

Prophylaxis in Hemophilia:
Do Immunologic Danger
Signals or Pharmacokinetics
Hold Relevance?



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Learning Objectives



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

- Recognize variation in prophylaxis utilization practices among hemophilia treatment centers
- Discuss recent studies concerning the impact of prophylaxis on inhibitor development in patients with hemophilia
- Analyze emerging data about immunologic danger signals and the effect of low-dose prophylaxis on inhibitor risk reduction in hemophilia patients
- Integrate learning on the role of factor VIII pharmacokinetics into the implementation of individualized prophylaxis regimens for patients with severe hemophilia A

Hemophilia Background



- Hemophilia A most common^{1,2}
 - ≈80% of all cases^{1,2}
 - 20%-30% of patients develop inhibitors³⁻⁵
- Hemophilia B less prevalent^{1,2}
 - ≈15%-20% of all cases^{1,2}
 - 1%-6% of patients develop inhibitors^{3,4}
- Inhibitors are the most important complication impacting current hemophilia care worldwide⁶

1. Aledort LM. *Haemophilia*. 2010;16(suppl 6):1-2; 2. Chitlur M, et al. *Haemophilia*. 2009;15:1027-1031; 3. Carcao M, et al. *Haemophilia*. 2010;16(suppl 2):16-23; 4. DiMichele DM. *Inhibitors in Hemophilia: A Primer*. 4th ed. World Federation of Hemophilia. April 2008; 5. Gouw SC, et al. *Blood*. 2007;109:4648-4654; 6. DiMichele DM. *Int J Hematol*. 2006;83:119-125.

Prophylaxis in Hemophilia—The Standard of Care

Prophylaxis = infused factor replacement before the occurrence of, and to prevent, bleeding^{1,2}

- Since the 1990s, supported by WHO, NHF, and WFH as first-line treatment for children with severe hemophilia^{2,3}
- Usage increasing for adult patients⁴
- Demonstrated benefits
 - Prevents joint damage and decreases frequency of joint and other hemorrhages⁵
- 21st century standard of care for severe hemophilia⁶

1. Berntorp E, et al. *Haemophilia*. 2003;9(suppl 1):1-4; 2. Carcao M, et al. *Haemophilia*. 2010;16(suppl 2):4-9; 3. Rodriguez NI, et al. *Hematol Oncol Clin North Am*. 2010;24:181-198; 4. Collins PW, et al. *J Thromb Haemost*. 2010;8:269-275; 5. Manco-Johnson MJ, et al. *N Engl J Med*. 2007;357:535-544; 6. van den Berg HM. *Haematologica*. 2004;89:645-650.

Long-term Goals of Prophylaxis



- Prevention of chronic arthropathy and sequelae^{1,2}
- Prevention of intracranial and other serious bleeds³
- Prevention of pain and suffering¹
- Improvement in individual/family QoL³
- Reduction in long-term societal costs through prevention of disability, improved outcome, and maximization of human potential^{1,3}

1. Shapiro AD, et al. The Role of Prophylaxis in Managing Hemophilia in Adult and Pediatric Populations. Available at: http://cme.medscape.com/viewarticle/703176_print. Accessed July 6, 2010;
2. Fischer K, et al. *Haemophilia*. 2008;14(suppl 3):196-201; 3. Berntorp E, et al. *Haemophilia*. 2003;9(suppl 1):1-4.

US Prophylaxis Utilization Practices



Summary Report of Universal Data Collection (UDC) Activity—National Treatment/Clinical Characteristics

Report Date:

October 4, 2010

Hemophilia A

Hemophilia B

Characteristic

Severity level

Severe

Severe

No. of patients

7383*

1379*

Treatment Type

Episodic

3292

766

ITI

137

8

Prophylaxis

3959

606

*Sum of numbers in treatment categories does not equal total number of patients, as some patients received no treatment and other patients received more than one type of treatment.

Centers for Disease Control and Prevention. Bleeding and Clotting Disorders Surveillance.

Available at:

https://www2a.cdc.gov/ncbddd/htcweb/udc_report?UDC_view1.asp?para1=NATION¶2=A¶3=&ScreenWidth=1024&ScreenHeight=768. Accessed September 2, 2010.

