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HEMOPHILIA: RECOGNIZING INDICATORS PRIOR TO PERILOUS CIRCUMSTANCES AN AWARENESS PIECE

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HEMOPHILIA: RECOGNIZING INDICATORS PRIOR TO PERILOUS CIRCUMSTANCES
AN AWARENESS PIECE

By

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A capstone project submitted for Graduation with University Honors

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Abstract

Hemophilia is a rare bleeding disorder that affects only 400,000 individuals worldwide. This small number gives an idea that there is an abundance of individuals who have no idea about what hemophilia is, who it affects, how to prevent it, or what to expect after being diagnosed. There are countless stories of hemophiliacs discovering their disorder after minor to severe incidents that change their lives forever. In some cases, the spontaneity/rarity of this disorder unfortunately allows people to realize they are a hemophiliac only after they have already encountered a life-threatening circumstance. The experiences of a fair share of hemophilia patients serves as a canvas for just how significant it is to recognize symptoms of hemophilia before it becomes fraught with danger. A look into the lives of those affected by hemophilia may potentially bring awareness to how treacherous this health disparity is and also display what can be done to prevent the unexplained bleeding from relinquishing our health. The objective of this project is to inform the public of statistics on hemophilia that could essentially avert some health disparities from reaching fatalities within the disorder.

Acknowledgements

First and foremost, I would like to express my praise, gratefulness and glory to my God in Heaven. None of my accomplishments/successes would have come to light without Him.

The fulfillment of this project would also not have been attained without the assistance of my mentor, Professor Subir Ghosh. Thank you for being so kind and encouraging throughout the duration of this capstone project. Each meeting was full of new insight for different pieces of my project; all questions I had were answered with great advice- for that, I thank you endlessly.

My sincere gratitude goes to my dear friend, Samuel. I would have never known about hemophilia had it not been for you. Thank you for allowing me to take a dive into a hidden aspect of your life and make this project truly come to life. All of this research and my newly discovered preventative measures are for your well-being.

My deepest, most unfeigned appreciation is to my family. Mom, thank you for instilling in me all of my most significant morals. You are my backbone, my world and the reason I work so hard is to make you proud. Dad, your work ethic has truly been my motivation through school. Any obstacle you've ever faced has been overcome with grace. You are my inspiration. Danny, you stepped in while I was young and I know life would never be the same had you not. Thank you for loving me as your own- you know I love you just the same. To my big brother, thank you for giving me shoes I always wish to fill. You are, without a doubt, my whole heart. Lastly, to my sisters- I try my hardest in life so you both know that women can do anything we wish to in this world. Always take the road less traveled on; you will accomplish anything you set your minds to. I love you all tremendously, thank you.

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Introduction

Imagine living a life feeling as though you are walking on eggshells in order to maintain your health and proper physical condition. Nearly 25 million Americans are forced to tread life carefully with enduring a constant battle of becoming victims to rare, undiagnosed diseases (Buckles, 2019). Amongst the plethora of diseases that continue to go undiagnosed lies a disorder called hemophilia. Hemophilia is a rare disorder in which the blood comes short of efficiently clotting in comparison to the average person (CDC, 2020). For many individuals suffering with the troubles that come along with having hemophilia, they do not know how to manage the excessive bleeding disorder prior to learning about their diagnosis.

What is hemophilia? Hemophilia is a disease that usually stems from the unfortunate inheritance of a deficiency of a coagulation factor (National Hemophilia Foundation, 2021). This deficiency does not allow the blood to clot properly which is the possible source of minor injuries becoming critical. Hemophilia is more than just a bleeding disorder. It is a disease that forces patients to encounter many trials and tribulations physically, mentally and emotionally. The biological effects that hemophilia has on one's body may generate physical differences that are easy to observe. In the same way, hemophilia patients are subject to the mental hardships that come with being diagnosed with a rare disease. To see your body go through changes when you are unaware of the cause may do damage to the mental state of a human. Similarly, the emotional toll it takes on an individual to be diagnosed with a disorder that pertains to how your body recuperates after injuries is immense. One may feel as though they have to be vigilant of all exertions in regards to the body. This could be the result of emotional damage if one is not used to keeping a close eye on every last movement they make.

