This chapter provides answers to these questions:

- What is clotting factor therapy?
- When was clotting factor therapy first used and how has it changed over the years?
- How are clotting factor concentrates made?
- What types of clotting factor concentrates are used in Canada?
- Are there special clotting factor concentrates for people with inhibitors?
- What other medications are used to treat bleeding?
- How are clotting factor concentrates and supplies stored?
- What type and what dosage of factor concentrate should you use for your child?
- How is the dose of clotting factor calculated by your doctors?
- How long does clotting factor work after infusion?
- How safe are clotting factor concentrates?
- Can modern factor concentrates transmit diseases?
- What are the differences between recalls, withdrawals and quarantines of clotting factor concentrates?
- Who looks after the blood system in Canada?

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Clotting Factor Therapy

5

NOTES

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What is clotting factor therapy?

When a child with hemophilia has a bleed, his body needs treatment to help form a clot and stop the bleeding. This treatment is called clotting factor therapy. The medication itself is clotting factor concentrate (also called factor concentrate). It is injected directly into a vein and is called an intravenous infusion. The clotting factor starts to work right away to stop the bleeding.

An infusion may also be given just before an activity, or on a regular basis, to prevent bleeds. Treatment of this kind is called prophylaxis. For more information on preventative treatment, see Chapter 6, The Role of Prophylaxis.

When was clotting factor therapy first used and how has it changed over the years?

The first clotting factor therapy was given in the 19th century but it was not until the 20th century that the clotting problem in hemophilia began to be understood, and effective treatments developed.

- In 1840, a whole blood transfusion was given to an 11-year-old boy with hemophilia. The boy was bleeding after an operation.
- In 1920, plasma was first used to treat bleeds in hemophilia. Plasma is a yellowish liquid in whole blood that remains after all of the blood cells are removed. Plasma can be frozen and stored for several months, then thawed when needed. Fresh frozen plasma (FFP) contains many proteins, including factor VIII and IX, needed for blood clotting. Unfortunately, the factor VIII or IX proteins were not concentrated enough in these blood products to stop serious bleeding. The body’s circulatory system would be overloaded before a sufficient quantity of clotting factor was administered.
In 1964, Dr. Judith Pool discovered that factor VIII was very concentrated in cryoprecipitate, the sediment that is formed when fresh frozen plasma is thawed in a certain way. This discovery revolutionized the treatment for hemophilia A. Care could now shift away from hospitals to outpatient clinics and the home.

Also in the late 1960s and early 1970s, clotting factor concentrates were developed by separating the various clotting proteins found in plasma. Because factor concentrates had more clotting factor protein in a smaller volume of liquid, they were even better than cryoprecipitate at stopping bleeds. They were also more convenient because these freeze-dried (lyophilized) powders could be refrigerated and then dissolved in sterile water when needed. This meant that a person with hemophilia could carry these products with him. Travel became possible.

At that time, clotting factor concentrates were made entirely from human plasma. However, ways to eliminate the human viruses sometimes contained in plasma were unknown. Tragically, the infusion of these blood products during the 1970's and 1980's sometimes caused infection by hepatitis and HIV. Today, plasma-derived factor concentrates available in Canada are safe and are free of hepatitis and HIV viruses. See the section called “How safe are clotting factor concentrates?” later in this chapter.

Today, recombinant clotting factor concentrates are available. Recombinant clotting factors are made in the laboratory by genetic engineering technology rather than from human plasma. They are the safest products currently on the market. Meanwhile, scientists are working to develop better and more convenient ways to treat hemophilia. One example is the development of longer-acting clotting factor concentrates to potentially allow for less frequent infusion for prophylaxis. Long-acting recombinant factor VIII is now undergoing clinical trial. Another example is the development of factor VIII concentrates that could achieve better responses in patients who have developed antibodies (called inhibitors) to regular factor VIII concentrates.
MYTH: THE BLOOD OF A PERSON WITH HEMOPHILIA IS “THIN”. THIS IS WHAT CAUSES HIM TO BLEED MORE.

REALITY: The blood of a person with hemophilia is no thinner or thicker than the blood of anybody else. It looks exactly the same. The number of red blood cells, white blood cells and platelets is absolutely normal. The only difference is the lack of factor VIII or IX protein. These proteins are extremely tiny. In fact, the total weight of factor VIII protein missing from the blood of an adult with hemophilia is about one ten-thousandth of a gram. In volume, this amount of factor VIII is roughly equivalent

