HEMOPHILIA-INHERITED BLEEDING DISORDER: AN OVERVIEW

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ABSTRACT

Hemophilia is an inherited bleeding disorder where one of the blood clotting proteins is absent or present in a reduced amount. People with Hemophilia, do not bleed faster than anyone else; but will bleed continuously at the normal rate until they are treated. Hemophilia has an estimated frequency of approximately one in 10000 births. Estimations based on the World Federation of Haemophilia’s (WFH) annual global surveys indicate that the number of people with Hemophilia in the world is approximately 400000. The history of Hemophilia shows the human mind attempting to define and encompass a mysterious yet fascinating phenomenon; and also the human heart responding to the challenge of repeated adversity. There is obviously a need to establish facilities and treatment options that will help the patient with Hemophilia, to manage their life with ease. As this is a genetic disorder no complete cure is possible as of now. The available treatment for Hemophilia is by replacing the missing clotting factor in the blood through an intravenous infusion of clotting factor concentrate. Several new technologies are also being implemented to advance Hemophilia, treatment. Multiple trials and studies are underway to examine the possibility to use gene therapy to replace the defective genes in Hemophilia. To date, stable and sustained production of the deficient clotting factors has not been achieved in humans, but this is an area of active investigation that holds great promise for the new delivery systems of the existing therapies or new treatment options has to be driven by pharmacy professionals. The present review
broadly describes an overview of the management of various aspects of Hemophilia in order to draw the attention of medical as well as pharmacy professionals for the benefit of millions of hemophilic patients.

**Keywords:** Hemophilia, Clotting factors, Hemostasis, Inheritance, Prophylaxis, Treatment.

**INTRODUCTION**

Hemophilia is a bleeding disorder that results from genetic alteration in production of coagulation factors that are important to maintain hemostasis. It is a genetic condition that causes people to keep on bleeding for a long time unless treated. The commonest type is Hemophilia A due to deficiency of factor VIII (FVIII), which is important zymogene co factor for clot formation. Hemophilia A is an X-linked disease that affects males at prevalence of 1:5000-10000. Hemophilia B is due to deficiency in factor (FIX) but less common with prevalence of 1:34,500 males. It is inherited also as X- linked.\(^1\) People with Hemophilia do not bleed faster than anyone else; but will bleed continuously at the normal rate until they are treated. This is because the blood is unable to clot without any therapy. Internal bleeding is the major concern in Hemophilia. Bleeding is common into joints such as knees, ankles and elbows. This may be caused by injury, but in severe Hemophilia, can begin spontaneously.\(^2\)

Hemophilia has an estimated frequency of approximately one in 10000 births. Estimations based on the WFH’s annual global surveys indicate that the number of people with Hemophilia in the world is approximately 400 000. Hemophilia A is more common than Hemophilia B, representing 80–85% of the total Hemophilia population. Hemophilia generally affects males on the maternal side. However, both F8 and F9 genes are prone to new mutations, and as many as 1/3 of all cases are the result of spontaneous mutation where there is no prior family history.\(^3\)

Hemophilia is the standard international spelling, also known as Haemophilia in the UK, other translations include: hémophilie, hemofilie, hemofili, hemofilia, hämophilie, emofilia.\(^4\)

We will use the standard international spelling for the purpose of this section.

Bleeding disorders are due to defects in the blood vessels, the coagulation mechanism, or the blood platelets. An affected individual may bleed spontaneously or for longer than a healthy
person after injury or surgery. When coagulation factors are missing or deficient the blood does not clot properly and bleeding continues.

Patients with Hemophilia A or B have a genetic defect which results in a deficiency in one of the blood clotting factors.\(^5\) A more precise definition can be given in terms of which part of the clotting mechanism is defective. The clotting factors, which are present in blood, are numbered with Roman Numerals from I to XIII. In normal blood the clotting factors act like a row of dominoes toppling against each other to create a chain reaction (figure 1)\(^6\);

![Figure 1 Normal Clotting Process](image1)

Figure 1 Normal Clotting Process

When one of the factors is missing the clotting mechanism is not activated (figure 2);

![Figure 2 Clotting process in a person with Hemophilia where a clotting factor is missing](image2)

Figure 2 Clotting process in a person with Hemophilia where a clotting factor is missing.

