Facts about Inhibitors
Hemophilia is an inherited bleeding disorder affecting approximately 18,000 people in the United States. The primary treatments available to stop and prevent bleeds in these individuals, namely plasma-derived and recombinant factor products, have improved dramatically over the course of the last several decades. In the mid-1970s, the establishment of a nationwide network of hemophilia treatment centers (HTCs) emphasizing comprehensive care further enhanced the outlook for people with hemophilia.

While U.S. hemophilia patients in the 21st century experience a quality of life as high as it has ever been, complications still exist. Ironically, one of the major complications is linked to the very life-saving factor products that are so highly valued and to the crucial defense system that protects every human from disease—the body’s immune system. This occurrence, which is seen in as many as 1/3 of Americans with hemophilia, results when the body’s immune system recognizes infused factor protein—factor VIII (FVIII) in the case of hemophilia A and factor IX (FIX) in hemophilia B—as a foreign substance and produces proteins to attack it. These proteins, or antibodies, “inhibit” the factor treatment’s intended purpose of stopping bleeding.

By hampering the work of FVIII or FIX, vital to the formation of a healthy clot, these inhibitors can become a costly, perplexing and stressful complication for patients, their families, and their health care providers. These individuals and their families face an often daunting set of challenges. This publication was written to help explain inhibitor formation, testing, treatment, and the physical and emotional issues facing this unique segment of the hemophilia community.
The immune system protects the body from diseases. Its first line of defense is a set of barriers such as the skin and mucous membranes. However, the body needs other defenses. Some microorganisms make it past these barriers, causing the body to mount an immune response by certain white blood cells that results in the production of antibodies.

An antibody is produced in response to the presence of an antigen, a foreign substance in the body. In most cases, antibodies destroy these foreign substances, usually viruses and bacteria, which can cause disease.

People with severe hemophilia do not produce enough of the clotting protein needed for bleeding to stop. When some people receive replacement factor, their body’s immune system perceives the clotting factor as an antigen. The body then produces an antibody against it. This antibody, or inhibitor, binds to the infused clotting factor and neutralizes it.

The inhibitor inactivates the factor so that it cannot work in the body to form a clot and help stop bleeding. This makes it difficult to raise the factor level high enough to control bleeding.

Who is at Risk for Developing an Inhibitor?

Approximately 10% to 30% of people with severe hemophilia A may develop an inhibitor sometime in their lives, while the incidence is about 1% to 4% among people with severe hemophilia B.

People with hemophilia have the greatest risk for developing an inhibitor during childhood, especially during the first 50 exposures to clotting factor. The incidence of inhibitors is highest among those with severe hemophilia because they make no clotting factor at all, so the infused factor is truly a foreign protein; in addition, they use more factor product, exposing the immune system to more of the perceived antigen. The risk of inhibitor development is higher among African-Americans and among individuals with a family history of inhibitors.

How Do You Know If You Have an Inhibitor?

An inhibitor is usually suspected when bleeding does not stop after treatment with factor concentrate. A screening test called an inhibitor screen or mixing study is done. If it is positive for an inhibitor, then a second blood test called the Bethesda inhibitor assay is done to measure the amount of the antibodies directed against the clotting factor. The results of the Bethesda inhibitor assay are measured in Bethesda units.

In individuals who are asymptomatic (people without symptoms), the inhibitor may be discovered by specialized laboratory testing during a regular physician visit.

Inhibitors are divided into two categories based on the highest number of units (the inhibitor titer) measured in the blood. Individuals with a Bethesda unit titer of 5 or higher have a high-titer inhibitor; those with a titer below 5 Bethesda units have a low-titer inhibitor.
People with high-titer inhibitors often have fast, strong immune system responses against FVIII or FIX, meaning that the inhibitor can quickly increase to very high levels. If there is no further exposure to the missing factor, the antibody levels may drop over a period of months to years, even to an undetectable range. However, this does not mean that the inhibitor is gone. It may reappear with new exposure to clotting factor products months or even years later.

For people with a low-titer inhibitor, the body’s immune response produces a persistently low level of antibodies despite the person’s continued exposure to factor concentrate.

A positive test result does not mean a person will always have an inhibitor. In some people, inhibitors have spontaneously disappeared without treatment. Although rare, these cases are classified as transient inhibitors.

