This chapter provides answers to these questions:

- What are mild and moderate hemophilia? How do they differ from severe hemophilia?
- How are mild and moderate hemophilia diagnosed?
- What are the treatment options for these types of hemophilia?
- What complications can occur in boys with mild or moderate hemophilia?
- Can girls have mild hemophilia?
- What should be remembered about mild and moderate hemophilia?

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What are mild and moderate hemophilia? How do they differ from severe hemophilia?

Hemophilia is an inherited bleeding disorder transmitted through the X chromosome. The usual transmission is from mother to son at conception. A boy inherits his X chromosome from his mother and Y chromosome from his father. If the X chromosome from his mother has the genetic mutation, the boy will have hemophilia.

Hemophilia A occurs when there is a mutation in the gene for clotting factor VIII. Hemophilia B occurs when there is a mutation in the gene for clotting factor IX.

There are many different inheritable genetic mutations that can cause hemophilia. Certain types of mutations result in severe forms of the disease; others cause mild or moderate hemophilia. For more information on inheritance, see Chapter 2, How a Child Gets Hemophilia.

The consequences of having hemophilia — recurrent bleeds into muscles and joints —depend on the severity of the hemophilia. Severity is determined by the level of clotting factor activity. Normal clotting factor activity is described as 100 percent, but can be anywhere within the range of 50 to 150 percent.

In people with hemophilia, the clotting factor activity is much lower than normal levels. The lower the clotting factor activity level, the more frequent the bleeding. Table 1 shows the three classifications of hemophilia, the corresponding percentages of clotting factor activity, and the percentage of people with hemophilia in each classification.
People with severe hemophilia can have frequent bleeding episodes and bleeding into major joints, muscles and soft tissues. Sometimes bleeds can occur without anyone recognizing it right away or knowing what caused it. If left untreated, these bleeds can eventually lead to joint disease, muscle damage or arthritis that makes movement difficult or painful.

People with moderate hemophilia usually have fewer bleeds than those with the severe form. Their bleeds are frequently the result of minor trauma, such as a sports injury. However, some people with moderate hemophilia, especially those with a factor VIII or IX level of 1 to 2 percent, can have bleeding into joints and muscles without a known or apparent cause of trauma, similar to people with severe hemophilia.

In contrast, people with mild hemophilia rarely have unexplained bleeding episodes. In people with mild hemophilia, bleeding episodes are most commonly the result of serious injury, surgery or dental extractions. Therefore, some people with mild hemophilia remain undiagnosed until they have a significant trauma or undergo surgery; this sometimes only occurs when they are adolescents or even adults. In these patients, not knowing a bleeding disorder is present may lead to extreme blood loss, which can be life threatening.
### How are mild and moderate hemophilia diagnosed?

Accurate diagnosis of mild hemophilia can be difficult. It requires measuring the amount of clotting factor in the bloodstream. This testing procedure is generally not available in small community laboratories nor in small hospitals. It usually requires a more specialized centre to make or confirm the diagnosis.

Basic screening tests such as the aPTT (*activated partial thromboplastin time*) do not identify all cases of mild hemophilia. Other bleeding disorders such as von Willebrand disease may also show similar laboratory abnormalities — this makes the diagnosis of mild hemophilia more difficult.
There are many reports of individuals not being diagnosed until they are adults. While this can be an encouraging sign that the disorder is mild, it can also mean that the condition is sometimes not discovered until an individual has an accident or undergoes surgery. Therefore, if you or your family doctor suspects your child has a bleeding disorder, it is important to go to a hospital that specializes in diagnosing and treating coagulation problems, such as a hemophilia treatment centre. There, specialists can take a careful clinical and family history of bleeding and do the laboratory tests for diagnosis. It is important to get diagnosed as soon as possible — do not wait for a serious bleed in the midst of an emergency.

If hemophilia is diagnosed, it is important to inform other family members. Some of them may be affected as well. They also need to get a proper diagnosis in case they ever have a serious bleed or potentially life-threatening injury.

“When I attend family events with other families dealing with hemophilia, I feel very fortunate. Our son is 12 and needs to be treated a couple of times a year. He plays sports and hasn’t had many bleeds. It surprises me to share stories with other families and to see how different all our experiences are.”
What are the treatment options for these types of hemophilia?

