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?
- How is the dose of clotting factor calculated?
- How long does clotting factor work after infusion?
- How safe are clotting factor concentrates?
- What are the differences between recalls, withdrawals and quarantines of clotting factor concentrates?
- Who looks after the blood system in Canada?

Man-Chiu Poon, M.D., Director, Pat Klein, BASc, R.N., Clinical Resource Nurse, Southern Alberta Hemophilia Clinic, Calgary, AB
What is clotting factor therapy?

When a child with hemophilia has a bleed, his body needs a treatment to help form a clot and stop the bleeding. This treatment is called clotting factor therapy. The medication itself is clotting 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.

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. It 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 internal 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. Concentrates were even better than cryoprecipitate at stopping bleeds. These freeze-dried 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, concentrates were made entirely from human plasma. Ways to eliminate the human viruses sometimes contained in plasma were unknown. Tragically, the infusion of these blood products caused infection by hepatitis and HIV. (For more information, see Chapter 8, Complications of Hemophilia.)

• Today, recombinant clotting factor concentrates are available. They are the safest products currently on the market. Meanwhile, scientists are working to develop better and more convenient ways to treat hemophilia.
### Table 1
The History of Clotting Factor Therapy in Canada

<table>
<thead>
<tr>
<th>Generation</th>
<th>Product</th>
<th>Introduction in Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fresh whole blood</td>
<td>1947</td>
</tr>
<tr>
<td></td>
<td>Fresh frozen plasma (FFP)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cryoprecipitate (factor VIII)</td>
<td>1965</td>
</tr>
<tr>
<td>3</td>
<td>Factor VIII concentrate</td>
<td>1968</td>
</tr>
<tr>
<td></td>
<td>(lyophilized, unheated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor IX concentrate</td>
<td>1969</td>
</tr>
<tr>
<td></td>
<td>(lyophilized, unheated)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Factor VIII, IX concentrate</td>
<td>1985</td>
</tr>
<tr>
<td></td>
<td>(lyophilized, dry heat-treated)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Factor VIII concentrate</td>
<td>1987</td>
</tr>
<tr>
<td></td>
<td>(enhanced viral inactivation: vapour heat, solvent detergent treatment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor IX concentrate</td>
<td>1988</td>
</tr>
<tr>
<td></td>
<td>(enhanced viral inactivation: vapour heat, solvent detergent treatment)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>High purity factor VIII concentrate</td>
<td>1987</td>
</tr>
<tr>
<td></td>
<td>(monoclonal antibody purified)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High purity factor IX</td>
<td>1991</td>
</tr>
<tr>
<td>7</td>
<td>Genetically engineered (recombinant) factor VIII concentrate</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Genetically engineered (recombinant) factor IX concentrate</td>
<td>1997</td>
</tr>
<tr>
<td>8</td>
<td>Second-generation genetically engineered (recombinant) factor VIII concentrate</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>without albumin as a stabilizer</td>
<td></td>
</tr>
</tbody>
</table>

**MYTH:**

**THE BLOOD OF A PERSON 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 to the head of a pin.
How are clotting factor concentrates made?

There are two main types of clotting factor concentrates — plasma-derived 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 removed from the plasma.
2. It is purified and concentrated.
3. It is made into a freeze-dried powder and put in bottles.

Because the plasma comes from humans, it can contain human viruses. To make it safe, the concentrate goes through many steps to make it pure and to inactivate, or kill, the viruses. (See *How safe are clotting factor concentrates?* in this chapter.)

*Recombinant clotting factor concentrates* are made in these steps:

1. A human gene that directs clotting is placed in a non-human cell line.
2. The cell culture then manufactures clotting factor proteins that closely resemble human ones.
3. The clotting factor is then removed from the cell culture.
4. The proteins are purified. This is done through a series of steps that removes all materials except the desired clotting factor.
5. Finally, the clotting factor is made into a freeze-dried powder and put in bottles.
Scientists are working hard to create clotting factor concentrates which 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. New versions of these recombinant factor VIII concentrates have now been developed. Kogenate® FS, Helixate® FS, and ReFacto™, use sucrose, rather than albumin, as a stabilizer. However, all of these products still require very small amounts of human albumin in the cell culture medium to feed cells that manufacture the proteins. Recombinant factor VIII clotting factor concentrates currently in development will be manufactured without the addition of albumin to the cell line.

