INTRODUCTION

Hemophilia A and B are X-linked inherited bleeding disorders caused by deficiency of factor VIII (FVIII) or factor IX (FIX), respectively. One out of 5000 men are born with hemophilia A, whereas 1 out of 30,000 men are born with hemophilia B. Hemophilia A and B vary as to their severity; persons with severe hemophilia essentially produce no active FVIII or FIX (ie, factor activity levels <1% of normal), whereas persons with moderate or mild hemophilia have factor activity levels of 1% to 5% and greater than 5% to 40%, respectively.1 Bleeding is crudely proportional to baseline factor activity levels; accordingly, persons with severe hemophilia bleed considerably, whereas those with moderate hemophilia bleed less and those with mild hemophilia seldom bleed.

KEY POINTS

- Prophylaxis with factor replacement has been the mainstay of treatment for persons with hemophilia but may be challenged by several novel treatment options in development.
- Emicizumab has been recently approved for persons with hemophilia A and inhibitors and may dramatically alter the care of patients with inhibitors.
- “Rebalanced hemostasis” by inhibition of natural anticoagulants is a potential strategy for managing hemophilia that is currently under intensive research.
- Gene therapy for hemophilia A and B seems very promising and is likely to change hemophilia management drastically in the future.
Historical Perspective

Until the early 1960s, very little could be offered to persons with hemophilia: consequently, severe hemophilia was a devastating disease resulting in repeated musculoskeletal bleeding, causing not only terrible acute pain but, over time, leading to hemophilic arthropathy, chronic pain, and disability. Furthermore, persons with severe hemophilia would experience life-threatening or fatal bleeding, such as intracranial hemorrhage.

The management of hemophilia has focused on the intravenous replacement of the missing/reduced factor. Beginning in the 1960s, the availability of fresh frozen plasma, cryoprecipitate, and, later, lyophilized (powdered) factor concentrates began transforming the lives of patients. Lyophilized factor concentrates allowed persons with hemophilia to maintain concentrates in their homes and use them as needed.

Initially treatment was given simply to stop bleeding when bleeds occurred (on-demand therapy). Many centers gradually started recognizing that instead of waiting for bleeds to occur, it was better to prevent bleeds by giving frequent regular infusions of factor (prophylaxis), providing persons with hemophilia at least some circulating factor to reduce the likelihood of bleeding. With home prophylaxis, persons with hemophilia could treat themselves and live relatively free of bleeds. Several clinical trials have shown clear superiority of prophylactic treatment with FVIII or FXI for severe hemophilia, compared with on-demand replacement. Clearly the lives of persons with hemophilia were steadily improving throughout the 1970s. But some clinicians/researchers worried as to the safety of using factor concentrates that were not virally inactivated and were procured from thousands of mainly paid donors.

Tragedy struck in the late 1970s and early 1980s with the contamination of blood products with human immunodeficiency virus (HIV) and hepatitis B and C. Thousands of persons with hemophilia, along with their partners and children, were infected leading to shattered lives and tragic deaths. Researchers and pharmaceutical companies were driven to develop and implement effective viral inactivation technologies involving heat, solvent detergent, and/or nanofiltration. In addition, discovering the genes for FVIII and FIX became a priority, to create recombinant (synthetic) factor therapies. Over the next 20 years, factor concentrates became increasingly virally “safe” and prophylaxis continued to gain acceptance over on-demand therapy. However, there continues to be issues in the management of hemophilia, mainly due to the limitations of available plasma-derived and recombinant replacement therapies.

Limitations of Current Standard Replacement Therapies

Standard half-life (SHL) factor concentrates have many limitations, which the hemophilia community has traditionally tolerated in the absence of an adequate treatment alternative. With the advent of other therapies, these drawbacks are becoming increasingly unacceptable. Firstly, FVIII and FIX coagulation factors are only available intravenously and have had short half-lives of 8 to 12 hours and 16 to 24 hours, respectively. Thus, prophylactic therapy requires an intravenous infusion usually 3 to 4 times weekly for hemophilia A and 2 times weekly for hemophilia B, leading to a significant burden for persons with hemophilia and their families. The difficulties arising from the repeated intravenous treatments is such that adherence to therapy is far from ideal.