The problem in hemophilia is the absence or decreased level of clotting factors — factor VIII in hemophilia A and factor IX in hemophilia B. Today, the treatment of children with hemophilia aims at preventing bleeds. Nevertheless, bleeds sometimes occur despite all the best efforts at prevention. In the event of a bleed, it is important to seek medical attention quickly so that steps are taken to raise the level of the deficient clotting factor.

Factor concentrates

The most common way of raising the level of the missing clotting factor is by simply administering it to the child. Clotting factor concentrates are available in two forms:

- **Plasma-derived factor concentrates** – These blood products, derived from human plasma, are screened for blood-borne viruses, such as the human immunodeficiency virus (HIV), and hepatitis B and C viruses. Then they are treated in order to destroy any potential viruses that were not eliminated by the screening procedures. Since the late 1980s these products have been extremely safe and effective.

- **Recombinant factor concentrates** – As a result of the transmission of various blood-borne viruses through contaminated blood products during the 1970s and early 1980s, recombinant factor concentrates were developed. They are manufactured using recombinant technology rather than plasma as the source of the clotting factor. There are now several recombinant factor VIII products and one recombinant factor IX product in widespread use.

For more information on clotting factor concentrates, see Chapter 5, Clotting Factor Therapy.
Mild and Moderate Hemophilia

A small number of children with moderate hemophilia, especially those whose clotting factor VIII or IX activity levels are about or less than 2 percent of normal, may need factor concentrates on a regular basis.

For most individuals with mild or moderate hemophilia, factor concentrates may not always be required for bleeding episodes. In many cases, other treatments can be used to reduce or avoid the use of factor concentrates.

Desmopressin acetate (for factor VIII deficiency)

Desmopressin acetate is a synthetic drug — not a blood product — that is helpful in the treatment of the majority of individuals with mild hemophilia A. It works by raising the patient’s factor VIII level. This is achieved by releasing into the bloodstream factor VIII that has been previously produced and stored in the linings of blood vessels.

Desmopressin can be given in different ways:

- Intravenously — The drug is injected into a vein. This is usually the preferred method for children. This product goes by the brand names of Octostim® and DDAVP® Injection. Outside Canada, the same medication is known as Stimate®.

- Subcutaneously — The drug is injected just under the skin. Octostim® and DDAVP® Injection can be given in this way.

- Intranasally — The drug is taken into the nostrils using an inhaler, in the same way that people with asthma take their medications. This form of desmopressin goes by the brand name of Octostim® Nasal Spray. Outside Canada, it is known as Stimate® Nasal Spray. The intranasal form of desmopressin used in the management of individuals with mild or moderate hemophilia is 15 times more concentrated than the standard intranasal desmopressin used in the treatment of diabetes.
insipidus and enuresis (bed-wetting). Generally, nasal sprays are
not used in very young children, as the absorption through the
nasal mucosa (moist membranes of the nose) is not reliable in
early childhood.

There is an oral form of desmopressin — DDAVP tablets — that is
used as an anti-diuretic for bed-wetting. At present there is no
reliable information on its use in hemophilia. Therefore it cannot
be recommended for the treatment of bleeds in patients with
hemophilia.

Desmopressin can triple the level of factor VIII in the bloodstream.
As a result, a patient with mild hemophilia A may be given
desmopressin to raise his factor VIII level to within the normal
range, to prevent or treat bleeds.

Unfortunately, the effect of desmopressin in raising factor VIII
levels is short-lived. The maximum response usually occurs 1 hour
after its administration, although there is some lasting benefit
even after 12 hours. Desmopressin can be used again after waiting
at least 12 to 24 hours but it can only be used for a few days in a
row. After that it no longer produces much of an effect as the
body’s stores of factor VIII become exhausted. If further treatment
is needed to control bleeding, factor concentrates will likely be
needed.

After several days of being off desmopressin, it can be used once
again, as the body has built up its stores of factor VIII again.

Side effects with desmopressin are minimal but include:

- mild facial flushing
- headache
- nausea
- lightheadedness
Desmopressin also acts as an anti-diuretic. Anti-diuretics cause the kidneys to retain water. In young children who drink large amounts of fluids (water, juice, milk, etc.), this side effect of desmopressin may result in hyponatremia — a condition in which the sodium or salt content in the blood is low. In rare cases, this may result in a seizure. Hence when this drug is used, especially in very young children, it is important that they not be given large amounts of fluid. In young children, blood sodium levels should be checked.

