Management of Inhibitors in Patients with Hemophilia A

Information for Healthcare Professionals

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Key to Abbreviations

- aPCC: Activated Prothrombin Complex Concentrate
- aPTT: Activated Partial Thromboplastin Time
- BU: Bethesda Units
- CVAD: Central Venous Access Device
- DIC: Disseminated Intravascular Coagulation
- FVIII: Factor VIII
- FVIII:C: Factor VIII Coagulation Activity
- FX: Factor X
- HTC: Hemophilia Treatment Center
- ITI: Immune Tolerance Induction
- pdFVIII: Plasma-Derived Factor VIII
- PUP: Previously Untreated Patient
- rFVIIa: Recombinant Activated Factor VII
- rFVIII: Recombinant Factor VIII
- VWF: Von Willebrand Factor

Glossary

- Anamnesis: A marked rise in the inhibitor titer in response to FVIII exposure
- Low-Titer Inhibitor: Inhibitor levels ≤5 BU
- High-Titer Inhibitor: Inhibitor levels >5 BU
- Low-Responding Inhibitor: An inhibitor that does not rise above 5 BU despite immunologic challenge with FVIII; may be transient
- High-Responding Inhibitor: Inhibitor that displays anamnesis within a few days after FVIII exposure; over time, inhibitor may become low-titer/high-responding, but high-responder status is persistent
Introduction

The development of inhibitors that bind to active sites on the factor VIII (FVIII) molecule and neutralize its function is the most serious adverse event associated with the treatment of hemophilia A. An estimated 22% to 52% of patients with severe hemophilia (baseline FVIII <1%) and 3% to 13% of individuals with mild or moderate hemophilia develop these IgG antibodies, typically within the first 10 to 20 exposure days to FVIII replacement concentrates. The presence of an inhibitor does not increase bleeding frequency, but it makes the treatment of bleeding episodes more difficult. Consequently, patients with inhibitors are at increased risk of uncontrollable hemorrhage, disability (especially due to arthropathy), and premature death.
A variety of genetic factors are implicated in the development of inhibitors. As discussed, inhibitors are more common in patients with severe hemophilia, and this may be due, at least in part, to the presence of mutations in the FVIII gene. The severe hemophilia phenotype often is associated with large gene defects (ie, inversions, insertions, deletions) in multiple domains that lead to a total failure of endogenous FVIII protein synthesis. When FVIII replacement is administered, it is immediately recognized as a foreign protein by the immune system, thereby triggering an anti-FVIII immune response. Other genetic risk factors include a family history of inhibitors, which is linked to a 3-fold increased risk of inhibitor development, and African heritage, which doubles this risk.

Environmental factors also increase the likelihood of inhibitors. Risk may be higher in infants less than 6 months of age who are exposed to FVIII and among patients who receive high-dose or continuous FVIII infusions over a number of days—perioperatively, for example. In addition, immunologic, inflammatory, and/or infectious events—such as vaccination, surgery (eg, for central line placement), or bacterial or viral illness—may stimulate the immune system to produce inhibitors. Accumulating evidence suggests that recombinant FVIII (rFVIII) concentrates may be another contributor to inhibitor development. Goudemand et al analyzed data from 62 previously untreated patients (PUPs) with severe hemophilia who were administered the same brand of high-purity plasma-derived FVIII (pdFVIII) containing von Willebrand factor (VWF) and 86 PUPs treated with full-length rFVIII. The researchers found the risk of inhibitor development was substantially higher (adjusted relative risk 2.4 to 3.2) in patients treated with rFVIII compared with those given pd FVIII, regardless of other risk factors (Table 1).

### Genetic and Environmental Factors Associated with the Development of Inhibitors

<table>
<thead>
<tr>
<th>Genetic Factors</th>
<th>Environmental Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of hemophilia</td>
<td>Young age (&lt;6 months) at first exposure to FVIII*</td>
</tr>
<tr>
<td>FVIII gene mutation (eg, inversions, insertions,</td>
<td>Intensive FVIII treatment (high-dose of continuous</td>
</tr>
<tr>
<td>deletions)</td>
<td>infusions over several days)</td>
</tr>
<tr>
<td>Family history of inhibitors (3-fold increased risk)</td>
<td>Immunologic/inflammatory/infectious events (ie, vaccination,</td>
</tr>
<tr>
<td></td>
<td>surgery, illness)</td>
</tr>
<tr>
<td>Race/ethnicity (2-fold increased risk of inhibitors</td>
<td>Use of rFVIII products*</td>
</tr>
<tr>
<td>among patients of African descent)</td>
<td></td>
</tr>
</tbody>
</table>

*May increase risk, although further research is needed for confirmation.

