

# HEMOPHILIA: UNDERSTANDING INHIBITORS

Patients with *hemophilia* (a blood clotting disorder) can develop *inhibitors* (also called antibodies) when they have an immune response to *factor concentrates* (the treatment for hemophilia). Treatment of inhibitors is one of the biggest challenges in hemophilia care because patients with inhibitors can face greater risk of bleeding and the technique to get rid of inhibitors requires specialized medical expertise, is expensive, and can take a long time. Read below for more information about the development, diagnosis, and treatment of hemophilia with inhibitors.

This tear sheet was produced in collaboration with the World Federation of Hemophilia ([wfh.org](http://wfh.org)).

## What Are Inhibitors?

Inhibitors are antibodies that the immune system develops when it reacts to the proteins in *factor concentrates* (hemophilia treatment) as if they were harmful substances. Inhibitors fight against the proteins, as if they are foreign substances, thereby preventing the treatment from effectively managing a patient's bleeding risk.

## Who Is Affected by Inhibitors?

Inhibitors occur more often in individuals with *hemophilia A* (factor VIII deficiency) and *severe hemophilia* (those with <1% of normal clotting factor activity that is associated with bleeding into the muscles or joints, bleeding that occurs one to two times per week, or bleeding for no clear reason).

Most patients develop inhibitors within the first 75 exposures to factor concentrates, with the greatest risk occurring within the first 10 to 20 rounds of treatment.

Children and adults with newly diagnosed hemophilia should be tested regularly for inhibitors, as well as before any major surgery.

Other factors linked to an increased risk of developing inhibitors include:

- a family history of inhibitor development
- severe defects in the factor gene
- African ancestry
- early intensive treatment with high doses of factor concentrates (particularly in the first 50 doses)

## What Are the Symptoms of Inhibitors?

A person with hemophilia who develops inhibitors does not get better after standard treatment with factor concentrates.

Signs and symptoms of inhibitors include:

- bleeding that is not promptly controlled with the usual dose of factor concentrates
- treatment becoming less effective
- bleeding becoming more difficult to control

## How Are Inhibitors Diagnosed?

Inhibitors are often discovered during a routine laboratory test for *activated partial thromboplastin time*, which measures how long it takes for blood to clot. When inhibitors are present, the blood takes longer to clot and does not coagulate fully.

To confirm the diagnosis, a *Bethesda assay* is performed (measured in Bethesda units [BU]); it determines the *titer*

(strength) of the inhibitor, either *high titer* (>5 BU) or *low titer* (<5 BU). Generally, high-titer inhibitors quickly counteract infused factor concentrates, whereas low-titer inhibitors act more slowly.

Inhibitors are also classified by response, according to how strongly a patient's immune system reacts to factor concentrates:

- *Low-responding* inhibitors have stayed below 5 BU, and the patient has a weaker inhibitor response to factor concentrates.
- *High-responding* inhibitors have exceeded 5 BU at least once, and repeated exposure to factor concentrates will quickly trigger the formation of new inhibitors.

## What Are the Treatment Options?

Decisions regarding treatment of hemophilia with inhibitors should take into account the person's inhibitor titer and anamnestic response, the site and severity of the bleed, and whether the patient has started or is planning to start immune tolerance induction therapy.

Treatment options include:

- *High-dose factor concentrates*: administering factor concentrates at higher doses and/or at more frequent intervals
- *Bypassing agents*: activated prothrombin complex concentrates and recombinant factor VIIa (These agents carry a risk for blood clot formation, are expensive, and are not always available in every country.)
- *Tranexamic acid*: an antifibrinolytic drug given as an additional therapy to help stop blood clots from breaking down
- *Epsilon aminocaproic acid*: an antifibrinolytic drug given as an additional therapy to help hold clots in place in certain parts of the body, such as the mouth, bladder, and uterus
- *Plasmapheresis*: a procedure that removes inhibitors from the patient's bloodstream, usually performed when the inhibitor titer needs to be brought down quickly
- *Immune tolerance induction therapy*: administering frequent doses of factor concentrates over several months to train the body to recognize the treatment without adversely reacting to it (This type of treatment requires specialized medical expertise, is expensive, and requires a lengthy process.) ●



**WFH**

WORLD FEDERATION OF HEMOPHILIA

## Resources From the World Federation of Hemophilia

For over 50 years, the World Federation of Hemophilia (WFH) has provided global leadership to improve and sustain care for people with inherited bleeding disorders, including hemophilia, von Willebrand disease, rare factor deficiencies, and inherited platelet disorders. Their vision of "Treatment For All" is that one day, all people with a bleeding disorder will have proper care, no matter where they live. The WFH is a global network of patient organizations in 134 countries and has official recognition from the World Health Organization.

For more Patient Information tools, visit [elearning.wfh.org](http://elearning.wfh.org).