

GLOBAL NEWS SERIES FOR HEMOPHILIA NURSES



October 2007 Issue

Message from the Editor

Welcome to the Global News Series for Hemophilia Nurses. The purpose of the Global News Series is to share knowledge, experience and current events among hemophilia nurses from around the world. The topics for each edition are chosen from suggestions received from our readers and the content is developed by subject matter experts from the global hemophilia community. We believe subject matter experts are the best source of information, ensuring its accuracy, applicability and usefulness. Please continue giving us suggestions for topics, and share your knowledge by participating on the Advisory Board. To provide feedback, suggestions or express your interest as a subject

matter expert, please e-mail us at contactus@solutionsight.com or write us at SolutionSight, Inc., 2191 Avalon Drive, Buffalo Grove, Illinois 60089.

The newsletter is sponsored by an educational grant from Baxter Healthcare Corporation. This month we will present information about inhibitors. It's an area with much research in progress and multiple treatment approaches. Due to the variation in approved therapies and practices, we will not provide specific prescriptive recommendations. ❖

Cindy Jo Ping, RN, BSN, MBA, CPP

Advisory Board October 2007

We are pleased to introduce the subject matter experts for this edition of the Global News Series for Hemophilia Nurses. We would like to acknowledge Jennifer Maahs, RN, PNP, MSN and Laurel McKernan, MSN, RN for their support in the development of this edition. Their knowledge, expertise and creativity in dealing with inhibitors have been instrumental in providing you with this information. Jennifer Maahs is a Pediatric Nurse Practitioner at the Indiana Hemophilia and Thrombosis Center, located in Indianapolis, Indiana, USA. Laurel McKernan is a Clinical Nurse Specialist at the Hemophilia and Thrombosis Center, Dartmouth Hitchcock Medical Center, in Lebanon, New Hampshire, USA.

This Issue's Focus

Living with Inhibitors

Inhibitors are a very serious complication of hemophilia. Currently there are three primary-treatment goals for patients with inhibitors. The first goal is the prevention of bleeding episodes. While this is the goal for all hemophilia patients, it is emphasized in patients with inhibitors, due to the challenges encountered in the treatment of these patients. The second goal is the effective treatment of acute bleeding episodes and the ultimate goal of treatment is to eliminate the inhibitor.

In this issue, we will review the current information available about

inhibitors - what they are, how they are detected, how they are classified, who is at risk, their frequency and their implications. Next we will provide information on the current treatment options, including: high-dose factor VIII, bypassing agents, immune tolerance induction (ITI) and some other adjunctive therapies. Teaching tools are provided to use with your patients to prevent bleeding occurrences. Two case studies are provided to illustrate the impact of inhibitors and some creative ways of dealing with them. ❖

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Living with Inhibitors Overview

What is an Inhibitor?

Inhibitors are antibodies (immunoglobulin G, IgG) directed against any clotting factor proteins. There are two types of inhibitors; *alloantibody* and *autoantibody*. Autoantibody refers to IgG antibodies directed against clotting proteins that develop in people without a bleeding disorder. This is known as acquired hemophilia. Alloantibody refers to IgG antibodies that develop in persons with hemophilia that are directed against clotting proteins.

The IgG antibodies can be directed against any clotting factor proteins, i.e. factor VIII, factor IX, etc. Developing an antibody is a normal reaction of the body and is usually beneficial, as antibodies destroy substances in the body that are believed to be foreign. However, when factor VIII or IX is not recognized as a normal protein, the antibody attaches itself to the factor and inhibits the factor's ability to stop bleeding. This inactivation occurs as soon as the body identifies the factor, thereby rendering the factor (including factor concentrates) ineffective. The exact mechanism of this activity is not known. If inhibitors last a short time, they are called transient and if they exist for a long time, they are called persistent.

