



TABLE OF CONTENTS

Introduction

Current Treatments

Inhibitor Development

Risk Factors for Inhibitor Development

Inhibitor Prevention Strategies

Looking Ahead: Current Research Goals

References

Expert Commentary

Faculty

Practical Strategies for Managing Hemophilia and Preventing Inhibitor Development

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April 4, 2011

Introduction

Approximately 400,000 males worldwide have hemophilia, an X-linked recessive disorder that results in decreased or absent levels of factor VIII (FVIII; hemophilia A) or factor IX (FIX; hemophilia B) and a predisposition for bleeding.¹ Roughly 70% of people with hemophilia A and 40% of those with hemophilia B have the severe form of the disease, which is defined as plasma FVIII or FIX activity <1%. In such cases, >90% of severe bleeding episodes occur in joints and 80% occur in the ankles, knees, and elbows, the most common target joints.¹ When bleeding occurs, iron is deposited into the synovium of the target joint, leading to inflammation, hypertrophy, and neovascularization. Repeated episodes of bleeding and inflammation—the “vicious cycle” of hemophilia—ultimately lead to the loss of joint cartilage and bony destruction, as well as profound deformity and disability.^{1,2}

The goal of hemophilia therapy, therefore, is to treat and prevent bleeding episodes and related complications by replacing the deficient clotting factor.^{1,2} Therapy is often complicated, however, by its high cost, the need for frequent intravenous infusions, and the development of inhibitors, the latter being the most serious complication associated with hemophilia therapy.¹⁻³

Research to improve hemophilia care and confront the challenges associated with it is ongoing. In recent years, a number of important advances have been made that have led to vastly improved outcomes for hemophilia patients. In the pivotal [US Joint Outcome Study](#) by Manco-Johnson et al, the efficacy of prophylaxis with recombinant FVIII for the prevention of bleeding episodes and joint damage was decisively established.^{4,5} Progress is now being made in understanding the mechanisms of inhibitor development and developing novel treatment strategies that circumvent this grim complication.¹

Listen to Dr. Valentino discuss the benefits and risks of prophylaxis in patients without inhibitors in [“Prophylaxis in Hemophilia Patients Without Inhibitors and Its Impact on Inhibitor Development.”](#)



Listen to expert commentary derived from the symposium titled, [“Perspectives in Hemophilia: Clinical Challenges and Current Issues in Managing Patients With Inhibitors.”](#) which was held at the American Society of Pediatric Hematology/Oncology (ASPHO) Annual Meeting on April 8, 2010. In this CME activity, Victor S. Blanchette, MD, FRCP, Manuel D. Carcao, MD, MSc, and Amy D. Shapiro, MD, offer their insights on the challenges clinicians need to be aware of and

prepared to address in the management of hemophilia patients with inhibitors.

Current Treatments

Purified plasma-derived (pd) FVIII, pdFIX, recombinant (r) FVIII, and FIX products are currently available for the treatment of hemophilia.⁶ Purified plasma-derived FVII became available in the early 1970s, followed by plasma-derived FIX concentrates in 1992. The first recombinant products became available in 1992 and 1999, respectively (Table 1).¹

Table 1. FVIII and FIX Concentrates and Bypassing Agents Available in the US	
Product	Manufacturer/manufacturing site
pdFVIII concentrates	
Alphanate	Grifols, Los Angeles, CA
Hemofil M AHF	Baxter BioScience, Los Angeles, CA
Humate P	CSL Behring, Marburg, Germany
Koate CVI	Talecris, Clayton, NC
Kogenate FS	Bayer, Berkeley, CA
Helixate FS	Bayer, Berkeley, CA
Monoclate P	CSL Behring, Kankakee, IL
rFVIII concentrates	
Advate rAHF PFM	Baxter BioScience, Neuchatel, Switzerland
Helixate FS	Bayer, Berkeley, CA
Kogenate FS	Bayer, Berkeley, CA
Recombinate rAHF	Baxter BioScience, Thousand Oaks, CA
ReFacto*	Wyeth, Stockholm, Sweden
Xyntha*	Wyeth, Stockholm, Sweden
pdFIX concentrates	
AlphaNine SD	Grifols, Los Angeles, CA
Mononine	CSL Behring, Kankakee, IL
rFIX concentrates	
BeneFIX	Wyeth, Andover, MA
Bypassing agents	
FEIBA VH	Baxter BioScience, Vienna, Austria
NovoSeven	Novo Nordisk, Copenhagen, Denmark
*B-domain-deleted recombinant factor VIII. FVIII=factor VIII; FIX=factor IX.	

