilia A
- Bumped head on school playground equipment, did not appear to have any significant injury
- Parents noted change in behavior later that evening

Clinical Features of Hemophilia:
Soft tissue bleeding



Severe hemophilia A with inhibitor, neck bleed provoked by coughing

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Inhibitors in Congenital Hemophilia

- Some hemophilia patients "see" factor VIII or factor IX as a foreign protein
- Infusion of factor concentrate to prevent or treat bleeding triggers an immune response
- Antibodies ("inhibitors") directed against factor VIII or factor IX neutralize the procoagulant effect and render standard treatment useless

Inhibitors in Congenital Hemophilia

- Development of inhibitors is currently the most severe complication of factor replacement therapy
- Typically seen in those with severe hemophilia
- Hemophilia A – inhibitors develop in ~25%
- Hemophilia B – inhibitors develop in < 5%
- No longer associated with increased mortality

However . . .

- *Bleeding more difficult to control*
- *Devastating joint disease and disability*
- *Major clinical and economic challenges*

Inhibitors in Congenital Hemophilia

Factor VIII

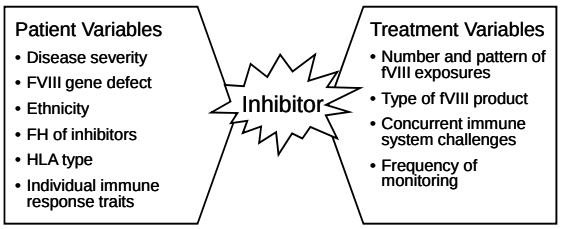
- **Common (~25%)**
- **Well-studied and characterized**
- **Eradicated in ~70% with ITT (immune tolerance therapy)**

Factor IX

- **Rare (< 5%)**
- **Risk factors poorly defined**
- **ITT often fails**
- **Allergic reactions, nephrotic syndrome**

- **May develop following treatment with both plasma derived and recombinant factor products**
- **Similar bleeding patterns, diagnosis, and management**

Factors Influencing Inhibitor Development in Hemophilia A



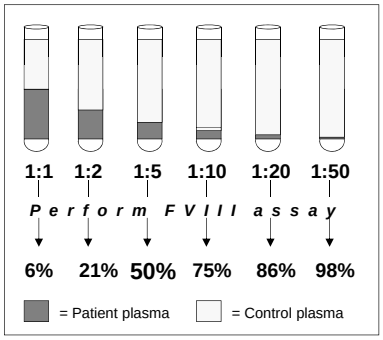
A complex interaction of many variables leads to inhibitor development in a particular individual

Gouw SC. *Semin Thromb Hemost*. 2009; 35:723-34.

Clinical Recognition of Inhibitors

- Usually develop in small children, after only a small number of factor exposures
- Change in bleeding pattern
- Poor response to treatment with factor
- Allergic reactions often herald the development of factor IX inhibitors
- May develop later in life in those with mild or moderate hemophilia
  - ➢ Often after intense factor exposure following surgery or trauma

Measurement of Factor VIII Inhibitors: *Bethesda Assay*



Reciprocal of dilution at which 50% of normal FVIII activity is observed

1 / 5

Inhibitor Titer = 5 BU/mL

Treatment of Inhibitors

- "Bypassing Agents"
  - Prothrombin complex concentrates
  - Recombinant factor VIIa
- Bypassing agents have unpredictable efficacy (50 – 90%)
  - More bleeding, more joint damage
  - Surgery is risky
- Immune Tolerance Therapy
  - Expensive: ~ $1 million per patient
  - Only ~ 70% effective
- Overall costs
  - Routine treatment: $200,000 – 250,000 per year
  - Major bleed, surgery: $500,000 – 1,000,000 ++

Acquired Hemophilia

- Inhibitors can develop in those who are not genetically deficient in factor VIII
- Rare autoimmune condition
- Occurs in 0.2 – 1 per million per year
- Must have a high index of suspicion to make a timely diagnosis
- Delayed diagnosis and lack of appreciation of risk to patient are common mistakes

Why You Should Care About Acquired Hemophilia

✓ Morbidity: > 80% have *serious* bleeding
✓ Mortality: as high as 20%

(Translation: 1 in 5 patients may *bleed to death*)

Challenges in Managing Acute Bleeding in Patients with Hemophilia

Acquired Hemophilia: *Clinical Features*

- Median age at presentation: 60 - 67 yrs; range: 2 - 89 yrs
- Males and females both affected
- Bleeding pattern
  - Hemarthroses rare
  - Mucocutaneous bleeding common (epistaxis, ecchymosis, gastrointestinal bleeding, hematuria)
  - Severe intramuscular bleeding
  - Intracranial hemorrhage
  - Postsurgical or postpartum bleeding

Ma AD, Carrizosa D. *Hematology Am Soc Hematol Educ Program*. 2006:432-7.