AUTOANTIBODIES

Autoantibody or Acquired Hemophilia is when a person develops antibodies to their own factor VIII, however, this is rare. It occurs in about one in one million people each year.³ It may occur following pregnancy, surgery, a serious injury, the development of cancer, intake of certain antibiotics or for no apparent reason. Fortunately, in most cases these inhibitors can be

overcome with medical treatment and causing the person's blood to regain its normal ability to coagulate. These patients do not have the same understanding of their condition that patients with hemophilia have developed through years of learning. For that reason, patient education is very important.

ALLOANTIBODIES

How are inhibitors detected?

An inhibitor may be discovered during a routine comprehensive evaluation, when there are increased incidences of breakthrough bleeding or may be suspected when bleeding does not stop as quickly as it should in response to factor. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) suggests that children be tested for inhibitors every three months up to the age of 10 years and for two years after changing products at any age.¹ The first test performed is a mixing study, also known as an inhibitor screen. A mixing study consists of a process where normal plasma is mixed with an equal amount of patient's plasma. The abnormal aPTT will not be corrected and with incubation, the aPTT will actually lengthen as a result of the inhibitor binding to the factor VIII or factor IX in the normal plasma. The presence of an inhibitor is usually confirmed using a specific blood test called the Bethesda inhibitor assay. The amount of antibody is reported as a number of Bethesda units (BU), and expressed as a Bethesda titer. The higher the number of Bethesda units, the higher

the inhibitor concentration.

How are inhibitors classified?

Inhibitors are usually classified as either high- or low-responding, depending on how a person's immune system reacts with repeated exposure to factor VIII or IX. If the immune system reacts briskly and strongly, the amount of inhibitor directed against factor can rise quickly, to high levels, generally called "high-responding." Without further exposure to the factor, the Bethesda titer may drop down to a lower level, but this process could take months to occur. In comparison, the immune system's response may be slower and weaker, and the Bethesda titer will remain low. This type of inhibitor is generally characterized as "low-responding." The characteristics of an inhibitor can change over time, and can disappear spontaneously without apparent treatment. As the immune system changes following the stimulus of clotting factor, the production of antibodies falls. When stimulated again by clotting factor, it reacts by increasing production of antibodies again. This is known as the anamnestic response.



Who is at risk of developing an inhibitor?

Although anyone can develop an inhibitor, genetics play a major role in their development. If one child in a family has an inhibitor, his brother with hemophilia is also at significant risk. The majority of patients who develop inhibitors have severe or moderately severe hemophilia. The

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Key
Term

Anamnestic response: Refers to the increase in the Bethesda titer as a result of exposure to factor VIII.

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median number of factor-exposure days prior to inhibitor detection is between 9 and 12 days, but it most commonly develops in the first 50 factor-exposure days, and is rare after 200 factor-exposure days. Therefore, the majority of the patients who develop inhibitors are children. In a patient with mild hemophilia, the inhibitor may not present until later, due to the limited exposure to factor concentrates.

Since factor concentrate may trigger the body's immune system to react, many doctors who treat people with hemophilia change concentrate brands as little as possible. Persons with hemophilia A are much more likely to develop inhibitors than those with hemophilia B. The risk of inhibitor development in people with hemophilia A increases if they are of African or Latino descent. Doctors think there may also be an environmental cause of inhibitors.³ Environmental influences under consideration include: age at first infusion; immune system challenges, such as immunizations; inflammation, trauma or surgery.⁵ Environmental factors suspected, but not proven to increase the risk of inhibitor development, include: continuous infusion of factor VIII concentrates, presence of ongoing inflammation and exposure to concentrates when younger than six months of age.

How common are inhibitors?

The risk of developing an inhibitor does not remain the same during the lifetime of a person with hemophilia. The majority of inhibitors have been found to develop during childhood. Based on a number of studies from around the world, it is estimated that the incidence of antibody development in persons with severe (less than 1% factor) or moderately severe (1% to 5% factor) hemophilia A is between 20% and 33%.² This information suggests that one third to one fifth of persons with factor VIII levels of 5% or less may develop an inhibitor sometime in their lives. However, among persons with hemo-

philia B, inhibitors are much less frequent, affecting only 1% to 4%.