- Despite acceptance of prophylaxis as the standard of care, no standardized best practices¹
 - Unresolved differences concerning regimen implementation and dosing schedules
- UDC data analysis conducted by Soucie of boys aged 2-14 years with severe hemophilia demonstrated wide variation in prescription of prophylaxis among US hemophilia treatment centers (HTCs)²
 - Data from visits during 2 study periods
 - Period 1: 2937 visits, Jan 2006-Dec 2007
 - Period 2: 2416 visits, Jan 2008-Dec 2009
 - During both periods, the proportion of patients on prophylaxis varied from **0%-100%**^{*†}

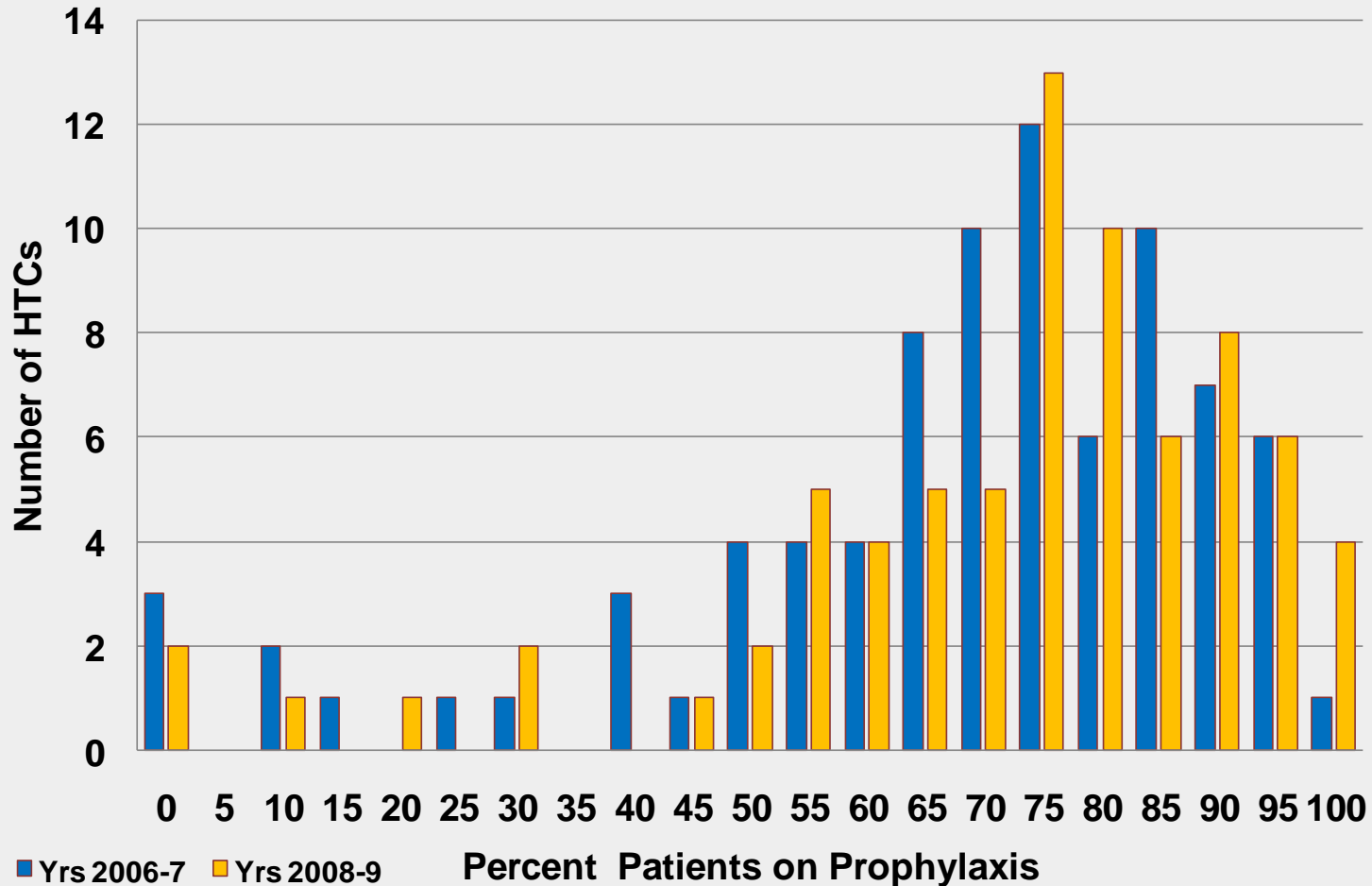
*Period 1 represented 84 HTCs with at least 10 boys with severe hemophilia; †Period 2 represented 75 HTCs with at least 10 boys with severe hemophilia.

