Complications of Hemophilia

This chapter provides information on complications of hemophilia. It includes the following sections:

PART 1 - Inhibitors

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PART 2 - Joint and muscle damage

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PART 3 - Pain in hemophilia

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Introduction

In recent decades, great progress has been made in the care and treatment of hemophilia. Today, the majority of children with severe hemophilia in Canada are treated with prophylaxis. Prophylaxis involves treatment with regular infusions of clotting factor according to a regular schedule, to help prevent bleeds and reduce complications such as loss of mobility, joint damage, pain, related psychological challenges.

However, people with hemophilia still face certain risks and complications. The first complication that can occur when children are first exposed to clotting factor concentrates is the development of inhibitors against the factor product infused to prevent or stop bleeds. The second complication is joint damage called hemophilic arthritis, caused by bleeding into a joint and gradual loss of mobility of the joint. Finally, the third complication is pain. This chapter explains how each complication can be prevented and treated.
PART 1 – Inhibitors

This section provides answers to these questions:

- What are inhibitors?
- What are the symptoms of inhibitor development?
- What tests are available to detect inhibitors?
- What are the treatment options?

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The development of an inhibitor is a serious complication of hemophilia because it interferes with effective treatment for bleeds. Fortunately, a number of treatment options are available to deal with inhibitors. The hemophilia treatment centre (HTC) team will guide you through the options if your child develops this complication and provide support at all times.

What are inhibitors?

In about 30 per cent of people with severe hemophilia, the immune system reacts to clotting factor concentrate by developing antibodies. The immune system is made up of several biological mechanisms that are vital to the body’s ability to recognize and fight off foreign substances such as bacteria and viruses. Sometimes, the factor concentrate is perceived as a foreign substance. The body’s defenses do not recognize it so they produce antibodies. The antibodies eliminate or neutralize the factor concentrate and thus prevent it from doing its job of stopping a bleed. These antibodies are called inhibitors.

This complication usually tends to occur sometime during the first 50 exposures to the clotting product. After this critical period, the risk of developing inhibitors is very low. Despite a lot of research and many ongoing studies, doctors do not yet fully understand all the factors that may influence the development of inhibitors. Factors such as age and type of hemophilia, and possibly infection arising from an implanted venous access device (port-a-cath) may increase the risk and development of inhibitors. Your HTC medical director will determine the best treatment approach to avoid, as much as possible, this complication.
PART 1 – Inhibitors

■ **What are the symptoms of inhibitor development?**

The HTC team is always available to discuss any issues or questions related to response to treatment. The nurse coordinator will stay in frequent communication with you through a clinical follow-up or by telephone to make sure that the treatment initiated is adequate.

The HTC doctor and nurse coordinator will perform a physical assessment and blood test at the slightest signs or symptoms. The first noticeable signs include the appearance of bruises on the body and bleeding that does not seem controlled by appropriate treatments.

■ **What tests are available to detect inhibitors?**

The inhibitor screening test and inhibitor assay are blood tests that are routinely done at all assessments at the HTC including the annual check-up, and before any surgery. The doctor could also decide to do an inhibitor screening test or assay if there seems to be a problem with the effectiveness of treatment. An inhibitor screening test can detect the presence, or not, of inhibitors. An inhibitor assay is done when the presence of an inhibitor has been confirmed by a screening test—it measures the level of the inhibitors, in Bethesda Units, produced by the immune system in reaction to the infused factor concentrate.

The blood analysis is done at a hemostasis laboratory and test results can be obtained within a few hours in the event of an urgent medical emergency.
What are the treatment options?

There are several treatment options to eliminate inhibitors and make it possible to resume normal treatment. The HTC medical director will explain the differences between the various options, and the particularities, advantages and disadvantages of each type of treatment.