The Canadian Hemophilia Society reports that inhibitors affect about 1 in 5 people with severe hemophilia A at some time in their lives.³ Most people develop these inhibitors when they are very young, soon after they receive their first infusions of factor VIII concentrate, however, some people develop them later in life. Inhibitors also affect about 1 in 15 people with mild or moderate hemophilia A. These inhibitors usually develop during adulthood.³ They not only destroy factor VIII concentrates infused, but they also destroy the body's own factor VIII. As a result, mild and moderate hemophiliacs become severe. Fortunately, in 60% of these hemophiliacs, the inhibitors disappear on their own within, on average, nine months. For the other 40%, the inhibitors persist and are problematic. In hemophilia B, inhibitors are much rarer. They affect about 1 in 100 people.³ In most cases, these inhibitors develop after the first infusions of factor IX concentrate. Unfortunately, inhibitors in people with hemophilia B can be extremely serious because they can be accompanied by allergic reactions.

What are the implications of inhibitors?

Although there is no increase in the number of spontaneous hemorrhages in patients with inhibitors, this complication impacts every aspect of their life. Bleeding episodes in these patients become less responsive to treatment, since the infused factor VIII becomes ineffective by the circulating antibody.

Therefore, these patients develop significant health challenges, such as joint disease, related to uncontrolled bleeding. They may also experience increased hospitalizations and difficulty with other medical and dental procedures.

The effects of inhibitors on the mental well being of the person with hemophilia will vary, depending where they are in their life cycle. As inhibitor development often occurs in children, the development of inhibitors often has a psychosocial impact.⁴ The care of a child with hemophilia is difficult enough without additional challenges. Adolescence is marked by independence and risk-taking activities, which often creates a dynamic that can impact medical compliance with prescribed therapy. Many of the patients face the fear of disability, decreased quality of life and death. Providing tools, education and support are an important part of the healthcare team's role.

Medical costs for patients with inhibitors increase significantly due to the cost of treatment and increased occurrence of complications, placing additional burdens on the patients and their families. Healthcare providers need to discuss the cost of treatment with patients and their families, as well as provide appropriate referrals to alternative programs and resources whenever possible. ❖



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Living with Inhibitors Treatment Options

The treatment of an inhibitor is challenging for both the patient and the medical team. In persons with low-responding inhibitors (<5 BU/ml¹), successful hemostasis can be achieved with higher doses of factor VIII replacement. For high-responding patients (>5 BU/ml¹), treatment with factor is usually not possible because the factor is made ineffective by the inhibitor and alternative treatment strategies need to be adopted.

Inhibitor eradication is accomplished by Immune Tolerance Induction (ITI), and is the main goal of treatment for the hematology team. Alternative therapies need to be used for those patients that are not suitable for ITI or if a patient has failed ITI.

Acute Bleeding

Acute bleeding episodes can be managed with bypassing agents that contain activated coagulation factors that achieve hemostasis by bypassing the typical coagulation process.

Bypassing Agents

Bypassing agents, either prothrombin complex concentrates (PCCs), activated prothrombin complex concentrates (aPCCs) and activated recombinant factor VII (rFVIIa), are the mainstay of therapy for both hemophilia A and B. These products enhance thrombin generation, which leads to the formation of a clot and hemostasis, thus bypassing the specific requirement for factor VIII or factor IX. PCCs and aPCCs contain a variety of activated and non-activated clotting factors that contribute to the hemostatic process. rFVIIa differs in that it is a recombinant product created by expressing the human gene for factor VII in mammalian cells. Data shows that bypassing agents control at least 80% of bleeding episodes in inhibitor patients.^{11,12,13,14}