Table 1

<table>
<thead>
<tr>
<th>Year Introduced in Canada</th>
<th>Product</th>
<th>Manufacturing Process, Virus Inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>Fresh whole blood</td>
<td>No viral inactivation process</td>
</tr>
<tr>
<td></td>
<td>Fresh frozen plasma (FFP)</td>
<td></td>
</tr>
<tr>
<td>1965</td>
<td>Cryoprecipitate (factor VIII)</td>
<td>No viral inactivation process</td>
</tr>
<tr>
<td>1968</td>
<td>Plasma-derived factor concentrate (lyophilized)</td>
<td>No viral inactivation process</td>
</tr>
<tr>
<td>1969</td>
<td>Factor VIII concentrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor IX concentrate</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>Plasma-derived factor concentrate (lyophilized) – with virus inactivation</td>
<td>Virus inactivation by dry heat-treatment</td>
</tr>
<tr>
<td></td>
<td>Factor VIII, IX concentrate</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Plasma-derived factor concentrate (lyophilized) – with enhanced virus inactivation</td>
<td>Virus inactivation by vapour heat, pasteurization, solvent-detergent treatment</td>
</tr>
<tr>
<td>1987</td>
<td>Factor VIII concentrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High purity factor VIII concentrate: Monoclate®</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Factor IX concentrate</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>High purity factor IX concentrate: Immunine®</td>
<td></td>
</tr>
</tbody>
</table>

continued on page 5-4
<table>
<thead>
<tr>
<th>Year Introduced in Canada</th>
<th>Product</th>
<th>Manufacturing Process, Virus Inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Factor IX concentrate: BeneFIX®</td>
<td>Cell culturing/manufacturing/purification/stabilization without animal or human proteins.</td>
</tr>
<tr>
<td>2000</td>
<td>Factor VIII concentrates: Kogenate®FS, Helixate®FS</td>
<td>Human plasma proteins in cell culturing and mouse protein needed for factor VIII purification step during manufacturing, but final product stabilized in sucrose instead of albumin.</td>
</tr>
<tr>
<td>2008</td>
<td>Factor VIII concentrate: Xyntha®</td>
<td>As above, but mouse antibody is not used for purification.</td>
</tr>
</tbody>
</table>
How are clotting factor concentrates made?

There are two main types of clotting factor concentrates — plasma-derived (manufactured from plasma) and recombinant.

Plasma-derived clotting factor concentrates are made from human plasma. Plasma contains many clotting factors as well as other proteins.

Plasma-derived clotting factor concentrates are made in these steps:

1. The specific clotting factor is extracted from the plasma.
2. It is purified and concentrated.
3. It is treated to inactivate or kill any viruses that may be present; because the plasma comes from humans, it can contain human viruses.
4. It is made into a freeze-dried powder and put in glass bottles (vials).

For more details on the steps used to physically remove, inactivate or kill possible viruses, see “How safe are clotting factor concentrates?” later in this chapter.

Recombinant clotting factor concentrates are made in these steps:

1. A human gene that directs the assembly of clotting factor is placed in an animal cell line.
2. The cell line is grown in culture and manufactures clotting factor proteins that closely resemble human ones.
3. The clotting factor is then extracted from the cell culture.
4. The proteins are purified. This is done through a series of steps that removes all substances from the cell culture fluid except the desired clotting factor.
5. Finally, the clotting factor is made into a freeze-dried powder and put in glass bottles.
Scientists are working hard to develop clotting factor concentrates that contain no trace of human blood. The first recombinant factor VIII concentrates (Kogenate®/Helixate® and Recombinate®) added albumin, a human protein found in plasma, to stabilize the factor VIII in the final formulation. New versions of these recombinant factor VIII concentrates have now been developed.

The currently available recombinant factor VIII concentrates use sucrose, rather than albumin, as a stabilizer in the final formulation. Although albumin is removed from the final product, some of these products (Kogenate® FS/Helixate® FS) still require very small amounts of human plasma proteins in the cell culture medium to feed cells that manufacture the proteins. These products use a mouse antibody (which is subsequently removed) in the purification procedure. Another recombinant factor VIII concentrate currently available (Advate®) is manufactured without the addition of human plasma proteins to feed the cell line, although a mouse antibody is still used for factor VIII purification. Recently, a new recombinant factor VIII concentrate (Xyntha®) has used a synthetic man-made protein to replace the mouse antibody in the purification procedure. This recombinant factor VIII concentrate (Xyntha®) has one un-needed portion of the molecule removed. For added safety, recombinant factor VIII concentrates now available have additional virus inactivation steps incorporated into the manufacturing process.

Recombinant factor IX (BeneFIX®) uses no albumin, nor does it contain any other human protein in the manufacturing process.

For more information on future clotting factor concentrates, see Chapter 16, The Future of Hemophilia Care.
What types of clotting factor concentrates are used in Canada?

In Canada, almost all people with hemophilia A, and most with hemophilia B, use recombinant factor concentrates. Some people still use plasma-derived concentrates that are highly purified and virally inactivated.

Since these purer, safer products are now available, cryoprecipitate (which is not virus inactivated) is no longer used to treat factor VIII deficiency. Nor is plasma used nowadays to treat factor IX deficiency.

Are there special clotting factor concentrates for people with inhibitors?

Inhibitors are antibodies produced by the body’s own immune system. A factor VIII inhibitor destroys the clotting activity of the infused factor VIII concentrate. A factor IX inhibitor does the same with factor IX concentrate.

Inhibitors develop in some people receiving factor VIII or IX concentrates. When an inhibitor is present, the usual treatments for hemophilia A and B work less well. For more information on inhibitors, see Chapter 8, Complications of Hemophilia.