Secondly, even with such frequent intravenous infusions most people receiving SHL concentrates can only achieve factor trough levels of 1% to 3%. It has increasingly been recognized that these trough levels result in occasional clinical and subclinical bleeds, resulting in a slow, steady progression of joint disease over a lifetime.
A third limitation of SHL factor concentrates has been their very high price, which has made them unaffordable and consequently unavailable in many parts of the world. This fortunately is improving, as prices of SHL factor concentrates are dropping.

Finally, 25% to 40% of persons with severe hemophilia A, 10% in those with mild/moderate hemophilia A, and 5% of those with severe hemophilia B develop inhibitory antibodies to factor, thereby making factor replacement therapy ineffective. In patients with inhibitors, bleeds are currently managed with high doses of factor concentrates (for low-titer inhibitors) or with bypassing agents, including recombinant factor VIIa (rFVIIa; NovoSeven) or activated prothrombin complex concentrates (FEIBA).

In this article, the authors focus on new therapies for hemophilia (Tables 1 and 2) and how they may influence principles of hemophilia care. Given the limitation of any paper to describe in depth all the new therapies in development, this article instead focuses on how we envision these therapies potentially fitting into hemophilia care.

NOVEL THERAPIES

Extended Half-Life Replacement Factors

To reduce treatment burden and increase compliance, several extended half-life (EHL) products have been developed, using technologies that involve attaching long-lasting molecules (Fc, albumin, or polyethylene glycol [PEG]) to recombinant FVIII or FIX.

Table 1
Extended half-life products available and/or in development

<table>
<thead>
<tr>
<th>Product</th>
<th>Ref</th>
<th>Technology</th>
<th>Half-Life (h)</th>
<th>Cell Line</th>
<th>FDA Approval</th>
</tr>
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<tbody>
<tr>
<td>FVIII</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFVIII-Fc (Eloctate/Elocta)</td>
<td>44-47</td>
<td>Fusion protein of BDD rFVIII and the Fc fragment of IgG1</td>
<td>19</td>
<td>HEK</td>
<td>Jun 2014</td>
</tr>
<tr>
<td>BAX 855 (Adynovate/Adynovi)</td>
<td>48-50</td>
<td>Random PEGylation to parent drug Advate (full length rFVIII)</td>
<td>14–16</td>
<td>CHO</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>BAY94–9027 (Jivi)</td>
<td>51-54</td>
<td>Site-specific addition of PEG side chain to a BDD rFVIII</td>
<td>19</td>
<td>CHO</td>
<td>Aug 2018</td>
</tr>
<tr>
<td>N8-GP</td>
<td>55,56</td>
<td>Site-specific glycoPEGylation of BD-modified FVIII</td>
<td>19</td>
<td>CHO</td>
<td>NA</td>
</tr>
<tr>
<td>BIVV001</td>
<td>57</td>
<td>Fusion protein with addition of a region of VWF and XTEN polypeptides</td>
<td>37</td>
<td>HEK</td>
<td>NA</td>
</tr>
<tr>
<td>FIX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFIX-Fc (Alprolix)</td>
<td>11,58,59</td>
<td>Fusion protein with the Fc fragment of IgG1</td>
<td>82</td>
<td>HEK</td>
<td>Mar 2014</td>
</tr>
<tr>
<td>rFIX-FP (Idelvion)</td>
<td>10,60</td>
<td>Fusion protein with recombinant albumin</td>
<td>102</td>
<td>CHO</td>
<td>Mar 2016</td>
</tr>
<tr>
<td>N9-GP (Rebinyn/Refixia)</td>
<td>9,61</td>
<td>Site-specific glycoPEGylation</td>
<td>93</td>
<td>CHO</td>
<td>May 2017</td>
</tr>
</tbody>
</table>

