This chapter provides answers to these questions:

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

- How are mild/moderate hemophilia diagnosed?

- What are the treatment options for these types of hemophilia?

- What complications can occur to boys with mild/moderate hemophilia?

- Can girls have mild hemophilia?

- What should be remembered about mild/moderate hemophilia?
What are mild/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. The mother has two X chromosomes as part of her 46 chromosomes and, at conception, gives one to her son. He gets a Y chromosome from his father. If the X chromosome the boy gets from his mother is defective, he will have hemophilia.

The disease is caused by a genetic mutation—a change in the gene. 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—the frequency and severity of bleeding—depend on the severity of the hemophilia, which is determined by the level of clotting factor activity. Clotting factor activity in a normal person is said to be 100 percent, ranging anywhere from 50 percent to 150 percent.

In people with hemophilia, the clotting factor activity is much lower than this. The lower the clotting factor, the more frequent the bleeding. The following table shows the three classifications of hemophilia, the percentage of clotting factor activity and the percentage of children with hemophilia in each classification.
### Table 1

<table>
<thead>
<tr>
<th>Classification of Hemophilia</th>
<th>Percentage of clotting factor activity</th>
<th>Percentage of children with hemophilia in each classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Less than 1 percent</td>
<td>40 percent</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 to 5 percent of normal</td>
<td>20 to 25 percent</td>
</tr>
<tr>
<td>Mild</td>
<td>5 to 30 percent of normal</td>
<td>35 to 40 percent</td>
</tr>
</tbody>
</table>

A child with severe hemophilia has frequent spontaneous bleeding episodes usually involving major joints, muscles and soft tissues. If left untreated, these bleeds lead to crippling arthritis.

Children with moderate hemophilia usually bleed less often. Their hemorrhages are frequently the result of minor trauma, such as a sports injury. However, some people with moderate hemophilia, especially those whose levels of factor VIII or IX are between 1 and 2 percent, can have frequent spontaneous bleeds in the same way as a person with severe hemophilia.

In contrast, a child with mild hemophilia rarely has spontaneous bleeding episodes. Bleeding most commonly occurs as a 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. In these patients, not knowing a bleeding disorder is present may lead to extreme blood loss which can be life threatening.

Still a Mystery...

We still don’t know why some children with severe hemophilia hardly bleed at all and some children with moderate hemophilia bleed quite often. There’s obviously something else besides factor level at work here. It’s still a mystery.
Table 2

<table>
<thead>
<tr>
<th>Classification of hemophilia</th>
<th>Most common types of bleeding</th>
<th>Usual causes of bleeding</th>
<th>Frequency of bleeding (in the absence of prophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>• Mucosal bleeding</td>
<td>• Serious sports injuries</td>
<td>• Quite rare</td>
</tr>
<tr>
<td></td>
<td>• Internal bleeding</td>
<td>• Serious trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dental extractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>• All of the above plus...</td>
<td>• All of the above plus...</td>
<td>• Variable, depending on individual differences and factor levels</td>
</tr>
<tr>
<td></td>
<td>• Joints</td>
<td>• Minor sports injuries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Muscles</td>
<td>• Spontaneous (no obvious cause, especially for those with factor levels of less than 2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>• All types</td>
<td>• All of the above plus...</td>
<td>• Several episodes per month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spontaneous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minor twists or bumps</td>
<td></td>
</tr>
</tbody>
</table>

How are mild/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 not available in most small community laboratories nor in smaller 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 patients with mild hemophilia. As well, 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 patients not being diagnosed until they are adults. While this is an encouraging sign that the disorder is mild, it can also mean that the condition is not discovered until the person has an accident or undergoes surgery. Therefore, if you or your family doctor suspect a bleeding disorder, it is crucial 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 needed to make the diagnosis.

It is better to do this when a person is not experiencing a bleed than in the midst of an emergency.

If hemophilia is found, it is important to inform other family members. Some of them may be affected, too. They also need to get a proper diagnosis before an emergency threatens their lives.

