

Hemophilia

Case #5

The mother of six-month-old Steven cannot stop his bleeding after he hits his mouth on the kitchen floor. Find out what happens to this infant who has a disease that is credited for bringing down the last tsar of Russia

Case Objectives

- 1) Define
 - a. Hemostasis.
 - b. Define the processes involved in primary hemostasis, and secondary hemostasis. Include in your definition.
 - i. How clotting factors work together to form a clot.
 - ii. A brief explanation of the intrinsic, extrinsic, and common pathways.
 - iii. Define what clotting factors are involved in each pathway.
 - iv. The end result of the clotting pathway.
- 2) Summarize the basic principles of genetics and genetic testing to include the following:
Helpful sites: [Understanding Gene Testing](#), [X Linked Disorders](#), [Males are at Risk](#).
 - a. Define the following terms: gene, DNA, chromosome, autosome, sex chromosome.
 - b. Summarize the chromosomal makeup of a human cell to include.
 - i. The number of chromosomes.
 - ii. The number of autosomes and sex chromosomes.
 - iii. The differentiation of gender by chromosomes.
 - c. Describe how gene mutations are linked to disease.
 - d. Differentiate between a hereditary mutation and an acquired mutation.
 - e. Define recessive allele, dominant allele, and carrier.
 - f. Discuss how a recessive or dominant allele affects the hereditary influence of a disease.
 - g. Define gene testing and predictive gene testing.
 - h. List benefits, risks, and limitations of genetic testing.
 - i. Define an x-linked disorder.
 - j. Describe the hereditary pattern of an x-linked disorder.
 - k. Define what gender is at risk for diseases with this type of disorder.
 - l. Discuss the value of a pedigree chart in a family with a known hemophiliac.
- 3) Define which hemostasis function(s) is/are tested for in each of the following tests
 - a. Platelet count.
 - b. Bleeding time.
 - c. PT.
 - d. APTT.
 - e. Factor Assays.
- 4) Define hemophilia.

- 5) List the symptoms of a patient with hemophilia to include complications that may arise from symptoms.
- 6) Summarize treatment of a hemophilia to include:
 - a. The goals of treatment.
 - b. advantages and disadvantages of each of the following methods of treatment:
 - i. freeze dried cryoprecipitate.
 - ii. direct donor cryoprecipitate.
 - iii. purified cryoprecipitate.
 - iv. recombinant DNA.
 - c. Discuss methods by which cryoprecipitate is purified.
 - d. Discuss the process by which recombinant factor VIII is made.
 - e. Discuss blood borne diseases and their impact on hemophiliacs.
 - f. Describe how gene therapy may become a cure for hemophilia.
- 7) Discuss the roles of a pediatrician and/or hematologist, nurses, clinical laboratory scientists, and genetic counselors in diagnosing and treating a patient with hemophilia.
- 8) Define how a hemophiliac can stop the transmission of the disease.

Steven had just turned 6 months old. He had recently discovered the freedom of being mobile and was attempting to follow his 3 year old sister Heather up the stairs. He had almost mastered crawling up the first step when he slipped and fell, hitting his mouth on the linoleum floor of the kitchen. The screaming brought his mother running who initially thought the baby must have split his head open because of the amount of blood that was everywhere. As she cleaned the injury, she realized that the blood was coming from the baby's mouth. After applying cold compresses for 15 minutes, the bleeding eventually stopped. Five minutes later, the bleeding started up again. She decided to call the pediatrician.

The baby had stopped bleeding by the time the mother arrived at the pediatrician's office. During a thorough checkup of the baby, the pediatrician noticed bruises on the legs and arms. He noted that the baby had not been circumcised. Upon examination of the injured gum area, bleeding started again.

The pediatrician asked the mother if there was any history of bleeding disorders on the maternal side of her family. The mother was not sure, although she thought she may have had a great uncle who died when he was young of a blood disorder.

Instructor's Note: At this point in the case, it would be helpful for the student to review [mechanisms of blood coagulation](#). The student should also review this process in their text.

Mechanisms of Blood Coagulation

Blood coagulation refers to the process of forming a clot to stop bleeding. Coagulation is a complicated subject and is greatly simplified here for the student's understanding.

To stop bleeding, the body relies on the interaction of three processes:

Primary [hemostasis](#) involves the first two processes.

- 1) Vasoconstriction. Vasoconstriction is the body's first response to injury in the vascular wall. When injury occurs, vessel walls constrict, causing reduced blood flow to the site of injury.
- 2) [Platelet](#) plug. Platelets aggregate to the site of the injury. They stick together acting as a "plug." Platelets also activate the process which causes a fibrin clot to form, known as secondary hemostasis.