Table 1
Clinical Presentation and Laboratory Diagnosis

FVIII inhibitors often are diagnosed on routine surveillance in the absence of symptoms. However, clinicians should suspect the presence of an inhibitor when a bleeding event is not promptly controlled by a patient's usual dose of clotting factor concentrate, or when a patient on FVIII prophylaxis experiences increased breakthrough bleeding.1

The activated partial thromboplastin time (aPTT) is the most common screening test used to detect inhibitors. 1 When an inhibitor is present, the aPTT after incubation (1 to 2 hours at 37°C) is prolonged and cannot be corrected by mixing patient plasma with normal plasma (mixing study). Measurement of FVIII in vivo recovery and half-life, performed 1-hour after a bolus infusion of FVIII, is more sensitive than the aPTT to traces of inhibitor.

Inhibitors are quantified with the Bethesda assay, in which normal pooled plasma (used as a source of FVIII) is incubated with undiluted patient plasma for 2 hours at 37°C and then assayed for residual FVIII. 1 Titers are expressed in Bethesda units (BU). One BU is the amount of inhibitor needed to inactivate 50% of FVIII in pooled normal plasma after the incubation period. In situations where the Bethesda assay yields inconclusive results, a more sensitive modification of this test may be helpful. The Nijmegen assay, which was introduced in 1995, now is in widespread use. The control consists of normal plasma incubated with FVIII-deficient plasma rather than with buffer, and the normal plasma used in the incubation mixture is buffered with imidazole to a pH of 7.4.19
Classification of Inhibitors

Inhibitors are classified as low- or high-titer. Low-titer inhibitors measure 5 BU or less. High-titer inhibitors exceed 5 BU and may surpass 1000 BU or even higher in some patients.

Inhibitors are further categorized as low- or high-responding. Low-responding inhibitors are not anamnestic—that is, they do not rise markedly following exposure to FVIII, and they often are transient. In contrast, high-responding inhibitors are anamnestic and exhibit a sharp rise in antibody titer within 4 to 6 days of FVIII exposure. (Figure 1) High-responding inhibitors are persistent and account for 70% of all inhibitors.

Management of FVIII Inhibitors

Low titer inhibitors (≤5 BU) usually can be overcome with large doses of FVIII replacement concentrate. High-titer inhibitors, on the other hand, generally render factor replacement therapy ineffective and require the use of alternative means of hemostatic support, primarily bypassing agents.

Bypassing Therapy

Two bypassing products are in current use: activated prothrombin complex concentrate (aPCC) and recombinant activated factor VII (rFVIIa). aPCC contains factors II, VII, IX, X, and trace amounts of FVIII. It acts at several sites in the coagulation cascade and induces thrombin generation by direct activation of factor X (FX), which is required for the formation of a fibrin clot. The recommended dose of aPCC is 50-100 IU/kg every 8 to 12 hours, not exceeding 200 IU/kg daily to prevent thrombotic events. rFVIIa likely induces hemostasis by forming a complex with tissue factor and enhancing FX activation on platelet surfaces, thus generating thrombin without the need for FVIII. The optimal dose of rFVIIa is unclear. Standard doses range from 90-120 µg/kg every 2 to 3 hours, but doses up to 3 times standard have been used and reported effective.

Both bypassing agents successfully control at least 80% of bleeding episodes, including perioperative bleeding, in patients with high-titer inhibitors. Sequential therapy using alternating doses of aPCC and rFVIIa may be considered for very serious bleeding events that are not controlled by either agent used alone. The combination of both products may have a synergistic effect. However, both fatal and nonfatal thrombotic events have been reported in patients treated with sequential therapy. Because of the risks and uncertainties, it is strongly recommended that combination therapy with aPCC and rFVIIa be reserved for severe, acute, refractory bleeding; provided only a trained hemophilia treatment center (HTC) by clinicians with expertise in coagulation disorders; and monitored with frequent clinical and laboratory screening to quickly detect thrombosis or disseminated intravascular coagulation (DIC).
Supportive Adjunctive Therapy

Several supportive adjunctive therapies are helpful in managing bleeding events in patients with inhibitors. Plasmapheresis with or without extracorporeal immunoadsorption is used to temporarily decrease high circulating antibody levels. Treatment must be followed immediately with FVIII replacement (100-200 IU/kg) to achieve hemostasis. Plasmapheresis and immunoadsorption, although not always practical for the management of severe acute bleeds, are often useful for patients undergoing elective surgery. These techniques require specialized equipment and training, however, and are not readily available to most physicians.

