

What are inhibitors?



WORLD FEDERATION OF
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FÉDÉRATION MONDIALE DE L'HÉMOFILIE
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Treatment for All

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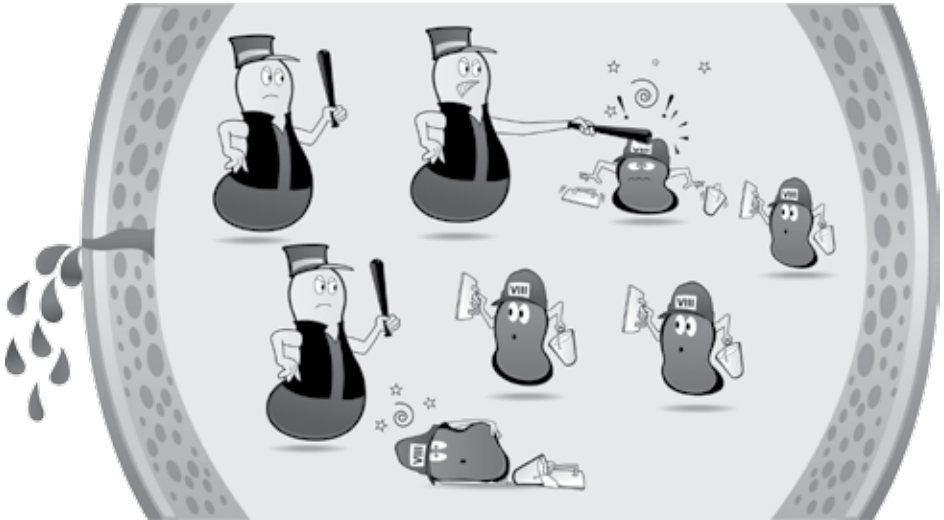
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WHAT ARE INHIBITORS?

Inhibitors are a serious medical problem that can occur when a person with hemophilia has an immune response to treatment with clotting factor concentrates.

The immune system defends the body from harmful germs and viruses. Sometimes in the case of an inhibitor, a person's immune system reacts to proteins in factor concentrates as if they were harmful foreign substances because the body has never seen them before. When this happens, inhibitors (also called antibodies) form in the blood to fight against the foreign factor proteins. This stops the factor concentrates from being able to fix the bleeding problem.

How inhibitors neutralize treatment products



Bleeding is very hard to control in someone with hemophilia who develops inhibitors. A person with inhibitors faces more bleeding and pain because treatment with factor concentrates does not work. If bleeding into the muscles and joints (the most common type of bleeding in hemophilia) is not controlled, permanent joint damage is likely.

Treatment of inhibitors is one of the biggest challenges in hemophilia care today. It is possible to get rid of inhibitors using a technique called immune tolerance induction (see page 11). However, this type of treatment requires specialized medical expertise, is expensive, and takes a long time.

Drugs called bypassing agents can be used to work around inhibitors and help blood clot.

WHO IS AT RISK OF DEVELOPING INHIBITORS?

Inhibitors occur more often in individuals with severe hemophilia than in those with moderate or mild hemophilia (see severity figure below). Most people who develop inhibitors do so within the first 75 exposures to factor concentrates, with the greatest risk occurring between the first 10–20 treatments. This means that inhibitors occur mostly in children with severe hemophilia, though they can also occur later in life in individuals with mild or moderate hemophilia following treatment.

About 25–30% of children with severe hemophilia A (factor VIII deficiency) develop inhibitors. Fewer individuals with hemophilia B (factor IX deficiency) develop inhibitors — about 1–6%. For this reason, less information is available on the risk of inhibitors to factor IX concentrates. We do know that

Severity of Hemophilia

The level of severity depends on the amount of clotting factor that is missing from a person's blood.

MILD HEMOPHILIA

5%–30% of normal clotting factor activity

- Might bleed for a long time after surgery or a very bad injury
- Might never have a bleeding problem
- Do not bleed often
- Do not bleed unless injured

MODERATE HEMOPHILIA

1%–5% of normal clotting factor activity

- Might bleed for a long time after surgery, a bad injury, or dental work
- Might bleed about once a month
- Rarely bleed for no clear reason

SEVERE HEMOPHILIA

Less than 1% of normal clotting factor activity

- Bleed often into the muscles or joints
- Might bleed one or two times per week
- Might bleed for no clear reason

some people with hemophilia B who develop inhibitors may experience a severe allergic reaction called anaphylaxis if they continue to receive factor IX concentrates. Because of this danger, it is very important for people with hemophilia B to be treated at a hemophilia treatment centre, particularly for the first 10–20 treatments, with factor IX concentrates.

Ideally, children and adults who are newly diagnosed with hemophilia should be tested regularly for inhibitors between the 1st and 50th days of treatment. Even after the 50th day of treatment, they should be checked at least twice a year until they have received 150–200 doses and at least once a year after that. Testing for inhibitors should also be done before any major surgery.

