HAEMOPHILIA: FACTS FOR HEALTH CARE PROFESSIONALS

Haemophilia is an X-chromosome-linked inherited bleeding disorder which occurs in all races and social groups.

Haemophilia management requires adequate supplies of blood products and comprehensive medical care.

The problems of haemophilia can be reduced if information, scientific research and proper medical services are available.
EDUCATIONAL MATERIAL ABOUT HAEMOPHILIA
FOR HEALTH CARE PROFESSIONALS

This edition has been updated by Dr Peter Jones
and reviewed by
Dr Carol Kasper and Professor Ian Peake
on behalf of the
Human Genetics Programme,
World Health Organization
and the
World Federation of Hemophilia

Originally prepared in 1992 by
Dr Elizabeth Berry, Dr Margaret Hilgartner,
Dr Guglielmo Mariani, Dr Yvette Sultan
and Members of the Medical Advisory Board,
World Federation of Hemophilia
# LIST OF CONTENTS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Introduction</td>
</tr>
<tr>
<td>2.</td>
<td>Normal Blood Coagulation</td>
</tr>
<tr>
<td>3.</td>
<td>Mode of Inheritance</td>
</tr>
<tr>
<td>4.</td>
<td>Carrier Identification</td>
</tr>
<tr>
<td>5.</td>
<td>Use of Polymorphisms</td>
</tr>
<tr>
<td>6.</td>
<td>Identification of Specific Gene Defects</td>
</tr>
<tr>
<td>7.</td>
<td>Advantages of DNA Analysis</td>
</tr>
<tr>
<td>8.</td>
<td>Prevention of Haemophilia</td>
</tr>
<tr>
<td>9.</td>
<td>Severity of haemophilia</td>
</tr>
<tr>
<td>10.</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>11.</td>
<td>Management of Bleeding</td>
</tr>
<tr>
<td>12.</td>
<td>Therapy</td>
</tr>
<tr>
<td>13.</td>
<td>Dosage</td>
</tr>
<tr>
<td>14.</td>
<td>Complications of Treatment</td>
</tr>
<tr>
<td>15.</td>
<td>Viruses</td>
</tr>
<tr>
<td>16.</td>
<td>Inhibitors</td>
</tr>
<tr>
<td>17.</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>18.</td>
<td>Other Side Effects</td>
</tr>
<tr>
<td>19.</td>
<td>Total Care of the Person with Haemophilia</td>
</tr>
<tr>
<td>20.</td>
<td>Haemophilia and the Family</td>
</tr>
<tr>
<td>21.</td>
<td>Conclusion</td>
</tr>
<tr>
<td>22.</td>
<td>Further Information</td>
</tr>
</tbody>
</table>

Annex: Storage of DNA | 27
1. **INTRODUCTION**

This booklet is for health care professionals who manage families with haemophilia.

The haemophilias are inherited, life-long, sex-linked disorders occurring predominantly in males. The incidence is about 1:5,000 male births and all races and socioeconomic groups are affected. Clinical features of severe haemophilia include haemorrhages into joints, muscles and other tissues either spontaneously or following minor trauma. If untreated, crippling deformity and arthritis will result and life expectancy is considerably reduced.

Modern management includes administration of virally safe, effective concentrates of the deficient clotting factor, self treatment and prophylaxis, a professional team approach to the total care of the person with haemophilia and access to genetic technology for carrier detection and prenatal diagnosis. Early and adequate replacement of the deficient coagulation factor is therapy for the majority of bleeding episodes.

Using this approach, a baby newly diagnosed with severe haemophilia can expect to lead a near normal life, to share responsibilities both for himself and future generations and live to old age.

There is a companion booklet for families which contains complementary information.

2. **NORMAL BLOOD COAGULATION**

Within the coagulation system of proteins, clotting Factor VIII (FVIII) is a large protein which acts as a cofactor in the activation of Factor IX (FIX) and Factor X (FX) in the intrinsic pathway. Factor VIII circulates loosely bound to a larger protein, von Willebrand Factor (vWF) which protects it from enzymatic degradation. Quantitative and qualitative abnormalities in these
proteins result in the three most common inherited disorders of coagulation. Abnormalities in FVIII and FIX produce Haemophilia A and B respectively, and abnormalities on vWF produce von Willebrand disease. Haemophilia A is about five times more common than haemophilia B, but is clinically indistinguishable. Within the older literature, haemophilia B may be referred to as Christmas disease, after the first family in which factor IX deficiency was diagnosed.

3. MODE OF INHERITANCE

Haemophilia is the classical example of a sex linked recessive disorder. The genes which control FVIII and FIX production are both located on the X chromosome. As males have only one X chromosome, the synthesis of FVIII or FIX will be deficient if the relevant gene is defective. A person with haemophilia passes his abnormal X chromosome on to all of his daughters, and his Y chromosome, which is normal, to his sons (Fig 1). Thus, all of his sons will be normal and cannot pass on the defective gene, and all his daughters will be carriers of the defective X gene. A woman who is a carrier (Fig 1) has four possible outcomes with each pregnancy; a normal boy, a normal girl, a girl who is a carrier, or a boy with haemophilia. Thus the risk of having a baby with haemophilia is 1 in 4 for each pregnancy. There are rare instances of females with haemophilia. They are descendants of a haemophilic father and a carrier mother.