There are several clotting factor concentrates that are used to treat bleeds in people with factor VIII inhibitors:

- **Factor VIII concentrates** (Kogenate® FS/Helixate® FS, Advate® and Xyntha®) are used when the inhibitor level is low. In these cases, the inhibitor can be overcome by using a higher dose of factor VIII concentrate. Factor VIII concentrates can also be used for immune tolerance induction therapy.
Activated prothrombin complex concentrates (FEIBA® VH, which stands for Factor Eight Inhibitor Bypassing Activity) are plasma-derived concentrates that contain activated and non-activated clotting factors that can “bypass” the inhibitor’s actions. However, they may cause unwanted clotting in the bloodstream and therefore your child’s doctor may limit the number of doses to be given over a period of time. Also, they should not be given along with antifibrinolytic medication. Together, they increase the risk of unwanted blood clots. See “What other medications are used to treat bleeding?” later in this chapter.

Recombinant factor VIIa (Niastase®) is an activated factor VII concentrate that can bypass the inhibitor's actions and is effective in treating bleeding in people with inhibitors to factor VIII.

Porcine factor VIII (Hyate:C) was used in the past but is no longer available. It was purified from screened pig plasma and used for treating bleeding in people with inhibitors because it was more resistant to inhibitors against human factor VIII. However, people sometimes developed inhibitors to the porcine factor VIII, too. A recombinant form of porcine factor VIII is now undergoing clinical trial and will likely become available in the near future.

There are several clotting factor concentrates that are used to treat bleeds in people with factor IX inhibitors:

Factor IX concentrates (BeneFIX® and Immunine® VH) are used when the inhibitor level is low and it can be overcome by using a higher dose of factor IX.

Recombinant factor VIIa (Niastase®) is an activated factor VII concentrate that can bypass the inhibitor’s actions and is effective in treating bleeding in children with inhibitors to factor IX.
What other medications are used to treat bleeding?

Desmopressin acetate (also called DDAVP) is a synthetic drug that is a close copy of a natural hormone. It acts by releasing stored factor VIII and von Willebrand factor protein into the bloodstream. Von Willebrand factor is the protein missing or improperly functioning in another bleeding disorder, called von Willebrand disease.

Desmopressin is useful for some children with mild hemophilia A. Desmopressin can be given by:

1. Infusion into a vein (intravenous) or injection under the skin (subcutaneous) – These forms of desmopressin are called DDAVP® Injection or Octostim®. Note that DDAVP® Injection contains 4 micrograms (mcg) per 1 milliliter (mL) vial and Octostim® contains 15 mcg per 1 mL vial. These are the same drugs in different strengths.

2. Nasal spray – This medication is Octostim® Nasal Spray and delivers 150 mcg per spray.

The doctor will usually test your child with this medication (at a time when he does not have a bleed) to see how well it works for him. Desmopressin is not effective for all children with mild hemophilia A. The test may be repeated as your child grows.

Desmopressin has anti-diuretic activity causing water retention that may result in decreased plasma sodium level. This effect can be more problematic in very young children. Desmopressin is therefore generally not used for children younger than two years old.
Desmopressin helps the body release naturally stored-up factor VIII and von Willebrand factor. Once these clotting factors are released, it takes a while for the body to make more and replenish the factor levels. So, even if your child responds well to this medication, he may still need clotting factor concentrates for more serious bleeds or surgery.

Desmopressin does not work for individuals with hemophilia B (factor IX deficiency).

**Antifibrinolytic medication** called tranexamic acid (Cyklokapron®) helps stop enzymes in the body from breaking down clots. Use of an antifibrinolytic agent lowers the risk of bleeding starting again. They are especially helpful for bleeds in the mouth, tooth extractions and nose bleeds.

- Cyklokapron® comes as a large tablet, which can be crushed and mixed in food or drink if your child can’t swallow tablets well.
- Cyklokapron® also comes in liquid form, given by intravenous (IV) infusion which may be used if your child is in hospital for surgery. It can also be given as a mouthwash for dental procedures.
- Another antifibrinolytic agent is epsilon-aminocaproic acid (Amicar ®) but this product is no longer available in Canada.

Antifibrinolytics are often used in combination with clotting factor concentrates. They may reduce the number of doses of clotting factor concentrate that your child needs for a bleed. Remember these important points when using antifibrinolytics:

- Give antifibrinolytic medication for the full length of time recommended by your child’s doctor, even if no more bleeding has occurred. This is because antifibrinolytics work to prevent further bleeding and allow the wound to heal.
• Do not give antifibrinolytic medication to your child if he has blood in his urine. Large clots could form in the kidneys or bladder. Clots in these locations can behave like stones and cause pain and/or blockage, as they pass through the ureter — the tube connecting the kidney to the bladder — and the urethra — the tube connecting the bladder to the outside of the body.

• Do not give antifibrinolytic medication to your child if he is using FEIBA® VH or low purity factor IX concentrates (also called prothrombin complex concentrates or PCC). Unwanted clots could form in the bloodstream.

• Always check with your child’s doctor before giving antifibrinolytic medication.

