# A Guide to the Management of Patients with Inhibitors to Factor VIII and Factor IX

AHCDC

THE ASSOCIATION OF HEMOPHILIA CLINIC DIRECTORS OF CANADA

L'ASSOCIATION CANADIENNE DES DIRECTEURS DES CLINIQUE D'HEMOPHILIE

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# Index


| | |
|---|---|
| Introduction | 3 |
| Epidemiology, mechanisms, and risk factors for inhibitor development | 7 |
| Clinical picture of inhibitors in patients with congenital hemophilia | 13 |
| Laboratory diagnosis and monitoring of inhibitors | 17 |
| Clinical management of inhibitor patients | 19 |
| Primary prevention of inhibitors and future prospects | 35 |
| Acquired hemophilia (AH): background | 39 |
| Acquired hemophilia: clinical presentation and management | 43 |

# Introduction

The familiar term "inhibitors" is used to refer to antibodies to FVIII or FIX which arise in some patients with hemophilia A or B respectively, and which inhibit the functional activity of the target coagulation protein. The development of inhibitors has emerged as the most serious and feared complication of substitution therapy for hemophilia, as the other serious adverse effects of treatment have been substantially ameliorated. We are beginning to define the risk factors for inhibitor development, which may lead to strategies for primary prevention. Meanwhile, treatment strategies aimed at achieving hemostasis and at antibody eradication have achieved gratifying degrees of success.

This Guide presents a brief summary of key aspects of the epidemiology, immunology, risk factors, mechanisms, and clinical presentation of inhibitors, and provides practical recommendations regarding their prevention, diagnosis, and management. It is intended as a quick reference guide for physicians who have the expertise to manage patients with hemophilia and its complications, and who practice in recognized Hemophilia Treatment Centres (HTC). We strongly recommend that patients with inhibitors be managed in these specialized settings. We hope that this publication will also be valuable to our students, the hematology residents and fellows who are called upon to help manage these patients, and who will become

our colleagues and successors as Medical Directors of HTCs.

The reader is encouraged to visit the AHCDC website at http://www.ahcdc.ca/ for a link to the online version of this publication, which will be updated regularly.

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# List of abbreviations

| | |
|---|---|
| **AHCDC** | Association of Hemophilia Clinic Directors of Canada |
| **APCC** | Activated prothrombin complex concentrate |
| **AH** | Acquired hemophilia |
| **BU** | Bethesda unit |
| **FVIII** | Factor VIII |
| **FIX** | Factor IX |
| **HTC** | Hemophilia treatment centre |
| **ITI** | Immune tolerance induction |
| **IU** | International unit |
| **rFVIIa** | Recombinant activated factor VII |
| **VWF** | von Willebrand factor |

# Epidemiology, mechanisms, and risk factors for inhibitor development

## Epidemiology of FVIII inhibitors

- The cumulative *incidence* of FVIII inhibitors is approximately 25% in patients with severe hemophilia A, ranging in various studies from 0-52%. Approximately half of these are low titer or transient. In those with moderately severe and mild hemophilia the incidence is lower (<10%).
- The *prevalence* of FVIII inhibitors is approximately 5-10% in the hemophilia A population.
- The risk of inhibitor development diminishes with repeated exposures to FVIII. After >150 FVIII exposure-days, the incidence is approximately 2 to 3 per 1,000 person-years.
- The median number of FVIII exposure days to inhibitor development is between 9 and 36.
- "Methodologic" factors that artifactually influence the incidence and prevalence figures for inhibitors include the frequency of inhibitor testing and the inhibitor testing protocol.
- FVIII inhibitors develop twice as frequently in Blacks and Hispanics as in Caucasians.
- The incidence and prevalence of non-inhibitory anti-FVIII antibodies in patients with hemophilia is unknown.

- The antibody response to FVIII is oligo/polyclonal in nature with both IgG1 and IgG4 subclass involvement.
- The immunodominant B and T cell epitopes are in the C2, A2 and A3 domains of the FVIII protein.

## Epidemiology of FIX inhibitors

- The incidence and prevalence of inhibitors to FIX is approximately 3%.
- FIX inhibitors occur more frequently in patients with severe disease (9-20% incidence).
- FIX inhibitor development occurs most frequently during the early stages of FIX replacement therapy.
- The incidence and prevalence of non-neutralizing anti-FIX antibodies is unknown.

