**Virtual Grand Rounds:**

**Individualized Prophylaxis in Hemophilia: Best Practices**

Jointly Provided by the American Academy of CME and E&S MedEd Group, Inc.

Support for this activity has been made possible through an educational grant from Bayer HealthCare Pharmaceuticals

Estimated time to complete: 1.0 hour

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**Program Overview**

This program will provide education for hematologists, nurses, pharmacists, and other healthcare providers involved in hemophilia care on how to better determine individualized prophylaxis strategies for patients with severe hemophilia. In addition, the multidisciplinary team will hear about strategies to monitor the effects of prophylaxis and adherence to therapy to ensure optimal and cost-effective patient management. The expert faculty will discuss critical time points in a patient’s life that are associated with changing treatment regimens and adherence so that prophylaxis can be continued or initiated in children and adults. Implementing appropriate strategies to improve adherence can lead to successful outcomes in both pediatric and adult patients on prophylaxis. In addition, how different HTCs design and implement prophylactic regimens, address challenges with adherence, and utilize prophylactic treatment to manage non-standard clinical situations (eg, activity-related prophylactic infusions, management of microbleeds) will be discussed.

**Target Audience**

The proposed educational initiative is targeted toward hematologists and hemophilia specialists, nurses, physicians-in-training, pharmacists, and other members of the comprehensive care teams at HTCs, as well as professionals in managed care, specialty pharmacy, and home health care settings.

**Learning Objectives**

*Upon completion of this educational activity, participants should be better able to:*

- Identify the clinical benefits of and barriers to prophylaxis vs. on-demand treatment for management of patients with congenital hemophilia
- Review approaches to hemophilia prophylaxis, including assessment of response to prophylactic treatment, to better individualize patient prophylactic regimens
- Evaluate the potential role of newer therapeutic agents, including extended half-life factor concentrates, in prophylactic regimens
- Incorporate strategies to promote adherence to hemophilia prophylaxis for improved patient outcomes
Agenda

40 minutes  Presentation by Faculty
20 minutes  Live Q&A Session

During the 40-minute presentation and live Q&A, you will have the opportunity to submit questions via a message window. Following the presentation, two faculty will respond to many of these questions in a live, 20-minute Q&A.

Accreditation and Credit Designation

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This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of American Academy of CME, Inc., (Academy) and E&S MedEd Group, Inc. American Academy of CME, Inc., is accredited by the ACCME to provide continuing medical education for physicians.

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Mary Pham, PharmD, discloses that she is on the Provider Advisory Committee for Cal-Optima. Dr. Pham is also the Director for the World Federation of Hemophilia as well as the Alliance for Integrated Medication Management. She serves as Director of the Coalition of Orange County Community Health Centers. Her employer, Center for Inherited Blood Disorders, receives HHS grants and provides research support for USC Hemophilia Utilization Group Study.

Michael Recht, MD, discloses that he is on the Advisory Board for scientific information for Kedrion and is a Consultant for clinical trial design for Novo Nordisk. Dr. Recht has received Grant/Research support from Baxalta, Biogen Idec, and Novo Nordisk.

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Guy Young, MD, discloses that he is on the Advisory Board for scientific information for Baxalta, Bayer, Biogen Idec, Kedrion and Novo Nordisk. He is a Consultant for clinical trial design for Biogen Idec, Kedrion, and Novo Nordisk.

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Planning Committee

John JD Juchniewicz, MCIS, CHCP, Edward Moylan, RP, and Natalie Kirkwood, RN, BSN, JD (Lead Nurse Planner),
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Virtual Grand Rounds:
Individualized Prophylaxis in Hemophilia

**Individualized Prophylaxis in Hemophilia**

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**Prophylaxis in Hemophilia: Benefits and Barriers**
Prophylaxis in Factor VIII and Factor IX Deficiency

Definition

- Regular intravenous infusions of factor replacement to prevent bleeding

Considerations

- Patient diagnosis
- Patient bleeding pattern
- Activity level

Types of Prophylaxis

<table>
<thead>
<tr>
<th>Type</th>
<th>Time Frame</th>
<th>Age Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>regular continuous replacement before</td>
<td>by age 3 years or 2nd evident joint bleed</td>
</tr>
<tr>
<td></td>
<td>documented joint disease</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>regular continuous replacement started after</td>
<td>age agnostic</td>
</tr>
<tr>
<td></td>
<td>≥ 2 joint bleeds but before documented joint</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>regular continuous therapy started after onset</td>
<td>age agnostic</td>
</tr>
<tr>
<td></td>
<td>of documented joint disease</td>
<td></td>
</tr>
</tbody>
</table>

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Individualized Prophylaxis in Hemophilia