Recombinant factor IX, BeneFIX®, contains no human protein, and is inherently free from the risk of human blood-borne viruses.

(For more information on future clotting factor concentrates, see Chapter 12, 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 is no longer used to treat factor VIII deficiency. Nor is plasma used nowadays to treat factor IX deficiency.
Are there special clotting factors for people with inhibitors?

Inhibitors are antibodies produced by the body’s own immune system. A factor VIII inhibitor destroys the clotting activity in an infusion of factor VIII concentrate. A factor IX inhibitor can do 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, Recombinate®, ReFacto™) 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 many activated clotting factors. These activated clotting factors can “bypass” the inhibitor’s action. However, they may cause unwanted clotting in the bloodstream. 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 antifibrinolytics. (See What other medications are used to treat bleeding? in this chapter.) Together, they increase the risk of unwanted blood clots.
• **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 VIII.

• **Porcine factor VIII** (Hyate: C) is purified from screened pig plasma. Because it does not contain human plasma, it cannot transmit human viruses. It is often useful for treating bleeding in children with inhibitors. However, people sometimes develop inhibitors to the porcine factor VIII, too. Then, it can no longer be used.

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

• **Factor IX concentrates** (*e.g.*, BeneFIX®, Immunine® VH *etc.*) 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**, is a synthetic drug that is a close copy of a natural hormone. It acts by releasing the von Willebrand factor and factor VIII stored in the lining of blood vessels. (Von Willebrand factor is a protein missing in a disease similar to hemophilia A, called von Willebrand disease.)

Desmopressin is useful for some children with mild hemophilia A. Desmopressin can be given by:
intravenous infusion or injection under the skin. This medication is DDAVP® Injection or Octostim®. Note that DDAVP® Injection (4 micrograms per 1 ml. ampoule) and Octostim® (15 micrograms per 1 ml. ampoule) are the same drug in different strengths.

nasal spray. This medication is Octostim® Nasal Spray.

The doctor will usually test your child with this drug (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 helps the body release naturally stored-up clotting factors. Once these clotting factors are released, your child’s body takes a while to make and store more. So, even if your child responds well to this medication, he may still need clotting factor concentrates for more serious bleeds or surgery.

Antifibrinolytics (Amicar® or Cyklokapron®) are drugs that help stop enzymes in the body from breaking down clots. Their use lowers the chance of bleeding starting again. They are especially helpful for bleeds in the mouth, tooth extractions and nose bleeds.

Amicar® and Cyklokapron® come in large pills. They can be crushed and mixed in food or drink if your child can’t swallow them. Cyklokapron® also comes in liquid form which is given by intravenous infusion. It may be given this way if your child is in hospital for surgery.

Antifibrinolytics are often used in combination with clotting factor concentrates. They may reduce the number of doses of clotting factor concentrate your child needs for a bleed.

Remember these important points when using antifibrinolytics.
• Give these drugs 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 these drugs 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 urethra—the tube connecting the bladder to the exit.

• Do not give these drugs to your child if he is using FEIBA® VH or low purity factor IX concentrates. Unwanted clots could form in the bloodstream.

• Always check with your child’s doctor before giving these medications.

Topical Thrombin (Thrombostat®) is purified from bovine plasma. 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 surface wound 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.
How are clotting factor concentrates and supplies stored?

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° – 46°F). If not stored in the refrigerator, they will start to lose potency.
  - 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.

- 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.

- Talk to your HTC staff 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 the 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 advice regarding safe storage and handling of these supplies.

How is the dose of clotting factor calculated?

Deciding how much clotting factor to give is based on five points:

• **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.

• **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 staff may ask you to bring your child to the clinic for blood tests to determine how 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 than older boys and adults. Sometimes the dose of clotting factor needs to be adjusted to the individual.

