GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA

WORLD FEDERATION OF HEMOPHILIA








WORLD FEDERATION OF
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FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
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World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel.: (514) 875-7944
Fax: (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

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INTRODUCTION

Although effective therapy has been available for hemophilia for at least 30 years, many issues remain unresolved regarding the management of this condition, particularly with reference to doses and duration of factor replacement therapy for different types of bleeding, immune tolerance induction, and surgical prophylaxis.

Many countries that are starting to establish care for hemophilia do not have standard protocols to ensure the proper management of hemophilia. As the World Federation of Hemophilia (WFH) has expanded its various programs to improve care for people with hemophilia worldwide, more and more requests have been made for standard guidelines that are appropriate for countries where economic resources are limited, to ensure a basic level of care.

As there were no guidelines for the management of hemophilia with a universal outlook, the WFH established a working group in 2003 to develop such guidelines. This group, consisting of Paul Giangrande, Man Chiu Poon, Mary Chua, Angus McCraw, Jerome Wiedel, and Alok Srivastava (Chair), has worked to put together this document with the exemplary editorial help of Elizabeth Myles at WFH headquarters.

In the absence of good evidence for current protocols in practice in the management of hemophilia, the information included here is mainly adapted from published consensus guidelines from different centres or countries, including Hemophilia of Georgia (USA), the Association of Hemophilia Clinic Directors of Canada, the National Hemophilia Foundation (USA), Italian Association of Hemophilia Centres, Hemophilia Federation, India, and the South African Hemophilia Foundation. Directors of the International Hemophilia Training Centres of the WFH as well as all the centres involved in the WFH Twinning Program were consulted. The current version of these guidelines incorporates the suggestions from many of these physicians, for which we are extremely grateful and welcome further comments. As and if new evidence is generated on different aspects of the management of hemophilia, these guidelines will be updated and revised as necessary.

The purpose of these guidelines is to provide protocols for treatment to centres that are beginning to establish care for people with hemophilia. They may also help standardize care at the more established ones. The WFH hopes that as well as helping those less familiar with the management of this condition, this publication will be a small step towards harmonizing care of people with hemophilia in the world until evidence-based practice is possible.

Alok Srivastava, MD
WFH Treatment Guidelines Working Group

SECTION 1

GENERAL MANAGEMENT OF HEMOPHILIA

What is Hemophilia?

- Hemophilia is an X-linked congenital bleeding disorder with a frequency of about one in 10,000 births.
- Hemophilia is caused by a deficiency of coagulation factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B) related to mutations of the clotting factor gene.
- The number of affected persons worldwide is estimated to be about 400,000.
- Hemophilia A is more common than hemophilia B, representing 80-85% of the total.
- The life expectancy of persons born with hemophilia, who have access to adequate treatment, should approach normal with currently available treatment.

Diagnosis of Hemophilia

Accurate diagnosis is important and essential for effective management. Hemophilia should be suspected in patients presenting with a history of:

- Easy bruising in early childhood;
- Spontaneous bleeding (particularly into the joints and soft tissue); and
- Excessive bleeding following trauma or surgery.

While the history of bleeding is usually lifelong, some severe hemophilic children may not have bleeding symptoms until after the age of one or later when they begin walking and exploring their world. Patients with mild hemophilia may not have excessive bleeding unless they experience trauma or surgery.

- A family history of bleeding is commonly obtained. Hemophilia generally affects males on the maternal side. However, both FVIII and FIX genes are prone to new mutations, and as many as 1/3 of all patients may not have a family history of these disorders.
- Screening tests will show a prolonged activated partial thromboplastin time (aPTT) in severe and moderate cases but may not show prolongation in mild hemophilia. A definitive diagnosis depends on factor assay to demonstrate deficiency of FVIII or FIX.
- The severity of bleeding manifestations in hemophilia is generally correlated with the clotting factor level as shown in the following table.

Severity	Clotting factor level % activity (IU/ml)	Bleeding episodes
Severe	1% (< 0.01)	Spontaneous bleeding, predominantly in joints and muscles
Moderate	1%-5% (0.01-0.05)	Occasional spontaneous bleeding. Severe bleeding with trauma, surgery
Mild	5%-40% (0.05-0.40)	Severe bleeding with major trauma or surgery

Bleeding Manifestations in Hemophilia

Sites of bleeding

Serious

- Joints (hemarthrosis)
- Muscle/soft tissue
- Mouth/gums/nose
- Hematuria

Life-threatening

- Central nervous system (CNS)
- Gastrointestinal (GI)
- Neck/throat
- Severe trauma

Incidence of different sites of bleeding

- Hemarthrosis: 70%-80%
- Muscle/soft tissue: 10%-20%
- Other major bleeds: 5%-10%
- Central nervous system (CNS) bleeds: < 5%

Incidence of bleeding into different joints

- Knee: 45%
- Elbow: 30%
- Ankle: 15%
- Shoulder: 3%
- Wrist: 3%
- Hip: 2%
- Other: 2%

Chronic Complications of Hemophilia

- Musculoskeletal complications:
  - Chronic hemophilic arthropathy;
    - Chronic synovitis;
    - Deforming arthropathy;
  - Contractures;
  - Pseudotumour formation (soft tissue and bone);
  - Fracture;
- Inhibitors against FVIII/FIX;
- Transfusion-related infections of concern in people with hemophilia:
  - Human immunodeficiency virus (HIV);
  - Hepatitis B virus (HBV);
  - Hepatitis C virus (HCV);
  - Hepatitis A virus (HAV);
  - Parvovirus B19;
  - Others.

Carriers

Being an X-linked disorder, the disease typically affects males, while females are carriers.

- Most carriers are asymptomatic.
- A few carriers may have clotting factor levels in the hemophilia range — mostly in the mild category — but in rare instances, carriers can be in the moderate or severe range due to extreme lyonization.
- Carriers with factor levels in the hemophilia range may have bleeding manifestations commensurate with their degree of clotting factor deficiency, particularly during trauma and surgery.
- Menorrhagia is a common manifestation among those with significantly low factor levels (< 30%). Birth control pills and antifibrinolytic agents are useful in controlling symptoms.
- These carriers should be categorized as having hemophilia of appropriate severity and managed accordingly.
- Immediate female relatives (mother, sisters, and daughters) of a person with hemophilia should have their factor level checked, especially prior to any invasive procedure or if any symptoms occur.

Comprehensive Care

Hemophilia is a relatively rare but complex disorder in terms of diagnosis and management. Optimal management of these patients, especially those with severe forms of the disease, requires more than the treatment and prevention of acute bleeding.

Keys to improvement of health and quality of life include:

- Prevention of bleeding;
- Long-term management of joint and muscle damage and other sequelae of bleeding;
- Management of complications from treatment including:
  - Inhibitor development; and
  - Viral infection(s) transmitted through blood products requiring long-term management.

These management goals are best met by a team of healthcare professionals providing comprehensive care.

Comprehensive care team

Hemophilia patients should ideally be managed in a comprehensive care centre staffed by the following core team members:

- Hematologist(s);
- Nurse coordinator;
- Physiotherapist; and
- Social worker.

These staff members should have expertise and experience in treating bleeding disorders. The core team members should have access to the following support resources:

- A coagulation laboratory capable of clotting factor assays and inhibitor detection;
- Appropriate clotting factor concentrates, either plasma derived or recombinant; and
- If clotting factor concentrates are not available, a blood bank with expertise in preparing fresh frozen plasma (FFP) and cryoprecipitate.

Specialists should be available as consultants, as needed, and should include, among others, the following:

- Orthopedic surgeon;
- Physiatrist/rheumatologist;
- Occupational therapist;
- Dentist;
- Geneticist;
- Hepatologist;
- Infectious disease specialist; and
- Immunologist.

In centres where there are many patients with chronic musculoskeletal problems from frequent bleeding, an orthopedic surgeon should be a core team member. Additional specialists could also be members of the core team, depending on the needs of the patient population served.

Functions of comprehensive care program

- To provide or coordinate care and services to patients and family:
  - Patients should be seen by all team members at least yearly (children every 6 months) and a comprehensive management plan should be communicated to the patient and all treaters.
  - Smaller centres and personal physicians can provide day-to-day care in coordination and consultation with the comprehensive care centre, particularly for patients who live a long distance from the nearest hemophilia treatment centre. Communication is important.
- To provide education to patients and family members (parents, spouse, children, and others), other healthcare workers, schools, and the workplace to ensure that the needs of the person with hemophilia are met.
- To conduct research to further our knowledge and improve the management of this condition. Because the number of patients in each centre may be limited, clinical research could best be conducted in collaboration with other hemophilia centres.
- Documentation of the treatment given and measurement of long-term outcome, particularly with reference to musculoskeletal function, is very important.

The family

Since hemophilia is a lifelong condition, requires expensive treatment, and can be life-threatening, it significantly affects many aspects of family life. It is, therefore, important that parents, spouses, and other family members are educated, supportive, and active participants in all aspects of the patient's care.

The comprehensive care team should have the resources to support family members of a person with hemophilia. This may include identifying resources and strategies to help cope with:

- Risks and problems of everyday living, particularly with management of bleeding;
- Changes during different stages of the patient's growth and development;
- Issues regarding schooling and employment; and
- Risk of another affected child and the options available.

This is accomplished through education and counselling, as well as identifying and using community resources. All family members are encouraged to become involved with the comprehensive care team in order to best meet the needs of the patient.

Management of Hemophilia

Principles of care

The general principles of care for hemophilia management include the following:

- Prevention of bleeding should be the goal.
- Acute bleeds should be treated early (within two hours, if possible).
- Home therapy should be used to manage only uncomplicated mild/moderate bleeding episodes.

- All severe bleeds should be managed in the clinic or hospital setting.
- Clotting factor concentrate replacement or DDAVP should be given to achieve appropriate factor levels prior to any invasive procedures.
- As much as possible, patients should avoid trauma by adjusting their lifestyle.
- Patients should be advised to avoid use of drugs that affect platelet function, particularly acetylsalicyclic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors. The use of paracetamol/acetaminophen is a safe alternative for analgesia.
- Intramuscular injections, difficult phlebotomy, and arterial punctures must be avoided.
- Regular exercise should be encouraged to promote strong muscles, protect joints, and improve fitness.
- Contact sports should be avoided, but swimming and cycling with appropriate gear should be encouraged.

Management of bleeding

- During an episode of acute bleeding an assessment should be performed to identify the site of bleeding and treatment should be given early.
- Patients usually recognize early signs of bleeding even before manifestation of physical signs – they often experience a tingling sensation or "aura". Treatment at this stage will stop bleeding early, resulting in less tissue damage and the use of less clotting factor concentrates.
- All patients should carry easily accessible identification indicating the diagnosis, severity, inhibitor status, type of product used, and contact information of the treating physician/clinic. This will facilitate management in an emergency and prevent unnecessary investigations before treatment.
- In severe bleeding episodes, especially in the head, neck, chest, and gastrointestinal and abdominal regions that are potentially life-threatening, treatment should be initiated immediately, even before assessment is completed.
- If bleeding does not resolve, despite adequate treatment, clotting factor level should be monitored and inhibitors should be checked if the level is unexpectedly low.
- Administration of desmopressin (DDAVP) can raise FVIII level sufficiently high (2-8 times baseline levels) in patients with mild to moderate hemophilia A.