Acquired Hemophilia: *Associated Conditions*

- 50 – 60% of AH cases are idiopathic
- 40 – 50% of AH cases are associated with other underlying conditions . . .

Pregnancy
Autoimmune disorders
Malignancy
Drugs
Infections

Ma AD, Carrizosa D. *Hematology Am Soc Hematol Educ Program*. 2006:432-7.

Treatment of Acquired Hemophilia

1. *Stop Bleeding*
   - Factor VIII
   - Prothrombin complex concentrates
   - Recombinant factor VIIa
2. *Eradicate inhibitor*
   - Plasma exchange
   - Immunosuppression (steroids)
   - Cyclophosphamide
   - Rituximab

Acquired Hemophilia: *Diagnostic Barriers, Management Pitfalls*

1. *Delay in establishing correct diagnosis*
   - Dismissal of prolonged aPTT
   - Not included in differential diagnosis
   - Requires specialized coagulation lab testing
2. *Failure to recognize seriousness of diagnosis*
   - Immunosuppressive therapy should begin as soon as the diagnosis is established
   - Optimal treatment requires expertise rarely found outside of a hemophilia treatment center

Clinical Challenges in Managing Congenital Hemophilia with Inhibitors and Acquired Hemophilia

- Rare patients, higher risk of bleeding, increased morbidity
- Unpredictable and incomplete efficacy of bypassing agents
- No routine lab monitoring available
- Extremely expensive
- Optimal management of acute bleeding and surgery requires HTC expertise

Clinical Considerations in Managing Acute Bleeding in Patients with Hemophilia

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University of Virginia Health System
Charlottesville, Virginia

Timeline of Hemophilia Treatment

- Before 1940s: supportive care, transfusions of whole blood or fresh plasma
  - Average life expectancy 27 years
  - Disabled by age 20
- 1960: transfusion medicine improved
  - Average life expectancy 40 years
  - Still severely disabled and unemployed
- 1964: expanding treatment options with cryoprecipitate
- 1968: development and availability of plasma-derived factors products
  - Average life expectancy 60 years
  - Hemophiliacs able to travel, work, and attend school with regularity

Timeline of Hemophilia Treatment

- 1982: First reported case of AIDS in patients with hemophilia
- 1985: Virally inactivated factor concentrates introduced
- 1992: Recombinant factor VIII
- 1997: Recombinant factor IX

Treatment of Hemophilia

- Hemophilia A or B
  - Severity of factor deficiency
  - Past clinical course
- Develop an ongoing relationship with regional hemophilia treatment center
  - Assist in day-to-day management and provide information on available therapeutic products

Q2: Prophylactic administration of clotting factor concentrate is recommended as standard of care by the World Federation of Hemophilia.

a. True
b. False

Rodriguez NI et al. *Pediatric Clin North Am*. 2008; 55:357-76, viii.

Strategies for Bleeding Management

- Goal is rapid and effective replacement of missing coagulation factor
  - Episodic or "on demand"
    - Conventional treatment approach
  - Prophylactic
    - Primary
      - Given at early age to prevent expected complication
    - Secondary
      - Begun after complication has occurred to prevent recurrence
  - Bolus vs. continuous infusion
    - Surgical procedures

Q3: The choice of factor VIII product for hemostasis is usually based upon the safety, purity, cost and risk of inhibitory antibodies.

a. True
b. False

Factor VIII Products

Plasma Derived		
Products Containing von Willebrand Factor	**Immunoaffinity Purified**	
Alphanate®	Hemofil M™	
Koate®-DVI	Monoclate-P®	
Humate-P®	Monarc-M™	
Recombinant		
First Generation	**Second Generation**	**Third Generation**
Recombinate™	Kogenate® FS	Advate®
Kogenate®	Helixate® FS	Xyntha®
Helixate®	Refacto®	

Wong T et al. *Drugs*. 2011; 71:305-20.
Also see prescribing information (PI) in reference list.

