WHAT ARE RARE CLOTTING FACTOR DEFICIENCIES?
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Additional print copies can be ordered from:
World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel.: (514) 875-7944
Fax: (514) 875-8916
E-mail: wfh@wfh.org

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Introduction

WHAT ARE CLOTTING FACTORS?
Clotting factors are proteins in the blood that control bleeding.

When a blood vessel is injured, the walls of the blood vessel contract to limit the flow of blood to the damaged area. Then, small blood cells called platelets stick to the site of injury and spread along the surface of the blood vessel to stop the bleeding. At the same time, chemical signals are released from small sacs inside the platelets that attract other cells to the area and make them clump together to form what is called a platelet plug.

On the surface of these activated platelets, many different clotting factors work together in a series of complex chemical reactions (known as the coagulation cascade) to form a fibrin clot. The clot acts like a mesh to stop the bleeding.

Coagulation factors circulate in the blood in an inactive form. When a blood vessel is injured, the coagulation cascade is initiated and each coagulation factor is activated in a specific order to lead to the formation of the blood clot. Coagulation factors are identified with Roman numerals (e.g. factor I or FI).

WHAT ARE RARE CLOTTING FACTOR DEFICIENCIES?
If any of the clotting factors is missing or is not working properly, the coagulation cascade is blocked. When this happens, the blood clot does not form and the bleeding continues longer than it should.

Deficiencies of factor VIII and factor IX are known as hemophilia A and B, respectively. Rare clotting factor deficiencies are bleeding disorders in which one or more of the other clotting factors (i.e. factors I, II, V, V+VIII, VII, X, XI, or XIII) is missing or not working properly. Less is known about these disorders because they are diagnosed so rarely. In fact, many have only been discovered in the last 40 years.
Factor I (Fibrinogen) Deficiency

Factor I (also called fibrinogen) deficiency is an inherited bleeding disorder that is caused by a problem with factor I. Because the body produces less fibrinogen than it should, or because the fibrinogen is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor I deficiency is an umbrella term for several related disorders known as congenital fibrinogen defects. Afibrinogenemia (a complete lack of fibrinogen) and hypofibrinogenemia (low levels of fibrinogen) are quantitative defects, meaning the amount of fibrinogen in the blood is abnormal. Dysfibrinogenemia is a qualitative defect in which fibrinogen does not work the way it should. Hypodysfibrinogenemia is a combined defect that involves both low levels of fibrinogen and impaired function.

Afibrinogenemia is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. Like all autosomal recessive disorders, afibrinogenemia is found more frequently in areas of the world where marriage between close relatives is common. Hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia can be either recessive (both parents carry the gene) or dominant (only one parent carries and transmits the gene). All types of factor I deficiency affect both males and females.

SYMPTOMS

The symptoms of factor I deficiency differ depending on which form of the disorder a person has.

AFIBRINOGENEMIA

Common symptoms
- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- muscle bleeds
bleeding into joints (hemarthrosis)
bleeding from the umbilical cord stump at birth
bleeding in the mouth, particularly after dental surgery or tooth extraction
abnormal bleeding during or after injury, surgery, or childbirth
abnormal bleeding after circumcision
problems during pregnancy (including miscarriage)

Other reported symptoms
- bleeding in the gut (gastrointestinal hemorrhage)
- bleeding in the central nervous system (the brain and spinal cord)
- formation of blood clots (thrombosis)

HYPOFIBRINOGENEMIA
Symptoms are similar to those seen in afibrinogenemia. As a general rule, the less factor I a person has in his/her blood, the more frequent and/or severe the symptoms.

DYSFIBRINOGENEMIA
Symptoms depend on how the fibrinogen (which is present in normal quantities) is functioning. Some people have no symptoms at all. Other people experience bleeding (similar to those seen in afibrinogenemia) and others show signs of thrombosis (abnormal blood clots in blood vessels) instead of bleeding.

HYPODYSFIBRINOGENEMIA
Symptoms are variable and depend on the amount of fibrinogen that is produced and how it is functioning.