FIG. 1 Family Tree

In some texts you will see the X and Y chromosomes used to denote a family tree. An X with a small "o" or "+" (X° or X+) signifies a female chromosome with the gene for haemophilia.

X X = normal female chromosome.
X°X = carrier female.
X°X° = normal male.
X°Y = haemophilic male.
4. CARRIER IDENTIFICATION

Carriers are classified as ‘obligatory’ or ‘possible’ from the family history. Obligatory carriers are women whose fathers have haemophilia, or women who have two or more sons with haemophilia, or women who have one affected son and a male relative on the mother’s side with the disorder. Possible carriers are women who have one or more relatives with haemophilia on their mother’s side but no affected sons, or women who have only one son with haemophilia and no other known relatives with the disorder.

Most women who are carriers are asymptomatic, but a few with particularly low levels of FVIII or FIX activity may bruise easily, bleed abnormally following surgery or dental extractions or have other symptoms including menorrhagia.

The range of factor activity in the carrier population overlaps the normal range and thus detection of carriers by coagulation factor assay alone presents problems.

The first step in deciding if a woman is a carrier for haemophilia A or B is to obtain an accurate family tree. Carriers will be related to a haemophilic male through their mother and her female relations. The next step is to determine the factor VIII clotting activity and von Willebrand Factor antigen for haemophilia A and factor IX clotting activity for haemophilia B. Because of natural variability, it is advisable to measure an individual’s clotting activity on at least three separate occasions.

Roughly 80% of the carriers of haemophilia A and 50% of the carriers of haemophilia B will be detected by these assays.

A normal level of FVIII and FIX clotting activity does not exclude carrier status.
The third and most precise step in carrier detection is DNA analysis. This is also the most important test in prenatal diagnosis.

5. **USE OF POLYMORPHISMS**

A commonly used strategy for DNA based carrier detection and prenatal diagnosis is to study the inheritance of DNA polymorphism either within the FVIII or FIX gene (intragenic) or closely linked to them (extragenic). Such polymorphisms (either restriction fragment length polymorphism RFLP or variable number tandem repeats VNTR) result in up to 95% of families being informative using intragenic polymorphism where a degree of certainty >99% can be expected. Where only linked polymorphisms are useful this figure is reduced to 95% certainty. This information is an important component in prenatal diagnosis. At 10 weeks or later of pregnancy, fetal DNA is extracted from chorionic villus samples and analyzed for the appropriate informative polymorphic marker identified in the mother.

Carrier identification by family study requires DNA analysis from several key family members including a haemophilic male, and the parents of the possible carrier. As many relatives as possible are preferable for completeness and for the identification and exclusion of other carriers.

6. **IDENTIFICATION OF SPECIFIC GENE DEFECTS**
   (e.g., a deletion, point mutation, insertion or inversion)

These are being identified with increasing frequency using technology based on Southern blotting or polymerase chain reaction (PCR) amplification of specific sequences of DNA to give adequate quantities for analysis. These techniques are performed only in specialized centres and require high levels of expertise. It is probable that future developments within this area will result in an increased simplification of these procedures making them more applicable to routine genetic studies. One of the most important recent developments, which allows immediate identification of an abnormal gene in
approximately 50% of haemophilia A probands tested by Southern blot, involves identification of an inversion of a portion of the X chromosome. This results in the separation of the FVIII gene into two distinct parts, and the subsequent incapacity of the gene.

7. ADVANTAGES OF DNA ANALYSIS

Both specific gene defect detection and polymorphism analysis require DNA, which is generally obtained from whole blood (white blood cells). The advantages of DNA analysis over measurement of clotting factors are both its greater precision in terms of carrier state assignment and prenatal diagnosis and that DNA is stable in its frozen state (in whole blood for example). Samples can therefore be readily transported and analyzed after years of storage. It is particularly important to collect samples of whole blood from many people with haemophilia (and relevant family members) and to store these samples in case of future need. World Federation of Hemophilia recommendations on collection and storage of DNA can be found in the Annex.

8. PREVENTION OF HAEMOPHILIA

Avoiding the birth of children with haemophilia can be done only on the basis of accurate identification of carriers and with counselling to provide information on prenatal diagnosis. The earlier counselling is provided the less the emotional impact concerning maternity and possible termination of the pregnancy should be. It is therefore advisable to perform genetic studies on all members of at-risk families as soon as the diagnosis of haemophilia is made in a family member. Children should preferably be told of their carrier status when they are able to fully understand it. This is usually around 12 years but may be obvious earlier if their factor VIII or IX clotting levels are low enough to warrant therapy.
Not only are carriers identified, but there is positive exclusion of non-carriers.