From the moment I learned about hemophilia, I realized that this was something that should be elucidated. I first learned about this disorder from my boyfriend who suffers from being diagnosed with hemophilia. My experiences with having a loved one suffering from a medical disorder are nothing short of arduous. You truly do not ascertain the substance of diseases until they are affecting you or your loved ones. The shocking realization that my boyfriend's hardships that he kept facing could possibly be much worse for other individuals diagnosed with the same disorder gave me the push to conduct this research.

Coincidentally, I was also continuously being scheduled to work alongside the daughter of a severe hemophiliac patient. When conversing with this coworker about the misfortunes of hemophilia, I started to realize how uncommon it was for others to have heard about hemophilia. Without proper knowledge of this bleeding disorder, there could be struggles in finding the right diagnosis. For my boyfriend, figuring out that he had hemophilia was no small feat. From the time that he was a child, he would become injured, have a bleeding episode, and nurses/doctors in our very small hometown had no answers. I was once an individual who attained an undiagnosed disorder for so long. This disorder ended up being revealed as rheumatoid arthritis. Even rheumatoid arthritis was a medical condition that people were familiar with; so, I became engrossed with figuring out a solution to bringing awareness to hemophilia.

In this paper, I explore the multitude of different aspects that are associated with hemophilia. I address particular features connected with hemophilia such as: characteristics, hemophilia population, and even treatments. With the intention of bringing awareness to this rare disorder, I also incorporate personal accounts of a certain hemophiliac patient. The experiences offered within this paper aim to permit more individuals to understand the significance of

becoming educated in this area. Hemophilia, if not treated properly, has the capability of dwindling down the amount of years in the average life expectancy for hemophiliacs (Green, 2007). Any disorder that has the potential of being life-threatening should be analyzed in a higher regard. In this connection, I have created a review of valuable literature pieces alongside powerful personal experiences with an eye toward further unraveling the complexities of hemophilia.

Literature Review

Characteristics of Hemophilia

Considering the rarity of hemophilia, a bleeding disorder that can come in different forms, it is crucial that its characteristics be unveiled. In identifying characteristics, it is more feasible to determine if the bleeding disorder is Hemophilia A (lack of blood clotting factor VIII), Hemophilia B (diminishing blood clotting factor IX), or Hemophilia C (factor levels are deficient in factor XI); which is important for diagnosis (Hemophilia Federation of America, 2021). Characteristics of hemophilia named by the Centers for Disease Control and Prevention include: bleeding within the joints that results in swelling, bleeding clots (hematomas), raised/elevated bruises, blood in the urine/stool, frequent and excessive bleeding episodes, and even bleeding in the muscles/soft tissues. These characteristics can be major identifiers that an individual may be suffering from a certain type of hemophilia.

Recognizing these characteristics of hemophilia early on can be a lifeline for some patients. For instance, hemophilia may reveal itself earlier than we may expect in children like newborns. In some births of hemophilia patients, there may be bleeding on the scalp or

immoderate bleeding on the genitals after circumcisions (CDC, 2021). As these children begin to develop, if they had not already figured out that hemophilia was affecting their lives, it could possibly come in the form of uncontrolled bleeding after losing teeth. These cumbersome bleeding experiences for hemophiliacs are generally very unmanageable; additionally, they are extremely rare and hard to recognize without prior knowledge of characteristics. These episodes can gradually become worse and more hazardous if not identified in the early stages of life.