**HISTORY**

In the 20\(^{th}\) century doctors looked for the cause of Hemophilia. Until then, they had believed that the blood vessels of Hemophiliacs were simply more fragile. In the 1930s doctors looked at defective platelets as the likely cause. Then, in 1937, Patek and Taylor, two doctors at Harvard, found they could correct the clotting problem by adding a substance which came from the plasma in blood. This was called *anti-hemophilic globulin*\(^7\). In 1947, Pavlosky, a doctor from Buenos Aires, Argentina, did a lab test which showed that blood from one Hemophiliac could correct the clotting problem in a second Hemophiliac and vice-versa. He had stumbled upon two Hemophiliacs each with a deficiency in different proteins - factor VIII and factor IX.\(^8\) This led to the recognition in 1952 of Hemophilia A and Hemophilia B as two distinct diseases. In the 1960s the clotting factors were identified and named. An
article in Nature in 1964 described the clotting process in detail. The interaction of the different factors in blood clotting was named the coagulation cascade.

In the 1950s and early 1960s, Hemophiliacs were treated with whole blood or fresh plasma. Unfortunately, there weren’t enough of the factor VIII or IX proteins in these blood products to stop serious internal bleeding. Most people with severe Hemophilia and some people with mild or moderate Hemophilia died in childhood or early adulthood. The most common causes of death were bleeding in vital organs, especially the brain, and bleeding after minor surgery or after an injury.

Those who survived were usually crippled by the long-term effects of repeated hemorrhages into the joints. The pressure of massive bleeding into joints and muscles made Hemophilia one of the most painful diseases known to medicine. Then, in the 1960s, cryoprecipitate was discovered by Dr. Judith Pool. Dr. Pool found that the sludge that sunk to the bottom of thawing plasma was rich in factor VIII. For the first time, enough factor VIII clotting factor could be infused to control serious bleeding. Even surgery became possible.\[9\]

Then, later in the 1960s and early 1970s, concentrates containing factor VIII and IX began to be available. These freeze-dried powdered concentrates could be kept at home and used as needed. They revolutionized Hemophilia care. Hemophiliacs were now independent of hospitals. They could travel, hold steady jobs and hope to lead normal lives. Tragically, these same blood products carried blood-borne viruses like hepatitis C and HIV. Many Hemophiliacs were infected.

In the 1990s, modern treatment, using safer factor concentrates, again improved the outlook (Table 1)[10]. Most children born with Hemophilia in Canada today can look forward to long, healthy, active and productive lives.

Unfortunately, only 25% of the world's Hemophiliacs enjoy this level of care. The ones who do not have access to modern Hemophilia care face the same fate as Queen Victoria's offspring in the 1800s - a life of pain and crippling, and an early death.[11]
European royalty

Hemophilia has featured prominently in European royalty and thus is sometimes known as 'the royal disease'. Queen Victoria passed the mutation for Hemophilia B to her son Leopold and, through some of her daughters, to various royals across the continent, including the royal families of Spain, Germany, and Russia (Figure 3).[11]

Figure 3 Queen Victoria and her family

In Russia, Tsarevich Alexei Nikolaevich, son of Nicholas II, was a descendant of Queen Victoria through his mother Empress Alexandra and suffered from Hemophilia (Figure 4). It
was claimed that Rasputin was successful at treating Tsarevich's Hemophilia. At the time, a common treatment administered by professional doctors was to use aspirin, which worsened rather than lessened the problem. It is believed that, by simply advising against the medical treatment, Rasputin could bring visible and significant improvement to the condition of Tsarevich.

![Image of Tsarevich Alexis]

Figure 4  The Tsarevich Alexis, aged 10 years. Note the position of the left leg with flexed hip and knee. This was probably due to previous muscle and joint bleeding.

In Spain, Queen Victoria's youngest daughter, Princess Beatrice, had a daughter Victoria Eugenie of Battenberg, who later became Queen of Spain. Two of her sons were Hemophiliac sand both died from minor car accidents. Her eldest son, Prince Alfonso of Spain, Prince of Asturias, died at the age of 31 from internal bleeding after his car hit a telephone booth. Her youngest son, Infante Gonzalo, died at age 19 from abdominal bleeding following a minor car accident where he and his sister hit a wall while avoiding a cyclist. Neither appeared injured or sought immediate medical care nor Gonzalo died two days later from internal bleeding.\[12\]