Abbreviations: BD, B-domain; BDD, B-domain deleted; CHO, Chinese Hamster Ovary; FDA, Food and Drug Administration; FIX, factor IX; FVIII, factor VIII; h, hours; HEK, human embryonic kidney; NA, not available; PEG, polyethylene glycol; rFVIII, recombinant factor VIII; VWF, von Willebrand factor.
EXTENDED HALF-LIFE FACTOR VIII FOR HEMOPHILIA A

EHL FVIIIs currently available or in development are shown in Table 1. Adequate control of bleeding has been seen with all EHL factors currently available. However, the half-life of the current EHL FVIIIs is only 1.4- to 1.6-fold higher compared with SHL FVIIIs; thus, most patients will need greater than 1 dose/week for effective prophylaxis. The modest extension of half-life is due to the binding of EHL FVIIIs to endogenous von Willebrand factor (VWF), which results in EHL FVIIIs still being subject to the clearance of VWF. This binding to VWF creates a “ceiling effect” for prolonging the half-life of FVIII. Despite the marginal improvement in half-life, there are increasing reports showing that EHL FVIIIs improve the quality of life (QOL) of persons with hemophilia and compliance to treatment by reducing the number of infusions. Clinical trials have not raised substantial safety concern of EHL FVIIIs.

A recombinant FVIII is in development, which avoids attachment to VWF by covering the FVIII binding site to VWF with a recombinant D′-D3 molecule. This D′-D3-FVIII is...
then attached to 2 Fc molecules and 2 XTEN polypeptides (protein polymers designed to increase the half-life of other proteins conjugated to them). Preliminary results showed that this modified molecule exhibits a much longer half-life (37h), resulting in a median FVIII trough level of 5% with once weekly dosing.²

EXTENDED HALF-LIFE FACTOR IX FOR HEMOPHILIA B

Three EHL FIXs are currently commercially available (see Table 1). Unlike EHL FVIIIs, which all achieve similar half-life extension, EHL FIXs show significant variability in pharmacokinetic parameters. Both rFIXFP (Idelvion) and N9-GP (Rebinyn/Refixia) show substantially longer half-lives than rFIXFc (Alprolix), whereas N9-GP additionally shows a much higher recovery (ie, “peak” level following an infusion) than the others.

All 3 products allow for once weekly dosing in most patients with few or no bleeds reported; rFIXFP and N9-GP additionally allow for once every 2-week dosing while still maintaining protective FIX trough levels after 2 weeks. When given once per week, both rFIXFP and N9-GP (but not rFIXFc) can lead to FIX trough levels greater than 20% and in the case of N9-GP greater than 30% in many adults. All products have shown acceptable safety profiles in phase 3 clinical trials in previously treated patients.⁹–¹¹

EHL factor concentrates, however, still carry some of the limitations of SHL concentrates; they are given intravenously, can lead to inhibitor development (the current literature does not allow to determine if the incidence of inhibitors with EHL factor concentrates will be more, less, or the same compared with SHL factor concentrates), and do not benefit persons with hemophilia and inhibitors. In addition, some of these products are more difficult to monitor using conventional laboratory assays such as the one-stage clotting assay.¹²,¹³ Consequently, there is still room for improvement for hemophilia treatment.

FACTOR VIII REPLACEMENT PRODUCTS

Emicizumab (licenced as Hemlibra) is a humanized monoclonal antibody that mimics the cofactor activity of FVIII. Much like FVIII, emicizumab binds to both activated FIX and FX, leading to a significant acceleration of FIXa-mediated FX activation and ultimately to increased thrombin generation.¹⁴ A series of clinical studies, the HAVEN trials, have been conducted in adults and children with or without inhibitors. These studies have shown substantial reductions in bleeding rates and improvement of health-related QOL.¹⁵–¹⁷

Obvious advantages of emicizumab are that it can be given subcutaneously and infrequently (weekly to potentially monthly). Moreover, emicizumab can be used in persons with inhibitors, offering such individuals for the first time a convenient and effective prophylactic option. Furthermore, emicizumab achieves steady state levels without the constant peak and troughs associated with factor replacement. It has been conjectured that at regular maintenance doses (1.5 mg/kg/wk), emicizumab provides similar hemostatic protection to a constant FVIII level of around 10% to 15%.¹⁶ Such levels should be adequate to prevent most spontaneous bleeding and many minor trauma-induced bleeds, although they are likely insufficient to prevent bleeding in the setting of major trauma or surgery.