Adjunctive management

The following treatment strategies are important, particularly where clotting factor concentrates are limited or not available, and may lessen the amount of treatment products required.

- RICE (rest, ice, compression, and elevation) is an important adjunctive management for bleeding in muscles and joints in addition to increasing factor level with clotting factor concentrates or desmopressin in mild hemophilia A. Bleeding muscles and joints can be kept at rest by splinting, casting, or using crutches or a wheelchair. Application of cold/ice packs is useful to decrease inflammation, but ice should be wrapped in a towel and not be applied directly to the skin. It is recommended that ice be applied for 20 minutes, every four to six hours, until swelling and pain decrease.
- Antifibrinolytic drugs (e.g., tranexamic acid, epsilon amino caproic acid) for 5-10 days is effective as adjunctive treatment for mucosal bleeds (e.g., epistaxis, mouth bleed) and is used to decrease the use of coagulation products in dental extractions. These

drugs should be avoided in renal bleeding as unlysed clots in the renal pelvis and ureter can behave like stones resulting in ureteric colic and obstructive nephropathy. Antifibrinolytic drugs should not be given concurrently with non-activated or activated prothrombin complex concentrates because of potential thrombotic complications. (See Section 4: Guidelines for the Selection of Clotting Factor Concentrates and Other Drugs)

- Certain COX-2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis.

Home therapy

Home therapy allows immediate access to treatment, and hence optimal early treatment. This is ideally achieved with clotting factor concentrates or other lyophilized products that are safe and can be stored in a domestic fridge and reconstituted easily. However, home therapy is possible (though may be difficult) even with cryoprecipitate, provided the patients have a simple but reliable storage freezer at home – but concentrates should not be frozen.

- Home treatment must be supervised closely by the comprehensive care centre and be started after adequate education and preparative teaching. A certification program can be instituted and the technique monitored at comprehensive visits.
- Teaching should include recognizing a bleed and its common complications, dosage calculation, preparation, storage, and administration of clotting factor, aseptic techniques, performing venipuncture (or access of central venous catheter), record keeping, as well as proper storage and disposal of needles and handling of blood spills.
- Encouragement, support, and supervision are key to successful home therapy and periodic reassessment of educational needs, techniques, and compliance must be performed. A periodic re-certification program can be instituted.
- Patients or parents should keep bleeding records that include date and site of bleeding, dosage and lot numbers of product used, as well as any adverse effects.
- Home care can be started on young children with adequate venous access and motivated family members who have undergone adequate training. Older children and teenagers can learn self-infusion with family support.
- An implanted venous access device (Port-A-Cath) can make injecting treatment much easier, however, they can be associated with local infection and thrombosis. Therefore, the risks and benefits should be weighed and discussed with the patient and/or parents.

Prophylaxis

Prophylaxis is the administration of clotting factors at regular intervals to prevent bleeding and must be the goal of all hemophilia care programs until a cure is available.

- The practice of primary prophylaxis was conceived from the observation that moderate hemophilia patients with clotting factor level > 1% seldom have spontaneous bleeding and have much better preservation of joint function. Prophylactic replacement of clotting factor has been shown to be useful even when factor levels are not maintained above 1% at all times.
- In patients with repeated bleeding, particularly into specific joints (target joints), short-term secondary prophylaxis for 4-8 weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis.

- Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury to prevent bleeding.
- Currently the most commonly suggested protocol for prophylaxis is the infusion of 25-40 IU/kg of clotting factor concentrates three times a week for those with hemophilia A and twice a week for those with hemophilia B. However, it should be recognized that many different protocols are followed for prophylaxis, even within the same country, and the optimal regimen remains to be defined. Different clotting factor replacement protocols for prophylaxis are currently being evaluated.
- Such a regimen in younger children often (but not always) requires the insertion of a venous access device that must be kept scrupulously clean to avoid infectious complications and be adequately flushed after each administration to prevent clots developing in the line. The risks and morbidity associated with such devices should be weighed against the advantages of starting prophylaxis early.
- Primary prophylaxis, as currently practiced, is an expensive treatment and can be accomplished only if significant resources are allocated to hemophilia care, as in developed countries, and for a few patients in developing countries who can afford it. However, prophylaxis has been shown to decrease joint bleeding with preservation of joint function and improve quality of life. Therefore, it is cost-effective in the long term because it eliminates the high cost associated with subsequent management of damaged joints. Cost-efficacy studies designed to identify minimum dosage are necessary to reduce the cost of care and allow access to prophylaxis in more of the world.

Surgery

The following issues are of prime importance when performing elective surgery on persons with hemophilia:

- Surgical procedures should be performed in co-ordination with a team experienced in the management of hemophilia.
- Procedures should take place in a centre with adequate laboratory support for reliable monitoring of clotting factor level.
- Pre-operative assessment should include inhibitor screening.
- Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.
- Availability of sufficient quantities of clotting factor concentrates should be ensured before undertaking major surgery for hemophilia.
- The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed (see Table 1, page 45).

Inhibitors

About 10%-15% of hemophilia A patients and 1%-3% of hemophilia B patients may develop persistent inhibitors rendering treatments with factor concentrates difficult. The following should be kept in mind:

- The majority of patients who develop inhibitors do so early – within the first 10-20 exposure days.
- Patients more likely to develop inhibitors are those with severe gene defects such as gene deletion or inversion, nonsense, and frameshift mutations.

- Inhibitors may be transient despite continual specific factor replacement, usually when the titre is low (< 5 BU).
- Patients whose inhibitor titres are ⩾ 5 BU (high responders) tend to have persistent inhibitors. If not treated for a long period, titre levels may fall but there will be a recurrent anamnestic response in 3-5 days when challenged again.
- For children, inhibitors should be screened once every 3-12 months or every 10-20 exposure days, whichever occurs first, and for adults as clinically indicated.
- Inhibitors should also be screened prior to surgery, and when clinical response to adequate treatment is sub-optimal.
- Very low titre inhibitors may not be detected by the Bethesda inhibitor assay, but by a poor recovery and/or shortened half-life (T-1/2) following clotting factor infusions.

Management of bleeding

- Management of bleeding in patients with inhibitors must be in consultation with a centre experienced in the management of such patients, and all serious bleeds should be managed in these centres.
- Choice of product should be based on titre of inhibitor, records of clinical response to product, and site and nature of bleed.
- Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralize the inhibitor with excess factor activity and stop bleeding.
- Patients with a history of a high responding inhibitor but with low titres may be treated similarly in an emergency, until an anamnestic response occurs, usually in 3-5 days, precluding further treatment with treatment products.
- With an inhibitor level ⩾ 5 BU, the likelihood is low that specific factor replacement will be effective in overwhelming the inhibitor without high dose continuous infusion therapy.
- Alternative agents for hemophilia inhibitor patients include bypassing agents, such as recombinant factor VIIa and prothrombin complex concentrates, including the activated ones such as FEIBA® and Autoplex®.

Allergic reactions in hemophilia B patients with inhibitors

Hemophilia B patients with inhibitors have special features, in that up to 50% of cases may have severe allergic reactions, including anaphylaxis to FIX administration. Thus, newly diagnosed hemophilia B patients, particularly those with a family history and/or with genetic defects predisposed to inhibitor development, should be treated in a clinic/hospital setting capable of treating severe allergic reactions during the initial 10-20 treatments with FIX concentrates. Reactions can occur later but may be less severe.

Immune tolerance induction

- In patients with hemophilia A and inhibitors, eradication of inhibitors is often possible by immune tolerance induction (ITI) therapy. Different dosing regimens have been used and the optimal regimen remains to be defined.
- Before ITI therapy, high responding patients should avoid FVIII products to allow inhibitor titres to fall and to avoid persistent anamnestic rise. Some patients may react to the inactive FVIII molecules in FEIBA® as well.
- There is no general agreement on the optimal dosage and frequency of dosage for ITI

and an international trial is ongoing to compare 50 IU/kg three times a week to 200 IU/kg daily.

- Experience with ITI for hemophilia B inhibitor patients is limited. The principles of treatment in these patients are similar to those mentioned above, but the success rate is much lower, especially in persons whose inhibitor is associated with an allergic diathesis. Furthermore, hemophilia B inhibitor patients with a history of severe allergic reactions to FIX may develop nephrotic syndrome during ITI, which is not always reversible upon cessation of ITI therapy.

Patients switching to new concentrates

For the vast majority of patients, switching products does not lead to the development of inhibitors. However, in rare instances inhibitors in previously treated patients have occurred with the introduction of new FVIII concentrates. In those patients, the inhibitor disappeared only after withdrawal of the offending product. Therefore, patients switching to a new factor concentrate should be monitored for inhibitor development.

Genetic Counselling/Prenatal Diagnosis

- Genetic counselling is an important part of hemophilia care to help people with hemophilia, carriers, and their families make more informed choices about having children where there is a possibility of having a child with hemophilia. It includes a wide range of tests for diagnostic and carrier detection, as well as individual counselling.
- Prenatal diagnosis is usually offered when termination of the pregnancy would be considered if an affected fetus was identified. However, it may also be done for helping the family to be prepared and for planning delivery. Assisted delivery is best avoided if the fetus has hemophilia.
- Chorionic villous sampling (CVS), or biopsy, is the main method of prenatal diagnosis and can be done at 10-11 weeks of gestation. It should not be carried out before this, as earlier biopsy may be associated with fetal limb abnormalities.
- Amniocentesis can be done at 12-15 of weeks of gestation.
- All invasive methods used for prenatal diagnosis may cause feto-maternal hemorrhage, and anti-D immunoglobulin should be given if the mother is Rh D negative.
- Because these procedures are carried out early in a pregnancy before the factor VIII level has risen significantly, hemostatic support may be required to prevent maternal bleeding, if the maternal levels are below 50%.

Delivery of Infants with Known or Suspected Hemophilia

- The delivery of infants with known or suspected hemophilia should be atraumatic to decrease the risk of bleeding. Avoid using forceps or vacuum extraction in vaginal delivery, and invasive procedures to the fetus, such as fetal scalp blood sampling and internal fetal scalp electrodes.
- In carriers with significantly low factor levels (< 50%), clotting factor replacement is necessary for surgical or invasive procedures, including delivery, even though FVIII levels usually rise into the normal range during the second and third trimesters. The need for clotting factor replacement should be planned in the prenatal period.

Vaccination

Persons with bleeding disorders should be vaccinated, but should receive the vaccine subcutaneously, not intramuscularly. The following points should be considered:

- Live virus vaccines (such as oral polio vaccine, MMR) should be avoided in those with HIV infection.
- People with hemophilia who have HIV should be given pneumococcal and annual influenza vaccines.
- Immunization to hepatitis B and A is important for all persons with hemophilia and can be given by subcutaneous rather than intramuscular injections.
- Family members handling treatment products should also be vaccinated; however, this is less critical for those using viral-inactivated products.