Most importantly, counselling must be provided in a way that whatever the decision of the carrier, she should not be made to feel guilty about her choice. It is important not to neglect people with haemophilia themselves in discussing genetic aspects. Ideally, a skilled genetic counsellor who is knowledgeable about haemophilia should be available, but in many countries haemophilia centre staff carry out this task. Whoever undertakes genetic counselling should appreciate that no testing is foolproof and that possible carriers can sometimes only be given an assessment of likely risk, rather than a definite diagnosis of being (or not being) a haemophilia carrier.

Options available to carriers and their partners include not having children or choosing adoption, pre-implantation diagnosis as part of in vitro fertilization, prenatal diagnosis, or accepting the choice of having a haemophilic son or carrier daughter. Prenatal options include chorionic villus sampling at 10 weeks or later for genetic analysis, amniocentesis at 14-15 weeks to determine fetal sex, and fetal blood sampling at 18 weeks to determine clotting factor levels. These tests all require to be done in specialized units.

Even with effective family planning there will still be haemophilic births since 20-30% of those with haemophilia are in families not known to be at risk and are presumably the result of new mutations.

9. SEVERITY OF HAEMOPHILIA

The clinical severity of the disorder varies markedly between families, but within a kindred all affected members will have essentially the same baseline levels of FVIII or FIX clotting activity.

The normal range of factor activity varies from 50-150%, but patients with more than 30% very rarely have any bleeding problems unless subjected to major surgery or trauma.
### Table 1

**CLASSIFICATION OF HAEMOPHILIA**

<table>
<thead>
<tr>
<th>% of factor</th>
<th>Degree of haemophilia</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIII or IX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% or less</td>
<td>Severe (&lt; 0.01 units/mL)</td>
<td>Frequent spontaneous bleeds. Coagulation screening tests always abnormal.</td>
</tr>
<tr>
<td>&gt;1 - 5%</td>
<td>Moderate (&gt;0.01 - 0.05 units/mL)</td>
<td>Few spontaneous bleeds. Bleeding after minor trauma. Prolonged partial thromboplastin time.</td>
</tr>
<tr>
<td>&gt;5 - 30%*</td>
<td>Mild (&gt;0.05 - 0.03 units/mL)</td>
<td>Bleed only after trauma or surgery. Coagulation screen tests may be low normal.</td>
</tr>
<tr>
<td>&gt;30 - 50%*</td>
<td>Very mild (&gt;0.3 - 0.5 units/mL)</td>
<td>May or may not bleed abnormally after major trauma or surgery. Coagulation screen tests often normal.</td>
</tr>
</tbody>
</table>

* About one third of carriers have levels between 15 and 50%.

**Severe Haemophilia (less than 1% FVIII or FIX)**

Prolonged or repeated bleeding may occur at one or more sites at a time an trauma which is so slight as to be unrecognized may produce bleeding which therefore appears to be spontaneous. Bleeding is mainly internal producing haemorrhage into joints (haemarthroses), muscle and soft tissue (haematoma), other organs or the central nervous system (Tables 2 and 3).
TABLE 2
BLEEDING SITES

<table>
<thead>
<tr>
<th>Type of Haemorrhage</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemarthroses</td>
<td>70 - 80</td>
</tr>
<tr>
<td>Muscle and subcutaneous</td>
<td></td>
</tr>
<tr>
<td>haematoma</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Other major bleeds</td>
<td>5 - 10</td>
</tr>
<tr>
<td>CNS bleeds</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

TABLE 3
JOINT INVOLVEMENT

<table>
<thead>
<tr>
<th>Haemarthrosis</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>45</td>
</tr>
<tr>
<td>Elbow</td>
<td>30</td>
</tr>
<tr>
<td>Ankle</td>
<td>15</td>
</tr>
<tr>
<td>Wrist</td>
<td>3</td>
</tr>
<tr>
<td>Shoulder</td>
<td>3</td>
</tr>
<tr>
<td>Hip</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
</tbody>
</table>

Bleeding episodes may be noted in early infancy, for example after circumcision. Bruising is common and often lumpy. It may be sufficiently extensive to raise the suspicion of child abuse. Joint and muscle bleeds occur when crawling and walking start. Swelling or reluctance to use a limb are often signs of joint or muscle bleeds at this age. Bleeding from the mouth and tongue are also common at this age, and are often associated with falls.
Recurrence of untreated or inadequately treated bleeding into joints leads to early disability from synovial and joint surface damage. Secondary muscle wasting will occur and the resulting weakness contributes to recurrent bleeding. If one joint has recurrent bleeding it is referred to as a "target joint".

Haematuria, epistaxes, gastrointestinal and oral bleeding occur and may be persistent. Local causes should always be excluded in these instances. In the past, central nervous system and intracranial bleeding were common and often fatal but their frequency has decreased as a result of early therapy for all head injuries. Haemorrhages in the neck and retroperitoneal region are also potentially life threatening.

Bleeding occurs after trauma as well as any surgical intervention, dental extraction or intramuscular injections. Immunizations should preferably be given subcutaneously taking special care, using a fine needle and applying local pressure for five minutes afterwards.