Reports of Hemophiliacs

In the grand view of hemophilia and who it affects, the specific numbers are shocking: 1 in 5,000 male births are hemophiliacs in the United States. Worldwide, approximately 400,000 people are diagnosed with this rare bleeding disorder and 20,000 of that small worldwide number come from the United States (Hemophilia Federation of America, 2021). These numbers are mind-boggling considering the current amount of humans inhabiting this earth. Within the small number of people who are diagnosed with hemophilia are even smaller amounts for specific hemophilia types. For example, hemophilia A is the most common form of hemophilia. Whereas, hemophilia B is reported to be more rare than hemophilia A. Due to the sole fact that there is such a small number in comparison to the world population that are diagnosed with hemophilia; this project is dedicated to bringing awareness to every morsel of individuals in order to emphasize the importance of learning about such a rare disorder.

Hemophiliac Population

Bearing in mind the rarity of hemophilia as stated before, questions may begin to arise about who this disorder actually affects. Hemophilia is a bleeding disorder that contains a sex-link gene (Bertamino et al. 2017). This means that the hemophilia gene is located on a

chromosome. For this bleeding disorder specifically, the gene will start its course on the X chromosome. Similarly, hemophilia has recessive traits. In the majority of cases of hemophilia, the family affected generally has a history of hemophilia already (CDC, 2021).

Therefore, those who are born male at birth (containing one X and one Y chromosome) will likely have increased chances of being affected by this disorder and have a higher chance of being diagnosed with hemophilia. Since females have two X chromosomes, they have a less chance that they would get hemophilia due to the fact that they would require two parents with hemophilia in order to inherit the bleeding disorder. However, females will become carriers of the gene even if only one of their parents is diagnosed with hemophilia. For this purpose, education about hemophilia ought to be more widespread and prevalent since half of the population (females) would not necessarily know that they are carriers of such a precarious disorder.

As an illustration, if a father has hemophilia and a mother does not have any trace of even being a carrier of hemophilia, their sons will all be born without hemophilia or carrier genes, but their daughters will solely become carriers of the gene (Bertamino et. al 2017). In contrast (Figure 1), if a father does not have hemophilia, but the mother is a carrier, there only lies a 50% chance of their sons being hemophiliacs and their daughters being carriers (Bertamino et. al 2017).

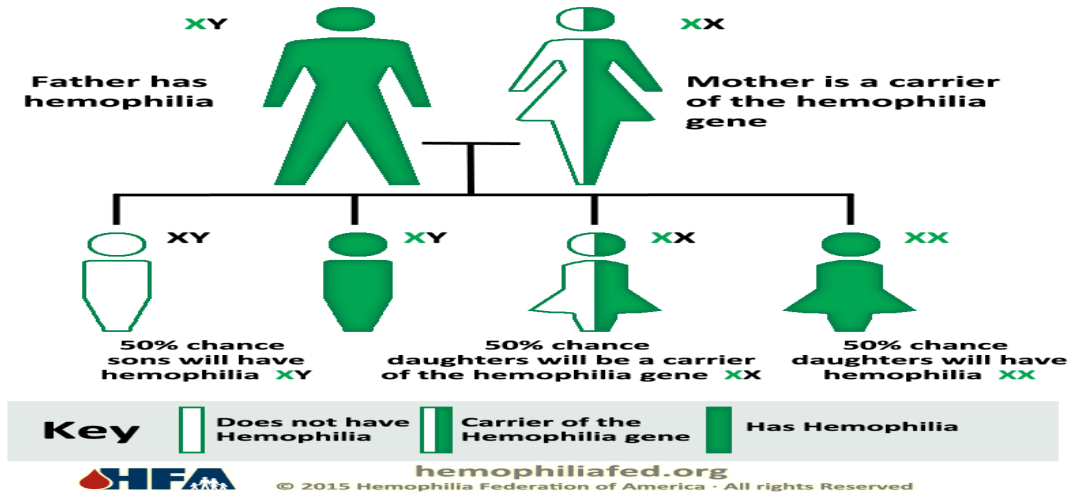


Figure 1. The passing down of hemophilia changes based on whether the mother obtains hemophilia or the father obtains hemophilia.