Other adjunctive therapies include:

- Rest, immobilization, local pressure, cold applications, analgesics (avoiding aspirin and aspirin-containing medications)
- Topical hemostatic agents (eg, thrombin, fibrin sealants, gelatin sponges, microfibrillar collagen)
- Antifibrinolytic agents (ie, aminocaproic acid, tranexamic acid)
  - Particularly helpful in managing mucosal bleeding
  - Contraindicated in DIC and hematuria
  - Relatively contraindicated in patients who have received aPCC in previous 12 hours

Limitations of Current Therapies

Despite the efficacy of aPCC and rFVIIa, the use of bypassing agents to manage bleeding episodes in patients with high-titer inhibitors has several limitations. First, there is no method for monitoring therapy, as there is with FVIII (ie, FVIII recovery and half-life). This lack of an effective assay can lead to prolongation of bypassing therapy before the need to adjust dosage and/or employ other agents is recognized. Second, both aPCC and rFVIIa have a higher potential for thrombosis than does FVIII. Although the risk is low with either bypassing agent, the thrombogenicity of these products is well-recognized, and adverse thromboembolic events are increasingly being reported for rFVIIa used to stop bleeding both in patients with hemophilia and for off-label indications. Another disadvantage of bypassing products is their cost, which is considerably higher than FVIII replacement concentrates. The shorter half-life of rFVIIa (2 to 3 hours) makes it especially expensive, particularly in pediatric patients, who have significantly faster clearance rates than adults and require more frequent dosing.

The most worrisome drawback to bypassing therapy, however, is that it cannot reliably achieve hemostasis. Neither aPCC nor rFVIIa is as predictably effective in controlling bleeding in inhibitor patients as FVIII is in noninhibitor or low-titer inhibitor patients, and it often becomes necessary to switch products during the course of a single bleeding event. As a result, patients with high-titer, high-responding inhibitors are at increased risk for life- or limb-threatening bleeding episodes and developing devastating joint disease. Because of these therapeutic limitations, immune tolerance induction (ITI) is usually attempted in patients with new-onset, high-responding inhibitors.
The goal of ITI is to eradicate inhibitor production, thus restoring normal replacement FVIII kinetics and, possibly, improving quality of life and increasing life expectancy. All ITI protocols involve ongoing frequent exposure to FVIII, and in young children, difficulties with venous access may require placement of a central venous access device (CVAD). Complications associated with CVADs include repeated infection and thrombosis, both of which may impede the ultimate success of ITI.

**ITI Protocols**

**Bonn Protocol (High-dose).** The Bonn protocol, described by Brackmann and Gormsen in 1977, was the first ITI regimen. In the original protocol, patients with high-responding inhibitors received FVIII 100-150 IU/kg every 12 hours as well as aPCC 50-100 IU/kg every 12 hours until their inhibitor titers fell below 1 BU. The current Bonn regimen omits aPCC except in patients with a high bleeding tendency.

The Bonn protocol is intensive for patients and families and extremely costly due to high FVIII consumption. As a result, it is uncommonly used in the United States.

**van Creveld/Dutch Protocol (Low-dose).** The low-dose van Creveld or Dutch protocol calls for FVIII 25 IU/kg every other day. Dosage is decreased each time absolute FVIII recovery exceeds 30%, with these reductions continuing until a prophylactic dose of 10-15 IU/kg every other day is reached. The Dutch protocol is considerably less demanding for patients and families than the Bonn regimen and also is more economical.

**Malmö Protocol.** The Malmö protocol combines an intensive high-dose FVIII regimen (Bonn protocol) with prior elimination of FVIII antibodies through extracorporeal immunoabsorption accompanied by immunosuppression with cyclophosphamide or azathioprine and followed by intravenous gammaglobulin replacement. The Malmö regimen requires hospitalization, but it may allow ITI to be quickly completed, potentially resulting in cost savings.

