

Inhibitor Antibodies to Factor VIII and Factor IX: Management

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ABSTRACT Inhibitor antibodies directed against factor VIII or factor IX present challenges to the clinician. Fortunately, several management options are available, although each has disadvantages as well as advantages. Alloantibodies against factor VIII (which develop in 25 to 50% of children with severe hemophilia A, as well as in a small percentage of children with mild or moderate hemophilia A) may be low titer and transient or may be high titer. Most patients with high-titer problematic inhibitors now try to eliminate the inhibitor by using one of several immune tolerance induction (ITI) regimens. For treatment of bleeding episodes in patients who have high-titer (≥ 5 Bethesda units) inhibitors, one can use a prothrombin complex concentrate (PCC) (preferably an activated PCC [APCC]), recombinant (r) factor VIIa, or porcine factor VIII. The choice of product is generally dependent on the type and severity of the patient's bleeding, degree of cross-reactivity of the patient's inhibitor with porcine factor VIII, physician familiarity with the product, product availability, and cost.

In persons with hemophilia B, alloantibodies occur in only 1 to 3% of severely affected individuals.

However, in roughly half of those who develop inhibitors, anaphylaxis or severe allergic reactions occur on infusion of any type of factor IX-containing product. This phenomenon usually develops after relatively few exposures to factor IX; thus it is recommended that the first 10 to 20 infusions of factor IX given to children with severe hemophilia B be given in a setting equipped for treatment of shock. For treatment of bleeding episodes in patients with severe allergic reactions, rF VIIa is the treatment of choice. ITI has been less successful in hemophilia B patients with inhibitors than in those with hemophilia A, and in a subgroup of patients with severe allergic reactions who were desensitized to factor IX and then tried on ITI, results were even poorer. Additionally, several developed nephrotic syndrome while on ITI. For hemophilia B patients with inhibitors who do not have allergic reactions to factor IX, bleeding episodes can be treated with PCC or APCC or with rF VIIa.

Autoantibodies directed against factor VIII are rare but can occur in a variety of settings. They occur mainly in adults, and bleeding is often severe and life threatening. Although some factor VIII autoantibodies disappear spontaneously, most require immuno-

Objectives

Upon completion of this article the reader should be able to (1) recognize the frequency with which hemophilia A and B patients develop inhibitors, (2) list the options for suppressing or eradicating inhibitors, and (3) describe the treatment modalities presently available to manage hemophilia A patients with bleeding.

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suppression. Corticosteroids and cyclophosphamide are generally recommended. For treatment of bleeding, therapeutic options include (human) factor VIII concentrates, porcine factor VIII, APCC, and rFVIIa. The choice of product is generally determined by the consulting hematologist's familiarity with the product, product availability and cost, as well as response to treatment.

Keywords: Factor VIII inhibitors, factor IX inhibitors, immune tolerance induction, prothrombin complex concentrates, porcine factor VIII, rF VIIa, autoantibodies to factor VIII, anaphylaxis to factor IX, nephrotic syndrome

Although inhibitors occasionally develop against other coagulation factors, by far the most common are those directed against factor VIII or factor IX. This review of management considerations will be divided into three parts: (1) management of factor VIII inhibitors developing in persons with hemophilia A, 2) management of factor IX inhibitors developing in persons with hemophilia B, and (3) management of factor VIII autoantibodies developing in nonhemophilia individuals.

FACTOR VIII INHIBITORS DEVELOPING IN PERSONS WITH HEMOPHILIA A

Although occasional persons with mild (5 to 30% factor VIII) or moderate (1 to 5% factor VIII) hemophilia A develop inhibitors,¹ most factor VIII inhibitors develop in severely affected individuals (those whose baseline factor VIII is < 1%). It is now recognized that a variety of genetic and immunologic factors play a role in inhibitor development (for example, the underlying defect in the factor VIII gene causing the person's hemophilia, race, or human leukocyte [HLA] antigen type),¹⁻⁶ thus, some hemophilic individuals are at much greater risk of inhibitor development than are others.