Dosage Calculation – Tables 2 and 3 below show the amount of clotting factor suggested 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 and Table 3 for factor IX.)*
### Table 2
Dosing Suggestions for Factor VIII to Prevent or Stop Bleeding in Different Circumstances

<table>
<thead>
<tr>
<th>Minor bleeding</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>Early joint or muscle bleed</td>
<td>20 - 30%</td>
<td>10 - 15 IU/kg</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 Amicar® or Cyklokapron®</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Major bleeding (large dose)**
- Advanced joint or muscle bleed
- Bleed into neck, tongue or throat
- Prophylaxis following severe physical trauma without bleeding

<table>
<thead>
<tr>
<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>40 - 50%</td>
<td>20 - 25 - IU/kg</td>
</tr>
</tbody>
</table>

**Life-threatening bleeding**
- Severe head injury
- Surgery (except dental)
- Bleeding after major trauma
- Bleeding into the abdomen

<table>
<thead>
<tr>
<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>70 - 100%</td>
<td>35 - 50 - IU/kg</td>
</tr>
</tbody>
</table>

**Dental Extraction**

<table>
<thead>
<tr>
<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>40 - 50%</td>
<td>20 - 25 - 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, Amicar® or Cyklokapron® should be given in addition to the clotting factor.

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%.
Table 3
Dosing Suggestions for Factor IX to Prevent or Stop Bleeding in Different Circumstances

<table>
<thead>
<tr>
<th>Desired blood factor IX level (% of normal)</th>
<th>Initial dose of factor IX – BeneFIX® (International Units per kilogram of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td></td>
</tr>
<tr>
<td>• Early joint or muscle bleed</td>
<td>20-30%</td>
</tr>
<tr>
<td>• Severe nose bleed</td>
<td>25-35 IU/kg</td>
</tr>
<tr>
<td>• Persistent blood in the urine</td>
<td></td>
</tr>
<tr>
<td>• Mouth bleed that does not respond to Amicar® or Cyklokapron®</td>
<td>40-50%</td>
</tr>
<tr>
<td>• Major bleeding (large dose)</td>
<td>50-60 IU/kg</td>
</tr>
<tr>
<td>• Advanced joint or muscle bleed</td>
<td></td>
</tr>
<tr>
<td>• Bleed into neck, tongue or throat</td>
<td></td>
</tr>
<tr>
<td>• Prophylaxis following severe physical trauma without bleeding</td>
<td>70-100%</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>85-120 IU/kg</td>
</tr>
<tr>
<td>• Severe head injury</td>
<td></td>
</tr>
<tr>
<td>• Surgery (except dental)</td>
<td></td>
</tr>
<tr>
<td>• Bleeding after major trauma</td>
<td></td>
</tr>
<tr>
<td>• Bleeding into the abdomen</td>
<td></td>
</tr>
<tr>
<td>Dental Extraction**</td>
<td>50-60 IU/kg</td>
</tr>
<tr>
<td>** For dental extractions, Amicar® or Cyklokapron® should be given in addition to the clotting factor.</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 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 625 IU of recombinant 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.

**Table 4** below shows how to calculate the dosage depending on weight and units per kilogram needed. To use this chart:

- find the Weight in kilograms closest to your child’s weight (on the left)
- choose the Units per kilogram desired (along the top) recommended for the type of bleed (according to Tables 2 and 3)
- find the number where the row and column meet. This number is the desired dose.

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

*e.g.* If your child weighs 20 pounds, calculate 20 pounds divided by 2.2, equals 9.1 kilograms.
Table 4

Dosage Calculation Table

<table>
<thead>
<tr>
<th>Wt. in kilos</th>
<th>Units per kilogram desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100 150 200 250 300 350 400 500</td>
</tr>
<tr>
<td>15</td>
<td>250 375 500 625 750 875 1000</td>
</tr>
<tr>
<td>20</td>
<td>300 450 600 750 900 1050 1200</td>
</tr>
<tr>
<td>25</td>
<td>350 525 700 875 1050 1225 1400</td>
</tr>
<tr>
<td>30</td>
<td>400 600 800 1000 1200 1400 1600</td>
</tr>
<tr>
<td>35</td>
<td>450 675 900 1125 1350 1575 1800</td>
</tr>
<tr>
<td>40</td>
<td>500 750 1000 1250 1500 1750 2000</td>
</tr>
<tr>
<td>45</td>
<td>550 825 1100 1375 1650 1925 2200</td>
</tr>
<tr>
<td>50</td>
<td>600 900 1200 1500 1800 2100 2400</td>
</tr>
<tr>
<td>55</td>
<td>700 1050 1400 1750 2100 2450 2800</td>
</tr>
<tr>
<td>60</td>
<td>1000 1500 2000 2500 3000 3500 4000</td>
</tr>
</tbody>
</table>

Example: If your child’s weight is 30 kilograms (on the left) and you want to give 25 units per kilogram for a minor joint bleed (along the top), you see that your child should receive around 750 units (also called IU’s for International Units) of clotting factor.