DIAGNOSIS
Factor I deficiency is diagnosed by a variety of blood tests, including a specific test that measures the amount of fibrinogen in the blood. However, low fibrinogen levels or abnormal function may be a sign of another disease, such as liver or kidney
disorders, which should be ruled out before a bleeding disorder is diagnosed. Diagnostic tests should be performed by a specialist at a hemophilia/bleeding disorders treatment centre.

**TREATMENT**

There are three treatments available for factor I deficiency. All are made from human plasma.

- Fibrinogen concentrate
- Cryoprecipitate
- Fresh frozen plasma (FFP)

Treatment may also be given to prevent the formation of blood clots, as this complication can occur after fibrinogen replacement therapy.

Many people who have hypofibrinogenemia or dysfibrinogenemia do not need treatment. Excessive menstrual bleeding in women with factor I deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

For more information on **TREATMENT OPTIONS**, please turn to page 22
Factor II (Prothrombin) Deficiency

Factor II (also called prothrombin) deficiency is an inherited bleeding disorder that is caused by a problem with factor II. Because the body produces less prothrombin than it should, or because the prothrombin is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor II deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor II deficiency is very rare, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common.

Factor II deficiency may be inherited with other factors deficiencies (see “Combined deficiency of vitamin K-dependent clotting factors” on page 16). It can also be acquired later in life as a result of liver disease, vitamin K deficiency, or certain medications such as the blood-thinning drug Coumadin®. Acquired factor II deficiency is more common than the inherited form.

**SYMPTOMS**

The symptoms of factor II deficiency are different for everyone. As a general rule, the less factor II a person has in his/her blood, the more frequent and/or severe the symptoms.

*Common symptoms*

- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding into joints (hemarthrosis)
- muscle bleeds
- bleeding in the mouth, particularly after dental surgery or tooth extraction

*Other reported symptoms*

- bleeding in the gut (gastrointestinal hemorrhage)
What are rare clotting factor deficiencies?

- bleeding from the umbilical cord stump at birth
- abnormal bleeding during or after injury, surgery, or childbirth

**Rare symptoms**
- bleeding in the central nervous system (the brain and spinal cord)
- blood in urine (hematuria)

**DIAGNOSIS**

Factor II deficiency is diagnosed by a variety of blood tests. The doctor will need to measure the amount of factors II, V, VII, and X in the blood. Diagnostic tests should be performed by a specialist at a hemophilia/bleeding disorders treatment centre.

**TREATMENT**

There are two treatments available for factor II deficiency. Both are made from human plasma.

- Prothrombin complex concentrate (PCC)
- Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with factor II deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

For more information on **TREATMENT OPTIONS**, please turn to page 22
Factor V Deficiency

Factor V deficiency is an inherited bleeding disorder that is caused by a problem with factor V. Because the body produces less factor V than it should, or because the factor V is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor V deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor V deficiency is very rare, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common.

SYMPTOMS

The symptoms of factor V deficiency are generally mild. Some people may experience no symptoms at all. However, children with a severe deficiency of factor V may bleed very early. Some patients have experienced bleeding in the central nervous system (the brain and spinal cord) very early in life.

Common symptoms
- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding in the mouth, particularly after dental surgery or tooth extraction

Other reported symptoms
- bleeding in the gut (gastrointestinal hemorrhage)
- muscle bleeds
- abnormal bleeding during or after injury, surgery, or childbirth
**Rare symptoms**

- bleeding into joints (hemarthrosis)
- bleeding in the central nervous system (the brain and spinal cord)

**DIAGNOSIS**

Factor V deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a hemophilia/bleeding disorders treatment centre. People with abnormal levels of factor V should also have their factor VIII levels checked to rule out combined factor V and factor VIII deficiency, which is a completely separate disorder (see page 10).

**TREATMENT**

Treatment for factor V deficiency is usually only needed for severe bleeds or before surgery. Fresh frozen plasma (FFP) is the usual treatment because there is no concentrate containing only factor V. Platelet transfusions, which contain factor V, are also sometimes an option.