As described elsewhere in this issue, for sake of uniformity, most coagulation laboratories performing inhibitor assays use the Bethesda Assay,⁷ and most use a cut-off of 0.6 Bethesda units for positive or negative (0.6 Bethesda unit is considered positive; < 0.6 Bethesda unit is considered negative). For equivocal values (e.g., 0.6 to 1.5 Bethesda units), the Nijmegen modification of the Bethesda Assay is often quite helpful in separating true inhibitors from false-positives.⁸

If one looks prospectively for factor VIII inhibitors (as has been done in several prospective, multicenter studies in previously untreated patients with hemophilia A), it is apparent that most inhibitors develop quite early in life, after relatively few exposure days (median in

prospective studies, 8 to 12 E.D.).^{4,9-11} These studies have also demonstrated a much higher incidence of inhibitor development than was previously thought to exist. It is now apparent that 25 to 50% of persons with severe hemophilia A develop inhibitors to factor VIII. Although approximately one third of these inhibitors remain low titer (< 5 Bethesda units) or are transient, the remainder are high-titer more problematic inhibitors.

Although the presence of an inhibitor does not increase the likelihood of bleeding (except indirectly, where poor response to treatment has resulted in a "target joint" or large pseudotumor), it does make management of bleeding more difficult.

In the case of low titer inhibitors (< 5 Bethesda units), the patient's bleeding episodes often respond to factor VIII in usual or slightly increased dosage. It should be noted that we are still not certain of the minimal level of factor VIII (or factor IX) needed to stop an acute joint bleed, and currently used dosages of factor VIII in noninhibitor patients may be higher than necessary. Also, it is recommended that one always use the entire vial of clotting factor (i.e., without discarding any), which often results in giving a somewhat increased dosage, especially in the case of infants and small children. Thus, low-level inhibitors would probably be missed if inhibitor assays were not being done in a regular, prospective fashion. This is particularly true because many of these low-level inhibitors are transient, disappearing despite continued episodic ("on demand") treatment with factor VIII.

For higher titer factor VIII inhibitors—those that cannot easily be overcome with an increased dosage of factor VIII—management considerations fall into two broad categories: attempts to suppress or eradicate the inhibitor and treatment of bleeding episodes.

Attempts to Suppress or Eradicate Inhibitors

Immune Tolerance Induction Regimens

In the 1970s, Professor Brackmann in Bonn, Germany, developed an ITI regimen that became known as "the Bonn Regimen." The original Bonn regimen involved large, twice-daily infusions of factor VIII and daily doses of the APCC, FEIBA®. A later version of the Bonn regimen omitted the requirement for daily doses of APCC.¹² Although generally successful in eradicating inhibitors, the Bonn regimen was very expensive, time consuming, demanding of both patients and physicians, and often took many months. The Bonn regimen never became popular in the United States because of the cost and time involved, plus the fact that transfusion-transmitted hepatitis and then human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) became recognized as complications of clotting factor concentrates being used in the early

1980s. However, by the late 1980s and early 1990s, much safer plasma-derived clotting factor concentrates and then recombinant (r) factor VIII concentrates had become available, and other investigators began trying less costly, less demanding modifications of the Bonn regimen. Whereas some of these incorporated prednisone¹³ or cyclophosphamide and intravenous gammaglobulin (IVIg),¹⁴ several groups reported successful eradication (or at least suppression) of factor VIII inhibitors with factor VIII alone. Success rates of approximately 80% were reported with daily doses of factor VIII (in a dosage of 50 to 100 IU/kg).^{15,16} Some groups reported success with every other day, twice weekly, or even weekly doses of factor VIII (25 to 50 IU/kg).^{17,18} Kreuz and colleagues,¹⁹ however, have recommended the use of ≥ 100 factor VIII U/kg per day, starting as soon as possible, and have had excellent results in pediatric patients.¹⁹ Three ITI registries have been established, one international (maintained by Professor Mariani in Palermo, Italy),²⁰ one North American (maintained by Dr. DiMichele in New York),²¹ and one German (maintained by Dr. H. Lenk).²² Although the registries are retrospective in nature and dependent on voluntary reporting by physicians, analysis of data submitted to them suggests that one is more likely to be successful with ITI if the patient's inhibitor titer has never been ≥ 100 Bethesda units and is < 10 Bethesda units when ITI is begun. However, the optimal ITI approach has yet to be defined. At present, in Germany, larger doses, given twice daily (e.g., 100 IU/kg per dose, twice daily) are used; in The Netherlands a very low dose regimen is employed. The latter regimen has apparently converted a number of high responders into low-titer inhibitor patients whose bleeding episodes can be controlled with factor VIII.¹⁸

Among U.S. physicians using daily doses of factor VIII for ITI, many use a sliding scale for factor VIII dosage, starting with 50 IU/kg per dose if the patient's inhibitor level has always been < 50 Bethesda units, 100 IU/kg if the patient's historical maximum inhibitor level has been between 50 and 100 Bethesda units, and 150 to 200 IU/kg if it has been > 100 Bethesda units. Once the patient's inhibitor titer becomes negative (< 0.6 Bethesda units) and the factor VIII recovery is normal or near normal (e.g., 60% of that expected), the dosage of factor VIII is reduced. If, after several weeks at the reduced dosage, the patient's inhibitor is still negative and factor VIII recovery is still $\geq 60\%$ of that expected, the dose and dosage interval can be further reduced. However, it should be noted that the optimal method for such dose reduction has not been established.