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Plasma-derived FVIII and rFVIII have identical hemostatic efficacy, but rFVIII is preferred due to ongoing concerns about infectious risk and emerging pathogens, including variant Creutzfeldt Jakob disease (Figure 1).¹

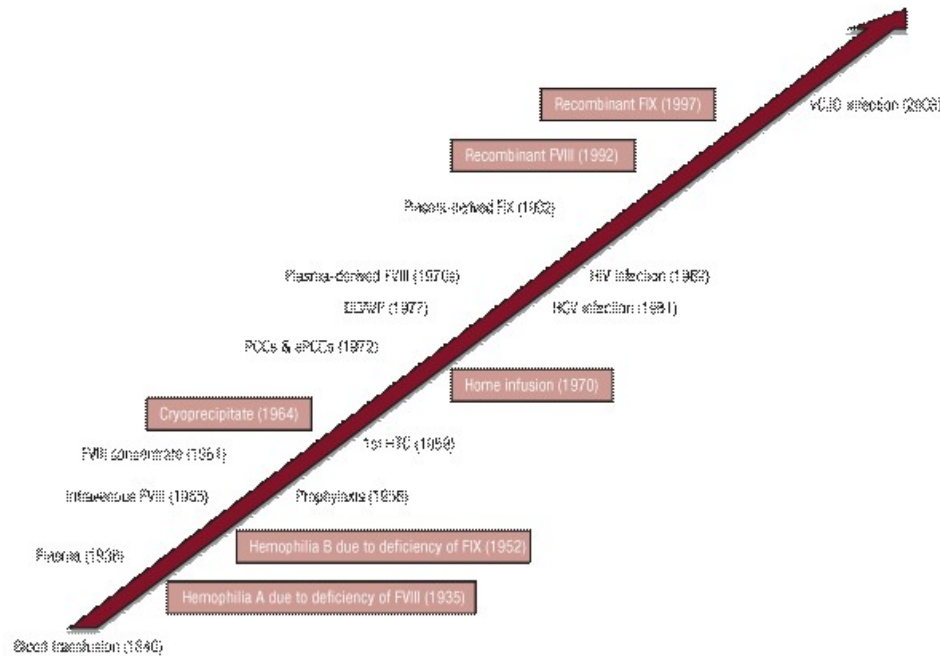


Figure 1

Advances and challenges in the evolution of hemophilia therapies. Key advances are boxed. Reproduced with permission from Valentin LA, et al. *Expert Opin on Emerging Drugs*. 2013; 16(6):597-613. ©2013 Informa Healthcare.

Bypassing agents (aPCC and rFVIIa) are generally used in patients anti-FVIII antibodies; rFVIIa is generally used for hemostasis in patients with FIX inhibitors, but aPCC may be safe and effective in some.¹ These agents bypass the missing coagulation factor, augment the coagulation process, and have been shown to control at least 80% of bleeding in patients with high-titer inhibitors.¹ However, their hemostatic efficacy is unpredictable and has not been found to be as efficacious as FVIII or FIX replacement in patients without inhibitors.¹

Inhibitor Development

Undoubtedly, inhibitor development is the most serious complication associated with factor replacement therapy.^{1-3,7,8} Up to 30% of patients with severe hemophilia A develop FVIII inhibitors^{8,9} and it has been estimated that 1% to 7% of patients with mild to moderate hemophilia A and 3% of patients with hemophilia B also develop inhibitors.⁹

When inhibitors are present, activity of the administered factor is compromised⁷ and disease-related morbidity is increased, with a corresponding significant impact on the patient's quality of life.^{8,9} In the presence of inhibitors, bleeding episodes are unresponsive to standard treatment⁸ and there is an increased incidence of target joint development.⁶ Moreover, patients with inhibitors have the greatest risk of arthropathy and orthopedic complications secondary to hemophilia¹⁰ and the highest reported economic burden for a chronic disease.⁸