Excessive menstrual bleeding in women with factor V deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

For more information on **TREATMENT OPTIONS**, please turn to page 22
Combined Factor V and Factor VIII Deficiency

Combined factor V and factor VIII deficiency is an inherited bleeding disorder that is caused by low levels of factors V and VIII. Because the amount of these factors in the body is lower than normal, the clotting reaction is blocked prematurely and the blood clot does not form. The combined deficiency is completely separate from factor V deficiency and factor VIII deficiency (hemophilia A).

Combined factor V and factor VIII deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. The deficiency is very rare, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common. Most cases are found around the Mediterranean Sea, especially in Israel, Iran, and Italy.

Normally the disorder is caused by a single gene defect that affects the body’s ability to transport factor V and factor VIII outside the cell and into the bloodstream, and not by a problem with the gene for either factor.

**SYMPTOMS**

The combination of factor V and factor VIII deficiency does not seem to cause more bleeding than if only one or the other of the factors were affected. The symptoms of combined factor V and factor VIII deficiency are generally mild.

*Common symptoms*

- skin bleeding
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding in the mouth, particularly after dental surgery or tooth extraction
- bleeding after circumcision
- abnormal bleeding during or after injury, surgery, or childbirth
Other reported symptoms:
- nosebleeds (epistaxis)

Rare symptoms
- bleeding into joints (hemarthrosis)
- muscle bleeds

**DIAGNOSIS**

Combined factor V and factor VIII deficiency is diagnosed by a variety of blood tests to determine if the levels of both factors are lower than normal. These tests should be performed by a specialist at a hemophilia/bleeding disorders treatment centre.

**TREATMENT**

There are three treatments available for combined factor V and factor VIII deficiency.

- Factor VIII concentrate
- Fresh frozen plasma (FFP)
- Desmopressin

Excessive menstrual bleeding in women with combined factor V and factor VIII deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

For more information on TREATMENT OPTIONS, please turn to page 22
Factor VII Deficiency

Factor VII deficiency is an inherited bleeding disorder that is caused by a problem with factor VII. Because the body produces less factor VII than it should, or because the factor VII is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor VII deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor VII deficiency is very rare, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common.

Factor VII deficiency may be inherited with other factor deficiencies (see “Combined deficiency of vitamin K-dependent clotting factors” on page 16). It can also be acquired later in life as a result of liver disease, vitamin K deficiency, or certain medications such as the blood-thinning drug Coumadin®.

SYMPTOMS

The symptoms of factor VII deficiency are different for everyone. As a general rule, the less factor VII a person has in his/her blood, the more frequent and/or severe the symptoms. People with very low levels of factor VII can have very serious symptoms.

Common symptoms
- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding in the mouth, particularly after
dental surgery or tooth extraction
- bleeding in the head (newborns)
- heavy bleeding at circumcision

Other reported symptoms
- bleeding in the gut (gastrointestinal bleeding)
bleeding into joints (hemarthrosis)
• muscle bleeds
• bleeding in the central nervous system (the brain and spinal cord)
• abnormal bleeding during or after injury, surgery, or childbirth

**Rare symptoms**
• blood in urine (hematuria)
• bleeding from the umbilical cord stump at birth

**DIAGNOSIS**

Factor VII deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a hemophilia/bleeding disorders treatment centre.

**TREATMENT**

There are several treatments available for factor VII deficiency.

• Recombinant factor VIIa concentrate (rFVIIa)
• Factor VII concentrate
• Prothrombin complex concentrate (PCC) containing factor VII
• Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with factor VII deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

For more information on **TREATMENT OPTIONS**, please turn to page 22
Factor X Deficiency

Factor X deficiency is an inherited bleeding disorder that is caused by a problem with factor X. Because the body produces less factor X than it should, or because the factor X is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor X deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor X deficiency is one of the rarest inherited clotting disorders, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common.

Factor X deficiency may also be inherited with other factor deficiencies (see “Combined deficiency of vitamin K-dependent clotting factors” on page 16).

**SYMPTOMS**

As a general rule, the less factor X a person has in his/her blood, the more frequent and/or severe the symptoms. People with severe factor X deficiency can have serious bleeding episodes.