**Moderate Haemophilia (> 1 - 5%)**

Bleeding episodes are similar to those in severe haemophilia but are less frequent and more clearly related to trauma. There is less handicap. Bleeding also occurs with all forms of surgery and dental extractions. Drugs should be given orally, rectally or intravenously and not by the intramuscular route.

**Mild Haemophilia (> 5 - 30%)**

Many people with mild haemophilia are diagnosed late in life after surgical or dental procedures or after trauma when abnormal bleeding occurs. They may also present with muscle or joint bleeds following significant injury.

Children with haemophilia should be encouraged to lead a normal life but they and their parents do need to be aware of potential dangers of trauma.
10. **DIAGNOSIS**

The first step in diagnosis is a detailed personal and family history with specific questions about increased bruising (both superficial and deep), bleeding after circumcision, bleeding after dental extractions or tonsillectomy and the occurrence of bleeding episodes in close relatives. In any person with prolonged or unexplained bleeding the possibility of haemophilia should be considered and tests done.

The second step is the performance of tests for haemostasis: bleeding time, activated partial thromboplastin time (APTT) and prothrombin time (PT). The bleeding time is usually normal as platelet function is unaffected in haemophilia. Depending on the sensitivity of the test, the APTT, a relatively simple test, should be prolonged with factor levels less than 30%. However, in some mild haemophiliacs screening tests may be normal. If the APTT is abnormal or bleeding history is suggestive then specific factor assays are performed and these may need to be referred to a more specialized hospital. It should be noted that the diagnosis of mild haemophilia can be difficult in situations such as post operative bleeding, because the FVIII level rises in response to stress and baseline levels may need to be obtained at a later date.

At the initial investigation and at the regular reviews, blood should be taken for factor inhibitor screening and for hepatitis and human immunodeficiency virus (HIV) testing. Mild and moderate haemophilia A (FVIII deficient) patients should have their response to DDAVP (desmopressin, minirin) assessed, as use of this pharmaceutical agent may avoid exposure to blood products (see therapy).

11. **MANAGEMENT OF BLEEDING**

The person with severe haemophilia can usually tell when bleeding occurs by the nature of the pain he experiences. Often bleeding is felt by the patient
before swelling, loss of movement and other physical signs are evident. The physician or nurse should pay close attention to the patient’s complaint and proceed with therapy despite the absence of physical findings. Bleeding may occur at any time without warning and treatment should be given as soon as possible for the following:

- Bleeding into a joint,

- Bleeding into a muscle. Delayed treatment may result in blood vessel and nerve compression,

- Injury to the neck, mouth, tongue, face or eye. Persistent bleeding has the potential to cause airway obstruction,

- Bumps to the head and unusual headache. 30% of intracranial haemorrhages have no previous history of trauma,

- Heavy or persistent bleeding from any site,

- Severe pain or swelling in any site. Bleeding can mimic other pathology, e.g., iliopsoas haemorrhage and a hip bleed can both resemble acute appendicitis,

- All open wounds requiring stitches. Repeated treatment will be needed until the wound is healed,

- Following any accident that may result in a bleed. Less blood product is needed for prophylaxis than to treat established bleeding.

In most instances treatment is by increasing the level of the deficient factor by transfusion. Ancillary measures may include rest, ice, limb splinting and local or systemic antifibrinolytic agents followed by physical therapy until rehabilitation is complete. Additional products may need to be given during
mobilization after muscle and joint bleeds to enable rehabilitation to succeed without further haemorrhage, and to decrease long term sequelae which include chronic synovitis, arthritis, pseudotumour (bone cyst) formation, and contractures. **WHEN IN DOUBT, TREAT!**

12. **THERAPY**

For haemophilia A fresh or frozen plasma can be used but it is difficult to achieve levels of FVIII greater than 20 - 25% because of the volume needed. The discovery of FVIII rich cryoprecipitate in 1964 enabled satisfactory haemostatic levels of FVIII to be attained and this product forms the starting point for many factor concentrates. Although cryoprecipitate can readily be made in a hospital blood bank, its preparation requires blood collection into a system with multiple satellite plastic bags as well as the use of a refrigerated centrifuge. Each bag of cryoprecipitate contains about 80 FVIII units and an adult would need 8 - 16 bags for a treatment. It has to be kept deep frozen (below minus 25°C) in order to maintain its FVIII activity. This limits its use for home therapy unless a suitable freezer is available. Freeze-dried (lyophilized) plasma and cryoprecipitate can be prepared and make home treatment much easier as they can be kept in a refrigerator.

As most of these products have not undergone viral inactivation procedures, it is essential that donors are carefully selected by questionnaire and interview, and individually tested for hepatitis viruses and HIV.

In mild haemophilia A the first treatment option should be DDAVP. This vasopressin analogue releases the FVIII/von Willebrand Factor complex from storage sites (endothelial cells, platelets), and the increase of FVIII may achieve haemostatic levels. The average rise is 3 - 4 times baseline values. It is administered intravenously, subcutaneously or as an intranasal spray and has few side effects, the most common being headache and facial flushing. Excess fluid intake should be avoided especially in children as water overload with hyponatremia may occur. The drug may be used to treat traumatic
bleeds and to increase levels for dental extractions and surgery. Haemostatic levels may not be attained if baseline FVIII levels are below 10% and DDAVP is thus of no use in severe haemophilia and of limited use in moderate haemophilia.

