

WHAT IS PROPHYLAXIS?



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YEARS OF ADVANCING
TREATMENT FOR ALL

WORLD FEDERATION OF HEMOPHILIA
Fédération mondiale de l'hémophilie
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WHAT IS PROPHYLAXIS?

Prophylaxis is the regular infusion of clotting factor concentrates in order to prevent bleeding.

The idea of prophylaxis came from the observation that people with moderate or mild hemophilia (who have clotting factor levels of 1% or more) rarely experience spontaneous bleeding. They also have less joint damage than people who have severe hemophilia.

Doctors believed that if they could keep minimum factor levels around 1% with regular infusions of clotting factor concentrates, they might reduce the risk of bleeding and prevent joint damage.

Since then, important studies have shown that children who receive prophylaxis do have fewer bleeds and healthier joints.

DID YOU KNOW?

Prophylaxis will not help repair joints that are already damaged. However, it will decrease the frequency of bleeding, may slow progression of joint disease, and may improve quality of life.

Prophylaxis is now the goal of treatment for people with severe hemophilia, allowing them to remain active and participate more fully in daily life.

Is 1% sufficient to prevent sub-clinical bleeding, or is it based on historical supply constraints, economics, and treatment protocol burdens?

TYPES OF PROPHYLAXIS

Unlike episodic or “on demand” treatment, which is given at the time of a bleed to make it stop, prophylaxis is given to prevent bleeding before it starts.

There are several types of prophylaxis. Continuous prophylaxis (primary, secondary, and tertiary) is given regularly over a period of several months and often years. Intermittent or periodic prophylaxis is given for shorter periods of time, usually a few weeks or months.

Type of treatment	Definition
Episodic (“on demand”) treatment	Treatment given at the time of bleeding
Continuous prophylaxis	
Primary prophylaxis	Regular continuous treatment, started before the second large joint bleed and age of 3 years
Secondary prophylaxis	Regular continuous treatment started after 2 or more large joint bleeds but before the onset of joint disease
Tertiary prophylaxis	Regular continuous treatment started after the onset of joint disease to prevent further damage
Intermittent (“periodic”) prophylaxis	Treatment given to prevent bleeding for short periods of time, such as during and after surgery

Adapted from: *Guidelines for the Management of Hemophilia*, World Federation of Hemophilia, 2012.

Note: These definitions are consistent with those published by the Factor VIII & IX Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis. National or regional programs may rely on other definitions.

ADMINISTRATION AND DOSING SCHEDULES

Prophylaxis is the regular infusion of clotting factor concentrates in an attempt to raise clotting factor levels and to keep them at 1% or higher at all times. There are a number of ways to achieve this; however, how it is done varies both from country to country and even within the same country.

Studies are still underway to determine the best dosing schedule (also called a ‘protocol’).

A prophylaxis schedule should outline:

- The type of factor product to be used
- The dose of factor administered with each injection
- The frequency at which treatment is administered
- The time (of day, or week) that treatment is administered

There are currently two protocols in use for which there is long-term data:

- The Malmö protocol: Injections of 25–40 IU/kg, administered three times a week for those with hemophilia A and twice a week for those with hemophilia B.
- The Utrecht protocol: Injections of 15–30 IU/kg, administered three times a week for those with hemophilia A and twice a week for those with hemophilia B.

In countries with significant resource constraints, lower doses of prophylaxis given more frequently (e.g., 10–15 IU/kg, 3 times per week) may be an effective option.

While these are the protocols that have been studied most extensively, the ultimate protocol has not yet been defined. (See also Personalized Prophylaxis, below)

Factors to consider when designing prophylaxis protocol:

- age at which prophylaxis started
- current age
- venous access
- bleeding symptoms
- joint status
- level and timing of physical activity
- availability of clotting factor concentrates
- size(s) of vials of clotting factor concentrates available

Personalized prophylaxis

We are entering an era in which it is becoming possible to treat an individual patient, rather than treating their disease. To be most effective, a prophylaxis protocol should be tailored to the individual based on their age, bleeding pattern, joint health, the level and timing of physical activity they engage in, their clotting factor levels, and their ability to adhere to a protocol. Prophylactic regimens should also be flexible enough to change with time as the individual patient's circumstances change.

Knowledge of a patient's pharmacokinetics – i.e. how the body absorbs, distributes, and eliminates a drug – is likely to help personalize prophylaxis when combined with other information.

Long-acting concentrates

New formulations of clotting factor concentrates with extended half-lives (they remain at higher levels for longer periods in the body) are designed to sustain the level of clotting factor concentrates in the blood for longer periods of time, meaning that less frequent and/or fewer injections will be needed to achieve the same result. The availability of these medications could change how prophylaxis is administered. They have the potential to increase the adoption of prophylaxis among patients, to improve patient adherence, and to improve outcomes.

