Challenges in Managing Acute Bleeding in Patients with Hemophilia

Presented as a Midday Symposium at the 47th ASHP Midyear Clinical Meeting and Exhibition

Tuesday, December 4, 2012
Las Vegas, Nevada

Planned and conducted by ASHP Advantage and supported by an educational grant from Novo Nordisk Inc.
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Challenges in Managing Acute Bleeding in Patients with Hemophilia

A G E N D A

11:30 a.m. – 11:35 a.m. Welcome
William E. Dager, Pharm.D., BCPS (AQ-Cardiology)

11:35 a.m. – 12:10 p.m. Hemophilia and Bleeding Disorders: Diagnosis and Clinical Features
Mark T. Reding, M.D.

12:10 p.m. – 12:45 p.m. Clinical Considerations in Managing Acute Bleeding in Patients with Hemophilia
Surabhi Palkimas, Pharm.D.

12:45 p.m. – 1:10 p.m. Patient Scenarios: Innovative Strategies for Managing Patients with Hemophilia in the Hospital Setting
William E. Dager, Pharm.D., BCPS (AQ-Cardiology)

1:10 p.m. – 1:30 p.m. Faculty Discussion and Audience Questions
All Faculty

Box lunch will be provided.

F A C U L T Y

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Activity Chair
Pharmacist Specialist
UC Davis Medical Center
Sacramento, California

Surabhi Palkimas, Pharm.D.
Pharmacy Clinical Coordinator, Hematology
University of Virginia Health System
Charlottesville, Virginia

Mark T. Reding, M.D.
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University of Minnesota Medical Center, Fairview
Associate Professor
University of Minnesota Medical School
Minneapolis, Minnesota
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Dr. Dager declares that he has no relationships pertinent to this activity.

**Surabhi Palkimas, Pharm.D.**
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**Mark T. Reding, M.D.**
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**Susan R. Dombrowski, M.S., B.S.Pharm.**
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**Carla J. Brink, M.S., B.S.Pharm.**
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ACTIVITY OVERVIEW

Patients with hemophilia who are acutely ill with bleeding issues or having surgery are a challenge in the hospital setting, and pharmacists can provide assistance in initiating therapy with hemostatic agents and play a key role in dosing, monitoring, and revising patient regimens. This educational activity will provide an overview of the epidemiology and pathophysiology of hemophilia and will outline various strategies for treatment of patients with hemophilia, specifically those with acute bleeding or planned surgery. Factors to consider when making formulary decisions regarding coagulation factors will be presented. The activity will conclude with a discussion of patient scenarios illustrating innovative strategies for managing acute bleeding using available treatments in patients with hemophilia in the hospital setting.

ACTIVITY OBJECTIVES

After attending this application-based educational activity, participants should be able to

- Discuss the epidemiology and pathophysiology of various types of hemophilia.
- Examine the various pharmacologic approaches to the treatment of patients with hemophilia, including patient-specific factors to consider.
- Consider key factors when making formulary decisions on the selection of coagulation factors.
- Devise a plan for using laboratory values and physical signs to influence selection of available treatments in a patient with hemophilia.
- Monitor patients with hemophilia who are receiving hemostatic agents for acute bleeding for signs that bleeding is resolving.
- Discuss selected treatment strategies for patients requiring hemostatic agents.
Challenges in Managing Acute Bleeding in Patients with Hemophilia

CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 2 hours (0.2 CEUs) of continuing pharmacy education credit (ACPE activity # 0204-0000-12-446-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP CE Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are on the next page. Be sure to record the session code beginning with “A” announced during the activity.

New! PRACTICE REMINDER EMAIL

During this educational activity, we encourage you to jot down points about what YOU want to remember to do as a result of what you are learning.