Treating a person who has an inhibitor can be a challenging experience for both the patient and the healthcare team. Often, the treatment is a two-fold process. The first step is to manage bleeding episodes. The second step is dealing with the inhibitor itself. Eliminating the inhibitor requires a different treatment regimen for each individual, since no two patients or situations are identical. The process can take months or even years of treatment. Proper diagnosis and treatment of inhibitors is complex, and many variables affect treatment choice. In all cases, these choices should be discussed with healthcare providers who have expertise managing inhibitors.

For people with low-titer inhibitors, minor and major bleeds can often be treated effectively with factor replacement therapy. To overcome the presence of inhibitors in these cases, physicians may use a greater amount of factor per dose and/or prescribe additional doses to treat each bleeding episode.

For people with high-titer inhibitors, treatment of bleeding is more problematic. Increasing the amount of factor is typically not an option because the inhibitor can neutralize even very large doses of factor. In these cases, treatment is based on the type of hemophilia and the nature of the bleed. Most bleeding episodes in these patients are treated with bypassing products or recombinant factor VIIa.

Bypassing Agents

Most bleeding episodes experienced by inhibitor patients can be treated with a bypassing agent. These are factor products that can circumvent or “bypass” the need for the deficient clotting factor (VIII or IX) while stimulating blood clot formation. The most commonly used bypassing agents that are licensed by the U.S. Food and Drug Administration to treat inhibitors are activated prothrombin complex concentrate (aPCC) and recombinant factor VIIa (rFVIIa).

FEIBA VH® (Baxter Healthcare), the only aPCC available in the U.S., is a plasma-derived therapy containing activated clotting factors Ila, VIIa and Xa. It has been used to treat bleeds in hemophilia patients with inhibitors to FVIII and FIX for more than 30 years.
While this product is derived from human plasma, it is treated with vapor steam heat to eliminate potential viruses. Today the risk for transmission of HIV and hepatitis B and C in this type of product is now very low as a result of improved donor screening and viral inactivation methods.

NovoSeven®RT (Novo Nordisk), a recombinant factor VIIa drug made by recombinant DNA technology, has been available to individuals with inhibitors to FVIII or FIX in the U.S. since 1999. It is licensed for the treatment of bleeding episodes and the prevention of bleeding related to surgery or other invasive procedures in hemophilia A and B patients with inhibitors. No human plasma proteins are used in its production, and it is not stabilized with albumin. Thus, the risk of transmission of human viruses is essentially zero. However, since multiple doses may be required to stop bleeding, treatment can be very expensive, particularly if treatments continue for an extended period of time. FEIBA® and NovoSeven® are used separately and, in some cases, in combination.

While these products are largely effective, they do have limitations. One problem is the lack of uniform and/or universal standards to demonstrate a bypassing agent’s capacity to stem bleeding. The lack of standardized lab tests showing a bypassing agent’s effectiveness means that doctors must often adjust dosages and even change product, before finding the most effective treatment.

Bypassing agents can also trigger excessive blood clotting, called thrombosis. The production of excessive clots may also be increased if the person is being treated with antifibrinolytic drugs such as aminocaproic acid (Amicar®, manufactured by Xanodyne Pharmaceuticals). In addition, certain bypassing agents contain small amounts of the deficient clotting factor IX, which can stimulate the continued production of inhibitors rather than allowing the inhibitor level to fall over time.

Porcine Factor VIII

Porcine factor VIII, which is made from pig plasma, is similar enough to its human FVIII counterpart to work effectively in the human clotting system of people with hemophilia A. It is different enough that most individuals’ immune systems do not recognize it to the same extent as human factor VIII. However, in 20% of patients, their inhibitor reacts with the porcine FVIII; after 5 days of therapy, up to 80% of patients will make an antibody to porcine FVIII.

This product effectively stops major bleeds in patients whose inhibitor does not destroy porcine factor VIII. However, allergic reactions and a temporary drop in platelet count have been associated with the use of this product, which is currently not available. A recombinant form of porcine factor VIII, rpFVIII, is currently in clinical trials and will hopefully be available soon.