Replacement factor therapy for Haemophilia B may be with fresh or frozen plasma but volume limitations will usually prevent the achievement of satisfactory levels.

For both haemophilia A and B methods have been developed for preparing concentrates of FVIII and FIX. The first FIX concentrates to be made are often known as PCCs (for prothrombin complex concentrates) as they contain other vitamin K dependent factors (FII, FVII, FX). PCCs are known to be thrombogenic, especially when used to treat patients immobilized after major surgery. They are being superseded by purer factor IX preparations.

Freeze dried products are very easy to use because of their small volume on reconstitution, their known factor activity, and their stability at room temperatures. Concentrates are either made from plasma pooled from thousands of donations using a variety of fractionation procedures, or by DNA technology. The goal is to produce a sterile product of high purity.

Concentrates can and should be treated by virucidal methods to attain a high degree of sterility. Methods presently in use include heat (for example 80°C treatment of freeze-dried material for 72 hours), solvent detergent exposure, affinity chromatography separation and ultrafiltration. Despite these measures no blood derived product has total safety guaranteed. This proviso also applies to presently available DNA factor VIII products because they contain human albumin as a stabilizer.
13. DOSAGE

An adequate dose depends on plasma volume, the resting factor level, activity of the material being used and the "in vivo" recovery of that material.

Transfused FVIII has a metabolic half life of 8 - 12 hours and remains largely in the intravascular space, whereas transfused FIX has a half life of 16 - 32 hours but only about half of the FIX remains in the intravascular space. Thus, approximately twice the dose needs to be given for the same effect. The half life of the factor determines the frequency of treatment. FVIII may need to be given every 8 - 12 hours while FIX may be given daily to maintain levels. It is important to remember that during bleeding (and as a result of surgery) the equilibration phase for each of the clotting factors is shorter than usual as they are being depleted during clot formation.

A wide variety of doses of FVIII or FIX are used to treat or prevent haemorrhage and suggested doses, expressed as units per kilogram of body weight, to achieve desired levels (expressed as percentages) in different clinical situations are given in Table 4 overleaf.

On average, one unit FVIII per KG raises the FVIII level 1.5% and one unit FIX raises the FIX level by 0.9%.

1 Unit FVIII/FIX activity is that present in 1 ml normal plasma and is equivalent to 100% activity.

In general doses of factor IX need to be higher than for factor VIII (see text).

The dose chosen for a given haemorrhage should be that which doctor and patient have found to be promptly effective in such instances. Such doses will vary from patient to patient, and will also vary according to the condition of the individual joint and severity of the haemorrhage. Lower doses may be effective if given early.
**TABLE 4**

**SUGGESTED HAEMOSTATIC LEVELS OF FVIII AND FIX IN DIFFERENT CLINICAL SITUATIONS AND DOSAGES OF FVIII OR FIX CONCENTRATES**

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Plasma concentration to be achieved</th>
<th>Dose needed for haemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of pooled normal plasma</td>
<td>iu/Kg body weight</td>
</tr>
<tr>
<td>Haemarthrosis and minor haematomas</td>
<td>15-25</td>
<td>10-15</td>
</tr>
<tr>
<td>Severe haemarthrosis and haematomas</td>
<td>30-60</td>
<td>20-35</td>
</tr>
<tr>
<td>Surgery, life threatening bleeds</td>
<td>60-100</td>
<td>40-60</td>
</tr>
</tbody>
</table>

Repeated doses over a period of days are frequently necessary after major trauma and surgery as well as for resolution of large muscle haematomas.

Treatment may also need to be given for mobilization after muscle or joint bleeds to enable rehabilitation to succeed without further haemorrhage.

With higher dosages of PCC, for instance as needed for surgery, the risk of thrombosis is increased. Smaller doses given several times daily may be safer. Antifibrinolytic therapy (Cyklokapron, Amicar) should not be given concurrently with PCC therapy.

If the clinical response is unsatisfactory to a presumed appropriate dosage then either the product lacks activity or factor inhibitors may have developed (see complications of therapy).
Inhibitors occur in 30% of people with severe haemophilia A and fewer with haemophilia B. Individuals show differing levels of inhibitor in response to therapy. Patients with low inhibitor levels may be treated with larger than usual doses of factor.

Those with high inhibitor (high titre) levels to FVIII are very difficult to treat but may respond to PCC and "activated" FIX concentrates, animal derived products (porcine FVIII) and other activated products (rVIIa).

Prophylactic (maintenance) therapy given on a regular basis to avoid haemorrhage is used in some countries, particularly in children and adolescents. Short term prophylaxis with regular doses, e.g., three times a week for several weeks, is frequently used to prevent recurrent bleeding in a "target joint" particularly during active rehabilitation, and is also accepted therapy for chronic synovitis which occurs mainly in the elbows, ankles and knees. A single prophylactic treatment in advance of a solitary stressful event, e.g., examinations, travel and unaccustomed exercise, can also be beneficial.