**Topical Thrombin** currently available is made from cow (bovine) plasma, but a recombinant human preparation (Recothrom®) is expected to be licensed in Canada. It is used to stop bleeding on the skin or in the mouth. It is a powder that can be put directly on the bleeding area, or placed on a moist gauze or gelatin sponge and then applied with pressure.

**Fibrin Glue** is sprayed directly on a wound surface to form a clot and stop bleeding. It is made of two components — fibrinogen and thrombin. These components also contain an enzyme to strengthen the clot and an antifibrinolytic to prevent the clot from breaking down. The product is made from screened human plasma and undergoes procedures to inactivate viruses.
Clotting factor concentrates are very important to your child’s care and are very expensive. Handle them with care by following these instructions.

- Read the product insert. Every box of factor concentrate has an insert, which explains how your specific product should be stored and used.

  - Some clotting factor concentrates must be stored in the refrigerator at temperatures between 2° and 8°C (36° to 46°F). If not stored in the refrigerator, they will start to lose potency (clotting factor activity or effectiveness).

  - Other factor concentrates can be stored at room temperature (up to 25°C or 77°F) for short periods of time. This may be up to 3 to 6 months depending on the specific clotting factor concentrate that your child uses. After this time, the factor concentrate will start to lose potency. Keep track of how long the product has been out of the refrigerator by writing on the box the time and date that the factor concentrate was removed from the refrigerator.

- Do not expose the factor concentrate to freezing temperatures or temperatures above 25° C. If frozen, bottles could be damaged, compromising sterility. If exposed to heat, the clotting factor activity could be lost.

- When travelling with factor concentrate, it should be kept in a cooler with ice or a cold pack.
• Talk to your HTC care team if you have any questions. If you think the clotting factor has not been stored properly, talk to the people at your HTC. Do not discard any clotting factor concentrates on your own.

• Store supplies needed for infusing factor concentrate (syringes, needles, etc.) in a clean, safe place, where children will not be able to get into them.

• Discard used needles and supplies that have blood on them into an approved “sharps” container. Follow your HTC’s advice regarding safe storage and handling of these supplies.

### What type and what dosage of factor concentrate should you use for your child?

If your child is on a home infusion program, your HTC will give you specific instructions on:

- treatment of bleeding
  - what factor concentrate to use (as prescribed)
  - what dose to use
- prevention of bleeding (prophylaxis)
  - what factor concentrate to use (as prescribed)
  - what dose to use
  - how often to infuse

These instructions will be updated:

- depending on how your child responds to the dose and frequency of infusion; and
- as your child grows.
It is important to always follow your HTC’s instructions, and ask questions if you have any problems. You must:

- Infuse factor concentrate as scheduled or immediately following a bleed.
- Complete the “bleed log” after each factor concentrate infusion.
- Always contact your HTC or go to the hospital if the bleed does not respond well to the first treatment.

**FactorFirst Card**

For your convenience and for your child’s safety, your HTC will provide you with a *FactorFirst* card that will advise hospital and emergency room doctors:

- what factor concentrate to use; and
- what dose to give for various bleeding episodes.

The card will be updated periodically as your child grows or as his condition changes.

**You must carry the FactorFirst card at all times in case emergency care is necessary.**
How is the dose of clotting factor calculated by your doctors?

Normally, your doctor decides on how much clotting factor to give based on five principles:

- **Body weight** – As your child grows, the amount of factor concentrate needed to treat a bleed increases.

- **Type of bleed** – The more severe the bleed, the more factor concentrate is needed to treat it.

- **How quickly the bleed is treated** – A bleed that has been left untreated for several hours usually needs a larger dose and sometimes even a repeat dose. Therefore it is always important to treat bleeds early.

- **Type of hemophilia** – Dosage is calculated differently for factor VIII and factor IX.

- **The level of clotting factor recovery in a child’s bloodstream after infusion** – Recovery is the amount of factor concentrate a child’s body can actually use to stop bleeding compared to the amount infused. Occasionally, your HTC team may ask you to bring your child to the clinic for blood tests to determine how well the clotting factor is working. This is particularly important if your child’s bleeds are not stopping as expected or if your child is using recombinant factor IX. Doctors have found that the level of recovery of factor IX can vary from child to child. Small infants may need more clotting factor per kilogram of body weight than older boys and adults. Sometimes the dose of clotting factor needs to be adjusted to the individual.

**Dosage Calculation** – Tables 2 and 3 show the amount of clotting factor your doctor will usually use for different types of bleeds. The dosage is shown as the number of *international units* (IU) of concentrate per kilogram of body weight. See Table 2 for factor VIII dosing and Table 3 for factor IX dosing.
Table 2

Dosing Suggestions for Factor VIII to Prevent or Stop Bleeding in Different Circumstances*

