

EDUCATIONAL MATERIALS ON HAEMOPHILIA FOR HEALTH CARE PROFESSIONALS

Haemophilia is a sex-linked inherited bleeding disorder which occurs in all races and social groups.

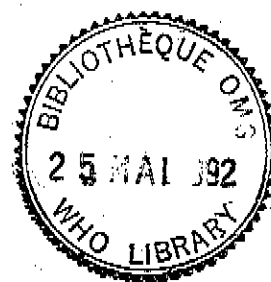
Haemophilia management requires adequate supplies of blood products and comprehensive medical care.

The problems of haemophilia can be reduced if information, scientific research and proper medical services are available.



WORLD HEALTH ORGANIZATION
HEREDITARY DISEASES PROGRAMME

1992



**EDUCATIONAL INFORMATION ABOUT HAEMOPHILIA
FOR HEALTH CARE PROFESSIONALS**

Prepared by

Members of the Medical Advisory Board, World Federation of Hemophilia,
in particular, E. Berry, G. Mariani, Y. Sultan, and reviewed by P. Jones

on behalf of the

Joint WHO/WFH Meeting on the
Possibilities for the Prevention and Control of Haemophilia
Geneva, 26-28 March 1990

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, 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 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.

NORMAL BLOOD COAGULATION

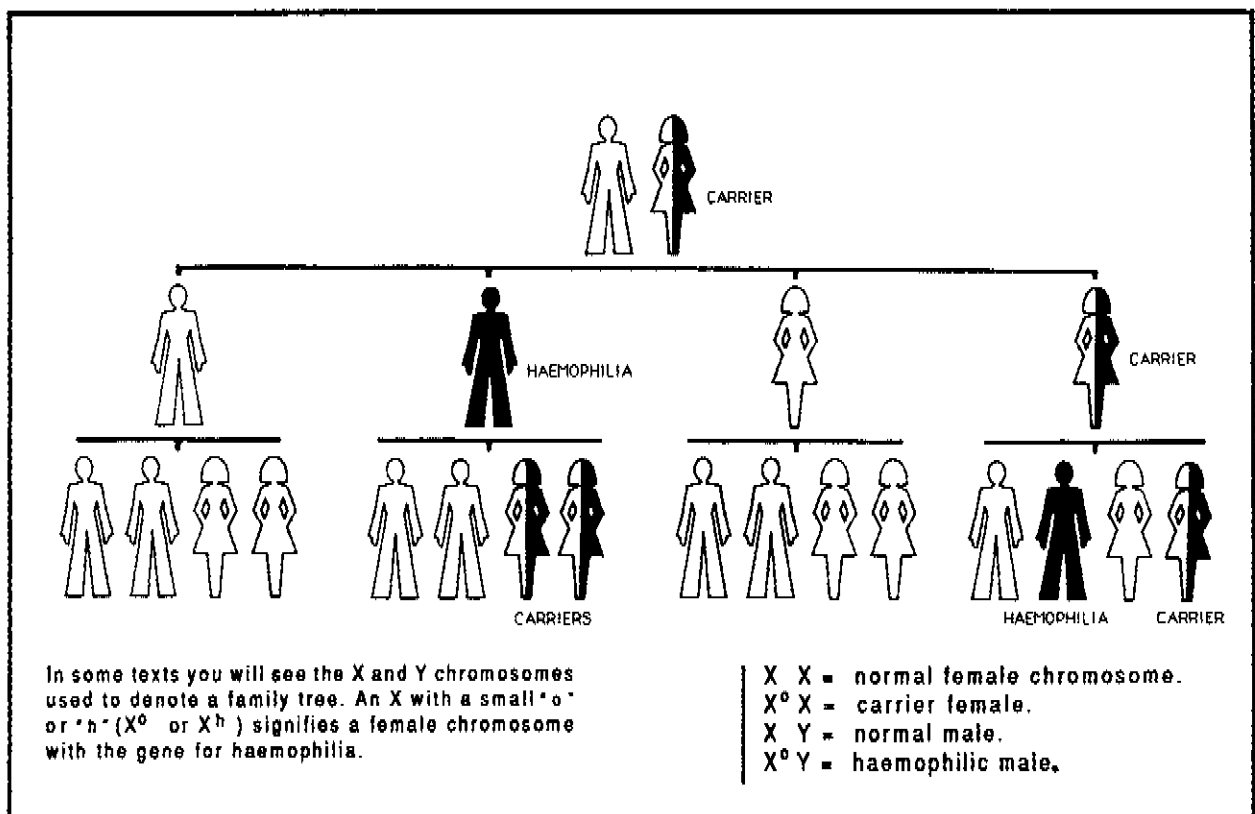
Within the coagulation system of proteins, clotting Factor VIII (FVIII) is a large protein which acts as a cofactor in the activation of Factor IX (FIX) and Factor X (FX) in the intrinsic pathway. Factor VIII circulates loosely bound to a larger protein, von Willebrand factor (vWF) which protects it 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 in vWF produce von Willebrand's 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.