A North American–European randomized trial, scheduled to begin in early 2000, will compare a low-dose regimen (50 IU/kg, twice weekly) to a high-dose regimen (200 IU/kg per day); once patients have negative inhibitor assays and factor VIII recoveries of $\geq 60\%$ expected, they will be further randomized to one of two dose-reduction schemes.

For high-titer, very problematic inhibitors in which it is deemed necessary to eradicate the inhibitor (as for impending surgery), Nilsson and colleagues in Malmö, Sweden, have reported success in some using extracorporeal adsorption of IgG antibodies on a staph A column, followed by high-dose factor VIII (or factor IX), cyclophosphamide, and IVIg.^{14,23,24}

Other Attempts to Suppress the Anamnestic Response

Although still under investigation, an anti-CD40 ligand developed by scientists at Biogen (Cambridge, MA) is being tried (in conjunction with factor VIII infusions) in persons with hemophilia A who have “high-responder” factor VIII inhibitors.

Treatment of Bleeding Episodes

For persons with factor VIII inhibitors > 5 Bethesda units (or some even lower than this whose bleeding episodes do not respond to factor VIII), there are several therapeutic options for treatment or prevention of bleeding.

Prothrombin Complex Concentrates

PCCs, either “standard” or purposely activated (APCCs), have been used to treat bleeding in hemophiliacs with factor VIII (or factor IX) inhibitors for more than 25 years. Although the unit systems differ from product to product (e.g., Baxter-Immuno's FEIBA®-VH is labeled in “factor VIII inhibitor bypassing units,” and Nabi's Autoplex®-T is labeled in “factor VIII correctional units” [FECU]) and the mechanism of action of these products in bypassing the need for factor VIII (or factor IX) is still not entirely clear, most physicians calculate dosage in the same way for each of them. Generally, 75 U/kg per dose is used (which is a considerably higher dose for PCC than is used for hemophilia B patients without inhibitors). If repeat doses are needed they are generally given at 6- to 12-hour intervals. The package insert for FEIBA®-VH recommends 12 hour intervals, whereas that for Autoplex®-T recommends 6 hours.

Although controlled trials conducted 20 years ago demonstrated very little superiority of APCC over “standard” PCC in controlling joint or muscle bleeding in inhibitor patients,^{25,26} the majority of physicians treating inhibitor patients prefer APCC, feeling that APCC is more effective than is PCC.

Advantages of PCCs and APCCs include the facts that these products have been used for many years, can generally be used safely at home, and often work fairly well in stopping bleeding. Disadvantages are as follows: (1) none of the PCCs or APCCs is predictably effective in stopping or controlling bleeding in inhibitor patients. They may be quite effective on some occasions and not

at all on others. As a result, few would rely on these products for surgical procedures. Additionally, most inhibitor patients who have been treated with PCCs or APCCs, or both, have more progressive musculoskeletal problems than do noninhibitor patients. (2) Their mechanism(s) of action are not known with certainty, and there is no readily available laboratory test for monitoring their efficacy. (3) The unit systems on the product labels may or may not have relevance to the active “bypassing” ingredients. (4) Repetitive doses may result in disseminated intravascular coagulation (DIC), thrombosis, or even fatal acute myocardial infarction.^{27,28} There have been more than 15 reported instances of acute myocardial infarction in young inhibitor patients receiving these products.

In view of the risks of thrombogenicity and acute myocardial infarction with repeated large doses of PCC or APCC, it is recommended that the patient not exceed 4 doses for a particular bleeding episode. If longer treatment is deemed necessary, one should use an alternate product (rF VIIa or porcine factor VIII).