## Pathophysiologic mechanisms of FVIII inhibitors

**Inhibitors may inhibit FVIII function by:**

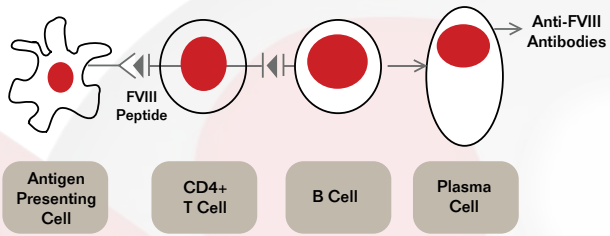
- Blocking binding of FVIII to von Willebrand factor (VWF) or phospholipid
- Preventing dissociation of FVIII from VWF

- Preventing FVIII light chain cleavage (activation) by thrombin
- Blocking the interaction of activated FVIII with factor X or IXa
- Accelerating dissociation of activated FVIII

### Possible additional mechanisms:

- Antibody-induced proteolysis of FVIII
- Enhanced clearance of FVIII

### The Cellular Immune Response to Factor VIII




## Risk factors for FVIII inhibitor development

The development of antibodies to FVIII represents a complex interaction among multiple genetic and environmental factors, as well as stochastic influences:

| Genetic Factors | Environmental Factors |
|---|---|
| Family history of inhibitors | Coexistent inflammation |
| FVIII genotype | Treatment intensity |
| HLA genotype | Age at initial treatment |
| Immunoregulatory genotype | Type of clotting factor replacement |

The best characterized genetic risk factor for inhibitor development is the FVIII mutation type:

| FVIII Mutation Type | FVIII Inhibitor Risk in a Previously Untreated Patient |
|---|---|
| Multidomain deletion | ~70% |
| Light chain nonsense mutation | ~30% |
| Intron 22 inversion mutation | ~20% |
| Single domain deletion | ~20% |
| Small non-A run insertion/ deletion | ~20% |
| Heavy chain nonsense mutation | ~15% |
| Factor VIII missense mutation | <10% |
| Small A run insertion/deletion | <5% |
| Splice site mutation | <5% |

There is preliminary evidence to indicate that components of the "immunogenotype" also play a role in determining the FVIII inhibitor risk:

| Effect of known polymorphisms in immunogenetic factor | Odds Ratio for FVIII Inhibitor Development (95% CI) |
|---|---|
| IL-10 | 5.4 (2.1 – 13.7) |
| TNFα | 4.0 (1.4 – 11.5) |
| CTLA4 | 0.3 (0.1 – 0.8) |

### Situational and exogenous risk factors:

- Administration of FVIII at the time of a coexistent inflammatory state (in the presence of immunologic "danger" signals) is especially provocative for inhibitor development.
- Thrombin generation (and possibly signaling through protease activated receptors) represents one form of inflammatory signal.
- While there have been rare examples of immunogenic concentrates that have clearly been associated with an increased incidence of inhibitors, the influence of the type of concentrate (especially plasma-derived FVIII/VWF versus recombinant FVIII) remains controversial.

## Risk factors for FIX inhibitor development

Due to the relative frequencies of FVIII and FIX inhibitor development, much less is known about the pathophysiologic mechanisms involved in FIX inhibitor generation.

- FIX genotype is a major risk factor for inhibitor development. The incidence of inhibitors in patients with FIX gene deletions is ~25%.
- Due to the infrequent occurrence of FIX inhibitors, information relating to the risk of inhibitor development with other FIX mutations is lacking.

- Although not systematically characterized, the available evidence suggests that the process of FIX inhibitor development often involves an IgE mediated hypersensitivity response.
- In at least 50% of cases, FIX inhibitor development is associated with anaphylactic/anaphylactoid reactions.

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1. Wight J, Paisley S. The epidemiology of inhibitors in hemophilia A: a systematic review. *Hemophilia*. 2003;9:418-435.

2. UK Haemophilia Directors' Organization. The incidence of factor VIII and Factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977-1999. *J Thromb Haemost*. 2004;2:1047-1054.

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# Clinical picture of inhibitors in patients with congenital hemophilia

- The clinical manifestations that draw attention to the possibility of inhibitors are:
    - Bleeding that does not respond as expected to factor concentrate
    - Bleeding that stops only after higher than expected doses of substitution therapy
    - Bleeding that occurs despite previously effective prophylactic therapy
- There may be no clinical manifestations if inhibitors are first detected by routine screening, which should be performed frequently in very young children.
- Bleeding patterns in severe congenital hemophilia patients do not differ among those with and without inhibitors. However, the treatment of bleeding episodes may be less successful in inhibitor patients, as bypassing agents are not as reliably effective as is replacement therapy.
- Patients with inhibitors generally do not bleed more frequently than those without inhibitors (excluding the influence of prophylactic treatment). The exceptions are those patients with non-severe hemophilia, in whom the inhibitor usually reduces their baseline plasma factor level.
- It is possible that inhibitor patients are at higher risk of intracranial hemorrhage than those without inhibitors, but more data are needed to confirm this association.