Concern has arisen when patients on emicizumab experience bleeds and require additional treatment with FVIII or bypassing agents (rFVIIa or FEIBA). As described by Lenting and colleagues,¹⁸ emicizumab does not function exactly like FVIII and its activity is not subject to the same degree of self-regulation. Several cases of thrombotic microangiopathy, thrombosis, and death have occurred in patients on emicizumab.
receiving repeated, high doses of FEIBA (>100 U/kg/d for >1 day). The hypothesis is that FEIBA provides large doses of substrate (FIXa and FX) for emicizumab, leading to a massive synergistic effect on increasing thrombin generation. In vitro experiments showed that an analogue of emicizumab, combined with FEIBA, led to a 17-fold increase in thrombin generation, well above the normal physiologic range. It is now recommended not to administer FEIBA to persons treated with emicizumab unless absolutely indicated and only in an inpatient setting. In contrast, rFVIIa or FVIII when given with emicizumab (in presence or absence of inhibitors, respectively), do not seem to create a huge synergistic burst in thrombin formation and thus seem safer.

**Inhibitors of Natural Anticoagulants**

Coagulation represents a balance between procoagulants and anticoagulants. Factor concentrates and emicizumab aim to replace the missing/reduced procoagulant (FVIII or FIX). Of late, much research has gone toward improving clotting by instead reducing anticoagulants in an attempt to offset the procoagulant deficiency and rebalance coagulation (Fig. 1). There are analogies in nature in which persons with hemophilia...
and co-inherited thrombophilic traits, such as Factor V Leiden, prothrombin gene mutation, or deficiencies in antithrombin, protein C, or S, have milder bleeding phenotypes.  

**Downregulation of antithrombin**

Antithrombin is an endogenous anticoagulant that inhibits thrombin, FX and, to a lesser degree, other procoagulant factors. Fitusiran is a small interfering RNA (siRNA) that silences posttranscriptional hepatic expression of the SERPINC1 gene, thereby reducing antithrombin levels in a dose-dependent manner. Fitusiran, when given as a subcutaneous once-weekly or once-monthly infusion to either healthy volunteers or persons with hemophilia A or B, has been shown to reduce antithrombin levels to 70% to 80% of normal, which results in persons with hemophilia achieving thrombin generation values comparable to that observed in healthy individuals without hemophilia. Early studies were very encouraging; however, studies were placed on hold when a fatal cerebral thrombosis occurred in a patient who, on fitusiran, had received therapeutic doses of FVIII concentrates for a musculoskeletal bleed. Much like persons with hemophilia on emicizumab who are given FEIBA, when persons receiving fitusiran experience breakthrough bleeds and are given a prothrombotic agent such as FVIII, they may become excessively prothrombotic. The study was reopened after institution of a plan to use significantly lower doses of prothrombotic agents (FVIII and/or bypassing agents) to manage breakthrough bleeds. Several phase 3 clinical trials are underway, in persons with severe hemophilia with and without inhibitors, to further assess the efficacy and safety of fitusiran.

**Inhibition of tissue factor pathway inhibitor**

Tissue factor pathway inhibitor (TFPI) inhibits the initiation pathway of coagulation through inhibition of FVIIa by its K (Kunitz) 1 domain and inhibition of FXa via its K2 domain. Various companies have been developing different agents that inhibit TFPI. Concizumab is a humanized monoclonal antibody targeting the TFPI binding site for FXa. In a phase 1 study in healthy volunteers and persons with hemophilia, Concizumab led to a concentration-dependent reduction in the residual level of TFPI and was generally well tolerated. Phase 2 clinical trials are underway in persons with hemophilia with or without inhibitors. Other anti-TFPI monoclonal antibodies are currently under investigation. As with emicizumab and fitusiran, TFPI inhibitors can be given subcutaneously. Like other rebalancing agents, the concern of potential thrombotic complications remains when persons with hemophilia on an anti-TFPI receive additional procoagulant therapy in the setting of a bleed or surgery.