Porcine Factor VIII

Whereas older porcine factor VIII preparations (produced in the 1950s and 1960s) were associated with a high rate of adverse reactions, Hyate:C® (Speywood Pharmaceuticals, Wrexham, UK) is a much more highly purified porcine factor VIII concentrate that has a low rate of untoward side effects. This preparation has been widely used since 1980 and has proved to be life- or limb-saving in a number of serious hemorrhagic events.^{29–33} The rationale for its use is that there is often some degree of species specificity of factor VIII inhibitor antibodies, with those developing in humans often inactivating human factor VIII to a greater degree than they inactivate another species' factor VIII. In the case of hemophiliacs with factor VIII inhibitors that have little or no cross-reactivity to porcine factor VIII, one can infuse them with Hyate:C® and then follow their circulating factor VIII levels with a standard factor VIII assay. The author has successfully used Hyate:C® for surgical coverage (for both major and minor procedures), for treatment of central nervous system (CNS) hemorrhages and iliopsoas hemorrhages, and for other large intramuscular hemorrhages requiring several days of effective hemostasis.

In order to determine whether or not an inhibitor patient is a candidate for treatment with porcine factor VIII, one can measure the patient's antiporcine inhibitor titer by substituting Hyate:C® for human factor VIII in the Bethesda Assay (substituting porcine factor VIII that has been diluted to 1 porcine unit/mL in hemophilic plasma). Persons whose inhibitor titer to porcine factor VIII is < 15 Bethesda units (or whose inhibitor titer to human factor VIII is < 50 Bethesda units) are likely to respond well to porcine factor VIII.^{29–31} It is helpful to

measure an inhibitor patient's antiporcine factor VIII inhibitor levels whenever a “standard” inhibitor assay is being run. Then, should an emergency situation arise, one would know whether or not porcine factor VIII is an option.

The recommended starting dose of porcine factor VIII is 100 to 150 factor VIII units/kg of body weight, with subsequent dosing based on the recipient's circulating factor VIII level. Factor VIII levels often increase by day 2 or 3 of treatment, after the patient's inhibitor has been saturated with infused porcine factor VIII. The product should be infused slowly in order to avoid allergic reactions. Although some recipients will eventually develop antibodies to porcine factor VIII, others do not.

Porcine factor VIII can also be given by continuous infusion, thereby decreasing the amount (and cost) of product.³⁴ When stored at room temperature, Hyate:C® has been shown to retain 90% activity for at least 24 hours.³⁵

Advantages of porcine factor VIII are as follows: (1) the recipient's factor VIII level can be measured and followed, thus allowing dosage adjustments to maintain the desired factor VIII level; (2) the product has an excellent track record of viral safety in human recipients; (3) the inhibitors of many hemophiliacs have little or no cross-reactivity to porcine factor VIII. Disadvantages include the fact that (1) Hyate:C® is a foreign species protein, and thus its use is associated with a slight risk of severe allergic reaction; (2) the product is only useful in persons with factor VIII inhibitors that have no or low cross-reactivity to porcine factor VIII; (3) an inhibitor antibody to porcine factor VIII may develop after 5 to 10 days of treatment with Hyate®; (4) occasionally, mild thrombocytopenia may occur during a course of treatment with porcine factor VIII; however, this has been much less of a problem with Hyate:C® than it was with older porcine factor VIII preparations (presumably because of a much lower content of porcine von Willebrand factor in Hyate:C®); (5) most physicians do not feel comfortable prescribing porcine factor VIII for home use because of concern that a severe allergic reaction might occur or that an anti-porcine factor VIII inhibitor might develop, rendering treatment suboptimal. However, Hay (in the U.K.) and colleagues (in France) have used Hyate:C® at home in carefully selected patients.³⁶

Recombinant Factor VIIa

rFactor VIIa is the newest of the treatment options for persons with inhibitors against factor VIII (or factor IX). In the mid-1980s, Hedner et al³⁷ demonstrated that a plasma-derived, activated (a) factor VII concentrate was effective in controlling bleeding in two hemophilic patients with factor VIII inhibitors; however, a recombinant product would have obvious advantages. Thus, a rF VII product was developed by scientists at Novo

Nordisk (Bagsvaerd, Denmark) for treatment of bleeding in persons with factor VIII or factor IX inhibitors. rF VIIa (Novo Seven®) is produced in baby hamster kidney (BHK) cells that are transfected with the gene for human factor VII. rFactor VII is then harvested from the cell culture medium and undergoes a series of ion exchange and antibody affinity chromatographic steps. During the final ion exchange chromatographic step, rFactor VII undergoes autoactivation to rF VIIa. It is noteworthy that no human proteins are used in the manufacture of rF VIIa, nor are they added later. However, fetal calf serum is used during manufacture, and a murine monoclonal antibody step is used in purification.³⁸