Secondary hemostasis.

- 3) Platelets alone are not enough to secure the damage in the vessel wall. A clot must form at the site of injury. The formation of a clot depends upon several substances called clotting factors. These factors are designated by roman numerals I through XIII. These factors activate each other in what is known as the clotting cascade. The end result of this cascade is that fibrinogen, a soluble plasma protein, is cleaved into fibrin, a non-soluble plasma protein. The fibrin proteins stick together forming a clot. The clotting cascade occurs through two separate pathways that interact, the intrinsic and the extrinsic pathway.
 - a. Extrinsic Pathway - The extrinsic pathway is activated by external trauma that causes blood to escape from the vascular system. This pathway is quicker than the intrinsic pathway. It involves factor VII.
 - b. Intrinsic Pathway - The intrinsic pathway is activated by trauma inside the vascular system, and is activated by platelets, exposed endothelium, chemicals, or collagen. This pathway is slower than the extrinsic pathway, but more important. It involves factors XII, XI, IX, and VIII.
 - c. Common Pathway - Both pathways meet and finish the pathway of clot production in what is known as the common pathway. The common pathway involves factors I, II, V, and X.

*Instructor's Note: A diagram may be found in your text illustrating the clotting cascade. The student **does not** need to be concerned about learning the details of these pathways. The student **does** need to realize that different factors are involved in each pathway. If a patient does not clot normally, it is usually due to a platelet abnormality or deficiency, or by a defect or deficiency in one of the clotting factors. There are diagnostic tests which test for deficiencies in the intrinsic pathway, the extrinsic pathway, and platelet abnormalities. These tests allow the physician to narrow down and eventually discover the defect which is causing a patient to bleed excessively.*

The interested student may want to study a more in depth chart and explanation of the coagulation cascade. See [Coagulation Cascade](#)

- 1) *What 3 processes are involved to stop bleeding?*
- 2) *Define the two processes of primary hemostasis.*
- 3) *What 2 pathways are involved in secondary hemostasis?*
- 4) *What factors can lead to the activation of each pathway?*
- 5) *What pathway is factor VIII involved in?*
- 6) *What is the end result of the clotting cascade?*
- 7) *How can a physician determine what is causing a bleeding disorder?*

The pediatrician ordered the following tests:

[Platelet count](#)
[Bleeding time](#)

Protime (PT)

Activated partial thromboplastin time (APTT)

- 8) *Why has the physician ordered all of these tests?*
- 9) *What conditions might cause an elevated or decreased platelet count?*
- 10) *What is a bleeding time?*
- 11) *Which pathway is measured with a PT?*
- 12) *Which pathway is measured with an APTT?*
- 13) *Which health care professional is responsible for the above testing?*

Testing Results

Based on the coagulation study results, the pediatrician ordered factor assays on factors VIII, IX, and XI and XII.

- 14) *From the testing results, which factor would you suspect might be abnormally low or missing in this patient?*

Factor Assay Results

Based on the coagulation studies, the Pediatrician diagnosed Steven with severe [hemophilia A](#). He referred Steven to a hematologist for further treatment.

- 15) *Why did the physician label Steven's hemophilia as severe?*
- 16) *What can be predicted by the degree of severity of the disease?*
- 17) *What sex carries the hemophilia gene?*
- 18) *What sex can inherit the hemophilia gene?*
- 19) *If a woman is a carrier for the hemophilia gene, what percentage of her daughters will also be carriers? What percentage of her sons will have hemophilia?*
- 20) *Typically, why do males and not females have hemophilia? Why are females typically only carriers of the disease?*
- 21) *If a male has hemophilia, what percentage of his sons will have hemophilia? What percentage of his daughters will be carriers? Why?*

The hematologist reviewed Steven's case, and recommended that he be treated with recombinant factor VIII. Steven's doctor explained that in the past, the hemophilia population was largely affected by blood borne viruses, especially the hepatitis viruses and HIV. Although more expensive, this genetically engineered replacement product virtually eliminates the risk of blood borne viruses.

See [Hemophilia Methods of Treatment](#).

- 22) *Why were males with hemophilia at such great risk for acquiring AIDS and other blood borne viruses in the 1980's?*
- 23) *How have researchers helped to alleviate the problem of viral contamination?*
- 24) *How is recombinant DNA made?*
- 25) *What is gene therapy? Why is this looked at as a possible cure for hemophilia?*

The hematologist recommended that Steven's parents make an appointment with a genetic counselor. The counselor could help them piece together the family history, and identify other siblings whose children may be at risk.