PCCs are defined by their absence of activated clotting factors, and although indicated for the treatment of inhibitors, are typically only used in patients who are intolerant to aPCCs. If PCCs are chosen, they should be used with caution and are contraindicated if signs and symptoms of dis-

seminated intravascular coagulation (DIC) are present. Repetitive dosing may result in DIC. (DIC is when your body's blood-clotting mechanisms are activated throughout the body instead of being localized to an area of injury. Small blood clots form throughout the body, and eventually the blood-clotting factors are used up and not available to form clots at sites of real tissue injury. Clot dissolving mechanisms are also increased.)

aPCCs contain both activated and non-activated coagulation factors. aPCCs achieve hemostasis by facilitating thrombin generation, essential for clot formation. The essential components of aPCCs are factors II and Xa. It is important to follow the manufacturer recommendations for dosing and rate of infusion. Thrombotic risk with aPCCs is low—about 4 episodes per 100,000 infusions.^{6,7} Patients at greatest risk are those receiving more than the recommended dose and patients with underlying risk of cardiovascular disease. aPCCs contain a small amount of factor VIII and factor IX, therefore, anamnesis is possible.^{6,7}

Recombinant Factor VIIa (rFVIIa) is a recombinant bypassing agent containing only one active component. The infusion volume per dose is smaller than other agents, but the short half-life of two hours requires more frequent infusions. There is no risk of human viral transmission; however mouse and bovine immunoglobulin G may be present in trace amounts. People who have ever had a bad reaction to proteins from mice, hamsters, or "bovines" (such as an ox or cow) should not be treated with rFVIIa.

Thrombosis is a rare, but well recognized, potential complication of bypassing therapy and includes myocardial infarction, pulmonary embolism and disseminated intravas-

cular coagulation. The extent of the risk of thrombotic adverse events after treatment with rFVIIa in patients with hemophilia and inhibitors is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs or PCCs (activated or non-activated prothrombin complex concentrates) may have an increased risk of developing thrombotic events due to circulating tissue factor or predisposing coagulopathy. The extent of the risk of arterial and venous thromboembolic adverse events after treatment with rFVIIa in patients without hemophilia is also not known. A clinical study in elderly, non-hemophilia intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of rFVIIa, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or cerebral infarction. Also, people taking aPCCs/PCCs at the same time that they're taking rFVIIa may be at increased risk for thrombosis.

Development of antibodies against factor VII has been reported in factor VII-deficient patients after treatment with rFVIIa. These patients had previously been treated with human plasma and/or plasma-derived factor VII.

Antifibrinolytics (for example tranexamic acid) have been reported to reduce blood loss in hemophilia patients, however they should be used with extreme caution with bypassing agents.

Immune Tolerance Induction

In 1970, a procedure for eliminating inhibitors in patients with hemophilia was developed, called immune

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tolerance induction (ITI) or immune tolerance therapy (ITT). ITI involves the frequent, regular administration of factor VIII or factor IX over a period of time, until tolerance is achieved. The goal of this therapy is to eliminate the inhibitor, thus allowing patients to be treated using factor, with a more predictable response. Immune tolerance induction, although time-consuming and costly, is effective 60% to 80% of the time, based on almost twenty years of experience with its use.² Low responders have a greater chance of success with ITI than high responders.³ Unfortunately, ITI does not seem to work as well with hemophilia B and inhibitors; these patients can have severe allergic reactions to the continued infusion of factor IX.

There are many ITI protocols available. An international panel of hemophilia opinion leaders developed consensus recommendations for ITI in patients with severe and mild hemophilia A and hemophilia B. These recommendations draw on the available published literature and the collective clinical experience of the group, and are rated based on the level of supporting evidence. The recommendations have been developed into decision-tree algorithms for healthcare professions to utilize and individualize, according to the unique needs of each patient. Recommendations are provided for many critical decision points for managing a patient with an inhibitor, such as, when to start, dosing and defining outcomes.⁸ We have listed a few of their recommendations below.