When infused, rF VIIa interacts with endogenous tissue factor sites exposed by injured cells. Although its exact mechanisms of action are still not known with certainty, it appears that rF VIIa is hemostatically active only at a local level and enhances the natural pathway of coagulation.^{39–41}

Following extensive in vitro and preclinical studies, Hedner et al⁴² reported the successful use of rF VIIa in a patient with severe hemophilia A and high titer inhibitor who underwent open synovectomy. Hemostasis was maintained during and after this procedure, and no blood products were needed.⁴² Shortly thereafter, phase I safety and pharmacokinetic studies were conducted. The latter demonstrated that the biological half-life of rF VIIa is approximately 2.5 hours⁴³ but may be shorter in infants and children. rF VIIa has now been used and evaluated in more than 2500 surgical and nonsurgical bleeding episodes in persons with hemophilia A and B, with or without inhibitors, and in factor VII-deficient persons. Over the past decade (in addition to the compassionate use program), rF VIIa has been evaluated in a dose-finding study,⁴⁴ in open label home treatment studies in the United States,⁴⁵ in France and Denmark, and in a U.S. controlled, double-blind surgical study in which two dosage regimens of rF VIIa were compared.⁴⁶

Recommended Dosage and Administration

The currently recommended dosage for rF VIIa is 90 µg/kg per dose. Because of its short half-life, repeat doses (if necessary) should be given at 2.5- to 3-hour intervals. rF VIIa appears to have a wide safety margin, with much higher doses (in the order of 300 µg/kg per dose) causing no ill effects.⁴⁷ If given soon after the onset of joint or soft tissue bleeding, one or two doses of rF VIIa may suffice (see Table 1).^{45,48}

Although some physicians have given rF VIIa by continuous infusion (with the aim of reducing the amount of product needed and thus reducing cost),⁴⁹ there are no established guidelines for doing this and no simple way of monitoring therapeutic efficacy in the recipient. An initial bolus dose of 90 µg/kg should be given; this can be followed by a continuous infusion of 20 to 30 µg/kg per hour. The dosage is then adjusted based on the patient's factor VII level. Some have attempted to keep the recipient's factor VII level at ≥ 10 IU/mL; however, this has not always been successful. With additional experience and more published data, however, continuous infusion of rF VIIa may become the method of choice in situations requiring longer hemostatic control (e.g., during and after major surgery and for serious, life-threatening bleeding episodes).

OVERALL APPROACH TO MANAGEMENT OF INHIBITORS IN PERSONS WITH HEMOPHILIA A

One should consider an immune tolerance regimen in any individual with a problematic inhibitor (i.e., an inhibitor that cannot be easily overcome by factor VIII in usual or somewhat increased dosage). The choice of regimen will depend on one's analysis and interpretation of published results with various ITI regimens, as well as one's own experience, product availability, and cost. The

TABLE 1. Overall Comparison of Results of Treatment with rF VIIa for Acute Hemarthrosis from Three Databases in Which Time from Onset of Bleeding until Treatment with rF VIIa Began Differed Considerably

<i>Study</i>	<i>Dosage (µg/kg per dose)</i>	<i>Mean Time from Onset of Bleed until First Treatment with rF VIIa</i>	<i>% Achieving Excellent or Effective Response</i>	<i>Mean Number of Doses of rF VIIa Given to Control Bleeding</i>
Compassionate use	60–120	2.5 days (0.3–20.7 days)	61	22
Dose-finding study	a) 70	10 h (median)	71	3.1
	b) 35	8.4 h (median)	71	2.7
U.S. home Treatment Study	90	1.2 h	92	2.2

(Adapted from Lusher.⁴⁸)

patient or the patient's family, or both, should be given sufficient information concerning what the proposed ITI regimen involves (length or time, need for frequent venipunctures or placement of a central line, need for follow-up laboratory studies, likelihood of success, costs involved, and so on), in order for them to make an informed decision.

For those who are not candidates for ITI or for those who have failed ITI or are undergoing ITI but still have an inhibitor of ≥ 5 Bethesda units, how should bleeding episodes be treated? Many still use an APCC (or even PCC) for first-line treatment, citing familiarity with the product(s) and the fact that PCCs and APCCs have been used at home for many years and are less costly than are porcine factor VIII and rF VIIa. At the time of this writing, there has been no head to head comparison of APCCs and rF VIIa. However, should such a trial be done, with analysis of overall efficacy, cost, and number of doses needed, results would probably influence treatment practices.