Instructor's Note: At this point it would be helpful to review the following links reviewing basic genetics and genetic testing:

[Understanding Gene Testing](#) This is an excellent "booklet" describing basic genetic principles as well as information about genetic testing. Links to subsequent pages of the booklet are included at the bottom of each page.

[X Linked Disorders, Males are at Risk](#)

26) What is a gene?

27) What is DNA?

28) What is a chromosome?

29) How are genes linked to disease?

30) What is the difference between hereditary and acquired mutations?

31) What is an allele, a dominant allele, and a recessive allele?

32) What is a carrier?

33) What is gene testing?

34) What is a predictive gene test?

35) Bob Smith does not have hemophilia but his brother does. Can Bob's children inherit the disease?

36) Could Bob's brother's sons also have hemophilia?

Case Summary

- 1) Hemophilia is a sex-linked recessive disorder affecting males. Severe hemophiliacs produce less than 1% of clotting Factor VIII (Hemophilia A) or Factor IX (Hemophilia B). Absence of either of these clotting factors causes a defect in the intrinsic clotting mechanism and the patient is unable to produce normal fibrin clots to stop bleeding.
- 2) The symptoms of Hemophilia include excessive bleeding. This bleeding may occur externally due to injury but more often occurs spontaneously as bleeding into the joints. Symptoms are often first evident during circumcision. In this case, the infant had not been circumcised. Symptoms did not become evident until the infant became mobile. These symptoms manifested themselves as bleeding from the mouth due to injury, and bruising due to internal bleeding. Spontaneous bleeding into the joints can lead to joint deformities and arthritis.
- 3) The diagnosis of Hemophilia was made based upon the patient's symptoms, family history, and bleeding tests. Diagnostic tests included a platelet count, bleeding time, PT, and APTT. A prolonged APTT led to Factor Assay testing which showed less than 1% of factor VIII present in the blood.
- 4) Treatment of Hemophilia consists of replacing the deficient factor. Factor can be replaced routinely to control spontaneous bleeding but often is used only when the patient has started to bleed spontaneously or is undergoing dental work or surgery. Limited factor replacement is done to avoid expense and also to avoid unnecessary exposure to blood borne viruses. Directed donor cryoprecipitate is the least expensive method of treatment. Patients use a donor they know is "safe" who donates plasma as needed. Cryoprecipitate, rich in factor VIII,

is made from the donor plasma. Varying levels of purified cryoprecipitate are also available to the patient. Recombinant Factor Replacement is genetically engineered factor VIII. This is free of contaminating viruses but the most expensive treatment alternative.

- 5) The prognosis for hemophiliacs is much better than in the past. New treatment methods are relatively safe from AIDS and Hepatitis viruses. With frequent injections of factor replacements, joint deformities and arthritis can be alleviated. Scientists are currently experimenting with using genetic engineering as a "cure." Genes that produce the missing factor are inserted by viral vectors into the patient's cells. These cells now begin to produce the missing factor. This method is currently being tested in humans.
- 6) The only method of prevention for Hemophilia is to not pass the x-linked gene. This poses a very difficult and personal dilemma for women who are carriers of the gene or for hemophiliac males; the question of having children who are at risk or to not have children.
- 7) Although the healthcare workers listed in this case are minimal, many healthcare workers will be involved throughout Steven's life. In this case, the pediatrician made the diagnosis. He referred Steven to a hematologist, a doctor specializing in disorders of the blood. A clinical laboratory scientist performed the coagulation studies on the blood which provided the data for diagnosis. A genetic counselor was involved to map out a pedigree chart and counsel with family members who are carriers of the gene. As Steven matures and encounters spontaneous bleeding into the joints, he will most likely need the services of a radiologist and radiologic technician for imaging studies as well as a physical therapist to help rehabilitate the joints after a bleed. Nurses, in this case, would be responsible for injecting cryoprecipitate, and educating the family so that injections can be given at home.

Answers to Case Questions

Question 1

Vasoconstriction, the formation of a platelet plug, and secondary hemostasis.

Question 2

Vasoconstriction which is the narrowing of vessel walls to reduce blood flow, and the formation of a platelet plug from aggregating platelets.

Question 3

The intrinsic and extrinsic pathways.

Question 4

Extrinsic: external trauma that allows blood to leak from the vessel. Intrinsic: internal trauma inside the vascular system. Platelets, exposed endothelium, chemicals, or collagen may activate this pathway.

Question 5

The intrinsic pathway.