**Others (inhibition of activated protein C or protein S)**

Activated protein C (APC) inhibits FVa and thus is an additional target to reduce endogenous anticoagulant activity. Several strategies are being investigated to block APC, including aptamers and mutated α-1-antitrypsin, thereby promoting thrombin generation. Similarly, preliminary investigation is occurring in targeting protein S as a way of rebalancing coagulation. These compounds are in early preclinical stages of development.

**Gene Therapy**

Nearly two decades after the first reports of gene therapy, several successful phase 1/2 gene therapy trials have recently been published. Most have used liver-specific tropic adenovirus-associated virus (AAV) as viral vectors to deliver the missing/faulty gene to liver hepatocytes. AAV viruses are thought to be non-pathogenic and do not integrate
into the human genome (or if so, to a minimal degree), thus carrying a low theoretic risk of insertional mutagenesis compared with other viral vectors.

In hemophilia B, successful gene transfers have been reported with single infusions of both wild-type FIX and Padua FIX. The latter is a naturally occurring gain-of-function mutation (R338L), which increases the activity of FIX by 5 to 10 fold. The Padua FIX gene allows for a reduced vector dose, which may translate into reduced immune cellular response to the viral capsid. Long-term steady state FIX levels of between 1% and 7% have been obtained with wild-type FIX, whereas levels between 14% and 81% have been obtained using the Padua FIX. Consequently, after gene therapy, these individuals have FIX levels in the normal or mild hemophilia range with significant reductions in annualized bleeding rates (ABRs) and factor consumption.

Before wide implementation of gene therapy, several questions remain. Firstly, all trials have enrolled persons with hemophilia without preexisting antibodies to AAV. However, it is estimated that approximately 30% of the population carry antibodies to AAV. These antibodies can also develop following gene therapy raising potential difficulties in children who may require additional future gene therapy due to the inability of AAV to integrate into the genome of dividing hepatocytes. Secondly, the efficacy and safety of gene therapy in persons with liver disease, including hepatitis C, who until now have been excluded from gene therapy trials, remains unknown. Thirdly, elevation of liver enzymes has been witnessed with infusion of high doses of AAV, usually within the first 12 weeks following infusion; this is probably related to dose-dependent cellular immunity to the viral capsid. Although not harmful to the individual, antcapsid cellular immunity has been associated with reduced FIX expression and thus mandates quick institution of immunomodulation, which may be associated with additional morbidity.

Gene therapy in hemophilia A carries several specific challenges. First, FVIII (even in its B-domain deleted form) is a large molecule, making it difficult to be packaged within a viral genome. Also, for reasons that remain unclear, in vivo protein expression and secretion of FVIII is less efficient than FIX. Finally, FVIII is quite immunogenic and the risk of inhibitor development following gene therapy remains unknown. Nonetheless, early results of FVIII gene therapy trials are also promising: one trial has shown FVIII activity levels of 19% to 164% 52 weeks following a single gene therapy infusion.

An alternate curative approach for hemophilia is gene editing to replace the mutant FVIII or FIX gene. This approach minimizes the risk of insertional mutagenesis. Preclinical trials with designer zinc finger nucleases, CRISP/Cas9, and nuclease-free targeting approach are underway.

**PRINCIPLES OF HEMOPHILIA TREATMENT**

Over the past 50 years, several key principles of care have been established: persons with hemophilia should be offered a treatment that is

1. Safe;
2. Timely;
3. Available at home;
4. Oriented toward prevention of bleeds;
5. Individualized; and
6. Focused on clinically relevant outcomes.

Finally, inhibitor development should be avoided, and inhibitors should be eradicated whenever possible. Although most of these principles will continue because...
new therapies are incorporated into practice, the paradigm may change for some of them.