There is a definite role for the other two types of products (rF VIIa and porcine factor VIII) in certain situations. For surgery, one cannot count on PCCs or APCCs to be effective in controlling hemostasis. Here the choice would be to use porcine factor VIII or rF VIIa. If the patient's inhibitor has little or no cross-reactivity to porcine factor VIII, Hyate:C® would be a good choice, because one can monitor the recipient's factor VIII level and adjust the dose accordingly. On the other hand, if the patient's anti-porcine factor VIII level precludes the use of Hyate:C®, one should use rF VIIa. Some would prefer to use rF VIIa in *all* instances, because it is a recombinant product and has a very low incidence of adverse reactions, and inhibitors to it do not develop in persons with hemophilia A or B.

For patients who have an intracranial hemorrhage, iliopsoas hemorrhage, bleeding into a large muscle mass such as the thigh, or other bleeding that is likely to require at least several days of treatment, the use of rF VIIa or porcine factor VIII would be safer and more likely to be effective than giving frequent, repetitive doses of PCCs or APCCs.

FACTOR IX INHIBITORS IN PERSONS WITH HEMOPHILIA B

Unique Considerations

Although many of the approaches used for factor VIII inhibitors in persons with hemophilia A apply to factor IX inhibitors as well, there are a number of unique considerations that have an impact on management. Factor IX inhibitors in hemophilia B develop much less often (1 to 3%) than do factor VIII inhibitors in hemophilia A. This fact, coupled with the much lower percentage of hemophiliacs who have hemophilia B (20%) rather than

hemophilia A (80%), results in relatively few persons with inhibitor antibodies to factor IX. To put this in numbers, there are probably 70 to 80 persons with factor IX inhibitors in the United States. As in hemophilia A, certain defects in the factor IX gene (large deletions, stop codons, and frameshift mutations) are associated with a greater likelihood of inhibitor development.^{50–52} However, quite unlike factor VIII inhibitors, factor IX inhibitor development is associated with the development of anaphylaxis or severe allergic reactions to factor IX in approximately one half of the patients. This phenomenon occurs most often in infancy or early childhood, after relatively few exposure days to any type of factor IX-containing product(s).^{53,54} Because of this, when treating infants and children with severe hemophilia B, it is recommended that the first 10 to 20 or so infusions of factor IX be given in a setting equipped for treatment of shock.⁵³

Another difference between factor VIII and factor IX inhibitors is that the likelihood of response to ITI appears to be poorer in hemophilia B patients⁵⁴ than in hemophilia A patients (in whom the response rate is approximately 85%).

Attempts to Suppress or Eradicate the Inhibitor: Immune Tolerance Regimens

Although there are fewer persons with hemophilia B and inhibitors and thus far fewer individuals have been tried on an ITI regimen, those reported to the registries or published, or both, have had poorer responses to ITI than have persons with hemophilia A and factor VIII inhibitors. Although numbers are small, the likelihood of response in hemophilia B appears to be on the order of 50% or less. Among persons who have had anaphylactic or severe allergic reactions to factor IX-containing products and have then been desensitized and started on ITI with large doses of factor IX, the response rate has been even lower, and at least eight have developed nephrotic syndrome 7 to 8 months after the start of ITI.^{54–57} Thus, one should avoid ITI in persons with factor IX inhibitors and a history of severe allergic reactions or should at least proceed with caution.

Treatment of Bleeding Episodes

For treatment of bleeding episodes in persons with low-titer factor IX inhibitors, one can try a very high purity factor IX concentrate (either rF IX or plasma-derived factor IX), either in standard or somewhat increased dosage. For problematic, higher titer (usually ≥ 5 Bethesda units) factor IX inhibitors, one can use a factor IX complex concentrate (APCC or PCC) in a dosage of 75 factor IX IU/kg per dose (or 75 U/kg per dose in the case of APCC). However, another good therapeutic option is rF VIIa.

rF VIIa has the following advantages over PCC and APCC: (1) it is a recombinant product, thus providing an added measure of viral safety; (2) its mechanism of action appears to be local, at the site of injury, where tissue factor is exposed on cell surfaces; (3) it has fewer side effects than PCC or APCC has; (4) it can be safely used in patients who have severe allergic reactions to factor IX-containing products^{53,58}; (5) it has proved to be effective in maintaining hemostasis during and after major and minor surgery in a controlled, double-blind study.⁴⁶ On the other hand, rF VIIa is more costly than PCC and APCC are, and repeat doses (when necessary) must be given at 2- to 3-hour intervals because of the short half-life of rF VIIa.