## Natural history of inhibitors

- Because inhibitors generally arise after limited exposure to FVIII or FIX (see "Epidemiology") one-third of cases occur before the age of 1 year, two-thirds by 3 years, and most of the rest by 6 years. It is unusual for inhibitors to develop later, except in cases of moderate or mild hemophilia.
- The overall *prevalence* of inhibitors (i.e., the percentage currently affected) is 5-10%. This may be declining with the more widespread use of immune tolerance induction programs.
- The *incidence* of inhibitors (i.e., the risk of their development over a specified period of time) exceeds the prevalence, particularly in children with severe hemophilia, in whom it is >25%. The difference reflects the success of immune tolerance regimens and the fact that some inhibitors resolve spontaneously. The incidence falls sharply with age, to negligible levels by adulthood.
- Approximately 15% of inhibitors arise in patients with moderate or mild hemophilia A. In these cases the FVIII level usual becomes undetectable, and the bleeding frequency and severity approximates that seen in severe hemophilia.

- Inhibitor titers may decrease to undetectable levels if factor concentrate is not given for a few months. Subsequent administration of factor VIII will often be effective for a few days but usually results in an anamnestic rise in the inhibitor titer. This sequence is seen more often in mild and moderate hemophilia in which the necessity for treatment is infrequent.

- Transient low titer inhibitors appear to be common in severe hemophilia, but spontaneous sustained disappearance of high titer inhibitors is rare.

- Before the availability of effective bypassing therapy, the presence of inhibitors clearly increased the mortality of hemophilia. Recent data from Canada and elsewhere suggest that inhibitors no longer affect survival in hemophilia patients. If this is confirmed it could be attributable to more successful hemostatic therapy (with bypassing agents) and eradication therapy (immune tolerance induction).

- Historically, the prevalence of inhibitors in a population has remained constant, new cases balancing those that resolve or cause fatality. The introduction of more successful immune tolerance induction programs may change this recurring pattern.

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1. Kessler CM. Clinical Manifestations and Therapy of the Hemophilias. In: Colman RW, Clowes AW, Goldhaber SZ, Marder VJ, George JN, eds. *Hemostasis and Thrombosis: Basis Principles and Clinical Practice*. 5th ed. Philadelphia: Lillipott, Williams and Wilkins:887-904.

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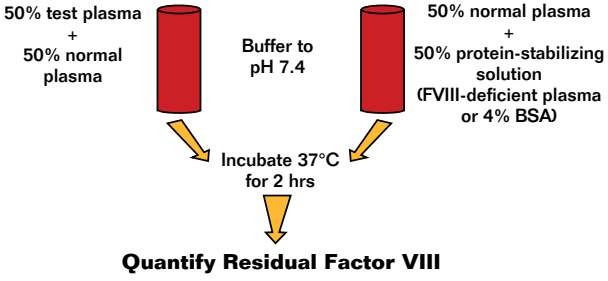
# Laboratory diagnosis and monitoring of inhibitors

- Genetic testing for the disease-causing mutation should be undertaken as a matter of high priority in any newly diagnosed patient with severe hemophilia. This is especially important for new cases of severe hemophilia B. This information will assist in predicting the risk of inhibitor generation during the critical early exposures to clotting factor concentrate.
- Inhibitor testing should be performed in a laboratory with extensive experience in measuring coagulation factor levels.
- Inhibitor testing frequency should be guided by several factors: the age of the patient, the frequency of concentrate exposure, the number of prior concentrate exposure days, and the clinical response to concentrate infusion.
- Young patients with high-risk hemophilia mutations should undergo frequent inhibitor testing during their first 50 exposure days to concentrate (every 5 to 10 infusions or every 3 to 6 months).
- Patients being treated on a regular basis with coagulation concentrate should be tested for inhibitors annually.
- FVIII inhibitor testing should employ either the standard Bethesda assay or preferably the Nijmegen-modified version of the assay.

## Nijmegen-modified Factor VIII Inhibitor Assay




- One Bethesda Unit (BU) is defined as the dilution of patient plasma that results in a 50% reduction in FVIII activity in normal plasma after 2 hours incubation at 37°C.
- Using a regular Bethesda assay or a Nijmegen-modified assay the cut-off value for clinically significant inhibitory activity is 0.5-0.6 BU.
- High titer antibodies are defined by inhibitory titers >5 BU.
- The inactivation of FVIII by inhibitors is time-dependent, and a 2-hour incubation is necessary for complete inhibition. This is not a requirement for FIX inhibitors.
- The clinical significance of non-inhibitory FVIII and FIX binding antibodies, and the role of testing for them, is currently unclear. These antibodies will not be detected by the Bethesda assay.