Psychosocial Issues

A person with hemophilia and his family need psychological and social support in coping with an illness that is chronic, often painful, and sometimes life-threatening. It is a financial burden and places restrictions on several aspects of normal living.

The following are guidelines for helping persons with hemophilia and their families to deal with the psychosocial aspects of this illness.

- When delivering the news about the diagnosis, prepare the patient for bad news, discuss it with them in simple terms, and allow them to express their feelings about the news. What they need is reassurance that help as well as treatment is available.
- When there are setbacks, acknowledge them, and assist the patient to work through his emotions. Provide care and support patiently.
- When a patient has to undergo a procedure of any kind, explain the procedure carefully and in terms he can understand. Be open about the amount of pain involved and possible complications. Answer questions that the patient may have.
- Coping with a chronic illness can result in burnout. Be aware of the signs and assist the patient in working through this period in his life. Provide suggestions and support for coping mechanisms.
- In the case of children, talk to them, not just their parents. Many children can understand a good deal about their illness and can work with the physician if properly informed and educated.
- Do not neglect the siblings that are healthy.
- The social worker should provide support for the patient and the family. Where social workers are unavailable, enlist the assistance of local groups and organizations to provide much-needed support.
- The physician should serve as a resource person for these important support networks.

Daily living

- Persons with hemophilia can perform usual tasks and, therefore, should be encouraged to engage in productive and leisure activities at home, in the workplace, and in recreation areas.

- Persons with hemophilia must be reassured that they have the care and moral support of others so they do not become isolated and experience depression.

The following are basic guidelines for the various persons/groups concerned.

For the person with hemophilia

The person with hemophilia should be encouraged to:

- Accept himself as a person with hemophilia who can successfully function in society despite this chronic condition.
- Accept his own strengths and limitations and not blame himself or others for having hemophilia.
- Think and act positively. Continue with his usual tasks, choosing activities that have lower risk of injury.
- Feel confident sharing with a family member or a friend his feelings and experiences of his health condition.
- Always have contact numbers or addresses of people, clinics, and health centres that can provide immediate information and necessary medical attention when needed.

For the family

- The patient and all family members must recognize and acknowledge the presence of hemophilia within the family.
- Every member of the family must be provided with at least basic information on the physical, psychological, and economic dimensions of hemophilia.
- Family members with no hemophilia must be available to provide emotional, physical, and spiritual support, if needed, to the member with hemophilia.
- Family members must become aware of emotional or attitudinal changes of the person with hemophilia as this may indicate stress that may be related to bleeding occurrences, physical pain, or emotional difficulty that may need immediate intervention.
- Family members, as caregivers, must try to be calm when bleeding, pain, and other hemophilia signs and symptoms occur in the patient in order to demonstrate that this condition can be calmly managed at home or anywhere.
- When the need for medical attention or hospitalization is necessary, family members must be able to recognize this need and be available to assist immediately and in whatever way possible to avoid further complication.
- The person with hemophilia should always be encouraged to socialize with other members of the family and within the community.
- Indoor as well as outdoor activities with lesser risks of injury or harm to the person with hemophilia must be encouraged.
- A young, active child with hemophilia commonly has numerous bruises. Parents may be *wrongfully* accused of child abuse.

For the community

- Basic information and education should be given to the community where there is an identified member with hemophilia, provided the patient/family consents. By doing so community members will be more willing and available to respond to the

person with hemophilia's needs. Community members must be fully informed that hemophilia is not a communicable disease and, therefore, a person with hemophilia should be encouraged to participate in any community activity.

Dental Care

For persons with hemophilia, good oral hygiene is essential to prevent gingival and periodontal disease.

- Teeth should be brushed *at least* twice daily for plaque control.
- Toothpaste containing fluoride should be used.
- Mouthwashes of triclosan or chlorhexidine can also help reduce plaque.
- Dental floss or interdental brushes help reduce plaque.
- People with bleeding disorders need close cooperation between their physician and their dental practitioner to receive safe, comprehensive dental care.

Guidelines for regular dental treatment of persons with bleeding disorders are as follows:

- Dental appointments for children with bleeding disorders, as well as education in preventive dentistry of children and caregivers, should be started when the baby teeth begin to erupt.
- Deep injections, surgical procedures – particularly those involving bone (extractions, dental implants) – or regional local anesthetic blocks should be performed only after clotting factor level has been appropriately increased.
- Oral infections should be treated with antibiotics before any surgical procedure is performed.
- Comprehensive dental assessment is needed at the age of about 12 or 13, to plan for the future and to decide how best to forestall difficulties resulting from overcrowding or misplaced third molars or other teeth.
- For people with mild or moderate hemophilia, non-surgical dental treatment can be carried out under antifibrinolytic cover (tranexamic acid or epsilon aminocaproic acid), but a hematologist must be consulted before other procedures are done.
- For people with mild hemophilia A (FVIII > 5%), scaling and some minor surgery may be possible under desmopressin (DDAVP) cover. (See Section 4, Guidelines for the Selection of Clotting Factor Concentrates and Other Drugs)
- For those with severe hemophilia, factor replacement is necessary before surgery or regional block injections or scaling. (See Section 5, Treatment of Bleeding in Hemophilia for details)
- Local use of fibrin glue and swish-and-swallow rinses of tranexamic acid before and after dental extractions are safe and cost-effective methods to help control bleeding.
- Tranexamic acid used topically significantly reduces bleeding. Ten ml of a 5% solution used as a mouth rinse for two minutes, four times daily for seven days is recommended. It may be used in combination with oral tranexamic acid tablets for up to five days. (See Section 4, Guidelines for the Selection of Clotting Factor Concentrates and Other Drugs)
- Bleeding can be aggravated by painkillers (analgesics) such as ASA or other NSAIDs such as indomethacin. Paracetamol/acetaminophen and codeine are safe alternative analgesics.

- After tooth extraction, a diet of cold liquid and minced solids should be taken for 5-10 days. Smoking should be avoided.
- Any swelling, difficulty swallowing (dysphagia), or hoarseness must always be reported to the dentist/hematologist immediately.
- Presence of blood-borne infections in the person with hemophilia should not influence access to dental care.
- Antibiotic prophylaxis should be administered to patients with prosthetic joint replacements.
- All precautions, as for any surgical procedure, should be taken.

People with hemophilia or congenital bleeding tendencies are a priority group for dental and oral health care, since bleeding after dental treatment may cause severe or even fatal complications. Maintenance of a healthy mouth and prevention of dental problems is of great importance, not only to quality of life and nutrition but also to avoid the dangers of surgery.

Monitoring Outcome of Treatment

Patients should be evaluated once every 6-12 months for the following:

- Musculoskeletal status: measure clinical scores annually, and radiological scores, as indicated;
- Use of clotting factor concentrates;
- Inhibitor development: perform screening tests for inhibitors as mentioned above;
- Transfusion-related infections (if appropriate): evaluate for HIV, HCV, and HBV infections commonly, and other infections if indicated; and
- Quality of life.

Sports and Hemophilia

- Sports activities should be encouraged to promote muscle strengthening and increased self-esteem. The choice of sports should reflect an individual's preference, ability, physical condition, local customs, and resources.
- Low impact activities such as swimming and golf should be encouraged. High contact sports such as football, rugby, boxing, and wrestling are not advised. The patient should consult with a physician before engaging in sports activities to discuss appropriateness, protective gear, and prophylaxis prior to the activity.
- Organized sports programs should be encouraged as opposed to unstructured activities, where protective equipment and supervision may be lacking.

SECTION 2

LABORATORY DIAGNOSIS

Introduction

Different bleeding disorders may have very similar clinical symptoms. In order to ensure that a patient gets the appropriate treatment, a correct diagnosis is essential. This section provides general guidelines for the diagnosis of hemophilia. For detailed information on technical aspects and specific instructions on screening tests and factor assays, please consult the WFH laboratory manual, *Diagnosis of Hemophilia and Other Bleeding Disorders*.

Accurate diagnosis can only be made with the support of a comprehensive and accurate laboratory service. It is dependent on the laboratory following strict protocols and procedures, which require:

- Knowledge and expertise in coagulation laboratory testing;
- Use of the correct equipment and reagents; and
- Quality assurance.

Knowledge and Expertise in Coagulation Laboratory Testing

Principles of diagnosis

- Understanding the clinical features of hemophilia and the appropriateness of the clinical diagnosis.
- Using screening tests to identify the potential cause of bleeding, for example, platelet count, bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (APTT).
- Confirmation of diagnosis by factor assay.

Technical aspects

Preparation of the patient prior to taking a blood sample

- Patients should be told to fast before blood tests. Fasting allows the blood to clear excess lipids, which may affect measurement of proteins in automated analysers.
- Patients should be told to avoid medications that can affect test results — such as ASA, which can severely affect platelet function and prolong the bleeding time.

Collecting the sample

- The sample should preferably be collected near the laboratory to ensure quick transport

to the lab. In case of a delay in transportation (> 1 hour), the sample should be transported on ice – in such cases, the sample should be drawn only after the patient has rested for 15-30 minutes.

- Venipuncture must be clean and the sample collected within one minute of tourniquet application without much venous stasis.
- Blood should be withdrawn into a plastic syringe with a butterfly short needle (19-21 standard wire gauge [SWG] for adults and 22-23 SWG for small children).
- Blood from an indwelling catheter should be avoided for coagulation tests. Frothing of the blood sample should also be avoided. It is often useful to discard the first 2 ml of blood collected.
- The sample should be collected in citrate tubes (3.2% aqueous trisodium citrate dihydrate or 3.8% aqueous trisodium citrate pentahydrate are suitable anticoagulants) maintaining the proportions of blood to citrate as 9:1.
- Prompt and adequate mixing with citrate solution should be done by gentle inversion.
- The sample should be processed immediately. If there is delay in doing the tests, the platelet-poor plasma (PPP) (see below) should be prepared and stored at 4°C where it can remain for two hours before performing the assay. If the tests are to be done much later, the plasma should immediately be frozen at -30°C where it can be stored for a few weeks, or up to six months if stored at -70°C.

Preparation of platelet-poor plasma (PPP)

- This is prepared by centrifugation of a sample at 2,000 g (3,500 rpm in ordinary standard bench centrifuge) for 15 minutes (at 4°C if possible).
- PPP may be kept at room temperature (20°-25°C) for PT and factor VII assay, but for all other tests it is better kept at 4°C.
- Testing should preferably be done within two hours of collection; otherwise PPP should be frozen at -30°C to -70°C as explained above.

End-point detection

Many laboratories now have some form of semi- or fully automated coagulation analysers. However, for those using a manual technique, detecting the clotting end point accurately requires considerable expertise, particularly if the clotting time is prolonged and the clot is thin and wispy.

- It is important to adopt a uniform convention to be followed in the laboratory for consistency to detect the end point of the clotting.
- The tube should be dipped in and out of the water bath at an angle to observe the clot so that the temperature at which clotting proceeds remains constant (37°C).