<table>
<thead>
<tr>
<th>Type of bleeding or procedure</th>
<th>Desired blood factor VIII level (% of normal)</th>
<th>Initial dose of factor VIII (international units per kilogram of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>20 - 30%</td>
<td>10 - 15 IU/kg</td>
</tr>
<tr>
<td>• Early joint or muscle bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Severe nose bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Persistent blood in the urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mouth bleed that does not respond to Cyklokapron®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding (large dose)</td>
<td>40 - 50%</td>
<td>20 - 25 IU/kg</td>
</tr>
<tr>
<td>• Advanced joint or muscle bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bleed into neck, tongue or throat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prophylaxis following severe physical trauma without bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>70 - 100%</td>
<td>35 - 50 IU/kg</td>
</tr>
<tr>
<td>• Severe head injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Surgery (except dental)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bleeding after major trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bleeding into the abdomen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Extraction**</td>
<td>40 - 50%</td>
<td>20 - 25 IU/kg</td>
</tr>
<tr>
<td>** For dental extractions, Cyklokapron® should be given for several days in addition to the clotting factor.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from Clinical Practice Guidelines, Hemophilia and von Willebrand disease: Diagnosis, comprehensive care and assessment (Edition 2, Update 2 [1999-07-01]), Association of Hemophilia Clinic Directors of Canada.

As a general rule, one IU of factor VIII concentrate infused for each kilogram of body weight increases the factor VIII activity by 2%. For example, a 10-kilogram child with severe hemophilia A needs 250 IU to increase the factor VIII level from 0 to 50%.

“It is always important to treat bleeds early.”
### Table 3

<table>
<thead>
<tr>
<th>Type of bleeding or procedure</th>
<th>Desired blood factor IX level (% of normal)</th>
<th>Initial dose of recombinant factor IX – BeneFIX® (international units per kilogram of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early joint or muscle bleed</td>
<td>20 - 30%</td>
<td>25 - 35 IU/kg</td>
</tr>
<tr>
<td>Severe nose bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent blood in the urine</td>
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<td></td>
</tr>
<tr>
<td>Mouth bleed that does not respond to Cyklokapron®</td>
<td></td>
<td></td>
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<tr>
<td><strong>Major bleeding (large dose)</strong></td>
<td>40 - 50%</td>
<td>50 - 60 IU/kg</td>
</tr>
<tr>
<td>Advanced joint or muscle bleed</td>
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<td></td>
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<tr>
<td>Bleed into neck, tongue or throat</td>
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<td>Prophylaxis following severe physical trauma without bleeding</td>
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<td></td>
</tr>
<tr>
<td><strong>Life-threatening bleeding</strong></td>
<td>70 - 100%</td>
<td>85 - 120 IU/kg</td>
</tr>
<tr>
<td>Severe head injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery (except dental)</td>
<td></td>
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<td>Bleeding after major trauma</td>
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<tr>
<td><strong>Dental Extraction</strong></td>
<td>40 - 50%</td>
<td>50 - 60 IU/kg</td>
</tr>
</tbody>
</table>

*Adapted from Clinical Practice Guidelines, Hemophilia and von Willebrand disease: Diagnosis, comprehensive care and assessment (Edition 2, Update 2 [1999-07-01]), Association of Hemophilia Clinic Directors of Canada.

** For dental extractions, Cyklokapron® should be given in addition to the clotting factor.

Did you know…

that Christmas Disease, the original name for factor IX deficiency, was named after a Torontonian named Stephen Christmas? He was the first person in the world to be diagnosed with this distinct form of hemophilia. The study by Biggs and MacFarlane was published in the British Medical Journal on Christmas Eve, 1952.

As a general rule, one IU of recombinant factor IX concentrate (BeneFIX®) infused for each kilogram of body weight increases the factor IX activity by 0.8%. For example, a 10-kilogram child with severe hemophilia B needs 600 IU of recombinant factor IX concentrate to increase the factor IX activity from 0% to 50%.
Clotting Factor Therapy

**Note:** If plasma-derived factor IX concentrate (Immunine® VH) is used, one IU of factor IX concentrate infused for each kilogram of body weight increases the factor IX activity by 1.0%. For example, a 10-kilogram child with severe hemophilia B needs 500 IU of plasma-derived factor IX concentrate to increase the factor IX activity from 0% to 50%.

Because the dose of recombinant factor IX varies from child to child and can change as your child grows, it is recommended that your child have blood tests to determine the right dose. Your HTC may arrange this every year as your child is growing.

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To calculate your child’s weight in kilograms, take your child’s weight in pounds and divide by 2.2.

Example: If your child weighs 20 pounds, calculate 20 pounds divided by 2.2, equals 9.1 kilograms.
How long does clotting factor work after infusion?

Your child’s doctor may talk about the half-life of the clotting factor. This is the time taken for half the infused factor activity to disappear from your child’s bloodstream. Knowing the half-life helps you decide how soon another dose of clotting factor concentrate should be given, if needed. This is particularly important for severe bleeds and following surgery.

A series of blood tests over 24 to 48 hours, or longer, is done to find out the half-life of the clotting factor concentrate in a particular individual. The series of tests is called a survival study. Your child’s doctor may suggest this if bleeds are not stopping as expected.

Normally, the half-life of factor VIII is about 8 to 12 hours. In other words, after 8 to 12 hours, half the factor VIII infused has disappeared from the bloodstream. For factor IX, the half-life is about 18 to 24 hours.

The glasses illustrate the principle of half-life. In this example, the child’s clotting factor half-life is 12 hours. The infusion raised his factor VIII level to 100% of normal.