# Clinical management of inhibitor patients

## What to do when an inhibitor develops

### A. Classify the inhibitor as to type

#### 1. Anamnestic responsiveness

**Low responding inhibitor, defined as:**

- Inhibitor level ≤5 BU
- No anamnestic response to FVIII after immunologic challenge

**High responding inhibitor, defined as:**

- Any inhibitor for which the titer exceeds 5 BU at any time

#### 2. Inhibitor titer

**Low titer (≤5 BU)**

- Usually low responding, although a high responding inhibitor can become low titer if patient is not exposed to factor for long period

**High titer (>5 BU)**

- Always high responding

**Transient Inhibitors: Low titer inhibitors (<5 BU) that disappear spontaneously with continuation of the same replacement therapy within 6 months from occurrence**

## B. Make a therapeutic plan

**For low responding inhibitors (always low titer)**

- No change in replacement therapy
- Treat bleeds with sufficient FVIII to achieve therapeutic levels (typically 2 to 3-fold higher doses than in non-inhibitor patients)

**For high responding inhibitors (usually high titer)**

- Stop further exposure to FVIII until ready to start ITI; treat bleeding with bypassing agent, preferably rFVIIa (to avoid exposure to FVIII in APCC)
- Initiate ITI to eradicate inhibitor (see below)
- During ITI, treat bleeding episodes with bypassing agent of choice, either rFVIIa or APCC

# Treatment of bleeding in congenital hemophilia A with inhibitors

## Desmopressin

- Rarely has a role in management; restricted to minor bleeding in some patients with mild hemophilia and low titer inhibitors.

## Human FVIII (recombinant or plasma-derived)

- Can be used in much higher doses (up to 3-fold) in patients with low-titer inhibitors (≤5 BU). In actual practice, FVIII is usually not very effective if inhibitor titer >3 BU, as extremely high doses would be required.
- In patients with high responding inhibitors an anamnestic response will usually occur within several days, making ongoing use of FVIII ineffective.

## Porcine FVIII

- Plasma-derived product is no longer produced but a recombinant porcine FVIII may soon become available. It is unclear at this time what its role will be in inhibitor management.

| | Activated prothrombin complex concentrates (APCCs; FEIBA®) | Recombinant FVIIa (rVIIa; Novoseven®; NiaStase® in Canada) |
|---|---|---|
| **Composition** | Activated and nonactivated FII, VII, IX, X; proteins C and S (all components are believed to be necessary, but FII and activated FX appear to be most critical for procoagulant activity)<br><br>Contains some FVIII which may induce an anamnestic response and compromise future ITI | FVIIa |
| **Vial sizes** | 1000 units / 20 mL diluent | Currently 1.2 mg, 2.4 mg and 4.8 mg. All are reconstituted in diluent volumes <10 mL. The product will soon be re-formulated in vials containing 1 mg, 2 mg and 5 mg. |
| **Administration** | Give over 30-45 min; some patients are known to administer faster but safety is not established | Give as bolus in 1-3 min. |
| **Dosing** | 50–100 U/kg every 8-12 hours, maximum cumulative daily dose 200 U/kg | Conventional: 90 µg/kg q2-4 hours; most bleeds require 2-3 doses; severe bleeds require additional doses<br><br>High dose: 270 µg/kg X 1 dose; equally effective for joint bleeds – no experience in life threatening bleeds or in surgery |
| **Pharmacokinetics** | Effective half-life of 4–7 h | Effective half-life of 2-3 h |
| **Effectiveness** | 70-90% of bleeds or surgical procedures<br><br>Efficacy independent of inhibitor titer | 70–100% of bleeds or surgical procedures<br><br>Efficacy independent of inhibitor titer |
| **Safety** | Thrombosis (rare)*<br>venous thromboembolism, MI, DIC reported; estimated incidence 4–8 events per $10^5$ infusions<br>Viral transmission – theoretically possible but no evidence in 30 yrs | Thrombosis (rare)*<br>MI, stroke, DIC and other thromboses reported, often with off-label use |
| **Monitoring** | No easily available method<br><br>Possibly thrombin generation assays; not yet validated | FVII:C or FVIIa levels – but do not predict success of treatment<br><br>Possibly thrombin generation assays; not yet validated |
| **Anti-fibrinolytics** | Generally avoided because of risk of thrombogenicity, and lack of empirical safety data | Can be given concurrently, particularly for oral or nasal bleeding, or for dental or other mucosal surgery |
| **Continuous infusion** | No studies, therefore not recommended at present | Has been used but in general appears less effective than bolus therapy |

*Thrombosis risk is increased in certain situations: surgery, elderly, liver disease, ischemic heart disease. The risk is also greater when very large doses of FEIBA® (>200 U/kg/day) or possibly of rFVIIa are used.