Primary Options for Treatment

Factor VIII and factor IX products

- Plasma-derived factor replacement therapy
- Recombinant factor replacement therapy
  – 1st, 2nd and 3rd generation
- Recombinant extended half-life products

Benefits of Prophylaxis

Findings similar in children and adults:

- Improved joint health\(^1,^2\)
- Decreased bleeding in joints, muscles, other\(^2\)
- Improved HRQoL over on-demand therapy\(^2^4\)

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Barriers to Prophylaxis

- Venous access
- Adherence
- Direct costs\(^1,\,^2\)
- Burden of illness\(^3\)
- Availability of factor replacement therapy


Considerations for Comprehensive Care Team

Comprehensive care team must account for many parameters that affect treatment:

- Baseline factor levels\(^1\)
- Bleeding phenotype \(^2,\,^3\)
- Joint status\(^4\)
- Activity levels

\(^1\)den Uijl et al. Haemophilia. 2011;17(1):41-44.
Considerations for Comprehensive Care Team

- Adherence by the patient: caregiver may ‘tailor’ treatment for better results
  - Child with venous access challenges
  - Adolescent
  - Adult with long-term care challenges
- Comorbidities
  - Hepatitis C/HIV
  - Arthritis/heart disease/kidney failure
- Medication use (over the counter, herbal, diet)

Considerations for Comprehensive Care Team

- Level of physical activity

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>Considerations*</th>
</tr>
</thead>
</table>
| Very active lifestyle (athletes, active adults) | • Multiple peaks are beneficial  
  - Use standard half-life factors 3-4x per week (sometimes even more)  
  - Troughs are less important |
| Sedentary/less active                   | • Troughs are key to preventing bleeds  
  • Peaks for high-risk activity not important  
  - An extended half-life factor is more convenient and provides same trough level |

* Based on expert opinion.
Considerations for Comprehensive Care Team

- Pharmacokinetic profile
  - Adult vs child
  - Obese patients
  - Previous inhibitor patients
- Relationship with HTC staff (trust)
- Social factors (attitudes, beliefs)
- Literacy level of patients

Current MASAC Recommendations

- Should be considered optimal therapy for individuals with severe hemophilia A or B
- Should be instituted early (before onset of frequent bleeding)
- Goal: keep trough levels > 1%
- Patients may continue to benefit from prophylaxis throughout their life

MASAC. Medical and Scientific Advisory Council of the US National Hemophilia Foundation.
MASAC Recommendation Concerning Prophylaxis. Available at:
**MASAC Recommendations for Prophylaxis Regimens**

**Children**
- 25-50 FVIII units/kg 3 x week or every other day
- 40-100 FIX units/kg 2-3 x week

**Adults**
- Dosing same as for children
- May continue to benefit from prophylaxis throughout their life

**Each Center Decides Own Protocol**

- MASAC recommendations: Very broad dosing and treatment intervals
- Extended half-life products: dosing per manufacturer; currently not addressed in any standardized recommendations
Devising Protocols for Prophylaxis

Prophylaxis Regimens

- Historically based on patient's
  - Weight
  - Bleeding pattern
  - Trough level

- More recent
  - Annualized bleeding rate (ABR)
  - Individual pharmacokinetics (PK)
Prophylaxis Based on Annualized Bleeding Rate (ABR)

- ABR measures the estimated number of bleeding episodes per year
  - Spontaneous
  - Traumatic
- Recent studies have achieved ABR’s close to zero


ABR with Extended Half-Life Products

<table>
<thead>
<tr>
<th></th>
<th>Individualized Prophylaxis</th>
<th>Weekly Prophylaxis</th>
<th>On-Demand</th>
</tr>
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<tbody>
<tr>
<td>recFVIIIFc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.6</td>
<td>3.6</td>
<td>33.6</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>0.0</td>
<td>1.9</td>
<td>20.2</td>
</tr>
<tr>
<td>Traumatic</td>
<td>0.0</td>
<td>1.7</td>
<td>9.3</td>
</tr>
<tr>
<td>recFIXFc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.1</td>
<td>2.4</td>
<td>18.7</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>1.0</td>
<td>0.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Traumatic</td>
<td>1.0</td>
<td>0.0</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Pharmacokinetic Studies (PK)

- Hemophilia treatment well suited to optimization by PK studies
- “Tailored” dosing: based on patient’s rAHF-PFM PK (infusion interval, estimate $t_{1/2}$, and recovery)
- PK study: performed after 3-5 half-life washout period
  - Dose product to 100%
  - Factor activity measured at various time points
- Superior results to episodic treatments with respect to annualized bleeding rate and qualify of life measures