Basically, the treatments consist of desensitizing the immune system or masking the factor VIII or IX from the inhibitor. The first approach involves giving regular, high doses of factor concentrates to wear out the antibody production and get the immune system used to the factor so that it no longer rejects it. This approach is similar to allergy desensitization. The second approach involves giving treatment with other clotting factors (not just pure factor VIII or IX) to bypass the inhibitor. The factor VIII domain that triggers inhibitor production can be masked by the von Willebrand factor (VWF) molecule, which is bound to factor VIII in the bloodstream.

These treatments are called immune tolerance therapy. These treatments can take several months to several years to succeed and are effective about 80 per cent of the time. Meanwhile, other products such as FEIBA® and NiaStase® are used at home to stop the bleeding that may occur during the treatment of the inhibitors. These products may occasionally be used to prevent bleeding.
Conclusion

Hemophilia is a medical condition that requires infusions of a factor replacement product to help prevent or stop bleeding and avoid complications such as joint damage. Sometimes an individual will develop an inhibitor against the infused factor because his body recognizes it as a foreign substance. However, there are treatments to eliminate inhibitors as well as treatments to stop bleeding despite the presence of inhibitors. The success rate of these treatments is encouraging but it can be a long and demanding process for the patient and his family.

If your child develops an inhibitor, the HTC team will be there to guide and support you. More comprehensive information is available on inhibitors, including through the Quebec Centre of Inhibitors of Coagulation.

For more information on inhibitors, we recommend that you consult these two publications:

- *All About Inhibitors*, a booklet prepared by the Canadian Hemophilia Society for patients with inhibitors.

Complications of Hemophilia

PART 2 - Joint and Muscle Damage

This section provides answers to these questions:

- How can a bleeding disorder cause joint damage?
- What are the types of joint damage?
- What is a target joint?
- How will you know if your child has a target joint?
- What is synovitis?
- What is chronic synovitis?
- How will you know if your child has chronic synovitis?
- What is arthritis?
- What are the symptoms of arthritis?
- Can synovitis and arthritis be prevented?
- How is joint disease treated once it exists?
- How do muscle bleeds happen?
- What are the complications of muscle bleeds?
- How should muscle bleeds be treated?
Many adults with severe hemophilia in Canada have permanent damage in one or more joints. When they were children, treatment was less advanced. Preventative treatment with regular clotting factor infusions (prophylaxis) was not prescribed routinely, home infusion programs were not as well developed, and joint bleeds were less well controlled.

Today, prophylaxis starting at a very early age helps prevent bleeding and joint damage. This preventative treatment approach has greatly improved the child’s chances of reaching adulthood without developing serious joint disease. Many Canadian children with hemophilia grow up with nearly normal joints. However, while prophylaxis helps decrease the frequency and severity of bleeds and early joint damage, it does not prevent all bleeds. If the bleeding continues and is not promptly controlled, early joint damage can develop. Repeat bleeding can result in permanent joint damage.
PART 2 - Joint and Muscle Damage

How can a bleeding disorder cause joint damage?

Bleeding into the joints and muscles is common in people with hemophilia. These bleeds can eventually lead to joint or muscle damage in three ways:

1. Damage to a joint can start to develop when there is bleeding into the joint cavity. In some cases, joint damage can begin after one major joint bleed. But more often, joint damage is the result of large or repeated bleeds over a period of time.

2. After a joint bleeds, the lining of the joint (synovium) can remain inflamed for several weeks. This is called acute synovitis. An inflamed synovium can bleed again very easily, creating a new bleed before the first bleed has had a chance to heal completely.

3. Muscle bleeds, if they are not treated correctly, can cause scarring and loss of flexibility of muscles. This can place additional stress on the nearby joints, and place them at risk to bleed.

Some joints are more likely to be affected by bleeds than others. The joints that bleed most often are the knees, ankles and elbows. These are hinge joints and have little protection from side-to-side stresses.

Joints like the shoulder and the hip are ball-and-socket joints. They are well protected by large muscles, and are designed to move in many directions without being injured.
Complications of Hemophilia

PART 2 - Joint and Muscle Damage

■ What are the types of joint damage?

Joint damage can affect two parts of the joint: the synovium and the cartilage. Inflammation of the synovium is called synovitis. Synovitis can be acute or chronic. Erosion and damage to the cartilage is called arthritis.

