SDM
WFH SHARED DECISION MAKING TOOL

SHL/EHL

CLOTTING FACTOR REPLACEMENT THERAPIES

What is clotting factor replacement therapy?

Clotting factor replacement therapies are a prophylactic treatment of hemophilia A and hemophilia B. Clotting factor replacement therapies provide the missing factor VIII or factor IX, which allows the blood to clot efficiently. These therapies can also be used on demand.

Clotting factor replacement therapies provide a short-term increase in factor levels by injecting the needed clotting factor protein. The body does not produce this replacement factor; therefore, the effects are temporary, and injections must be administered frequently and regularly to maintain effective clotting factor levels and prevent bleeds (prophylaxis) or as needed to stop bleeds (on-demand).

What are the different types of replacement therapies?

The two clotting factor replacement therapy types are standard half-life (SHL) and extended half-life (EHL). Half-life refers to how long the treatment lasts inside your body. Both SHL and EHL increase your factor levels. After injecting SHL therapies, your factor levels increase immediately but decrease quickly over the next few days. The same is true for EHL, except that factor levels remain higher for longer.

There are many different SHL and EHL medications available for both hemophilia A and hemophilia B. The most recently approved EHL for hemophilia A, ALTUVIIIO, has a 3- to 4-fold longer half-life compared to other FVIII products, and therefore, requires less frequent infusions compared to other EHLs for hemophilia A.[1]

Standard Half-Life Factor Therapy

Extended Half-Life Factor Therapy

How is the mechanism of action for clotting factor replacement therapies different from other treatments for hemophilia?

The main treatment types for hemophilia are clotting factor replacement therapy (standard half-life (SHL) and extended half-life (EHL)), bispecific antibodies, re-balancing agents, and gene therapy. All these treatments help the blood clot more efficiently, but they all work in different ways.

Clotting factor replacement therapy provides a short-term increase in factor levels by injecting the needed clotting factor protein directly into the blood of a person with hemophilia.

Bispecific antibodies are Y-shaped proteins that act as a bridge between factor IXa and factor X, which helps the blood to clot more efficiently. This antibody bridge mimics the function of the missing activated factor VIII (i.e., factor VIIIa-mimetic).

Rebalancing therapies restore the disrupted balance between the levels of anticoagulation (i.e., anti-clotting) factors and clotting factors in the blood, thereby improving blood clotting.

Gene therapy introduces a working copy of the missing clotting factor gene. Once the gene is introduced, the body can produce the missing protein and maintain adequate clotting factor levels, on its own, for an extended time.

TREATMENT WITH CLOTTING FACTOR REPLACEMENT THERAPIES

Who is eligible to use clotting factor replacement therapies?	Adults and children with hemophilia A or B who do not have inhibitors are eligible for clotting factor replacement therapy.[1]
How are prophylactic clotting factor replacement therapies administered?	Clotting factor replacement therapies are administered through an injection into your vein. The injection usually takes 5–10 minutes and can be done at home or a clinic.
What is the treatment frequency for prophylaxis with clotting factor replacement therapy?	Prophylactic treatment with clotting factor replacement therapies aims to maintain enough clotting factor levels to prevent bleeding. The frequency and dosage of the infusion depend on the individual's specific needs, hemophilia severity, and the type of factor replacement product being used. SHL and EHL must be injected regularly to keep factor levels high and prevent bleeding. SHL is typically administered 2–4 times per week, and EHL is typically administered 1–2 times per week or less.[1,2]
Can clotting factor replacement therapies be used in combination with other hemophilia treatments?	Yes. Clotting factor replacement therapies can be used in combination with other hemophilia treatments.[1]

EFFICACY OF CLOTTING FACTOR REPLACEMENT THERAPIES

How will clotting factor levels be affected?	Clotting factor levels will increase immediately after treatment and decrease rapidly and return to baseline within a few days without repeat treatment. The rapid decrease in factor levels necessitates frequent and regular treatment to keep factor levels high. The time that it takes the replacement clotting factor to decrease by half is called the "half-life." Extended half-life replacement therapies remain in the blood longer, and therefore require less frequent dosing to maintain adequate factor levels.[1,2]
How will clotting factor replacement therapies affect my annual bleed rate?	Any form of regular prophylactic treatment is likely to reduce your annual bleed rate. Annual bleed rate is calculated as the sum of all bleeds experienced over a 12-month period and is highly dependent on individual factors such as age, prior bleeding history, physical activity, lifestyle, dosing regimen, and adherence to the dosing regimen. In clinical trials, the median annual bleed rates with SHL clotting factor therapies range from 0–2 for hemophilia A and 1–2 for hemophilia B, and the reported annual bleed rates with EHL clotting factor therapies range from 1–2 for hemophilia A and 1–2 for hemophilia B.[1]

SAFETY OF CLOTTING FACTOR REPLACEMENT THERAPIES

What are the potential side effects of clotting factor replacement therapies?

The most common side effects of clotting factor replacement therapies can include injection site reactions and allergic reactions. Side effects vary by the medication.

Are there any known serious side effects or risks?

One of the most significant side effects associated with clotting factor replacement therapy is the potential for the development of inhibitors, which are antibodies that can bind to and neutralize the replacement clotting factors. Inhibitors can reduce the effectiveness of treatment and increase the risk of bleeding. If inhibitors are going to occur, they typically develop within the first 75 days of exposure. Inhibitors occur in approximately 20–30% of people with hemophilia A and in about 3–5% of people with hemophilia B.[2] People with hemophilia who develop inhibitors are no longer eligible to use factor replacement therapies.

MONITORING AND FOLLOW-UP AFTER CLOTTING FACTOR REPLACEMENT THERAPY TREATMENT

How often will you need follow-up and monitoring with clotting factor replacement therapies?

As with all hemophilia treatment classes, regular monitoring by your health care team is recommended. Clinical review should be conducted annually and as needed.

What will happen in the event of a bleed, injury or surgery?

Your healthcare team will work with you to develop a personalized plan for managing any bleeds, injuries, or surgeries while taking clotting factor replacement therapies for prophylaxis. This is likely to include additional doses of clotting factor, additional medications, and/or physical therapy to manage bleeding and pain.

If you need to have surgery your healthcare team will carefully manage your treatment to ensure that you have enough clotting factor for the procedure. This may involve increasing your dose of clotting factor replacement therapy before and after the surgery.

1 Prescribing information from approved SHL and EHL products from the FDA and EMA.
2 Srivastava, A, Santagostino, E, Dougall, A, et al. *WFH Guidelines for the Management of Hemophilia*, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1–158.

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This is a living document that will be updated as new evidence becomes available.