Considerations in Individualized Prophylaxis

- Bleeding phenotype
- Physical activity
- Tailored prophylaxis
- Pharmacokinetics
- Joint status
Individualizing Prophylaxis

Personalized Medicine

President’s Council of Advisors on Science and Technology (PCAST)

- Tailoring of medical treatments to the individual characteristics of each patient
- Classify individuals into subpopulations based on
  - susceptibility to a particular disease or
  - responses to a specific treatment
- Potentially optimize targeted delivery and dosing of treatments

US Food & Drug Administration.
Starting Prophylaxis

All protocols are individualized. No existing protocol stating:
- When (or even if) to start prophylaxis
- Which dosing approach to start prophylaxis

When
After first joint bleed or by age 3 years, whichever is first

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
</tr>
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<tbody>
<tr>
<td>Full-dose</td>
<td>3-4x per week</td>
</tr>
<tr>
<td>Step-up</td>
<td></td>
</tr>
<tr>
<td>• Rapid</td>
<td>As quickly as possible to 3x per week</td>
</tr>
<tr>
<td>• Bleed-related</td>
<td>Increase to 3x per week only with bleeding event</td>
</tr>
</tbody>
</table>

Transitions and Prophylaxis

<table>
<thead>
<tr>
<th>Age</th>
<th>Transition Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>Infancy (pre-prophylaxis)</td>
</tr>
<tr>
<td>1-3 years</td>
<td>Toddlerhood (initiation of prophylaxis, venous access issues)</td>
</tr>
<tr>
<td>3-5 years</td>
<td>Pre-school (limited “dangerous” activities)</td>
</tr>
<tr>
<td>6-12 years</td>
<td>School age (increased physical activity)</td>
</tr>
<tr>
<td>13-18 years</td>
<td>Teens (increased risk taking, some with decreased physical activity, adherence)</td>
</tr>
<tr>
<td>Adults</td>
<td>Various lifestyles</td>
</tr>
</tbody>
</table>
Assessing Outcomes

Whatever treatment regimen is chosen, assessing outcomes is crucial to determining if the regimen needs to be changed.

Let’s Get Practical
Infancy, Toddlerhood, and Preschool

- Limited “dangerous” physical activity
- Risk for falls/injuries
- Venous access issues
- Options include:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Full-dose</td>
<td>3-4x per week</td>
</tr>
<tr>
<td>Tailored dosing</td>
<td>• Aiming for a set trough&lt;br&gt;• Requires PK studies</td>
</tr>
<tr>
<td>Step-up</td>
<td></td>
</tr>
</tbody>
</table>

School Age

- Physical activities/sports often begin and/or become more serious at this age

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>Considerations</th>
</tr>
</thead>
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<tr>
<td>Active, athletic children</td>
<td>• May need more peaks per week&lt;br&gt;– Full-dose prophylaxis with 3-4x per week dosing</td>
</tr>
<tr>
<td>Less active children</td>
<td>• Can use a less intense regimen&lt;br&gt;– PK-tailored dosing aiming for a low trough (1%-3%)&lt;br&gt;– Less frequent dosing regimen (2x a week regardless of trough)&lt;br&gt;– Consideration for extended half-life factors with even less frequent dosing</td>
</tr>
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</table>
Teen Years: Three Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Activity Level</th>
<th>Regimen</th>
</tr>
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<tbody>
<tr>
<td>Athletes</td>
<td>• Supervised physical activity</td>
<td>• Frequent, high peaks organized around their specific activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– High school soccer player</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– May dose even daily before practice, games; not infuse when not playing</td>
</tr>
<tr>
<td>Physically active</td>
<td>• Unsupervised activities (skateboarding, street</td>
<td>• Routine prophylaxis with additional dosing around specific activities</td>
</tr>
<tr>
<td>individuals</td>
<td>games/pickup games)</td>
<td></td>
</tr>
<tr>
<td>Gym rats</td>
<td>• Gym rats</td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>Limited/no physical activity</td>
<td>• Low intensity regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Less frequent dosing with low troughs</td>
</tr>
</tbody>
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Case Study 1

- 14-year-old boy with severe hemophilia A
- On prophylaxis 3x per week since infancy
- Joints are pristine
- Outstanding soccer player
  – Has played club soccer for years
- He wishes to join the high school team
- You are advising him in his pre-school visit
Case Study 1

• Current regimen
  – SHL rFVIII 29 IU/kg/dose every other day
  – Has had one trauma-related bleed (not soccer-related) in the past year

• Soccer schedule
  – Daily practice 3:30 – 5:30 pm
  – Games on Wednesdays at 3:30 pm and Fridays at 6:00 pm

SHL, Standard half-life product.