Surgery requires thorough preparation and should only be carried out in hospitals where staff have the experience to manage the patient with haemophilia safely.

Before surgery the patient should be screened for the presence of inhibitors. Sufficient factor must be available to cover both the procedure and the post operative period. The factor levels will need to be raised to >60% and maintained there for at least a week after major surgery and at a somewhat lower level until healing is completed. Twice daily (for FVIII) or daily (for FIX) infusions will be needed in the immediate post operative period. There must be a laboratory and personnel able to monitor factor levels. In a surgical situation patients with mild haemophilia need as much care and attention as patients with severe haemophilia, remembering that any complication of surgery usually requires additional therapy.
Antifibrinolytic drugs, which work by preventing the natural breakdown of formed blood clots, are an important adjunct to replacement therapy after dental extraction and are also useful in management of open wounds and menorrhagia. The main side-effect is nausea. The two most widely used are Epsilon Aminocaproic Acid (Amicar) and Tranexamic Acid (Cyklokapron). These agents should not be used at the same time as PCC because of the increased risk of thromboembolic problems.

Aspirin and aspirin containing compounds should be avoided because of their adverse platelet effects, and other medications known to alter platelet function used with caution. Nonsteroidal anti-inflammatory agents (NSAIDs) may be useful for chronic pain but should only be taken after food and stopped in the event of epigastric discomfort or gastrointestinal haemorrhage.

Adequate treatment allows even the most severely affected patient to have a near normal life expectancy and to be able to play a full role in society.

In summary, the cornerstone of haemophilia treatment is an adequate supply of safe, effective products which must be administered early in the course of haemorrhagic events.

14. COMPLICATIONS OF TREATMENT

The main complications of therapy are related to infection with blood borne viruses and the appearance of inhibitors.

15. VIRUSES

Hepatitis
Liver disease is frequent in the present generation, and may be caused by hepatitis B virus (HBV) with or without delta, hepatitis C virus (HCV), and other non A non B hepatitis viruses. The consequences vary from biochemical changes only to liver cirrhosis and hepatoma. Hepatitis B has
been virtually eliminated in many countries by screening out hepatitis B antigen positive blood donors and by immunization. Anti HCV testing should further reduce the incidence of non A non B hepatitis, and the goal of current viral attenuation procedures is to eliminate transmission of all hepatitis viruses as well as the more labile human immunodeficiency virus (HIV) which causes AIDS. Careful donor history, laboratory screening and use of well known repeat donors has significantly reduced risks from plasma and cryoprecipitate, and improved viral inactivation and purification procedures and the introduction of recombinant products have made concentrates much safer. Hepatitis B vaccination is strongly recommended for all people with haemophilia and their families, if they are not already immune. In addition, hepatitis A vaccine is now recommended because transmission of this virus has recently been associated with concentrate transfusion.

**HIV Infection and AIDS**

The human immunodeficiency virus (HIV) was transmitted to many patients with haemophilia in blood products before donor testing and virucidal processing techniques were introduced. Transmission rates varied, from 10% in some European countries to over 70% of patients with severe haemophilia in the USA treated prior to 1984. As of mid 1991 no seroconversions to HIV antibody positivity have been identified in patients who have received only viral inactivated products prepared from screened donor plasma since 1987.

Currently, identification of HIV infection is by antibody detection for both blood donors and recipients, although other more sensitive test systems are available.

Collection and storage of serial plasma samples from all treated individuals is important in determining status as well as for future infective agent review.

When an individual is found to have HIV antibody, regular review at 3 - 6 monthly intervals, depending on clinical grading, is recommended.
Transmission to others must be avoided and, in those who are sexually active, appropriate instructions given. Cultural attitudes to condom usage may need to be confronted. Safe disposal of intravenous apparatus must be carefully controlled and instruction given concerning avoidance of needle-stick injuries. Used needles must be placed in proper containers and not re-sheathed, and blood spillages are best HIV inactivated with household bleach. Universal precautions, including use of gloves when handling body fluids, should be rigorously applied.

It is important that a sympathetic and knowledgeable staff member is available to provide support, to discuss the problems of everyday life and to lessen the feelings of loneliness and isolation that can develop in infected individuals and their families. Joint haemorrhages and other bleeding episodes should continue to be treated with blood products in the same way as for HIV negative individuals. The possibility of septic arthritis should be considered when a haemarthrosis does not respond to conventional treatment. Prophylactic treatment with factor concentrate or DDAVP will also be needed before invasive diagnostic procedures. Therefore the treatment co-ordination has to remain under the control of Haemophilia Centre staff members.

In children, recommended vaccination schedules should be followed with the exception of BCG. Immune globulin therapy may be considered after exposure to infectious viral agents such as varicella and measles.