■ What is a target joint?

A target joint is a joint that bleeds often. Different definitions have been suggested, such as a joint that bleeds more than other joints or a joint that bleeds a certain number of times in a certain time period. The most important points are that a target joint is one that does not return to a healthy state between bleeds. A target joint is at (higher) risk of developing early joint disease.

■ How will you know if your child has a target joint?

You may recognize that a certain joint seems to bleed more often than the others. Or your hemophilia team may notice this when they review your bleeding/treatment diary. This is one of the reasons that keeping an accurate diary is so important.

“When I was little, I fell off my bike and hit my elbow really bad. It gets sore a lot since then and I have to use a sling to keep it still. I’m not supposed to throw a baseball if it is sore.”
**What is synovitis?**

The insides of joints are covered by a thin lining called the *synovium* or *synovial membrane*. The function of this layer of special cells is to...

- lubricate the joint
- feed the cartilage
- remove fluid and debris from the joint.

The synovium has many blood vessels that feed the joint and carry away debris. Because there are so many blood vessels in the area, they can easily be injured when the joint is twisted or strained and a bleed into the joint begins.

Following a joint bleed, the synovium can remain inflamed for several weeks. This is a **danger period** when the joint is more likely to bleed again — sometimes the pain may be gone and the joint seems to look and move normally, but the joint has not yet healed completely. Many *target joints* develop during this danger period.

**What is chronic synovitis?**

When there are repeated bleeds, the synovium becomes overwhelmed with the job of cleaning up the old blood. In an attempt to keep up, the synovium will grow more blood vessels and become thickened. This is called chronic synovitis.
How will you know if your child has chronic synovitis?

Synovitis looks and feels different from an acute bleed. The joint looks “puffy” or swollen all the time. The swelling does not go away after a treatment of factor concentrate. If the joint has become permanently stretched from chronic swelling, it may not be painful. While a bleeding joint will quickly lose motion as blood fills the joint cavity, joints that are swollen from chronic synovitis usually continue to move without pain (that is, when they are not bleeding). However, they may lose motion over months or years.

### Table 1

<table>
<thead>
<tr>
<th>Differences between an acute bleed and synovitis</th>
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<tbody>
<tr>
<td><strong>Acute bleed</strong></td>
</tr>
<tr>
<td>• Painful</td>
</tr>
<tr>
<td>• Motion limited</td>
</tr>
<tr>
<td>• Swelling may diminish with factor therapy</td>
</tr>
</tbody>
</table>
**What is arthritis?**

*Arthritis* means “inflammation of the joint.” In addition to inflammation of the synovial lining, there is also damage to the cartilage and bones of the joint surfaces.

There are two types of cartilage in joints. The most important is the one that forms the smooth hard cap on the ends of the bones and allows the joints to move with very little friction. When there has been a lot of blood inside a joint, either after a very large bleed, or after repeated bleeds, the old blood and the fluid that the synovium makes to try to heal itself begin to eat away at the cartilage. This is arthritis.

**What are the symptoms of arthritis?**

These are some of the symptoms of arthritis.

- The joint becomes stiff, especially in the morning or after sitting for a long time.
- The joint may be painful when it is used.
- The muscles around the joint may become weak and wasted from lack of use.
- If the joint is a knee or an ankle, the person may have difficulty walking, climbing stairs, or getting in and out of a car. Running is out of the question.
Can synovitis and arthritis be prevented?

Yes. It is much easier to prevent joint damage than it is to treat it after it starts to develop. The best way to prevent joint damage is to prevent bleeds into the joints. This is done with prophylactic clotting factor therapy. Clotting factor can be given before bleeding actually occurs. Many children with severe hemophilia receive factor infusions on a regular basis. People with moderate hemophilia sometimes infuse factor concentrate before they participate in sports or other activities that can place stress on joints and cause bleeds. See Chapter 4, Management of Bleeds; Chapter 5, Clotting Factor Therapy; and Chapter 6, The Role of Prophylaxis.