*Common symptoms*

- nosebleeds (epistaxis)
- easy bruising
- bleeding in the gut (gastrointestinal hemorrhage)
- bleeding into joints (hemarthrosis)
- muscle bleeds
- bleeding from the umbilical cord stump at birth
- bleeding from the mouth, particularly after dental surgery or tooth extraction
- bleeding during or after surgery or injury
Other reported symptoms

- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding after circumcision
- abnormal or prolonged bleeding after childbirth
- first-trimester miscarriage (spontaneous abortion)
- blood in urine (hematuria)
- bleeding in the central nervous system (the brain and spinal cord)

**DIAGNOSIS**

Factor X deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a hemophilia/bleeding disorders treatment centre.

**TREATMENT**

There are two treatments available for factor X deficiency. Both are made from human plasma.

- Prothrombin complex concentrate (PCC) containing factor X
- Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with factor X deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

For more information on TREATMENT OPTIONS, please turn to page 22
Inherited combined deficiency of the vitamin K-dependent clotting factors (VKCFD) is a very rare inherited bleeding disorder that is caused by a problem with clotting factors II, VII, IX, and X. In order to continue the chain reaction of the coagulation cascade, these four factors need to be activated in a chemical reaction that involves vitamin K. When this reaction does not happen the way it should, the clotting reaction is blocked and the blood clot does not form.

VKCFD is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. VKCFD is very rare, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common.

VKCFD can also be acquired later in life as a result of disorders of the bowel, liver disease, dietary vitamin K deficiency, or certain medications such as the blood-thinning drug Coumadin®. Acquired VKCFD is more common than the inherited form. Some newborn babies have a temporary vitamin K deficiency, which can be treated with supplements at birth.

**SYMPTOMS**

The symptoms of VKCFD vary a great deal from one individual to another but are generally mild. The first symptoms may appear at birth or not until later in life. Symptoms at birth must be differentiated from the acquired deficiency. People with severe deficiencies can have serious bleeding episodes, but the more serious symptoms are generally rare and only occur in those individuals with very low factor levels.

*Reported symptoms*

- bleeding from the umbilical cord stump at birth
- bleeding into joints (hemarthrosis)
What are rare clotting factor deficiencies?

- bleeding in soft tissue and muscle
- bleeding in the gut (gastrointestinal hemorrhage)
- easy bruising
- excessive bleeding after surgery

**Rare symptoms**

- bleeding in the brain (intracranial hemorrhage)
- skeletal abnormalities and mild hearing loss (in severe cases)

**DIAGNOSIS**

VKCFD is diagnosed by a variety of blood tests that should be performed by a specialist at a hemophilia/bleeding disorders treatment centre. Care should be taken, particularly in newborns, to exclude causes of acquired vitamin K deficiency or exposure to certain medications.

**TREATMENT**

There are three treatments available for VKCFD.

- Vitamin K
- Prothrombin complex concentrates (PCC)
- Fresh frozen plasma (FFP)

For more information on **TREATMENT OPTIONS**, please turn to page 22
Factor XI Deficiency

Factor XI deficiency is an inherited bleeding disorder that is caused by a problem with factor XI. Because the body produces less factor XI than it should, or because the factor XI is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor XI deficiency is also called hemophilia C. It differs from hemophilia A and B in that there is no bleeding into joints and muscles. Factor XI deficiency is the most common of the rare bleeding disorders and the second most common bleeding disorder affecting women (after von Willebrand disease).

Some people have inherited factor XI deficiency when only one parent carries the gene. The disorder is most common in Ashkenazi Jews, that is, Jews of Eastern European ancestry.

SYMPTOMS

Most people with factor XI deficiency will have little or no symptoms at all. The relationship between the amount of factor XI in a person’s blood and the severity of his/her symptoms is unclear; people with only a mild deficiency in factor XI can have serious bleeding episodes. Symptoms of factor XI deficiency vary widely, even among family members, which can make it difficult to diagnose.

Common symptoms
- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- abnormal bleeding during or after injury, surgery, or childbirth

Other reported symptoms
- bleeding in the gut (gastrointestinal hemorrhage)
- bleeding in the mouth, particularly after dental surgery or tooth extraction
- blood in the urine (hematuria)
**DIAGNOSIS**

Factor XI deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a hemophilia/bleeding disorders treatment centre.