Desmopressin is a useful drug for two reasons:
- It is effective in the majority of patients with mild hemophilia.
- It can help reduce or altogether avoid the use of factor concentrates in these patients.

See the staff at your hemophilia treatment centre to find out if desmopressin would be effective treatment for your child, the best form of desmopressin for your child and how to administer it.

**Antifibrinolytics (for both factor VIII and IX deficiency)**

Antifibrinolytic drugs such as tranexamic acid (also called Cyklokapron® or TA) are also helpful for the treatment of both hemophilia A and B. Another antifibrinolytic agent is epsilon amino caproic acid (also called Amicar® or EACA) but this product is no longer available in Canada.

These agents act by strengthening blood clots that form. This prevents the clots from being dislodged and bleeding to re-start. Antifibrinolytic agents are particularly useful for bleeding from the mouth (gums, teeth, tongue) as well as from the nose. These drugs are not recommended for bleeding in the urinary tract as they may result in a clot forming that blocks urine flow, much like a kidney stone.

*For more information on desmopressin and antifibrinolytics, see Chapter 5, Clotting Factor Therapy, “What other medications are used to treat bleeding?”*
Physiotherapy

It is important for individuals with mild/moderate hemophilia to be followed by a physiotherapist experienced in managing patients with hemophilia. Your HTC physiotherapist will help you and your child learn how to recognize and treat a joint or muscle bleed and provide advice on appropriate exercises and other physical activities for rehabilitation and/or the prevention of bleeds and joint damage.

The basic steps of first aid commonly used to slow bleeding are called **RICE** — which stands for **Rest**, **Ice**, **Compression** and **Elevation**.

- **Rest** – Resting an injured leg or immobilizing an injured arm is helpful as continued use of an injured limb may make a joint or muscle bleed more.

- **Ice** – Ice is used to shrink blood vessels and slow the flow of blood to an injured area. This process is called **vasoconstriction**.

- **Compression** – Compression, such as by wrapping a tensor bandage around an injured joint, provides support and also helps to slow bleeding.

- **Elevation** – By elevating an injured limb above the level of the patient’s heart, blood flow to the site of bleeding may be reduced.

For more information on the four techniques of **RICE**, see Chapter 4, Management of Bleeds, “How are bleeds treated?”
All of these measures are important in the management of a bleed in any child with hemophilia. However, they are even more important in children with mild hemophilia who may never have received factor concentrates. The use of desmopressin, antifibrinolytics and other treatments may help avoid the use of factor concentrates altogether and reduce the risk of complications such as the development of an inhibitor.

For more information on the importance of physiotherapy and exercise in the treatment of bleeds, see Chapter 12, Physical Activity, Exercise and Sports.

What complications can occur in boys with mild or moderate hemophilia?

Most boys with mild or moderate hemophilia will only rarely have prolonged bleeding episodes. This usually only happens as a result of major trauma or surgery. Therefore, most children with mild or moderate hemophilia lead quite healthy lives participating in a full range of activities. They may often go years or even a lifetime without requiring the infusion of factor concentrates. Nevertheless, occasionally and unexpectedly, they may have bleeding problems that require treatment in the form of desmopressin, antifibrinolytic drugs and/or factor concentrates. Sometimes, they can also experience complications such as joint and muscle damage, life-threatening bleeds and inhibitors.

Joint and Muscle Damage

Given that people with mild and moderate hemophilia typically have fewer symptoms and bleeding problems, some often do not seek prompt medical attention when an injury occurs. However, waiting can make the bleed worse. Prolonged bleeding can lead to joint or muscle damage. Also, a bleed that is not treated promptly

“Moderate hemophilia sounded so much better to us in the beginning, than severe hemophilia. Over time however, we have experienced serious ankle and knee bleeds, an internal bleed, and difficult muscle bleeds. Our son needs prophylaxis, even though we started with on demand treatment. He needed a port to provide the regular access to his veins. He developed a target joint and has arthritis as a result. We are working with a physiotherapist to help him strengthen his weaker leg and to walk better. He doesn’t present like a typical moderate, if there is such a thing.”
can ultimately require several days or weeks of therapy, instead of
the single infusion of factor that would likely have been required
had medical attention been sought right away. It is therefore very
important for those with mild and moderate hemophilia to seek
prompt medical attention when a bleed occurs.