Plasmapheresis

During a life- or limb-threatening bleeding episode, physicians can remove the inhibitor antibodies from the body using a process called plasmapheresis. The procedure involves taking plasma from a patient using a small, thin tube inserted into a large vein, typically in the arm, while a second tube is put in the opposite hand or foot. The blood is removed through the outflow tube and put through a device called a cell separator. The device can work two ways: by “spinning” the blood at a high speed to separate the cells from the plasma or by filtering the blood through a membrane with tiny pores through which only the fluid-like plasma can pass. The separated blood cells, combined
with other replacement fluids such as saline or albumin, are eventually returned to the individual through the other tube while the antibody-filled plasma is discarded. The process, which can be done in an out-patient setting, is often conducted in conjunction with other immunosuppressive drug treatments.

Depending on the patient, successful plasmapheresis may require plasma exchanges from once a week to several days in a row. It may require as many as six to 10 procedures during a two- to 10-week period. When completed, plasmapheresis lowers antibody levels enough to allow infused factor concentrate to treat the bleed. However, this is only a temporary solution because within a few days, the body will begin producing large amounts of new antibodies.

**Immune Tolerance Induction**

While the treatments discussed in the previous sections provide immediate options for treating a bleed, they do not have the same positive, long-term effects as standard factor VIII or IX replacement therapy in patients without inhibitors. Continued use of these less-than-optimal treatments can also lead to secondary problems such as infections and more bleeding into joints or organs.

Because of these serious complications, many healthcare providers believe that ridding the body of inhibitors offers an optimal long-term solution. This is done using a course of therapy known as **immune tolerance induction (ITI)** or **immune tolerance therapy**.

The goal is to eventually “teach” the body to accept the factor and not mount an immune response. Normal factor replacement therapy can then be used to prevent or control bleeding.

Most of the treatment regimens for ITI involve repeated exposure to the deficient clotting factor over a long time, similar to allergy desensitization. Patients receive daily doses of factor over a period of weeks, months or even years. ITI is very effective, eliminating the inhibitor in approximately 60% to 80% of cases. However, the individual may need to stay on prophylactic factor replacement therapy for several years afterward. Some people going through this therapy are also given immune suppressive drugs, which can decrease the amount of new inhibitor produced but may also predispose the body to infection.

The risks and benefits of ITI should be discussed in detail with a healthcare provider. The HTC can play an important role in assessing a family’s support system, especially as it relates to the time and dedication that this type of therapy requires, such as the necessity of more frequent intravenous (IV) treatments and clinic visits. A treatment regimen as intensive as ITI often calls for supportive counseling from the HTC social worker. As a family adjusts to the “fits and starts” sometimes associated with immune tolerance – therapy can be interrupted because of complications such as infections and blood clots – ongoing adherence can become challenging. Despite the hurdles that may arise, a relatively high rate of success and the promise of a long-term solution to the inhibitor problem explains why many providers still favor ITI. A team effort involving HTC staff and drawing on the ongoing support of family and peers can go a long way to ensuring adherence to the ITI regimen and its ultimate success.
People with inhibitors experience musculoskeletal bleeds (into joints and muscles), just like people without inhibitors, but they are often harder to control and require longer recovery and rehabilitation time. Re-bleeding, a recurrence of a specific bleed while a patient is still recovering from the initial bleed, is also more common in people with inhibitors. It is important for an individual to recognize the signs of joint and muscle bleeding and call the HTC, so that these recurring bleeds can be treated promptly.

To prevent musculoskeletal bleeding, the HTC physical therapist will help develop an individualized treatment plan and exercise program, focusing on strengthening supportive structures around the joints to decrease the likelihood of bleeding. In addition, protective gear and/or assistive devices may be recommended to further prevent injury. Participating in recreational sports activities can provide musculoskeletal conditioning, as well as many other physical and psychosocial benefits. When choosing which activities to participate in, people with inhibitors should avoid high-contact, high-risk activities and discuss appropriate activities with their HTC staff.

People with inhibitors often experience joint damage from repetitive bleeding, which is an accumulation of bleeding episodes over the course of many years. There are many beneficial nonsurgical and surgical options to help relieve the pain and limited motion caused by this joint damage. The best treatment option for joint damage is prevention.

Additional Life Challenges

Musculoskeletal & Physical Activity Concerns

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Social & Emotional Concerns

Patients with inhibitors and their families face many challenges, especially from the ongoing financial, physical and emotional strain associated with such intense, frequent and long-term therapy. Many families live in areas where they do not have access to immediate treatment and must travel long distances to get appropriate care. Coping with frequent bleeds and repeated infusions means patients with inhibitors also need to deal with the additional issues of how to manage their pain. A rise in school absences and time lost at work for parents and caregivers can cause added strain.