1. Chambost H. *Haemophilia*. 2010;16(suppl 2):1-3; 2. Soucie M. Treatment Center Variations and Trends in the Use of Prophylaxis for Hemophilia. Presented at: National Conference on Blood Disorders in Public Health; March 9, 2010; Atlanta, GA.

US Prophylaxis Utilization Practices Epidemiologic Data



Distribution of Percent of Boys With Severe Hemophilia on Prophylaxis in HTC's by Time Period



- Various treatment regimens employed

Regimen			
	Swedish (Malmö model)	Canadian	French (COMETH recommendations)
Initiation criteria	Treatment is initiated early at 1–2 years of age or younger before the onset of joint bleeds	Treatment is initiated between 1 and 2.5 years of age; in the context of normal joints	Treatment is initiated before the age of 3, after the occurrence of the second haemarthrosis or when two spontaneous joint bleeds occur during a 6-month period (any joint)
Study protocol	FVIII (haemophilia A) or FIX (haemophilia B) at 20–40 U kg ⁻¹ every second/third day or minimum 3 or 2 times/week respectively, following initiation period (initiated at 250 IU/dose) All patients escalated to full-dose prophylaxis by approximately 2 years of age	Step 1* – FVIII administration at 50 U kg ⁻¹ once per week Step 2* – 30 U kg ⁻¹ twice weekly Step 3* – Full-dose prophylaxis 25 U kg ⁻¹ on alternate days (or three times per week)	Step 1 [†] – FVIII administration at 50 U kg ⁻¹ once per week Step 2 [†] – 30 U kg ⁻¹ twice weekly on fixed days Step 3 ^{†‡} – 25 U kg ⁻¹ on Days 1 and 3, 30 U kg ⁻¹ on Day 5 each week, or 25 U kg ⁻¹ at a fixed interval of 72 h Step 4 ^{†‡} – 25 U kg ⁻¹ on alternate days

*Escalate if unacceptable bleeding is detected at any stage; unacceptable bleeding defined as 3+ bleeds into any one joint, or 4+ bleeds into any muscle/joint over 3 months, or 5+ bleeds into one joint while on a treatment step.

[†]Escalate after the first additional spontaneous haemarthrosis.

[‡]Doses pharmacokinetically tailored according to residual plasma level of anti-haemophilic factor.

Prophylaxis Treatment Regimens (cont)



- Optimal regimen for primary prophylaxis still not identified
 - Primary prophylaxis generally recommended in children with severe hemophilia
 - Prophylaxis initiated before age of 2 years, prior to clinically evident joint bleeding or joint damage
 - Precisely when to implement?
 - Frequency?
 - Dose?
 - When to escalate the regimen?

Prophylaxis and Inhibitor Risk

Hemophilia Background



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Prophylaxis and Risk of Inhibitors: Data From Clinical Studies



Santagostino et al (2005)

- Multicenter case-control study of 108 children with hemophilia A with and without inhibitors suggests that early prophylaxis is associated with a 70%-80% lower risk of inhibitor development compared with on-demand treatment

Gouw et al (2007)

- CANAL Study (retrospective, multicenter cohort study of 366 consecutive previously untreated patients with severe hemophilia A) reported that prophylaxis was associated with a 60% decreased risk of inhibitor development compared with on-demand treatment

Santagostino E, et al. *Br J Haematol*. 2005;130:422-427; Gouw SC, et al, for the CANAL Study group. *Blood*. 2007;109:4648-4654.

Immunologic Danger Signals and Inhibitor Development



- Recent paradigm: presence of pro-inflammatory “danger signals” may determine effector immune response versus induced tolerance
- Effector immune response may be triggered by intensive exposure to FVIII in presence of such danger signals
 - Bleeding associated with tissue damage
 - Surgery
 - Trauma
 - Additional immunologic stimuli
 - Vaccination
 - Infection
- Results in increased risk of inhibitor formation?