Treatments

Following the diagnosis of hemophilia, most patients urgently set in motion a search for treatments and prevention strategies. The National Hemophilia Foundation (2021) provides information in regards to treatments such as factor replacement therapies (most commonly used), oral liquids and capsules, and even nasal sprays. According to the NHF (2021), different treatments could be more beneficial for certain patients. It is advised that hemophilia patients contact a medical provider who specializes in hematology in order to determine which treatment would be more serviceable to their specific condition (mild, moderate, or severe hemophilia).

Specifically, factor replacement therapies have seemed to be the most common treatments utilized for hemophiliacs. Though there are many new treatments on the rise for the hemophilia community, factor replacement therapies have demonstrated themselves to be a swift remedy to patients who are in dire need. Replacement therapies bear resemblance to a normal IV injection

(intravenous). They also operate in a similar fashion when being infused, in view of the fact that it injects replacement clotting factors in order to rejuvenate the blood so it can clot properly. The Indiana Hemophilia and Thrombosis Center (2022) suggests that the infusion of certain doses of clotting factor is heavily reliant on what type of hemophilia a patient has (Figure 2).

| Severity of hemophilia | Blood clotting factor level |
|-------------------------------|------------------------------------|
| Normal | 50% - 150%* |
| Mild | > 5%- <40% ¹ |
| Moderate | 1%-5% |
| Severe | < 1% |

* The classification of individuals with FVIII levels between 40 and 50% remains unresolved.² Some patients can bleed more than normal with FVIII levels >40%.¹

1. Makris M, Oldenburg J, Mauser-Bunschoten EP, et al. The definition, diagnosis and management of mild hemophilia A: communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis* 2018;16:2530-3.
2. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis* 2014;12:1935-9.

Figure 2. *This table is vital in determining which doses of clotting factor are required for each category that a hemophilia patient would be classified as. Less severe cases of hemophilia will require lower doses of clotting factor.*

For hemophiliacs who possibly have fears of needles and/or have experienced adverse reactions to replacement therapy methods; there are oral liquids and capsules that treat hemophilia in which some patients have found success with utilization. Amino Caproic Acid, also known as Amicar® (CDC, 2021), is one of the more prominent medications well known for treating hemophilia. Amicar® is typically given orally by means of pills or liquids but also has

the potentiality of being offered through injection sites as well (CDC, 2021).

Information provided by the CDC (2021) suggests that additional remedies proven to be advantageous to the treatment of hemophilia include: DDAVP®, Stimate®, and Hemlibra®. DDAVP® and Stimate® have similar forms of restoring clotting factor 8 into the body when a patient is in need. They both take existing factor 8 from tissues within the body and release the factor into the system (CDC, 2021). According to the CDC (2021), the difference between DDAVP® and Stimate® is that DDAVP® is typically given through injections (IV's) whereas Stimate® is able to be offered in a nasal spray form.

Behavioral Tactics

In an effort to assist the general public in comprehending hemophiliacs and the bleeding disorder they are burdened with, we must also understand how to cope with it. Some safety/preventative measures that may help hemophiliacs subsist with this bleeding disorder include: medications, therapies and even physical activity. Medications such as antifibrinolytics assist patients with hemophilia in slowing down their blood clotting (National Organization for Rare Disorders, 2021). Essentially, this medication stimulates the body of a hemophiliac to reduce the breaking down of blood-clotting factors which can help these patients minimize their excessive bleeding episodes.

To reiterate, some therapies have been shown to strengthen the blood circulation and white blood cells in hemophiliacs to support blood clotting. Therapies like replacement therapy and prophylactic therapy have been proven to slow down the bleeding where severe bleeding events have occurred (NORD, 2021). Replacement therapy is when the patient is given a clotting factor (from an immanent source) during a bleeding episode. This type of therapy is

also known as on-demand therapy. Likewise, prophylactic therapy encourages blood clotting during these bleeding episodes by infusing hemophilia patients with the factor that corresponds to the type of hemophilia they are diagnosed with (NORD, 2021).