Comparison of Recombinant Factor VIII Products (rFVIII)

- First generation
  - Required bovine or human serum for stabilization
- Second generation
  - Required plasma during manufacturing process, but plasma is removed in final product
- Third generation
  - Serum free during manufacturing process and final product
  - Smaller infusion volumes
  - Safety advantage is theoretical only

Wong T et al. *Drugs*. 2011; 71:305-20.

Factor VIII Products: Choice of Product

- Safety and purity
  - No documented cases of viral transmission with any plasma-derived or recombinant factor concentrate in more than 25 years
  - All rFVIII products are hemostatically equivalent
  - There is no difference in immunogenicity between different generations of rFVIII products

Mannucci PM et al. *Blood*. 2012; 119:4108-14.

Factor VIII Products: Choice of Product

- Risk of occurrence of inhibitory antibodies
  - Data suggest, but do not prove, that plasma-derived products elicit fewer inhibitors than rFVIII
- Cost

Mannucci PM et al. *Blood*. 2012; 119:4108-14.

Factor VIII Products: Dosing

- Administration of 1 international unit per kg increases plasma factor VIII level by 2%
  - Number of units depends upon
    - Body weight
    - Volume of distribution
    - Desired factor level
- Half life approximately 8 to 12 hours
- Check factor VIII level near end of 12-hour period

Factor VIII Products: Control and Prevention of Bleeding

Type of Bleeding Episode	Factor VIII Level Required (% of normal)	Dosage and Frequency
Minor Early hemarthrosis Minor muscle or oral bleed	20 - 40	• 10 – 20 units/kg • Repeat dose every 12 - 24 hours or add antifibrinolytic
Moderate Bleeding into muscles or oral cavity, definite hemarthrosis, known trauma	50 - 80	• 25 – 40 units/kg every 12 - 24 hours until bleeding resolved
Major GI, intracranial, intra-abdominal, intrathoracic, CNS, or retroperitoneal bleeding	80 - 100	• Initial dose: 40 – 50 units/kg • Repeat dose 20 – 50 units/kg every 8 - 12 hours until bleeding resolved

Advate (antihemophilic factor [recombinant], plasma/albumin-free method) PI; 2012 Jul.
Helixate FS (antihemophilic factor [recombinant], formulated with sucrose) PI; 2011 Apr.

Factor VIII Products: Monitoring Parameters

Concept	Factor VIII
Blood pressure and heart rate	✓
Partial thromboplastin time (PTT)	✓
Factor levels	✓
Development of factor inhibitors	✓
Signs of bleeding (hemoglobin, hematocrit)	✓

Adjuvant Therapy: Desmopressin Acetate

- Increase circulating level of factor VIII by 2 to 10 fold (mild to moderate hemophiliac)
- Dose 0.3 mcg/kg IV over 30 min or 150-300 mcg intranasal
  - Repeated at 12-24 hour interval
- Limited use
- Adverse effects
  - Flushing, headache, tachycardia, nausea, abdominal cramping

Stimate (desmopressin acetate nasal spray) PI; 2011 Sep.
Desmopressin acetate injection PI; 2012 Apr.

Adjuvant Therapy: Antifibrinolytics

- Used for mild bleeding episodes
- Stabilizes clot and discourages re-bleeding
- Aminocaproic acid
  - Adult dose: 5 g orally or IV during the first hour then 1g/hr for 8 hours or until bleeding is controlled
  - Pediatric dose: 50 – 100 mg/kg orally or IV every 6 hours
- Tranexamic acid
  - Adult and pediatric dose: 10 mg/kg IV every 8 hours for 2 to 8 days

Amicar (aminocaproic acid) PI; 2012 Jan.
Cyklokapron (tranexamic acid injection) PI; 2011 Jan.

Adjuvant Therapy: Fresh Frozen Plasma (FFP)

- Same factor VIII and IX concentrations as normal plasma
  - 1 unit of FFP contains 200-250 units of factors VIII, IX and XI
- Each unit increases patient's factor VIII level by only 5-10%
  - Large volumes needed to get factor levels above 50%
- Limited use
- Complications
  - Allergic reactions, transmission of viral infections

Adjuvant Therapy: Cryoprecipitate

- Prepared from FFP: contains high levels of factor VIII, XIII, vWF, and fibrinogen
- One unit of cryo contains 80-150 units of factor VIII
  - 30-fold more concentrated compared with FFP
- Limited use
- Complications
  - Allergic reactions, transmission of viral infections

vWF = von Willebrand factor

Factor IX Products

Plasma Derived	
AlphaNine® SD	Mononine®
Recombinant	
BeneFix®	
Prothrombin Complex Concentrates (PCCs)	
Profilnine® SD	Bebulin® VH
Activated Prothrombin Complex Concentrates	
Factor VIII inhibitor bypassing activity (FEIBA® NF)	

Wong T et al. *Drugs*. 2011; 71:305-20.
Also see prescribing information (PI) in reference list.