WHAT OTHER FACTORS CAN AFFECT A PERSON'S RISK OF DEVELOPING INHIBITORS?

Some other things that can increase an individual's risk of developing inhibitors are:

- History of inhibitors in the family.
- Severe defects in the factor gene.
- African ancestry.
- Early intensive treatment with high doses of factor concentrates (particularly in the first 50 doses).

Some studies have shown that people who receive regular treatments with factor concentrates to prevent bleeds (prophylaxis or prophylactic treatment) have a lower chance of developing inhibitors. Little is known about

whether the type of factor concentrates (recombinant or plasma-derived) that is used plays a role, but there are ongoing studies to shed light on this matter.

WHAT ARE THE SIGNS AND SYMPTOMS OF INHIBITORS?

A person with hemophilia who develops inhibitors does not get better after standard treatment with factor concentrates. Inhibitors are suspected when the person, family members or medical staff notice that treatment is less effective than it used to be. Signs and symptoms of inhibitors include:

- A bleed is not promptly controlled with the usual dose of factor concentrates.
- Normal treatment seems less and less effective.
- Bleeding is more and more difficult to control.

A diagnosis based on signs and symptoms of inhibitors should be confirmed by repeated laboratory tests. Sometimes, inhibitors are discovered during a routine laboratory test.

HOW ARE INHIBITORS DIAGNOSED?

Inhibitors are often suspected during a routine blood test called the activated partial thromboplastin time (APTT) assay. The APTT test measures how long it takes for blood to clot. When inhibitors are present, the blood takes longer to clot and does not coagulate fully, even after mixture with normal

plasma. In order to diagnose inhibitors, a Bethesda assay, or a modification thereof, the Nijmegen method, is performed. This test can determine the strength (titer) of the inhibitor. However, the Bethesda/Nijmegen method is not available in many laboratories because it requires specialized expertise.

Inhibitor levels vary from one individual to another and can also vary within the same person over time. The amount of inhibitors in a person's blood is measured in Bethesda Units (BU) and referred to as "high titer" (more than 5 BU) or "low titer" (less than 5 BU). Generally, high titer inhibitors act strongly to quickly neutralize infused factor concentrates, while low titer inhibitors are weaker and act more slowly. However, this is not always the case.

Inhibitors are also classified as "low responding" or "high responding" according to how strongly the person's immune system reacts to factor concentrates based on memory from a previous encounter – this is called the anamnestic response. A high responder is someone whose titer has exceeded 5 BU at least once and in whom repeated exposure to factor concentrate will quickly trigger the formation of new inhibitors. A low responder is someone whose titer has never exceeded 5 BU and who will have a weaker inhibitor response to factor concentrates.

HIGH TITER INHIBITORS

> 5 BU

- Inhibitors act strongly
- They quickly neutralize factor

HIGH RESPONDING

- Inhibitor titer exceeded 5 BU at least once
- Repeated exposure to factor will quickly trigger new inhibitors

LOW TITER INHIBITORS

< 5 BU

- Inhibitors act weakly
- They slowly neutralize factor

LOW RESPONDING

- Inhibitor never exceeded 5 BU
- Exposure to factor will more slowly trigger new inhibitors

WHAT ARE THE TREATMENT OPTIONS FOR PEOPLE WITH INHIBITORS?

People with inhibitors are more difficult to manage and treat than people without inhibitors. There are a number of different approaches. Decisions regarding treatment should take into account the person's inhibitor titer and anamnestic response, the site and severity of the bleed, and whether he/she has started or is planning to start immune tolerance induction therapy (see page 11). Ideally, a person with inhibitors should be treated at a hemophilia treatment centre with specialized expertise.

- **HIGH-DOSE FACTOR CONCENTRATES:** Administering factor concentrates at higher doses and/or more frequent intervals is the preferred treatment for acute bleeding in low responders. The person's factor level should be measured right after each infusion to make sure that target levels are reached. Continuous infusion may be useful. High-dose factor concentrate is also the preferred treatment option for acute bleeding in previous high responders with current low titer inhibitors – however, it is vital to take into account that the anamnestic response will get stronger within five to seven days, at which time treatment should be switched to bypassing agents.
- **BYPASSING AGENTS:** Bypassing agents, such as activated prothrombin complex concentrates (APCC) and recombinant factor VIIa (rFVIIa), are used to treat

acute bleeding in people with high titer inhibitors. However, these treatment products are expensive and not always available in every country.