- Use your smart device to link directly to the reminder tool and type in your ideas.
- Next month, we will send you an email as a reminder from YOURSELF about what YOU want to do after attending this activity.
- Do it more than once…multiple entries for this activity from the same email address will be combined into one email.
- If you do not have a smart device, go to the reminder tool on the activity website http://www.ashpadvantage.com/stopbleeding/?qr=1
Challenges in Managing Acute Bleeding in Patients with Hemophilia

PROCESSING CPE ONLINE

The ASHP CE Center allows participants to obtain statements of continuing pharmacy education (CPE) conveniently and immediately using any computer with an internet connection. To obtain CPE statements for ASHP Advantage activities, please visit http://ce.ashp.org

1. Log in to the ASHP CE Center using your e-mail address and password.
   - If you have not logged in to the ASHP CE Center and are not a member of ASHP, you will need to set up an account by clicking on “Become a user” and follow the instructions.

2. Once logged in to the site, click on Process Meeting CE.

3. If you are a registered attendee at the ASHP Midyear Clinical Meeting, click on the start button to the right of ASHP Midyear Clinical Meeting 2012.
   - If you are not registered to attend the ASHP Midyear Clinical Meeting, click on the start link to the right of the activity title. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The activity code is noted below. Click submit when prompted and then click on the start link to the right of the activity title. Do not click on “remove” next to an activity title unless you did not attend that activity.

4. Click on the click here link to view sessions associated with the day of the activity.

5. Enter the session code announced during the activity (e.g., A12XXX and note that the letter is case sensitive) and select the number of hours equal to your participation in the activity.

6. Click submit to receive the attestation page.

7. Confirm your participation and click submit.

8. Complete the evaluation and click the finish button. You will then be able to view and print your transcript.

<table>
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<th>Activity Code</th>
<th>Session Code (announced during the live activity)</th>
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</table>

NEED HELP? Contact ASHP Advantage at support@ashpadvantage.com.
Your educational opportunities related to the management of acute bleeding in patients with hemophilia extend beyond today’s symposium...

**Available in 2013**

- A live webinar where faculty will explore issues raised by participant questions in today’s symposium (1 hour CPE)
- Informational podcasts featuring the faculty in a roundtable discussion about important issues related to the management of acute bleeding in patients with hemophilia
- e-Newsletters featuring tips for incorporating information from this symposium into practice, as well as updates on emerging information related to hemophilia management
- Web-based activity based on today’s live symposium (2 hours of CPE, but please note that individuals who claim CPE credit for the live symposium or webcast are ineligible to claim credit for the web-based activity)

For more information and to sign up to receive e-mail updates about this educational series, go to

www.ashpadvantage.com/stopbleeding
Challenges in Managing Acute Bleeding in Patients with Hemophilia

Mark T. Reding, M.D.
Director, Center for Bleeding and Clotting Disorders
University of Minnesota Medical Center, Fairview
Associate Professor
University of Minnesota Medical School
Minneapolis, Minnesota

Mark T. Reding, M.D., is Director of the Center for Bleeding and Clotting Disorders at University of Minnesota Medical Center in Minneapolis. In this role he is responsible for providing and coordinating patient care in the clinic and hospital for all adult patients followed by the Center, which is a hemophilia treatment center supported by the Centers for Disease Control and Prevention. Dr. Reding also serves as Medial Director of the Inpatient Hematology/Oncology Unit at University of Minnesota Medical Center. In addition, he is Associate Professor of Medicine in the Division of Hematology, Oncology, and Transplantation at the University of Minnesota.

Dr. Reding received his Bachelor of Science degree in Microbiology and Biology at South Dakota State University in Brookings. He then earned a Doctor of Medicine degree at University of Minnesota Medical School in Minneapolis. He is board certified in hematology.

Dr. Reding’s clinical interest is the treatment of non-malignant hematologic disorders with particular emphasis on disorders of hemostasis and thrombosis, including hemophilia. His current research efforts focus on the immune response to factor VIII, the cellular mechanisms involved in the synthesis of factor VIII inhibitors, and the immunologic consequences of gene therapy. He has also served as the local principal investigator for multi-center clinical trials. His research has been published in peer-reviewed journals.

Dr. Reding considers teaching to be the most important and rewarding aspect of his work, and he twice was awarded the Outstanding Clinical Mentor Award from his division at the Medical School. In addition to teaching responsibilities at the University, he frequently speaks at educational programs for physicians and other health care professionals.