Even with prophylaxis, there is no way to prevent all bleeds, especially in active toddlers. Padding the furniture, using carpeting on floors, and protective gear such as a helmet and kneepads may help to prevent and reduce bruises. However, joint bleeds are almost always caused by stress — a twist or a sprain — on the joint.

The second best way to prevent joint damage is to recognize and treat each new joint bleed immediately. In very young children, it is often difficult to tell if there is swelling in a joint. However, in the early stages of a bleed you may notice that your child refuses to use an arm or a leg, or cries if that limb is moved. If clotting factor is given at this point, there will be only a small amount of bleeding that needs to heal. It is also important to rest the joint — this means no walking after a knee or ankle bleed, no crawling after an elbow bleed, and no sports until the joint has fully recovered.

“Our child was only seven when his x-ray showed serious joint damage in his target joint. He was on prophylaxis, yet it still developed.”
PART 2 - Joint and Muscle Damage

If the bleeding is not stopped at this point, the joint becomes increasingly painful as the capsule is stretched. It becomes more and more difficult to bend. The skin over the joint feels warm to the touch. These signs mean that a large amount of bleeding has occurred into the joint space, and it will therefore take a longer time for the joint to completely return to normal. The joint is then more at risk for repeated bleeding. It could become a target joint. It may require several treatments with factor, as well as several days or weeks of rest, and physiotherapy to restore range of motion and muscle strength.

Prevention of bleeding and aggressive management of all new bleeds helps to prevent synovitis and the development of target joints. Aggressive management of new bleeds and of synovitis should prevent arthritis.

How is joint disease treated once it exists?

Remember! Once a joint has been damaged, it is unlikely that it will ever be as good as new. However, if synovitis or a target joint has developed, there are several treatment options.

• **Prophylaxis** – Preventative treatment may be recommended for a period of three to six months. This means that clotting factor therapy is given, usually every second day, to prevent new bleeds and allow the synovium to heal.

• **Exercise** – A program designed by the HTC physiotherapist is also used to strengthen the surrounding muscles and protect the joint from further injury.
• **Splinting or bracing** – This may be used to protect the joint. This is sometimes used in combination with prophylaxis. Strengthening exercises are very important if a brace is worn because some braces restrict motion and allow the muscles to become weak.

• **Steroid injections** – Steroid treatment can be used to speed the healing. First, factor concentrates are given. Then a small needle is used to inject medicine directly into the joint to settle the inflammation. This is usually done by an expert in joints, such as a rheumatologist or an orthopedic surgeon.

• **Synovectomy** – This is a procedure used to remove the inflamed synovium. This can dramatically reduce the number of bleeding episodes, allow some healing, reduce pain, and lessen the severity of damage to the joint surfaces. Over time, a new synovium will grow back. However, synovectomy cannot make the joint like new, nor restore motion that has been lost. There are different types of synovectomy:

  * **Arthroscopic synovectomy** – A small tube fitted with a tiny camera (arthroscope) is inserted into the joint through a small incision. Special tools allow the surgeon to remove the thickened synovium. Clotting factor must be given during and after the procedure. Physiotherapy is important after the procedure, to regain maximum strength and function of the joint, but the recovery time is fairly short.

  * **Radioactive or chemical synovectomy** – A substance is injected into the joint to “burn” the synovial tissue. The swollen synovium dies and is eventually replaced by a healthy one. This procedure does not require large amounts of factor replacement or physiotherapy. It has been used in special cases, such as to treat target joints in children with inhibitors.
PART 2 - Joint and Muscle Damage

- **Arthrodesis** – Two bones are fused together with screws, steel rods or staples. The resulting fused joint loses flexibility but is stabilized and can bear weight better leading to decreased pain. Arthrodesis has been the operation of choice for the ankle joint to date as total ankle joint replacements are still being tested and perfected. It is generally not recommended for larger joints such as the hip or knee, where joint replacement would be superior.

