Evolving Complexity in Hemophilia Management

Stacy E. Croteau, MD, MMS

KEYWORDS

• Bleeding • Hemarthrosis • Factor concentrate • Factor VIII • Factor IX • Inhibitors • Gene therapy • Bispecific antibody

KEY POINTS

- The goals of hemophilia care, long-term outcomes, and expectations for burden of therapy are changing.
- Use of factor concentrates should be tailored to the needs of the individual patient. Musculoskeletal health, physical activity level, bleed frequency, and adherence must be considered.
- Nonfactor therapies are an exciting frontier in hemophilia, but attention to safe use in conjunction with factor replacement and bypassing therapies and interactions with standard coagulation assays must be incorporated into planning.
- Gene therapy for both factor VIII and factor IX deficiency is beginning to emerge as a potential cure or at least significant modulator of disease severity.

INTRODUCTION

Rapid expansion of therapeutic options has increased the complexity of hemophilia care. Previously, on-demand therapy aimed to reduce morbidity and early mortality; however, early initiation of prophylaxis decreases morbidity and encourages an active lifestyle. The integrated hemophilia care model available to patients in the United States and many developed countries globally is key to quality hemophilia management; ensuring accurate diagnosis, recognition of early threats to musculoskeletal health, and optimization of therapy for both males and females affected by hemophilia. The diversity of emerging hemophilia therapies, from modified factor proteins, to gene therapy, to nonfactor hemostatic strategies, provides an exciting opportunity to target unmet needs. Considerations for how these therap alter hemostasis, coagulation

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Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA
E-mail address: stacy.croteau@childrens.harvard.edu

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monitoring, patient safety, and long-term outcomes for all subpopulations, inhibitor patients, noninhibitor patients, previously untreated patients, and patients with mild hemophilia, are critical for hemophilia providers today.

FUNDAMENTALS OF HEMOPHILIA A AND B

Epidemiology

Hemophilia A (factor VIII [FVIII] deficiency) and hemophilia B (factor IX [FIX] deficiency) have an estimated US prevalence of 25,000 individuals and more than 400,000 individuals worldwide. The incidence of each is estimated at 1 in 5000 and 1 in 30,000 male births, respectively. No racial or ethnic predilection has been observed in disease incidence; however, polymorphisms of *F8* and *F9* have ethnic variation.[1,2] Characterization of clinically significant hemophilia in females has not yet been well-described. Increasingly, the burden of bleeding symptoms and the impact on musculoskeletal health in women are being recognized.[3,4] Efforts such as the Annual Global Survey and the World Bleeding Disorders Registry aim to improve data capture on the prevalence and clinical care of hemophilia and other rare bleeding disorders worldwide.[5–7]

Genetics

Both *F8* and *F9* are located on the distal end of the long arm of the X chromosome, at Xq28 and Xq27, respectively. Point mutations are the most common of the more than 4000 pathogenic variants identified.[8,9] Deletions, insertions, and rearrangements/inversions also occur, leading to reduced or absent functional clotting protein.[2,8] The most common *F8* pathogenic variant in severe FVIII deficiency is an intrachromosomal inversion resulting from homologous recombination in male germ cells (maternal grandfather), which separates exons 1 through 22 from 23 to 26 by inversion of intron 22.[10,11] In contrast, the most common pathogenic variant in severe FIX deficiency is single nucleotide substitution. De novo mutations arise in approximately one-third of patients with severe hemophilia.

Pathophysiology

The absence or reduction of functional FVIII or FIX results in impaired thrombin generation and less stable fibrin clots. FVIII, a glycoprotein cofactor, and activated FIX, a serine protease, amplify the rate of factor X activation, yielding about a 50,000-fold increase in thrombin generation. FVIII circulates as a trace plasma protein with its carrier protein, von Willebrand factor. The noncovalent interaction between FVIII and von Willebrand factor seems to play an important role in modulating the clearance of FVIII as well as its immunogenicity.[12] FVIII and FIX deficiency are generally considered to produce the same clinical phenotype, because of their shared role in the tenase complex. Some data suggest that those with FIX deficiency may experience less severe or less frequent bleed events; this supposition remains controversial.[13]

Clinical Features

The hallmark clinical feature of FVIII and FIX deficiency is hemarthrosis, with ankles, knees, and elbows being most frequently affected. Abnormal or excessive bleeding can occur in any organ or tissue, particularly after trauma. Musculoskeletal bleeding is characteristic in hemophilia, but mucosal bleeding, and epistaxis in particular, is common.

A male infant with FVIII or FIX deficiency may present with postcircumcision bleeding, soft tissue/muscular bleeding, cephalohematoma, or intracranial hemorrhage owing to minimal birth trauma or subsequent head injury.[14] Mild factor deficiency may not come to clinical attention until school age or adulthood, at the time