Question 6

Fibrinogen, a soluble plasma protein, is cleaved into fibrin, a nonsoluble plasma protein. The fibrin proteins stick together forming a clot.

Question 7

By testing for platelet abnormalities, and factor deficiencies in the intrinsic and extrinsic pathways.

Question 8

To isolate the cause of the baby's excessive bleeding.

Question 9

Elevated: Certain malignancies (i.e. leukemia), certain blood disorders, and rheumatoid arthritis.

Decreased: Certain blood disorders, infections, and some medications.

Question 10

A test that measures how long a person takes to stop bleeding after several small cuts are made on the lower arm.

Question 11

Extrinsic pathway

Question 12

Intrinsic pathway

Question 13

Clinical laboratory scientist.

Question 14

Because the APTT was the only abnormal result, the physician would suspect a factor involved in the intrinsic pathway, factor VIII, IX, XI, or XII.

Question 15

He has less than 1% of factor VIII present in his blood.

Question 16

How often a person will bleed, how difficult it will be for them to form a clot, and how much medication they will need to control their bleeding.

Question 17

Female

Question 18

Male and female

Question 19

50% in both cases. A female carrier has two x chromosomes, one of them carries the hemophilia trait. She will pass this to half of her sons who will have the disease, and half of her daughters who will be carriers.

Question 20

The hemophilia trait is carried on the x chromosome. Males have only one x chromosome, therefore, if they have the hemophilia trait on the x chromosome they will have the disease. Females have two x chromosomes, if they have the hemophilia trait on one x chromosome they are carriers of the disease but generally do not display symptoms.

Question 21

His sons will not have hemophilia, all of his daughters will be carriers. Hemophilia is carried on the x chromosome. A male has an xy chromosome, a female xx. The hemophilia trait is linked to the x chromosome. He would pass the y chromosome to his sons and the x to his daughters.

Question 22

Freeze-dried factor VIII concentrate was the method of choice for replacement. This concentrate was pooled from multiple plasma donors, thus greatly increasing the risk for viral contamination. The HIV virus was not screened for at the time.

Question 23

By 2 different methods. The first is to purify the cryoprecipitate through heat, solvents, pasteurization, or with monoclonal antibodies. The second is to manufacture factor VIII through genetic engineering.

Question 24

The DNA for Factor VIII is cloned into bacterial DNA. The bacteria now produce Factor VIII. The bacteria multiply rapidly producing great quantities of factor VIII which is free from any viral contamination.

Question 25

Gene therapy uses viruses as vectors to insert missing genetic material directly into the patient's own cells. By inserting the missing genetic material that codes for factor VIII, patient's may produce factor VIII on their own. Gene therapy is undergoing experimental trials in humans and is hoped to be a cure for hemophilia.

Question 26

A gene is a working subunit of DNA.

Question 27

DNA is a chemical information database made up of 2 strands containing chemical bases. DNA carries the genetic code to make specific proteins.

Question 28

A chromosome is a pair of structures in a cell that house the DNA. Each cell contains 22 autosomes and 1 pair of sex chromosomes (xx female, xy male).

Question 29

A mutated gene will encode for a malfunctioning protein. This may manifest itself in a disease. A disease may be the result of 1 mutated gene, several, or a combination of gene mutations and environmental factors.

Question 30

Hereditary: a gene change in the egg or sperm that affects every cell in the body.

Acquired: gene changes in individual cells.

Question 31

An allele is a variation of the same gene. One allele is inherited from each parent. A dominant allele is expressed regardless of the other allele. A recessive allele is not expressed unless two recessive alleles are present.

Question 32

A carrier has a recessive mutated gene that is not expressed. A carrier can pass this mutated gene on to their children.

Question 33

Examining a person's DNA for genetic disorders.

Question 34

Examining a person's DNA to determine the probability of getting a disease before symptoms occur.

Question 35

No. If Bob carried the hemophilia gene it would be on his x chromosome and would be expressed. He does not have hemophilia so does not have the mutated x gene and cannot pass this on to his children.

Question 36

No. He has passed the y chromosome to his sons--they cannot have the mutated x chromosome or they would be girls! His daughters could have the mutated x chromosome and would be carriers of the disease.

Health Professionals Introduced in this Case

[Genetic Counselor](#)

[Nursing](#)

[Clinical Laboratory Scientist](#)

[Physician](#)

[Pediatrician](#)

[Hematologist](#)

Additional Links of Interest

[World Federation of Hemophilia Facts for Families](#)

[DNA Overview](#)

[A Pedigree of Hemophilia in the Royal Families of Europe](#)