Various intermediate-dose protocols — FVIII <200 IU/kg daily with or without immunosuppressive therapy — have been developed at and are used by individual HTCs worldwide.
Success Rates
Ultimately, 55% to 78% of patients respond to ITI within several months to 4 years, according to the results from 2 large ITI registries. Although the definition for success varies, it often is described as:

- A negative inhibitor titer (≤1 BU)
- Normal FVIII recovery (≥70% predicted)
- Normal FVIII half-life/survival (≥12 hours)
- Conversion from high- to low-responder status

Several factors are thought to be predictive of ITI success or failure, including age at inhibitor diagnosis, historical maximum inhibitor titer, titer at the initiation of ITI, peak titer during ITI, and whether treatment was interrupted and/or infections developed during ITI (Table 2).30,49,62-66

Cost Considerations
Regardless of the protocol used, ITI is an expensive undertaking, easily approaching $1 million for the average 5-year-old. Given the morbidity and high cost of less effective bypassing therapy, however, health economists at Harvard Medical School found ITI actually is cost-effective in the long-term. Colowick et al estimated that the total lifetime costs for ITI were approximately $1.7 million less than those associated with lifelong aPCC therapy. These savings would be even greater if more costly rFVIIa was used as a bypassing agent. Furthermore, ITI was associated with an increase in projected life expectancy of 4.6 years. The findings from this research underscore the need to take a long-term view regarding the cost of care for patients with high-responding inhibitors.

Unresolved Issues
Despite the widespread use of ITI to treat patients with high-responding inhibitors, many issues remain unresolved.

When should ITI be initiated?
A low inhibitor titer (<10 BU) at the start of ITI increases the likelihood of successful tolerization. However, it may take a year or longer for a patient’s titer to drop to this level, and the presence of a long-standing inhibitor increases the risk of ITI failure.
What is the optimal regimen?

Because no ITI protocol is uniformly effective, FVIII dosing is probably the most controversial unresolved issue. The International Immune Tolerance Study, launched in 2002, may finally provide answers about the efficacy, morbidity, and cost-effectiveness of low versus high-dose FVIII, although the results will not be known for several years. In this study, 150 patients aged 7 years or less who were diagnosed with a FVIII inhibitor no more than 12 months earlier and whose peak inhibitor titer ranged from 5 to 200 BU are being randomized to a high-dose modified Bonn regimen (200 IU/kg/day) or a low-dose modified Dutch protocol (50 IU/kg 3 times weekly). Success is defined as normalization of FVIII recovery (>66%) and half-life (>6 hours) and survival within 33 months of initiating ITI.

Which type of FVIII concentrate should be used?

Most children are tolerized using the product they were receiving when they developed an inhibitor. Consequently, ITI generally is performed using rFVIII, even though its use may double the cost of treatment compared with pdFVIII.

In actuality, disease transmission is a concern with rFVIII and all other recombinant DNA biologicals, as evidenced by a recent report from researchers at the US Food and Drug Administration describing the rigorous safety measures used in the production of recombinant biopharmaceuticals. Furthermore, the safety of plasma-derived products has dramatically improved with the adoption of measures for decreasing viral load in source plasma and for inactivating or eliminating residual infectious agents during the production process. As a result, not a single incident of disease transmission has resulted from infusions of human-derived, viral-inactivated products since 1985 in the United States and since 1987 in Canada. Experts agree that the risks of blood-borne infections transmitted by pdFVIII are more theoretical than real, and they argue that both pdFVIII and rFVIII should be considered equally safe.

Another issue surrounding the choice of FVIII concentrate for ITI is whether pdFVIII products containing VWF increase the likelihood of successful tolerization. VWF, a large glycoprotein contained in plasma, platelets, and endothelial cells, is a critical component of hemostasis, initiating platelet adhesion at sites of vascular injury. In addition, VWF plays a key role in FVIII function, production, and stabilization by:

- Transporting FVIII to sites where it can participate in the formation of fibrin clots
- Prolonging the half-life of FVIII in the circulation
- Protecting FVIII from proteolytic inactivation
- Increasing FVIII concentration within the forming hemostatic plug

VWF also is involved in FVIII immunogenicity. Inhibitors react with and bind to active sites on the FVIII molecule, primarily with epitopes in the A2, A3, C1, and C2 domains. VWF binds to a similar epitope on the FVIII molecule as inhibitors directed against the C2 domain (Figure 2). In vitro and in vivo research suggest that antibodies may be less inhibitory to FVIII complexed with VWF compared with recombinant and monodonal FVIII products. This observation appears to be borne out in clinical practice, as a growing number of hemophilia treaters report that FVIII concentrates containing high amounts of VWF are more successful than other FVIII products in achieving ITI (Figure 3).
**VWF Modulates the Ability of FVIII to React with Inhibitors**

![Diagram showing the modulation of FVIII by VWF](image)


**FVIII:C Activity in an Inhibitor Patient after Infusion of 5000 IU pdFVIII/VWF (blue bars) or Monoclonal FVIII (red bar)**

Bars denote FVIII:C activity after each of 4 consecutive infusions given 3 hours apart. Preinfusion FVIII:C concentrations were < 0.5-3.0 IU/dL.