- **Joint replacement** – In cases of severe joint destruction and loss of motion, joint replacement surgery may be an option.

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The best approach to joint disease in hemophilia is to prevent it.

Here’s how:

- Prevent bleeds with prophylactic clotting factor therapy and choose sensible physical activities and sports over risky ones.

- Treat each joint bleed with clotting factor promptly and completely. Rest the injury and modify physical activities until the joint is completely healed.

- Prevent the development of target joints and chronic synovitis through management of acute synovitis after each bleed. This should include resting the joint for at least 1 day following a bleed to prevent re-bleeding.

- Watch and treat for chronic synovitis aggressively.

- See the HTC physiotherapist for regular check-ups and treatment recommendations.
How do muscle bleeds happen?

Muscles can be injured if they are over-stretched or by direct impact. Some of the muscle fibres tear and start to bleed.

What are the complications of muscle bleeds?

Muscle bleeds can have very serious consequences. Bleeds into deep muscles can cause damage to nerves and blood vessels, leading to numbness, paralysis of the muscles or even muscle death.

Following a bleed, the muscle can be sore and weak for a long time. Returning to full activity too quickly can cause additional bleeding to the muscle itself or the nearby joints. Muscles can heal with scarring, which causes them to lose flexibility. This can also lead to further injury to the muscle itself, and can also place additional strain at the nearby joints.

See Figure 1: cross section of a muscle bleed causing compression of nerves, vessels.

How should muscle bleeds be treated?

Prevention of muscle bleeds, by choosing activity wisely, and using protective padding for riskier activities, can help. Early recognition of muscle bleeds is essential. All muscle bleeds must be rehabilitated fully, under the supervision of an experienced physiotherapist.

For information on physical movements and activities that can cause joint or muscle bleeds, see Chapter 12, Physical Activity, Exercise and Sports.
Complications of Hemophilia

PART 3 - Pain in Hemophilia

This section provides answers to these questions:

- What causes pain in a person with hemophilia?
- How can you relieve your child’s acute pain?
- What about painkillers?
- What if the pain does not go away?
- What can be done for chronic pain?

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What causes pain in a person with hemophilia?

There are two kinds of pain in people with hemophilia. The first is acute pain, caused by active bleeding into a joint or muscle. The second is chronic pain, caused by long-term joint damage. Chronic pain mainly affects older people with hemophilia who suffer more from arthritis.

Acute pain is a signal that something is wrong. It is usually the earliest sign of a bleed. A bleed that is ignored will go on to stretch a joint or put pressure on muscles and other structures. This will make the pain get much worse. Even if there are no other obvious signs of bleeding, such as swelling, clotting factor therapy is recommended. “If in doubt, treat” is the motto used by most experts in hemophilia care.

How can you relieve your child’s acute pain?

Pain from a bleed can be controlled by giving clotting factor concentrate to stop the bleeding as soon as a problem is identified. Resting the bleed by supporting the arm or leg on a pillow in a comfortable position or in a splint may help to lessen the pain. Use of ice will ease the pain by decreasing the ability of the nerves to send pain messages. For more information on how to use ice correctly, see Chapter 4, Management of Bleeds.

Pain will seem much worse if your child is upset or worried. Distractions such as reading a story, watching a favourite movie, or playing games can help him relax and think about things other than the pain. They can also help him stay calm. This will rest the injured joint or muscle to allow healing. Some children find that a warm bath and a back rub help them relax and rest more comfortably.
PART 3 - Pain in Hemophilia

What about painkillers?

Medications, such as acetaminophen, can be used to control or relieve pain. However, many of the painkillers that are available at the drug store without a prescription contain acetylsalicylic acid (ASA), the active ingredient in aspirin. People with hemophilia must not take products that contain aspirin. Aspirin stops platelets from grouping together to make a clot. Its use will make the bleeding worse.

Some other common painkillers such as Advil and Ibuprofen also affect platelets and can make the bleeding worse—these medications should also be avoided.

Make sure you know if the medicine you are thinking about using is safe. If you are not sure, check with your pharmacist, your nurse or your doctor.