As is true for patients with hemophilia A and factor VIII inhibitors, in hemophilia B with factor IX inhibitors, there has been no head to head comparison of rF VIIa and APCC.

However, for the subset of factor IX inhibitor patients who have severe allergic reactions to any factor IX-containing product, rF VIIa is clearly the treatment of choice.

FACTOR VIII INHIBITORS (AUTOANTIBODIES) DEVELOPING IN NONHEMOPHILIC PERSONS

Factor VIII inhibitors can develop in peripartum women, in association with systemic lupus erythematosus or other autoimmune disorders, lymphomas, other solid tumors (e.g., prostatic and lung cancer), and in older persons without identified underlying conditions.^{59–61} The incidence of such inhibitors is 0.2 to 1 per million persons annually. It has been postulated that a dysfunctional immune system may induce the development of an abnormal lymphoid clone with a subsequent humoral response that is T cell dependent.⁶⁰

These inhibitor autoantibodies differ from the alloantibodies seen in hemophilia in their clinical presentation, clinical manifestations, and often their reaction kinetics. An individual who has developed an autoantibody against factor VIII may present with severe, rapidly expanding ecchymoses, gross hematuria or other mucous membrane bleeding, postoperative hemorrhage, or life-threatening internal bleeding. Unrecognized gastrointestinal bleeding may lead to syncope. Others may seek medical attention because of uncontrolled epistaxis, large ecchymoses, or severe gum bleeding. In contrast to hemophilia, joint bleeding is uncommon. Bleeding proved fatal in 15% of patients in one series⁶⁰ and in 22% in another.⁵⁹ In contrast, in some individuals (e.g., peripartum women and elderly persons without underlying disease), spontaneous remission may occur.⁶⁰

As described elsewhere in this issue, coagulation screening tests will demonstrate an isolated prolongation of the activated partial thromboplastin time (aPTT), and

mixing studies will still show prolongation of the aPTT. A factor VIII assay will document that the inhibitor is directed against factor VIII. Although autoantibodies against factor VIII are generally measured using the Bethesda assay, it should be noted that the Bethesda assay was designed to quantitate hemophilic inhibitors that generally inactivated factor VIII in a linear fashion (type I, “second order kinetics”). Most nonhemophilic inhibitors exhibit more complex, type II kinetics, and often some residual factor VIII persists in the incubation mixture. This results in calculation of a falsely low inhibitor value.⁶²

MANAGEMENT OF PERSONS WITH AUTOANTIBODIES TO FACTOR VIII

Once an acquired autoantibody to factor VIII is suspected and documented by appropriate laboratory testing, a plan of management must be developed. If the patient is actively bleeding, prompt diagnosis and prompt institution of treatment (with rF VIIa, porcine factor VIII, or an APCC) may be lifesaving.

It is also important to avoid intramuscular injections, invasive diagnostic procedures, and any activities predisposing to trauma. Aspirin and other drugs that interfere with platelet function should be avoided.

In the case of peripartum inhibitors (which often disappear within weeks), one may elect to only treat bleeding, without the use of immunosuppressive agents. In most other situations, however, the goal should be to rapidly decrease the inhibitor level while treating bleeding as necessary.^{63–65} For treatment of bleeding, human factor VIII (preferably rF VIII), porcine factor VIII or rF VIIa, or, if none of these are readily available an APCC can be used.

If the patient's inhibitor titer is low (< 5 Bethesda units), rF VIII can be used, because the inhibitor often can be saturated and overcome. Most clinicians prefer to use rF VIII rather than plasma-derived factor VIII in this situation because most nonhemophilic individuals who develop a factor VIII autoantibody have had little or no exposure to blood products and are open to transfusion-transmitted viruses. rF VIII offers an added margin of viral safety, although the plasma-derived factor VIII concentrates in current use are no doubt safer than ever before.