Serial monitoring of CD4 (T4) lymphocyte levels is useful to determine when to start antiviral therapy. Prophylaxis for pneumocystis carinii pneumonia (PCP) is recommended. Clinicians should be alert to non-specific symptoms (e.g., fatigue, weight loss), direct effect on the nervous system (dementia, peripheral neuropathy), tumours (especially lymphomas) and opportunistic infections (herpes zoster in young patients; oral, oesophageal and disseminated candidiasis; tuberculosis variants and other bacterial infections; PCP; central nervous system cryptococcus or toxoplasmosis;
cytomegalovirus infection, cryptosporidiosis of the bowel). Treatment of these HIV associated problems should be carried out in consultation with other appropriate specialists including infectious disease physicians, and patients should have access to the best available treatment of HIV infection itself including zidovudine (AZT) and other drugs and to the best available treatment of tumours, opportunistic infections and other complications of HIV infection. Two complications of particular note to the haemophilic population are the increased incidence of septic arthritis, and/or osteomyelitis, as well as the additional haemorrhagic risk posed by HIV-related thrombocytopenia. The clinical course, including response to antiviral, is similar to that of other HIV infected patient groups.

Safety Measures for Staff
The risk of acquiring HIV and other blood borne infections in the work place is very low. However, all staff and relatives who are handling blood and blood products and caring for patients should observe recommended safety procedures. These include the use of gloves and protective clothing when appropriate. Needle-stick injury has the highest risk of transmission (around 0.4%) and needles should be meticulously handled, not recapped or bent, and disposed of in a puncture proof container. Protective equipment and education programs should be provided within the hospital system for staff protection. All those involved in haemophilia treatment who are not already immune to hepatitis A and B should be vaccinated.

16. INHIBITORS (ANTIBODIES)

Specific inhibitors will develop in about 30% of all patients with severe FVIII deficiency and 2 - 3% with severe FIX deficiency. Inhibitors are antibodies that can destroy infused FVIII or IX making treatment very difficult. An inhibitor may develop at any point in the life of a patient and must be specifically tested for if there is a poor response to the usual therapy, and prior to any surgical procedure including dental extractions. Patients with inhibitors may not bleed more frequently than other patients with haemophilia
although therapy is more difficult (see also section on treatment). A recent approach has been to induce immune tolerance to FVIII by giving frequent, often daily infusions of FVIII sometimes combined with courses of immunosuppressive agents. Success may be achieved after weeks to months of such therapy.

17. THROMBOSIS

Has been described following the use of FIX (PCC) concentrate when large doses are given, such as in surgery and also in patients with liver disease. Antifibrinolytic therapy is contraindicated when using factor IX preparations. It is too early to judge whether thromboembolism will be a feature of the purer IX preparations.

18. OTHER SIDE EFFECTS

Allergic reactions of all grades of severity may occur with any transfused product but are more common with plasma and cryoprecipitate. Antihistamines may be given prophylactically and adrenaline and steroids may be required for severe reactions. Volume overload limits use of plasma and administration of large quantities of product can result in haemolysis in patients who have blood type A or B. In this situation replacement red cells should be blood type O.

19. TOTAL CARE OF THE PERSON WITH HAEMOPHILIA

Optimal haemophilia management is based upon an interdisciplinary approach utilizing supervised self and home treatment. Comprehensive centralized care enables patients with a rare disorder to be treated by knowledgeable experts in an efficient way. With this approach most problems can be solved on an outpatient basis, the cost of haemophilia can be reduced and people with haemophilia integrated into society as functioning members.
The comprehensive care team usually includes a paediatrician or physician, haematologist, a nurse, an orthopaedic surgeon, a dentist, a physiotherapist (physical therapist), and a social worker. The nurse in association with the Centre Director handles many telephone enquiries, day-to-day problems, supervises home care patients and plays a major role in educating the patients, relatives and other staff about good haemophilia management.

Ideally, Haemophilia Centres should be located within a General Hospital to ensure facilities and specialist staff are available. Such Centres should also maintain a confidential Register of people with bleeding disorders for local and national use to identify those at risk, provide essential information on a 24 hour basis, and compile accurate statistical information for planning future therapeutic needs.

Patients should be seen at these Centres at regular intervals, depending on the overall clinical setting. For instance, patients with HIV infection should be seen at least every three months whereas mildly affected patients can be seen annually. Regular reviews include physical examination with musculoskeletal and joint motion assessment, review of therapeutic product usage and efficacy, dental examination and occupational and psychosocial assessment. Laboratory tests should include hepatitis serology and hepatic function. HIV antibody testing should be performed regularly in negative patients who have received blood products, and CD4 (T4) lymphocyte function should be monitored in those who are HIV positive.

Responsibilities and decisions for the management of each patient should be shared by members of the team in joint meetings and close liaison should be maintained with the primary care physician, for education as well as therapy. Preventive health should be encouraged, in particular regular dental care in order to prevent major "catch ups" for invasive dentistry with its added expense of hospital admission and therapeutic products.
Maintenance of physical fitness is very important in prevention of bleeding episodes and a fitness programme can be developed in association with a physiotherapist at the referral hospital. Regular involvement in sports should be encouraged. Swimming is especially recommended. Boxing and rugby football are contraindicated because of the danger of head and neck injury.