Low-Dose Prophylaxis and Inhibitor Development



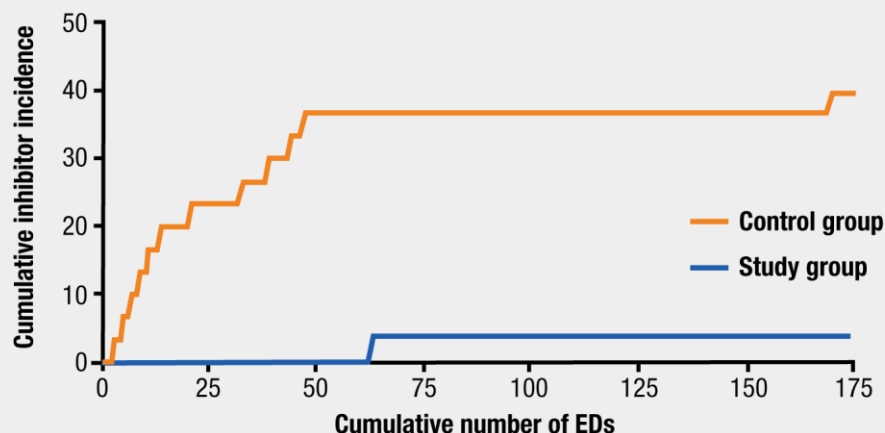
Kurnik et al (2010)

- Recent pilot study hypothesizing a role for danger signals in the development of inhibitors
- Exposure to danger signals purposefully minimized in cohort
 - Surgery avoided during first 20 EDs
 - Vaccination avoided on treatment days
 - Early treatment of bleeds with high doses of FVIII to minimize duration of tissue damage
- 26 PUPs with severe hemophilia A treated with low-dose prophylaxis weekly at time of first bleed manifestation of any severity, escalated to 2x-3x/wk, based on bleed severity; introduced after median of 1 ED
- Historical control group of 30 consecutive PUPs treated with standard prophylaxis regimen of 40-50 IU/kg FVIII 3x/wk; introduced after median of 30 EDs

Low-Dose Prophylaxis and Inhibitor Development (cont)

Kurnik et al (2010)

- Results suggest that early start of low-dose prophylaxis 1x/wk with minimization of immunologic danger signals during first 20 EDs to FVIII may reduce incidence of inhibitors
 - 14/30 patients on standard regimen developed inhibitor vs 1/26 patients on low-dose regimen ($P=.0003$; OR .048; 95% CI .001-.372)



Cumulative inhibitor incidence with increasing number of EDs: control vs study group

Prophylaxis and Pharmacokinetics

Impact of FVIII Trough Levels on Prophylaxis Efficacy

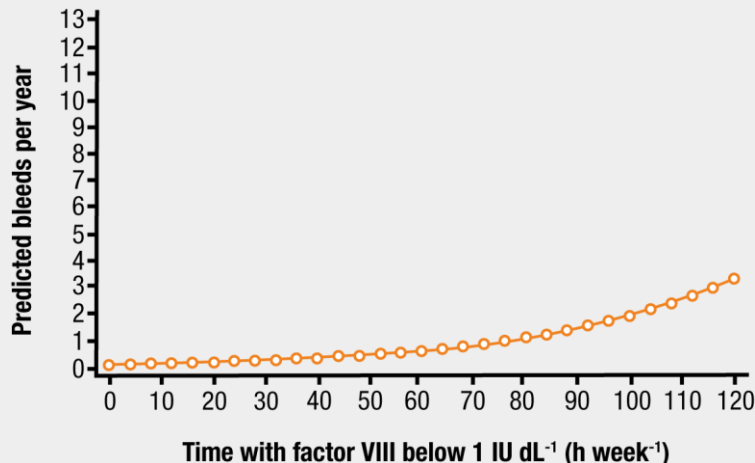


- The observation that patients with moderate hemophilia (factor levels 1%-5% of normal) bleed less than those with severe disease (<1% normal) led to the concept of factor prophylaxis^{1,2}
 - “Convert” a severe phenotype to moderate by maintaining factor levels at or above 1% of normal through regular factor infusions^{2,3}
 - Outcome: reduced bleeding and arthropathy, improved quality of life
 - Caveat: Some patients require higher levels to prevent bleeds (eg, patients with damaged joints); others do not bleed despite trough level <1 IU/dL
 - 1% should be viewed as a “rule of thumb”³
 - Infusions are periodic: regimens that maintain adequate levels over longer periods of time are clinically superior to those that give occasional high peak levels (daily or 3x/week better than weekly)³