**Safety of Treatments**

Since the hepatitis C and HIV tragedies, safety has become the main priority of persons with hemophilia and clinicians. Although contemporary products are considered safe for transmission of known viral pathogens, there remains a theoretic risk of transmission of unknown pathogens, in particular prions, such as variant Creutzfeldt-Jakob disease. Thus, there is a keen interest to avoid plasma-derived products. However, the consequences of manipulating recombinant products remain a concern, especially for inhibitor development. In addition, in altering the procoagulant-anticoagulant pendulum, many new therapies may lead to an increased risk of thrombosis. It is crucial for clinicians to remain vigilant of possible side effects (both expected and unexpected) of new therapies.

**Rapid Treatment of Bleeds**

A key principle of hemophilia management has been immediate treatment of a bleed to rapidly halt bleeding. This “treat first and fast” approach when there is any suspicion of a bleed has worked well until now. With factor replacement strategies, there is a significant margin of safety in that inadvertent factor overdose almost never results in harm. However, with future therapies there may be reason to alter this approach. This seems particularly true with inhibitors of natural anticoagulants, because the concurrent infusion of procoagulant agents (FVIII/FIX or bypassing agents) may transiently be associated with a prothrombotic state.

**Home Care**

In the 1960s, it was recognized that to accomplish immediate treatment of bleeds and, later, to allow persons with hemophilia to be on prophylaxis, treatment needed to be administered at home, ideally by the persons with hemophilia themselves or their families or, if that was not possible, through visiting nurses. Thus, a large part of any hemophilia management program has been to empower persons with hemophilia and their families, so that they can administer treatment at home.

Subcutaneous treatments are very appealing for prophylactic therapy. However, subcutaneous therapies do not lend themselves to rapid treatment of bleeds and consequently persons with hemophilia will still need occasional intravenous infusions. It is unclear if individuals will still be able to acquire and retain the ability to self-infuse intravenous therapies if they primarily use subcutaneous therapies.

**Prevention of Bleeds**

The current standard of care for severe hemophilia in most industrialized countries is regular prophylactic infusion of FVIII or FIX to prevent hemorrhage and hemophilic arthropathy. Yet because of the limitations of available treatments, prophylaxis has not been easy or as effective as desired and certainly has not been widely adopted in low- to middle-income countries. Newer therapies, both those administered subcutaneously as well as gene therapy, will substantially increase the bleed protection traditionally offered through FVIII or FIX trough levels of 1% to 3%.

**Interindividual Heterogeneity of Hemophilia**

Despite the generally accepted fact that bleeding is proportional to factor levels in hemophilia A and B, there is significant interindividual variability in bleeding phenotype and response to treatment, even between persons with comparable factor levels.
This variability is likely attributed to particular differences between persons with hemophilia (Box 1). Given these differences, individualization of prophylaxis has become a major focus of hemophilia care. Until now, individualization of hemophilia care has simply revolved around interpatient pharmacokinetic differences in how they use the same type of therapy—factor concentrates. In the future, individualization of therapy is likely to additionally involve interindividual differences in the type of therapy (eg, EHL factor replacement vs FVIII-mimetic agent vs rebalancing agent) from which an individual would most benefit. This is likely to increase the complexity of hemophilia care.

**Focus on Outcomes**

Currently, the efficacy of most hemostatic products is assessed using the ABR. This short-term outcome is fraught with limitations, in that it is very subjective and, as such, error prone. Furthermore, current therapies already achieve very low ABRs limiting the comparative value of the ABR to evaluate newer therapies. In addition, arthropathy can develop without clinically evident joint bleeds, and consequently, low ABRs do not necessarily translate into the absence of hemophilic arthropathy, adequate functioning, and good QOL.

New indicators of treatment efficacy are therefore needed; these need to be clinically relevant, integrate patient-reported outcomes and economic evaluations. Moreover, long-term outcomes will be of utmost importance, especially with newer therapies that may be associated with long-term complications.

**Inhibitor Management**

Inhibitors are the most common complication of hemophilia and should be suspected in all patients who do not respond as expected to treatment. Several patient, disease, and treatment-related risk factors for the development of inhibitors have been reported (Table 3). Although research has led to a greater understanding of what triggers inhibitor development, there have been no effective strategies to reduce the incidence of inhibitors within clinical practice. Inhibitor development leads to two broad issues: (1) management and prevention of bleeds and (2) eradication of the inhibitor.