Three factors may cause your child’s factor half-life to be shorter than expected:

- individual differences
- active bleeding or
- the presence of an inhibitor.
5 Clotting Factor Therapy

How safe are clotting factor concentrates?

A brief history of plasma-derived factor concentrates and blood-borne infections

In the 1970s and 1980s, it became apparent that blood-borne infections were a serious complication of treating hemophilia with factor concentrates. Many people with hemophilia around the world were infected with HIV (human immunodeficiency virus), hepatitis B and hepatitis C during those years. These viruses entered blood and blood products from blood donors who were themselves infected. People with hemophilia received these infections from the plasma, cryoprecipitate and plasma-derived factor concentrates prescribed to control bleeding.

In Canada:

- Approximately 35 percent of people with hemophilia were infected with HIV, including approximately 90 percent of those with severe hemophilia A and 40 percent of those with severe hemophilia B. HIV weakens the body’s immune system and leaves it open to disease. This disease is called AIDS (acquired immune deficiency syndrome).

- By the year 2000, approximately 400 of these people (more than half of those infected), had died from AIDS.

- Approximately 70 percent of people with hemophilia were infected with hepatitis C, including all those who used blood products regularly before 1988. The hepatitis C virus causes liver damage, which usually takes many years to develop. In approximately 20 percent of cases, the damage leads to scarring of the liver (cirrhosis). This can be fatal. Hepatitis C is even more dangerous for people infected with HIV because their weakened immune systems are less able to fight the virus.
These events were an unprecedented catastrophe to patients, families and the medical community alike. The tragedy, however, brought about very rapid changes to the way blood products are manufactured beginning in 1984. As a result, clotting factor concentrates currently available in Canada are safe and doctors are not aware of any blood-borne infections from factor concentrates with HIV since 1987 and with hepatitis C since 1988.

**Plasma-derived clotting factor concentrates available today**

Plasma-derived clotting factor concentrates are now safe because of improvements in *blood donor screening* and *testing of blood donations*, and modern *factor purification* and *viral inactivation* procedures.

**Blood donor screening and testing of blood donations**

There are strict guidelines for donor selection in Canada and many other regions of the world. Each blood donor is questioned each time he/she donates. This screening means that only healthy donors, without risk factors and symptoms for viral infection, can donate blood and plasma.

Each blood donation undergoes a series of tests to look for signs of infection by HIV, hepatitis B, hepatitis C and other viruses. If a donation is found to contain any sign of these pathogens, it is discarded. The donor can no longer give blood.
Factor concentrate purification and viral inactivation

Before the manufacture of factor concentrates, the plasma is again tested for viruses. It is discarded if there is any sign of virus present.

During manufacture, all clotting factor concentrates go through a series of steps to remove impurities and remove or kill viruses that may be present. This “viral inactivation/removal process” may include heating the factor concentrate with different heat treatments, treating the factor concentrate with solvent detergents or nanofiltration. These methods are very effective in killing or removing a wide variety of viruses including hepatitis B and C and HIV.

Once the final product is ready, it is again tested to ensure it is safe and that it meets all manufacturing standards, including potency (clotting factor activity or effectiveness).

All persons with hemophilia are advised to get hepatitis A and B immunization, if they do not already have immunity. This is one extra step you can take to protect against these diseases.

For more information on immunization, see Chapter 10, Growing with Hemophilia.
Because of what happened with HIV, hepatitis B and hepatitis C, those responsible for hemophilia care and the blood system are watchful of new dangers. One concern in the late 1990s was classical Creutzfeldt-Jakob Disease (cCJD). This rare fatal disease is believed to be caused by a misshapen protein, called a prion, that invades the brain. In rare cases, it has been transmitted from person-to-person. Each of these infections involved material from the brain of one person coming into contact with material from the brain of another person. For example, some people were infected by contaminated instruments used in brain surgery.

It was feared that the prion could also be transmitted by blood. Studies around the world have not turned up a single case of cCJD transmitted by blood to people with hemophilia or to others receiving blood transfusions. cCJD is now called only a “theoretical risk” for those who receive blood or blood products. Recombinant factor concentrates are considered extremely safe from cCJD.

However, a variation of cCJD emerged in the United Kingdom in the 1990s. Called variant CJD (vCJD), this equally fatal disease is caused by eating beef products from animals infected with bovine spongiform encephalopathy (BSE). The animal form is commonly called “mad cow disease.” Cases of vCJD in humans have turned up in several European countries, notably the United Kingdom.

Authorities are concerned that vCJD is more infectious than the older and better-known form of cCJD. One reason for concern is that vCJD has jumped the “species barrier” from bovine to human. It is the only spongiform encephalopathy known to do this. As a precaution, public health authorities in North America have excluded people who have spent long periods in certain European countries from donating blood. Factor VIII or factor IX concentrates distributed to Canadian patients have always been manufactured from plasma collected in North America, and not from the United Kingdom or European countries. vCJD is a huge
health concern in Europe because of the large number of people who have eaten infected beef. Public health authorities are following this disease very closely. They also have a surveillance program on hemophilia patients in the United Kingdom.