Professor Bulloch meticulously traced out the spread of Victoria's mutant gene through the Royal houses of Europe. The family trees which he drew are still preserved in the Library of the Royal Society of Medicine of London. Sir Paul Fildes made his contribution to Hemophilia largely while still a medical student, indeed publishing an independent paper in the London Hospital Gazette in 1909, the year in which he qualified. In later years he became famous, of course, in microbiology.\[13\]
CLINICAL PRESENTATIONS IN HEMOPHILIA \(^{[14]}\)

A. Acute bleeding
   (i) Superficial, e.g. cutaneous, epistaxis, gum bleeding due to loss of deciduous teeth.
   (ii) Deeper mucosal bleeds, e.g. genito-urinary tract and gastro-intestinal tract.
   (iii) Acute joint bleeding (major joints, e.g. knee, elbow, ankle are most often affected).
   (iv) Bleeding comprising
      (a) Musculo-skeletal bleeds;
      (b) Compartment syndromes – Volkman’s contracture;
      (c) Femoral nerve palsy or other nerve palsy.

B. Life-threatening bleeding
   (i) Bleeding in the central nervous system;
   (ii) Road traffic accident and multiple trauma;
   (iii) Severe bleeding from the gastro-intestinal tract.

C. Consequences of repeated acute or chronic bleeding
   (i) Anaemia;
   (ii) Chronic synovitis;
   (iii) Chronic haemophilic arthropathy;
   (iv) Contractures, caused by repeated joint bleeds and abnormal postures;
   (v) Unequal length of limbs, because of repeated joint bleeds resulting in varus or valgus deformity;
   (vi) Chronic haematoma leading to pseudocyst formation.

D. Hemophiliacs needing surgical intervention.

E. Inhibitor development in Hemophiliacs.

F. Transfusion-transmitted disease in Hemophiliacs.

MOST COMMON TYPES OF HEMOPHILIA

Hemophilia-A (Classic Hemophilia)
It is otherwise called as the classic Hemophilia. It is “X” linked recessive disorder occurred due to the absence or deficiency of clotting factor VIII (FVIII). Hence it affects only males. Females are said to be carriers. Carrier females usually are asymptomatic but can have bleeding symptoms (e.g., are easily bruised or have menorrhagia or excess bleeding after trauma) when they have significant reductions in factor VIII levels, which are caused by the greater (extreme) inactivation of the normal FVIII gene, compared with the hemophilic FVIII gene, during early embryogenesis. The occurrence of Hemophilia –A is 1:5000-10000.\(^{[15]}\)
Hemophilia B (Christmas disease)

It is also an “X” linked recessive disorder occurring due to the absence or deficiency of the clotting factor IX. The inheritance pattern and the symptoms of Hemophilia B are same as that of the classic Hemophilia. The occurrence of Hemophilia –B is 1: 20000-34000,\(^\text{[15]}\)

Hemophilia C

It is an autosomal recessive disorder exhibits bleeding symptoms because of the absence/deficiency of the factor XI. For inheriting the disease both parents must carry the defective gene. Reports are there as exceptions, that people have bleeding problems when only one of their parents has the gene which causes Factor XI Deficiency. Factor XI Deficiency affects males and females in equal numbers. The occurrence of the Hemophilia C is1:100000,\(^\text{[15]}\)

Acquired Hemophilia

This is very rare disease occurring in approximately one in 5 million persons in contrast with the 10 to 20% of Hemophiliacs who develop alloantibodies\(^\text{[16,17]}\). It is characterized by the presence of an autoantibody (mainly IgG) to factor VIII protein (FVIII), with a clinical presentation resembling Hemophilia A\(^\text{[18]}\). The patient develops the condition during his/her lifetime and it does not have a genetic or heritable cause. It occurs when the body forms antibodies that attack one or more blood clotting factors, (usually factor VIII), thus preventing the blood clotting mechanism from working properly. Patients may be male or female and the pattern of bleeding is rather different from that of classical Hemophilia, the joints being rarely affected. It is associated with various autoimmune or dermatologic
diseases, pregnancy, cancer, or drug ingestion, but in almost 50% of patients, no underlying disorder is found.[5]