Impact of FVIII Trough Levels on Prophylaxis Efficacy (cont)

Collins et al (2009)

- Analysis of PK and bleeding data from 143 patients receiving a recombinant FVIII product as prophylaxis during clinical studies
- Time per week subjects spent below 1% factor level calculated from collected PK data and factor infusion data recorded in treatment diaries; bleeding events also tracked in diaries



Predicted bleed count per year vs time spent with a factor VIII (FVIII) less than 1 IU dL⁻¹ for patients aged 1-6 years. The predicted hemarthroses per year (represented with an open circle) dependent on time per week spent with a FVIII less than 1 IU dL⁻¹ are shown for the patients aged 1-6 years.

- Increasing time per week with FVIII level <1% associated with increased total bleeds and hemarthroses
- In young children (1-6 yr), annual bleed rate increased 2.2% for every additional hour spent with FVIII <1% (CI 1.6-2.8%)
- Lack of adherence to frequency the most important determinant of low FVIII and increased bleeding

Role of FVIII Pharmacokinetics in Designing a Prophylaxis Regimen

Collins et al (2010)

- Study utilized PK parameters (half-life and recovery) from 147 patients from same series of clinical trials of the same FVIII product to explore effect of interpatient PK variability and different dosing regimens on trough levels

Observed Factor VIII Half-life and Recovery

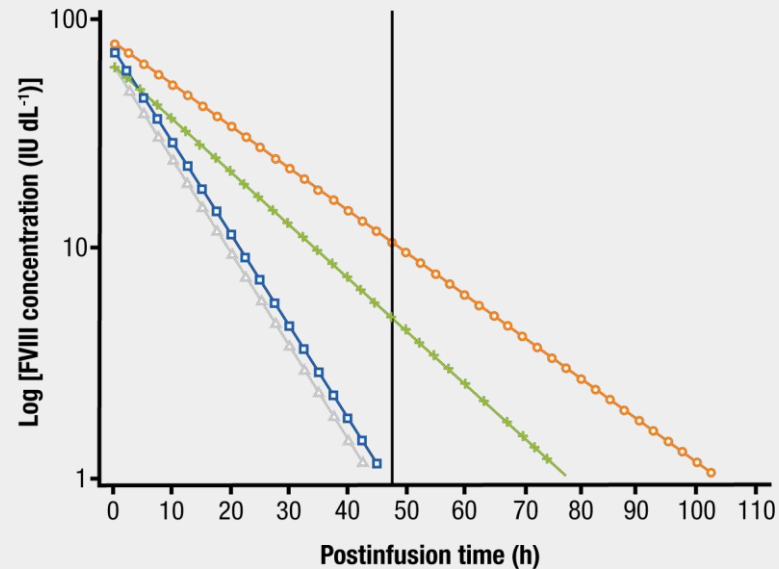
	Age 1–6 years		
	5%	Median	95%
Half-life (h)	7.4	9.4	13.1
Recovery (IU dL ⁻¹ per IU kg ⁻¹)	1.35	1.83	2.76

Role of FVIII Pharmacokinetics in Designing a Prophylaxis Regimen (cont)



Collins et al (2010)

- Following a single infusion of FVIII (30 IU kg^{-1}), the time taken for the FVIII level to fall below 1 IU dL^{-1} varied widely, dependent on half-life