Table 2

<table>
<thead>
<tr>
<th>Pain Killers that Should Not Be Used by People with Hemophilia</th>
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<tbody>
<tr>
<td><strong>Drugs that contain aspirin/ASA</strong></td>
</tr>
<tr>
<td>Aspirin</td>
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<tr>
<td>Entrophen</td>
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<tr>
<td>Anacin</td>
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<tr>
<td>Norgesic</td>
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<tr>
<td>222’s, 282’s, 292’s</td>
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<tr>
<td>Coricidin Cold</td>
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<tr>
<td>Coricidin D and Non-Drowsy</td>
</tr>
<tr>
<td>Robaxinal</td>
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<tr>
<td>Midol</td>
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<tr>
<td>Dristan</td>
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</table>
What if the pain does not go away?

Ice, rest and medication may help to reduce pain, but they do not stop the bleeding. Clotting factor therapy is the only way to stop bleeding.

If the regular treatment of clotting factor does not seem to relieve the pain, contact your hemophilia treatment centre immediately. Perhaps an inhibitor has developed. Or there may be another reason, besides a bleed, for your child’s pain. He could have a more serious injury, such as a broken bone, or a problem that is not related to his hemophilia.

What can be done for chronic pain?

Some people with hemophilia, particularly those with joint damage, suffer from chronic pain. There are several options available for the management of chronic pain.

Physiotherapy

Physiotherapists have many ways to help reduce pain and will advise you regarding what’s right for your child. This is a short list of some of them.

- **Exercise** – Specific exercises may help relieve joint or muscle stiffness. Exercises that strengthen muscles may also help to support damaged joints.

- **Walking aids** – Using a cane or crutches can help to take the pressure off sore joints.

- **Splints or braces** – These can help support damaged joints and prevent further injury.

“Throughout my life I have had to deal with pain. Not all kids my age are in the same boat. My pain ranges quite a bit, from arthritic pain to the pain of bleeds caused by hemophilia.”
PART 3 - Pain in Hemophilia

- **Electrical modalities** – Physiotherapists may use TENS (transcutaneous electrical nerve stimulation) to control pain. This works by sending a very mild current of electricity to the nerves which normally send pain messages to the brain. The electricity blocks the pain signals.

- **Hydrotherapy** – Exercise in water is a good way to move joints and strengthen muscles. The buoyancy of the water takes the weight and pressure off the joints as they are exercised.

- **Relaxation and biofeedback** – When a child is tense or worried, the pain may seem worse. Techniques to help relax and concentrate on other things besides the pain can help.

**Medications**

Medications may be used to reduce inflammation and to control pain. You and your child’s doctor should work together to find the right combination of medicine for his particular needs. Some people may be referred to a pain clinic where specialists assess and treat chronic pain. Always discuss your child’s pain management with your health care team.

**Other Alternatives**

There are many other ways to treat pain, such as acupuncture and chiropractic treatments. However, some of these alternatives may not be completely safe for people with hemophilia. Always check with your comprehensive care team before you try these kinds of treatments.

**Test Your Knowledge**

Which of these over-the-counter medications contain ASA and should never be given to a child with hemophilia?

a) aspirin  
b) Anacin  
c) Dristan  
d) 222

(For some help in finding the answers, see page 21 in this chapter.)

(The correct answers are on page 17-18.)
Conclusion

Pain is a feature of acute bleeds as well as chronic joint damage in hemophilia. The best way to manage pain in hemophilia is to prevent bleeds altogether, and when a bleed does happen, to treat it early. This will decrease the amount of acute pain and prevent joint disease. If the joints are healthy, the chances of developing chronic pain are reduced.

For more information, see the Canadian Hemophilia Society publication, Pain the Fifth Vital Sign: A Resource on Managing Pain for People with Bleeding Disorders.

“When I have pain, I just can’t wait until it goes away and I can be me again. I know this will happen so I keep looking forward to getting better and doing the things I can to make that happen.”