SEVERITY OF HEMOPHILIA
The severity of Hemophilia is related to the degree of deficiency of the relevant clotting factor in the blood. Normal clotting factor activity is described as between 50% and 200%. There are three levels: severe, moderate and mild. A person with less than 1% of normal clotting activity is described as having severe Hemophilia. A person with between 1% and 5% of normal clotting activity is described as having moderate Hemophilia and a person with over 5% but less than 50% of normal activity is described as having mild Hemophilia.[19]

Those who have mild or moderate Hemophilia generally only experience bleeding problems after an obvious injury or an operation, and many mild cases only experience bleeding after, for example, a tooth extraction or surgery.[6]

HEMOSTASIS AND BLOOD COAGULATION
Blood travels around inside the body through blood vessels. These include Veins, arteries, and capillaries. When any of these is damaged the blood can spill out. Sometimes this happens when the skin is cut or scratched. Other times the blood can leak out of a blood vessel inside the body. In both the cases, body must work to stop the leak and repair the injury. The process of blood clotting (Coagulation), the subsequent dissolution of the clot and the beginning of the repair of the injured tissue, is termed as hemostasis. Blood clotting is considered as an important step in the hemostasis. This is a process that leads to the formation of fibrin clot. During an injury the sequential steps that lead to the formation of clot are: [15]

Step I) Vascular constriction
This limits the flow of blood to the area of injury.
Step II) Platelets become activated by thrombin and aggregate at the site of injury, forming a temporary, loose platelet plug.
Step III) Formation of a strong fibrin clot

Blood coagulation entails the interaction of a large number of plasma glycoprotein with blood platelets and vascular endothelial cells. Blood clotting (Coagulation) proceeds through following pathways which leads to the fibrin production (Figure 5).[20]
It consists of two processes: Primary and Secondary hemostasis.

Primary hemostasis involves the aggregation of platelets at an injury site. An initial platelet plug is established and subsequently replaced by a more stable fibrin clot through secondary hemostasis.

Secondary hemostasis involves the coagulation cascade: a sequence of reactions that ultimately leads to the formation of the stable fibrin clot. FVIII and FIX are both part of the intrinsic pathway of the coagulation cascade and are necessary to convert FX to FXa, the first step of the common pathway. A deficiency or defect in either FVIII or FIX decreases the activation FXa, impairing subsequent reactions necessary to create fibrin clots.\[^{20}\]

**Intrinsic pathway**

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {Kallikrein};
  \node (b) at (1.5,0) {Pre-kallikrein};
  \node (c) at (0,-1) {Factor XII};
  \node (d) at (1.5,-1) {Factor XIIa};
  \node (e) at (0,-2) {Factor XI};
  \node (f) at (1.5,-2) {Factor Xlla};
  \node (g) at (0,-3) {Factor IX};
  \node (h) at (1.5,-3) {Factor IXa. Factor VIIIa};
  \node (i) at (0,-4) {Factor X};
  \node (j) at (1.5,-4) {Factor Xa. Factor Va};
  \node (k) at (0,-5) {Factor II (prothrombin)};
  \node (l) at (1.5,-5) {Factor IIa (thrombin)};
  \node (m) at (0,-6) {Fibrogen};
  \node (n) at (1.5,-6) {Fibrin};
  \draw[->] (a) -- (b);
  \draw[->] (c) -- (d);
  \draw[->] (e) -- (f);
  \draw[->] (g) -- (h);
  \draw[->] (i) -- (j);
  \draw[->] (k) -- (l);
  \draw[->] (m) -- (n);
  \draw[->] (n) -- (a);
\end{tikzpicture}
\end{center}

**Extrinsic pathway**

**Figure 6 Hemophilia: A deficient hemostatic System**

**CAUSES OF HEMOPHILIA**

Hemophilia is caused by a problem in one of the genes that tells the body to make the clotting factor proteins needed to form a blood clot. These genes are located on the X chromosome. All males have one X and one Y chromosome (XY) and all females have two X chromosomes (XX).

Males who inherit an affected X chromosome have Hemophilia. Rarely, a condition called "female Hemophilia" occurs. In such cases both X chromosomes are affected or one is missing or inactive. In these women, bleeding symptoms may be similar to males with Hemophilia.
A female who inherits one affected X chromosome becomes a "carrier" of Hemophilia. A female who is a carrier sometimes can have symptoms of Hemophilia. In addition, she can pass the affected gene on to her children.