In similar fashion, physical therapy has been promoted as a preventative measure for hemophilia patients. For many years, hemophilia was deemed as a disorder that would drastically change the lives of individuals forever. These people that were diagnosed with hemophilia felt as though they would have to retire from their leisure activities for a life of constant paranoia about the next bleeding episode. These leisure activities included anything that would involve physical activity that could possibly result in injury or trauma. However, it has been studied and proven that physical activity is one of the best preventative measures that hemophilia patients can use to cope with their bleeding disorder.

Physical activity has the potential to strengthen the joints that are known to become damaged in those who are diagnosed with hemophilia. Likewise, physical activity has been identified as a factor in decreasing obesity in the hemophilia community, improving the effectiveness of treatments, and ultimately preventing the bleeding episodes from becoming too severe (Goto et al. 2016). In a similar manner, this physical activity for the elderly has been shown to decrease obesity, osteoporosis, fractures and more complications that occur in those who have previously been diagnosed with hemophilia (Goto et al. 2016). Since hemophilia patients are prone to injury from their high chances of getting unexpected bruises and bleeding episodes, hemophiliacs were generally told to refrain from physical activity as much as possible. However, this type of activity has been proven to have more potential to strengthen the muscles, joints, and the body at large.

Awareness

Hemophilia, being the rare disorder that it is, needs to have more light shed on it in order to prevent more individuals from risking their lives when doing laborious work that they are so used to doing. In no way should individuals have to shift their lives completely when diagnosed with hemophilia which is why this project is an advocate for the awareness of the disease as a whole. In an effort to make this disease as easily comprehensible as possible, my dear friend will be participating in allowing me to share stories of his own since having been diagnosed with hemophilia. He will be able to share about how he found out about hemophilia, how he changed his lifestyle to cope, the preventative techniques he uses, and how the general public can help in an event that a bleeding episode is occurring. Since there are cases of mild, moderate, and severe hemophilia, these stories will be able to serve as a canvas as to how life-threatening this bleeding disorder may be if not identified and treated correctly. The objective is simple, to bring awareness to the rare bleeding disorder, hemophilia. Nonetheless, this awareness will serve to make those suffering with hemophilia feel as though they are being heard, their bleeding disorder is not going unseen, and their peers are willing to offer support and a helping hand in a scenario where assistance is required. Recognizing each aspect of hemophilia will hopefully play a part in demonstrating how the efforts of this project will benefit the hemophilia community and our society contemporaneously.

Case in Point

Exemplary Template

Authentic examples of hemophilia patients can give us a look into this bleeding disorder that words alone (literature) may not be able to. For this purpose, I intend to raise awareness with the portrayal of a dear friend, Samuel's experience with hemophilia through different photographs. My main goal in revealing these photographs is to convey the uncomfortable,

troublesome obstacles that arise when a patient is enduring an uncontrollable bleeding incident.

Bleeding episodes for hemophiliacs can arise with mild, moderate, or severe consequences. For Samuel, he would be categorized as a mild, type A hemophiliac. Specifically, treatments for this class of hemophilia would encompass doses of factor 8 (at approximately 40%) being infused into the blood. Mild cases of hemophilia are just as difficult to approach and cope with. Samuel's most recent bleeding occurrence can function as a testimony to the difficulties faced when diagnosed with even mild hemophilia.

On January 7th, 2022, Samuel was scheduled for a rhinoplasty (a surgery for nasal reconstruction). This surgery, like any other, required that the patient (Samuel) be cleared medically and physically in order to have it completed. Samuel went to urgent care for a medical clearance, but just as he was being physically cleared, his blood work and labs came back with abnormalities. Unfortunately, Samuel's blood work indicated that his blood was not clotting at an efficient time or at a time that the typical 24 year old's blood would clot. Normal clotting times for the average human without hemophilia is typically around 10-13 seconds (MFMER, 2022). Paying regard to this, doctors would be forced to decline Samuel of the ability to move forward with anything pertaining to the nose surgery without taking the appropriate precautions first. Due to the irregularity in the labs, Samuel would then be sent to a cardiologist to make sure his heart was able to handle the amount of stress it would be put under during surgery (anesthesia). Then, he would be required to have an electrocardiogram (EKG) and an echocardiogram taken to examine if there were abnormalities in his heart in regards to its structure and rhythm. Typically, the average person does not need to take all of these steps in order to get a rhinoplasty done. However, for Samuel, his blood would engender a multitude of issues in getting this very common surgery executed. This would only be the beginning of the

struggles that would soon present themselves.