## When treating bleeding or managing surgery in patients with inhibitors

### Evaluate and consider

- Severity of bleed
- Current inhibitor titer
- Previous anamnestic response
- Previous response to bypassing therapy
- Patient preference

### To treat minor bleeds (usually requires 1 to 3 doses)

**In low responders**

- Use higher doses (3-fold) of FVIII – monitor with FVIII assays
- If hemostasis is not obtained, use bypassing agent

**In high responders**

- Use a bypassing agent

*Is one bypassing agent better than the other?*

**Both agents appear equally successful**

**Either agent may be tried first**

### To treat major bleeds (will need ongoing treatment for many days)

**In low responders**

- Use higher doses (3-fold) of FVIII – monitor with FVIII assays; consider continuous infusion
- If hemostasis is not obtained, use bypassing agent

**In high responders**

- Human FVIII is reserved for life-threatening bleeding; if current inhibitor titer is high, to be effective this will require removal of antibody by plasmapheresis or preferably immunoadsorption, which is not usually available
- Usually need to use bypassing agents

## Additional considerations

### Some patients respond better to one or the other bypassing agent. It is not known why. Observations suggest that:

- The response to rFVIIa may be better when given early after first evidence of bleeding or immediately peri-operatively
- For later treatment FEIBA might be the preferred agent

### If adequate hemostasis is not achieved with bypassing therapy

- Consider switching to the alternative bypassing agent
- If hemostasis still not achieved consider combined sequential therapy
- Concurrent use of rFVIIa and APCC cannot be recommended at present. However in rare cases of life threatening refractory bleeding, this option should be considered, using reduced doses of each agent.

## Concomitant use of antifibrinolytic agents

- Clinical experience has validated the safety of the concurrent use of rFVIIa and tranexamic acid or aminocaproic acid. This is especially useful for management of mucocutaneous bleeding
- Concurrent use of FEIBA and these antifibrinolytic drugs is not recommended, since published data demonstrating the safety of the combination are lacking

## Vaccination in inhibitor patients

- The optimal route of vaccination is not clear. The subcutaneous or intradermal routes may be considered, but conventional intramuscular vaccination has been used safely, using a small-gauge needle and applying pressure for several minutes.

## Surgery in hemophilia patients with inhibitors

### The following principles should be understood:

- These are high risk procedures
- Surgery should preferably be done in hemophilia treatment centres
- Procedures should ideally be performed by surgeons with experience in hemophilia
- Diagnostic and therapeutic facilities must be available to maintain hemostasis and monitor patients for up to 14 days post-operatively
- Bypassing agents are generally needed; one can consider using FVIII when inhibitor titer is low, recognizing that switch to a bypassing agent may be required if there is anamnestic rise in inhibitor titer

## Prophylaxis in inhibitor patients

- There is increasing evidence for the clinical benefit of bypassing agent prophylaxis
- It is not clear when to start but this should be considered for inhibitor patients who experience frequent or life threatening (e.g., intracranial) bleeding
- The regimens are very expensive regardless of the agent used. However, they may occasionally be associated with reduction in costs in patients who have very frequent bleeding
- APCC (FEIBA, usually 50-100 U/kg) might be effective when given every other day; in some cases it is given daily
- rFVIIa must generally be given daily for prophylaxis. Limited data support doses of 90 or 270 µg/kg. At this time there is no evidence to suggest that additional benefit is derived from the 270 µg/kg regimen
- Morning dosing is strongly suggested
- Prophylaxis requires good venous access – in many patients this means a central venous line is necessary

# Immune tolerance induction (ITI)

***All patients who develop high titer inhibitors should be offered ITI, which is the only method of potentially eradicating the inhibitor***

**Ideally all patients on ITI should be on a clinical trial or registry**

**The ideal regimen is not known. Prototypes are:**

## Bonn-type regimens

**High dose FVIII (100–200 IU/kg/day)**

- More costly than lower dose regimens
- Greater need for central venous lines
- Associated with fewer bleeds during ITI
- May achieve tolerance faster than lower dose regimens
- Probably more successful than low dose regimens in poor-risk patients

**Low dose FVIII (25–50 IU/kg daily to 3 times weekly)**

- Less costly
- Less need for central venous line
- Associated with more bleeds during ITI

- May be slower to induce tolerance, but the ultimate success rate may be similar to high dose regimen

### Malmö type regimen

**This is generally now reserved for failure of Bonn-type regimens. This regimen, substituting FIX for FVIII, may also be considered for hemophilia B patients with inhibitors. It consists of a combination of:**

- High dose FVIII
- IVIG
- Immunoadsorption (not readily available; difficult in young patients due to venous access)
- Cyclophosphamide (reluctance to use in young children)

## Predictors of ITI outcome

**Generally accepted as predictors of ITI success:**

- Inhibitor titer at start of ITI <10 BU
- Peak historical inhibitor titer <200 BU