Even though Hemophilia is genetic, it does occur among families with no prior history. About one-third of newly diagnosed babies have no family history of Hemophilia. These cases are thought to be due to a change to the gene's instructions for making the clotting factor protein, called a "mutation." This change or mutation can prevent the clotting protein from working properly or to be missing altogether. [21]

Inheritance of Hemophilia [22,23]
The following examples show how the Hemophilia gene can be inherited. It is important to note that in one-third of people with Hemophilia, there is no family history of the disorder.

1. In this example, the mother is a carrier of the Hemophilia gene, and the father does not have Hemophilia.
   - There is a 50% chance that each son will have Hemophilia.
   - There is a 50% chance that each daughter will be a carrier of the Hemophilia gene.

![Figure 7](image.png)

Figure 7 The inheritance pattern of Hemophilia when the mother is a carrier of Hemophilia.
2. In this example, the father has Hemophilia, and the mother does not carry the Hemophilia gene.

- All daughters will carry the Hemophilia gene.
- No sons will have Hemophilia.

Figure 8 The inheritance pattern of Hemophilia when the father has Hemophilia.

3. In this example, the father does not have Hemophilia, and the mother does not carry the Hemophilia gene.

- None of the children (daughters or sons) will have Hemophilia or carry the gene.

Figure 9. The inheritance pattern of Hemophilia when the father does not have Hemophilia, and the mother does not carry the Hemophilia gene.
SYMPTOMS AND DIAGNOSIS

Hemophilia symptoms vary, depending on the degree of blood clotting factor (coagulation factor) deficiency and they also depend on the nature of any injury.\(^{19}\)

The major signs of Hemophilia are bleeding that is unusually heavy or last a long time, or bleeding and bruising that happens without obvious cause. The amount of bleeding depends on the type and severity of Hemophilia and how serious it is. Three levels of Hemophilia are recognized, according to the level of clotting factor amounts in the blood. These are often expressed as percentages of normal.\(^{24}\)

- Above 5% - mild Hemophilia
- 1% to 5% - moderate Hemophilia
- Less than 1% - severe Hemophilia

**Mild Hemophilia**

People with inherited mild Hemophilia may not have any symptoms until an event occurs which wounds the skin or tissue, such as a dental procedure or surgery, and results in
prolonged bleeding. In societies where male circumcision is carried out soon after birth, mild Hemophilia will be detected earlier. Joint bleeding is uncommon.

**Moderate Hemophilia**

Those with inherited moderate Hemophilia will be noticeable early on. The child will bruise easily and may also experience internal bleeding symptoms, especially around the joints, and after a blow or a fall. Bleeding that occurs inside a joint is usually referred to as a *joint bleed*.

**Symptoms of a joint bleed:**
- Tingling sensation in the joint
- Pain in the joint
- Irritation in the joint

Any surgical intervention, circumcision, dental procedure or injury will result in prolonged bleeding in a person with Hemophilia.

**Severe Hemophilia**

Symptoms are similar to those found in moderate Hemophilia, but occur more frequently and are usually more severe. A child with severe Hemophilia will often bleed for no apparent reason, often referred to as spontaneous bleeding. Most commonly, in early childhood from about 18 months of age, the nose or mouth start to bleed or apparently spontaneous bruises appear, particularly on the legs. Parents are sometimes suspected of causing non-accidental injury (deliberate harm) to their children.

**Symptoms of Hemophilia type bleeding may include:**
- Several large or deep bruises
- Joint pain or swelling
- Unexplained bleeding or bruising in nose and gum bleeding
- Blood in feces (stools) and urine
- Tightness in the joints

**Intracranial hemorrhage (bleeding inside the skull)**

About 1 in every 30 patients with Hemophilia will have intracranial hemorrhage at least once during their lives. This should be treated as a medical emergency. Spontaneous intracranial hemorrhage is rare and in many cases bleeding inside the skull will be the result of a blow to the head.
Symptoms of intracranial hemorrhage include:

✓ A bad headache
✓ Vomiting
✓ Confusion
✓ Fitting (Convulsion)
✓ Loss of balance
✓ Slurred speech, or other speaking difficulties
✓ Stiff neck
✓ Vision problems
✓ Loss of coordination
✓ Some of the facial muscles do not work (sometimes all of them)\textsuperscript{[24]}

DIAGNOSIS OF HEMOPHILIA

Prenatal testing - if a pregnant woman has a history of Hemophilia, a Hemophilia gene test can be done during pregnancy. A sample of placenta is removed from the uterus and tested. This test is known as a CVS (chorionic villus sampling) test.