“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 raise the level of the missing 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. These 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), 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 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 the manufacture of clotting factor concentrates, see Chapter 4, Clotting Factor Therapy.)*
For patients 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 majority of patients 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 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 in children. This product goes by the brand names of Octostim® and DDAVP® Injection. Outside Canada, the same medication can be called Stimate®.

- **subcutaneously.** The drug is injected just under the skin. Octostim® and DDAVP® Injection are also used.

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

Desmopressin may triple the level of factor VIII in the child’s bloodstream. As a result, a patient with mild hemophilia may raise his factor VIII level high enough to stop further bleeding.

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 this time, it no longer produces much of an effect as the body’s stores of factor VIII become exhausted. If further treatments were needed to control bleeding, factor concentrates would be considered.

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

Side effects with desmopressin are minimal but do 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 excessive fluids (water, juice, or milk), 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 occurring. 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. In the majority of patients with mild hemophilia, it...

- is effective
- can help to reduce or altogether avoid the use of factor concentrates.

See the staff at your hemophilia treatment centre to find out which is the best form of desmopressin for your child and how to administer it.

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

Other medications that are helpful include antifibrinolytic drugs such as epsilon amino-caproic acid (also called Amicar® or EACA) or tranexamic acid (also called Cyklokapron® or TA).

These agents act by strengthening blood clots that form. This prevents the clots from being dislodged and bleeding to re-start. Amicar® and Cyklokapron® are particularly useful in 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 4, Clotting Factor Therapy, “What other medications are used to treat bleeding?”)*
Other Treatments

In addition to medications such as desmopressin, Amicar® and Cyklokapron®, non-drug treatments should also be used when a child with mild or moderate hemophilia has a bleed. Called R-I-C-E, these treatments include...

- **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 what would be provided by a tensor bandage wrapped 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 R-I-C-E, see Chapter 5, 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 to avoid the use of factor concentrates altogether and reduce the risk of complications such as the development of an inhibitor.
What complications can occur to boys with mild/moderate hemophilia?

Most boys with mild or moderate hemophilia will only rarely bleed. This usually happens because of major trauma or surgery. As a result, most of these boys 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 require their administration. A small number of boys with moderate hemophilia, especially those whose levels of factor VIII or IX are close to 2 percent or less, need factor concentrates on a regular basis.

Currently the biggest risk from receiving a factor concentrate is that of developing an inhibitor.

What causes an inhibitor? The body’s immune system can react to the clotting factor concentrate that is infused to stop or prevent a bleed. The factor concentrate is seen as a foreign substance. The body’s defenses do not recognize it, so the immune system fights the invader by producing antibodies, natural chemical substances that circulate in the blood. The antibodies eliminate 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.

“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 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.”
It is not known why inhibitors develop in some people with hemophilia and not in others. Researchers think there may be some 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 into one who has many spontaneous 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 this happening that physicians treating patients with 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, Part 1 - Inhibitors, A Complication of Hemophilia.)

In the 1970s and 1980s certain viruses were transmitted through various factor concentrates. With improved donor screening and viral inactivation steps, today’s plasma-derived factor concentrates have shown themselves to be safe over many years of use. No clotting factor concentrate in current use in North America or Europe has been shown to transmit HIV, hepatitis A, B or C. Furthermore, none of the recombinant factors available has been known to transmit any infectious agent. Nevertheless, there remains a fear that any product that originates from human or animal sources may harbour some as yet unknown infectious agent. (For more information, see Chapter 8, Part 4 - Blood-borne Infections, A Complication of Hemophilia.)
Can girls have mild hemophilia?

Yes, they can.

Severe hemophilia is almost exclusively a disease of boys. A girl may carry one abnormal X chromosome and, if so, she is referred to as a carrier of hemophilia. As a carrier, she can transmit the disease 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 may 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.
What should be remembered about mild and moderate hemophilia?

- Most children with mild and moderate hemophilia have less frequent bleeding than those with the most severe form of the disease; some of them may never need factor concentrates. However, there are exceptions. These boys 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 is unexpected, and might go untreated.

- Caregivers, and the children themselves, need to learn the signs of bleeding, so as to get treatment quickly.

- Children with mild and moderate hemophilia need to be cared for in a hemophilia treatment centre, where the family can learn all it needs to know about the disease.