Factor IX Products: Dosing

- Administration of 1 international unit per kg increases plasma factor IX level by 1%
  - Number of units depends upon:
    - Body weight
    - Volume of distribution
    - Desired factor level
- Half life approximately 18 to 24 hours
- Check factor IX level near the end of 24-hour period

Factor IX Products: Control and Prevention of Bleeding

Type of Bleeding Episode	Factor IX Level Required (% of normal)	Dosage and Frequency
Minor Uncomplicated hemarthrosis Superficial muscle or soft tissue bleed	15 – 30	• Initial dose: 15 – 30 units/kg • Maintenance dose: 20 units/kg every 12 - 24 hours
Moderate Bleeding into muscles or oral cavity, definite hemarthrosis, and known trauma	25 – 50	• Initial dose: 30 – 60 units/kg • Maintenance dose: 30 units/kg every 12 - 24 hours
Major GI, intrathoracic, CNS, or retroperitoneal bleeding	50 – 100	• Initial dose: 60 – 100 units/kg • Maintenance dose: 60 units/kg every 12- 24 hours

BeneFIX (coagulation factor IX [recombinant]) PI; 2011 Nov.

Factor VIII and Factor IX Products: Monitoring Parameters

Concept	Factor VIII	Factor IX
Blood pressure and heart rate	✓	✓
Partial thromboplastin time (PTT)	✓	✓
Factor levels	✓	✓
Development of factor inhibitors	✓	✓
Signs of bleeding (hemoglobin, hematocrit)	✓	✓
Signs of hypersensitivity reactions		✓

Comparison of Factor VIII and IX Products

Concept	Factor VIII		Factor IX	
	Plasma Derived	Recomb	Plasma Derived	Recomb
Easy to store and prepare	✓	✓	✓	✓
Straightforward dosing	✓	✓	✓	✓
May contain immunomodulatory proteins	✓		✓	
Contains vWF	✓			
Biologically identical to human factor		✓		✓
No risk of pathogen transmission	?✓	✓	?✓	✓
More expensive*		✓		✓
Increase dose up to 1.5x vs. plasma derived				✓

*Compared with plasma-derived products.

Inhibitors in Hemophilia

- Antibody against factor VIII or factor IX
  - Most serious treatment-related complication in hemophilia
- Higher incidence in hemophilia A than hemophilia B
- Appear following median of 8 to 12 exposure days

Makris M et al. *Haemophilia*. 2012; 18(Suppl 4):48-53.

Challenges in Managing Acute Bleeding in Patients with Hemophilia

Inhibitors in Hemophilia

- Risk factors
  - Type of mutation in the factor VIII or factor IX gene
  - Human leukocyte antigen types and polymorphisms in gene that codes for cytokines
  - rFVIII products pose increased risk?
- Low inhibitor titer is <5 BU/mL
  - May have historically had higher titers
  - Higher (4-5 times) doses of exogenous factor may be required
- High inhibitor titer is ≥ 5 BU/mL
  - Control of acute bleeding episodes
  - Reduction of inhibitor titer

BU = Bethesda unit

Makris M et al. *Haemophilia*. 2012; 18(Suppl 4):48-53.

Management of Acute Bleeding in Patients with High Inhibitor Titer

- Goal: to "bypass" the need for factor VIII or IX in coagulation cascade
  - Led to exploring the efficacy and safety of PCCs
- Two bypass products
  - Factor VIII inhibitor bypassing agent (FEIBA)
    - Activated PCC
  - Recombinant factor VIIa (rFVIIa)

FEIBA® NF

- Consists of
  - Factors II, IX, X (mainly non-activated)
  - Factor VII (activated form)
- Provides both factor II and Xa at site of the bleed
- Dose
  - 50 – 100 units/kg every 6 to 12 hours (not to exceed daily dose 200 units/kg)
- Risk of DIC or thromboembolism
- Cannot monitor clinical efficacy
  - Thrombin generation time (TGT)?

FEIBA NF (anti-inhibitor coagulant complex, nanofiltered and vapor heated) PI; 2011 Feb.