**Life-threatening bleeds**

Injury or trauma can cause internal bleeding that does not show,
but can become life-threatening. It is therefore especially
important that any injury involving the head, neck, chest or
abdomen be given immediate medical attention.

**Inhibitors**

Currently, the biggest risk from receiving factor concentrate is that
of developing inhibitors.

What is an inhibitor? The body’s immune system can sometimes
react to the clotting factor concentrate that is infused to stop or
prevent a bleed. The factor concentrate is seen by the person’s
immune system as a foreign substance, and as a result of this his
immune system produces antibodies, natural chemical substances
that circulate in the blood. The antibodies destroy the infused
factor concentrate and thus prevent it from doing its job of
stopping the bleeding. These antibodies are called inhibitors.
They develop in...

- 15 to 35 percent of people with severe hemophilia A (factor
  VIII deficiency)
- 1 to 5 percent of people with mild or moderate hemophilia A
- 1 to 3 percent of people with severe hemophilia B (factor IX
  deficiency)
- less than 1 percent of people with mild or moderate
  hemophilia B
It is not known why inhibitors develop in some people with hemophilia and not in others. Researchers think there may be a genetic predisposition in certain people, making them more susceptible to inhibitor development.

Unfortunately, when these inhibitors do develop in people with mild or moderate hemophilia, they are an extremely serious complication. They may change a patient who seldom experiences bleeding problems into someone who has many joint and muscle bleeds. This is because the inhibitor not only destroys the factor VIII or IX administered to the patient, but also reacts with the patient’s own factor and destroys that, thereby decreasing the patient’s clotting factor level to less than 1 percent. This puts him into the range of severe hemophilia.

It is to avoid the risk of inhibitor development that physicians treating patients with mild or moderate hemophilia will, if possible, use other treatment measures such as desmopressin (for mild hemophilia A) and antifibrinolytic drugs rather than simply administering factor concentrates.

For more information on inhibitors, see Chapter 8, Complications of Hemophilia, Part 1 – Inhibitors.
Can girls have mild hemophilia?

Yes, they can.

Severe hemophilia is almost exclusively a disorder that affects boys. A girl can carry one abnormal X chromosome and, if so, she is referred to as a *carrier of hemophilia*. As a carrier, she can transmit the genetic mutation to her sons. Her second X chromosome, being normal, produces certain quantities of factor VIII or IX. This protects her from the moderate or severe forms of hemophilia with clotting levels less than 5 percent of normal.

However, a hemophilia carrier can have clotting factor levels less than 30 percent of normal. This puts her into the same category as a boy with mild hemophilia. Therefore, she may bleed more frequently than a normal girl and may have to be followed in a bleeding disorders clinic. Indeed, even some carriers of hemophilia with factor levels greater than 30 percent are known to have an increased tendency to bleed.

Menstrual bleeding is of special concern, especially during a girl’s first period when bleeding can be heavier. In the event of surgery, a girl with low clotting factor levels may need treatment with factor concentrates.

For more information, see Chapter 14, Symptomatic Carriers of Hemophilia.
What should be remembered about mild and moderate hemophilia?

- Most people with mild and moderate hemophilia have less frequent bleeding than those with the most severe form of the disorder; some of them may never need factor concentrates. However, there are exceptions. Some people with the mild and moderate forms can bleed like those with severe hemophilia.

- Bleeding in mild and moderate hemophilia can be serious, even if it happens less frequently. In fact, in some ways, mild and moderate hemophilia can be more dangerous, because the bleeding problem is unexpected and might go untreated. Delays in seeking treatment will make bleeds worse and more difficult to treat, and may predispose patients to developing joint damage.

- Parents, caregivers, and children with hemophilia themselves, need to learn the signs of bleeding, so as to get treatment quickly.

- Children with mild and moderate hemophilia need to be followed by a hemophilia treatment centre, where the family can learn all it needs to know about the bleeding disorder.