Prophylaxis & Arthropathy
Coagulation factor replacement may be given when a bleed occurs (on-demand therapy) or before bleeding occurs, to prevent bleeds (prophylactic therapy).

The goal of prophylaxis treatment is to reduce the number of bleeds that occur, and to prevent progressive joint damage.

You may wonder why this is necessary. Why not just treat a bleed once it has occurred (ie, on-demand)?

Compared with on-demand treatment, prophylaxis results in a reduced risk of hemarthroses (bleeding into the joint space) and has been shown to protect joints from the development and progression of arthropathy (disease/damage of the joint)

This is thought to happen by preventing subclinical joint bleeds, that is, bleeding into the joint that you do not notice. Over time, this bleeding into the joint leads to arthropathy. Damage may become permanent.
Research carried out over the past decade has shown that even brief exposure to blood, as can occur after a limited number of bleeding episodes (or as a result of sub-clinical bleeding), can result in lasting cartilage damage.

As a result of joint bleeding, the components of red blood cells can accumulate in the joint space. One of these components is hemosiderin, an iron-containing complex. When it accumulates in tissues it can cause damage.

Prophylaxis is required to break the cycle of repeated bleeding and to prevent joint damage.
Iron deposits can be detected within the joints of people with hemophilic arthropathy. Iron can cause joint damage by triggering inflammation of the synovial tissue. This leads to chronic inflammation and accumulation of tissue-destructive enzymes.

These enzymes may damage both cartilage and bone. Iron can also destroy cartilage by interfering with the ability to make proteoglycans, an important component of cartilage.

Once joint damage occurs, many patients can be managed conservatively with clotting factor replacement, therapeutic exercises, anti-inflammatory drugs, orthotics, and activity restriction.

However, some patients have severe pain and disability and may require interventions such as synovectomy, joint fusion, and joint replacement.
Which Joints Are Most Commonly Affected?

Incidence of bleeding into different joints

- Shoulder: 3%
- Elbow: 30%
- Hip: 2%
- Knee: 45%
- Ankle: 15%
- Wrist: 3%

Who Needs Prophylaxis?

The decision to begin prophylaxis is yours and your hemophilia treatment team’s. Which type (frequency and dose) will be tailored to your needs. The majority of people using some form of prophylaxis in Canada have severe hemophilia. However, sometimes prophylaxis is recommended for patients with moderate or mild hemophilia. Your hemophilia treatment centre can help determine if prophylaxis is right for you.

There are many different possible treatment regimens. Your hemophilia treatment centre and physician will help find the optimal regimen for you.
How Does Prophylaxis Work?

**Prophylaxis** is defined as the infusion of factor concentrate in a non-bleeding state, in order to prevent bleeding.

Much of the sub-clinical bleeding into the joint can be prevented by maintaining at least 1% (or 1 IU/dL) of the normal levels of factor in the blood. **Routine prophylaxis** consists of infusions provided in a routine timeline that attempts to maintain levels at or above this target. Likewise, **episodic prophylaxis** may be given in anticipation of activities or events where a bleed is expected, and the goal is to maintain factor levels at an adequate level to prevent bleeding.

A prophylaxis regimen is tailored based on dose and frequency of dosing. Frequency of treatment is important as factor is slowly cleared from the body over time. Doctors often refer to “half-life”, which means the amount of time required for half the factor that was infused to disappear, or be cleared from the body. In general, for hemophilia A the factor has a half-life of ~12 hrs. The half-life of factor IX, used for hemophilia B, is ~18 hrs. Prophylaxis regimens for hemophilia A are often administered three times per week or more, while those for hemophilia B are often administered twice weekly.
How Do We Know Prophylaxis Makes a Difference? The Pediatric Experience

There is now good evidence that the early initiation of prophylactic treatment in children with severe hemophilia results in fewer joint bleeds, reduced arthropathy and improved quality of life.

One study by Dr Marilyn Manco-Johnson and others examined the benefit of prophylaxis in 65 boys with hemophilia. The boys received either prophylactic therapy (32 boys received this treatment) or on-demand therapy (33 boys), and the two groups were compared.

Boys included in this study were younger than 30 months, with severe hemophilia (factor VIII activity level of <2 IU/dl) and a history of bleeding into joints. By the time the boys reached 6 years of age, 45% of those in the on-demand therapy group already had joint damage as seen by magnetic resonance imaging (MRI). Only 7% of those in the prophylaxis group had detectable joint damage.

In another study, called ESPRIT (Evaluation Study on Prophylaxis: a Randomized Italian Trial), 40 children were studied. They had severe hemophilia A, aged <7 years, with no detected joint damage and at least 1 bleed during the previous 6 months.

They received prophylactic therapy (factor VIII 25 IU/kg body weight 3 times a week) or on-demand therapy (25 IU/kg body weight when they experience a bleed, treated daily until complete resolution of the bleed).

Children on prophylactic treatment had fewer breakthrough bleeds compared to children treated on-demand and fewer bleeds into joints. X-rays showed signs of joint damage in 29% of patients in the prophylaxis group, compared to 74% in the on-demand group.

How Do We Know Prophylaxis Makes a Difference? The Canadian Experience

The Canadian Hemophilia Primary Prophylaxis Study looked at a tailored prophylaxis approach to see if clotting factor use could be reduced (to keep cost at a minimum) while still preventing joint damage. Ten Canadian hemophilia clinics participated in this study that enrolled twenty-five children with severe hemophilia A.