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 haemophiliac passes his abnormal X gene 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 girl, a normal boy, 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 descendents of a haemophilic father and a carrier mother.

FIG. 1 FAMILY TREE



CARRIER IDENTIFICATION

There are approximately five potential carriers of haemophilia for every haemophiliac.

Carriers are classified as obligatory or possible from the family history.

Obligatory carriers are women, whose fathers have had 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 and may bleed with surgery or have other symptoms including menorrhagia. These women may be called symptomatic carriers.

The range of factor activity in the carrier population overlaps the normal range and thus detection of carriers by coagulation factor assay 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 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 step and most precise step in carrier detection is DNA analysis which is also the most important test in prenatal diagnosis. Although direct mutational analysis is highly desirable and a goal for the near future, such a programme is not yet achievable, at least for haemophilia A.

USE OF POLYMORPHISMS

The most commonly used strategy for DNA based carrier detection and prenatal diagnosis is to study the inheritance of DNA polymorphisms either within the FVIII or FIX gene (intragenic) or closely linked to them (extragenic). Such polymorphisms (either restriction fragment length polymorphisms RFLP or variable number tandem repeats VNTR) result in up to 95% of families being informative using intragenic polymorphisms where a degree of certainty of >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.

IDENTIFICATION OF SPECIFIC GENE DEFECTS

(e.g., a deletion, point mutation, insertion)

These are being identified with increasing frequency using recently described technology based on the polymerase chain reaction-PCR amplification of specific sequences of DNA to give adequate quantities for analysis. These techniques are at present 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.

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 haemophiliacs (and important family members) and to store these samples in case of future need.

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 about prenatal diagnosis and selective abortion. The earlier counselling is provided, the less the emotional impact concerning maternity and abortion should be. It is therefore advisable to do 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 or older.

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. Ideally, a skilled genetic counsellor who is knowledgeable about haemophilia should be available, but in many countries there are few or no such people and haemophilia centre staff carry out this task. It is also important not to neglect haemophiliacs themselves in discussing genetic aspects, to be sure that they are aware that all of their daughters will be carriers. Testing options during pregnancy include amniocentesis at 14 - 15 weeks to determine foetal sex, foetal blood sampling at 18 weeks to determine clotting factor levels, and chorionic villus sampling at 10 weeks or later for genetic analysis. 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 haemophiliacs are in families not known to be at risk and are presumably the result of a new mutation.

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 base line levels of FVIII or FIX and the same clinical severity.

The normal range of factor activity varies from 50-150% and patients with more than 30%, very rarely have any bleeding problems.

TABLE 1 CLASSIFICATION OF HAEMOPHILIA

% of factor VIII or IX	Degree of haemophilia	Characteristics
1% or less	Severe	Frequent spontaneous bleeds. Coagulation screening tests always abnormal.
2 - 5%	Moderate	Few spontaneous bleeds. Bleeding after minor trauma. Prolonged partial thromboplastin time.
6 - 30%*	Mild	Bleed only after trauma or surgery. Coagulation screen tests may be low normal.
30 - 50%*	Very mild	May or may not bleed abnormally after major trauma or surgery. Coagulation screen tests often normal.

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

Severe Haemophilia (less than 1%)

Prolonged or repeated bleeding may occur at one or more sites at a time and 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 (haemarthrosis), muscle and soft tissue (haematomata), other organs or the central nervous system (Tables 2 and 3).