**TREATMENT**

There are several treatments available to help control bleeding in people with factor XI deficiency.

- Factor XI concentrate
- Antifibrinolytic drugs
- Fibrin glue
- Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with factor XI deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

For more information on **TREATMENT OPTIONS**, please turn to page 22
Factor XIII Deficiency

Factor XIII deficiency is an inherited bleeding disorder that is caused by a problem with factor XIII. Because the body produces less factor XIII than it should, or because the factor XIII is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor XIII deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor XIII deficiency is very rare, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common.

**SYMPTOMS**

Most people with factor XIII deficiency experience symptoms from birth, often bleeding from the umbilical cord stump. Symptoms tend to continue throughout life. As a general rule, the less factor XIII a person has in his/her blood, the more frequent and/or severe the symptoms.

*Common symptoms*

- bleeding from the umbilical cord stump at birth
- nosebleeds (epistaxis)
- easy bruising
- bleeding into joints (hemarthrosis)
- bleeding in the central nervous system (the brain and spinal cord)
- bleeding in the mouth, particularly after dental surgery or tooth extraction
- poor wound healing and abnormal scar formation
- bleeding in soft tissue
- problems during pregnancy (including recurrent miscarriages)
bleeding after circumcision
abnormal bleeding during or after injury or surgery

**Other reported symptoms**
- heavy or prolonged menstrual bleeding (menorrhagia)
- blood in urine (hematuria)
- bleeding in the gut (gastrointestinal hemorrhage)
- muscle bleeds

**Rare symptoms**
- bleeding in the spleen, lungs, ears, or eyes

**DIAGNOSIS**

Factor XIII deficiency is difficult to diagnose. Standard blood clotting tests do not detect the deficiency, and many laboratories are not equipped with more specialized tests that measure the amount of factor XIII in a blood sample or how well factor XIII is working. The high rate of bleeding at birth usually leads to early diagnosis.

**TREATMENT**

There are several treatments available to help control bleeding in people with factor XIII deficiency.

- Factor XIII concentrate
- Cryoprecipitate
- Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with factor XIII deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

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For more information on **TREATMENT OPTIONS**, please turn to page 22.
Treatment Options

FACTOR CONCENTRATES
When they are available, factor concentrates are the ideal and safest treatment for rare bleeding disorders. Unfortunately, individual concentrates are available only for factors I, VII, VIII, XI, and XIII. Factor concentrates for rare bleeding disorders are usually made from human plasma and are treated to eliminate viruses like HIV and hepatitis B and C. Recombinant factor VIII and recombinant factor VIIa are also available. They are made in the laboratory and not from human plasma, so they carry no risk of infectious disease. Factor concentrates are administered intravenously.

PROTHROMBIN COMPLEX CONCENTRATE (PCC)
This concentrate is made from human plasma and contains a mixture of clotting factors, including factors II, VII, IX, and X (however, some products do not contain all four factors). PCC is suitable for individual deficiencies of factor II and X as well as inherited combined deficiency of the vitamin K-dependent clotting factors (VKCFD). It is treated to eliminate viruses like HIV and hepatitis B and C. Some PCCs have been reported to cause potentially dangerous blood clots (thrombosis). PCC is administered intravenously.

FRESH FROZEN PLASMA (FFP)
Plasma is the portion of blood that contains all the clotting factors, as well as other blood proteins. FFP is used to treat rare bleeding disorders when concentrates of the specific factor that is missing are not available. FFP is the usual treatment for factor V deficiency. However, it usually does not undergo viral inactivation, so the risk of transmission of infectious diseases is higher. Viral-inactivated FFP is available in some countries and is preferable. Circulatory overload is a potential problem with this treatment: since the concentration of each coagulation factor in FFP is low, a large volume of it must be given over several hours in order to achieve an adequate rise in factor level. This large amount of FFP needed can overload the circulatory system and stress the heart. Other complications of treatment with FFP can occur, particularly allergic reactions or lung problems (transfusion-related lung injury [TRALI]). These
What are rare clotting factor deficiencies?

problems are much less common if viral-inactivated pooled FFP is used. FFP is administered intravenously.