MONITORING OUTCOMES

More than three decades of research has shown that continuous prophylaxis is preferable to on-demand therapy to reduce the frequency of bleeding and to prevent or delay joint damage.

People with hemophilia who are receiving prophylaxis should have an assessment on a regular basis to ensure that the goals of therapy are being met and to make any necessary adjustments to the treatment plan. These assessments should include an evaluation of:

- Joint health/status
- Bleed frequency
- Limitations in activities
- Psychosocial integration

A number of assessment tools are available to measure and monitor joint status and function, bleeding patterns, and quality of life. For more information on outcome assessment tools, consult the WFH's online Compendium of Assessment Tools (www.wfh.org/assessment_tools).

Inhibitor development should also be monitored in all patients. Inhibitor development is particularly common in people with severe hemophilia within the first 75 treatments with clotting factor concentrates. More than 50% of inhibitors develop within the first 15 exposure days.

WHEN TO START AND STOP

There are still varying opinions regarding the best time to start and stop prophylaxis.

The most cost-effective approach is to start prophylaxis early in order to preserve normal joints. Prophylaxis has been the standard of care in many European countries for more than 50 years, however the associated high cost has hampered its wide-scale adoption.

Access to large quantities of clotting factor concentrates needed for prophylaxis is certainly an important factor in determining when to start treatment and how long it should be continued.

In countries where treatment is readily available, most agree that prophylaxis should be started before irreversible joint damage has occurred. Some doctors believe it should begin after the first joint bleed, or by a certain age (typically two or three years old). Others recommend waiting until two or more bleeds have occurred.

Where access to clotting factor concentrates is limited, lower doses of prophylaxis given more frequently may be an effective option. To allow greater access to prophylaxis, cost-efficacy studies are needed to determine the minimum effective dosage, thereby maximizing treatment product for the greatest number of patients.

It is also unclear whether all patients should remain on prophylaxis indefinitely as they become adults. Although some studies suggest that young adults can do well without prophylaxis, more studies are needed before a clear recommendation can be made. Patients often decide for themselves whether to continue prophylaxis or not.

BARRIERS AND CHALLENGES

Cost and access to treatment products

The biggest barrier to long-term prophylaxis is the cost of treatment. Prophylaxis is only possible if significant resources are allocated to hemophilia care. However, it is cost-effective in the long-term because it eliminates the high cost associated with subsequent management of damaged joints and improves quality of life.

It is very important to collect and provide scientific evidence that justifies the high cost of treatment, even in countries that have traditionally invested significantly in hemophilia treatment and where prophylaxis is well-established as a standard of care.

In countries where access to clotting factor concentrates is limited, prophylaxis is not possible for most patients. However, some countries are now starting low-dose prophylaxis in children. Follow-up data of these patients will be very important in confirming the effects on their joints. Patients and healthcare providers must work together to advocate for a national hemophilia care program and the purchase of sufficient clotting factor concentrates.

Adjustments to the prophylaxis protocol, such as administering lower doses of factor concentrates more frequently, may also be an effective option. Cost-efficacy studies designed to identify minimum dosage are necessary to allow access to prophylaxis across the world.

Venous access

Prophylaxis requires frequent injections and it can be difficult to find suitable veins in very young children with hemophilia.

An implanted venous access device (e.g. Port-A-Cath) can make injections much easier and may be required for administering prophylaxis in young children. However, there are risks involved with the use of these devices, including the risk of local infection and the formation of blood clots that may cause blockage. These risks need to be weighed against the advantages of starting intensive prophylaxis early. In 70% of children early prophylaxis is possible without venous access devices. An important option is starting prophylaxis once a week as it does not require the implantation of a Port-A-Cath which makes the treatment easier for patients and families to accept.

Adherence

Adherence to (or compliance with) a treatment plan is generally defined as the extent to which patients take medications as prescribed by their healthcare providers. According to the World Health Organization, rates of non-adherence with any medication treatment may vary from 15% to 93%, with an average estimated rate of 50%.

Adherence to a prophylaxis protocol is critical to its success. Prophylaxis is most effective if factor levels are continuously maintained above the target level. Missing or skipping a dose can cause clotting factor levels to fall below this target, which increases the risk of bleeding. Bleeding that occurs while a patient is on prophylaxis is called 'breakthrough bleeding'.

Patients and healthcare providers must work together to ensure that the protocol is manageable for the person with hemophilia and their family. A patient's adherence to the protocol should be assessed regularly during clinic visits and strategies to improve adherence, including changes to the protocol, should be explored wherever possible.

For more detailed information about prophylaxis, please visit the World Federation of Hemophilia's website: www.wfh.org



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