**Not completely accepted as predictors of ITI success:**

- Start by age 6 years
- Start within 2 years of onset of inhibitor

**Predictor of ITI failure:**

- Patients in whom the inhibitor titer rises to >500 BU after starting ITI

## When to start ITI

- If possible defer ITI until inhibitor titer <10 BU; this may take 3–6 months without further exposure to FVIII
- Some advocate starting ITI immediately regardless of inhibitor titer
- While waiting to start ITI, rFVIIa is the preferred agent for on-demand or prophylactic management of bleeding; the rationale is to avoid an anamnestic rise in inhibitor titer, which may occur with FEIBA

## Type of factor concentrate for ITI

**There is conflicting evidence that tolerance may be more readily achieved using low-purity (plasma-derived) concentrates containing both FVIII and VWF**

- It is not known if this is because of presence of VWF or of other components in plasma-derived concentrates
- VWF may mask inhibitor epitopes of FVIII in the concentrate, leading to a longer half-life of FVIII in inhibitor patients receiving FVIII:VWF concentrates

- This is the subject of an international randomized clinical trial (RESIST study)

## Role of concomitant immunosuppressive treatments is not clear

- Usually reserved for patients who previously failed ITI
- Rituximab – variable responses

## Evaluating outcome of ITI

- Definition of success (adapted from the International ITI study, terminated in November 2009)
    - Negative Bethesda titer (X 2)
    - Normal recovery (>66%)
    - Normal half-life (>6 hrs)
- Partial success can be defined as the ability to successfully resume replacement therapy with FVIII concentrate, without satisfying all the above criteria
- Most patients achieve tolerance within 9-15 months – likely should continue for 2-3 years before declaring failure

- After successful ITI it is recommended that patients continue on prophylaxis for a minimum of 1 year and that surveillance continue for inhibitors. The specific prophylaxis regimen is at the discretion of the physician and the patient and his family
- Where an ITI regimen has been partially successful the physician may also recommend switching to a prophylactic schedule, which in this case could be considered as continuation of ITI at lower intensity
- Recurrence rate after successful ITI is up to 15%
- Suggested criteria for declaring failure of ITI (note that it is more difficult to define what constitutes failure than success)
    - Lack of success within approximately 3 years (there is no acceptable definition for this)
    - Failure of inhibitor titer to drop by 20% in a 6 month infection-free period – following initial 3 months of ITI

## Use of bypassing agents during ITI

- Bleeding episodes during ITI should be treated with bypassing agents exactly as for patients not on ITI
- Prophylactic bypassing therapy should be considered in high responder patients with a bleeding tendency, although bleeding frequency often declines during ITI

- In addition to providing hemostasis, prophylactic bypassing agents may enhance the success rate of ITI by reducing the immunologic "danger signals" associated with the cycle of bleeding and inflammation; plasma-derived components in APCC (such as cytokines) may also contribute
- The combination of immune tolerance therapy plus bypassing therapy potentially has both added hemostatic efficacy and thrombogenicity. During ITI, it is recommended that bypassing agent prophylaxis be stopped when FVIII activity becomes detectable, or the inhibitor titer falls to 2 BU

## Inhibitors in mild hemophilia

- To avoid inhibitor development consider using desmopressin whenever possible, particularly in those at high risk for inhibitor formation, based on family history or FVIII mutations
- The natural history of inhibitors in patients with mild hemophilia is variable. In some cases inhibitors disappear spontaneously, but the risk of anamnestic responses with further FVIII exposure remains

## Immune tolerance in hemophilia B

- Regimens consist of conventional ITI approach with FIX infusions in low or high dose

- Relatively poor (25%) overall success rate of ITI
- High risk of complications:
    - Anaphylaxis – therefore administer first 10-20 exposures in hospital
    - Nephrotic syndrome – this may be irreversible even after stopping ITI
- Steroids and antihistamines have limited value
- Modified Malmö regimen may be considered

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# Primary prevention of inhibitors and future prospects

There is a very small pool of data on which to base recommendations for the prevention of inhibitor development. Therefore what follows cannot be considered as medical guidelines, but rather as practical recommendations based on what is known at the time of writing this Guide. There is much less information on inhibitors to FIX than to FVIII. Most of the following recommendations apply to either of the deficiencies.

## Primary prevention

**Knowing the genetics of the causal mutation:**

- Whenever possible potential carriers should be tested to facilitate prenatal diagnosis, in order to plan optimal delivery and neonatal treatment strategies as necessary, or to assist in decisions regarding early therapeutic termination or the possibility of pre-implantation embryo selection (PES).
- Early genetic diagnosis of newly diagnosed hemophilia might assist in optimizing plans for replacement therapy and timing of elective surgery, if needed.