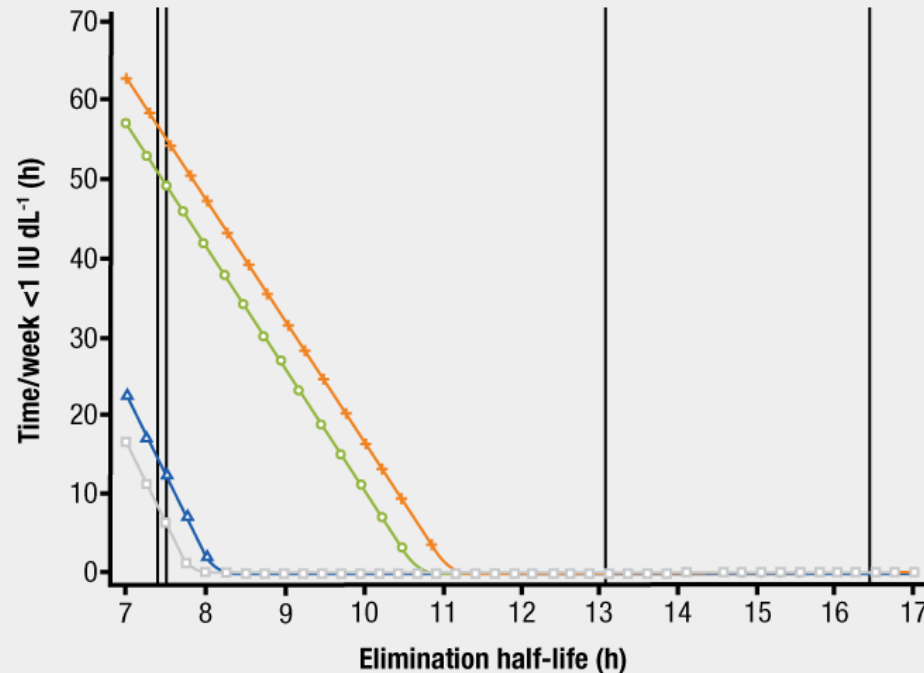
Time for factor VIII (FVIII) to reach 1 IU dL^{-1} dependent on half-life. The FVIII concentration over time after a single infusion of 30 IU kg^{-1} is shown and demonstrates a wide variation dependent on half-life. In contrast, in vivo recovery (assuming a median half-life) had a smaller effect on the time to reach 1 IU dL^{-1} , with a difference of 9.7 h between the 5th and 95th percentile in the 1-6 year olds and 12.6 h in the 10-65 year olds. $\Delta\Delta\Delta$ and xxx = half-life at 5th and 95th percentiles for 1-6 year olds; $\square\square\square$ and $\circ\circ\circ$ = half-life at 5th and 95th percentile for 10-65 year olds.

Role of FVIII Pharmacokinetics in Designing a Prophylaxis Regimen (cont)



Collins et al (2010)

- The combined effect of half-life and frequency of infusion on FVIII levels was also analyzed, based on qod vs q3d dosing



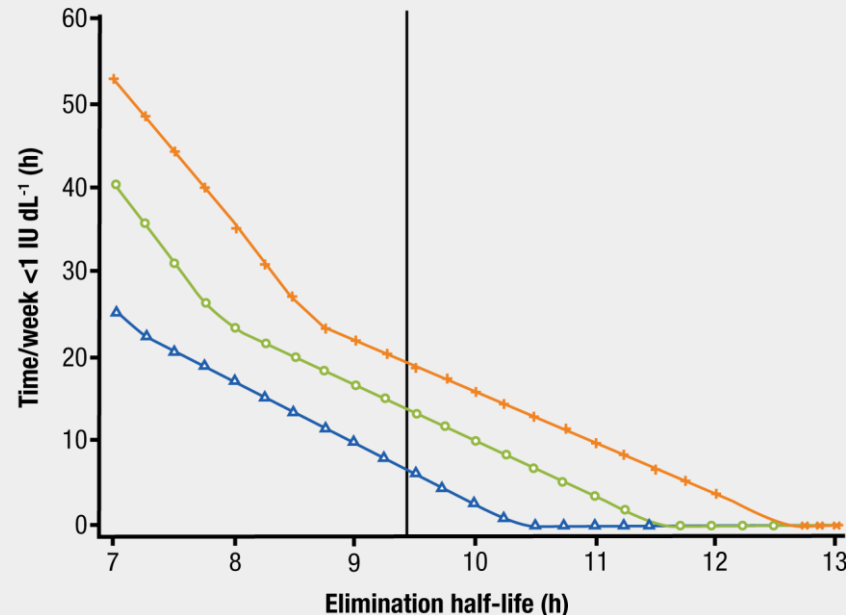
The amount of time per week a patient would spend with FVIII <1 IU/dL dependent on half-life and frequency is shown. $\Delta\Delta\Delta$ = alternate day dosing with 30 IU/kg for 1- to 6-year-olds; $\square\square\square$ = alternate day dosing with 30 IU/kg for 10- to 65-year olds; xxx = every third day dosing with 45 IU/kg for 1- to 6-year-olds; $\circ\circ\circ$ = every third day dosing with 45 IU/kg for 10- to 65-year-olds.