Clinical Consequences of Hemophilia

- Inhibitor patients experience hemorrhagic episodes that are less controlled compared to noninhibitor patients¹
- Increased incidence of target joint development⁶
- Common bleeding sites⁶:
 - Knee: 45%
 - Elbow: 30%
 - Ankle: 15%
 - Shoulder: 3%
 - Wrist: 3%
 - Hip: 2%
 - Other: 2%

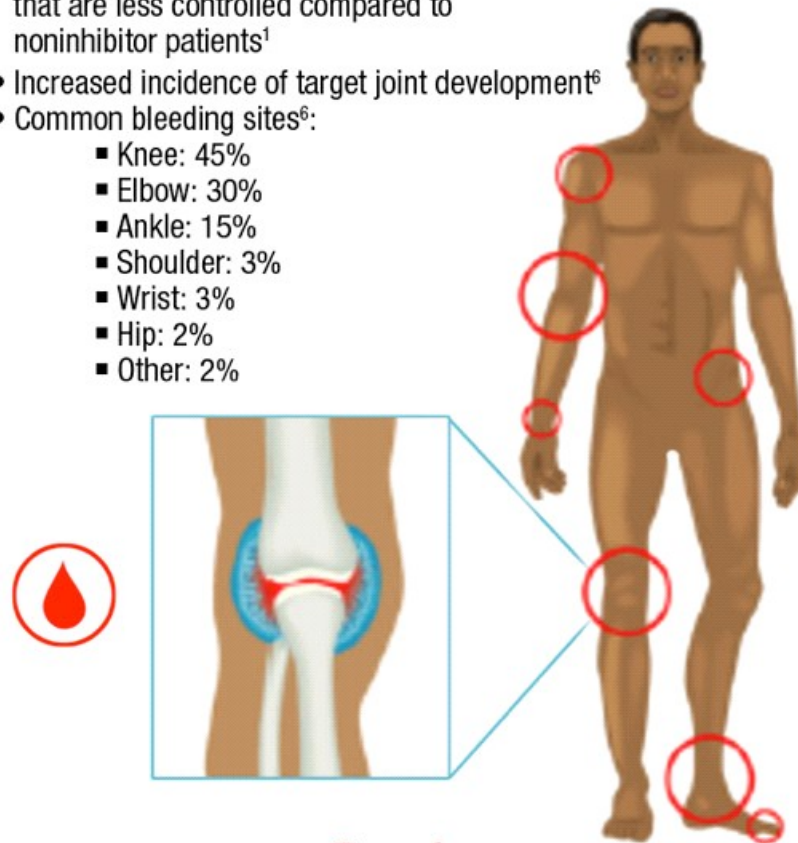


Figure 2

World Federation of Hemophilia. Guidelines for the Management of Hemophilia.
Available at: www.wfh.org. Accessed November 3, 2010.

Risk Factors for Inhibitor Development

Most inhibitors develop during the first 20 days of factor exposure and are the result of a complex interplay of various genetic and nongenetic factors.⁸ An understanding of the mechanisms of inhibitor development as well as associated risk factors allows for heightened prevention strategies and risk stratification to improve outcomes.

A number of genetic risk factors for inhibitor development have been identified. The most extensively studied is the FVIII gene mutation.⁸ Subsequent studies have found that the development of inhibitors corresponds with the type and location of *F8* mutations. In general, it is believed that patients with null mutations (large deletions, inversions, and nonsense mutations) are more susceptible to developing inhibitors, while missense mutations are usually associated with a low risk of inhibitor development.⁸

The seminal [Malmö International Brother Study](#) established that a family history of inhibitor development is associated with approximately a three-fold higher risk of inhibitor development. For reasons not yet completely understood, there is approximately a two-fold increased risk of inhibitor development in non-Caucasian patients.⁸

Unlike genetic factors, environmental and treatment-related risk factors are potentially modifiable and may therefore offer the hope of improved outcomes. Increasing evidence supports the concept of an immune response based on the “danger model.” In this model, alarm signals arise from injured tissues, thereby activating the immune system and leading to inhibitor development.⁸ Danger conditions include severe bleeds, trauma, and surgery that involves major tissue injury. When danger conditions are present, high-dose and/or prolonged hemophilia treatment occurs in association with signals that upregulate cellular T and B lymphocyte response.⁸ The intensity of treatment at first factor exposure has been found to play a key role.^{8,11}

The most controversial treatment-related risk factor is the type of FVIII concentrate administered.