Dr. Reding is a member of American Society of Hematology, Hemostasis and Thrombosis Research Society (HTRS), and International Society for Thrombosis and Hemostasis. He recently completed a two-year term on the board of directors for HTRS.
Hemophilia and Bleeding Disorders: Diagnosis and Clinical Features

Mark T. Reding, MD
Director, Center for Bleeding and Clotting Disorders
University of Minnesota Medical Center, Fairview
Associate Professor
University of Minnesota Medical School
Minneapolis, MN

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

<table>
<thead>
<tr>
<th>Protein</th>
<th>Prevalence</th>
<th>Genetics</th>
<th>Specific Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>1 : 1,000,000</td>
<td>AR</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor II</td>
<td>1 : 2,000,000</td>
<td>AR</td>
<td>No</td>
</tr>
<tr>
<td>Factor V</td>
<td>1 : 1,000,000</td>
<td>AR</td>
<td>No</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>1 : 500,000</td>
<td>AR</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor X</td>
<td>1 : 1,000,000</td>
<td>AR</td>
<td>No</td>
</tr>
<tr>
<td>Factor XI</td>
<td>1 : 1,000,000</td>
<td>AD</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>1 : 2,000,000</td>
<td>AR</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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%

Clinical phenotypes are indistinguishable

Hemophilia B

- Factor IX deficiency
- Christmas disease
- 1 in 30,000 male births
- 20% of total cases
- Spontaneous mutations = 20%
**Hemophilia affects all racial and socioeconomic groups equally**

- There are ~ 20,000 hemophiliacs in the United States
- More than 500,000 hemophiliacs worldwide

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**Age Distribution of the U.S. Hemophilia Population**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 19</td>
<td>8584</td>
<td>48%</td>
</tr>
<tr>
<td>20 – 44</td>
<td>6418</td>
<td>36%</td>
</tr>
<tr>
<td>45 – 64</td>
<td>2274</td>
<td>13%</td>
</tr>
<tr>
<td>65+</td>
<td>524</td>
<td>3%</td>
</tr>
</tbody>
</table>


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**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

+ 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

<table>
<thead>
<tr>
<th>Mild ( &gt; 5% )</th>
<th>Moderate (1-5%)</th>
<th>Severe ( &lt; 1 % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bleed only after severe injury, trauma, or surgery</td>
<td>• Bleed after injury, surgery</td>
<td>• Frequent spontaneous bleeding</td>
</tr>
<tr>
<td>• May not be diagnosed until adulthood</td>
<td>• May have occasional spontaneous bleeding</td>
<td>• Diagnosis made in early childhood</td>
</tr>
</tbody>
</table>

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

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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.


Blood in joint space

Recurrent bleeding

Inflammation

Acute and chronic synovitis

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.

SK
Clinical Features of Hemophilia:

Joint bleed (hemarthrosis)

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

Patient: LF, 22-yo male with severe hemophilia A

March 2008, May 2010, June 2010

• Underwent total knee arthroplasty
• Infected prosthesis had to be removed 3 months later
Severe hemophilia A, no inhibitor, morbidly obese

Clinical Features of Hemophilia:

Joint bleed (hemarthrosis)

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

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

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**

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

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Clinical Features of Hemophilia: 

**Deep muscle bleeds**

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

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Acquired hemophilia, non-traumatic elbow bleed
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
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

<table>
<thead>
<tr>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Common (~25%)</td>
<td>• Rare (&lt; 5%)</td>
</tr>
<tr>
<td>• Well-studied and characterized</td>
<td>• Risk factors poorly defined</td>
</tr>
<tr>
<td>• Eradicated in ~70% with ITT (immune tolerance therapy)</td>
<td>• ITT often fails</td>
</tr>
<tr>
<td></td>
<td>• Allergic reactions, nephrotic syndrome</td>
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</table>

- 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

Patient Variables
- Disease severity
- FVIII gene defect
- Ethnicity
- FH of inhibitors
- HLA type
- Individual immune response traits

Treatment Variables
- Number and pattern of FVIII exposures
- Type of FVIII product
- Concurrent immune system challenges
- Frequency of monitoring