Recombinant Factor VIIa (rFVIIa)

- Complexed with tissue factor can activate coagulation factor X and factor IX
- Minimizes risk of systemic coagulation seen with FEIBA
- Dose
  - 90 mcg/kg every 2 hours until hemostasis is achieved

NovoSeven RT (coagulation factor VIIa [recombinant] room temperature stable) PI.; 2012 Jan.

Review of Literature

- FEIBA vs. rFVIIa[1]
  - Both had an efficacy rate of 80 to 90%
  - Neither product was superior to the other
- FEIBA plus rFVIIa[2]
  - Hemostatic efficacy appears to be satisfactory
  - Higher incidence of thrombotic complications
  - Reserved for life-threatening bleed

[1]Astermark J et al. *Blood*. 2007; 109:546-51.
[2]Ingerslev J et al. *Br J Haematol*. 2011; 155:256-62.

Formulary Considerations

- Product considerations
  - Dosage and storage
  - Safety and purity
- Availability
- Physician's experience
- Cost

Conclusion

- Patients with hemophilia require life-long integrated care
- Use of either plasma or recombinant factor product for the treatment or prevention of bleeding in patients with hemophilia
- A serious complication of hemophilia is the development of an inhibitor

Patient Scenarios: Innovative Strategies for Managing Patients with Hemophilia in the Hospital Setting

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Could this occur on your watch?

- A 26 yo male with factor IX deficiency presents to the ED with trauma, including a fractured leg after crashing his motorcycle
- A 50 yo male with factor VIII deficiency is scheduled for surgery

Changes in the Hemophilia Population Needs

- Established management considerations
  - Younger population
  - Hemarthrosis
- New challenges – population getting older
- Diseases of older populations
  - Atrial fibrillation
  - Coronary artery disease
  - Cancer

The Hemophilia Management Team

- Multidisciplinary
  - Medicine (primary physician, hematologist, surgeon, …)
  - Nursing (bedside, hematology program,…)
  - Pharmacy
  - Genetics
  - Coagulation laboratory
  - Social work
  - Physical therapy
- Coordinated
- Easy to notify
- Communication

Clinicians who are current on hemophilia management considerations

Escobar M et al. *Haemophilia*. 2012; 18:971-81.

Skill: Assess the Situation

- Active bleeding vs. planned procedure
  - Confirm type of hemophilia
    - Insights from patient's hemophilia treatment center or hematologist
    - Inhibitors present
  - Laboratory assay
  - What additional or related therapies may be necessary
- Urgency of situation

Surgical Considerations

- Is the center familiar with hemophilia
  - Multidisciplinary team present
  - Experience
    - Surgical procedure
    - Hemophilia as a special population
  - Site: risk of a complication
- Discuss with the patient and family
- Type of anesthesia
  - General preferred over epidural or spinal block
- Preoperative - Intraoperative - Postoperative Plan

Kulkarni R. *Haemophilia*. 2012 Aug 27 [Epub ahead of print].

Challenges in Managing Acute Bleeding in Patients with Hemophilia

Avoiding Complications

- Frequent bleeding a concern
  - Consider minimally invasive procedure
- Advanced age
  - More conservative procedures
- Risk assessment
  - Scar tissue from multiple procedures
  - Other non-invasive options
  - Patient's physical and clinical presentation
- Simplify agents used
  - Singular therapies vs. multiple agents
- Clinical support nearby or easy to contact
  - Consider when scheduling

Pharmacology Considerations

- Hemostatic agents
  - Recombinant vs. pooled sources
  - rFVIIa, PCC, FEIBA
  - Is supply adequate?
  - Reimbursement evaluated and handled accordingly
- Antifibrinolytic agents
  - Tranexamic acid
  - Aminocaproic acid
- Topical therapies
- Immunomodulators

Preoperative Management Considerations

- Consider ability to perform the procedure before accepting the case
- Develop plan in advance of surgery
  - Adequate hemoglobin
- Arrange availability of the agents
- Determine what should be withheld
- Prophylactic hemostatic agent pre-op
  - Pre-surgical factor concentration (level)
  - Type of surgery
  - Type of hemophilia

Escobar M et al. *Haemophilia*. 2012; 18:971-81.
Kulkarni R. *Haemophilia*. 2012 Aug 27 [Epub ahead of print].

Perioperative Management Considerations

- Maintaining hemostasis
  - Hemostatic agents
  - Antifibrinolytic agents
- Catheter insertion
- Antibiotic prophylaxis

Escobar M et al. *Haemophilia*. 2012; 18:971-81.
Kulkarni R. *Haemophilia*. 2012 Aug 27 [Epub ahead of print].