Case Study 1

• Would you alter his regimen?
• Would you consider an EHL FVIII product?
• What would be the ideal regimen to prevent bleeding?

EHL, Extended half-life.
Adults

• Similar to teenagers
• Some may elect to forgo prophylaxis
  – Not recommended in general
• Activity may change over younger years
• Knowledge of personal bleeding “triggers”
  can affect treatment regimen

Case Study 2

• 25-year-old man with severe hemophilia A
• Started prophylaxis at age 8 years after a target
  joint developed
• Target joint has been resolved for many years
• He is married and works as an IT supervisor for
  a small company
• He exercises daily in low-impact activities
• He doesn’t play sports or engage in any
  physically risky activities
Case Study 2

• Current regimen
  – SHL rFVIII 40 IU/kg/dose every M-W-F
  – He has had no bleeds in the past year

• Exercise routine
  – Exercises in a gym 4 days per week
  – 20 minutes aerobic activity on a stair climber
  – Light weight lifting

M-W-F, Monday-Wednesday-Friday.

Case Study 2

• Would you alter his regimen?
• Would you consider an EHL FVIII product?
• What would be the ideal regimen to prevent bleeding?
The Importance of Adherence

“Drugs don’t work in patients who don’t take them.”
Former United States Surgeon General C. Everett Koop

Definition of Adherence

- “The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.”

Hemophilia Patient’s Perspective

• General studies:
  – 41% of patients reported not following their treatment regimen
  – 41.2% rated their adherence as ‘less than excellent’


Barriers to Adherence

Forgetfulness
• Dealing with it on a daily basis
• Social/family stresses (lack of discipline)
• Costs
• Transition to adulthood
  – Lack of supervision
  – Lack of commitment
• Poor venous access
• Risk of complications
• Adults: unwillingness to allow HTC to interfere with their daily lives

Adherence: Link to Quality Outcomes

Prophylaxis & better adherence resulted in lower ABR than with episodic treatment

Clinical Outcomes
- Morbidity
- Mortality
- Bleeding episodes

Medication Adherence
- Quality of Care
  - Adverse events
  - Control of disease

Quality of Life
- Absenteeism from work/school
- Participation in activities

Health Care Utilization
- ED visits
- Dose optimization
- Cost of care

Hemophilia Physicians’ Perceptions of Adherence to Prophylaxis

Adherence is suboptimal (N = 59)
- ~60% infuse more than 75% - 80% of recommended infusions
- 54% believed that 76% - 100% of their patients infuse prophylactically > 80% of doses
- 42% believed that 51% - 75% of patients infuse > 80% of doses

Ways to Improve Adherence: Patient’s Perspective

- Education about prophylaxis
- Tracking prophylaxis
  - Diary/log
  - PC/palmtop database
- Improvements in factor
- Contracts
- Communication
  - Internet dialog page
  - More frequent visits
  - Reminder telephone calls


Ways to Improve Adherence: Healthcare Provider’s Perspective

- Education about prophylaxis
  - Promote it as a way to decrease inhibitor formation, enhance participation in physical activities, decrease subclinical bleeds
- Improve ease of venous access
  - Psychological interventions to decrease anxiety w/ PIV
  - Training for independence
- Individualized therapy

How Healthcare Providers Can Change Adherence Patterns

- Health professionals’ job satisfaction (communication/body language)
- Discuss patients’ beliefs (motivational Interviewing)
- Keep regimens simple; fit into patient’s lifestyle
- Assess available social support, family structure
- Screen and refer for depression
- Just trying to convince them that treatment is good for them is unlikely to work


Cost of Nonadherence

Nonadherence has been estimated to cost the US health care system between $100 billion and $289 billion annually in direct costs

Cost Effectiveness of Prophylaxis

• Point of view
  – Affected individual/family
  – Payer
  – Society

• Costs considered
  – Direct costs
  – Indirect costs
    ▪ Loss of productivity
    ▪ Benefits for other family members


Annual Cost of Prophylaxis

Healthcare Coverage

- Affordable Care Act (ACA) eliminated some of the barriers:
  - Lifetime caps removed
  - Insurance coverage cannot be dropped for pre-existing conditions
- Navigate through various coverages; remember to ask:
  - Premium costs and coverages (medical versus pharmacy)
  - Copays and deductibles
  - Direct cost to consumer: out of pocket costs
  - Coverage and access to available services and providers
    - Ensure access to comprehensive hemophilia treatment centers for clinical treatment
    - Ensure options to access pharmacy services for clotting factor

Individualizing Prophylaxis for Cost Effectiveness

1. Prophylaxis is expensive; important to ensure access and adequate treatment to sustain measurable and effective factor levels for optimal outcomes
2. Demonstrated relationship:

   Better adherence = Better outcomes