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


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

Perform FVIII assay

<table>
<thead>
<tr>
<th>Dilution</th>
<th>1:1</th>
<th>1:2</th>
<th>1:5</th>
<th>1:10</th>
<th>1:20</th>
<th>1:50</th>
</tr>
</thead>
<tbody>
<tr>
<td>P  e  r  f  o  r  m    F  V  I  I  I    a  s  s  a  y</td>
<td>6%</td>
<td>21%</td>
<td>50%</td>
<td>75%</td>
<td>86%</td>
<td>98%</td>
</tr>
</tbody>
</table>

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)
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


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


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
SELECTED REFERENCES


ONLINE RESOURCES

National Hemophilia Foundation
http://www.hemophilia.org

World Federation of Hemophilia
http://www.wfh.org
SELF-ASSESSMENT QUESTIONS

1. Hemophilia A accounts for what percentage of all hemophilia cases?
   - a. 20%.
   - b. 30%.
   - c. 50%.
   - d. 80%.

2. A poor response to treatment with recombinant factor VIII (i.e., increased bleeding) in a 3-year old boy with congenital hemophilia A is most likely the result of
   - a. Misdiagnosis.
   - b. Inhibitor development.
   - c. Infection.
   - d. Overdosing error.

3. A 65-year-old man presents with severe gastrointestinal bleeding, and it is determined that he has acquired hemophilia. Which of the following would be most appropriate to use for inhibitor eradication in this man?
   - a. Immunosuppressive therapy.
   - b. Recombinant factor VIII.
   - d. Prothrombin complex concentrates.

Answers
1. d
2. b
3. a
Challenges in Managing Acute Bleeding in Patients with Hemophilia
Challenges in Managing Acute Bleeding in Patients with Hemophilia

Surabhi Palkimas, Pharm.D.
Pharmacy Clinical Coordinator, Benign Hematology
University of Virginia Health System
Charlottesville, Virginia

Surabhi Palkimas, Pharm.D., is Pharmacy Clinical Coordinator in Benign Hematology at University of Virginia (UVA) Health System in Charlottesville, Virginia. In this role, she provides pharmacy services for the adult hematology inpatient consult team. Dr. Palkimas also serves as pharmacy chair of the Anticoagulation Committee and is an active member of the Patient Education and Communication Committee. In addition, she is a preceptor for the postgraduate year one (PGY-1) pharmacy residency and postgraduate year two (PGY-2) oncology residency at UVA Health System, both of which are accredited by the American Society of Health-System Pharmacists (ASHP).

Dr. Palkimas earned a Bachelor of Science degree in biochemical pharmacology from State University of New York at Buffalo and a Doctor of Pharmacy degree from Massachusetts College of Pharmacy & Health Sciences, Worcester Campus. She completed an ASHP-accredited PGY-1 pharmacy practice residency at Hospital of Saint Raphael in New Haven, Connecticut.

Dr. Palkimas is a member of ASHP, American College of Clinical Pharmacy, Virginia Pharmacists Association, and Anticoagulation Forum. In addition, she serves as a peer reviewer for *The Annals of Pharmacotherapy*. 
Clinical Considerations in Managing Acute Bleeding in Patients with Hemophilia

Surabhi Palkimas, Pharm.D.
Pharmacy Clinical Coordinator, Hematology
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

• 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

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

<table>
<thead>
<tr>
<th>Factor VIII Products</th>
</tr>
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<tbody>
<tr>
<td><strong>Plasma Derived</strong></td>
</tr>
<tr>
<td>Products Containing von Willebrand Factor</td>
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<tr>
<td>Alphanate®</td>
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<td>Helixate®</td>
</tr>
</tbody>
</table>

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
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


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


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

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

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

<table>
<thead>
<tr>
<th>Concept</th>
<th>Factor VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure and heart rate</td>
<td>✓</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>✓</td>
</tr>
<tr>
<td>Factor levels</td>
<td>✓</td>
</tr>
<tr>
<td>Development of factor inhibitors</td>
<td>✓</td>
</tr>
<tr>
<td>Signs of bleeding (hemoglobin, hematocrit)</td>
<td>✓</td>
</tr>
</tbody>
</table>

## Adjuvant Therapy: Desmopressin Acetate

- Increase circulating level of factor VIII by 2 to 10 fold (mild to moderate hemophilia
- 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 1 g/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