Blood test - If a doctor suspects a child may have Hemophilia a blood test can determine whether the patient has Hemophilia A or B, and how severe it is. Blood tests can be performed from the time of birth onwards.\textsuperscript{[24]}

TREATMENT FOR HEMOPHILIA

Hemophilia is treated by replacing the missing clotting factor in the blood through an intravenous infusion of clotting factor concentrate. Each bleeding episode must be promptly treated. Once the bleeding stops, pain rapidly diminishes and use of the limb returns. The clotting factor concentrate is manufactured as a white powder and is reconstituted with the sterile water provided with the factor concentrate. The Factor VIII and Factor IX used for the treatment of Hemophilia is called “recombinant factor”. What cannot be emphasised enough is that a person with Hemophilia must have treatment as soon as a bleed starts. It prevents further bleeding, pain and most importantly, reduces the likelihood of permanent damage to joints (target joints).\textsuperscript{[19]}

Hemophilia treatment will mainly depend on its severity and for patients with Hemophilia A or B involves clotting factor replacement therapy. There are two approaches:
• **On demand** - giving treatment to stop prolonged bleeding when it occurs. This is more common in the management of patients with mild Hemophilia.

• **Preventative treatment (prophylaxis)** - medication to prevent bleeding episodes, and subsequent complications, such as joint and/or muscle damage. More commonly used for patients with moderate or severe Hemophilia.[25]

Good quality medical care from doctors and nurses who know a lot about the disorder can help prevent some serious problems. Often the best choice is a comprehensive Hemophilia Treatment Center (HTC). An HTC provides care to address all issues related to the disorder, as well as education.[26]

- A CDC-sponsored randomized clinical trial found that children who were treated on a regular basis to prevent bleeding had less evidence of joint damage by 6 years of age than did those who were treated only after a bleed had started.
- About 70% of people with Hemophilia in the United States receive multidisciplinary, comprehensive care in a network of federally funded Hemophilia treatment centers.
- Mortality rates and hospitalization rates for bleeding complications from Hemophilia were 40% lower among people who received care in Hemophilia treatment centers than among those who did not receive this care.[27,28]

**Surgery**

All surgical procedures, including dental extractions and fillings, will require treatment beforehand and should be organised through your Hemophilia Treatment Centre.[19] Surgery, once considered prohibitive for this population, especially for patients with high-titer inhibitors, has become routine, with procedures such as radiosynovectomy further improving quality of life for affected individuals due to the advent of factor concentrates and the bypassing agents.[29]

**Home Treatment**

Both preventive and on demand treatment can be administered at home. Home treatment is the ideal method of treatment from a medical viewpoint as a minimum amount of time is lost between the recognition of a bleed and treatment. This has many advantages, it reduces the disruption caused by a bleeding episode to the person with Hemophilia and his family and the patient feels more able to control his condition. The benefits of self in fusion at home not only include increased independence and the bonus of not having to travel to the hospital for
treatment, but school and work attendance is more regular. If bleeds are treated promptly, the period of incapacity caused by each episode can be reduced. In adults and teenagers home treatment is usually carried out by the affected person. From a young age children will be taught how to self infuse. Alternatively, a device called a Port-a-Cath (Freddie) can be used to facilitate venous access until self infusion using the veins is practical.\textsuperscript{[19]}

**PORT-A-CATHS**

In some young children where venous access is difficult and injections are stressful for both the child and the parent it is recommended that a Port-a-Cath be fitted. Port-a-Caths are used to provide access to veins and are inserted under general anaesthetic. The Port-a-Cath is inserted under the skin usually in the chest area. When the Port has been inserted there is no longer a need for injections into veins so treatment is painless and therefore less stressful.\textsuperscript{[19]}

![Port-a-Cath](image)

**Figure 11 Port-a-Cath**

**Clotting factor concentrates**

Clotting factor concentrates can be made in two different ways;\textsuperscript{[30]}

- **Plasma-derived clotting factors** - prepared from the plasma of donated human blood.