Screening tests

- The following tests may be used to screen a patient suspected to have a bleeding disorder: platelet count, BT, PT, and APTT.
- Based on these tests, the category of bleeding disorder may be identified (See table below).
- These screening tests may not detect abnormalities in patients with mild bleeding disorders and in those with factor XIII (FXIII) deficiency or those with low fibrinolytic inhibitor activity (alpha 2 antiplasmin, PAI-1).

Possible condition	PT	APTT	BT	Platelet count
Normal	Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Prolonged	Normal	Normal
VWD	Normal	Normal or prolonged	Normal or prolonged	Normal or reduced
Platelet defect	Normal	Normal	Normal or prolonged	Normal or reduced

Correction (mixing) studies

- Correction or mixing studies using normal pooled plasma (NPP) will help to define whether prolonged coagulation times are due to factor deficiency or circulating anticoagulants of inhibitors. (For details of testing for inhibitors, see the WFH Laboratory Manual.)
- Correction studies with FVIII/IX-deficient plasma may be used to identify the particular deficiency if a factor assay is not possible.

Factor assay

Factor assay is required in the following situations:

- **To determine diagnosis** (For technical details, see WFH Laboratory Manual.)
- **To monitor treatment**
  - The laboratory monitoring of clotting factor concentrates is possible by performing pre- and post-infusion clotting factor levels.
  - The actual amount of infused clotting factor given to the patient should predict the rise in blood levels. This approach is especially important when surgical procedures are to be performed. It is also useful for documenting dose-response relationship.
  - Lower than expected recovery may be an early indicator of the presence of inhibitors.
- **To test the quality of cryoprecipitate**
  - It is useful to check the FVIII concentration present in cryoprecipitate as part of

the quality control of this product. The American Association of Blood Banks guidelines currently recommend a factor VIII content of 80 units per bag.

- **To detect carriers**
  - The phenotypic or genetic analysis of carriers of hemophilia requires an expertise that may not be available in many laboratories.
  - In the case of phenotypic analyses, a ratio of the factor VIII:C (FVIII:C) to von Willebrand factor antigen (VIII:C/VWF:Ag) is normally 1.0. A result of less than 0.7 gives an 80% chance of a female being a carrier. These tests should be repeated before a diagnosis is confirmed. (For more details, see the WFH Laboratory Manual.)
  - Because some obligate carriers may have a normal FVIII:C/VWF:Ag ratio, it may not be possible to detect carriers of hemophilia phenotypically in all cases. Genotypic testing is, therefore, a more precise method of carrier detection based on linkage analysis or direct identification of the mutation.

Trained personnel

Even the simplest coagulation screening tests are complex by nature. A technologist with an interest in coagulation requires an in-depth understanding of the tests in order to achieve accurate results. It is beneficial to have a technologist who has had further training in a specialist centre.

- The WFH offers fellowships for more specialized laboratory training usually at an international hemophilia training centre.
- A training-the-trainers course has been devised by the WFH so that trained technologists can train others who then return to their countries and continue the process.
- Lab workshops are a key part of WFH activities. The aim of these workshops is to demonstrate and teach practical coagulation skills, conveying the message that good results can be obtained using basic equipment and technology provided that "good laboratory practice" is observed. These skills can then be adapted to more automated technology.

Use of the Correct Equipment and Reagents

Equipment and reagents are the tools of the trade of any laboratory. The following requirements are requisite for accurate laboratory testing.

Equipment

- A water bath – this should be placed in a well-lit area. The temperature of the bath should be 37°C ± 0.5°C.
- A good light source should be provided near the water bath to accurately observe the clot formation.
- Stopwatches are needed for timing.
- Automated pipettes (either fixed or variable volume) capable of delivering 0.1 ml and 0.2 ml accurately are required.
- Clean soda glass test tubes (7.5 cm x 1.2 cm) should be used for clotting tests and reuse is not recommended.

- Similarly, reutilization of plastic or glassware consumables should be avoided whenever possible, unless strict washing guidelines are followed. *Plasticware used in coagulation analysers should not be reused*.
- A number of semi-automated and fully automated coagulometers are now available. This equipment has the following advantages:
  - Accuracy of end-point reading.
  - Ability to perform multiple clot-based assays.
  - Reduction of observation errors. The end point of the reaction is measured electromechanically or photoelectrically.
  - The reactions are carried out in polystyrene (clear) cuvettes instead of glass tubes.

All equipment requires maintenance to be kept in good working order.

- When equipment is purchased, consideration should be given to and resources put aside for regular maintenance by a product specialist.
- Pipettes should be checked for accurate sample delivery.
- Water baths, refrigerators, and freezers should have regular temperature checks.

Reagents

- It is good practice to ensure continuity of supply of a chosen reagent, with attention paid to continuity of batches and long shelf life. This can be achieved by asking the supplier to batch hold for the laboratory, if possible.
- Changing to a different source of material is not recommended unless there are supply problems or because of questionable quality with results. Different brands may have completely different sensitivities and should not be run side by side.
- Instructions supplied with the reagent should be followed. A reference centre should be contacted when in doubt.
- Particular attention should be paid to reagent stability. Once a reagent is reconstituted or thawed for daily use, its quality will deteriorate rapidly, especially at high temperatures.
- Once an appropriate test and reagents have been decided upon, normal ranges ideally should be defined.

Quality Assurance

- Quality assurance (QA) is an overall term used to describe all measures taken to ensure the reliability of laboratory testing and reporting.
- QA covers all aspects of the diagnosis process from sample-taking, separation and analysis, and internal quality control (IQC) through to reporting of the result and ensuring that it reaches the clinician.
- IQC is used to establish whether a series of techniques and procedures is being performed consistently over a period of time. Normal and abnormal plasma samples should be included for this.
- It is the responsibility of everyone involved to make sure that the procedures are followed in the correct manner.
- Participation in an external quality assessment scheme is an essential part of QA.

External quality assessment scheme (EQAS)

It is strongly advised that laboratories participate in an external quality assessment scheme (EQAS). Essentially this is a scheme that audits the effectiveness of the internal QA systems in place in a laboratory and gives a measure of the laboratory's competence.

- EQAS helps to identify the degree of agreement between the laboratory results and those obtained by other laboratories.
- Participation in such a scheme helps build the confidence between a laboratory and its users.
- The WFH/World Health Organization (WHO) EQAS is specifically designed to meet the needs of hemophilia treatment centres worldwide. The scheme includes analyses relevant to the diagnosis and management of bleeding. Details of this scheme, which is operated from the U.K. National Quality Assessment Scheme in Sheffield, can be obtained from the WFH.
- Other national and international quality assessment schemes are also available.

In order for a laboratory to attain a high level of testing reliability and to participate successfully in EQAS, it must have access to international reference materials and standards and must ensure adequate and ongoing training of its staff.

Reference materials and standards

Reference materials and standards are essential for standardization of tests and assay procedures being used in the laboratory. They provide an easy reference without which accurate results cannot be guaranteed.

- Normal pooled plasma traceable to a WHO international reference material can be used. See below for a method of how to produce a normal pool.
- It is important to be consistent and to use a plasma standard when assaying plasma samples and a concentrate standard when assaying concentrates.
- Standards and reference plasmas are commercially available and can be used to calibrate local reference plasmas, as they are traceable to WHO international standards.
- WHO international standards are available directly from the National Institute for Biological Standards and Control (NIBSC), which is based in the United Kingdom.

Preparation of normal pooled plasma (NPP)

- At least 20 blood samples (10-20 ml each) from healthy subjects should be collected in citrate and spun immediately at 2,000 g for 15 minutes (at 4°C if possible).
- The plasma from all of these samples should be pooled together and 500 ul aliquots of these should be frozen immediately at -70°C. Sufficient care should be taken not to produce froth during mixing.
- During each assay, an aliquot may be removed, thawed at 37°C after which it is gently mixed and kept immediately in ice. Once thawed, it should not be frozen and reused.
- Vigorous shaking of the plasma samples should be avoided.

SECTION 3

MUSCULOSKELETAL COMPLICATIONS OF HEMOPHILIA

Introduction

The most common sites of bleeding in a person with hemophilia are the joints and muscles of the extremities. Depending on the severity of the disease, based on factor levels, the bleeding episodes are frequent and spontaneous in severe hemophilia (< 1%) or occur mostly after minor trauma in moderate hemophilia (1–5%). In the person with mild hemophilia (5–40%) bleeding usually occurs only with major trauma or surgery.

Common orthopedic complications of hemophilia are described below.

Acute Hemarthrosis

- In the child with severe hemophilia, the first spontaneous hemarthrosis typically occurs before two years of age, but may occur later.
- If inadequately treated, repeated bleeding will lead to progressive deterioration of the joint and muscles.
- This will lead to severe loss of function due to joint deformity, loss of motion, muscle atrophy, and contractures within the first one to two decades of life.
- The origin of the bleeding is the synovium. This is a very delicate and highly vascular tissue that lines and lubricates the joint space.
- Very early bleeding in joints may be recognized by the person experiencing it as a tingling sensation and tightness within the joint. This "aura" precedes the actual occurrence of the clinical features of acute hemarthrosis – pain, swelling, and limitation of motion.
- Once blood fills the joint cavity, the joint will appear swollen and feel warm and tender. This will cause the joint to seek the most comfortable position, which is flexion. Any attempt to change this position causes more pain, thus limiting motion. Secondary muscle spasm follows as the patient tries to prevent any motion.
- The goal of treatment of acute hemarthrosis is to stop the bleeding as soon as possible. Ideally, this should occur when the person recognizes the "aura".
- The most important initial step in the management of the acute hemarthrosis is factor replacement as soon as possible at a level sufficiently high to stop the bleeding. (See Table 1, page 45)
- The most effective method of providing immediate factor replacement is to have a home therapy program in place that allows the informed patient with hemophilia (or his family members) to give the factor at the appropriate time. *Joint bleeding that does not respond within 12-24 hours should be evaluated by a healthcare provider.*

- Other measures to help control the bleeding and provide pain relief are as follows:
  - Rest in the position of comfort.
  - Immobilization (partial and temporary) with splints, pillows, slings, and crutches depending on the joint affected.
  - Ice packs can be applied immediately and continued for at least the first 12 hours. Ice should not be in direct contact with the skin.
  - Elevation of the affected joint.
  - Tolerable pressure bandage can be used.
  - Use of narcotics as analgesics should be carefully monitored, but preferably avoided because of the chronic nature of the bleeding episodes and the risks of addiction.
  - Non-steroidal anti-inflammatory drugs (NSAIDS) and medications containing ASA are contraindicated during the acute bleeding episode. However, certain COX-2 inhibitor NSAIDs may be used judiciously.
- Physiotherapy must be stressed as an active part of the management of acute joint bleeding episodes.
  - As soon as the pain and swelling begin to subside, the patient should attempt to change the position of the affected joint from a position of comfort to a position of function.
  - This means gradually decreasing the flexion of the joint and striving for complete extension.
  - This should include gentle, passive stretching and, more importantly, active muscle contractions to gain extension.
  - The sooner the joint is in a position of function, the sooner active muscle control is instituted and this will in turn prevent muscle atrophy and loss of joint motion.