The use of home or self therapy and prophylaxis has altered the lifestyle of families with haemophilia in a positive way and early treatment has significantly reduced the number, severity and sequelae of joint and other haemorrhages. However, home therapy is not a substitute for comprehensive care. Continuing education, record review and regular medical follow-up are all required.

A well functioning supervised treatment service may reduce the work load of the Haemophilia Centre thus allowing personnel to concentrate on education, and on the most severely affected patients including those with transfusion acquired HIV infection whose care has been integrated into the comprehensive care system.

In areas where there is no established Centre it is important for one interested hospital physician to develop a long term commitment to the care of patients with bleeding disorders. In this way a team of people can build up expertise, regular reviews can be established, a register developed and records kept. In addition, consultation and advice will be available for physicians at peripheral hospitals thus improving the overall care for families with haemophilia in the region.

20. HAEMOPHILIA AND THE FAMILY

Haemophilia is a family affair. Mothers often feel responsible for their son's disorder because of their role in the genetic transmission of haemophilia. Unresolved guilt can lead to overprotection. Some fathers may have difficulty in accepting the diagnosis although others will take a major
responsibility in caring for their children. Negative spouse/parent/child interactions can leave the child with feelings of rejection and isolation. Health care professionals in haemophilia should recognize and address the psychosocial impact of this disorder and its complications on parents, siblings and extended family members. The focus of comprehensive haemophilia care has broadened to the entire family with the advent of hepatitis C and HIV infection, and the potential for development of acquired immune deficiency syndrome (AIDS) which presents the most challenging aspect of patient care in many Centres. Family evaluations and follow-up are essential early in the course of treatment when patients are diagnosed and on-going contact with the family must be maintained. Carrier detection and the possibility of intra-uterine diagnosis using DNA studies further underline the involvement of siblings and relatives of the patient with haemophilia. A social worker can play a major part in identifying stresses, providing psychosocial support and counselling (please also refer to "Haemophilia: Facts for Families").

21. CONCLUSION

Haemophilia is a congenital life-long disorder. The goals of therapy are to minimize disability and prolong life, to facilitate general social and physical well-being and to help each patient achieve his full potential. The cornerstone of haemophilia treatment is an adequate supply of safe effective therapeutic products which must be administered early in the course of haemorrhagic events.

Advances in therapeutic product technology and the introduction of a comprehensive care approach over the past 30 years have enabled these goals to be achieved in many areas. HIV infection continues to have a profound impact on the haemophilia community especially in developed countries, but the quest for viral free and purer blood products has resulted in much safer products. Molecular biology and recombinant DNA technology have provided synthetic factor concentrates, enabled accurate carrier detection and prenatal diagnosis, and made gene therapy a future possibility.
22. FURTHER INFORMATION

- "Guidelines for the Development of a National Programme for Haemophilia"
  WHO document 1996 (WHO/HGN/WFH/GL/96.1)

In addition, up-to-date information on haemophilia is available from:

- World Federation of Hemophilia
  1310 Greene Avenue
  Suite 500
  Montreal, Quebec
  Canada H3Z 2B2

  Tel: +1 514 933 7944
  Fax: +1 514 933 8916
  e-mail: wfh@wfh.org
  Internet Web Site: http://www.wfh.org
ANNEX

STORAGE OF DNA

The analysis of factor VIII and factor IX genes in patients with haemophilia A and B respectively is resulting in a greater understanding of the nature of these diseases, and in precise carrier detection and prenatal diagnosis within affected families.

In order to perform these studies, it is generally important that a sample of blood from which DNA can be extracted is obtained from the affected patient. Unfortunately because of the present position regarding HIV infection, situations have arisen when family studies to detect carriers and to enable prenatal diagnosis to be performed have been prevented because the affected family member has died and no blood sample from which DNA can be extracted is therefore available.

Blood for DNA extraction, and DNA itself, is extremely stable if stored under the right conditions and may be used for studies many years hence. The techniques of gene and DNA analysis are rapidly becoming simpler and DNA studies in haemophilia, particularly when performed to provide accurate carrier detection and prenatal diagnosis, will become more widespread. The World Federation of Hemophilia therefore recommends that samples of blood suitable for DNA extraction are obtained from all patients with haemophilia A and B and stored under suitable conditions (see below). This is, unfortunately, particularly important for those patients who are HIV antibody positive. WFH recommends the following procedure.

1. Counsel the patient and his family regarding the need for a sample. Explain that the sample will only be analyzed with the expressed permission of the patient and/or his family.
2. Collect up to 20 mls of citrated or heparinized blood.

3. Divide the whole anticoagulated blood into 2 or 3 aliquots and store at minus 20°C (in separate deep freezers if possible).

4. Keep and maintain a record of samples stored.

5. If possible extract DNA from one of the aliquots (using standard methods) and store at minus 20°C. Storage of samples as extracted DNA is not essential but may be performed in laboratories where extraction procedures are established.

It is expected that samples stored in this way will provide valuable material for family studies in years to come.

* * * * *