Plasma is the liquid part of blood. It is pale yellow or straw colored and contains proteins such as antibodies, albumin and clotting factors. Several factor concentrates that are made from human plasma proteins are available. All blood and parts of blood, such as plasma, are routinely tested for the viruses. The clotting proteins are separated from other parts of the plasma, purified, and made into a freeze-dried product. This product is tested and treated to kill any potential viruses before it is packaged for use. A blood safety surveillance system in place since 1998 has found no new infections with hepatitis or HIV associated with these products among Hemophilia patients.

- **Recombinant clotting factors** - The first generation of recombinant products use animal products in the culture medium and had human albumin (a human blood product) added as a stabilizer. Second generation products use animal-derived materials in the culture medium
but do not have added albumin and instead use sucrose or other non-human derived material as a stabilizer. Third generation clotting factors have no albumin present at any stage of their preparation. Mouse monoclonal antibodies have been routinely used in the purification of coagulation factors for many years but a recently licensed recombinant factor VIII employs a synthetic ligand for this step. This has resulted in the production of the first factor VIII concentrate to be free of all exogenous human and animal protein, a goal which was reached for Hemophilia B when the first recombinant factor IX was licensed in 1997.

**Prophylaxis**

It is recommended that all children with severe factor deficiencies should be commenced on a programme of factor concentrate prophylaxis. Prophylaxis involves small regular (2-3 per week) infusions of factor concentrate to prevent spontaneous bleeding and to minimise traumatic bleeding. This treatment regime, although it can be time consuming and at times difficult to learn, will prevent joint damage and lead to an improved quality of life.\[31\]

**Other treatment products**

**Desmopressin (DDAVP) (for mild Hemophilia A)**

It is a synthetic analog of the anti diuretic hormone vasopressin (1-deaminocys-8D arginini-vasopressin). It is useful in mild hemophilies. This medication is a synthetic hormone which encourages the body to produce more of its own Factor VIII. It is unsuitable for patients with Hemophilia B and those with severe Hemophilia A.\[32\] In patients with milder forms of Hemophilia A, factor VIII replacement therapy may be necessary, especially for severe bleeds, or after serious injury or major surgery. This medicine can be given through a vein (DDAVP®) or through nasal spray (Stimate®).

**Amicar® (Epsilon Amino Caproic Acid)**

Amicar® is a chemical that can be given in a vein or by mouth (as a pill or a liquid). It prevents clots from breaking down, resulting in a firmer clot. It is often used for bleeding in the mouth or after a tooth has been removed because it blocks an enzyme in the saliva that breaks down clots.

**Cryoprecipitate**

Cryoprecipitate, made through the cold precipitation of frozen plasma from1965 onwards, was the first really effective treatment for Hemophilia A. Freeze-dried concentrates made from human plasma containing the right levels of Factors VIII and IX became available in the
late 1960s and early 1970s. Being able to keep the treatment at home and use it as required meant that patients could travel, leave the home, go to work, and enjoy a level of independence. However, a large number of patients subsequently became infected with blood-borne pathogens, such as hepatitis –B, hepatitis-C and HIV. From the mid 1980s rigorous donor selection and viral inactivation procedures reduced the risk of blood-borne viral transmission to nearly zero. During the 1990s it became possible to prepare synthetic (recombinant) factors, using specially prepared mammalian cells and these recombinant concentrates are now widely used. By appropriate fast-freezing in ethanol-dry ice, cold-thawing at refrigerator temperature, and centrifuging, blood banks now process fresh blood to prepare two final products-cryoprecipitate and reconstituted whole blood-using a two bag set. Or they prepare three final products packed cells, cryoprecipitate, and supernatant plasma-using a three-bag set. The cryoprecipitate is stored at -20 degrees C.[33]

The disadvantages of cryoprecipitate are the variability in potency among individual units and the need for storage of -20 degrees C rather than at refrigerator or room temperature. When -20 degree C storage is not available, the commercial products of necessity must be used.[34]

**RICE (Rest, Ice, Compression, Elevation)**

RICE is a treatment many health care professionals recommend for joint bleeds. It also reduces swelling and tissue damage when used together with clotting factor concentrates.[25]

**Inhibitors**

Approximately 30% of people with severe Hemophilia A develop antibodies to transfused factor VIII, usually shortly after their first few treatments. These antibodies (also called inhibitors) prevent the factor VIII treatment working properly. It is often the case that, after a while, the inhibitors disappear and only about 10% or less of people with severe Hemophilia A will suffer from long term inhibitors. In recent years it has become possible to prevent inhibitors becoming persistent through immune tolerance induction therapy. Where inhibitors do not respond to this approach alternative treatments are available. Inhibitors rarely develop in mild Hemophilia A or in Hemophilia B of any severity.[35]