All children were initially treated with prophylaxis at a dose of 50 IU/kg weight, once weekly. The frequency and weekly dosage of rFVIII replacement was increased (see steps in diagram), when one of the following happened:

- At least 3 bleeds into any one joint (target joint) over a consecutive 3-month period; or
- At least 4 bleeds—either significant soft tissue bleeds or joint bleeds—into any number of joints over a consecutive 3-month period; or
- At least 5 bleeds occurred into any one joint while on the same dosage (step) of factor therapy over any period of time.

In this study, most children appeared to have little bleeding if treated with once-weekly FVIII prophylaxis, at least for several years. Just over half of the children (52%) eventually required an increase (Step 2) in their regimen. By 5 years, almost one-third (28%) of the children required alternate-day prophylaxis (Step 3).

As almost one-half of all children were able to have good outcomes with once-weekly dosing, this step-wise, tailored prophylaxis, would appear to require considerably less FVIII than some other reported prophylaxis strategies. This may make it a cost-effective approach. Tailored prophylaxis was associated with good joint function and normal or near-normal X-rays of joints in the preschool and early school-age years.

Most studies of prophylaxis have been carried out in children. However, there are a few studies that have examined the value of prophylaxis in adults either continuing on prophylaxis that they started as a child, or starting a prophylaxis regimen as an adult (secondary prophylaxis).

A recently reported study looked at the benefits of secondary prophylaxis in adults with severe hemophilia. Twenty men (aged 30-45 years) participated in the study and used “on-demand” treatment for 6 months, followed by “prophylaxis” for 7 months. While treated with prophylaxis, there were fewer joint bleeds. There were also fewer bleeds of any kind and fewer spontaneous bleeds. In fact, the median number of bleeds during the months on prophylaxis was zero. The Gilbert score, which measures joint function, was also improved.

In another study conducted in Italy, prophylaxis reduced the annual number of total and joint bleeds. There was also a meaningful improvement in orthopaedic score (a measure of joint function) in adolescents.

Aside from reduced number of bleeds, the benefits of prophylaxis may also have an impact on your daily activities. One study showed that those treated with prophylaxis have fewer days lost from school or work, as well as fewer days spent in the hospital.\(^1\) Another more recent study\(^2\) showed that, in addition to fewer days lost from work or school, those on prophylaxis had fewer surgeries (arthrodoses, prostheses implantations and synovectomies), compared to those receiving on-demand treatment.

The median annual number of days lost from work for those on prophylactic treatment was zero.

Annual number of days lost from work from 1989 to 1999. Demonstrated from retrospective case-book data and an 11-year panel of 156 Norwegian and Swedish patients with severe hemophilia A (n=133) and B (n=23) treated on-demand vs prophylaxis. Adapted from Steen Carlsson K, et al. Haemophilia 2003

If I’m Less Active Now Than When I Was Younger, Do I Still Need Prophylaxis?

Adults are often less physically active than children and therefore less prone to trauma-induced bleeds. However, the need for prophylaxis often remains. Subclinical bleeding can be a big concern for adults who have joint damage.

You may wonder if prophylaxis is necessary since you may have joint disease already; but, prophylaxis (routine or episodic) prevents new bleeds from occurring, which can impact your quality of life and your ability to work and remain active.

In the Italian study described previously, prophylaxis was started in adults at a median age of 30 (range from 18 to 72 years). Even starting prophylaxis at this age, resulted in fewer work/school days lost, fewer days of hospitalization, clinic visits, and orthopaedic visits, compared to on-demand treatment. This suggests a benefit to starting prophylaxis, even if damage already exists.

As you move through your life, your prophylaxis requirements may change and treatment doses and times may need to be adjusted. You may continue taking routine prophylaxis after adolescence, or you may start secondary prophylaxis later in life, either short-term or for prolonged periods.

You and the hemophilia treatment centre will evaluate all factors to develop a prophylaxis plan that is right for you.

**Glossary**

**Arthrodeses** - the surgical fixation of a joint, ultimately resulting in bone fusion

**Arthroplasty** - surgical repair of the joint; the joint surface may be remodelled, realigned, or actually replaced

**Arthropathy** - a disease or abnormality of a joint

**Hemarthroses** - bleeding into joint spaces.

**Hemosiderin** - an iron-storage complex

**Median** - relating to or constituting the middle value in a distribution of numbers

**Regimen** - a systematic plan (as of diet, therapy, or medication) especially when designed to improve and maintain the health of a patient

**Subclinical** - describes an early stage or mild form of a medical condition, no symptoms of which are detectable

**Synovectomy** - surgery done to remove inflamed joint tissue (synovium)

**Where Can I Read More About Prophylaxis?**

- ESPRIT study by Gringeri and others http://www3.interscience.wiley.com/journal/118851033/abstract?CRETRY=1&SRETRY=0
- Results of the 2006 Canadian national haemophilia prophylaxis survey http://www3.interscience.wiley.com/journal/120775269/abstract
- Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A. http://www3.interscience.wiley.com/journal/122647727/abstract?CRETRY=1&SRETRY=0
- EmbraceLife.ca was created to inspire active living and well-being for Canadians with hemophilia. http://www.embracelife.ca/en/home/

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