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)
- Profinin® SD
- Bebulin® VH

Activated Prothrombin Complex Concentrates
- Factor VIII inhibitor bypassing activity (FEIBA® NF)

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

<table>
<thead>
<tr>
<th>Type of Bleeding Episode</th>
<th>Factor IX Level Required (% of normal)</th>
<th>Dosage and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>15 – 30</td>
<td>Initial dose: 15 – 30 units/kg</td>
</tr>
<tr>
<td>Uncomplicated hemorrhage</td>
<td></td>
<td>Maintenance dose: 20 units/kg every 12 - 24 hours</td>
</tr>
<tr>
<td>Superficial muscle or soft tissue bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>25 – 50</td>
<td>Initial dose: 30 – 60 units/kg</td>
</tr>
<tr>
<td>Bleeding into muscles or oral cavity, definite hemorrhage, and known trauma</td>
<td></td>
<td>Maintenance dose: 30 units/kg every 12 - 24 hours</td>
</tr>
<tr>
<td>Major</td>
<td>50 – 100</td>
<td>Initial dose: 60 – 100 units/kg</td>
</tr>
<tr>
<td>GI, intrathoracic, CNS, or retroperitoneal bleeding</td>
<td></td>
<td>Maintenance dose: 60 units/kg every 13 - 24 hours</td>
</tr>
</tbody>
</table>

BeneFIX (coagulation factor IX [recombinant]) PI; 2011 Nov.
Factor VIII and Factor IX Products: Monitoring Parameters

<table>
<thead>
<tr>
<th>Concept</th>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure and heart rate</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Factor levels</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Development of factor inhibitors</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Signs of bleeding (hemoglobin, hematocrit)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Signs of hypersensitivity reactions</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Comparison of Factor VIII and IX Products

<table>
<thead>
<tr>
<th>Concept</th>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy to store and prepare</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Straightforward dosing</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>May contain immunomodulatory proteins</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Contains vWF</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Biologically identical to human factor</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>No risk of pathogen transmission</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Increase dose up to 1.5x vs. plasma derived</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*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

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


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)?
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

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


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
SELECTED REFERENCES


PRESCRIBING INFORMATION FOR PRODUCTS MENTIONED IN SLIDES

Plasma-Derived Factor VIII


Recombinant Factor VIII


*Plasma-Derived Factor IX*


*Recombinant Factor IX*


*Prothrombin Complex Concentrates*


17. Profilnine SD (factor IX complex, solvent detergent treated) prescribing information. Los Angeles, CA: Grifols Biologicals, Inc; 2010 Aug.

*Activated Prothrombin Complex Concentrate*


*Recombinant Factor VIIa*


*Adjuvant Therapy*


SELF–ASSESSMENT QUESTIONS

1. LJ is a 27-year-old man with hemophilia who experiences mild bleeding following a dental procedure. Which of the following is best used to manage his bleeding?
   a. Tranexamic acid 1.5 g IV every 8 hours.
   b. Aminocaproic acid 5 g orally every 6 hours.
   c. Desmopressin acetate 0.3 mcg/kg IV over 20-30 minutes, repeated 12-24 hours later if needed.
   d. Fresh frozen plasma 4 units IV over 2-4 hours.

2. You are evaluating several first-, second-, and third-generation recombinant factor VIII products for inclusion in the formulary at your health system. For which of the following factors is documentation available demonstrating a difference among the three generations of products that should be taken into consideration in making formulary decisions?
   a. Immunogenicity.
   b. Hemostatic efficacy.
   c. Infusion volume.
   d. Half-life.

3. A 30-year-old man with hemophilia A and a high inhibitor titer presents with acute upper gastrointestinal bleeding. Which of the following are the greatest concerns associated with the use of factor VIII inhibitor bypassing agent (FEIBA) in this patient?
   a. Potential lack of hemostatic efficacy and high cost.
   b. Risk of allergic reaction and high cost.
   c. Need for routine laboratory monitoring and high cost.
   d. Risk of thromboembolism and need for routine laboratory monitoring.