Aspiration

With an acute hemarthrosis, aspiration (removal of the blood from a joint) may be considered under certain circumstances. Once there is a large accumulation of blood in a joint, the early removal of the blood should result in a rapid relief of pain and theoretically reduce the damaging effects of the blood on the articular cartilage. Joint aspiration is usually not practical, however, because ideally it should be done very early following a bleeding episode (< 12 hours) and must be done in a medical facility by a physician.

- Situations when joint aspiration may be considered include:
  - A hemarthrosis that has not responded to factor replacement within 48–72 hours;
  - Pain and swelling out of proportion with bleeding alone, in which circumstances a septic joint must be ruled out.
- No aspiration should be done when there is overlying skin infection.
- The presence of inhibitors should also be considered as a reason for persistent bleeding in the face of adequate factor replacement and must be ruled out before aspiration is attempted.
- When aspiration is performed, it should be done under factor levels of at least 30–50% for 48–72 hours. *Joint aspiration should not be done in circumstances where such factor replacement is not available.*
- A large bore needle, at least 16-gauge, should be used.
- The joint should be completely immobilized for one hour after the aspiration.

Muscle Hematomas

The sites of soft tissue and muscle bleeding that need immediate management are those affecting the flexor muscle groups in the arms and legs. The most critical sites of bleeding are those that have a risk of compromising the neurovascular function. These include:

- The iliopsoas muscle which may cause femoral nerve palsy;
- The gastrocnemius muscle which causes posterior tibial nerve injury and muscle contracture leading to an equinus deformity; and
- The flexor group of forearm muscles causing a Volkmann's ischemic contracture.

Management of these bleeds include the following:

- These muscle bleeds require thorough clinical evaluation and monitoring.
- Factor replacement should be initiated immediately.
- Severe bleeds in these critical sites may require higher levels of factor replacement and for longer duration. (see Table 1, page 45)
- Other measures as discussed above for the acute joint bleed, such as elevation of the affected limb and physiotherapy, should also be included in the management of the acute muscle bleed.

Chronic Hemarthrosis

Once a joint develops recurrent bleeding episodes (target joint), chronic changes occur. These changes affect all of the tissues within and surrounding the joint: synovium and cartilage, capsule and ligaments, bone and muscles.

- Chronic synovitis is usually seen in the first and second decades of life.
- The management of chronic hemophilic arthropathy depends on the stage at which it is seen.

Chronic synovitis

With repeated bleeding in a joint, the synovium becomes chronically inflamed and eventually hypertrophies, causing the joint to appear grossly swollen. This swelling is usually not tense, nor is it particularly painful. Muscle atrophy is often present while a relatively good range of motion of the joint is preserved.

Diagnosis made by performing a detailed physical examination of the joint. The presence of synovial hypertrophy may be confirmed by ultrasonography and MRI. Plain radiographs and particularly MRI will assist in defining the extent of articular changes. The goal of treatment is to control the synovitis and maintain good joint function. Options include:

- Daily exercise to improve muscle strength and maintain joint motion is of prime importance. Factor concentrate replacement ideally should be given with the frequency and dose levels sufficient to prevent recurrent bleeding.
- If concentrates are available in sufficient doses, short treatment courses (6-8 weeks) of secondary prophylaxis with intensive physiotherapy is beneficial.
- NSAIDs (COX-2 inhibitors).
- Intra-articular injection of a long-acting steroid.

Synovectomy

Synovectomy should be considered if a chronic synovitis persists with frequent recurrent bleeding not controlled by other means. Options for synovectomy include chemical or radioisotopic synoviorthesis and arthroscopic or open surgical synovectomy.

- Surgical synovectomy, whether open or arthroscopic, requires enormous resources from an experienced team, a dedicated hemophilia treatment centre, and a large supply of clotting factor. Surgical synovectomy is seldom necessary today and is only considered when other less invasive and equally effective procedures fail.
- Non-surgical synovectomy should be the procedure of choice for treating chronic hemophilic synovitis. Clearly, radioisotopic synovectomy using a pure beta emitter (phosphorus-32 or yttrium-90) is the most effective and least invasive. It has the fewest side effects and is done in a simple out-patient setting. It also requires minimal if any follow-up physiotherapy. Only a single dose of clotting factor is required with the single dose of isotope.
- If a radioisotope is not available then chemical synovectomy is an appropriate alternative. Either rifampicin or oxytetracycline chlorhydrate can be used. Chemical synovectomy requires weekly injections until the synovitis is controlled. These painful injections require medication, and a dose of clotting factor is required for each injection. The low cost of the chemical agent is offset by the need for multiple injections.

Chronic hemophilic arthropathy

This can develop any time from the second decade of life, sometimes earlier, depending on the severity of bleeding and its treatment. It is caused by a persistent chronic synovitis and recurrent hemarthroses resulting in irreversible damage to the joint cartilage.

- With advancing cartilage loss, a progressive arthritis condition develops along with secondary soft tissue contractures, muscle atrophy, and angular deformities.
- With advancing chronicity of the arthropathy, there is less swelling due to progressive fibrosis of the synovium and the capsule.
- Loss of motion is common with flexion contractures causing the most significant functional loss.
- Pain may or may not be present.

The radiographic features of chronic hemophilic arthropathy depend on the stage of involvement.

- Early changes will show soft tissue swelling, epiphyseal overgrowth, and osteoporosis.
- Cartilage space narrowing will vary from minimal to complete loss.
- Bony erosions and subchondral bone cysts will develop, causing irregular articular bony surfaces which can lead to angular deformities.
- Fibrous/bony ankylosis may be present.

The goal of treatment is to improve joint function and relieve pain. Treatment options for chronic hemophilic arthropathy will depend on:

- The stage of the condition;
- The patient's symptoms; and
- The resources available.

Supervised physiotherapy is a very important part of management at this stage. Factor replacement is necessary if recurrent bleeding occurs during physiotherapy. Pain should be controlled with appropriate analgesics.

- Narcotics should be avoided when possible.
- NSAIDs (certain COX-2 inhibitors) may be used to relieve arthritic pain.

Conservative management techniques include:

- Serial casting to assist in correcting deformities; and
- Bracing and orthotics to support painful and unstable joints.

If these conservative measures fail to provide satisfactory relief of pain and improved function, surgical intervention may be considered. Adequate resources, including sufficient factor concentrates, must be available in order to proceed with any surgical procedure.

Surgical procedures, depending on the specific condition needing correction, may include:

- Radionucleotide synoviorthesis;
- Extra-articular soft tissue release to treat contractures;
- Arthroscopy to release intra-articular adhesions and correct impingement;
- Elbow synovectomy with radial head excision;
- Osteotomy to correct an angular deformity;
- Prosthetic joint replacement for severe disease involving a major joint (knee, hip, shoulder); and
- Arthrodesis of the ankle which provides excellent pain relief and correction of deformity with marked improvement in function.

Pseudotumours

A potentially limb- and life-threatening condition unique to hemophilia is the pseudotumour. It is most commonly seen in a long bone or the pelvis. It occurs as a result of inadequately treating a soft tissue bleed, usually in muscle adjacent to bone, which can be secondarily involved. If not treated, the pseudotumour can reach enormous size causing pressure on the neurovascular structures and pathologic fractures. A fistula can develop through the overlying skin.

- Diagnosis is made by the physical finding of a localized mass.
- Radiographic findings include a soft tissue mass with adjacent bone destruction.
- A more detailed and accurate evaluation of a pseudotumour can be obtained with CT scan and MRI.

Management depends on the site, size, rate of growth, and effect on adjoining structures. While some very small pseudotumours may be monitored when factor replacement therapy is used, most pseudotumours require surgery.

- Surgical excisions, including amputations, may be necessary for large tumours.
- Surgery may involve aspiration followed by injections of fibrin glue in some lesions located more peripherally and in well-localized positions.

Fractures

Fractures are not uncommon in the person with hemophilia and occur most commonly around the knee and hip. The person with hemophilia is at risk for fracturing around joints that have significant loss of motion and in bones that are osteoporotic. Treatment of a fracture in hemophilia requires immediate factor concentrate replacement.

- Levels of at least 50% should be obtained initially and maintained for 3–5 days.
- Lower levels may be maintained for 10–14 days while the fracture becomes stabilized.
- The actual management of the fracture should be performed in a manner appropriate for a specific fracture and this includes operative treatment under appropriate coverage of clotting factor concentrates.
- Care should be taken to avoid prolonged immobilization that could lead to significant limitation of range of movement in the adjacent joints.
- Physiotherapy should be started as soon as the fracture is stabilized.

SECTION 4

SELECTION OF CLOTTING FACTOR CONCENTRATES AND OTHER DRUGS

Clotting Factor Concentrates

Commercially prepared, lyophilized FVIII and FIX are available under a variety of brand names. All of these products have undergone viral attenuation. It is beyond the scope of this document to include details of all the available coagulation factor concentrates. This information is available in Dr. Carol Kasper and Dr. Meirione Costa e Silva's *Registry of Clotting Factor Concentrates*, which was originally set up by the Factor VIII and IX Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) in 1997. The registry is updated annually and is available from the WFH in print and on its web site. It includes information on:

- Donors (nationality, paid or unpaid);
- Method of obtaining plasma;
- Serological tests on donors;
- Testing of mini-pools for viruses using polymerase chain reaction (PCR) amplification;
- Location of fractionation facilities;
- Methods of fractionation;
- Methods of viral inactivation or filtration;
- Levels of purification;
- Identity of distributor and manufacturer; and
- Intended area of distribution (domestic or export).

The WFH has also published the *Guide for the Assessment of Clotting Factor Concentrates*. The guide covers the important principles involved in selecting suitable products for the treatment of hemophilia and is also available through the WFH web site. When selecting products consideration needs to be given to both the plasma quality as well as the manufacturing process. The key points may be summarized as follows:

- Fractionated plasma products have a history of transmitting blood-borne viruses (HBV, HCV, and HIV).
- Plasma-derived concentrates manufactured using today's processes and good manufacturing practices (GMPs) rank among the lowest risk therapeutic products in use today.
- Product safety is the result of efforts in several areas:
  - Improved donor selection (exclusion of at-risk donors);
  - Improved screening tests of donations, including nucleic acid testing (NAT);
  - Type and number of in-process viral inactivation and/or removal steps.

- In-process viral inactivation is the single largest contributor to product safety.
- Plasma types are distinguished based on:
  - Donor remuneration status (paid or unpaid), which, when regulated to current standards, is similar to the safety of manufactured products; and
  - Method of collection.
- In practice, all sources of properly screened blood will yield safe, effective products if processes are properly optimized and GMPs are observed.
- It is important to include, in the fractionation process, one or more steps with validated capability to inactivate or remove relevant viruses, primarily enveloped viruses such as HIV, HBV, and HCV. This results in plasma products that are essentially free from risk of these viruses. Inactivation and removal processes are less effective for non-enveloped viruses (mainly HAV and parvovirus B19).
- Currently, there is no screening test for variant Creutzfeldt-Jakob disease (vCJD), and no established manufacturing steps to inactivate the agent. vCJD in the U.K. donor population made it necessary to exclude plasma for fractionation from U.K. donors and has led to exclusion of perceived at-risk donors from other donor populations.
- There is no established risk of transmission of vCJD by plasma products.