Although effective in treating bleeds, currently available bypassing agents (rFVIIa and FEIBA) are inconvenient, and neither is an ideal prophylactic agent. Given the high morbidity, significant cost, and inconvenience of having an inhibitor, eradication through immune tolerance induction (ITI) is currently the goal when persons with hemophilia develop an inhibitor. In ITI, frequent doses of factor are administrated to

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**Box 1**

**Sources of interpatient variability in hemophilia phenotype**

- Underlying hemophilia mutations, leading to slight differences in factor levels
- Levels of other prothrombotic (eg, fibrinogen, thrombin, FV, FVII, FXI, etc.) and anticoagulant (antithrombin, protein C, protein S, TFPI) factors
- Blood group and other variables that affect clearance of infused FVIII/FIX
- Joint structure
- Levels and patterns of activity

*Abbreviations:* FV, factor V; FVII, factor VII; FVIII, factor VIII; FIX, factor IX; FXI, factor XI; TFPI, tissue factor pathway inhibitor.
gradually render a person’s immune system tolerant of factor. ITI usually requires several months of intensive treatment and is associated with high costs and burden of care for persons with hemophilia who tend to be very young children. Despite over 40 years of experience with ITI, the hemophilia community has still not resolved many important questions, including when to start ITI and whether ITI should be commenced immediately when a high titer inhibitor is detected or delayed until the inhibitor titer has fallen to a certain level. Other unresolved questions pertaining to ITI include when to discontinue when persons do not seem to respond; what is the ideal ITI regimen; and which is the type of factor to use. Overall, ITI is effective in 60% to 80% of cases. Why ITI is ultimately successful or not is unknown, although certain predictors of success include younger patient age, lower historical inhibitor titer (<200 Bethesda Units [BU]) and lower inhibitor titer pre-ITI (<10 BU), lower inhibitor peak titters on ITI, and low-risk FVIII mutations.

Emicizumab will almost certainly have a valuable role in the management of persons with hemophilia and inhibitors. Emicizumab will likely replace traditional bypassing agents for prophylaxis, but bypassing agents will likely still be needed for episodic treatment of bleeding. However, many questions remain regarding the adoption of emicizumab. Should one or more courses of ITI still be attempted? If so, should immunosuppressive therapies still be attempted for those who fail a first course of ITI? Will ITI regimens change with incorporation of emicizumab into inhibitor management? Can individuals stay on emicizumab exclusively following successful ITI or must they be maintained on some regular exposure to FVIII to maintain tolerance?

In addition to emicizumab, novel methods, several in the preclinical stage, are being studied to improve inhibitor eradication and care of persons with hemophilia and inhibitors. These methods have been recently reviewed elsewhere.

### SUMMARY

The future is promising for persons with hemophilia with the advent of so many new therapies. Clinicians caring for these individuals face a daunting future of how they will manage persons with hemophilia, with such an array of potential therapies. For now, it should be made clear to patients that treatment is changing, becoming more effective, and convenient. With gene therapy, many individuals with severe hemophilia will likely be cured of hemophilia or have factor levels in the mild hemophilia range. The authors envision a future in which joint disease from recurrent bleeds in persons with hemophilia will be incredibly rare. In anticipation of such a future, persons with hemophilia should be encouraged to prevent bleeds and their complication, recognizing that future therapies will be much more effective but are unlikely to reverse prior damage.

### Table 3

<table>
<thead>
<tr>
<th>Type of Risk Factors</th>
<th>Elements Associated with Higher Incidence of Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Nonmodifiable risk factors</td>
<td>• Causative mutations, especially null mutations&lt;br&gt;• Positive family history of inhibitors&lt;br&gt;• Ethnicity—higher incidence in people of African-American or Hispanic descent&lt;br&gt;• Polymorphisms in certain immune response genes</td>
</tr>
<tr>
<td>Treatment-related and environmental risk factors</td>
<td>• Type of factor concentrates&lt;br&gt;• Context of factor exposure—on-demand vs prophylaxis&lt;br&gt;• Intense exposure to factor concentrates at an early age</td>
</tr>
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