Consensus recommendations for when to start ITI

- Postpone the initiation of ITI until the inhibitor titer has dropped to <10 BU, although an even lower inhibitor titer may be more beneficial. The waiting time is usually short, and most children will still be very young at the start of ITI. Closely monitor inhibitory antibody levels during the waiting period to ensure that ITI is started promptly once the titer falls sufficiently. Avoid FVIII exposure during the waiting period.
- Consider starting ITI regardless of the inhibitor titre if the inhibitor titre does not fall below 10 BU within a one- or two-year period of close observation or if a severe life or limb-threatening bleeding event occurs.

Consensus recommendations for ITI dosing

- Among good-risk patients (i.e. peak historical titre <200BU, pre-ITI titre <10 BU, <5 years since diagnosis), no dosing regimen has shown to be superior to another. Among poor-risk patients (i.e. peak historical titre >200 BU and a pre-ITI titre >10 BU and/or above >5 years since inhibitor diagnosis) the evidence suggests a higher success rate with the use of high-dose regimens (>200 IU/day).

Consensus recommendations for managing incomplete or lack of response to ITI

- Continue the initial ITI regimen, particularly if a low-dose regimen is being used for reasons of preferential or default use of peripheral access.
- Maximize the ITI dose if a lower-dose regimen is being used and adequate venous access exists.
- Consider switching to FVIII/VWF product if ITI was initiated with a monoclonal or recombinant product.
- Consider adding rituximab or another immunomodulating drug to the current regimen.

Consensus recommendations for defining ITI outcome

- Pharmacokinetic parameters of success (level III): abnormal inhibitor titre; normal FVIII recovery (<66% of predicted); normal FVII half-life (>6 h) after a 72-h FVIII washout period; and, absence of anamnesis upon further FVIII exposure.
- Pharmacokinetic parameter of partial success (level III): an inhibitor titre <5 BU; FVIII recovery (<66% of predicted); FVIII half-life (<6 after a 72-h FVIII washout period); clinical response to FVIII; and, no increase in the inhibitor titre >5 BU over a 6-month period of on-demand therapy or a 12-month period of prophylaxis.
- Pharmacokinetic parameter of failure (level III): failure to fulfill criteria for full or partial success within 33 months; and, less than a 20% reduction in the inhibitor titre for any 6-month period during ITI after the first 3 months of treatment, which implies that: nine months is the minimum period for ITI; and, 33 months is the maximum

duration of ITI, although the decision may be made to continue immune tolerance induction.

The decision tree and details of all recommendations can be viewed in HAEMOPHILIA Volume 13, Supplement 1, July 2007.

Antifibrinolytic Agents

Antifibrinolytic agents (aminocaproic acid and tranexamic acid) work primarily by preventing clot lysis through the inhibition of plasminogen activators and to a lesser degree through anti-plasmin activity. Use on upper urinary tract bleeding is contraindicated due to potential glomerular capillary thrombosis as well as the development of clots in the renal pelvis or ureter.

Antifibrinolytic tablets are often used prior to teeth cleaning appointments. The tablets are crushed and put in water. The solution is used as a rinse and spit out.

Antifibrinolytic I.V. Topical

This preparation is used as a nasal solution or mouth rinse. The solution is stable for 24 hours and is typically used 2 to 3 days after the bleeding stops.

Plasmapheresis

In rare instances, when high levels of inhibitors exist, and there is life-threatening bleeding that can only be treated with specific factor therapy, some of the antibodies can be removed from the blood. The procedure, called plasmapheresis, withdraws whole blood from the person, removes the antibodies from the plasma, and the treated plasma is returned to the person.

Topical Therapies

Topical therapies can be useful as adjunctive therapies to treat bleeding in all patients with hemophilia. They work best on oozing blood. Topical therapies are not effective with brisk bleeding, but work best in conjunction with infusion products. They include bovine-derived products and collagen products that are a "glue" that allows cells to adhere to one another. Some examples are: Avitene®, Dermabond®, Floseal®, Helistat®, Tisseel® and Gelfoam®.