![Bar graph showing FVIII:C activity](image)

A compilation of data on ITI therapy from hemophilia centers in Bonn and Bremen, Germany showed that prior to 1990, ITI was successful in 44 of 51 patients (86%) treated exclusively with an intermediate purity FVIII/VWF concentrate.\textsuperscript{88} Success rates dropped to 55\% between 1990 and mid-1999, when high-purity FVIII concentrates without VWF were primarily used. With the resumed use of FVIII/VWF concentrates in July 1999, success rates have increased to 71\%. Specifically, 23/28 patients (82\%) treated with FVIII/VWF have been successfully tolerized compared with 6/14 patients (43\%) treated with rFVIII.

Findings from a retrospective analysis by Heisel K urth support the strategy of switching to FVIII/VWF products in patients whose inhibitors are refractory to ITI with rFVIII.\textsuperscript{83,85} FVIII/VWF was successful in achieving immune tolerance in 5/8 patients with high-titer FVIII inhibitors who had failed ITI with recombinant or monoclonal FVIII or whose history suggested a high likelihood of failing standard ITI.\textsuperscript{85} One patient achieved partial tolerization, another was in the process of being successfully tolerized, and only 1 patient failed ITI with a FVIII/VWF concentrate. Similar findings were reported by Kreuz et al.\textsuperscript{83} Among 10 patients who had failed ITI with a monoclonal FVIII product, 8 were successfully tolerized when they were switched to a FVIII/VWF concentrate (Table 3). Gringeri also described the enhanced efficacy of VWF-containing concentrates in achieving tolerization.\textsuperscript{86} Prospective surveillance showed that 6/13 patients at high risk for a poor response to ITI, including 3 patients who had previously failed ITI, were successfully tolerized using high-purity FVIII/VWF concentrates. The remaining 7 patients, who were still undergoing ITI at the time the report was presented, had converted from high-to low-responders.

### Experience with ITI at a Hemophilia Treatment Center in Frankfurt, Germany (1972–2000)\textsuperscript{89}

<table>
<thead>
<tr>
<th>Period</th>
<th>Type of Concentrate</th>
<th>Completed ITI (No. Patients)</th>
<th>Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979-1993</td>
<td>pd FVIII/VWF (n=21)</td>
<td>19</td>
<td>91</td>
</tr>
<tr>
<td>Since 1993</td>
<td>pd FVIII/VWF (n=2)</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>pd FVIII (n=14)</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Changes to pd FVIII/VWF* (n=10)</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Total (n=16)</td>
<td></td>
<td>14</td>
<td>88</td>
</tr>
</tbody>
</table>

*Due to failure of ITI regimen with monoclonal FVIII product


It is noteworthy that comparable high-purity FVIII/VWF products were used in the Heisel K urth, Kreuz, and Gringeri studies.\textsuperscript{85,86,89} In contrast to intermediate purity concentrates, high-purity products have specific FVIII coagulation activity values (FVIII:C) that range from 1000 to 3000 FVIII:C IU/mg.\textsuperscript{89}
The development of inhibitors to FVIII significantly complicates the management of patients with hemophilia A. FVIII usually is unsuccessful in controlling bleeding episodes in patients with high-titer inhibitors (>5 BU), making bypassing therapy and various adjunctive therapies necessary for hemostatic support. The efficacy of bypassing agents is unpredictable, however, which places patients at substantial risk for uncontrollable bleeding, the development of arthropathy, and early death. ITI generally is recommended in children to eradicate their inhibitors and allow the use of more reliable and less expensive FVIII replacement concentrates to treat bleeding events. ITI is successful in approximately 70% of patients. While some contributors to ITI success and failure have been established, several issues remain unresolved. Ongoing clinical trials may provide the answers that will improve the care of patients with hemophilia A and inhibitors in the coming years.

**Conclusion**

The development of inhibitors to FVIII significantly complicates the management of patients with hemophilia A. FVIII usually is unsuccessful in controlling bleeding episodes in patients with high-titer inhibitors (>5 BU), making bypassing therapy and various adjunctive therapies necessary for hemostatic support. The efficacy of bypassing agents is unpredictable, however, which places patients at substantial risk for uncontrollable bleeding, the development of arthropathy, and early death. ITI generally is recommended in children to eradicate their inhibitors and allow the use of more reliable and less expensive FVIII replacement concentrates to treat bleeding events. ITI is successful in approximately 70% of patients. While some contributors to ITI success and failure have been established, several issues remain unresolved. Ongoing clinical trials may provide the answers that will improve the care of patients with hemophilia A and inhibitors in the coming years.
References


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