**CRYOPRECIPITATE**

Made from human plasma, cryoprecipitate contains factor VIII, fibrinogen (factor I), and a few other proteins important for blood clotting. Cryoprecipitate does not undergo viral inactivation and should only be used when factor concentrate is not available. It contains higher concentrations than FFP of some (but not all) coagulation factors, so less volume is needed. It is only suitable for a few deficiencies. Cryoprecipitate is administered intravenously.

**DESMOPRESSIN**

Desmopressin is a synthetic hormone that raises the levels of factor VIII in patients with combined factor V and factor VIII deficiency. Since it is man-made, there is no risk of transmission of infectious diseases. Desmopressin has no effect on the levels of any of the other coagulation factors. It can be administered intranasally or intravenously.

**ANTIFIBRINOLYTIC DRUGS**

The antifibrinolytic drugs tranexamic acid and aminocaproic acid are used to hold a clot in place in certain parts of the body, such as the mouth, bladder, and uterus. They are also very useful in many situations, such as during dental work, but are not effective for major internal bleeding or surgery. Antifibrinolytic drugs are particularly useful for patients with factor XI deficiency. They are also used to help control excessive menstrual bleeding. Antifibrinolytic drugs can be administered orally or by injection.

**FIBRIN GLUE**

Fibrin glue can be used to treat external wounds and during dental work, such as a tooth extraction. It is not used for major bleeding or surgery. It is applied to the bleeding site.

**PLATELET TRANSFUSIONS**

Platelets are small blood cells that are involved in the formation of blood clots and the repair of damaged blood vessels. Certain clotting factors, including factor V, are stored in small sacs inside
them. Platelet transfusions are sometimes used to treat factor V deficiency.

**VITAMIN K**

Treatment with vitamin K (either in pill form or by injection) can help control symptoms of inherited combined deficiency of the vitamin K-dependent clotting factors (VKCFD). However, not everyone responds to this type of treatment. People who do not respond to vitamin K and have a bleed or need surgery will need factor replacement.

**HORMONAL CONTRACEPTIVES**

Hormonal contraceptives (birth control pills) help control menstrual bleeding.

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These treatments may have side-effects, so people with rare clotting factor deficiencies should talk to their physician about possible side-effects of treatment.
Tips for Living with Clotting Factor Deficiencies

COPING WITH THE DIAGNOSIS
Learning you or your child has a bleeding disorder is very upsetting and you may experience a range of different emotions. For some people, it inspires fear and anxiety while for others, being able to put a name to symptoms they have lived with for years can be a tremendous relief. Parents may feel guilty to learn their child has inherited a genetic disease. All these feelings are normal, and are likely to change over time as you learn more about the condition and the impact it will have on your life.

Talking to others—friends, parents, healthcare professionals, and other people with bleeding disorders—can be a great comfort. Learning as much as you can about the disorder will also help you feel more confident and soothe your fears. Get in touch with your local patient organization or hemophilia/bleeding disorder treatment centre to ask questions and discuss options.

HEALTHY LIVING
People with bleeding disorders should register with a treatment centre that specializes in the diagnosis and treatment of bleeding disorders, as they are likely to offer the best standards of care and information.

A healthy diet and regular exercise keep the body healthy and strong. Exercise can also help reduce stress, anxiety and depression, and reduce the frequency and severity of joint bleeds. People who are overweight place additional stress on the joints (particularly the knees and ankles), leaving them increasingly susceptible to bleeds.

People with severe forms of bleeding disorders who are at risk of joint bleeds should avoid high-impact activities and sports such as football, wrestling, and skateboarding. Ideally, exercises should be prescribed for people with bleeding disorders by a skilled and experienced doctor or physiotherapist.
DENTAL CARE
Good oral hygiene is essential to prevent tooth decay and gum disease. For people with bleeding disorders, maintaining good dental health is very important to reduce the need for dental surgery, which can be complicated by excessive or prolonged bleeding. People with bleeding disorders should:

- Brush teeth at least twice a day
- Floss regularly
- Use a toothpaste containing fluoride
- Get regular checkups

Any type of invasive procedure, such as a tooth extraction or root canal, can cause bleeding in people with bleeding disorders. The dentist should consult with the hemophilia/bleeding disorder treatment centre to identify potential risks and properly plan the procedure. Medication may be needed beforehand to help control bleeding and ensure a safe recovery.