## Optimizing environmental factors:

- Avoid birth trauma for babies with hemophilia by encouraging multidisciplinary participation in delivery (obstetrics, anesthesia, hematology, nursing, laboratory medicine), and considering Caesarean section in case of anticipated difficult vaginal delivery; perform a FVIII assay on cord blood at birth.
- Avoid elective surgery, especially in subjects with high risk mutations for inhibitor development.
- Consider early prophylaxis following the patient's first bleed.
- Consider postponing vaccination until after at least 50 exposure days of replacement therapy; the decision to vaccinate should be individualized, taking into consideration the known benefits of vaccination and the theoretical risk of stimulating the immune system in a patient predicted to be at high risk of inhibitor development.
- For patients considered to be at high risk for inhibitor development consider initiating replacement therapy with a doubly virus inactivated plasma-derived FVIII concentrate containing VWF for the first 50 to 150 exposure days.
- Initiate prophylaxis with once-a-week replacement therapy in order to avoid the need for a central venous access line.

- For hemophilia B patients with high-risk mutations (complete gene deletion, large deletion, stop codon), consider treatment with rFVIIa; the risk for inhibitor development in this small subgroup is very high, and their onset is often associated with anaphylactic reactions and/or nephrotic syndrome upon exposure to factor IX.

## Future and speculative prospects

### Knowing the genetics of non-synonymous FVIII gene polymorphisms:

- Early data suggest that in the future it may become possible to reduce the risk of inhibitor development by choosing the recombinant FVIII concentrate that corresponds best to the patient's own FVIII gene polymorphisms. Such an effect should be expected to be limited to subjects whose hemophilia is due to a mutation that allows the production of some endogenous FVIII (formerly referred to as CRM+ hemophilia). No prospective study has yet been done to support this hypothesis.

## Knowing the genetics of inflammatory cytokines:

- Genetic polymorphisms of some inflammatory cytokines (TNFα, IL10, CTLA4) are known to affect the risk of inhibitor development. A full discussion of the role of these mediators and their significance with respect to FVIII inhibitors is beyond the scope of this Guide. However, in light of the recent reports it is possible that for subjects with high-risk genotypes, immune modulating medication given at time of first FVIII exposure will reduce that risk.


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# Acquired hemophilia (AH): background

## Pathophysiology

- An autoimmune disease caused by autoantibodies to FVIII, which result in FVIII deficiency and a bleeding tendency
- The antibodies may interfere with the interaction of FVIII with phospholipids or VWF, or inhibit the activity factor of Xase, the reaction in which factor IXa proteolytically activates factor X, in the presence of phospholipid and thrombin-activated FVIII
- There is some evidence that some anti-FVIII antibodies in both congenital and acquired hemophilia patients have proteolytic activity specifically directed against FVIII

## Characteristics of the antibodies

- Autoantibodies in AH are usually polyclonal, and are predominantly of the IgG4 subtype
- They are directed against epitopes in the A2 domain of the FVIII heavy chain or the C2 domain of the light chain (less commonly the A3 domain)
- There are differences between antibodies in AH and congenital hemophilia, but it is not clear that these can explain the differences in bleeding pattern and severity (see below)

- Autoantibodies in AH are usually directed against a single target (most commonly a C2 epitope), inhibit FVIII activity only incompletely such that residual FVIII activity is usually detectable, and display complex non-linear inactivation kinetics
- Antibodies in congenital hemophilia most commonly react with epitopes in both the A2 and C2 domains, neutralize FVIII completely, and do so with linear kinetics

- Low titer circulating anti-FVIII antibodies, usually of the IgG1 or IgG2 subtype and with specificity in the C2 domain, can be detected in nearly 20% of the general population. They may be controlled by anti-idiotypic regulation. As these antibodies presumably react with polymorphisms in non-self FVIII, they are characterized as alloantibodies rather than autoantibodies

## Epidemiology

- The annual incidence of AH in the general population is approximately 1-2 per million/year
- AH is extremely rare in children, with an estimated incidence of 0.045 per million/year in those younger than 16
- There is a small peak in the 20-30 year age range and a much larger peak after age 65, the incidence progressively rising thereafter

- By age 85 the incidence approaches 15 per million/year
- There is no sex predominance except for those cases in the 20-30 year age bracket, most of whom are post-partum women
- About half of all cases are truly idiopathic. The others occur post-partum (10-15% of cases) and in association with other autoimmune diseases, solid tumors, hematological malignancies, inflammatory disorders, dermatologic diseases, infections (hepatitis B or C), or as an adverse effect of medications
- The validity of many cases of suspected "drug-induced AH" is problematic. The majority of AH patients are elderly and they are often taking many medications simultaneously
- There are fewer than 40 reported cases of drug-induced AH, and it is often difficult to demonstrate a clear causal relationship with a medication. The drugs for which there is reasonably good evidence for a causative association include penicillin, sulfonamides, phenytoin, interferon, and fludarabine

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# Acquired hemophilia: clinical presentation and management

For reasons that are not well understood, the clinical manifestations of acquired hemophilia (AH) A are quite distinct from those seen in congenital hemophilia.