Impediments with Hemophilia

Undoubtedly, anyone undergoing a surgery involving reconstruction of the face/body would encounter bruising, swelling, and bleeding. For a hemophiliac like Samuel, this bruising, swelling, and bleeding would begin and seem to never end. The bruising traveled from what was supposed to be solely his eyes and nose all the way to his cheeks (Figure 3). Moreover, the swelling was atypical and made its way down to his jaw (Figure 4). The average person going through the same surgery is claimed (by the surgeon) to have little to no swelling on these parts of the body at the time that Samuel was showing evidence of swelling. The most concerning part, from a post-surgery aspect, was the bleeding. Samuel would bleed non stop from morning to night. This bleeding was not the typical nosebleed; Samuel would find himself spitting out clots the size of a child's palm. To our surprise, Samuel's surgeon expressed that he had not seen as much blood from his other patients when performing postoperative practices. The bleeding was so excessive that it caused Samuel to make his way to the emergency room in the hospital two times in one week.

During these visits he would be injected with the factor 8 that he was lacking (Figure 5). Samuel's deficiency of factor 8 would induce a grueling battle with attempting to put an end to this overwhelming bleeding episode. In the course of getting factor 8 injected, Samuel had a tube available to him that would suction out the clumps of blood that would build up in the back of his throat (Figure 6). Although he was being treated at the hospital, the blood would not stop fueling out of his nose, so this tube was essential to his breathing getting back to normal. Samuel was unable to breathe out of his nose since the rhinoplasty procedure. Unfortunately, the excessive bleeding making its way down his throat made it almost impossible to get a deep

breath of air. The tube provided to Samuel would permit him to withdraw blood from his throat to make a pathway for air to get through. Not only did hemophilia cause issues with bleeding, but it forced Samuel to endure days of respiratory issues coupled with sleep-deprivation.

Content Warning:

Blood, bruising, and swelling are depicted below.



Figure 3. (10 days post-op) *By day 10 most of the bruising should have subsided; yet, he was still bruised not only on his nose and eyes (per typical rhinoplasty patient), but his cheeks too.*



Figure 4. After surgery, Samuel looked as though he gained weight all throughout his jaw and neck. This was shocking for a guy like him who weighs less than the average man his age. The swelling was distinguishably making his appearance altered.



Figure 5. The IV was injected into Samuel's arm. Factor 8 was infused into his blood in amounts of 4ml with increments of two minutes in a dosage that is appropriate for moderation of his mild hemophilia. This dosage allowed for his blood to clot within 30 minutes of the treatment.



Figure 6. *The blood collected in this tube was after only one suction out of Samuel's mouth.*

Although the photographs depict the strenuous circumstances that someone with mild hemophilia may confront, it is important to keep in mind that there are two, more severe cases of hemophilia that accompany more burdensome difficulties.

Discussion

After observing the photos of Samuel's prolonged recovery process, it was evident that his hemophilia played a huge factor in his healing being so delayed. After comparing these photos to a normal recovery for a rhinoplasty, it became clear to me that the severity of hemophilia should not be overlooked. As a reminder, the patient discussed above had been diagnosed with hemophilia A which is the most common form of hemophilia. This mild case still comes with numerous disparities that would impact the patient for his whole life. Even though these photos may be disturbing, I feel that it is necessary to convey how a mild form of hemophilia A would impact a young, healthy person. In the unfortunate event that someone is

diagnosed with an even more severe form of hemophilia, this awareness piece would be of service to educating that individual. The characteristics of hemophilia (excessive bleeding, swelling, bruising, and joint damage) would also serve as a template for someone who is concerned about their health and whether they have hemophilia or not. Overall, sharing stories of one's experiences with having hemophilia, even though it may feel personal, could be transformative to another person's life.