Intraoperative Management Considerations

- Monitor hemostasis
  - Thromboelastograms
  - Consider ability to perform the procedure before accepting
- Control bleeding (expected vs. non-expected)
  - Avoid diluting clotting factors
  - Mechanical
  - Topical
  - Systemic therapy
  - Cooling patient
- Consider thromboembolism vs. bleeding risks
- Determine what should be withheld
- Prophylactic hemostatic agent pre-op

Escobar M et al. *Haemophilia*. 2012; 18:971-81.
Kulkarni R. *Haemophilia*. 2012 Aug 27 [Epub ahead of print].

Postoperative Management Considerations

- Minimizing bleeding
  - Wound care (healing slower)
  - Timing of concentrated clotting factors
    - Drains
    - Suture removal
    - Physical therapy
- Monitoring and maintaining hemostasis
  - Avoid excessive blood draws
  - Monitor for inhibitor development
  - Hemostatic agents
  - Antifibrinolytic agents
- Transfusing to maintain HgB/Hct

Escobar M et al. *Haemophilia*. 2012; 18:971-81.
Kulkarni R. *Haemophilia*. 2012 Aug 27 [Epub ahead of print].

Postoperative Management Considerations (cont)

- Unexpected bleeding
- Supportive and preventive therapy
- VTE prophylaxis
  - Compression stockings
  - Pharmacologic: caution in patients with inhibitors

Escobar M et al. *Haemophilia*. 2012; 18:971-81.
Kulkarni R. *Haemophilia*. 2012 Aug 27 [Epub ahead of print].

Managing Acute Bleeding

- Increasing blood loss → ↑ morbidity and mortality
- Patients at risk for catastrophic bleeds
  - Trauma (major or to a vital location)
  - Gastrointestinal bleeding
  - Vascular injury (aneurysms, graft failure, postoperative)
  - Cerebral vascular bleed
  - Congenital or acquired coagulopathy

Q4: For a given concentrated clotting factor (hemostatic agent), the dose is the same no matter what type of hemophilia is present.

a. True
b. False

Hemostatic Agent Considerations

- Dosing: Prophylaxis vs. active bleeding
  - Baseline factor levels
  - Presence of inhibitors
  - Type of hemophilia (rFVIIA dose < in factor VII deficiency vs. Hemophilia A or B with inhibitors)
- Administration
  - Bolus
  - Continuous Infusion
  - Inhibitors
    - < 5 BU/mL – High dose factor replacement
    - ≥ 5 BU/mL – Agent bypassing the inhibitor (rFVIIa or FEIBA)
- Single or combined therapies

Berntorp E et al. *Lancet*. 2012; 379:1447-56.

Q5: What laboratory measure may be useful to determine if internal bleeding is occurring?

a. Bleeding time
b. Factor level <60%
c. Hemoglobin
d. Prothrombin time

Monitoring Hemostatic Agent

- Titrating infusion
  - Time assessment with revised dose
    - Change rate or dosing interval just prior to physician assessment
- Factor levels
  - Establish targets
  - Inhibitors developing?

Assessing Hemostasis with Hemostatic Agent in Use

- Assessing hemostasis
  - Onsite expert
  - Risk for undesirable clotting
- Severity of bleeding
  - Assessing wound (site, packing removed, etc.)
  - Hgb for internal bleeding
  - Improving or limited/no progress
- Thrombosis risks

Adjunctive Therapies

- Antifibrinolytic agents
- Desmopressin
- Steroids
- Cytotoxic immunosuppressants
  - IVIG
  - Cyclophosphamide
  - Rituximab
- Topical agents
- Plasma exchange
- Single or combined therapies

Toschi V et al. *Intern Emerg Med*. 2010; 5:325-33.

Systems Support

- Keep key personnel current
- 24/7 process
- Identify necessary hemostatic agents and labs
- Guidelines on using available therapies
  - Easy for clinicians to locate and follow
  - Adapted for patients with hemophilia
- Rapid ability to implement management
- Periodic review and quality improvement

Escobar M et al. *Haemophilia*. 2012; 18:971-81.

Key Pharmacy Considerations

- Is the right agent being sent out?
- Is the dose correct?
- Who and how is the dose being determined?
- Is it safe?
- Is it working?
- Do we have enough clotting factor concentrates available?
- Is a change in therapy being considered?
- Is the dose going to be adjusted?
- How can we minimize cost and wastage?
- Was the correct pre-authorization or billing done?

APPENDIX: COAGULATION CASCADE