Posted with permission of Collins PW, et al. *J Thromb Haemost.* 2010;8:269-275.

Role of FVIII Pharmacokinetics in Designing a Prophylaxis Regimen (cont)

Collins et al (2010)

- Prophylaxis regimens based on M-W-F dosing are not adequate to sustain a FVIII level above 1 IU dL^{-1} for the 3-day weekend gap



Effect of half-life and dose on factor VIII (FVIII) level for Monday, Wednesday, and Friday dosing. The amount of time per week a 1- to 6-year-old patient treated on Monday, Wednesday, and Friday would have with a FVIII $<1 \text{ IU dL}^{-1}$, dependent on half-life, for commonly used doses of FVIII is shown. xxx = 20 IU kg^{-1} ; ooo = 30 IU kg^{-1} ; and ΔΔΔ = 50 IU kg^{-1} .

Role of FVIII Pharmacokinetics in Designing a Prophylaxis Regimen (cont)



Collins et al (2010) – Summary

- FVIII half-life and dosing frequency had the largest influence on FVIII levels (more than recovery and dose/kg)
- Wide variation in total FVIII dose required to maintain a specific trough level in patients receiving regular prophylaxis infusions
- Less frequent dosing leads to increased total factor usage (eg, up to 33-fold difference for daily vs q3d dosing)
- Although commonly used, M-W-F dosing is significantly less cost-effective than qod dosing and requires large doses to sustain measurable trough at 72 hours
- Knowledge of patients' factor half-lives may allow for more cost-effective prophylaxis and could serve as a useful adjunct to clinical bleeding information in customizing dosing regimens
- Prospective trial comparing PK-based versus weight-based prophylaxis being planned by the authors

Dose Tailoring in Prophylaxis



- Holds promise for better cost-effectiveness and expanded access of prophylaxis in areas where resources are scarce due to optimized factor consumption for individual patients^{1,2}
- The full potential of cost-effectiveness is currently limited by available vial sizes—smaller and more varied vial sizes are required for small children and truly individualized dosing
- Although more frequent dosing is more cost-effective, another limitation is patient acceptance of the regimen—more frequent venipunctures and requirements for vascular access

- Current methods for obtaining PK data are cumbersome—emerging data suggest that “limited blood sampling” may be sufficient for dose tailoring^{1,2}
 - This must be better defined and validated for routine clinical practice, especially pediatrics^{3,4}
- Optimal dose tailoring must incorporate clinical outcomes (eg, bleeding frequency, joint status, quality of life)

1. Björkman S. *Haemophilia*. 2010;16:597-605; 2. Björkman S, et al. *J Thromb Haemost*. 2010;8:730-736; 3. Björkman S. *Haemophilia*. 2003;9(suppl 1):101-110; 4. Collins PW, et al. *J Thromb Haemost*. 2010;8:269-275.

- Prophylaxis is the recommended standard of care for children with severe hemophilia, and its use is on the rise among adult hemophilia patients
- Prophylaxis utilization practices vary widely among US hemophilia treatment centers and worldwide; there is no consensus among clinicians concerning the optimal regimen for, or implementation of, primary or secondary prophylaxis
- Clinical data suggest a protective effect of prophylaxis against inhibitor development, but this requires additional study
- Use of pharmacokinetic measures of FVIII trough levels may optimize prophylaxis regimens, leading to better clinical outcomes and lower costs of care; this also requires further validation, and various practical hurdles need to be overcome

Thank You



For additional programs on hemophilia and blood-related disorders, please visit:

www.BloodCMECenter.org