There have been mixed study results concerning the incidence of inhibitor development with recombinant versus plasma-derived factor concentrate. [The CANAL study](#) by Gouw and colleagues found no significant difference in the risk of inhibitor development between pdFVIII and rFVIII products, nor did switching between factor products appear to confer additional risk.^{8,11} These results are at variance with the prospective long-term rFVIII registration studies, however, which clearly showed an increased risk of inhibitor development with recombinant products ([Table 2](#)).^{8,11} The differences in study results may be attributed to different study designs, and older studies may have underestimated the overall incidence of inhibitor development.^{8,11}

In general, it is believed that environmental conditions at first FVIII exposure are involved in a delicate interplay with the patient's genetic background and *F8* mutation type, leading to the determination of risk ([Figure 3](#)).⁸

Table 2. Inhibitor Prevalence and Type and Distribution of Factors Affecting the Inhibitor Risk Profile in the rFVIII PUPS Registration Studies

Study, product	Inhibitors, n Prevalence, % in severe pts (<2%)	High-titre (>10 BU/mL), n Prevalence, %	Transient, n (LR/HR) % of inhibitors	Afro- American patients	High-risk mutations	Family history of inhibitors	Prophylaxis
Lusher <i>et al.</i> , KODENATE	19/65 29.2%	11 16.9%	7 (1/6) 37%	14 22%	n.a.	10* 15%	n.a.
Bray <i>et al.</i>	22/73 30.1%	7 9.6%	5 (0/5) 23%	19 27%	31/51 61%	6* 14%	24 34%
Rotschild <i>et al.</i>							
Goodeve <i>et al.</i> , RECOMBINATE							
Lusher <i>et al.</i> , REFACTO	32/101 31.7%	12 11.9%	9 (1/8) 28%	5 5%	n.a.	n.a.	45 45%
Kreuz <i>et al.</i>	9/60 15%	5 8.3%	2 (0/2) 22%	5 8%	38/57 67%	13 22%	43 72%
Oldenburg <i>et al.</i> , KODENATE BAYER							

*Data not available for all patients
n.a. = not available

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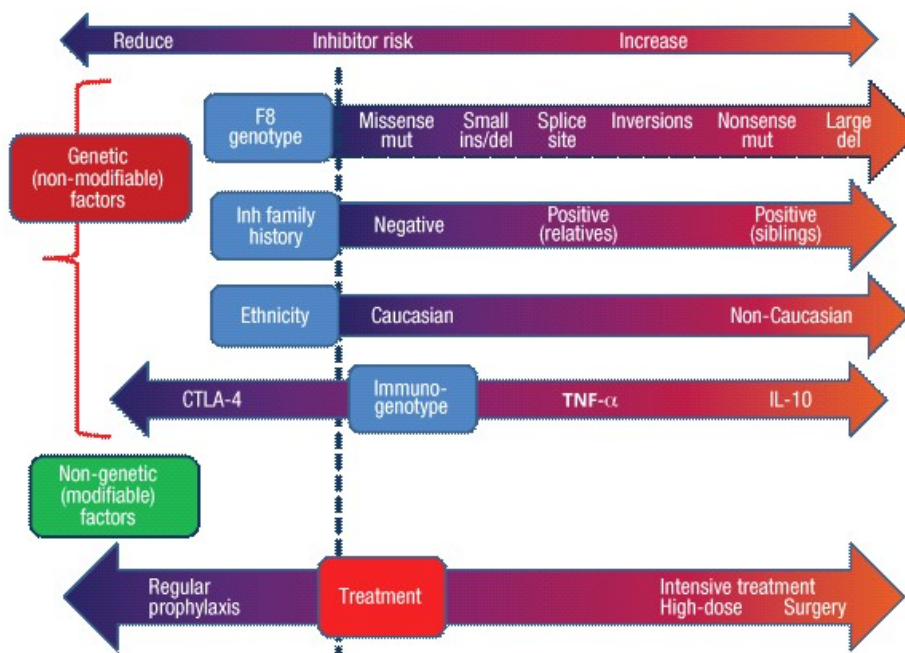


Figure 3

Protective or predisposing effects of genetic and non-genetic factors that may potentially influence the risk of inhibitor development.