TABLE 2 BLEEDING SITES

Type of Haemorrhage	Prevalence (%)
Haemarthrosis	70 - 80
Muscle and subcutaneous haematomas	10 - 20
Other major bleeds	5 - 10
CNS bleeds	<5

TABLE 3 JOINT INVOLVEMENT

Haemarthrosis	Prevalence (%)
Knee	45
Elbow	30
Ankle	15
Wrist	3
Shoulder	3
Hip	2
Other	2

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 possibility 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, associated with falls.

Recurrence of untreated or inadequately treated bleeding in specific 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, epistaxis, 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 minor and major trauma as well as any surgical intervention, dental extraction or intramuscular injections. Immunizations can be given subcutaneously taking special care, using a fine needle and applying local pressure for five minutes afterwards.

Moderate Haemophilia (2-5%)

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.

Mild Haemophilia (6 - 30%)

Many mild haemophiliacs 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.

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 screening tests for haemostasis; bleeding time, partial thromboplastin time (APTT), prothrombin ratio. 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).

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 airways 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., ileopsoas 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.

Treatment in most instances is by increasing the level of the deficient factor by transfusing products derived from blood donations. 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 decrease long term sequelae which include chronic synovitis, arthritis, pseudotumour (bone cyst) formation and contractures. **WHEN IN DOUBT, TREAT!**

THERAPY

For Haemophilia A fresh or fresh 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 - 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/interview and 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 should be avoided especially in children as water overload with hyponatremia may occur. Exhaustion of the stores may result in refractoriness after 3 - 5 doses, but the response returns after 1 - 2 days. 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 fresh frozen plasma but again volume limitations will often prevent the achievement of satisfactory levels.

For both haemophilia A and B methods have been developed for preparing concentrates of FVIII and FIX. FIX concentrates are often known as PCC for prothrombin complex concentrate as they contain other vitamin K dependent factors (FII, FVII, FX).

These freeze dried products are very easy to use because of the small volume on reconstitution, the known factor activity and stability at room temperatures. Concentrates are made from plasma pooled from thousands of donors using a variety of fractionation procedures. The goal is to produce a sterile product of high purity as it has been assumed that included extra protein may overload the immune system of the recipient. Newer products produced by immuno affinity chromatography contain FVIII concentrations up to 3500 units per gram protein, whereas for cryoprecipitate there is less than 1 unit FVIII per gram of protein. In addition, higher purity FIX products do not have the thrombogenic potential of PCC and can be more effectively viral inactivated.

Concentrates can and should be treated by virucidal methods (heat, solvent detergent, betapropionolactone plus Ultraviolet Irradiation) to attain a high degree of sterility. All methods inactivate HIV with pasteurization and solvent detergent treatment appearing to be most effective in eliminating hepatitis viruses. Purification and virucidal treatment result in higher cost of product because more starting plasma is required. Despite these measures no blood derived product has total safety guaranteed.

Some of the problems associated with human derived blood products should be eliminated with the development of high purity products from genetically engineered recombinant technology but for at least the next decade human derived factor treatment will be used for the majority of haemophiliacs worldwide.

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 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, 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.

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 percentage) in different clinical situations are given in Table 4.

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

TABLE 4 SUGGESTED HAEMOSTATIC LEVELS OF FVIII AND FIX IN DIFFERENT CLINICAL SITUATIONS AND DOSAGES OF FVIII OR IX CONCENTRATES

Clinical situation	Plasma concentration to be achieved % of pooled normal plasma			Dose needed for haemostasis IU/Kg Body Weight	
	FVIII	FIX	(PCC)	FVIII	FIX (PCC)
Haemarthrosis and minor haematomas	15-25	10-15		10-15	10-12
Severe haemarthrosis and haematomas	30-60	15-35		20-30	15-35
Surgery, life-threatening bleeds.	60-120	40-60		40-60	40-60

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

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 may vary from patient to patient and may vary according to the condition of the individual joint and severity of the haemorrhage. Lower doses may be effective if given early.

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 dosage of PCC such as is needed for surgery, the risk of thrombosis is increased. Smaller doses given several times daily may be safer. If higher purity FIX concentrates are used this issue is not critical, but these expensive products are not widely available.

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 10-15% 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 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 (FVIIa).

Prophylactic (maintenance) therapy 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 of chronic synovitis which

occurs mainly in 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 normal (50-150%) and maintained there for 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 (Cyclokapron). 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.

Adequate treatment allows even the severe haemophiliac to have a near normal life expectancy and to be able to play a reasonably full life in society.