In 2008, a 72-year old hemophilia A patient in the United Kingdom who had received factor VIII concentrate made from U.K. plasma before 1998 - but who died of an unrelated cause - was found to have the infectious agent for vCJD in his spleen on surveillance autopsy. The patient did not have symptoms of vCJD. Evidence strongly suggests the infection in this patient was caused by the clotting factor concentrate, and not from eating beef. As of 2010, it is the only suspected case of vCJD transmission by factor concentrates to a hemophilia patient.

**Recombinant clotting factor concentrates**

Recombinant clotting factor concentrates are considered to be extremely safe.

Several recombinant factor VIII concentrates (Advate®, Xyntha®) and factor IX concentrates (BeneFIX®) contain no human proteins in the cell culturing that manufactures the clotting factor protein or in the final product. They may or may not have used a mouse antibody in the purification procedure. The manufacturing process of recombinant factor VIII concentrates (Kogenate®FS, Helixate®FS) needs human plasma proteins to feed the cell line that makes the clotting factor protein, but these proteins are removed during purification. During processing, recombinant factor concentrates undergo all the purification and viral inactivation steps described above. Recombinant products are considered to be the safest clotting factor concentrates available and are used widely in Canada. The transmission of viruses has never occurred with any of these recombinant factor concentrates. See “**How are clotting factor concentrates made?**” earlier in this chapter.

“The factor concentrates used in Canada today, whether plasma-derived or recombinant, have never been known to transmit diseases like HIV, hepatitis B or hepatitis C.”
Other safety issues

Allergic reactions

Clotting factor concentrates may cause *allergic reactions*. These occur very infrequently. They can be mild, such as hives or rash; or severe, such as wheezing or *anaphylaxis* — a sensitivity reaction triggered by food or medicine characterized by difficulty breathing, nausea and vomiting among other symptoms.

Severe reactions need emergency treatment

Your HTC care team will explain what to do if your child has an allergic reaction. If you think that your child has had an allergic reaction from the clotting factor concentrate, you should inform your HTC right away so that the cause can be investigated and a plan put in place to prevent further problems. An allergic reaction can also occur if the clotting factor concentrate is given too fast or is too cold. Your HTC will provide training and guidelines on how to administer factor concentrate and how to deal with allergic reactions before your child goes on a home infusion program. For more information, see Chapter 7, Home Infusion.

Can modern factor concentrates transmit diseases?

The factor concentrates used in Canada today, whether plasma-derived or recombinant, have never been known to transmit diseases such as HIV, hepatitis B or hepatitis C.

However, some viruses, such as parvovirus B19 and hepatitis A, are resistant to certain viral inactivation methods and can be transmitted by plasma-derived factor concentrates.
5 Clotting Factor Therapy

- Parvovirus B19 is a virus that most people in the general population have been exposed to and they have immunity against it. It causes a common childhood infection called “Fifth Disease” which is usually mild and short-lived. In pregnant women or people with a weakened immune system, parvovirus B19 can cause serious problems.

- Hepatitis A causes liver inflammation and jaundice, usually lasting several weeks, that does not develop into chronic liver disease. Hepatitis A is transmitted by dirty water or contaminated food because of poor hygiene. However, in Europe in the 1990s, several lots of plasma-derived factor concentrates transmitted hepatitis A but there have since been no further reports of this happening. Effective vaccines against hepatitis A (often combined with a hepatitis B vaccine) exist. Therefore, as a precaution, it is recommended that all individuals with hemophilia be vaccinated against hepatitis A.

- Hepatitis B infection can result in chronic liver disease. With the present-day blood donor screening and viral inactivation procedures, infection has not been known to happen at all with modern factor concentrates. Nevertheless, hepatitis B is still a risk for the general population. It can be transmitted through sexual contact and contaminated needles. Many provinces have introduced hepatitis B vaccination programs for all children. Because this is a wise health precaution, and because people with hemophilia have a greater chance of needing a blood transfusion, it is recommended that they be vaccinated at a young age.

It is theoretically possible that a new unknown agent could infect the blood supply. It is for this reason that recombinant factor concentrates which have little or no exposure to human protein are the preferred treatment.

Test Your Knowledge

Your son has severe factor VIII hemophilia and is receiving on-demand therapy. He has the first signs of a joint bleed. He weighs 40 kg. How many units of factor VIII should be infused?

(For some help in calculating the dosage, see page 16 of this chapter.)

(The correct answer is on page 17-17.)
What are the differences between recalls, withdrawals and quarantines of clotting factor concentrates?

Recalls

At some time you may be advised by your HTC that a clotting factor concentrate has been recalled. This means that there may be a concern that the product is not safe. Such recalls occur very rarely. Recalls are done by the manufacturer of a product. The manufacturer informs Health Canada of the concern and what actions it has taken to deal with the problem. If Health Canada is not satisfied with the actions taken by the manufacturer, it can take action on its own.

In the case of factor concentrates in Canada, there is a chain of communication. The manufacturer informs Health Canada of the problem. It also informs the distributors of the product — either Canadian Blood Services or Héma-Québec (in the province of Quebec). Health Canada also informs the distributors. They in turn contact the hospital or HTC where the product was sent. Finally, patients are notified by their doctors or nurses. This is often done by telephone, especially if it is an urgent safety issue. Staff will work until everyone has been notified.