Choice of products for replacement therapy

Two issues deserve special consideration:

- Purity of product;
- Viral inactivation/elimination.

Purity

Purity refers to the percentage of the desired ingredient (e.g., FVIII) in concentrates, relative to other ingredients present. There is no universally agreed upon classification of products based on purity, but one can make the following generalizations:

- Low purity is less than 10 IU per mg of protein.
- Intermediate purity is 10–100 IU per mg of protein.
- High purity is 100–1,000 IU per mg of protein.
- Very high purity is more than 1,000 IU per mg of protein.
- Concentrates on the market vary widely in their purity. Some products may have high or very high purity at one stage of the production process but are subsequently stabilized by albumin, which lowers their final purity. Generally speaking, products with higher purity tend to be associated with low manufacturing yields. This is due in part to a lower percentage of von Willebrand factor (the natural carrier protein of FVIII). These concentrates are, therefore, costlier.
- In some products, higher purity leads to clinical benefit. For example, high purity FIX concentrates lacking factors II, VII, and X are more preferable for the treatment of hemophilia B than the so-called prothrombin complex concentrates made of a mixture of these factors. The risk of thromboembolic complications is decreased with the high purity products.
- The purity of FVIII concentrates has not been convincingly demonstrated to enhance the safety of these products, as long as adequate viral reduction measures are in place.

Viral inactivation/elimination

There is a growing tendency to incorporate two specific viral reduction steps in the manufacturing process of concentrates.

- Heat treatment is generally effective against a broad range of viruses, both with and without a lipid envelope, including HIV, HAV, and HCV.
- Solvent/detergent treatment is effective against both HCV and HIV, but does not inactivate non-enveloped viruses, such as HAV.

Some viruses (such as human parvovirus B19) are relatively resistant to both types of process and none of the current methods can inactivate prions. Nano (ultra) filtration can be used to remove small viruses such as parvovirus.

When choosing a product, the plasma quality and testing should be of primary consideration. A product created by a process that incorporates two viral reduction steps should not automatically be considered as a better product than one which only goes through just one specific viral inactivation step. If only one step is used, it is desirable that this step should inactivate both viruses with and without lipid envelopes.

Plasma-derived/recombinant products

The WFH does not express a preference for recombinant over plasma-derived concentrates and the eventual choice between these classes of product will be made according to local criteria.

Cryoprecipitate

- Cryoprecipitate is prepared by slow thawing of fresh frozen plasma (FFP) at 4˚C for 10–24 hours.
- When cryoprecipitate appears as an insoluble precipitate and is separated by centrifugation, it contains significant quantities of FVIII (about 5 IU/ml), von Willebrand factor (vWF), fibrinogen, and FXIII (but not FIX or XI). The resultant supernatant is called cryo-poor plasma and contains other coagulation factors such as factors VII, IX, X, and XI.

There are some concerns about cryoprecipitate:

- The coagulation factor content of individual packs is variable and is usually not controlled.
- Cryoprecipitate is not subjected to viral inactivation procedures (such as heat or solvent/detergent treatment) and this inevitably translates into a risk of transmission of viral pathogens, which is not insignificant with repeated exposure. The use of this product in the treatment of congenital bleeding disorders can only be justified, therefore, in situations where clotting factor concentrates are not available.

The WFH supports the use of coagulation factor concentrates in preference to cryoprecipitate. However, the WFH recognizes the reality that single donor cryoprecipitate is still widely used in countries around the world where it is the only affordable treatment option.

Certain steps can at least be taken to minimize the risk of transmission of viral pathogens. These include:

- Quarantining plasma until the donor has been retested for antibodies to HIV and hepatitis C and HBsAg – a practice that is difficult to implement in countries where the proportion of repeat donors is low;
- Polymerase chain reaction (PCR) testing for HIV, HBV and/or HCV – a technology which has a potentially much greater relevance for the production of cryoprecipitate than concentrates, as the latter are subjected to viral inactivation steps anyway; and
- Quality policy, involving the monitoring of FVIII content.

Fresh Frozen Plasma and Cryo-Poor Plasma

Much of what has been said about cryoprecipitate applies to the use of fresh frozen plasma (FFP), which is a source of all coagulation factors, or to cryo-poor plasma.

- As FFP and cryo-poor plasma contain FIX, they are still used for the treatment of hemophilia B in countries unable to afford plasma-derived FIX concentrates.
- FFP can also be used for the treatment of bleeding in patients with some of the rarer congenital disorders of coagulation where specific concentrates are not available (e.g., factor V).
- FFP and cryo-poor plasma may also be used for the treatment of patients with mild factor XI (FXI) deficiency when a specific concentrate is not available or when its use may be contraindicated because of the potential for thrombogenicity.
- It is possible to apply some forms of virucidal treatment to packs of FFP (including solvent/detergent treatment) and the use of treated packs is recommended. However, virucidal treatment may have some impact on coagulation factors. The industrial processing of solvent/detergent-treated plasma has been shown to reduce the proportion of the largest multimers of vWF.

The WFH supports the use of coagulation factor concentrates in preference to FFP or cryo-poor plasma. However, the WFH recognizes the reality that FFP and cryo-poor plasma are still used in countries around the world where they are the only affordable treatment options.

Other Pharmacological Options

In addition to conventional coagulation factor concentrates, there are other agents which can be of great value in a significant proportion of cases. These include:

- Desmopressin;
- Tranexamic acid; and
- Epsilon aminocaproic acid.

Desmopressin (DDAVP)

Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) is a synthetic analogue of antidiuretic hormone (ADH). The compound boosts the plasma levels of FVIII and vWF after administration. The following should be noted:

- The most common mode of administration is by intravenous infusion, but it may also be given by subcutaneous injection.
- A single intravenous infusion at a dose of 0.3 micrograms/kg body weight can be expected to boost the level of FVIII three- to sixfold.
- The peak response is seen approximately 90 minutes after completion of the infusion.
- Closely spaced repetitive use of DDAVP may result in decreased response (tachyphylaxis) after 1-2 days so that factor concentrates may be needed when higher factor levels are required for a prolonged period.
- Before therapeutic use, it is preferable to test the patient's response as significant individual differences are possible.
- The compound is ineffective in patients with severe hemophilia A.
- Desmopressin does not affect FIX levels and is of no value in hemophilia B.
- The decision to use DDAVP must be based on both the baseline concentration of FVIII and on the nature of the procedure. It would not, for example, be feasible to perform gastrectomy in a patient with a baseline FVIII level of 10% or less. The expected post-infusion level of 30-40% would not be sufficient to ensure hemostasis and the responses to subsequent doses would be even less. On the other hand, the same patient might be able to have a dental extraction after an infusion.
- Desmopressin is particularly useful in the treatment of bleeding in female carriers of hemophilia.
- Obvious advantages of DDAVP over plasma products are the much lower cost and the absence of any risk of transmission of viral infections.
- Many centres give a trial infusion of desmopressin to appropriate patients, so that the potential value may be assessed for possible future use.

Administration:

- DDAVP is usually diluted in at least 50-100 ml of physiological saline and given by slow intravenous infusion over 20-30 minutes.
- Rapid infusion may result in tachycardia, flushing, tremor, and abdominal discomfort.
- Water retention and hyponatremia is not usually a problem in adults, although concomitant administration of diuretic therapy can exacerbate the risk. However, children under two years old and women immediately post-partum appear to be at particular risk of hyponatremia that may provoke seizures.
- Consensus is that DDAVP should not be given to children under the age of two.
- The manufacturers caution against use of DDAVP in pregnancy although there is now growing anecdotal, but unpublished, experience that it is safe to use in pregnancy.
- There are case reports of thrombosis (including myocardial infarction) after an infusion of DDAVP. Therefore, it should be used with caution in elderly patients and others with evidence of arterial disease.
- DDAVP may also be useful to control bleeding and reduce the prolongation of the bleeding time associated with acquired disorders of hemostasis, including chronic renal failure and liver diseases and some platelet disorders.
- A concentrated nasal spray has recently become available and a spray dosage in an adult of 300 micrograms is equivalent to the standard intravenous dose of 0.3 micrograms/kg. A dose of 300 micrograms for those over 50 kg and 150 micrograms for those up to 50 kg is suggested. This preparation should not be confused with the more dilute nasal spray preparation of desmopressin which is used for treatment of diabetes insipidus, but which is of no value in the treatment of hemostatic disorders.

The nasal spray is likely to prove particularly useful for home treatment of relatively minor bleeding problems.

Tranexamic acid

Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin. It promotes clot stability and is useful as adjunctive therapy in hemophilia and some other bleeding disorders. Tranexamic acid is also of use in FXI deficiency, where its use to cover dental, gynecologic, or urologic surgery in FXI-deficient patients may obviate the need for replacement therapy with concentrates or plasma.

Trials several decades ago established that regular treatment with tranexamic acid alone is of no value in prevention of hemarthroses in hemophilia. However, it is certainly valuable in controlling bleeding from mucosal surfaces (e.g., oral bleeding, epistaxis, menorrhagia) in hemophilia and is particularly valuable in the setting of dental surgery.

Administration:

- Tranexamic acid is usually given in tablet form at a typical dose of 3 or 4 grams (in divided doses) daily for an adult and is generally very well tolerated.
- Gastrointestinal upset (nausea, vomiting and diarrhea) may rarely occur as a side effect, but these symptoms usually resolve if the dosage is reduced. It may also be given by intravenous injection, but it must be infused slowly as rapid injection may result in dizziness and hypotension.
- A syrup formulation is also available for pediatric use: the syrup contains 500 mg tranexamic acid in each 5 ml, and the usual dose for children is 25 mg/kg up to three times daily. If this is not available, a 500 mg tablet can be crushed and dissolved in clean water for topical use on bleeding mucosal lesions.
- The drug may be of particular use in controlling oral bleeding associated with eruption of teeth.
- The kidneys excrete the drug and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.
- The use of tranexamic acid is contraindicated for the treatment of hematuria in severe hemophilia, as treatment may precipitate clot colic and even obstruction of the outflow from the renal pelvis.
- Similarly, the drug is contraindicated in the setting of thoracic surgery, where it may result in the development of insoluble hematomas.
- Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrates. Please note:
  - It should not be given to patients with inhibitory antibodies receiving activated prothrombin factor concentrates (APCCs) (such as FEIBA® or Autoplex®) as this may exacerbate the risk of thromboembolism.
  - If treatment with both agents is deemed necessary, it is recommended that at least 4–6 hours elapse between the last dose of APCC and the administration of tranexamic acid.
  - By contrast, tranexamic acid may be usefully used in combination with recombinant factor VIIa to enhance hemostasis.

Aminocaproic acid

Epsilon aminocaproic acid (EACA) is a drug similar to tranexamic acid but it is less widely used nowadays as it has a shorter plasma half-life, is less potent, and is more toxic.