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

COMPLICATIONS OF TREATMENT

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

Viruses

Liver disease is frequent and may be caused by hepatitis B virus, (HBV) hepatitis C virus, (HCV) delta 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 by screening out hepatitis B antigen positive blood donors and by immunization. Recently introduced anti HCV testing in some countries 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 have made concentrates much safer. Hepatitis B vaccination is strongly recommended for all haemophiliacs and their families.

Studies are currently in progress to see if the higher purity products have a less suppressive effect on the immune system than standard products.

Inhibitors (antibodies)

Specific inhibitor will develop in about 10% 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. Patients with inhibitors may not bleed more frequently than other haemophiliacs 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.

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.

Other

Allergic reactions of all grades of severity may occur with any transfused product but are more common with plasma and cryoprecipitate. Anti-histamines 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.

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 disease to be treated by knowledgeable experts in an efficient way. With this approach most problems can be solved on an Outpatient basis, the cost for haemophilia care can be reduced and haemophiliacs may be 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 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 to provide accurate statistical information for planning future blood product 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 mild haemophiliacs can be seen annually. Regular reviews include physical examination with musculoskeletal and joint motion assessment, review of blood product usage and efficacy, dental examination and occupational and psychosocial assessment. Laboratory tests should include hepatitis serology and hepatic function, HIV antibody should be done regularly in negative patients who have received blood products and 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 conservative and/or extractive dentistry with the added expenses of hospital admission and blood products.

Maintenance of physical fitness is very important in prevention of bleeding episodes and a fitness programme can be developed in association with a physical therapist at the referral hospital. Regular involvement in swimming, cycling and other non contact sports should be encouraged.

The use of home or self therapy has altered the life-style 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 the most severely affected patients such as 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 haemophiliacs in the region.

HIV INFECTION AND AIDS

The human immunodeficiency virus (HIV) was transmitted to many haemophiliacs 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 sero-conversions 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 may ultimately be used.

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 in proper metal containers and blood spillage are best HIV inactivated with household bleach and 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, 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. Product cover 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 lymphocyte levels is useful to determine when to start Zidovudine (AZT) therapy and prophylaxis for pneumocystis carinii pneumonia (PCP), if these are available. Clinicians should be alert to non-specific symptoms (e.g., fatigue, weight loss), direct effect on the nervous system (dementia, peripheral neuropathy), tumours (e.g., lymphomas, Kaposi's sarcoma and opportunistic infections [e.g., Herpes Zoster in young patients; oral, oesophageal and disseminated candidiasis; tuberculosis variants and other bacterial infections; PCP, central nervous system cryptococcosis or toxoplasmosis; cytomegalovirus infection, cryptosporidiosis of the bowel]). Treatment of these HIV associated problems should be carried out in consultation with other appropriate specialists, such as infectious disease physicians and patients should have access to the best available treatment of HIV infection itself including AZT and other new drugs that may become available 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 AZT, 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.

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 psycho/social 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 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 ongoing contact with the family must be maintained. Carrier detection and the possibility of intra-uterine diagnosis using DNA studies further underlines 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.

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 full potential. The cornerstone of haemophilia treatment is an adequate supply of safe effective blood products which must be administered early in the course of a haemorrhagic event.

Advances in blood product technology and introduction of a comprehensive care approach over the past 20 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.

FURTHER READING

Kasper, C.K., Graham, J.B., Kernoff, P.B.A., Larrieu, M.J., Rickard, K.A. and Mannucci, P.M. "Hemophilia - State of the Art of Hematologic Care". 1988. *Vox Sanguin* 56 (3):141-144. 1989.

Weatherall, D., Ledingham, J.G.G., Warrell, D.A., eds. *Oxford Textbook of Medicine*. Oxford Medical Publications. 2nd ed., 1987. "Haemostasis and Thrombosis" (Chapter 19), Davies, J.A., Tuddenham, E.G.D.

Bloom, A.L., Thomas, D.P., eds. *Haemostasis and Thrombosis*. 2nd ed., 1987. Churchill Livingstone, Edinburgh.

Colman, R.W., Hirsh, J., Marder, V.J., Salzman, E.W. eds. *Hemostasis and Thrombosis*. 2nd ed., 1987. J.B. Lippincott Co., Philadelphia.