Conclusion

Awareness for hemophilia can take on a number of appearances such as: a visual representation (Figure 7), an interview with a hemophiliac patient, or even a piece of writing like this one. Despite the efforts of medical professionals, some rare diseases are simply just hard to recognize and diagnose. Optimistically, the content provided within this paper will permit more individuals to become educated on this disorder that has the capability of having perilous circumstances if not treated in a timely and efficient manner. The utter importance of recognizing how hemophilia is passed down from parent to offspring will also assist in treating the symptoms that arise. Hemophilia is a compound disorder that has many different layers to unfold in order to treat accordingly. There are a handful of treatments that are suitable for patients who have different classifications of hemophilia. In a similar manner, the behavioral tactics have the same objective of preventing serious bleeding outbursts for hemophiliacs. In the end, I have hope that the personal accounts of experiences with hemophilia that are offered within this piece are adequate enough to aid in the comprehension of this elaborate disease.

Hemophilia Awareness

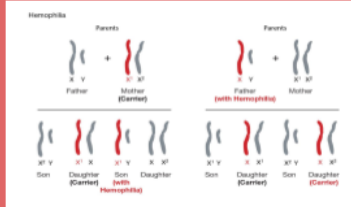
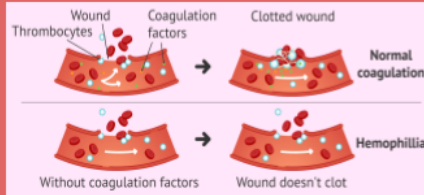


Characteristics:

- Blood is noticeably not clotting properly
- Unexpected, raised bruises
- Bleeding is continual

Damage in joints

Overview: Hemophilia is a bleeding disorder that arises from lack of the protein called clotting factor in one's body.



Who does it affect?

Males are generally affected by hemophilia. It is extremely rare for females to be diagnosed with hemophilia.

How is it passed down?...

Identifying hemophilia: Difficult birth, excessive bleeding, history within family, minor accidents result in severe injuries, etc.

Numbers: 20,000 people are currently living with Hemophilia in the U.S., only 400,000 worldwide

Treatments: infuse factor, collect plasma to inject, medication (pills), & newest form- patch

Preventative Tactics: physical therapy, physical activity/exercise, avoid high-contact sports, etc.

Personal Experiences:

Hemophilia is so rare that most people, if not aware of familial ties to hemophilia, will meet serious injuries before knowing what is truly going on with their bodies.

Figure 7. Hemophilia awareness is condensed here into one visual representation.

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Appendix A: Different Categories of Hemophilia & Rare Disorders with Respective Factor Deficiencies

| Rare Disorder | Factor Deficiency |
|---|---|
| Hemophilia A | Factor 8 (VIII) |
| Hemophilia B | Factor 9 (IX) |
| Hemophilia C | Factor 11 (XI) |
| Von Willebrand Disease (related to Hemophilia A) | Von Willebrand Factor & Factor 8 (VIII) |
| Owren's Disease | Factor 5 (V) |
| Parahemophilia (interchangeable with Owren's disease) | Factor 5 (V) |

[Rare Disorders](#)

Appendix B: Impacted Populations within Each Factor Deficiency

| Factor Deficiency | Impacted Population |
|--------------------------|---------------------------------------|
| Factor 1 (I) | 1 or 2 per 1 million individuals |
| Factor 2 (II) | 1 per 2 million individuals |
| Factor 5 (V) | 1 per 2 million individuals |
| Factor 7 (VII) | 1 per 300,000 - 500,000 individuals |
| Factor 8 (VIII) | 1 per 1 million individuals |
| Factor 10 (X) | 1 per 500,000 - 1 million individuals |
| Factor 11 (XI) | 1 per 100,000 individuals |
| Factor 12 (XII) | 1 per 1 million individuals |
| Factor 13 (XIII) | 1 per 5 million individuals |

[Impacted Populations](#)