VACCINATIONS
People with bleeding disorders should be vaccinated, but the vaccines should be given under the skin, not directly into the muscle. Vaccines against hepatitis A and B are particularly important for people that are treated with fresh frozen plasma and any other product that is not viral inactivated. Family members handling treatment products should also be vaccinated, though this is less critical for those using viral-inactivated products.

MEDICATIONS TO AVOID
Check all medications with your doctor. Some over-the-counter medications should be avoided because they interfere with clotting. People with bleeding disorders should not take acetylsalicylic acid (ASA or Aspirin®) or nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen) without medical advice.

HAVE MEDICAL INFORMATION ON HAND AT ALL TIMES
Carry information about your disorder, the treatment that has been prescribed, and the name and telephone number of your physician or treatment centre. In emergencies, a medical bracelet
or other identification, such as the WFH International Medical Card, notifies healthcare personnel of your bleeding disorder.

When travelling, find the addresses and telephone numbers of the hemophilia/bleeding disorders treatment centres at your destination(s) and bring the information with you.

**SPECIAL ISSUES FOR GIRLS AND WOMEN**

Women with clotting factor deficiencies tend to have more symptoms than men because of menstruation and childbirth. Girls may have especially heavy bleeding when they begin to menstruate. Women with clotting factor deficiencies may have heavier and/or longer menstrual flow, which can cause anemia (low levels of iron, which results in weakness and fatigue).

Women with clotting factor deficiencies should receive genetic counseling about the risks of having an affected child well in advance of any planned pregnancies and should see an obstetrician as soon as they suspect they are pregnant. The obstetrician should work closely with the staff of the hemophilia/bleeding disorder treatment centre in order to provide the best care during pregnancy and childbirth and to minimize the potential complications for both the mother and the newborn.

Women with certain factor deficiencies (such as factor XIII deficiency and afibrinogenemia) may be at greater risk of miscarriage and placental abruption (a premature separation of the placenta from the uterus that disrupts the flow of blood and oxygen to the fetus). Therefore, these women require treatment throughout the pregnancy to prevent these complications.

The main risk related to pregnancy is postpartum hemorrhage. All bleeding disorders are associated with a greater risk of increased bleeding after delivery. The risk and the severity of the bleeding can be reduced with appropriate treatment. This treatment is different for each woman and depends on her personal and family history of bleeding symptoms, the severity of the factor deficiency, and the mode of delivery (vaginal birth vs. cesarean section). Factor replacement may be necessary in some cases.

For more information and a list of resources in several languages, visit the rare bleeding disorders section of the WFH website at [www.wfh.org](http://www.wfh.org).
<table>
<thead>
<tr>
<th>Missing Factor</th>
<th>Incidence</th>
<th>Inheritance</th>
<th>Severity of Bleeding</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor I</td>
<td>5 in 10 million</td>
<td>Autosomal recessive</td>
<td>Usually mild, except in afibrogenemia</td>
<td>Fibrinogen concentrate</td>
</tr>
<tr>
<td>Afibrogenemia</td>
<td></td>
<td></td>
<td></td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Hypofibrogenemia</td>
<td>not available</td>
<td>Recessive or dominant</td>
<td></td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Dysfibrogenemia</td>
<td>1 in 1 million</td>
<td>Recessive or dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor II</td>
<td>1 in 2 million</td>
<td>Autosomal recessive</td>
<td>Usually mild</td>
<td>Prothrombin complex concentrate</td>
</tr>
<tr>
<td>Factor V</td>
<td>1 in 1 million</td>
<td>Autosomal recessive</td>
<td>Usually mild</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Combined factor V and factor VIII</td>
<td>1 in 1 million†</td>
<td>Autosomal recessive</td>
<td>Usually mild</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Factor VII</td>
<td>1 in 500,000</td>
<td>Autosomal recessive</td>
<td>Severe when factor levels are low</td>
<td>Recombinant factor VIIa concentrate</td>
</tr>
<tr>
<td>Factor X</td>
<td>1 in 1 million</td>
<td>Autosomal recessive</td>
<td>Moderate to severe when factor levels are low</td>
<td>Prothrombin complex concentrate</td>
</tr>
<tr>
<td>Combined deficiency of vitamin K-dependent</td>
<td>not available</td>
<td>Autosomal recessive</td>
<td>Usually mild, but a few families have reported</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>clotting factors</td>
<td></td>
<td></td>
<td>very low levels and more severe symptoms</td>
<td>Prothrombin complex concentrate</td>
</tr>
<tr>
<td>Factor XI</td>
<td>1 in 100,000</td>
<td>Recessive or dominant</td>
<td>Mild to moderate when factor levels are low</td>
<td>Factor XI concentrate</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>1 in 3 million</td>
<td>Autosomal recessive</td>
<td>Severe</td>
<td>Factor XIII concentrate</td>
</tr>
</tbody>
</table>