**Gene Therapy**

Gene therapy is currently being investigated as a treatment options for Hemophiliacs. Such therapy would reduce the need for long-term IV infusions of clotting factors. In 2011, a study
found adenovirus associated virus vector expressing human factor IX gene increased FIX levels in all participants with Hemophilia B. Though there results are encouraging, disease was not eliminated, but did reduce frequency of needed clotting factor transfusions.\cite{36}

**RNA Interference**

A novel way of treating Hemophilia, by Alnylam pharma ltd, outside of traditional factor replacement. The firm is looking to apply its RNA interference (RNAi) technology to Hemophilia by targeting protein C, and is poised to enter clinical trials in 2013 (preclinical proof of concept was achieved in July 2012, with data presented in December at the American Society of Hematology meeting). Because protein C typically reduces thrombin production, blocking the production of this protein would increase thrombin generation and blood clotting, making this a novel target for Hemophilia. Alnylam's ALN-AT3 could serve as a treatment for patients with Hemophilia A or B, in addition to patients with inhibitors or those with even rarer deficiencies of various factor proteins. This would also be administered subcutaneously, potentially offering a convenience advantage to current treatments.\cite{37}

**PREVENTION**

People who have Hemophilia should avoid situations that might cause bleeding. They should be careful about dental care so they won't need to have teeth extracted. People who have Hemophilia should also avoid certain drugs that can aggravate bleeding problems:

- Aspirin
- Heparin
- Warfarin
- Certain analgesics, such as NSAID (eg, Tylenol and Ibuprofen )

Genetic counselors can make a detailed family history. They will discuss risks and available testing options.\cite{38}

The transmittance of the Hemophilia to the next generation can be prevented by the following methods.

1) Prenatal diagnosis (PND): Preconceptual counselling should precede prenatal diagnosis in known Hemophilia carriers and women with bleeding disorders.\cite{39}

- **Chorionic villus sampling (CVS):** Under local anesthesia and ultrasound guidance, a fine needle is inserted through the abdomen or a thin catheter is inserted through the mother’s
vagina to take a sample of chorionic villi cells from the placenta. These cells contain the same genetic information as the fetus itself, and can be used to determine whether the fetus is affected by Hemophilia. CVS is carried out early between 11 and 14 weeks of pregnancy. It is the most widely used method for the prenatal diagnosis of Hemophilia and other inherited bleeding disorders.

- **Amniocentesis:** A small amount of amniotic fluid is removed, using a fine needle inserted into the uterus through the abdomen. Amniocentesis is done under ultrasound guidance, between the 15th and 20th week of pregnancy. The amniotic fluid contains cells from the fetus that can be analyzed to detect Hemophilia.

2) Preimplantation genetic diagnostic testing (PGD): PGD is a newly-emerging form of a very early prenatal diagnosis. The technique combines assisted reproductive technology with molecular genetics and cytogenetics to allow the identification of abnormality in embryos prior to implantation.[40]

3) IVF with egg/sperm donation.

**FUTURE**

Multiple trials and studies are underway to examine the possibility to use gene therapy to replace the defective genes in Hemophilia. To date, stable and sustained production of the deficient clotting factors has not been achieved in humans, but this is an area of active investigation that holds great promise for the future.

Several new technologies are also being implemented to advance Hemophilia treatment. These new technologies, once used to destroy viruses in blood, have been successful in virtually eliminating the risk of contracting HIV or hepatitis C from clotting factor today. Pharmaceutical companies are continuing to investigate genetically manufactured product alternatives derived from little to no human blood products. New products have consistently been developed which have an even higher purity than have ever been available before.
CONCLUSION

Hemophilia is a bleeding disorder that results from genetic alteration in production of coagulation factors that are important to maintain hemostasis. As the number of patients reported with Hemophilia is comparatively less than other major diseases like cancer, cardiac diseases, and diabetics it seems to be less concentrated area by researchers though almost 50 years many studies have addressed different aspects of Hemophilia and risk factors to diagnosis and management of patients with Hemophilia. Over the next couple of years it is widely anticipated that new technologies will develop to diagnose and treat the patients of Hemophilia and study continue to evolve and expand in many areas of Hemophilia.

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