Inhibitor development in children often has a significant psychosocial impact, since more intensive therapy may limit activities until the inhibitor is eliminated. On the other hand, physical activity, one of the most natural and healthy of children’s endeavors, has many physical and emotional benefits. Families need to work closely to contact the insurance company in advance to determine if a proposed treatment plan is covered or if there is additional justification needed. When contacting an insurance company, it may be helpful to ask for a nurse case manager who specializes in hemophilia to ensure clear and detailed answers to questions. Patients should be aware that there are significant differences in coverage and reimbursement for inpatient versus outpatient treatment.

Working closely with the social worker and the rest of the HTC team early on will go a long way in helping patients to verify insurance coverage benefits, coordinate care, identify any problems or potential gaps in coverage, and investigate eligibility through government and/or pharmaceutical assistance programs.

In many cases, insurance companies will not cover all treatment-related costs. Therefore, it becomes imperative for patients and their families to not only understand the initial costs of treatment but also how these costs will accrue over the projected length of the inhibitor therapy. This knowledge will provide consumers with a clearer sense of how treatment costs may affect their own out-of-pocket costs and the likelihood of reaching their health insurance plan’s lifetime limit or cap. When considering out-of-pocket costs, the HTC social worker is often able to assist patients in identifying potential resources to help defray the costs of treatment.

Treatment Costs & Financial Considerations

Factor replacement therapy for hemophilia is costly, even without the presence of an inhibitor. Once an inhibitor appears, treatment often becomes extraordinarily expensive.

It is important for the patient, as well as the HTC team,
**Antibody:** A protein formed by the body’s immune system in response to a foreign substance entering the body.

**Antigen:** The part of a foreign protein that provokes the formation of an antibody by the immune system.

**Bethesda inhibitor assay:** A blood test that measures the amount of antibody present. Measurements are given in “Bethesda units” or “Bethesda titer.”

**Bethesda units:** Also known as a “Bethesda titer,” a measurement of the level of inhibitor to clotting factor.

**Bypassing agents:** Factor concentrates that can “bypass” the need for the deficient clotting factors (VIII or IX), while still helping to ensure the formation of a clot to stop a bleed.

**High-titer inhibitor:** An inhibitor measured at 5 Bethesda units or higher signifying a powerful immune response to clotting factor.

**Immune tolerance induction:** Also known as immune tolerance therapy, this is a clinical therapy option for eliminating an inhibitor that involves regular (once daily or several times per week) doses of factor VIII or IX product to train the immune system to accept the therapy by ceasing to produce antibodies. It may take a few weeks to a few years.

**Inhibitor screen:** (Also known as a mixing study.) A lab test used to identify blood clotting abnormalities which may indicate the presence of an inhibitor. If results are positive, then the screen is often followed up by a specialized assay (like the Bethesda inhibitor assay), to confirm an inhibitor diagnosis.

**Low-titer inhibitor:** An inhibitor measured at lower than 5 Bethesda units signifying a less potent inhibitor response.

**Plasmapheresis:** A process used to separate the inhibitor antibodies from a patient’s plasma.

**Porcine factor VIII:** A factor VIII product used to treat serious bleeding episodes in hemophilia A inhibitor patients. This concentrate, derived from the plasma of pigs, is no longer available in the U.S. However, a recombinant form is in clinical trial development.

**Re-bleeding:** Recurrence of a specific bleed while a patient is still recovering from the initial bleed.

**Repetitive bleeding:** An accumulation of bleeding episodes over many years.

**Transient inhibitor:** A low-responding inhibitor that disappears without treatment.

Future Research

The scientific community is still seeking to fully understand why inhibitors occur in certain hemophilia patients. Research is underway to determine why some individuals with severe hemophilia develop inhibitors while others do not. This information will lead to ways to tailor therapy in order to prevent inhibitor formation in those individuals who are predisposed to making them.

For more information about inhibitors, please contact the information resource center of the National Hemophilia Foundation: 800.42.HANDI or info@hemophilia.org.
The National Hemophilia Foundation is dedicated to finding better treatments and cures for bleeding and clotting disorders and to preventing the complications of these disorders through education, advocacy and research. Its programs and initiatives are made possible through the generosity of individuals, corporations and foundations as well as through a cooperative agreement with the Centers for Disease Control and Prevention (CDC).