Administration:

- EACA is typically administered to adults at the following dosage: 5 gm immediately followed by 1 gm every hour for 8 hours or till bleeding stops. It is available as tablets and injection. A 250 mg/ml syrup formulation is available and the commonly used pediatric dosage is 50-100 mg/kg (maximum 5 gms) PO or IV every 6-8 hours.
- Myopathy is a rare adverse reaction specifically reported in association with aminocaproic acid therapy (but not tranexamic acid), typically occurring after administration of high doses for several weeks.
- The myopathy is often painful, and associated with elevated levels of creatine kinase and even myoglobinuria.
- Full resolution may be expected once drug treatment is stopped.

SECTION 5

TREATMENT OF BLEEDING IN HEMOPHILIA

Basic Principles of Treatment

- Bleeds should be treated with factor replacement therapy at the earliest possible moment, preferably within two hours of onset of symptoms. Do not wait for the appearance of physical symptoms.
  - Patients, even young children, can usually tell when a joint hemorrhage starts. Treatment at this early stage will often stop the bleed before tissue damage occurs. Also, less factor concentrates will be needed and the patient will recover more quickly.
  - *"If in doubt, treat."* If a person with hemophilia is injured or thinks he may be bleeding, treat him with factor replacement therapy if it is feasible.
- Veins must be treated with care. They are the lifelines for a person with hemophilia!
  - 23- or 25-gauge butterfly needles are recommended.
  - *Never* cut down into a vein, except in an emergency, as it destroys the vein.
  - After venipuncture, apply pressure for 3–5 minutes with one or two fingers.
- All products that cause platelet dysfunction, especially those containing ASA, should be avoided. Use non-steroidal anti-inflammatory drugs (NSAIDs) with caution. Paracetamol/acetaminophen, with or without narcotic analogues, is usually effective in controlling pain.
- Avoid intramuscular injections.
- Encourage home therapy with clotting factor concentrates. Home therapy is usually begun when a child is two to three years old.
- Communication between the patient, his physician, the hemophilia treatment centre, and the community is essential for optimal management.

Treatment of Hemophilia A (FVIII Deficiency)

FVIII concentrates

Commercially prepared, lyophilized FVIII is available under a variety of brand names. All plasma-derived products have undergone viral attenuation. Consult the product insert guide for specific instructions.

Dosage

- Vials of factor concentrates are available in dosages ranging from approximately 250 to 2000 units each.

- Each FVIII unit per kilogram of body weight infused intravenously will raise the plasma FVIII level approximately 2%. The half-life is approximately 8–12 hours. Verify the calculated dose by measuring the patient's factor level.
- Calculate the dosage by multiplying the patient's weight in kilograms by the factor level desired multiplied by 0.5. This will indicate the number of factor units required.

  Example: (50 kg x 40 (% level desired) x 0.5 = 1,000 units of FVIII).

  Refer to Table 1 on page 45 for suggested factor level and duration of replacement required based on type of hemorrhage.
- *Infuse FVIII by slow IV push at a rate not to exceed 3 ml per minute in adults and 100 units per minute in young children.*
- It is best to use the entire vial of FVIII once reconstituted, though many products have been shown to have extended stability after reconstitution.
- Continuous infusion will help avoid peaks and troughs and is considered by many to be safer and more cost-effective. This will reduce significantly the total amount of factor concentrates used to treat bleeding or during prophylaxis after surgery. Dosage is adjusted based on frequent factor assays and calculation of clearance. Since FVIII concentrates of very high purity are stable in IV solutions for at least 24-48 hours at room temperature with less than 10% loss of potency, continuous infusion for a similar number of hours is possible. The concentrates may be prepared by the pharmacy or blood bank under sterile conditions, and administered without concern for proteolytic inactivation, degradation, or bacterial contamination.

Cryoprecipitate/fresh frozen plasma

- Only use cryoprecipitate if factor concentrates are not available. Cryoprecipitate is best prepared from repeatedly tested and virus-negative donors.
- FVIII content per bag of cryoprecipitate is 60-100 units (average - 80 units) in a volume of 30-40 ml.
- Fresh frozen plasma may also be used if factor concentrates are not available. It is recommended that FFP be subjected to viral reduction procedures.
- One ml of fresh frozen plasma contains 1 unit of factor activity.

Desmopressin (DDAVP)

- DDAVP is useful in the treatment of persons with mild hemophilia who have a 5% or greater FVIII level and who have been shown to be responsive in pre-tests.

Treatment of Hemophilia B (FIX Deficiency)

FIX concentrates

- Commercially prepared, lyophilized FIX concentrates are available under a variety of brand names. All plasma-derived products have undergone viral attenuation. FIX concentrates fall into two classes:
  - Pure coagulation FIX products, and
  - Prothrombin complex concentrates (PCCs).

  Consult the product insert guide for specific instructions.

- Purified FIX products are largely free of the risks of that could cause patients to develop thrombosis or disseminated intravascular coagulation (DIC), which may occur with large doses of intermediate purity PCCs.
- Whenever possible, the use of pure FIX concentrates is preferable and it is particularly advisable in the following instances:
  - Surgery;
  - Liver disease;
  - Prolonged therapy at high doses;
  - Previous thrombosis or known thrombotic tendency;
  - Disseminated intravascular coagulation (DIC);
  - Concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents.

Dosage

- Vials of FIX concentrates are available in doses ranging from approximately 300 to 1200 units each.
- Each FIX unit per kilogram of body weight infused intravenously will raise the plasma FIX level approximately 1%. The half-life is about 18-24 hours. Verify calculated doses by measuring the patient's factor level.
- Recombinant FIX (rFIX; BeneFIX®, Wyeth) has a lower recovery, and each FIX unit per kg body weight infused will raise the FIX activity by approximately 0.8% in adults and 0.7% in children < 15 years of age. The reason for lower recovery of rFIX is not entirely clear.
- To calculate dosage, multiply the patient's weight in kilograms by the factor level desired. This will indicate the number of factor units required.

  Example: 50 kg x 40 (% level desired) = 2000 units of plasma-derived FIX. For rFIX, the dosage will be 2000 ÷ 0.8 (or 2000 x 1.25) = 2500 units for adults, and 2000 ÷ 0.7 (or 2000 x 1.43) = 2860 units for children.

  Refer to Table 1, page 45, at the end of this section, for suggested factor level and duration of replacement therapy based on type of hemorrhage.
- *Infuse FIX by slow IV push at a rate not to exceed a volume of 3 ml per minute in adults and 100 units per minute in young children. PCCs and APCCs should be infused at half this rate.*
- Continuous infusion will help avoid peaks and troughs and is considered by many to be safer and more cost-effective. This will reduce significantly the total amount of factor concentrates used to treat bleeding or during prophylaxis after surgery. Dosage is adjusted based on frequent factor assays and calculation of clearance. Since FIX concentrates of very high purity are stable in IV solutions for at least 24-48 hours at room temperature with less than 10% loss of potency, continuous infusion for a similar number of hours is possible. The concentrates may be prepared by the pharmacy or blood bank under sterile conditions, and administered without concern for proteolytic inactivation, degradation, or bacterial contamination.

Fresh frozen plasma (FFP)

- For patients with hemophilia B, fresh frozen plasma should only be used if FIX concentrates are unavailable.
- FIX levels above 25% are difficult to achieve. An acceptable starting dose is 15-20 ml/kg. Solvent/detergent-treated FFP is available in some countries.

Antifibrinolytic agents

- Due to increased risk for thromboses, antifibrinolytic agents, either as primary or adjunctive therapy, are not recommended for treatment of patients with FIX deficiency already receiving large doses of prothrombin complex concentrates. (See Choice of Products, page 45)

Treatment of Specific Hemorrhages

Joint hemorrhage

- Administer the appropriate dose of factor concentrate first and then evaluate the patient. X-rays usually are not indicated.
- Raise the patient's factor level (see Table 1, page 45) at the first sign of symptoms or after trauma.
- If symptoms persist, a second infusion may be required. If so, repeat the dosage in 12 hours (hemophilia A) or 24 hours (hemophilia B).
- The joint should be mobilized as soon as possible after pain subsides.
- Adjunctive care includes the local application of ice, temporary rest, and elevation of the joint.
- Further evaluation is necessary if the patient's symptoms continue longer than three days. Things to consider if symptoms and findings persist are presence of inhibitors, septic arthritis, or fracture.
- Control pain with adequate analgesics.

Muscle hemorrhage

- Administer the appropriate dose of factor concentrate first and then evaluate the patient.
- Raise the patient's factor level (see Table 1, page 45) at the first sign of symptoms or after trauma.
- Repeat infusions often are required for 2–3 days. Monitor the patient for neurovascular compromise.

Iliopsoas hemorrhage

- This type of muscle hemorrhage has a unique presentation. Signs may include pain in the lower abdomen, groin, and/or lower back and pain on extension, but not on rotation, of the hip joint. There may be paresthesia in the medial aspect of the thigh or other signs of femoral nerve compression. The symptoms may mimic acute appendicitis.
- Immediately raise the patient's factor level (see Table 1, page 45). Maintain the levels (see Table 1) for 48–96 hours, as symptoms indicate.
- Hospitalize the patient for observation and control of pain.
- If there is any doubt, confirm diagnosis with an imaging study (ultrasonography, CT scan).

- Hydrocortisone (100 mg IV) may reduce the muscle edema and pressure on the femoral nerve.
- Limit the patient's activity until the pain resolves. Physiotherapy is the key to restoring full activity.

Central nervous system hemorrhage/head trauma

- *This is a medical emergency. Treat first before evaluating*. All post-traumatic head injuries, confirmed or suspected, and significant headaches must be treated as intracranial bleeds. Do not wait for further symptoms to develop or for laboratory or radiologic evaluation. *Immediately* raise the patient's factor level (see Table 1, page 45) when significant trauma or symptoms occur. Further doses will depend on imaging results. Maintain factor level (see Table 1) until etiology is defined. If a bleed is confirmed, maintain the appropriate factor level for 2–3 weeks.
- Immediate medical evaluation and hospitalization is required. A CT scan or MRI of the brain should be performed.
- A severe headache may be a manifestation of meningitis in immunocompromised patients.

Throat and neck hemorrhage

- *This is a medical emergency. Treat first before evaluating*. *Immediately* raise the patient's factor level (see Table 1, page 45) when significant trauma or symptoms occur. Maintain the factor levels (see Table 1) until symptoms resolve.
- Hospitalization and evaluation by a specialist is essential.
- To prevent hemorrhage in patients with severe tonsillitis, treatment with factor may be indicated, in addition to culture and treatment with antibiotics.

Acute gastrointestinal (GI) hemorrhage

- Administer the appropriate factor concentrate dose first and then evaluate. *Immediately* raise the patient's factor levels (see Table 1, page 45). Maintain the factor levels (see Table 1) until etiology is defined.
- For signs of GI bleeding and/or acute abdomen, medical evaluation and possibly hospitalization are required.
- Treat anemia or shock, as needed.
- Treat origin of hemorrhage, as indicated.
- EACA or tranexamic acid may be used as adjunctive therapy for patients with FVIII deficiency and those with factor IX deficiency who are *not* being treated with prothrombin complex concentrates.