Answers
1. b
2. c
3. a
Challenges in Managing Acute Bleeding in Patients with Hemophilia
Challenges in Managing Acute Bleeding in Patients with Hemophilia

William E. Dager, Pharm.D., BCPS (AQ-Cardiology)
Pharmacist Specialist
UC Davis Medical Center
Sacramento, California

William E. Dager, Pharm.D., BCPS (AQ-Cardiology), is a pharmacist specialist at UC Davis Medical Center in Sacramento, California, where he is responsible for managing challenging cases in anticoagulation, pharmacokinetics, and critical care. He also is clinically active with the cardiology service and serves as the director of the postgraduate year two (PGY-2) residency in cardiology at UC Davis. In addition, Dr. Dager holds three academic positions. He is Clinical Professor of Pharmacy at the University of California, San Francisco (UCSF) School of Pharmacy and Clinical Professor of Medicine at the University of California, Davis (UC Davis) School of Medicine. He also serves as Clinical Professor at the Touro School of Pharmacy in Vallejo, California.

Dr. Dager earned his Doctor of Pharmacy degree at UCSF and completed a residency at the UC Davis Medical Center in Sacramento. In addition, he completed the University of Pittsburgh Nephrology Pharmaceutical Care Preceptorship. He is a board-certified pharmacotherapy specialist and fellow of the American College of Clinical Pharmacy (ACCP), American Society of Health-System Pharmacists (ASHP), California Society of Hospital Pharmacists, and Society of Critical Care Medicine (SCCM).

Dr. Dager’s research interests focus on anticoagulation, critical care medicine, cardiovascular disease, and pharmacokinetics and pharmacodynamics. He has authored numerous articles, book chapters, and scientific reviews, and he coauthored “Anticoagulation Therapy: A Point-of-care Guide” published by ASHP in 2011. He also regularly makes presentations at national and international educational conferences. Dr. Dager serves as a reviewer and editorial board member for several medical journals, and he currently is chair of the Editorial Advisory Board Panel on Anticoagulation for The Annals of Pharmacotherapy. He has served as a site coordinator for the ASHP Research and Education Foundation Antithrombotic Pharmacotherapy Traineeship. Dr. Dager has received multiple teaching and professional awards, including the 2008 ACCP Best Practice Award.
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


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

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
Perioperative Management Considerations

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


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


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

Postoperative Management
Considerations (cont)

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

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**


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


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

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?
SELECTED REFERENCES


SELF–ASSESSMENT QUESTIONS

1. In a patient with hemophilia, considerations prior to surgery should include all of the following EXCEPT
   a. Consultation with the patient and family regarding the risks.
   b. Use of spinal anesthesia.
   c. Notifying pharmacy purchasing of pending need of a selected concentrated clotting factor.
   d. Determine if the patient has inhibitors.

2. A postoperative patient with hemophilia is being treated with a hemostatic agent in your hospital. Which of the following indicators would be the most appropriate to monitor to assess the potential severity of internal bleeding?
   a. Hemoglobin.
   b. Serum potassium.
   c. Respiratory rate.
   d. Prothrombin time.

3. In a patient with factor VIII deficiency and an inhibitor titer >5 BU/mL post knee surgery, initiation of factor concentrate typically starts with
   a. High dose (100 units/kg) factor VIII concentrate should be used to initiate therapy.
   b. Low dose (1 mg) recombinant factor FVIIa (rFVIIa).
   c. Factor VIII inhibitor bypassing agent (FEIBA) as the proven first line of therapy.
   d. Either rFVIIa or FEIBA are options.

4. Key considerations for pharmacists related to managing hemostatic agents include all of the following EXCEPT
   a. Let the purchasing department worry about ordering factor concentrates.
   b. Check with the prescribing physician about any planned changes in clotting factor concentrate infusions.
   c. Check that the correct billing is done.
   d. Check to see if an alternative agent is needed should therapy continue and dosing is escalated.

Answers
1. b
2. a
3. d
4. a
Challenges in Managing Acute Bleeding in Patients with Hemophilia

APPENDIX: COAGULATION CASCADE

[Diagram of the coagulation cascade including intrinsic and extrinsic pathways, indicating key clotting factors and their interactions, such as Fibrinogen, Platelet Activation, and Clot Stabilization.]

LIVER