When your HTC receives notification of a recall, the staff take it very seriously.

- Once notified, they check which product and lot numbers are affected.
- They check their records to see who received these products.
- Patients affected by the recall are notified as soon as possible.
- Your HTC team will explain the concern and advise you what to do.
- If your child is affected, you may be advised to return the remaining stock of clotting factor.
- Your child may need a blood test or other follow-up.
Sometimes, information sessions will be organized to provide more information and answer questions. Everyone is usually anxious when a recall occurs and it is important that you ask questions and get the information that you need. If you are worried about what you have heard from other people or from the media, contact your HTC for accurate information.

It is important, in case of a product recall, that records with details of all infusions with clotting factor concentrates — date, product name and lot number — be immediately available. When your child receives treatment at the HTC or hospital, the nurse giving the infusion records this information. **When your child is on a home infusion program, it is essential that you record all infusions in the bleed diary provided by your HTC and that you submit this information on a regular basis.**

The Plasma Protein Therapeutics Association (PPTA) has developed a Patient Notification System that promptly alerts registered patients and healthcare providers about recalls or withdrawals of plasma-derived and recombinant products (www.patientnotificationsystem.org). The PPTA is a global organization of the world’s major collectors of source plasma and manufacturers of plasma-derived and recombinant products.

**Test Your Knowledge**

Your son is receiving prophylactic therapy. He receives 500 units of factor VIII every three days. He weighs 25 kg. This means that he receives 20 IU/kg. Since 1 IU/kg raises his factor level by 2%, then 20 IU/kg raises his factor VIII level to 40%. Your doctor has told you that your son’s factor VIII half-life is 12 hours. What percentage of factor VIII is left in his bloodstream after 3 days?

(For some help in figuring out the answer, see the illustration on page 19 of this chapter).

(The correct answer is on page 17-18.)
Withdrawals

A product withdrawal occurs when the manufacturer decides to remove the product from use. Although both Health Canada and the manufacturer consider the product to be safe, the manufacturer feels that the product does not meet its standards.

Health Canada does not consider a withdrawal to be a recall. This is because there is no safety concern. Nevertheless, staff at your HTC will follow the same procedures as in the case of a recall. You will be contacted and asked to return the product.

Quarantine

A quarantine occurs when a product is held back and not used for a short period of time because of a possible problem with its quality. During this time, manufacturers and Health Canada investigate. If the problem is found to be real, the product is recalled or withdrawn. If it is found that there is no problem, the product is released from quarantine.

In hemophilia care, people have clotting factor concentrates in their homes. As a result, they have to be notified of a quarantine so as not to use the products. The staff at the HTC will advise you to return them to the clinic in exchange for another supply. Usually, other products are used until the safety of the “held back” product is decided.
Who looks after the blood system in Canada?

The following groups are very important to Canada’s blood system:

• Canadian Blood Services (CBS) and Héma-Québec (for the province of Quebec) collect blood and produce the fresh blood components — red blood cells, platelets, fresh frozen plasma — for all Canadians. They also receive funding from provincial governments for the purchase and distribution of fractionated blood products, including all clotting factor concentrates. Clotting factor concentrates are manufactured by multi-national pharmaceutical companies.

• Health Canada’s Biologics and Genetic Therapies Directorate is responsible for the licensing and safety of blood and blood products for all Canadians.

• Health Canada’s Centre for Infectious Disease Prevention and Control (CIDPC) works to ensure the safety of blood products by surveillance work on old and new diseases that could infect blood and blood products.

• The Association of Hemophilia Clinic Directors of Canada (AHCDC) recommends which clotting factor concentrates should be made available for hemophilia care in Canada. It monitors the use and safety of clotting factor concentrates.

• The Canadian Association of Nurses in Hemophilia Care (CANHC) is a group of nurses from across Canada who specialize in the care of people with bleeding disorders.

• The Canadian Hemophilia Society (CHS) is a consumer group. It represents people with bleeding disorders. It advocates for access to the safest clotting factor concentrates and high-quality comprehensive care for people with hemophilia. It also works to promote blood safety for all Canadians.
The AHCDC, CHS and CANHC work closely with government agencies and people with hemophilia to ensure that clotting factor concentrates for Canadians are safe, effective, widely available and used in a responsible manner.

Clotting factor concentrates are very precious and expensive medicines. Canadians with hemophilia are privileged to have universal access to the highest quality of factor concentrates. Hundreds of dollars can be wasted each time a child is given an unnecessarily high dose of concentrate. Thousands of dollars can be wasted each time a vial is broken. Many thousands of dollars can be wasted if a supply of concentrate is stored incorrectly or allowed to expire without being used. It is important that you learn as much as you can about this precious resource and use it responsibly.

“A clotting factor concentrates are a very precious resource—Canadians with hemophilia must use them responsibly.”

A young boy with hemophilia and his father advocating for recombinant products on behalf of the CHS.

Parliament Hill, Ottawa, 1992