**Unique clinical features of AH:**

- Lack of correlation between inhibitor titer and measurable residual FVIII levels
- Lack of correlation between measured FVIII level and severity of bleeding (severe spontaneous bleeding occurring with FVIII levels > 5%)
- Hemarthrosis is very rare and extensive hematomas are common, in contrast to congenital hemophilia A (the photograph shows a typical presentation of AH); retroperitoneal or ilio-psoas hematomas are not infrequent in either disorder

### When to suspect AH:

- Unexplained prolonged APTT
- Elderly man or woman with a recent onset of extensive bruising and subcutaneous hematomas, in the absence of other more common hemostatic abnormalities (thrombocytopenia, drug-induced causes, etc)
- Continued bleeding despite stopping anticoagulant and antiplatelet medication
- Bleeding occurring weeks to months postpartum
- Note that the severity of AH is variable: fatal hemorrhage was described in up to 20% of cases in older series, and mild bleeding or bruising not requiring hemostatic treatment occurs in about 30% of cases

## AH: Principles of Management

### Overall treatment strategy:

- Avoid procedures that might cause iatrogenic bleeding
- Treat significant bleeding, usually with a bypassing agent
- Initiate eradication therapy without delay

### Prevention of bleeding:

- Meticulous care of venipuncture technique, and care of puncture sites
- Delay any procedure or surgical intervention until inhibitor is eradicated (FVIII will often normalize 3 to 6 weeks after starting immunosuppression)
- If a procedure is urgent (for instance, central line placement for venous access) provide coverage with a bypassing agent

### Deciding whether to treat bleeding:

- Extensive ecchymosis and subcutaneous hematomas may require only close observation, especially if they seem to have been present for more than a day
- In elderly patients with co-morbidities and risk factors for thrombosis, the risks and benefits of treatment with bypassing agents must be weighed carefully
- Clinical assessment and frequent monitoring of the hemoglobin level are more dependable signs of significant bleeding than imaging studies

### Treatment of acute severe/clinically significant bleeding:

- Both rFVIIa and APCC are approved and effective for the treatment of bleeding in patients with AH

- No comparative study allows one to recommend one product over the other
- rFVIIa 90 µg/kg is given by IV bolus injection every 2-3 hr until hemostasis is achieved. High dose regimen of 270 µg/kg is not recommended.
- APCC (FEIBA) 50-100 U/kg is given by slow IV injection (usually 20-30 minutes) every 8-12 hr (maximum of 200 U/kg/day) until bleeding is controlled.

### Duration of hemostatic treatment:

- Continue bypassing therapy until bleeding is controlled and then taper over 24 to 72 hrs depending on the severity, type and site of bleeding (this may not be necessary in some cases)
- If treatment fails, switch to the alternate bypassing agent
- Use alternating regimen of both agents only in exceptional circumstances with refractory bleeding

### Antifibrinolytic agents:

- These remain controversial in association with bypassing agents, but these are often used with rFVIIa in congenital hemophilia patients with inhibitors
- Most useful in mucosal bleeding

### Inhibitor Eradication:

- Should begin as soon as possible, to minimize time that patient is at risk of bleeding
- Most patients should be treated initially with corticosteroids alone or in combination with cyclophosphamide
- Prednisone 1 mg/kg/day PO for 2 weeks (then tapered over 6 weeks), either alone or in combination with cyclophosphamide 1.5-2 mg/kg/day for up to 12 weeks (for frail elderly patients consider doses as low as 1 mg/kg/day)
- Combined immunosuppressive therapy may result in a somewhat shorter time to remission

### Rituximab:

- If high dose prednisone $\pm$ cyclophosphamide is contraindicated or has failed, a regimen based on Rituximab 375 mg/kg weekly for 4 weeks is suggested
- Rituximab alone without steroids may not be as effective. However, this should be considered in cases of postpartum AH
- Rituximab is not approved for this indication in some jurisdictions

## Outcome and follow-up:

- Patients who survive the initial acute bleeding episode have a high likelihood of attaining a durable remission
- Relapses occur in 15-20% of cases and may happen a few months to a few years following the initial presentation
- Patients in complete remission should be followed every 1 to 2 months for 6 months, and then as needed.
- Patients should be taught to recognize signs of bleeding and to seek medical attention without delay if these occur

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