- Most clotting factor concentrates come in small (around 250 IU), medium (around 500 IU) and large (around 1000 IU) sizes.

- Dosages are approximate and the closest vial size to the desired dose should be given. It does not have to be exact.

- Use complete vials. Clotting factor should not be wasted by giving only part of a vial.
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 is done to find out the half-life of an individual child’s clotting factor. This test 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 your child’s 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.

Illustration 1: This shows the half-life of factor VIII after infusion.

Three factors may mean that your child's factor half-life is shorter than normal:

- individual differences
- active bleeding or
- the presence of an inhibitor.
How safe are clotting factor concentrates?

Clotting factor concentrates available in Canada are safe. The risk of HIV and hepatitis C transmission is extremely low. Doctors are not aware of any infection from clotting factor concentrates with HIV since 1987 or with hepatitis C since 1990.

In the past, transfusion of blood products was known to cause infection by human viruses. Hepatitis transmission was a known problem as early as the 1970s. The tragedy of HIV—the virus that causes AIDS—transmission in the early 1980s made blood product safety a most urgent issue.

Plasma-derived clotting factor concentrates

Plasma-derived clotting factor concentrates are now safe because of improvements in blood donor screening and the 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. These methods are very effective in killing 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.

- Surveillance studies, which follow a large number of people with hemophilia around the world over many years, continue to show that the risk of HIV and hepatitis C transmission is extremely low.

All persons with hemophilia are advised to get hepatitis A and B immunization, if they do not already have immunity. These vaccines are safe and effective. This is one extra step you can take to protect against these diseases. *(For more information on immunization, see Chapter 9, Growing with Hemophilia.)*
Recombinant clotting factor concentrates

Recombinant clotting factor concentrates are considered to be extremely safe.

Recombinant factor IX (BeneFIX®) contains no human proteins; therefore it cannot transmit human viruses. The manufacturing process used to make recombinant factor VIII (Kogenate® FS, Helixate® FS, Recombinate®, ReFacto™) adds albumin, a protein found in plasma, to the cell line. This is removed later, although Recombinate® still requires the addition of albumin in the final bottle as a stabilizer for factor VIII activity. During processing, recombinant clotting factor concentrates undergo all the safety measures (purification, viral inactivation) outlined above. They are considered to be the safest clotting factor concentrates available and are used widely in Canada.

Recombinant factor VIII clotting factor concentrates currently in development will be manufactured without the addition of albumin to the cell line.

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 (difficulty breathing).

Severe reactions need emergency treatment. Your HTC staff will discuss 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 so that the cause can be investigated and a plan put in place to prevent further problems. Reactions may also occur if the clotting factor concentrate is given too fast or is too cold. Your HTC will provide a teaching program before your child goes on a home infusion program. You will learn how to administer factor concentrate as well as how to deal with allergic reactions.

(For more information, see Chapter 6, Home Infusion.)

(For more information on the blood system and the safety of clotting factor concentrates, see Chapter 8, Complications of Hemophilia.)
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 Québec). 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. Those affected by the recall are notified as soon as possible. Your HTC staff 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 information.
It is important, in case of a 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 your 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 return this information on a regular basis.**

**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.
Recalls, withdrawals and quarantines are very different. But from the point of view of the consumer, they are hard to tell apart. That is why it is important to talk to the staff at the HTC. They can give you the full story.

Who looks after the blood system in Canada?

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

- The Canadian Blood Services (CBS) and Héma-Québec (for the province of Québec) 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 Biologics and Genetic Therapies is responsible for the licensing and safety of blood and blood products for all Canadians.

- Health Canada’s Laboratory Centre for Disease Control (LCDC) 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) is a group of hemophilia clinic directors from across Canada. The 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, freely available and used in a responsible manner.

Clotting factor concentrates are very precious and expensive. 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.

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 Illustration 1 on page 4-17.)

(The correct answer is on page 13-17.)