* Estimates only

** Can also be acquired later in life because of another medical condition, certain medications, etc.

† 1 in 100,000 in some populations, including Israel, Iran, and Italy

‡ Very rarely, factor VIII deficiency can be inherited separately from only one parent
## Table 2: Bleeding Symptoms of Rare Clotting Factor Deficiencies

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>FACTOR I</th>
<th>FACTOR II</th>
<th>FACTOR V</th>
<th>FACTORS V-VIII</th>
<th>FACTOR VII</th>
<th>FACTOR X</th>
<th>FACTOR XI</th>
<th>FACTOR XIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosebleed</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Occasional</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>Common</td>
<td>Not Available</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Heavy or prolonged menstrual bleeding</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Occasional</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Blood in urine</td>
<td>Absent</td>
<td>Rare</td>
<td>Absent</td>
<td>Absent</td>
<td>Rare</td>
<td>Occasional</td>
<td>Absent</td>
<td>Occasional</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Absent</td>
<td>Occasional</td>
<td>Common</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
<tr>
<td>Joint bleeding</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
<td>Occasional</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Muscle bleeds</td>
<td>Common</td>
<td>Common</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Common</td>
<td>Rare</td>
<td>Occasional</td>
</tr>
<tr>
<td>Umbilical cord bleeding</td>
<td>Common</td>
<td>Occasional</td>
<td>Absent</td>
<td>Absent</td>
<td>Rare</td>
<td>Common</td>
<td>Absent</td>
<td>Common</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>Occasional</td>
<td>Rare</td>
<td>Rare</td>
<td>Absent</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Absent</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding from mouth/gums</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Occasional</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding during pregnancy/childbirth*</td>
<td>Absent</td>
<td>Not Available</td>
<td>Absent</td>
<td>Absent</td>
<td>Occasional</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent ‡</td>
</tr>
<tr>
<td>Major surgery†</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Common</td>
<td>Occasional</td>
<td>Common</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Minor surgery‡</td>
<td>Common</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Other</td>
<td>Rare</td>
<td>Not Available</td>
<td>Rare</td>
<td>Occasional</td>
<td>Absent</td>
<td>Occasional</td>
<td>Rare</td>
<td>Absent</td>
</tr>
</tbody>
</table>

* treatment could not be ruled out
† percentages were calculated on the basis of the number of procedures
‡ percentage was calculated based on one patient

### LEGEND
- **Rare**: 0–10% of patients
- **Occasional**: 10–30% of patients
- **Common**: >30% of patients
- **Absent**: Patients reported absence of this symptom

### ABBREVIATIONS
- GI: Gastrointestinal (gut); CNS: Central nervous system (brain and spinal cord)

1. This chart was compiled with data from the International Rare Bleeding Disorders Database (www.rbdd.org) only and is not exhaustive. Other symptoms that have been reported in the literature are included in the text. Data for the combined deficiency of vitamin K-dependent clotting factors is not available.