Porcine factor VIII is another therapeutic option because nonhemophilic factor VIII inhibitors generally have low cross-reactivity to other species' factor VIII.^{60–63} Anamnestic responses are infrequent, and only 20% of persons develop anti-porcine factor VIII antibodies. Generally, an empiric starting dose of 100 factor VIII U/kg is given, with subsequent dosing being determined by measuring the recipient's factor VIII level. However, if the patient's anti-porcine factor VIII inhibitor level is known before treatment, one can cal-

culate the dose needed to neutralize the patient's autoantibody.⁶⁰

The newest therapeutic option, rF VIIa, has many potential advantages: it is recombinant (and thus virally safe), it has very few side effects, it acts locally where hemostasis is needed, it does not stimulate an anamnestic response, and it has proved to be effective in numerous nonhemophilic patients with inhibitors and serious bleeding episodes. The recommended dosage (as for hemophilic inhibitors) is 90 µg/kg per dose, given every 2 to 3 hours until bleeding has resolved.

Desmopressin (1-deamino-[8-D-arginine]-vasopressin; DDAVP), has also been used by some clinicians in treating persons with very low level inhibitors (< 3 Bethesda units).⁶⁰ The recommended dose is 0.3 µg/kg IV; doses can be repeated every 12 to 24 hours if necessary. Desmopressin acts by stimulating rapid release of factor VIII and von Willebrand factor from storage sites, and one may expect an increase in circulating factor VIII in patients with very low levels of inhibitor. However, one must keep in mind that this synthetic analogue of the naturally occurring antidiuretic hormone vasopressin is a potent antidiuretic agent. Thus, prevention of fluid overload and hyponatremia are important. Additionally, it has been recommended that the use of desmopressin be avoided in elderly persons and in person with a history of coronary or cerebral arterial disease.

THE USE OF IMMUNOSUPPRESSIVE AGENTS

Corticosteroids, cyclophosphamide, azathioprine, 6-mercaptopurine, and vincristine have all been successful in reducing the inhibitor titer in some persons. However, many of these agents have side effects and reported responses have been variable. Green and associates⁶⁵ conducted a randomized, prospective multicenter trial in which all persons initially received prednisone 1 mg/kg per day for 3 weeks. If the antibody persisted, patients were randomized to one of three regimens: continuation of prednisone in the same dosage for an additional 6 weeks; oral cyclophosphamide 2 mg/kg per day for 6 weeks; or a combination of prednisone and cyclophosphamide for 6 weeks. Ten of 30 persons had resolution of their inhibitors within the first 3 weeks; 10 of the 20 initially refractory persons responded well to the subsequent treatment, regardless of the treatment arm. However, the inhibitor returned in 3 persons in the prednisone-only arm when prednisone was discontinued.⁶⁵

Shaffer and Phillips⁶⁶ reported the successful suppression of eight consecutive autoantibodies using combined prednisone (1 mg/kg per day) and cyclophosphamide (2 mg/kg per day); treatment was continued for up to 240 days.

Toxicity associated with cyclophosphamide includes myelosuppression (with resulting infections), hemorrhagic cystitis (minimized by taking the drug in the morning and good hydration), and the risk of secondary malignancies such as myelodysplastic syndrome and acute nonlymphoblastic leukemia (although this risk is less with the relatively short-term use of cyclophosphamide).

Although the use of IVIg has resulted in a beneficial response in some persons,^{67,68} in the only published prospective trial, the response rate was between 25 and 37.5%.⁶⁸ The inconsistent and often short-lived response and high cost of IVIg would seem to argue against using this agent as first-line, single therapy. Cyclosporine⁶⁹ and human interferon alpha⁶⁰ have also been reported to be beneficial in isolated case reports.

OVERALL COMMENTARY CONCERNING NONHEMOPHILIC AUTOANTIBODIES

Treatment considerations should be individualized, depending on the person's underlying condition, extent of bleeding (if any), and inhibitor titer. Persons with high-titer inhibitors who are bleeding acutely will usually respond to rFVIIa, porcine factor VIII, or an APCC, whereas those with low-titer inhibitors and less serious bleeding may respond to a human factor VIII concentrate such as rF VIII or even desmopressin.

It is important to avoid trauma, intramuscular injections, invasive diagnostic procedures, and drugs known to interfere with platelet function. In most persons with autoantibodies to factor VIII, there should be a quick attempt to suppress the inhibitor. A combination of corticosteroids and cyclophosphamide would seem to offer the greatest likelihood of success; if this is not effective, other agents can be tried. The decision as to whether or not to start immunosuppression and the selection of agents will depend on the person's underlying condition, likelihood of spontaneous remission (as in postpartum inhibitors), risk of toxic side effects, and cost.

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