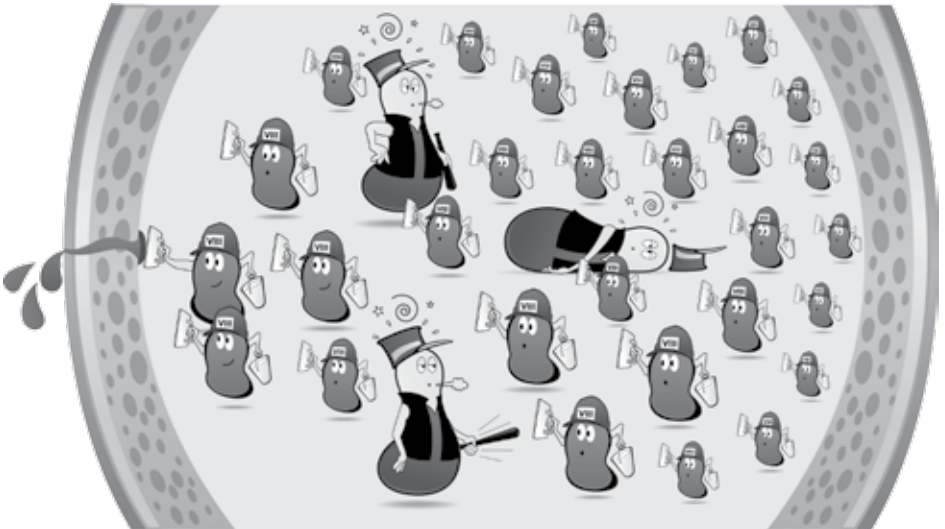
- APCCs like Factor Eight Inhibitor Bypassing Agent (FEIBA®) are made from human plasma and contain variable amounts of clotting factors such as factor VII, factor IX, and factor X. Treatment is given frequently (usually every eight to twelve hours) but should be limited to a maximum of five consecutive doses. A risk of blood clot formation has been associated with its use.
- Recombinant factor VIIa (rFVIIa, NovoSeven®) is a synthetic product that also has to be administered frequently (usually every two to three hours), which can lead to problems with access to veins.
- **TRANEXAMIC ACID:** Tranexamic acid is an antifibrinolytic drug that can be given as an additional therapy in pill form or by injection to help stop blood clots from breaking down. It is particularly useful for bleeding that involves mucous membranes such as those in the nose or mouth. However, it should not be used in combination with APCCs.
- **EPSILON AMINOCAPROIC ACID (AMICAR™):** Epsilon aminocaproic acid is an antifibrinolytic drug that can be given as an additional therapy in pill form or by injection to help hold clots in place in certain parts of the body, such as the mouth, bladder, and uterus.

- **PLASMAPHERESIS:** Plasmapheresis is a procedure that removes inhibitors from the person's bloodstream. It is usually done when the inhibitor titer needs to be brought down quickly (for example, before major surgery or in cases of severe bleeding that are not well controlled with bypassing agents).
- **IMMUNE TOLERANCE INDUCTION THERAPY:** Immune tolerance induction (ITI) therapy involves giving the person with inhibitors frequent doses of factor concentrates over several months, or sometimes years, to train the body to recognize the treatment product without reacting to it. This process is called tolerance induction. If a person plans to undergo immune tolerance induction therapy, but has not yet started, it is better not to use factor products to treat acute bleeding episodes prior to starting immune tolerance because they are likely to provoke a rise in inhibitor titer.

HOW DOES IMMUNE TOLERANCE INDUCTION WORK?

With immune tolerance induction therapy, factor concentrate is given regularly over a period of time until the body is trained to recognize the treatment product without reacting to it. When immune tolerance induction is successful, the inhibitors disappear and the person's response to factor concentrates returns to normal. The majority of people who undergo ITI therapy will see an improvement within 12 months, but more difficult cases can take two years or longer.

Concept of tolerance induction



Different dosing schedules are currently being used for ITI therapy, and the best one for eliminating inhibitors has not yet been defined. Daily, high doses of factor concentrates may induce tolerance faster, but this type of regimen is more expensive and carries different risks than do schedules that involve giving less factor concentrate, less frequently.

An ongoing study called the Immune Tolerance Induction Study (www.itistudy.com) is trying to compare the effectiveness and safety of different dosing regimens. The results of this study will help improve ITI therapy for people with factor VIII inhibitors in both developed and developing countries.

WHAT FACTORS INFLUENCE THE OUTCOME OF IMMUNE TOLERANCE INDUCTION THERAPY?

It is still unclear why ITI works better in some people than in others. Factors that have been associated with successful ITI therapy include:

- Beginning ITI in people whose inhibitor levels are below 10 BU/mL and ideally below 5 BU/mL.
- Beginning ITI in people whose inhibitor levels have never gone higher than 200 BU/mL and have ideally stayed below 50 BU/mL.
- Beginning ITI within five years of a person being diagnosed with the inhibitor.

Stopping treatment early or taking breaks in the treatment schedule (missed doses) may interfere with the success of ITI and/or increase the time it takes for the person with inhibitors to achieve tolerance.

Researchers are also looking at whether the type or brand of factor concentrate (intermediate or high-purity plasma-derived factor concentrates or recombinant products) used in ITI can influence the success of therapy. So far, similar success rates have been obtained with both recombinant and plasma-derived products.

**For more information
about inhibitors, visit the
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