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Inhibitor Prevention Strategies

Early prophylaxis is considered the optimal treatment modality for children with severe hemophilia and is recommended by the [National Hemophilia Foundation](#), the [World Federation of Hemophilia](#), and the [World Health Organization](#).¹² Prophylaxis is considered superior to on-demand treatment for the prevention of joint and other bleeding events and the preservation of joint function and the maintenance of quality of life,^{13,14} and has been associated with lower risk of inhibitor development versus on-demand treatment. Increasing attention is thus being paid to prophylaxis as a means of

Emerging data indicate that the avoidance of immunological “danger signals” during prophylaxis can reduce FVIII inhibitor development.³ Such danger signals include bleeding associated with tissue damage and immunological challenges like vaccination or infection.³ Emerging data suggest that the early start of low-dose escalating prophylaxis once weekly while minimizing the presence of danger signals during the first 20 exposure days may have the capacity to dramatically reduce the incidence of inhibitors, even in high-risk patients.³ Patients normally develop tolerance to FVIII after about 20 to 50 days on the low-dose regimen. Once this has occurred and venous access can be safely permitted, the normal 3 times weekly regimen can be instituted.³

Looking Ahead: Current Research Goals

The availability of less immunogenic factor replacements is a fundamental medical need in hemophilia care.¹ Such products would obviate the development of inhibitors and dramatically improve the quality of life for patients with hemophilia. Significant cost savings would also be realized. More potent, longer-acting drugs to reduce the number of infusions needed to treat acute bleeding and extend the time between prophylactic infusions would also dramatically change the face of hemophilia treatment. Obviously, no goal surpasses the development of unique hemostatic agents that could potentially cure FVIII or FIX deficiency. Generic/biosimilar drugs have the potential to reduce shortages and make treatment more accessible and affordable for everyone. Drugs requiring nonintravenous delivery systems would represent a major advance in hemophilia care and are eagerly anticipated. It is expected that several new agents will enter the market within the next 3 years. Novel agents for the treatment of hemophilia that are currently in Phase II clinical trials or beyond are listed in **Table 3**.¹

Compound	Company	http://www.clinicaltrials.gov	Structure	Indication	Stage of development	Mechanism of action	Study end points
PTC 124 (ataluren)	PTC Therapeutics	NCT00947193	Aminoglycoside-like compound	Hemophilia A or B	II	Selectively induces ribosomal read-through of premature termination codons	Safety/efficacy
IL-11	University of Pittsburgh	NCT00994929	rIL-11	Hemophilia A and vWD	II	Increased platelet vWF mRNA expression	Safety/efficacy
N8	Novo Nordisk	NCT00840086	rFVIII	Hemophilia A	III	FVIII replacement	Safety/efficacy
NN7128-1907	Novo Nordisk	NCT00951405	rFVIIa	Hemophilia A or B with inhibitors	II	Inhibitor bypassing	Safety/efficacy
IB-1001	Inspiration Biopharmaceuticals, Inc.	NCT00768287	rFIX	Hemophilia B	IV/III	FIX replacement	Safety, PK, efficacy
rFIXFc	Biogen Idec	NCT01027364	rFIXFc	Hemophilia B	II/III	Prolonged duration of FIX effect	PK, duration of effect

PTC 124 is a potential compound for the treatment of hemophilia A and B. It is a small molecule that selectively induces ribosomal read-through of premature termination codons. It is currently in Phase II clinical trials. It is expected that several new agents will enter the market within the next 3 years. Novel agents for the treatment of hemophilia that are currently in Phase II clinical trials or beyond are listed in Table 3.

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This initiative is supported by an educational grant from:



This initiative is jointly sponsored by:



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