Note: These products may not be approved for use in all countries.

Bleeding Prevention Safety Tips

- Make sure lighting is adequate to prevent tripping over obstacles. A night light can help illuminate dark areas.
- Remove throw rugs, eliminate clutter and keep extension cords out of the way. Tape the cords to the floor or carpet if necessary.
- Place important items where they can be reached easily. Do not use stepstools or reach for objects on your tiptoes.
- Tubs and showers should have non-skid surfaces or safety mats, both inside and outside. Use extreme caution on wet, tiled floors.
- Essential items should be stored on the upper shelves of the refrigerator.



- Use assistive devices to make items in cabinets easier to reach (i.e. "lazy Susan," extension pinchers).
- Store frequently used clothing in drawers at waist level.
- Do not sit in chairs that have wheels, unless the

wheels can be locked. Avoid chairs or sofas with soft cushions, as they make getting up and out difficult. Try to sit in chairs with armrests and a firm seat. Scoot to the edge of the chair and push from the armrests or sitting surface to stand.

- Make sure that assistive walking devices (canes, crutches or walkers) have rubber tips that are in good condition.
- Select footwear that stays securely on your feet, with soles that are not slippery. Do not walk on slippery surfaces without proper footwear. Place your shoes and assistive devices within easy reach of your bed, to keep them readily available.

Sidebar courtesy of Indiana Hemophilia and Thrombosis Center located in Indianapolis, Indiana, USA.

Living with Inhibitors Patient Education

What causes nosebleeds?

Nose bleeds are especially challenging for patients with inhibitors. The nose has a lot of blood vessels close to the surface and nasal membranes can dry out and crack. Bleeds are common in winter, with the use of household heaters and changes in temperature. Upper-respiratory infections may be more common. Posterior hemorrhage may not be seen.

Causes of nose bleeding

Infection, trauma, runny nose, high blood pressure, alcohol abuse, inherited bleeding problems, nose picking and dry air

Prevention of Bleeding

Nosebleeds often occur when the inside of the nose is dry. Some ways to prevent nose bleeds include:

- Using a humidifier at night.
- Applying non-prescription saline nasal spray or gels four times per day. Some examples are Ayr®-gel, or nasal mist or Ocean® nasal spray.
- Using an antihistamine may decrease the swelling of the tissue in the nose, especially if allergies are a problem; may be prescription medication.
- Blowing your nose gently, never pick and avoid blowing after bleeding has occurred.
- Taking stool softeners will help to prevent straining during bowel movements, which can result in a bleed.
- Avoid smoking, it irritates the mucous membranes.

Treatment Tricks

Salt Pork Nasal Plugs

Buy a package of salt pork at the grocery store. It comes packaged like bacon and is located in the meat section of the store. Cut small pieces

about the size of your little finger. Using a thread or dental floss and a needle, place a string through one end and tie a loop. This will allow easy removal from your nose.



Wrap the plugs in wax paper and place in the freezer. When nose bleeding occurs, remove from freezer, unwrap (you may need to run under warm water) and place in nose, frozen with the string hanging out of the nostril. The plug should be in place for about one hour, apply pressure over the plug.

Nosebleed QR (topical powder) can be ordered in the USA by calling Biolife, L.L.C. at 1-800-722-7559. It may also be available in the first-aid section of your local drug stores.

The **NoseBudd™** is a new device for use with nose bleeds. Created by Steve Riedle, a person with hemophilia, it is a reusable, gel-filled product that can be

easily grabbed from a freezer, and applied to the nose during a bleeding episode. Properly used, NoseBudd™ applies cold pressure only to the areas of the nose where needed, causing the capillaries in the nose to shrink, thus helping

the bleeding to stop. To be effective, the NoseBudd™ is taken from the freezer, and held on the nose for 3-4 minutes. More information about the product can be obtained at: www.nosebudd.com.



Handout courtesy of Indiana Hemophilia and Thrombosis Center located in Indianapolis, Indiana, USA.