Acute hemorrhage in the abdomen

- An acute abdominal hemorrhage can be mistaken for a number of infectious conditions and appropriate radiologic studies may be necessary. Rule out iliopsoas hemorrhage.
- *Immediately* raise the patient's factor levels (see Table 1, page 45). Maintain the factor levels (see Table 1) until the etiology can be defined, then treat appropriately in consultation with a specialist.

Ophthalmic trauma or hemorrhage

- Administer the appropriate dose of factor concentrate first and then evaluate. *Immediately* raise the patient's factor level (see Table 1, page 45). Maintain the factor level as indicated.
- Have the patient evaluated by an ophthalmologist as soon as possible.

Renal hemorrhage

- Do not use antifibrinolytic agents.
- Treat painless hematuria with complete bed rest and vigorous hydration (3 litres/m^2, body surface area) for 48 hours.
- Raise the patient's factor levels (see Table 1, page 45) if there is pain or persistent gross hematuria.
- Evaluation by an urologist is essential if hematuria (gross or microscopic) persists or if there are repeated episodes.

Oral hemorrhage

- Avoid using antifibrinolytic agents systematically for patients with FIX deficiency who are being treated with large doses of prothrombin complex concentrates.
- Bleeding may be controlled in patients with FVIII deficiency with the use of EACA or tranexamic acid alone, or with the use of factor and either EACA or tranexamic acid, if bleeding is prolonged, significant, or difficult to control. EACA or tranexamic acid may be used in the form of a mouthwash.
- Tell the patient to avoid swallowing blood.
- Evaluate the patient and treat for anemia as indicated.
- The application on the bleeding mucus membrane of topical agents such as thrombin/fibrin sealant may be effective. Ice in the form of "popsicles" (frozen flavoured water) may also be effective. A soft diet is recommended.
- Consultation with a dentist/otolaryngologist may be needed.

Epistaxis

- The formation of a platelet plug is often adequate so factor replacement therapy is usually not necessary unless bleeding is severe or recurrent.
- Place the patient's head in a forward position to avoid swallowing blood and ask him to gently blow out weak clots. Firm pressure with gauze soaked in ice water should be applied to the fleshy part of the nose for at least 20 minutes.
- Antihistamines and decongestant drugs are useful for bleeds specifically related to allergies, upper respiratory infections, or seasonal changes.
- If bleeding is prolonged or occurs frequently, watch for anemia and treat appropriately.
- Consult with an otolaryngologist if the bleed is persistent or recurrent. Anterior or posterior nasal packing may be needed to control bleeding.
- EACA or tranexamic acid is helpful.
- Nosebleeds can often be prevented by increasing the humidity of the environment, applying gels (e.g., Vaseline or saline drops/gel) to the nasal mucosa to preserve moisture, or administering saline spray to the nostrils.

Soft tissue hemorrhage

- For most superficial soft tissue bleeding, factor replacement therapy is not necessary. The application of firm pressure and ice may be helpful.
- Evaluate the patient for hemorrhage severity and possible muscular or neurovascular involvement. Rule out possible trauma to spaces containing vital organs, such as the head or abdomen. Open compartmental hemorrhage, such as in the retroperitoneal space, scrotum, buttocks, or thighs, can result in extensive blood loss. Treat with factor immediately if this situation is suspected.

Lacerations and abrasions

- Treat superficial lacerations by cleaning the wound, then applying pressure and steri-strips.
- Treat abrasions with cleaning and pressure.
- For deep lacerations, raise the factor level (see Table 1, page 45), and then suture. Suture removal occasionally requires another infusion of factor.

Other Management Issues

Dental care

- In general, routine examinations and cleaning can be done without raising the factor level. Ensure that adequate coverage (i.e., factor concentrates, DDAVP, or antifibrinolytic therapy) is given prior to, and possibly after, dental treatments for patients who need deep cleaning or have heavy plaque and/or calculus accumulation where bleeding could be induced with scaling. Where block local anesthesia is indicated, factor should *always* be given prior to dental procedures. If only local infiltration of anesthesia is going to be used for mild and some moderate patients, then infusion of factor may not be necessary prior to restorative work.
- DDAVP may be used for achieving hemostasis for procedures in people with moderate or mild hemophilia. (See section 4: Selection of Clotting Factor Concentrates and Other Drugs.)
- For hemophilia A, raise the factor level to 50% and for hemophilia B to 40% prior to giving a mandibular block. Local anesthesia is not contraindicated for hemophilia patients. In addition to local anesthesia, nitrous oxide and/or IV analgesia may be used.
- For dental extractions, ensure the patient receives a prior infusion of factor concentrate that raises the level appropriately (see Table 1, page 45). EACA or tranexamic acid may be started before factor infusion. The dose of EACA, which should be started the night before or morning of the procedure, is 50–100 mg/kg every 4–6 hours for 5–10 days (maximum 24 grams per 24 hours). The dose for tranexamic acid is 25–50 mg/kg orally every 6–8 hours for 10 days. A liquid preparation of these drugs may be used as a mouthwash.
- Extensive procedures – for example, those requiring sutures or multiple extractions – may require hospitalization for proper dental/medical management.
- Bleeding may occur when primary teeth are exfoliating. Use pressure and ice as a first attempt to control bleeding. If this is ineffective, antifibrinolytic drugs may be used (as above). In rare cases, factor may have to be administered. Patients with a history of prolonged bleeding may have to undergo dental extraction with appropriate factor cover.

Surgery

- A surgical patient is best managed at a hemophilia treatment centre. The centre where the surgery is to be performed must be capable of performing a factor inhibitor screen and measurement of serial factor levels.
- Once the coagulation defect is corrected by infusion with factor, operative and invasive procedures can be performed. A consultation with a hematologist who is familiar with surgery in hemophilia is necessary.
- Document the patient's individual response to the replacement material prior to surgery. Rule out an inhibitor if the patient does not respond adequately. (See section on factor inhibitors, page 10).
- Immediately prior to the procedure, the factor level must be raised to the appropriate level required for hemostasis (see Table 1, page 45).
- An appropriate factor level should be maintained for 5–7 days or till wound healing after minor surgery, and for 10–14 days after major surgery (see Table 1, page 45). After some orthopedic procedures, factor level may need to be maintained for a longer period of time.

Minor invasive procedures

- Infuse factor concentrates before invasive diagnostic procedures are performed. These procedures include lumbar puncture, arterial blood gas determination, bronchoscopy with brushings or biopsy, and gastrointestinal endoscopy with biopsy.

Allergic reactions to factor replacement products

- Use the filters included in factor packages to avoid the possibility of reaction.
- To prevent or reduce symptoms, use antihistamines.
- Changing the brand of clotting factor concentrate sometimes reduces symptoms.

SECTION 6

Plasma Factor Level and Duration of Administration

Tables 1A and 1B present commonly recommended plasma factor levels and duration of replacement that reflect the different practices in countries where there is no significant resource constraint (1A) and countries where treatment products are limited (1B).

TABLE 1A **Recommended Plasma Factor Level and Duration of Administration When There Is No Significant Resource Constraint**

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired level	**Duration (days)**	**Desired level**	**Duration (days)**
Joint	40%–60%	1–2, may be longer if response is inadequate	40%–60%	1–2, may be longer if response is inadequate
Muscle (except iliopsoas)	40%–60%	2–3, sometimes longer if response is inadequate	40%–60%	2–3, sometimes longer if response is inadequate
Iliopsoas • initial • maintenance	 80%–100% 30%–60%	 1–2 3–5, sometimes longer as secondary prophylaxis during physiotherapy	 60%–80% 30%–60%	 1–2 3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head • initial • maintenance	 80%–100% 50%	 1–7 8–21	 60%–80% 30%	 1–7 8–21
Throat and neck • initial • maintenance	 80%–100% 50%	 1–7 8–14	 60%–80% 30%	 1–7 8–14
Gastrointestinal • initial • maintenance	 80%–100% 50%	 1–6 7–14	 60%–80% 30%	 1–6 7–14
Renal	50%	3–5	40%	3–5
Deep laceration	50%	5–7	40%	5–7
Surgery (major) • Pre-op • Post-op	 80%–100% 60%–80% 40%–60% 30%–50%	 1–3 4–6 7–14	 60%–80% 40%–60% 30%–50% 20%–40%	 1–3 4–6 7–14

TABLE 1B Recommended Plasma Factor Level and Duration of Administration When There Is Significant Resource Constraint)

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired level	**Duration (days)**	**Desired level**	**Duration (days)**
Joint	10%–20%	1–2, may be longer if response is inadequate	10%–20%	1–2, may be longer if response is inadequate
Muscle (except iliopsoas)	10%–20%	2–3, sometimes longer if response is inadequate	10%–20%	2–3, sometimes longer if response is inadequate
Iliopsoas • initial • maintenance	20%–40% 10%–20%	1–2 3–5, sometimes longer as secondary prophylaxis during physio-therapy	15%–30% 10%–20%	1–2 3–5, sometimes longer as secondary prophylaxis during physio-therapy
CNS/head • initial • maintenance	50%–80% 30%–50% 20%–40%	1–3 4–7 8–14 (or 21 if indicated)	50%–80% 30%–50% 20%–40%	1–3 4–7 8–14 (or 21 if indicated)
Throat and neck • initial • maintenance	30%–50% 10%–20%	1–3 4–7	30%–50% 10%–20%	1–3 4–7
Gastrointestinal • initial • maintenance	30%–50% 10%–20%	1–3 4–7	30%–50% 10%–20%	1–3 4–7
Renal	20%–40%	3–5	15%–30%	3–5
Deep laceration	20%–40%	5–7	15%–30%	5–7
Surgery (major) • Pre-op • Post-op	60%–80% 30%–40% 20%–30% 10%–20%	1–3 4–6 7–14	50%–70% 30%–40% 20%–30% 10%–20%	1–3 4–6 7–14

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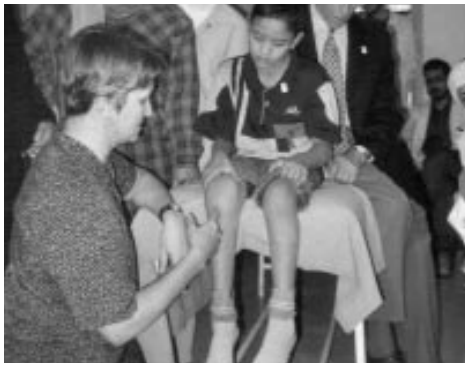

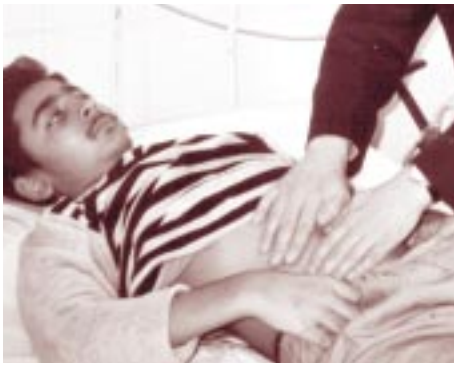

World Federation of Hemophilia

1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel.: (514) 875-7944
Fax: (514) 875-8916
E-mail: wfh@wfh.org
Web site: **www.wfh.org**

WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA