IRAQI GUIDELINES FOR THE MANAGEMENT OF HEREDITARY BLEEDING DISORDERS

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تم اعداد هذا الدليل الارشادي المحدث الخاص بالهيموفيليا وبقية امراض نزف الدم الوراثي من قبل الاطباء الاختصاص العاملين في هذا المجال في العراق. وبالاعتماد على الدليل العلاجي للهيموفيليا الصادر من قبل منظمة الهيموفيليا العالمية ، وبالتنسيق مع دائرة الامور الفنية في وزارة الصحة .

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Summery

Hemophilia is a rare hereditary disorder that is complex to diagnose and manage. These evidence-based guidelines offer practical recommendations on the diagnosis and general management of Hemophilia, and other rare bleeding disorders as well as the management of its complications including musclo _skeletal issues, inhibitors, and transfusion-transmitted infections.

By compiling these guidelines, we aims to assist healthcare providers seeking to initiate and or maintain Hemophilia care programs, encourage practice harmonization in Iraq and, where recommendations lack adequate evidence, stimulate appropriate studies.

Introduction

The edition of this guideline, compiling in 2017 by the Hemophilia Scientific Committee in MOH and our colleagues in all hemophilia centers all over Iraq, and Iraqi Hemophilia Society under sponsorship of Novo Nordisk Company, served its purpose of being a useful document for those looking for basic information on the comprehensive management of Hemophilia .We depend mainly on the Guideline for the management of Hemophilia issueed by World Federation of Hemophilia after few modification to become more convenient to our current health care condition in Iraq.

A question often raised when developing a guideline and its universal applicability given the diversity of health services and economic systems around the world. Our strongly held view is that the principles of management of Hemophilia are the same all over Iraq and the world. The differences are mainly in the doses of clotting factor concentrates (CFC) used to treat or prevent bleeding, given that the costs of replacement products comprise the major expense of Hemophilia care programs. Recognizing this reality, this guidelines continue to include a dual set of dose recommendations for CFC replacement therapy. These are based on published literature and practices in major centers around the world. It should be appreciated, however, that the lower doses recommended may not achieve the best results possible and should serve as the starting point for care to be initiated in resource-limited situations, with the aim of gradually moving towards more optimal doses, based on clinical situation and greater availability of CFC.

We hope this guide will continue to be useful to those initiating and maintaining hemophilia care programs

1. GENERAL CARE AND MANAGEMENT OF HEMOPHILIA

1.1 What is hemophilia?

1. Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in Hemophilia A) or factor IX (FIX) (in Hemophilia B). The deficiency is the result of mutations of the respective clotting factor genes.
2. Hemophilia A has an estimated frequency of approximately one in 10,000 births and in 40000-50000 in Hemophilia B.
3. Estimations based on the WFH's annual global surveys indicate that the number of people with Hemophilia in the world is approximately 400,000 [1].
4. Hemophilia A is more common than hemophilia B representing 80-85% of the total hemophilia population.
5. Hemophilia generally affects males on the maternal side. However, both *F8* and *F9* genes are prone to new mutations, and as many as 1/3 of all cases are the result of spontaneous mutation in Hemophilia A and 1/5 in Hemophilia B where there is no prior family history.
6. Accurate diagnosis of hemophilia is essential to inform appropriate management.

Hemophilia should be suspected in patients presenting with a history of:

- Easy bruising in early childhood.
- Spontaneous bleeding (bleeding for no apparent known reason), particularly into the joints, muscles, and soft tissues.
- Excessive bleeding following trauma or surgery.
- A family history of bleeding is obtained in about two thirds of all patients.
- A definitive diagnosis depends on factor assay to demonstrate deficiency of FVIII or FIX.

Bleeding manifestations

1. The characteristic phenotype in Hemophilia is the bleeding tendency.

2. While the history of bleeding is usually life-long, some children

with severe Hemophilia may not have bleeding symptoms until later when they begin walking or running.

3. Patients with mild Hemophilia may not bleed excessively until they experience trauma or surgery.

4. The severity of bleeding in Hemophilia is generally correlated with the clotting factor level, as shown in Table 1-1.

5. Most bleeding occurs internally, into the joints or muscles (see Table 1-2 and Table 1-3).

6. Some bleeds can be life-threatening and require immediate treatment

TABLE 1-1: RELATIONSHIP OF BLEEDING SEVERITY TO CLOTTING FACTOR

SEVERITY	CLOTTING FACTOR LEVEL	BLEEDING EPISODES
Severe	< 1 IU/dl (< 0.01 IU/ml) or < 1 % of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1-5 IU/dl (0.01-0.05 IU/ml) or 1-5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5-40 IU/dl (0.05-0.40 IU/ml) or 5-<40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

TABLE 1‑2: SITES OF BLEEDING IN HEMOPHILIA

Serious	Joints (hemarthrosis)
	Muscles, especially deep compartments (iliopsoas, calf, and forearm)
	Mucous membranes in the mouth, gums, nose, and genitourinary tract
Life-threatening	Intracranial
	Neck/throat
	Gastrointestinal

TABLE 1-3: APPROXIMATE FREQUENCY OF BLEEDING AT DIFFERENT SITES

SITE OF BLEEDING	APPROXIMATE FREQUENCY
Hemarthrosis more common into hinged joints: ankles, knees, and elbows less common into multi-axial joints: shoulders, wrists, hips	70%–80%
Muscle	10%–20%
Other major bleeds	5%–10%
Central nervous system (CNS)	<5%

1.2 Principles of Care

1. The primary aim of care is to prevent and treat bleeding with the deficient clotting factor.
2. Whenever possible, specific factor deficiency should be treated with specific factor concentrate.
3. People with hemophilia are best managed in a comprehensive care setting.
4. Acute bleeds should be treated as quickly as possible, preferably within two hours. If in doubt, treat.
5. Patients usually recognize early symptoms of bleeding even before the manifestation of physical signs. This is often described as a tingling sensation or “aura”.
6. During an episode of acute bleeding, an assessment should be performed to identify the site of bleeding (if not clinically obvious) and appropriate clotting factor should be administered.
7. In severe bleeding episodes that are potentially life-threatening, especially in the head, neck, chest, and gastrointestinal tract, treatment with factor should be initiated immediately, even before diagnostic assessment is completed.
8. To facilitate appropriate management in emergency situations, all patients should carry easily accessible identification card indicating the diagnosis, severity of the bleeding disorder, inhibitor status, type of treatment product used, initial dosage for treatment of severe, moderate, and mild bleeding, and contact information of the treating physician/clinic. [3]
9. Administration of Desmopressin (DDAVP) can raise FVIII level

adequately (three to six times baseline levels) to control bleeding in patients with mild, and possibly moderate, hemophilia A. Testing for DDAVP response in individual patients is appropriate.

10. 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.
    - Apply pressure for three to five minutes after venipuncture.
    - Venous access devices should be avoided whenever possible but may be required in some children.

11. Adjunctive therapies can be used to control bleeding, particularly in the absence of clotting Factor concentrates, and may decrease the need for them (see 'Adjunctive management').

12. If bleeding does not resolve despite adequate treatment, clotting factor levels should be measured. Inhibitor testing should be performed if the level is unexpectedly low (see Inhibitor testing).

13. Prevention of bleeding can be achieved by prophylactic factor replacement (see 'Prophylactic factor replacement therapy,).

14. Home therapy can be used to manage mild/moderate bleeding episodes (see Home therapy).

15. Regular exercise and other measures to stimulate normal psychomotor development should be encouraged to promote strong muscles, develop balance and coordination, and improve fitness (see Fitness and physical activity').

16. Patients should avoid activities likely to cause trauma (see Fitness and physical activity).

17. Regular monitoring of health status and assessment of outcomes are key components of care.

18. Drugs that affect platelet function, particularly Acetyl salicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors, should be avoided. Paracetamol/acetaminophen is a safe alternative for analgesia (see Pain management').

19. Factor levels should be raised to appropriate levels prior to any invasive procedure (see Surgery and invasive procedures').

20. Good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding (see Dental care and management).

1.3 Comprehensive care

1. Comprehensive care promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality.

2. Hemophilia is a rare disorder that is complex to diagnose and to manage. Optimal care of these patients, especially those with severe forms of the disease, requires more than the treatment of acute bleeding.

3. Priorities in the improvement of health and quality of life of people with hemophilia include:

Comprehensive care team

1. The wide-ranging needs of people with hemophilia and their families are best met through the coordinated delivery of comprehensive care by a multidisciplinary team of healthcare professionals, in accordance with accepted protocols that are practical and national treatment guidelines, if available.

2. The comprehensive care team should be multidisciplinary in nature, with expertise and experience to attend to the physical and psychosocial health of patients and their families.

3. The core team should consist of the following members:

- a medical director (preferably a pediatric and/or adult hematologist, or a physician with interest and expertise in hemostasis)
- a nurse coordinator who :
  - Coordinates the provision of care.
  - Educates patients and their families.
  - Acts as the first contact for patients with an acute problem or who require follow-up.
  - is able to assess patients and institute initial care where appropriate
- A musculoskeletal expert (physiotherapist, occupational therapist, psychiatrist, orthopedist, rheumatologist) who can address preventions well as treatment.
- A laboratory specialist.
- A psychosocial expert (preferably a social worker, or a psychologist) familiar with available community resources

Prevention of bleeding and joint damage.

- Prompt management of bleeding.
- Management of complications including :
  - Joint and muscle damage and other sequel of bleeding.
  - Inhibitor development.
  - Viral infection(s) transmitted through blood products.
- Attention to psychosocial health.

4. The roles assumed by core team members may differ, depending on the availability and expertise of trained staff and the organization of services within the center.

5. All members of the core team should have expertise and experience in treating bleeding disorders and should be accessible to patients in a timely and convenient manner. Adequate emergency care should be available at all times.

6. The following support resources are necessary:

- Access to a coagulation laboratory capable of performing accurate and precise clotting factor assays and inhibitor testing.
- Provision of appropriate clotting factor concentrates, either plasma-derived or recombinant, as well as other adjunct hemostatic agents such as Desmopressin (DDAVP) and Tranexamic acid where possible.
- Where clotting factor concentrates are not available, access to safe blood components such as Fresh Frozen Plasma (FFP) and Cryoprecipitate.
- Access to casting and/or splinting for immobilization and mobility support aids, as needed.

7. The comprehensive care team should also include or have access to, among others:

- Chronic pain specialist.
- Dentist.
- Geneticist.
- Hepatologist.
- Infectious disease specialist.
- Immunologist.
- Gynecologist/obstetrician.
- Vocational counselor.

8. Written management protocols are required to ensure continuity of care despite changes in clinic personnel.

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

- Risks and problems of everyday living, particularly with management of bleeding.
- Changes associated with different stages of the patients growth and development (especially adolescence and aging)
- Issues regarding schooling and employment.
- Risk of having another affected child and the options available.

10. Establishing a long-term relationship between patients/ families and members of the comprehensive care team promotes compliance.

Functions of a comprehensive care program

1. To provide or coordinate inpatient (i.e. during hospital stays) and

outpatient (clinic and other visits) care and services to patients and their family.

- Patients should be seen by all core team members at least yearly (children every six months) for a complete hematologic, musculoskeletal, and psychosocial assessment and to develop, audit, and refine an individual's comprehensive management plan. Referrals for other services can also be given during these visits.
- The management plan should be developed with the patient and communicated to all treaters and care facilities communication among treaters is important.
- Smaller centers and personal physicians can provide primary care and management of some complications, in frequent consultation with the comprehensive care center (particularly for patients who live a long distance from the nearest Hemophilia treatment center).

2. To initiate, provide training for, and supervise home therapy with clotting factor concentrates where available.
3. To educate patients, family members and other caregivers to ensure that the needs of the patient are met.
4. To collect data on sites of bleeds, types and doses of treatment given, assessment of long-term outcomes (particularly with reference to musculoskeletal function), complications from treatment, and surgical procedures. This information is best recorded in a computerized registry and should be updated regularly by a designated person and maintained in accordance with confidentiality laws and other national regulations. Systematic data collection will:

    - Facilitate the auditing of services provided by the Hemophilia treatment center and support improvements to care delivery.
    - Help inform allocation of resources.
    - Promote collaboration between centers in sharing and publishing data and exchange of resources wherever possible.

5. Where possible, to conduct basic and clinical research. Since the number of patients in each center may be limited, clinical research is best conducted in collaboration with other hemophilia centers.

1.4 Fitness and physical activity

1. Physical activity should be encouraged to promote physical fitness and normal neuromuscular development, with attention paid to muscle strengthening, coordination, general fitness, physical functioning, healthy body weight, and self-esteem.

2. Bone density may be decreased in people with Hemophilia.

3. For patients with significant musculoskeletal dysfunction, weight-bearing activities that promote development and maintenance of good bone density should be encouraged, to the extent their joint health permits.

4. The choice of activities should reflect an individual's preference interests, ability, physical condition, local customs, and resources.

5. Non-contact sports such as swimming, walking, golf, badminton, archery, cycling, rowing, sailing, and table tennis should be encouraged.

6. High contact and collision sports such as soccer, hockey, rugby, boxing, and wrestling, as well as high-velocity activities such as motocross racing and skiing, are best avoided because of the potential for life-threatening injuries, unless the individual is on good prophylaxis to cover such activities.

7. Organized sports programs should be encouraged as opposed to unstructured activities, where protective equipment and supervision may be lacking.

8. The patient should consult with a musculoskeletal professional before engaging in physical activities to discuss their appropriateness, protective gear, prophylaxis (factor and other measures), and physical skills required prior to beginning the activity. This is particularly important if the patient has any problem target joints.

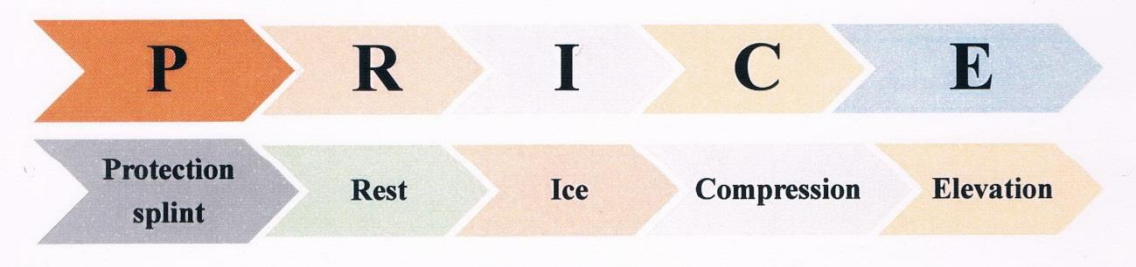
9. Target joints can be protected with braces or splints during activity, especially when there is no clotting factor coverage.

10. Activities should be re-initiated gradually after a bleed to minimize the chance of a re-bleed.

1.4 Adjunctive management

1. Adjunctive therapies are important, particularly where clotting factor concentrates are limited or not available, and may lessen the amount of treatment product required.
2. First aid measures: In addition to increasing factor level with clotting factor concentrates (or Desmopressin in mild Hemophilia A), protection (splint),rest, ice, compression, and elevation **(** PRICE **)** may be used as adjunctive management for bleeding in muscles and joints.

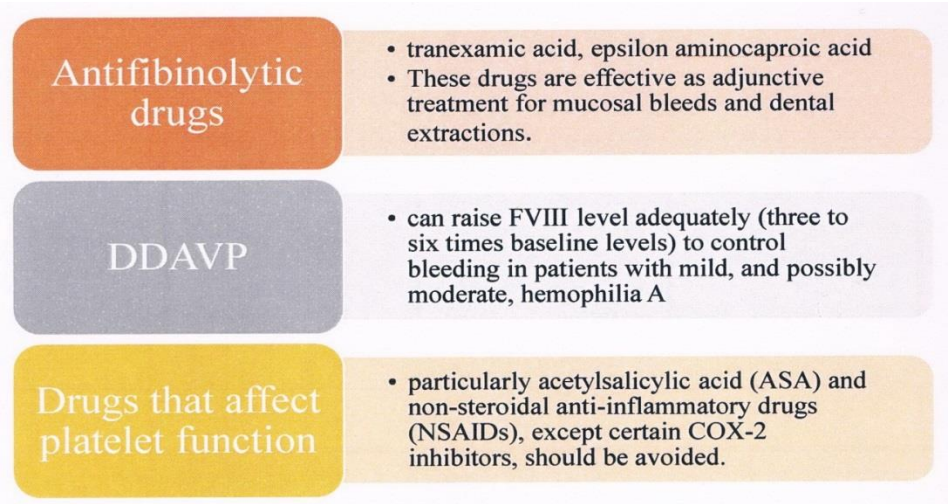
PRICE



Patients with intra articular hip bleeding should rest in bed with traction to relieve intra articular pressure.

3. Physiotherapy/rehabilitation is particularly important for functional improvement and recovery after musculoskeletal bleeds and for those with established hemophilic arthropathy

. 4. Drugs



1.5 Prophylactic factor replacement therapy

1. Prophylaxis is the treatment by intravenous injection of factor concentrate in order to prevent anticipated bleeding.
2. Prophylaxis was conceived from the observation that moderate hemophilia patients with clotting factor level >1 IU/dl seldom experience spontaneous bleeding and have much better preservation of joint function.
3. Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function.
4. Prophylactic replacement of clotting factor has been shown to be useful even when factor levels are not maintained above 1 IU/dl at all times.
5. In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for four to eight weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis.
6. Prophylaxis does not reverse established joint damage; however, it decreases frequency of bleeding and may slow progression of joint disease and improve quality of life.

TABLE 1-4: DEFINITIONS OF FACTOR REPLACEMENT THERAPY PROTOCOLS [64]

PROTOCOL	DEFINITION
Episodic (”on demand") treatment	Treatment given at the time of clinically evident bleeding
Continuous prophylaxis Primary prophylaxis	Regular continuous* treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging , and started before the second clinically evident large joint bleed and age 3 years**
Secondary prophylaxis	Regular continuous* treatment started after 2 or more bleeds into large joints** and before the onset of joint disease documented by physical examination and imaging studies.
Tertiary prophylaxis	Regular continuous* treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent ("periodic") prophylaxis	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

* Continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

**large joints = ankles, knees, hips, elbows and shoulders.

Administration and dosing schedules

1. There are two prophylaxis protocols currently in use for which there is long-term data:

- The Malmo protocol: [full dose prophylaxis]: 25-40 IU/kg per dose. Administered three times a week for those with Hemophilia A, and twice a week for those with Hemophilia B.
- The Dutch protocol: [Intermediate dose] 15-30 IU/kg per dose. Administered 2 -3 times a week for those with Hemophilia A, and twice a week for those with Hemophilia B.
- Chines and iranion protocol [low dose] 10-15 IU/Kg per dose. Administered 3 times a week for those with Hemophilia A, and twice a week for those with Hemophilia B.
-

2. However, many different protocols are followed for prophylaxis, even within the same country, and the optimal regimen remains to be defined.

3. The protocol should be individualized as much as possible, based on age, venous access, bleeding phenotype, activity, and availability of clotting factor concentrates and family understanding and cooperation.

4. One option for the treatment of very young children is to start prophylaxis once a week and escalate depending on bleeding and venous access. While in older children or those with two bleeding episodes or two or more large joint bleeding episods, it is better to start with twice injections / week than once weekly.

5. Prophylaxis is best given in the morning to cover periods of activity.

6. Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury.

7- Hemophiliac patients remain at risk of developing joint bleeding at their adulthood, and trial of switching to on demand, lead to Hemarthrosis, so our policy is to continue prophylaxis in to adult life.

8- Conclusion: Prophylaxis is given to:

- All boys with severe Hemophilia A & B.
- Around the age one year.
- At an intermediate dose usually 15-25 IU/ Kg and low dose at times of shortage of factors.
- Frequency: Twice weekly for Hemophilia A and B.
- Individualization.

1.6 Home Therapy

1. Where appropriate and possible, persons with Hemophilia should be managed in a home therapy setting.
2. Home therapy allows immediate access to clotting factor and hence optimal early treatment, resulting in decreased pain, dysfunction, and long term disability and significantly decreased hospital admissions for complications.
3. Further improvements in quality of life include greater freedom to travel and participate in physical activities, less absenteeism, and greater employment stability.
4. Home treatment must be supervised closely by the comprehensive care team and should only be initiated after adequate education and training

1.7 Monitoring health status and outcome

Regular standardized valuation at least every 12 months for severe bleeding episodes allows longitudinal assessment for individual patient and can identify new potential problems in their early stages so that treatment plans can be modified:

The following should be evaluated:

- Venous access.
- Bleeding records [paper or electronic] that include data and site of bleeding, dosage and lot number of product used and adversed effect.
- Use of products for replacement therapy and the response to them.
- Musculoskeletal status.
- Transfusion transmitted infection.
- Inhibitors.
- Psychological status.
- Dental/oral health.

Several Hemophilia-specific scores are available to measure joint impairment and function, including activities and participation these include:

- Clinical: Hemophilia Joint Health Score (HJHS).
- Radiological: Patterson score, MRI, and ultrasound scores.
- Activity: (Functional Independence Score in Hemophilia (FISH).

1.9 Pain management

- Acute and chronic pain are common in patients with hemophilia. Adequate assessment of the cause of pain is essential to guide proper management.

Pain caused by venous access

1. In general, no pain medication is given.
2. In some children, application of a local anesthetic spray or cream at the site of venous access may be helpful.

Pain caused by joint or muscle bleeding

- While clotting factor concentrates should be administered as quickly as possible to stop bleeding, additional drugs are often needed for pain control.

Post-operative pain

1. Intramuscular injection of analgesia should be avoided.
2. Post-operative pain should be managed in coordination with the anesthesiologist.
3. Initially, intravenous morphine or other narcotic analgesics can be given, followed by an oral opioid such as tramadol, codeine, hydrocodone, and others.
4. When pain is decreasing, Paracetamol/Acetaminophen may be used.

Pain due to chronic hemophilic arthropathy

1. Chronic hemophilic arthropathy develops in patients who have not been adequately treated with clotting factor concentrates for joint bleeding.
2. Treatment includes functional training, adaptations, and adequate analgesia as suggested in table 1.5.
3. COX-2 inhibitors have a greater role in this situation.
4. Other NSAIDs should be avoided.
5. When pain is disabling, orthopedic surgery may be indicated.

TABLE 1-5: Stepwise approach to use of analgesic for pain control in hemophilic patient

Step	Medication	Dosage &administration
1	Acetaminophen	Acetaminophen up to 650 mg dose* and 3250 mg day
2	COX-2 inhibitor	Celecoxib 100-200mg 1-2/ day
3	Acetaminophen + Codaine or acetominophine + tramadol	10-20 mg up to 6 time /day or 50-100 mg 3-4 time/day
4	Morphine or l Equivalent	Slow- release formulation 20 mg 2 time / day. allow rescue dose of rapid release 10 mg 4 time / day. Increase slow Dose if rapid release is used less than 4 time / day.

NSAID: Non-steroidal anti-inflammatory drug, COX-2: Cyclo-oxygenase-2 inhibitor.

1.10 Surgery and invasive procedures

1. Surgery may be required for hemophilia-related complications or unrelated diseases. The following issues are of prime importance when performing surgery on persons with Hemophilia.
2. Surgery for patients with hemophilia will require additional planning and interaction with the healthcare team than what is required for other patients.
3. A Hemophilia patient requiring surgery is best managed at or in consultation with a comprehensive Hemophilia treatment center.
4. The anesthesiologist should have experience treating patients with bleeding disorders. Spinal anesthesia should be avoided and General anesthesia is preferred.
5. Adequate laboratory support is required for reliable monitoring of clotting factor level and inhibitor testing.
6. Pre-operative assessment should include inhibitor screening and inhibitor assay, particularly if the recovery of the replaced factor is significantly less than expected.
7. Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.
8. Adequate quantities of clotting factor concentrates should be available for the surgery itself and to maintain adequate coverage post-operatively for the length of time required for healing and/or rehabilitation.
9. If clotting factor concentrates are not available, adequate blood bank support for plasma components is needed.
10. The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed
11. Patients with mild Hemophilia A, as well as patients receiving intensive factor replacement for the first time, are at particular risk of inhibitor development and should be re-screened 4–12 weeks post-operatively.
12. Careful monitoring for inhibitors is also advisable in patients with non-severe hemophilia A receiving continuous infusion after surgery.
13. Infusion of factor concentrates/hemostatic agents is necessary before invasive diagnostic procedures such as lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy.

1.11 Dental care and management

1. For persons with hemophilia, good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding.
2. Dental examinations should be conducted regularly, starting at the time the baby teeth start to erupt.
3. Teeth should be brushed twice a day with a medium texture brush to remove plaque deposits.
4. Dental floss or interdental brushes should be used wherever possible.
5. Toothpaste containing fluoride should be used in areas where natural fluoride is not present in the water supply. Fluoride supplements may also be prescribed if appropriate.
6. An orthodontic assessment should be considered for all patients between the ages of 10–14 in order to determine if there are any problems associated with overcrowding, which can result in periodontal disease if left untreated.
7. Close liaison between the dental surgeon and the Hemophilia team is essential to provide good comprehensive dental care.
8. Treatment can be safely carried out under local anesthesia using the full range of techniques available to dental surgeons. Infiltration, intrapapillary, and intra-ligamentary injections are often done under factor cover (20-40%) though it may be possible for those with adequate experience to administer these injections without it.
9. Treatment from the hemophilia unit may be required before an inferior alveolar nerve block or lingual infiltration.
10. Dental extraction or surgical procedures carried out within the oral cavity should be done with a plan for hemostasis management, in consultation with the hematologist.
11. Tranexamic Acid or Epsilon Aminocaproic Acid (EACA) is often used after dental procedures to reduce the need for replacement therapy.
12. Oral antibiotics should only be prescribed if clinically necessary.
13. Local hemostatic measures may also be used whenever possible following a dental extraction. Typical products include oxidized cellulose and fibrin glue.
14. Following a tooth extraction, the patient should be advised to avoid hot food and drinks until normal feeling has returned. Smoking

should be avoided as this can cause problems with healing. Regular warm salt water mouth washes (atea-spoon of salt in a glass of warm water) should begin the day after treatment and continue for five to seven days or until the mouth has healed.

15. Prolonged bleeding and/or difficulty in speaking, swallowing, or breathing following dental manipulation should be reported to the hematologist/dental surgeon immediately.

16. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin must be avoided.

17. An appropriate dose of Paracetamol/Acetaminophen every six hours for two to three days will help prevent pain following an extraction.

18. The presence of blood-borne infections should not affect the availability of dental treatment.

19. Prevention of bleeding at the time of dental procedures in patients with inhibitors to FVIII or FIX requires careful planning.

2 Special Management Issues

2.1 Carriers

1. Hemophilia is an X-linked disorder that typically affects males, while females are carriers.
2. Obligate carriers are:
    - Daughters of a person with hemophilia.
    - Mothers of one son with hemophilia and who have at least one other family member with Hemophilia.
    - Mothers of one son with Hemophilia and who have a family member who is a known carrier of the hemophilia gene.
    - Mothers of two or more sons with hemophilia.
3. The expected mean clotting factor level in carriers of hemophilia is 50% of the levels found in the healthy population.
4. Most carriers are asymptomatic.
5. Carriers with clotting factor levels of 40-60% of normal may have an increased bleeding tendency.
6. 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 lionization.
7. Carriers with clotting factor levels in the Hemophilia range may be symptomatic with bleeding manifestations commensurate with their degree of clotting factor deficiency, particularly during trauma and surgery.
8. Menorrhagia and bleeding after medical interventions are the most common manifestations among carriers with significantly low factor levels
9. Carriers with low clotting factor levels should be categorized as having hemophilia of appropriate severity and managed accordingly.
10. Birth control pills and antifibrinolytic agents are useful in

controlling symptoms of menorrhagia.

11. Levels of factor VIII increase significantly in pregnancy.Levels of factor IX, however, do not usually change significantly.

12. Immediate female relatives (mother, sisters, and daughters) of a person with hemophilia should have their clotting factor level checked, especially prior to any invasive intervention, childbirth, or if any symptoms occur.

2.2 Genetic testing / counselling and prenatal diagnosis

1. Where available and possible, genetic testing for carrier status should be offered to at-risk female family members of people with hemophilia to facilitate genetic counseling, and if desired by the family, prenatal diagnosis.

2. DNA-based mutation analysis to identify the specific mutation responsible for hemophilia in a particular family is becoming technically easier and more widely available. This facilitates identification of carriers and prenatal diagnosis for male fetuses.

3. Genetic counseling is key to helping people with Hemophilia, carriers, and their families make more informed choices.

4. 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 to help the family prepare and to plan delivery. Assisted delivery is best avoided in an affected fetus.

5. Fetal gender can be determined by ultrasonography. Beginning week 11 of gestation .Caesarian section is preferable if the fetus gender is male to decrease the chance of intra cranial bleeding.

6. Chorionic villus sampling (CVS), or biopsy, is the main method of prenatal diagnosis and is best done between 9-14 weeks of gestation. Biopsy carried out earlier may be associated with increased complications including fetal limb abnormalities.

7. Amniocentesis can be done at 15-17 weeks of gestation.

8. It is important to be aware of and to follow the relevant laws governing such procedures in the country where the service is being provided.

9. For carriers with low factor levels (< 50 IU/dl), hemostatic support may be required to prevent maternal bleeding during prenatal diagnosis procedures.

10. All invasive methods used for prenatal diagnosis may cause feto-maternal hemorrhage. Anti-D immunoglobulin should be given if the mother is Rh D negative.

11. Pre-implantation genetic diagnosis allows selection of embryos without specific mutation to be implanted into the uterus

2.3 Delivery of infants with known or suspected haemophilia

1. FVIII levels usually rise into the normal range during the second and third trimesters and should therefore be measured in carriers during the third trimester of pregnancy to inform decisions for factor coverage during delivery.

2. In carriers with significantly low factor levels (< 50 IU/dl), clotting factor replacement is necessary for surgical or invasive procedures including delivery.

3. The need for clotting factor replacement should be planned in the prenatal period.

4. Route of delivery in carriers with a normal fetus should be as per obstetric indications.

5. Delivery of infants with known or suspected Hemophilia should be atraumatic, regardless of whether it is vaginal or cesarean, to decrease the risk of bleeding.

6. Forceps and vacuum extraction should be avoided [in vaginal delivery, as well as invasive procedures to the fetus such as fetal scalp blood sampling and internal fetal scalp electrodes.

7. As soon as the baby is delivered, a sample of blood from the umbilical cord should be collected to measure clotting factor levels. Injections into the baby's muscle tissue and other surgical procedures should be avoided until the results of these blood tests are known.

- Postpartum hemorrhage PPH (up to six weeks after childbirth) is a major cause of maternal death and disability
- Certain precautions can be taken to reduce the risk of PPH :
  - Medications that keep the uterus contracted can be given.
  - The placenta should be delivered by controlled traction of the umbilical cord. This is called "active management" for placenta delivery and has been shown to significantly reduce the risk of PPH. Treatment may be recommended as a preventive measure, especially in carriers with low clotting factor levels.

2.4 Vaccinations

1. Persons with bleeding disorders should be vaccinated, but should preferably receive the vaccine subcutaneously rather than intramuscularly or intradermally, unless covered by infusion of clotting factor concentrates.

2. If intramuscular injection is to be given:

   - It is best done soon after a dose of factor replacement therapy.
   - An ice pack can be applied to the injection area for five minutes before injection.
   - The smallest gauge needle available (usually25-27 gauge) should be used.
   - Pressure should be applied to the injection site for at least five minutes.

3. Live virus vaccines (such as oral polio vaccine, MMR) may be contraindicated in those with HIV infection.

4. People with Hemophilia who have HIV should be given pneumococcal and annual influenza vaccines.

5. Immunization to hepatitis A and B is important for all persons with Hemophilia. These immunizations may not be as effective in those with HIV infection.

2.5 Ageing hemophilia patients

1. Ageing patients with Hemophilia will inevitably suffer from age-related diseases.

2. Comorbidities in ageing hemophilia patients should be managed appropriately as they may accentuate problems associated with Hemophilia and impact the patient's physical and psychosocial Health, and thus their quality of life.

Osteoporosis

1. Bone mineral density (BMD) is decreased in people with Hemophilia.

2. An increased number of arthropathic joints, loss of joint movement, and muscle atrophy leading to inactivity are associated with a lower BMD.

3. Weight-bearing activities (suitable sports) that promote development and maintenance of good bone density should be encouraged if joint health permits.

4. Calcium and vitamin D supplementation are also important and bisphosphonate therapy may be required. A dental evaluation is advisable before initiating long-term bisphosphonate therapy.

Obesity

1. The prevalence of overweight (BMI 25-30 kg/m2) and obesity (BMI > 30kg/m2) is increasing.

2. Lack of activity may contribute to an increase in BMI and increased body weight.

3. A high BMI has been associated with:

- A significant limitation in range of motion (ROM).
- Increased arthropathic pain.
- Increased risk of developing target joints.
- Increased risk of diabetes mellitus, atherosclerosis, and cardiovascular disease, which may further damage arthropathic joints.

4. Regular physical activity should be advised.

5. If functional limitations restrict daily activities, a physiotherapist familiar with hemophilia may be able to suggest appropriate alternatives.

6. In some cases referral to a dietician may be indicated.

Hypertension

1. Hemophilia patients have a higher mean blood pressure, are twice as likely to have hypertension, and use more anti-hypertensive medication compared to the general population.

2. In view of increased risk of bleeding, hypertensive patients with hemophilia should be treated adequately and have their blood pressure checked regularly.

3. In the absence of other cardiovascular risk factors, a systolic blood pressure ≤120 mmHg and a diastolic pressure ≤80 mmHg should be maintained.

Diabetes mellitus (DM)

1. The prevalence of DM in Hemophilia is not well documented, but was observed to be higher in a cohort of mild hemophilia.

2. In ageing hemophilia patients, especially among those who are overweight, glucose levels should be checked annually.

3. If treatment with insulin is indicated, subcutaneous injections can be administered without bleeding complications.

Hypercholesterolemia

1. Mean cholesterol levels in patients with Hemophilia have been reported to be lower than in the general population.

2. Cholesterol levels (total cholesterol, HDL, and LDL fraction) should be measured in ageing Hemophilia patients at risk of cardiovascular disease.

3. Treatment is indicated if cholesterol levels are high. As a general rule, the total cholesterol/HDL ratio should not be higher than 8.

Cardiovascular disease

1. Hemophilia patients appear to have a reduced risk of mortality from ischemic cardiovascular disease, but the number of deaths from this cause is increasing.

2 A possible association between the occurrence of myocardial infarction and previous administration of clotting factor concentrates has been described.

3. Hemophilia patients with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist.

4. For acute coronary syndromes requiring percutaneous cardiac intervention (PCI):

- Adequate correction with clotting factor concentrates before PCI and until 48 hours [after PCI is required.
- High factor levels should be avoided in order to prevent occlusive thrombi. During complete correction :
  - Heparin can be administered according to standard cardiologic treatment protocols.
  - Glycoprotein IIb/IIIainhibitors (abciximab, tirofiban] used in PCI with stenting can be administered.
- Radial artery access site, if technically possible, is preferred over femoral, in order to minimize retroperitoneal or groin bleeds.
- Factor concentrates should be given for the duration of dual antiplatelet therapy, usually about two weeks, aiming at trough levels of 30 IU/dl.
- Prolonged use of aspirin is not recommended in severe Hemophilia. Its use in patients on regular intensive prophylaxis is possible, though the data available is inadequate.

Psychosocial impact

1. In the ageing patient, the presence of crippling, painful arthropathy can affect quality of life and may lead to loss of independence.

2. Patients may be confronted with unexpected emotional problems due to memories of negative experiences related to hemophilia (such as hospitalization) during their youth.

3. Adaptations at home or at work and an adequate pain schedule are indicated to improve quality of life and preserve independence.

4. Active psychosocial support should be provided by a social worker, hemophilia nurse, physician and/or psychologist.

3 LABORATORY DIAGNOSIS

3.1 Knowledge and expertise in coagulation laboratory testing Principles of diagnosis

1. Understanding the clinical features of Hemophilia and the appropriateness of the clinical diagnosis.
2. Using screening tests to identify the potential cause of bleeding, for example, platelet count, bleeding time (BT; in select situations), or other platelet function screening tests, prothrombintime (PT), and activated partial thromboplastin time (APTT).
3. Confirmation of diagnosis by factor assays and other appropriate specific investigations.

Technical aspects

Preparation of the patient prior to taking a blood sample:

1. Fasting is not normally necessary before collection [of blood for investigation of possible bleeding disorders, although a gross excess of lipids may affect some automated analysers.
2. Patients should avoid medications that can affect test results such as aspirin, which can severely affect platelet function and prolong the bleeding closure time.
3. Patients should avoid strenuous exercise immediately prior to venipuncture.
4. If a patient is particularly stressed by the sample collection procedure, the levels of FVIII and von Willebrand factor may be temporarily elevated.

Sample collection

1. The sample should be collected as per standard guidelines.
2. The sample should preferably be collected near the laboratory to ensure quick transport.

3. Samples should be tested within four hours of collection.

4. Results of tests can change according to the sample storage conditions. Higher temperatures (>25°C) lead to loss of FVIII activity over time, whereas sample storage in the cold (2-8°C) leads to cold activation. The sample should therefore be maintained at temperatures between 20°C and 25°C where possible, but for no more than four hours.

5. Venipuncture must be clean and the sample collected within one minute of tourniquet application. Without prolonged venous stasis.

6. Blood should be withdrawn into a plastic syringe or an evacuated collection system. The needle should be 19-21 gauge for adults and 22-23 gauge. For small children. Collection through peripheral venous catheters or non-heparinized central venous catheters can be successful for many tests of hemostasis.

7. Blood from an indwelling catheter should be avoided for coagulation tests.

8. Frothing of the blood sample should also be avoided. It is often useful to discard the first 2 ml of blood collected.

9. The sample should be collected in citrate tubes containing 0.105M–0.109M (3.2%) aqueous tri sodium citrate dihydrate, maintaining the proportion of blood to citrate as 9:1. If the tube contains less than 80% of the target volume, results may be adversely affected. The higher strength concentration of 3.8% tri sodium citrate is no longer recommended.

10. Prompt and adequate mixing with citrate solution should be done by gentle inversion.

11. If the sample cannot be processed within four hours of collection, the platelet poor plasma can be frozen at -30°C and stored for a few weeks, or up to six months if stored at -70°C [3]. Storage at -20°C is usually inadequate.

12. Frozen samples must be thawed rapidly for four to five minutes at 37°C to avoid formation of cryoprecipitate.

Preparation of platelet-poor plasma (PPP)

1. PPP should be prepared as per standard guidelines.

2. PPP is prepared by centrifugation of a sample at a minimum of 1700g for at least 10 minutes at room temperature (i.e. not refrigerated).

3. PPP may be kept at room temperature (20–25°C) prior to testing.

4. Plasma that has been hemolysed during collection and processing should not be analysed.

End-point detection

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

2. For manual testing, the tube should be tilted three times every five seconds through an angle of approximately 90° during observation. The tube should be immersed in a water bath at 37C between tilting.

Screening tests

1. Platelet count, CBC, BT, PT, and APTT may be used to screen a patient suspected of having a bleeding disorder.

2. Bleeding time lacks sensitivity and specificity and is also prone to performance-related errors. Therefore other tests of platelet function such as platelet aggregometry are preferred when available.

3. Based on the results of these tests, the category of bleeding disorder may be partially characterized to guide subsequent analysis (see Table 3-1, above).

4. These screening tests may not detect abnormalities in patients with mild bleeding disorders including some defects of platelet function, FXIII deficiency, and those rare defects of fibrinolysis, which may be associated with a bleeding tendency.

TABLE 3-1: INTERPRETATION OF SCREENING TESTS

POSSIBLE DIAGNOSIS	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

* Results of APTT measurements are highly dependent on the laboratory method used for analysis.

** The same pattern can occur in the presence of FXI, FXII, prekallikrein, or high molecular weight kininogen deficiencies.

Correction studies [Mixing study]

1. Correction or mixing studies using pooled normal plasma (PNP) will help to define whether prolonged coagulation times are due to factor deficiency or circulating anticoagulants of inhibitors .Correction studies with FVIII/FIX-deficient plasma may be used to identify the particular deficiency if a factor assay is not available.

Factor assays

1. Factor assay is required in the following situations:-

- To determine diagnosis.
- To monitor treatment.
  - The laboratory monitoring of clotting factor concentrates is possible by measuring pre and post-infusion clotting factor levels.
  - Lower than expected recovery and/or reduced half-life of infused clotting factor 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.

2. Phenotypic tests lack sensitivity and specificity for the detection of carriers. Some obligate carriers may have a normal FVIII.C/VWF:Ag ratio. Genotypic testing is a more precise method of carrier detection and is therefore recommended.

3. One-stage Assays based on APTT are the most commonly used

techniques. The following assay features are important:

- FVIII- and FIX-deficient plasma must completely lack FVIII and FIX respectively, i.e. contain < 1 IU/dl, and have normal levels of other clotting factors.
- The reference/calibration plasma, whether commercial or locally prepared, must be calibrated in international units (i.e. against an appropriate WHO international standard).
- At least three different dilutions of the reference plasma and the test sample under analysis are needed for a valid assay.
- Use of a single dilution of test sample substantially reduces the precision of the test and may lead to completely inaccurate results in the presence of some inhibitors.
- When assaying test samples from subjects with moderate or severe hemophilia, an extended or separate calibration curve may be needed. It is not acceptable to simply extend the calibration curve by extrapolation without analyzing additional dilutions of the calibration plasma.
- Some cases of genetically confirmed mild Hemophilia A have normal FVIII activity when the one-stage assay is used for diagnosis, but reduced activity in chromogenic and two-stage clotting assays. The reverse can also occur. This means that more than one type of FVIII assay is needed to detect all forms of mild Hemophilia A.

Inhibitor testing

1. The presence of some form of inhibitor is suspected when there is a prolonged APTT that is not fully corrected by mixing patient plasma with PNP.

2. The most frequently encountered functional inhibitors of hemostasis are lupus anticoagulants (LA), which are not directed against specific clotting factors and which should be excluded.

3. Results of APTT testing on mixtures of test and normal plasma can be difficult to interpret, particularly since in acquired hemophilia there may initially be a full correction of APTT in the presence of a potent specific anti-FVIII antibody.

4. Most FVIII inhibitors that occur secondary to replacement therapy in subjects with hemophilia A show a characteristic pattern: the APTT of a patient/PNP mixture is intermediate, i.e. between the APTTs of the two materials, and is further prolonged when the mixture is incubated at 37°C for 1-2 hours.

5. Confirmation that an inhibitor is directed against a specific clotting factor requires a specific inhibitor assay.

6. The Nijmegen modification of the FVIII inhibitor assay offers improved specificity and sensitivity over the original Bethesda assay.

7. It is performed as follows:-

- Buffered PNP (providing FVIII) is mixed with test plasma and incubated at 37°C.
- After two hours, the residual FVIII is measured by comparison against the FVIII in a control mixture comprised of buffered PNP and FVIII deficient plasma, which has been incubated alongside the test mixture.
- Residual FVIII is converted into inhibitor units using a semi-log plot of the residual FVIII against inhibitor convention, which has been constructed using the assumption that 100% residual = 0 BU/ml inhibitor, and 50% residual= 1.0 BU/ml (the latter being the internationally agreed convention for defining inhibitor activity).
- When residual FVIII activity is < 25%, the patient plasma must be retested after dilution to avoid underestimation of the inhibitor potency.
- An inhibitor titer of ≥ 0.6 BU/ml is to be taken as clinically significant.

Trained personnel

1. Even the simplest coagulation screening tests are complex by nature.

2. A laboratory scientist/technologist with an interest in coagulation must have an in-depth understanding of the tests in order to achieve accurate results.

3. In some cases, it may be beneficial to have a laboratory scientist/technologist who has had further training in a specialist center.

3.3 Quality assurance

1. Quality assurance (QA) is an umbrella term used to describe all measures taken to ensure the reliability of laboratory testing and reporting.

2. QA covers all aspects of the diagnosis process from sample-taking, separation and analysis, and internal quality control through to reporting of the result and ensuring that it reaches the clinician.

3. It is the responsibility of everyone involved to make sure that the procedures are followed in the correct manner.

Internal quality control (IQC)

1. IQC is used to establish whether a series of techniques and procedures is being performed consistently over a period of time.

2. IQC measures are taken to ensure that the results of laboratory investigations are reliable enough to assist clinical decision making, monitor therapy and diagnose hemostatic abnormalities.

3. IQC is particularly useful to identify the degree of precision of a particular technique.

4. For screening tests of hemostasis, normal and abnormal plasma samples should be included regularly. At least one level of IQC sample should be included with all batches of tests.

External quality assessment (EQA)

1. Laboratories are strongly advised to participate in an external quality assessment scheme (EQAS) to audit the effectiveness of the IQC systems in place.

2. EQAS helps to identify the degree of agreement between the laboratory results and those obtained by other laboratories.

3. Participation in such a scheme helps build confidence between a laboratory and its users.

4. The WFH IEQAS is specifically designed to meet the needs of hemophilia treatment centers worldwide. The scheme includes analyses relevant to the diagnosis and management of this scheme, which is operated in conjunction with the U.K. National External Quality Assessment Service for Blood Coagulation in Sheffield, U.K., can be obtained from the WFH

5. Other national and international quality assessment schemes are also available.

6. In order for a laboratory to attain a high level of testing reliability and to participate successfully in EQAS, it must have access to appropriate reagents and techniques and an appropriate number of adequately trained staff.

4 HEMOSTATIC AGENTS

4.1 Clotting factor concentrates

- The WFH strongly recommends the use of viral inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate or fresh frozen plasma for the treatment of hemophilia and other inherited bleeding disorders.

FVIII concentrates

1. FVIII concentrates are the treatment of choice for Aemophilia A.

2. Vials of factor concentrates are available in dosages ranging from approximately 250 to 3000 units each.

2. In the absence of an inhibitor, each unit of FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level approximately 2 IU/dl.

3. The half-life of FVIII is approximately 8-12 hours.

4. The patient's factor level should be measured 15 minutes after the infusion to verify the calculated dose.

5. The dose is calculated by multiplying the patient's weight in kilograms by the desired rise in factor level in IU/dl, multiplied by 0.5.

Example:

50 kg × 40 (IU/dl desired rise in level) × 0.5 = 1,000 units of FVIII. Refer to Tables 7-1 and 7-2 for suggested factor level and duration of replacement required based on type of hemorrhage.

6. FVIII should be infused by slow IV injection at a rate not to exceed 3 ml per minute in adults and 100 units per minute in young children, or as specified in the product information leaflet.

7. Subsequent doses should ideally be based on the half-life of FVIII and on the recovery in an individual patient for a particular product.

8. It is best to use the entire vial of FVIII once reconstituted, though many products have been shown to have extended stability after reconstitution.

9. Continuous infusion avoids peaks and troughs and is considered by some to be advantageous and more convenient. However, patients must be monitored frequently for pump failure.

10. Continuous infusion may lead to a reduction in the total quantity of clotting factor concentrates used and can be more cost-effective in patients with severe Hemophilia. However, this cost effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions.

11. Dose for continuous infusion 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.

FIX concentrates

1. FIX concentrates are the treatment of choice for Hemophilia B.
2. A product containing only FIX is more appropriate than prothrombin complex concentrates, which also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture. Products containing activated clotting factors may predispose to thromboembolism.
3. FIX concentrates fall into two classes:
    - Pure FIX concentrates, which may be plasma derived or recombinant.
    - FIX concentrates that also contain factors II, VII, IX, and X, also known as prothrombin complex concentrates (PCCs), are only rarely used.
4. Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B as opposed to PCC.

Particularly in the following instances:

- Surgery.
- Liver disease.
- Prolonged therapy at high doses.
- Previous thrombosis or known thrombotic tendency
- Concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents.

5. Pure FIX products are free of the risks of thrombosis or disseminated intravascular coagulation (DIC), which may occur with large doses of PCCs.

Dosage/administration

1. Vials of FIX concentrates are available in doses ranging from approximately 250 to 2000 units each.

2. In absence of an inhibitor, each unit of FIX per kilogram of body weight infused intravenously will raise the plasma FIX level approximately 1 IU/dl.

3. The half-life is approximately 18–24 hours.

4. The patient's FIX level should be measured approximately 15 minutes after infusion to [verify calculated doses].

5. Recombinant FIX (rFIX) has a lower recovery than plasma-derived products, such that each unit of FIX per kg body weight infused will raise the FIX activity by approximately 0.8 IU/dl in adults and 0.7 IU/dl in children under 15 years of age. The reason for the lower recovery of rFIX is not entirely clear.

6. To calculate dosage, multiply the patient's weight in kilograms by the desired rise in factor levelin IU/dl.

Example:

50 kg × 40 (IU/dl desired rise in level) = 2000 units of plasma-derived FIX.

For rFIX, the dosage will be 2000 ÷ 0.8 (or 2000 × 1.25) =2500 units for adults, and 2000 ÷ 0.7 (or 2000 ×1.43) = 2860 units for children. Refer to Tables 7-1 and 7-2 for suggested factor level and duration of replacement therapy based on type of hemorrhage.

7. FIX concentrates should be infused by slow IV injection at a rate not to exceed a volume of 3 ml per minute in adults and 100 units per minute in young children, or as recommended in the product information leaflet. [12].

8. If used, PCCs should generally be infused at half this rate. Consult the product information leaflet for instructions.

9. Purified FIX concentrates may also be administered by continuous infusion (as with FVIII concentrates).

10. Allergic reactions may occur with infusions of FIX concentrates in patients with anti-FIX inhibitors. In such patients, infusions may need to be covered with hydrocortisone. Changing the brand of clotting factor concentrate sometimes reduces symptoms.

4.2 Other plasma products

1. The WFH supports the use of coagulation factor concentrates in preference to cryoprecipitate or fresh frozen plasma (FFP) due to concerns about their quality and safety. However, the WFH recognizes the reality that they are still widely used in countries around the world where it is the only available or affordable treatment option.

2. Cryoprecipitate and FFP are not subjected to viral inactivation procedures (such as heat or solvent/detergent treatment), leading to an increased risk of transmission of viral pathogens, which is [significant with repeated infusions

Fresh frozen plasma (FFP)

1. As FFP contains all the coagulation factors, it is sometimes used to treat coagulation factor deficiencies.

2. Cryoprecipitate is preferable to FFP for the treatment of hemophilia A.

3. Due to concerns about the safety and quality of FFP, its use is not recommended, if avoidable However, as FFP and cryo-poor plasma contain FIX, they can be used for the treatment of hemophilia B in countries unable to afford plasma-derived FIX concentrates.

Dosage/administration

1. One ml of fresh frozen plasma contains 1 unit of factor activity.

2. It is generally difficult to achieve FVIII levels higher than 30 IU/dl with FFP alone.

3. FIX levels above 25 IU/dl are difficult to achieve.

An acceptable starting dose is 15−20 ml/kg.

Cryoprecipitate

1. Cryoprecipitate is prepared by slow thawing of fresh frozen plasma (FFP) at 4°C for 10-24 hours. It appears as an insoluble precipitate and is separated by centrifugation.

2. Cryoprecipitate contains significant quantities of FVIII (about 3-5 IU/ml), VWF, fibrinogen, and FXIII but not FIX or FXI. The resultant supernatantis called cryo-poor plasma and contains other coagulation factors such as factors VII, IX, X, and XI.

3. Due to concerns about the safety and quality of cryoprecipitate, its use in the treatment of congenital bleeding disorders is not recommended and can only be justified in situations where clotting factor concentrates are not available.

Dosage/administration

- A bag of cryoprecipitate made from one unit of FFP (200-250ml) may contain 70–80 units of [FVIII in a volume of 30–40 ml.

4.3 Other pharmacological options

- In addition to conventional coagulation factor concentrates, other agents can be of great value in a significant proportion of cases. These include:
  - Desmopressin
  - Tranexamic acid
  - Epsilon aminocaproic acid

Desmopressin (DDAVP)

1. Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) is a synthetic analogue of vasopressin that boosts plasma levels of FVIII and VWF.

2. DDAVP may be the treatment of choice for patients with mild or moderate hemophilia A when FVIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using a clotting factor /concentrate.

3. Desmopressin does not affect FIX levels and is of no value in hemophilia B.

4. Each patient's response should be tested prior to therapeutic use, as there are significant differences between individuals. The response to intranasal desmopressin is more variable and therefore less predictable.

5. DDAVP is particularly useful in the treatment or prevention of bleeding in carriers of hemophilia.

6. Although DDAVP is not licensed for use in pregnancy, there is evidence that it can be safely used during delivery and in the post-partum period in an otherwise normal pregnancy. Its use should be avoided in pre-eclampsia and eclampsia because of the already high levels of VWF.

7. Obvious advantages of DDAVP over plasma products are the much lower cost and the absence of any risk of transmission of viral infections.

8. DDAVP may also be useful to control bleeding and reduce the prolongation of bleeding time associated with disorders of hemostasis, including some congenital platelet disorders.

9. The decision to use DDAVP must be based on both the baseline concentration of FVIII, the increment achieved, and the duration of treatment required.

Dosage/administration:

1. Though Desmopressin is given subcutaneously in most patients, it can also be administered by intravenous infusion or by nasal spray [Stemate]. It is important to choose the correct preparation of Desmopressin because some lower-dose preparations are used for other medical purposes. [Nocturnal enuresis].

2. Appropriate preparations include:

- 4 μg/ml for intravenous use.
- 15 μg /ml for intravenous and subcutaneous use
- 150 μg per metered dose as nasal spray

3. A single dose of 0.3 μg /kg body weight, either by intravenous or subcutaneous route, can be expected to boost the level of FVIII three- to six-fold.

4. For intravenous use, DDAVP is usually diluted in at least 50–100 ml of physiological saline and given by slow intravenous infusion over 20–30 minutes.

5. The peak response is seen approximately 60 minutes after administration either intravenously or subcutaneously.

6. Closely spaced repetitive use of DDAVP over several days may result in decreased response (tachyphylaxis). Factor concentrates may be needed when higher factor levels are required for a prolonged period.

7. Rapid infusion may result in tachycardia, flushing, tremor, and abdominal discomfort.

8. A single metered intranasal spray of 1.5 Mg/ml in each nostril is appropriate for an adult. For an individual with a bodyweight of less than 40 kg, a single dose in one nostril is sufficient. [35, 36]

9. Though the intranasal preparation is available, some patients find it difficult to use and it may be less efficacious than when given subcutaneously.

10. As a result of its antidiuretic activity, water retention and hyponatremia can be a problem. When repeated doses are given, the plasma osmolality or sodium concentration should be measured.

11. In most adults hyponatremia is uncommon.

12. Due to water retention, DDVAP should be used with caution in young children and is contraindicated in children under two years of age who are at particular risk of seizures secondary to cerebral edema due to water retention.

13. There are case reports of thrombosis (including myocardial infarction) after infusion of DDAVP. It should be used with caution in

patients with a history, or who are at risk, of cardiovascular disease.

Tranexamic acid

1. Tranexamic acid is an antifibrinolytic agent competitively inhibits the activation of plasminogento plasmin.

2. It promotes clot stability and is useful as adjunctive therapy in hemophilia and some other bleeding disorders.

3. Regular treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia.

4. It is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g. oral bleeding, epistaxis, menorrhagia).

5. Tranexamic acid is particularly valuable in the setting of dental surgery and may be used to control oral bleeding associated with eruption or shedding of teeth.

Dosage /administration

1. Tranexamic acid is usually given as an oral tablet three to four times daily. It can also be given by intravenous infusion two to three times daily, and is also available as a mouthwash.

2. Gastrointestinal upset (nausea, vomiting, or diarrhea) may rarely occur as a side effect, but these symptoms usually resolve if the dosage is reduced. When administered intravenously, it must be infused slowly as rapid injection may result in dizziness and hypotension.

3. A syrup formulation is also available for pediatric use. If this is not available, a tablet can be crushed and dissolved in clean water for topical use on bleeding mucosal lesions.

4. Tranexamic acid is commonly prescribed for seven days following dental extractions to prevent post-operative bleeding.

5. Tranexamic acid is excreted by the kidneys and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.

6. *The use of tranexamic acid is contraindicated for the treatment of hematuria* as its use may prevent dissolution of clots in the ureters, leading to serious obstructive uropathy and potential permanent loss of renal function.

7. Similarly, the drug is contraindicated in the setting of thoracic surgery, where it may result in the development of insoluble hematomas.

8. Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrates.

9. Tranexamic acid should *not* be given to patients with FIX deficiency receiving prothrombin complex concentrates, as this will exacerbate the risk of thromboembolism.

10. If treatment with both agents is deemed necessary, it is recommended that at least 12 hours elapse between the last dose of APCC and the administration of tranexamic acid.

11. In contrast, thromboembolism is less likely when tranexamic acid is used in combination with rFVIIa to enhance hemostasis.

12. Transexamic acid is contra indicated in patients with history of convulsion and thrombo - embolic disease.

Epsilon aminocaproic acid

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

Dosage/administration

1. EACA is typically administered to adults orally or intravenously every four to six hours up to a maximum of 24 g/day in an adult.

2. A 250 mg/ml syrup formulation is also available.

3. Gastrointestinal upset is a common complication,reducing the dose often helps.

4. 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.

5. The myopathy is often painful and associated with elevated levels of creatine kinase and even myoglobinuria.

6. Full resolution may be expected once drug treatment is stopped. Dose is 50 mg/Kg up to 4 doses/day.

5 TREATMENT OF SPECIFIC HEMORRHAGES

1. Bleeding in patients with hemophilia can occur at different sites (see Table 1-2 and Table 1-3), each of which requires specific management.
2. As a general principle in case of large internal hemorrhage, hemoglobin should be checked and corrected while other measures are being planned. Measures of hemodynamic stability, such as pulse and blood pressure, should be monitored as indicated.

5.1 Joint hemorrhage (hemarthrosis)

1. A joint bleed is defined as an episode characterized by rapid loss of range of motion as compared with baseline that is associated with any combination of the following pain or an unusual sensation in the joint, palpable swelling, and warmth of the skin over the joint.
2. The onset of bleeding in joints is frequently described by patients as a tingling sensation and tightness within the joint. This “aura” precedes the appearance of clinical signs.
3. The earliest clinical signs of a joint bleed are increased warmth over the area and discomfort with movement, particularly at the ends of range.
4. Later symptoms and signs include pain at rest, swelling, tenderness, and extreme loss of motion.
5. A re-bleed is defined as worsening of the condition either on treatment or within 72 hours after stopping treatment.
6. A target joint is a joint in which 3 or more spontaneous bleeds have occurred within a consecutive 6-month period.
7. Following a joint bleed, flexion is usually the most comfortable position, and any attempt to change this position causes more pain.
8. Secondary muscle spasm follows as the patient tries to prevent motion and the joint appears “frozen”.

9. The goal of treatment of acute hemarthrosis is to stop the bleeding as soon as possible. This should ideally occur as soon as the patient recognizes the "aura", rather than after the onset of overt swelling and pain.

10. Evaluate the patient clinically. Usually, X-rays and ultrasound are not indicated in the early stage.

11. Administer the appropriate dose of factor concentrate to raise the patient's factor level /suitably.

12. The definitions listed in Table 5-1 are recommended for the assessment of response to treatment of an acute hemarthrosis.

13. Instruct the patient to avoid weight-bearing, apply compression, and elevate the affected joint.

14. Consider immobilizing the joint with a splint until pain resolves.

15. Ice cold packs may be applied around the joint for 15-20 minutes every four to six hours for pain relief, if found beneficial. Do not apply ice in direct contact with skin.

16. If bleeding does not stop, a second infusion may be required. If so, repeat half the initial loading dose in 12 hours (hemophilia A) or 24 hours (hemophilia B).

17. Further evaluation is necessary if the patient's symptoms continue longer than three days. The presence of inhibitors, septic arthritis, or fracture should be considered if symptoms and findings persist.

18. Rehabilitation must be stressed as an active of the management of acute joint bleeding episode.

- As soon as the pain and swelling begin to subside, the patient should be encouraged to change the position of the affected joint from a position of comfort to a position of function, gradually decreasing the flexion of the joint and striving for complete extension.
- This should be done as much as possible with active muscle contractions. Gentle passive assistance may be used initially and with caution if muscle inhibition is present.
- Early active muscle control must be encouraged to minimize muscle atrophy and prevent chronic loss of joint motion.
- Active exercises and proprioceptive training must be continued until complete pre-bleed joint range of motion and functioning are restored and signs of acute synovitis have dissipated.
- If exercises are progressed judiciously, factor replacement is not necessarily required before exercising.

TABLE 5-1: DEFINITION OF RESPONSE TO TREATMENT OF ACUTE HEMARTHROSIS [1]

Excellent:

Complete pain relief within 8 hours and/or complete resolution of signs of bleeding after the initial injection and not requiring any further replacement therapy within 72 hours.

……
……

Good:

Significant pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but requiring more than one dose of replacement therapy within 72 hours for complete resolution

……
……

Moderate:

Modest pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection and requiring more than one injection within 72 hours but without complete resolution.

……
……

None:

No or minimal improvement, or condition worsens, within approximately 8 hours after the initial injection.

……
……

Note: The above definitions of response to treatment of an acute hemarthrosis relate to inhibitor negative individuals with hemophilia.

These definitions may require modification for inhibitor positive patients receiving bypassing agents as hemostatic cover or patients who receive factor concentrates with extended half-lives.

Arthrocentesis

1. Arthrocentesis (removal of blood from a joint) may be considered in the following situations:
    - A bleeding, tense, and painful joint which shows no improvement 24 hours after conservative treatment.
    - Joint pain that cannot be alleviated.
    - Evidence of neurovascular compromise of the limb.
    - Unusual increase in local or systemic temperature and other evidence of infection (septic arthritis).
2. Inhibitors should be considered as a reason for persistent bleeding despite adequate factorreplacement. The presence of inhibitors must be ruled out before arthrocentesis is attempted.
3. The early removal of blood should theoretically reduce its damaging effects on the articular cartilage and if there is a large accumulation of blood, early removal of blood will also decrease pain.
4. Arthrocentesis is best done soon after a bleed under strictly aseptic conditions.
5. When necessary, arthrocentesis should be performed under factor levels of at least 30–50 IU/dl for 48–72 hours. Arthrocentesis should not /be done in circumstances where such factor replacement is not available. In the presence of inhibitors, other appropriate hemostatic agents should be used for the procedure, as needed.
6. A large pore needle, at least 16-gauge, should be used.
7. The joint should be immobilized with mild compression.
8. Weight-bearing should be avoided for 24–48 hours.
9. Physiotherapy should be initiated as described above.

5.2 Muscle hemorrhage

1. Muscle bleeds can occur in any muscle of the body, usually from a direct blow or a sudden stretch.

2. A muscle bleed is defined as an episode of bleeding into a muscle, determined clinically and or by imaging studies, generally associated with pain and/or swelling and functional impairment e.g. a limp associated with a calf bleed.

3. Early identification and proper management of muscle bleeds are important to prevent permanent contracture, re-bleeding, and formation of pseudotumours.

4. Sites of muscle bleeding that are associated with neurovascular compromise, such as the deepflexor muscle groups of the limbs, require immediate management to prevent permanent damage and loss of function. These groups include:

    - The iliopsoas muscle (risk of femorocutaneous, crural, and femoral nerve palsy).
    - The superior-posterior and deep posterior compartments of the lower leg (risk of posterior. tibial and deep peroneal nerve injury).
    - The flexor group of forearm muscles (risk of Volkmann's ischemic contracture).

5. Bleeding can also occur in more superficial muscles such as the biceps brachii, hamstrings (triceps surae), gastrocnemius, quadriceps, and the gluteal muscles.

6. Symptoms of muscle bleeds are:

    - Aching in the muscle.
    - Maintenance of the limb in a position of comfort.
    - Severe pain if the muscle is stretched.
    - Pain if the muscle is made to actively contract.
    - Tension and tenderness upon palpation and possible swelling.

7. Raise the patient's factor level as soon as possible, ideally when the patient recognizes the first signs of discomfort or after trauma. If there is neurovascular compromise, maintain the levels for five to seven days or longer, as symptoms indicate.

8. Rest the injured part and elevate the limb.

9. Splint the muscle in a position of comfort and adjust to a position of function as pain allows.

10. Ice cold packs may be applied around the muscle for 15-20 minutes every four to six hours for pain relief if found beneficial. Do not apply ice in direct contact with skin.

11. Repeat infusions are often required for two to three days or much longer in case of bleeds at critical sites

causing compartment syndromes and if extensive rehabilitation is required.

12. The patient should be monitored continuously for neurovascular compromise; fasciotomy may be required in some such cases.

13. Hemoglobin level should be checked and corrected if needed as muscle bleeds can result in significant blood loss.

14. Physiotherapy should begin as soon as pain subsides and should be progressed gradually to restore full muscle length, strength, and function.

15. Factor coverage during this process is prudent, unless the physiotherapist is experienced with hemophilia management. Serial casting or splinting may be required. Supportive bracing will be required if there has been nerve damage.

16. Increasing pain during physical therapy can suggest re-bleeding and should be regularly evaluated.

Iliopsoas hemorrhage

1. 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 such as loss of patellar reflex and quadriceps weakness. The symptoms may mimic acute appendicitis, including a positive Blumberg's sign.

2. Immediately raise the patient's factor level. Maintain the levels for five to seven days or longer, as symptoms indicate.

3. Hospitalize the patient for observation and control of pain. Maintain *strict* bed rest. Ambulation with crutches is not permitted, as ambulation requires contraction of the muscle.

4. It is useful to confirm the diagnosis and monitor recovery with an imaging study (ultrasonography, /CT scan, or MRI).

5. Limit the patient's activity until pain resolves and hip extension improves. A carefully supervised program of physiotherapy is key to restoring full activity and function and preventing re-bleeding. Restoration of complete hip extension before returning to full activity is recommended.

6. If residual neuromuscular deficits persist, further orthotic support may be necessary.

7. Hydrocortizon 100mg iv may reduce edema pressure on the femoral nerve.

5.3 Central nervous system haemorrhage/head trauma

1. This is a medical emergency. Treat first before evaluating.

2. All post-traumatic head injuries, confirmed or suspected, and significant headaches must be treated as intracranial bleeds. Sudden severe pain in the back may be associated with bleeding around the spinal cord. Do not wait for further symptoms to develop or for laboratory or radiologic evaluation.

3. Immediately raise the patient's factor level when significant trauma or early symptoms occur. Further doses will depend on imaging results. Maintain factor level until etiology is defined. If a bleed is confirmed, maintain the appropriate factor level for 10-14 days.

4. Intracranial hemorrhage may be an indication for prolonged secondary prophylaxis (three to six months), especially where a relatively high risk of recurrence has been observed (e.g. in the presence of HIV infection).

5. Immediate medical evaluation and hospitalization is required. A CT scan or MRI of the brain should be performed. Neurological consultation should be sought early.

6. Severe headache may also be a manifestation of meningitis in immunocompromised patients.

5.4 Compartment syndrome and nerve compression

Just as CNS bleeding predisposes significant clinical neuronal damage from the space-occupying effect of blood in a confined volume, permanent debilitation can occur when the vascular and /or neural bundles are extremely compressed by blood. Such nerve that supply and blood vessels that supply and drain an extremity (e.g., arm or leg). Compression due to a closed space hemorrhage, known as "compartment syndrome," can compromise limb function. Predisposing injuries include blunt trauma. Arterial cannulation with iatrogenic bleeding from the puncture, and, particularly in neonates and young infants, perforation of large veins during venipuncture attempts. Initial swelling and engorgement will, if bleeding persists, result in loss of pulse and cold extremities. In addition, paresthesia or paresis accompany nerve compression. Early recognition of significant bleeding based on swelling in an extremity compartment (e.g. forearm, wrist, or calf) is essential so that CFC infusion can be initiated or accelerated. In most instances, bleeding that is recognized early can be stopped

before pulse and nerve function (indicated by peripheral pares- thesia) are impaired. However, once the distal part of the extremity becomes paler and cooler than the opposite corresponding distal extremity, surgical. Intervention with fasciotomy may be the only way to preserve function of the extremity. Fasciotomies are difficult in these circumstances, and the associated perioperative bleeding may be severe even after adequate" CFCs have been administered. Early recognition and intervention with appropriate doses (usually levels to achieve 1 IU/mL of plasma or 100% initially) will often forestall the need for fasciatomy.

5.5 Throat and neck haemorrhage

1. This is a medical emergency because it can lead to airway obstruction. Treat first before evaluating.
2. Immediately raise the patient's factor level when significant trauma or symptoms occur. Maintain the factor levels until symptoms resolve.
3. Hospitalization and evaluation by a specialist is essential.
4. To prevent hemorrhage in patients with severe tonsillitis, treatment with factor may be indicated, in addition to bacterial culture and treatment with appropriate antibiotics.

5.6 Acute gastrointestinal (GI) haemorrhage

1. Immediately raise the patient's factor levels. Maintain the factor level until hemorrhage has stopped and etiology is defined.
2. Acute gastrointestinal hemorrhage may present as hematemesis, hematochezia, or malena.
3. For signs of GI bleeding and/or acute hemorrhage in the abdomen, medical evaluation and possibly hospitalization are required.
4. Hemoglobin levels should be regularly monitored .Treat anemia or shock, as needed.
5. Treat origin of hemorrhage as indicated.
6. EACA or Tranexamic acid may be used as adjunctive therapy for patients with FVIII deficiency and those with FIX deficiency who are not being treated with prothrombin complex concentrates.

5.7 Acute abdominal haemorrhage

1. An acute abdominal (including retroperitoneal) haemorrhage can present with abdominal pain and distension and can be mistaken for a number of infectious or surgical conditions. It may also present as a paralytic ileus. Appropriate radiologic studies may be necessary.
2. Immediately raise the patient's factor levels. Maintain the factor levels) until the etiology can be defined, then treat appropriately in consultation with a specialist.

5.8 Ophthalmic hemorrhage

1. This is uncommon unless associated with trauma or infection.
2. Immediately raise the patient's factor level. /Maintain the factor level as indicated
3. Have the patient evaluated by an ophthalmologist as soon as possible.

5.9 Renal haemorrhage

1. Treat painless hematuria with complete bed /rest and vigorous hydration [3 litres / m bodysurface area] for 48 hours. Avoid DDAVP when hydrating intensively.
2. Raise the patient's factor levels (refer to Tables /7-1 and 7-2) if there is pain or persistent gross hematuria and watch for clots and urinary obstruction.
3. Do not use antifibrinolytic agents.
4. Evaluation by an urologist is essential for evaluation of a local cause if hematuria (gross or microscopic) persists or if there are repeated episodes.

5.10 Oral haemorrhage

1. Early consultation with a dentist or oral and maxillofacial surgeon is essential to determine the source of bleeding. The most common causes are:

    - Dental extraction.
    - Gingival bleeding often due to poor oral hygiene.
    - Trauma.

2. Local treatments must be considered to treat the hemorrhage. These may include:

    - Direct pressure on the area using a damp gauze swab, maintained for at Least 15 minutes.
    - Sutures to close the wound.
    - Application of local hemostatic agents.
    - Antibiotics, especially in gingival bleeding dueto poor oral hygiene.
    - Use of Tranexamic acid as a mouth wash.

3. An appropriate dose of regular Paracetamol/Acetaminophen will help control the pain.

4. Antifibrinolytic agents should not be used systemically in patients with FIX deficiency that are being treated with large doses of prothrombin complex concentrates or in /patients with inhibitors being treated with activated prothrombin complex concentrates (APCC).

5. Factor replacement may be required as directed by the Hemophilia Centre.

6. Oral tranexamic acid should be used if appropriate.

7. Advise the patient to avoid swallowing blood.

8. Advise the patient to avoid using mouthwashes until the day after the bleeding has stopped.

9. Advise the patient to eat a soft diet for a few days.

10. Evaluate and treat for anemia as indicated.

5.11 Epistaxis

1. 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 anterior softer part of the nose for 10-20 minutes.

2. Factor replacement therapy is often not necessary unless bleeding is severe or recurrent.

3. Antihistamines and decongestant drugs are useful for bleeds specifically related to allergies, upper respiratory infections, or seasonal changes.

4. If bleeding is prolonged or occurs frequently, evaluate for anemia and treat appropriately.

5. Tranexamic acid applied locally in a soaked gauze is helpful.

6. Consult with an otolaryngologist if the bleed is persistent or recurrent. Anterior or posterior nasal packing may be needed to control bleeding.

7. Epistaxis can often be prevented by increasing the humidity of the environment, applying gels [(e.g. petroleum jelly or saline drops/gel) to the nasal mucosa to preserve moisture, or administering saline spray.

5.12 Soft tissue haemorrhage

1. Symptoms will depend on the site of hemorrhage.

2. Factor replacement therapy is not necessary for most superficial soft tissue bleeding. The application of firm pressure and ice may be helpful.

3. Evaluate the patient for severity of hemorrhage and possible muscular or neurovascular involvement. Rule out possible trauma to spaces containing vital organs, such as the head or abdomen.

4. 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.

5. Hemoglobin levels and vital signs should be regularly monitored.

5.13 Lacerations and abrasions

1. Treat superficial lacerations by cleaning the wound, then applying pressure and steri-strips.

2. For deep lacerations, raise the factor level and then suture.

3. Sutures may be removed under cover of factor concentrate.

6 COMPLICATIONS OF HEMOPHILIA

6.1 Musculoskeletal complications

1. The most common sites of bleeding are the joints and muscles of the extremities.

2. Depending on the severity of the disease, bleeding episodes may be frequent and without apparent cause.

3. In the child with severe hemophilia, the first hemarthrosis typically occurs when the child begins to crawl and walk usually before two years of age, but occasionally later.

4. If inadequately treated, repeated bleeding will lead to progressive deterioration of the joints and muscles, severe loss of function due to loss of motion, muscle atrophy, pain, joint deformity, and contractures within the first one to two decades of life [1,2].

Synovitis

1. Following acute hemarthrosis, the synovium becomes inflamed, is hyperemic and extremely friable.

2. Failure to manage acute synovitis can result in repeated hemarthroses.

3. During this stage, the joint requires protection with a removal splint or compressive bandaging.

4. Activities should be restricted until swelling and temperature of the joint return to baseline.

5. In some cases, COX-2 inhibitors [Celecoxib] may be useful.

6. Range of motion is preserved in the early stages. Differentiation between hemarthrosis and synovitis is made by performing a detailed physical examination of the joint.

7. The presence of synovial hypertrophy may be confirmed by

ultrasonography or MRI. Plain radiographs and particularly MRI will assist in defining the extent of osteochondral changes.

8. With repeated bleeding, the synovium becomes chronically inflamed and hypertrophied, and the joint appears swollen this swelling is usually not tense, nor is it particularly painful) this is chronic synovitis.

9. As the swelling continues to increase, articular damage, muscle atrophy, and loss of motion will progress to chronic hemophilic arthropathy.

10. The goal of treatment is to deactivate the synovium as quickly as possible and preserve joint function. Options include:

- Factor concentrate replacement, ideally given with the frequency and at 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 are beneficial.
- Physiotherapy including:-
  - Daily exercise to improve muscle strength /and maintain joint motion.
  - Modalities to reduce secondary inflammation, if available.
  - Functional training.
- A course of NSAIDs (COX-2 inhibitors), which may reduce inflammation.
- Functional bracing, which allows the joint to move but limits movement at the ends of range where the synovium can be pinched and which may prevent new bleeding [15].
- Synovectomy

Synovectomy

1. Synovectomy should be considered if 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.

2. Non-surgical synovectomy is the procedure of choice.

3. Radioisotopic synovectomy using a pure beta emitter (phosphorus-32 or yttrium-90) is highly [effective, has few side effects, and can be accomplished [in an out-patient setting.)

- A single dose of clotting factor is often sufficient for a single injection of the isotope.
- Rehabilitation is less intense than after surgical synovectomy but is still required to help the patient regain strength, proprioception, and normal functional use of the joint.

4. If a radioisotope is not available, chemical synoviorthesis with either rifampicin or oxytetracycline chlorhydrate is an appropriate alternative.

- Chemical synoviorthesis involves weekly injections until the synovitis is controlled.
- These painful injections require the administration of intra-articular xilocaine a few minutes before injection of the sclerosing agent, oral analgesics (a combination of acetaminophen /Paracetamol and an opioid), and a dose of clotting factor concentrate prior to each injection.
- The low cost of the chemical agent is offset by the need for multiple injections of factor concentrate.
- Rehabilitation, as described for radioactive synovectomy, is recommended.

5. Surgical synovectomy, whether open or arthroscopic, requires a large supply of clotting factor for both surgery and the lengthy period of rehabilitation. The procedure must be performed by an experienced team at a dedicated Hemophilia treatment centre. It is only considered when other less invasive and equally effective procedures fail.

Chronic hemophilic arthropathy

1. Chronic hemophilic arthropathy can develop any time from the second decade of life (and sometimes earlier), depending on the severity of bleeding and its treatment.

2. The process is set in motion by the immediate effects of blood on the articular cartilage during hemarthrosis and reinforced by persistent chronic synovitis and recurrent hemarthroses, resulting in irreversible damage.

3. With advancing cartilage loss, a progressive arthritic condition develops that includes:

- Secondary soft tissue contractures.
- Muscle atrophy.
- Angular deformities.

4. Deformity can also be enhanced by contracture following muscle bleeds or neuropathy.

5. Loss of motion is common, with flexion contractures causing the most significant functional loss.

6. Joint motion and weight bearing can be extremely painful.

7. As the joint deteriorates, swelling subsides due to progressive fibrosis of the synovium and the capsule.

8. If the joint becomes ankylosed, pain may diminish or disappear.

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

- Radiographs will only show late osteochondral changes.
- Ultrasound or MRI examination will show early soft tissue and osteochondral changes.
- Cartilage space narrowing will vary from minimal to complete loss.
- Bony erosions and subchondral bone cysts will develop, causing collapse of articular surfaces that can lead to angular deformities.
- Fibrous/bony ankylosis may be present.

10. The goals of treatment are to improve joint function, relieve pain, and assist the patient to continue resume normal activities of daily living.

11. Treatment options for chronic hemophilic arthropathy depend on:

- The stage of the condition.
- The patient's symptoms.
- The impact on the patient's lifestyle and functional Abilities.
- The resources available.

12. Pain should be controlled with appropriate analgesics. Certain COX-2 inhibitors may be used to relieve arthritic pain (see 'Pain Management').

13. Supervised physiotherapy aiming to preserve muscle strength and functional ability is a very important part of management at this stage. Secondary prophylaxis may be necessary if recurrent bleeding occurs as a result of physiotherapy.

14. Other conservative management techniques include:

- Serial casting to assist in correcting deformities.
- Bracing and orthotics to support painful and unstable joints.
- Walking aids or mobility aids to decrease stress on weight-bearing joints.
- Adaptations to the home, school, or work environment to allow participation in community activities and employment and to facilitate activities of daily living.

15. If these conservative measures fail to provide satisfactory relief of pain and improved functioning, surgical intervention may be considered. Surgical procedures, depending on the specific condition needing correction, may include:

- Extra-articular soft tissue release to treat contractures.
- Arthroscopy to release intra-articular adhesions and correct impingement.
- Osteotomy to correct angular deformity.
- Prosthetic joint replacement for severe disease involving a major joint (knee, hip, shoulder, elbow).
- Elbow synovectomy with radial head excision.

- Arthrodesis of the ankle, which provides excellent pain relief and correction of deformity with marked improvement in function. Recent improvements in ankle replacement surgery may pose an alternative for persons with hemophilia in the future

16. Adequate resources, including sufficient factor concentrates and post-operative rehabilitation, must be available in order to proceed with any surgical procedure.

Principles of physiotherapy/physical medicine in hemophilia

1. Physiotherapists and occupational therapists and/or physiatrists should be part of the core hemophilia team. Their involvement with patients and their families should begin at the time of diagnosis, and they remain important to the patient throughout their lifespan.

2. Their role in the management of the patient with hemophilia includes the following:

- Assessment
  - determining the site of an acute bleed,
  - Regular assessment throughout life,
  - Pre-operative assessment.
- Education of the patient and family regarding musculoskeletal complications and their treatment of school personnel regarding suitable activities for the child, immediate care in case of a bleed, and modifications in activities that may be needed after bleeds.
- Treatment of acute bleeds, chronic synovitis, and chronic arthropathy using a variety of techniques including hydrotherapy, heat, ice, electrical nerve stimulation, pulsed diathermy, ultrasound as well as various orthoses for pain relief and restoration of function.

Pseudotumours

1. The pseudotumour is a potentially limb and life threatening condition unique to hemophilia that occurs as a result of inadequately treated soft tissue bleeds, usually in muscle adjacent to bone, which can be secondarily involved. It is most commonly seen in a long bone or the pelvis.

2. If not treated, the pseudotumour can reach enormous size, causing pressure on the adjacent neurovascular structures and pathologic fractures. A fistula can develop through the overlying skin.

3. Diagnosis is made by the physical finding of alocalized mass.

4. Radiographic findings include a soft tissue mass with adjacent bone destruction.

5. A more detailed and accurate evaluation of a pseudotumour can be obtained with CT scan and MRI.

6. Management depends on the site, size, rate of growth, and effect on adjoining structures .Options include factor replacement and monitoring, aspiration, and surgical ablation.

- A six-week course of treatment with factor is recommended, followed by repeat MRI. If the tumor is decreasing, continue with factor and repeat MRI for three cycles.
- Proceed to surgery if necessary, which will be much easier if the tumor has shrunk.
- Aspiration of the pseudotumour followed by injections of fibrin glue, arterial embolization, or radiotherapy may heal some lesion Surgery may be needed for others.
- Surgical excisions, including limb amputations, may be necessary for large pseudotumours, particularly if they erode long bones. Large abdominal pseudotumours present a special challenge in surgical management of hemophilia; surgery must only be performed by teams with experience in hemophilia.

Fractures

1. Fractures are not frequent in people with hemophilia, possibly due to lower levels of ambulation and intensity of activities. However, a person with hemophilic arthropathy may be at risk for fractures around joints that have significant loss of motion and in bones that are osteoporotic.

2. Treatment of a fracture requires immediate factor concentrate replacement.

3. Clotting factor levels should be raised to at least 50% and maintained for three to five days.

4. Lower levels may be maintained for 10–14 days while the fracture becomes stabilized and to prevent soft tissue bleeding.

5. The management plan should be appropriate for the specific fracture, including operative treatment under appropriate coverage of clotting factor concentrates.

6. Circumferential plaster should be avoided; splints are preferred.

7. Compound infected fractures may require external fixators.

8. Prolonged immobilization, which can lead to significant limitation of range of movement in the adjacent joints, should be avoided.

9. Physiotherapy should be started as soon as the fracture is stabilized to restore range of motion, muscle strength, and function.

Principles of orthopedic surgery in hemophilia

For important considerations related to performing surgical procedures in

persons with hemophilia, please see "Surgery and invasive procedures"

Specific issues in relation to orthopedic surgery Include:

1. Orthopedic surgeons should have had specific training in surgical management of persons with hemophilia.

2. Performing multiple site elective surgery in simultaneous or staggered fashion to use clotting factor concentrates judiciously should be considered.

3. Local coagulation enhancers may be used. Fibrin glue is useful to control oozing when operating in extensive surgical fields.

4. Post-operative care in patients with hemophilia requires closer monitoring of pain and often higher doses of analgesics in the immediate post-operative period.

5. Good communication with the post-operative rehabilitation team is essential. Knowledge of the details of the [surgery performed and intraoperative joint status will facilitate planning of an appropriate rehabilitation program.

6. Post-operative rehabilitation should be carried out by a physiotherapist experienced in hemophilia management.

7. Rehabilitation may have to progress more slowly in persons with hemophilia.

8. Adequate pain control is essential to allow appropriate exercise and mobilization.

9. These principles also apply to fixation of fractures and excision of pseudotumours.

6.2 Inhibitors

1. "Inhibitors" in hemophilia refer to IgG antibodies that neutralize clotting factors.

2. In the current era in which clotting factor concentrates have been subjected to appropriate viral inactivation, inhibitors to FVIII or FIX are considered to be the most severe treatment related complication in hemophilia.

3. The presence of a new inhibitor should be suspected in any patient who fails to respond clinically to clotting factors, particularly if he has been previously responsive. In this situation, the expected recovery and half-life of the transfused clotting factor are severely diminished.

4. Inhibitors are more frequently encountered in persons with severe

hemophilia compared to those with moderate or mild hemophilia.

5. The cumulative incidence (i.e. lifetime risk) of inhibitor development in severe Hemophilia A is in the range of 20-30% and approximately 5-10% in moderate or mild disease.

6. In severe hemophilia A, the median age of inhibitor development is three years or less in developed countries. In moderate mild hemophilia A, it is closer to 30 years of age, and is often [seen in conjunction with intensive FVIII exposure with surgery.

7. In severe hemophilia, inhibitors do not change the site, frequency, or severity of bleeding. In moderate or mild Hemophilia, the inhibitor may neutralize endogenously synthesized FVIII, thereby effectively converting the patient's phenotype to severe.

8. Bleeding manifestations in moderate/mild hemophilia complicated by an inhibitor are more frequently reminiscent of those seen in patients with acquired hemophilia A (due to auto-antibodies [to FVIII), with a greater predominance [of mucocutaneous, urogenital, and gastro intestinal bleeding sites . Consequently, the risk of severe complications or even death from bleeding may be significant in these patients.

9. Inhibitors are much less frequently encountered in hemophilia B, occurring in less than 5% of affected individuals.

10. In all cases, inhibitors render treatment with replacement factor concentrates difficult. Patients on clotting factor therapy should therefore be screened for inhibitor development.

Risk factors for inhibitor development are:- A history of inhibitors in the family

- Severe gene defects
- African ancestry,
- early intensive treatment with high doses of clotting factor in the first 50 exposure days

12. Confirmation of the presence of an inhibitor and quantification of the titre is performed in the laboratory, preferably using the Nijmegen /modified Bethesda assay

13 For children, inhibitors should be screened once every five exposure days until 20 exposure days, every 10 exposure days between 21and 50 exposure days, and at least two times a year until 150 exposure days.

14. For adults with more than 150 exposure days, apart from a 6-12 monthly review, any failure to respond to adequate factor concentrate replacement therapy in a previously responsive patient is an indication to assess for an inhibitor.

15. Inhibitor measurement should also be done in all patients who have been intensively treated for more than five days, [after surgery, ICH, G I Bleeding] within four weeks of the last infusion and exposure to severe trauma.

16. Inhibitors should also be assessed prior to surgery or if recovery assays are not as expected, and when clinical response to treatment of bleeding is sub-optimal in the post-operative period.

17. A low responding inhibitor is defined as an inhibitor level that is persistently < 5 BU/ml, whereas a high responding inhibitor is defined by a level≥ 5 BU/ml.

18. High responding inhibitors tend to be persistent. If not treated for a long period, titre levels may fall or even become undetectable, but there will be a recurrent anamnestic response in three to five days when challenged again with specific factor products.

20. Some low titre inhibitors may be transient, disappearing within six months of initial documentation, despite recent antigenic challenge with factor concentrate.

19. 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

1. Management of bleeding in patients with inhibitors must be in consultation with a centre experienced in their management.

2. Choice of treatment product should be based on titre of inhibitor, records of clinical response to product, and site and nature of bleed.

3. Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, [double or triple] if possible, to neutralize the inhibitor with excess factor activity and stop bleeding.

4. Patients with a history of a high responding inhibitor but with low titer may be treated similarly in an emergency until an anamnestic response occurs, usually in three to five days, precluding further treatment with concentrates that only contain the missing factor.

5. With an inhibitor level > 5 BU, the likelihood is low that specific factor replacement will be effective in overwhelming the inhibitor without ultra high dose continuous infusion therapy.

6. Alternative agents include bypassing agents such as recombinant factor VIIa (rFVIIa) and prothrombin complex concentrates (PCC), including the activated forms (APCC).

7. The efficacy of two doses of rFVIIa and one dose of APCC for management of joint bleeding has been shown to be essentially equivalent.

8. Notably, however, some patients respond better to one agent than the other, highlighting the need to individualize therapy.

9. An anamnestic immune response should be expected in patients with hemophilia B and aFIX inhibitor treated with prothrombin complex concentrates – whether activated or not – since these concentrates all contain FIX.

10. On the other hand, the risk of anamnesis in patients with hemophilia A and an inhibitor treated with a (n) (activated) prothrombin complex concentrate will vary depending on the concentrate and its content of FVIII, which is generally minimal. It is estimated that APCC leads to an anamnestic response in approximately 30% of FVIII inhibitor patients.

11. Although there has been interest in the use of immunosuppressive therapies in patients with inhibitors, their role is not yet defined, and there is no consensus as to whether they have a place in the management of these patients.

Allergic reactions in patients with hemophilia B

1. Up to 50% of hemophilia B patients with inhibitors may have severe allergic reactions, including anaphylaxis, to FIX administration. Such reactions can be the first symptom of inhibitor development.

2. 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 or 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

1. In patients with severe hemophilia A, eradication of inhibitors is often possible by immune tolerance induction (ITI) therapy.

2. Before ITI therapy, high-responding patients should avoid FVIII products to allow inhibitor titres to fall and to avoid persistent anamnestic rise. As noted, some patients may develop an anamnestic response to the inactive FVIII molecules in APCC as well.

Patients switching to new concentrates

1. For the vast majority of patients, switching products does not lead to inhibitor development.

2. However in rare instances, inhibitors in previously treated patients have occurred with the introduction of new FVIII concentrates.

3. In those patients, the inhibitor usually disappears after withdrawal of the new product.

4. Patients switching to a new factor concentrate should be monitored for inhibitor development.

5. Appropriate timing of switching is very important. Avoid danger signals which include:

- No switching at time of surgery.
- No switching at severe trauma.
- No switching if there is huge active bleeding.
- No switching during the tolerance phase i.e. the 1st 50 (EDs).

6.3 Transfusion-transmitted and other infection-related complications

1. The emergence and transmission of HIV, HBV and HCV through clotting factor products resulted in high mortality of people with hemophiliain the 1980s and early 1990s.

2. Many studies conducted all over the world indicate that HIV, HBV, and HCV transmission. Through factor concentrate has been almost completely eliminated.

3. This is a result of the implementation of several risk-mitigating steps, which include careful selection of donors and screening of plasma, effective virucidal steps in the manufacturing process, and advances in sensitive diagnostic technologies for detection of various pathogens.

4. Recombinant factor concentrates have been adopted over the past two decades, particularly in developed countries. Recombinant products have contributed significantly to infection risk reduction.

5. The new challenge remains emerging and re-emerging infections, many of which are not amenable to current risk reduction measures. These include the non-lipid enveloped viruses and prions, for which diagnosis and elimination methods are still a challenge.

6. As new treatments are continually emerging in this rapidly changing field, transfusion-transmitted infections in people with hemophilia are best managed by a specialist.

Principles of management of HIV infection in hemophilia

1. Knowledge and expertise in the treatment of /HIV-infected people with hemophilia is currently limited to case series and reports. HIV treatment in people with hemophilia is therefore

largely informed by guidelines used in the non-hemophilia population.

2. As part of the hemovigilance program, all people with hemophilia treated with plasma derived products that are not adequately virus-inactivated should be tested for HIV at least every 6-12 months and whenever clinically indicated.

3. The diagnosis, counsellin, initiation of treatment, and monitoring of HIV, as well as the treatment of HIV-associated complications in infected people with hemophilia, should be the same as in the non-Hemophilic population.

4. None of the currently available classes of anti-HIV drugs are contraindicated in people with Hemophilia.

Principles of management of HCV infection in hemophilia

1. Assessment of HCV in people with hemophilia should include:

- Anti-HCV serology to determine exposure.
- HCV polymerase chain reaction (PCR) in those who are anti-HCV positive
- HCV genotyping in those who are HCV PCR positive
- Liver function tests and non-invasive assessment of fibrosis and liver architecture.

2. The current standard of treatment for HCV is pegylated interferon (PEG-INF) and ribavirin, which give sustained virological response in 61% of people with hemophilia.

3. New antiviral therapies, in combination with these drugs, may improve sustained virologic response rates.

4. HCV genotype 1 and HIV coinfection predict poorer response to anti-HCV therapy.

5. Where HCV eradication cannot be achieved, regular monitoring (every 6-12 months) for end-stage liver complication is recommended.

Principles of management of HBV infection in hemophilia

1. All people with hemophilia treated with plasma derived products that are not adequately virus-inactivated should be screened for hepatitis B antigen and anti-hepatitis B at least every 6-12 months and whenever clinically indicated.

2. Active HBV infection should be managed as per local infectious disease guidelines and protocols.

3. Those without HBV immunity should be given the anti-HBV vaccine. Protective Sero conversion should be rechecked following vaccination.

4. People with hemophilia who do not seroconvert should be revaccinated with double the hepatitis B vaccine dose.

Principles of management of bacterial infection in hemophilia

1. The risk factors for bacterial infections in people with hemophilia are venous access catheter insertion,

surgical arthroplasty, and other surgical interventions.

2. In general, joint aspiration to treat hemarthros is should be avoided, unless done early under appropriate cover of factor replacement and with strict aseptic precautions to prevent infection.

3. Bleeding is likely to delay healing and worsen infection and should therefore be well controlled

4. Control of the source of infection is of paramount importance in PWH [109,110].

7 PLASMA FACTOR LEVEL AND DURATION OF ADMINISTRATION

7.1 Choice of factor replacement therapy protocols

1. Table 7-1 and Table 7-2 present commonly followed guidelines on plasma factor peak levels and duration of replacement that reflect the different practices in countries where there is no significant resource constraint (Table 7-1) and countries where treatment products are limited (Table 7-2).

2. With the lower doses for treating musculoskeletal bleeds listed in Table 7-2, it may only be possible to avoid major target joints and crippling deformities.

3. Higher doses listed in Table 7-1 have been shown to avoid joint damage, but the optimal dose needed to achieve this remains to be defined.

4. Observational studies documenting the musculoskeletal outcome of doses and protocols of factor replacement are extremely important in defining these issues.

5. Doses for prophylactic replacement of factor concentrates vary between different countries and also among centers in the same country.

TABLE 7-1: SUGGESTED PLASMA FACTOR PEAK LEVEL AND DURATION OF ADMINISTRATION (WHEN THERE IS NO SIGNIFICANT RESOURCE CONSTRAINT) [6]

		HEMOPHILIA A		HEMOPHILIA B
TYPE OF HEMORRHAGE	DESIRED LEVEL (lU/DL)	DURATION (DAYS)	DESIRED LEVEL(IU/DL)	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
Superficial muscle compromise/no NV (except iliopsoas)	40-60	2-3, sometimes longer if response is inadequate	40-60	2-3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
Initial	80-100	1-2	60-80	1-2
Maintenance	30-60	3-5, sometimes longer as secondary prophylaxis during physiotherapy	30-60	3-5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
Initial	80-100	1-7	60-80	1-7
Maintenance	50	8-21	30	8-21
Throat and neck				
Initial	80-100	1-7	60-80	1-7
Maintenance	50	8-14	30	8-14
Gastrointestinal				
Initial	80-100	7-14	60-80	7-14
Maintenance	50		30	
Renal	50	3-5	40	3-5

To be continue

Deep laceration	50	3-7	40	3-7
Surgery (major)				
Pre-op	80-100		60-80	
Post-op	60-80 40-60 30-50	1-3 4-6 7-14	40-60 30-50 20-40	1-3 4-6 7-14
Surgery (minor)				
Pre-op	50-80		50-80	
Post-op	30-80	1-5, depending on type of procedure	30-80	1-5, depending on type of procedure

- NV: neurovascular

TABLE 7-2: PLASMA FACTOR PEAK LEVEL AND DURATION OF ADMINISTRATION (WHEN THERE IS SIGNIFICANT RESOURCE CONSTRAINT)

		HEMOPHILIA A		HEMOPHILIA B
TYPE OF HEMORRHAGE	DESIRED LEVEL (lU/DL)	DURATION (DAYS)	DESIRED LEVEL(IU/DL)	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
Superficial muscle compromise/no NV (except iliopsoas)	10-20	2-3, sometimes longer if response is inadequate	10-20	2-3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
Initial	20-40		15-30	

To be continue

Maintenance	10-20	3-5, sometimes longer as secondary prophylaxis during physiotherapy	10-20	3-5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
Initial	50-80	1-3	50-80	1-3
Maintenance	30-50 20-40	4-7 8-14	30-50 20-40	4-7 8-14
Throat and neck				
Initial	30-50	1-3	30-50	1-3
Maintenance	10-20	4-7	10-20	4-7
Gastrointestinal				
Initial	30-50	1-3	30-50	1-3
Maintenance	10-20	4-7	10-20	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	60-80		50-70	
Post-op	30-40 20-30 10-20	1-3 4-6 7-14	30-40 20-30 10-20	1-3 4-6 7-14
Surgery (minor)				
Pre-op	40-80		40-80	
Post-op	20-50	1-5, depending on type of procedure	20-50	1-5, depending on type of procedure

8 VON WILLEBRAND & OTHER RAE BLEEDING DISORDER

8.1 Von Willebrand Disease

VWD is the most common bleeding disorder. The prevalence of VWD presenting with bleeding symptoms appears to be approximately 1 in 100. It affects both males and females. VWD is generally less severe than other bleeding disorders. For most people with VWD, the disorder causes little or no disruption to their lives except when there is a serious injury or need for surgery. It is caused by a problem with the von willebrand factor. (VWF) either low, or abnormal or absent). Bleeding symptoms can vary a lot within a family, symptoms can also change over time. Sometimes there is no family history and VWD occurs due to spontaneous mutation. It effects all ethnic groups.

Physiological functions of VWF

- To mediate platelet adhesion to the damaged vessel wall.
- To facilitate platelet aggregation, (VWF acts as abridging-protein between platelets) so enables platelet plug formation at the site of blood vessel injury.
- To bind to FVIII (carrier protein) and protect it from proteolytic degradation by activated protein C in the circulation.

Facts about VWF

- Neonates have a raised VWF at birth which reaches baseline at ~6 months of age.
- VWF levels increase with age at a rate of approximately 10 IU/dl per decade.
- Plasma VWF levels vary with blood group – (type O has the lowest vwf level) this becomes important in making a diagnosis of VWD when an individual has borderline value of VWF.
- 95% of values obtained in healthy populations lie between approximately 50 and 200 IU/dl.

Types of VWD

Type 1 VWD

- The most common and mildest form of VWD, which involves a quantitative defect of VWF.
- The condition is transmitted as an ***autosomal dominant*** trait with incomplete penetrance.
- The VWF functions normally, but levels are reduced to (20 to 50 %) of normal values, thus, a wide range of severities can be seen. Approximately (70 to 80 %) of patients with VWD have Type 1.

Type 2 VWD

- The current classification of VWD recognizes four distinct qualitative (VWF does not work properly) forms of VWD: types 2A, 2B, 2M, and 2N disease. The clinical manifestations of the type 2 variants of VWD are similar to those of type 1 disease.

Type 3 VWD

- Very low, often undetectable, levels of VWF.
- The rarest and most severe form of VWD.
- The incidence is one to three per million.

These individuals experience frequent, severe, life-threatening bleeds similar to individuals with hemophilia, and must be treated immediately.

Inheritance patterns of VWD

It is carried on chromosome 12 and occurs equally in men and women.

Type 1 VWD Autosomal dominant ~70%

Type 2 VWD 2A, 2B, and 2M (Autosomal-dominant)

2N –Autosomal recessive

Type 3 VWD Autosomal recessive

Symptoms of VWD

- Easy bruising.
- Menorrhagia.
- Frequent or prolonged epistaxis.
- Prolonged bleeding following dental work (bleeding gums), surgery, childbirth or injury.
- Muscle hematomas (type 3 VWD).
- Hemarthroses (type 3 VWD).

Diagnosis

The diagnosis of VWD requires attention to three clinical and laboratory components:

- A personal history of excessive mucocutaneous bleeding.
- A family history of excessive bleeding. Since most cases follow an autosomal dominant pattern of inheritance (However, spontaneous

genetic mutations of VWD can occur in approximately 30 percent of all cases).

- A laboratory evaluation that is consistent with a quantitative and/or qualitative defect in VWF.

Physicians should know the following facts about laboratory testing for VWD:

- Both VWF and FVIII are acute phase proteins and thus their plasma levels can vary significantly(temporarily increased) with a number of environmental variables include :

stress, exercise, the phase of the menstrual cycle, hormone treatment (pills), nursing and pregnancy cold temperatures, inflammation, infection, hyperthyroidism, patient who just have surgery or blood transfusion

- Additionally, individuals with Type 0 blood naturally have lower levels of VWF than people with other blood Types (type O has levels 20%-25%) less than those of non O persons), independent of whether or not they have VWD.
- Inter-laboratory standardization of some of the tests for VWD (i.e. VWF: RCo and the VWF multimer test) has proved to be challenging.

A VWF Antigen (VWF: Ag) estemation

An immunoassay, (ELISA) that measures the total amount of VWF present. Normal ranges are 50 to 200 IU/dl.

A von Willebrand Ristocetin Cofactor (VWF:RCoF):

A functional bioassay of VWF (it measures the ability of VWF to interact with normal platelets), it is based on the ability of the antibiotic ristocetin to promote platelet agglutination in the presence of VWF, thus, measuring VWF function. Normal ranges are 50 to 200 IU/dl.

Ratio of VWF:Rco /VWF:Ag

- In order to differentiate VWD type *1 & 2*, this ratio can be used because *VWD type 1* commonly results in a concomitant reduction in both *VWF: Rco &VWF: Ag*, Thus , a ratio of > *0.7 is often indicative of VWD type 1*,
- Conversely, in VWD type 2, where the function of VWF is decreased to a greater extent than the amount of protein, Thus, the ratio tends to be >0.7 in VWD type 2 (the VWF: RCo reduction is disproportionate to the VWF: Ag level).
- Interpretation of the laboratory results involved in making the diagnosis of VWD is often very difficult. To avoid misdiagnosis, it is strongly advised that physicians experienced in the clinical care of VWD perform this component of the diagnostic algorithm. (table 8.1).

(table 8.1)

Common laboratory findings associated with various types of VWD

	Type 1	Type 3	Type 2A	Type 2B	Type 2M	Type 2N
VWF: Ag	↓ or ↓↓	absent (<0.05 U/mL)	↓	↓	↓	normal or ↓
VWF: RCo	↓ or ↓↓	absent (<0.05 U/mL)	↓↓ or ↓↓↓	↓↓	↓↓	normal or ↓
FVIII:C	normal or ↓	0.01-0.10 U/mL	normal or ↓	normal or ↓	normal or ↓	↓↓ or ↓↓↓
VWF:RCo / VWF:Ag ratio	>0.6	not useful	<0.6	<0.6	<0.6	>0.6
Multimers	normal	absent	loss of high (and possibly intermediate) molecular weight multimers	loss of high molecular weight multimers	normal	normal

↓: slightly reduced ↓↓: moderately reduced ↓↓↓: severely reduced

VWF treatment options

- Adjunctive therapies
  - Anti-fibrinolytic agent.
  - Estragens
  - Topical hemostatic agent
- VWF/FVIII treatments
  - Desmopressin
  - VWF/FVIII concentrates

Adjunctive Therapies

- The use of antifibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid.
- The application of topical hemostatic preparations such as fibrin glue to exposed sites of bleeding.
- In women with menorrhagia, the administration of hormonal therapy in the form of combined contraceptives
- Additionally, replacement of iron stores in individuals with iron deficiency can result in an improved quality of life.

Strategies for increasing VWF levels

Release of intrinsic VWF stores.

Desmopressin (DDAVP) - IV, SC, nasal spray.

Administration of VWF concentrate.

Plasma-derived VWF/FVIII concentrate.

Cryoprecipitate

DESMOPRESSIN

- DDAVP cause the release of VWF & F.VIII from the storage site within the endothelium of the blood vessels. Desmopressin is a synthetic analogue of antidiuretic hormone Vasopressin, We have IV, SC, and Nasal routes of administration. It is important to notes that the hemostatic dose of DDAVP is higher than the dose for control of enuresis.
- The peak hemostatic effect of standard dose [0.3mcg /Kg] occur between 0,5-1hr following the administration within the average VWF/FVIII increment of 3-5 fold over base line value .
- The duration of the treatment not is longer than 2-3 days, the side effect of the DDAVP have been well characterized in the vast majority of cases. They are transient and minor in nature.
- Mild tachycardia, headache and facial flushing are not infrequent due to its antidiuretic effect, fluid intake should be limited to replacement volume only in 24hr. following the administration.
- Frequently episodes of fluid overload and severe hyponatremia [That can result in seizures] are rare.
- DDAVP has been used successfully and safely to prevent bleeding in early pregnancy.
- DDAVP is indicated for type 1 VWD and type 2 VWD but not for type 2B [No intrinsic VWD] and type 3 VWD [exacerbate thrombo cytopenia]. A test dose of DDAVP is usually given in a control medical setting to verify the patient whether he/or she is DDAVP responsive or non-responsive.

VWD/FVIII use in VWD

- For those VWD patients in whom DDAVP is either ineffective or contra indicated or in major bleeding, or where the duration of hemostatic support required longer then 2-3 days. VWF & FVIII level can be restored by the infusion of plasma derived conc.
- Faster Concentrate are Indicated for types 2A. 2B and 3. Clotting factors may also be used in individuals with type 1 VWD prior to surgery or injury
- VWF/FVIII concentrates work by raising the plasma levels of VWF and factor VIII.
- The prescribed quantity of factor will also vary depending on the Type of VWD the patient has as well as the severity of the bleeding episode.

9. Rare Clotting Factors Disorders

Rare clotting factor deficiencies are a group of inherited bleeding disorders caused by a problem with one or several clotting factors. These bleeding disorders are caused by deficiency of a soluble coagulation factor or factors, other than von Willebrand disease (VWD), Hemophilia A or Hemophilia B.

These disorders include heritable deficiencies of fibrinogen, prothrombin, factor V, FVII, FX, FXI and FXIII, combined FV and FVIII deficiency and vitamin K-dependent coagulation factor deficiency. These disorders have usually a low prevalence in the general population and constitute approximately 3 to 5% of all coagulation disorders. However, in some countries the prevalence is more in countries where consanguineous marriage is common. The clinical picture of RBDs are highly variable and could markedly vary from mild to severe, making either diagnosis or optimal treatment quiet challenging.

9.1 Factor I (fibrinogen) deficiency

Factor I (also called fibrinogen) deficiency is an inherited bleeding disorder that is caused by a problem with factor I. Because the body produces less fibrinogen than it should, or because the fibrinogen is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor I deficiency is an umbrella term for several related disorders known as congenital fibrinogen defects:

- Afibrinogenemia (a complete lack of fibrinogen) and *hypofibrinogenemia (low levels of fibrinogen) are quantitative defects,while
- Dysfibrinogenemia is a qualitative defect in which fibrinogen does not work the way it should.

Afibrinogenemia is an autosomal recessive disorder. Hypofibrinogenemia, and dysfibrinogenemia, can be either recessive or dominant.

Symptoms

The symptoms of factor I deficiency differ depending on which form of the disorder a person has.

Common Symptoms

- Epistaxis.
- Easy bruising.
- Menorrhagia.
- Muscle bleeds.
- Bleeding from the umbilical cord stump after birth.
- Bleeding in the mouth, particularly after dental surgery.

- Abnormal bleeding during or after injury, surgery, or childbirth.
- Abnormal bleeding after circumcision.
- Problems during pregnancy [including miscarriage].

Diagnosis

Normal value of factor I is 200 -400 mg/dl. Factor I deficiency is diagnosed by a variety of blood tests, including a specific test that measures the amount of fibrinogen in the blood. However, low fibrinogen levels or abnormal function may be a sign of another disease, such as liver or kidney disorders, which should be ruled out before a bleeding disorder is diagnosed. Expect PT and aPTT to be prolonged. Thrombin time is the most sensitive screening test and expect to be prolonged in patients with bleeding tendencies, and shortened occur in patients prone to thrombosis.

Treatment

There are three treatments available for factor I deficiency. All are derived from human plasma.

- Fibrinogen concentrate
- Cryoprecipitate
- Fresh frozen plasma (FFP)

Treatment may also be given to prevent the formation of blood clots, as this complication can occur after fibrinogen replacement therapy.

Many people who have hypofibrinogenemia or dysfibrinogenemia do not need treatment. Excessive menstrual bleeding in women with factor I deficiency may be controlled with hormonal contraceptives (birth control pills), intra-uterine devices (IUDs), or antifibrinolytic drugs.

9.2 Factor II (prothrombin) deficiency.

Factor II deficiency is an autosomal recessive disorder. It may be inherited with other factor deficiencies (Combined deficiency of vitamin K-dependent clotting factors). It can also be acquired later in life as a result of liver disease, vitamin K deficiency, or certain medications such as the blood-thinning drug Coumadin®. Acquired factor II deficiency is more common than the inherited form.

Symptoms

The symptoms of factor II deficiency are different for everyone. As a general rule, the less factor II a person has in his or her blood, the more frequent and/or severe the symptoms.

Common symptoms

- Epistaxis.
- Easy bruising.
- Menorrhagia.
- Hemarthrosis.
- Muscle bleeds
- bleeding in the mouth particularly after dental surgery.

Diagnosis

PT and aPTT prolonged, Factor II

deficiency is diagnosed by a variety of blood tests in patieut with low factor II. The doctor will need to measure the amount of factors V, V,II,IX and X in the blood to rate out combined defficy of dependent factors . Diagnostic tests should be performed by a specialist at a hemophilia/bleeding disorders treatment center.

Treatment

There are two treatments available for factor II deficiency. Both are made from human plasma.

- Prothrombin complex concentrates (PCCs)
- Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with factor II deficiency may be controlled with hormonal contraceptives (birth control pills), intra-uterine drugs (IUDs), or antifibrinolytic drugs.

9.3 Factor V deficiency

Factor V deficiency is an autosomal recessive disorder.

Symptoms

The symptoms of factor V deficiency are generally mild. Some people may experience no symptoms at all. However, children with a severe deficiency of factor V may bleed very early. Some patients have experienced bleeding in the central nervous system very early in life.

Common symptoms

- Epistaxis.
- Easy bruising.
- Menorrhagia.
- Bleeding in the mouth, particularly after dental surgery.

Diagnosis

PT and aPTT prolonged. Factor V deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a hemophilia/bleeding disorders treatment centre. People with abnormal levels of factor V should also have their factor VIII levels checked to rule out combined factor V and factor VIII deficiency, which is a completely separate disorder.

Treatment

Treatment for factor V deficiency is usually only needed for severe bleeds or before surgery. Fresh frozen plasma (FFP) is the usual treatment because there is no concentrate containing only factor V. Platelet transfusions, which contain factor V, are also sometimes an option. Excessive menstrual bleeding in women with factor V deficiency may be controlled with hormonal contraceptives (birth control pills), intra-uterine devices (IUDs) or antifibrinolytic drugs.

9.4 Combined Factor V and factor VIII deficiency

Combined factor V and factor VIII deficiency is an inherited bleeding disorder that is caused by low levels of

factors V and VIII. Because the amount of these factors in the body is lower than normal, the clotting reaction is blocked prematurely and the blood clot does not form. The combined deficiency is completely separate from factor V deficiency and factor VIII deficiency (hemophilia A). Combined factor V and factor VIII deficiency is an autosomal recessive disorder. The deficiency is very rare, but like all autosomal recessive disorders, it is found more frequently in areas of the world where marriage between close relatives is common.

Symptoms

The combination of factor V and factor VIII deficiency does not seem to cause more bleeding than if only one or the other of the factors were affected. The symptoms of combined factor V and factor VIII deficiency are generally mild.

Common symptoms:

- Skin bleeding.
- Menorrhagia.
- Epistaxis.
- Bleeding in the mouth, particularly after dental surgery or tooth extraction.
- Bleeding after circumcision.

Diagnosis

Combined factor V and factor VIII deficiency is diagnosed by a variety of blood tests including prolong PT and markly prolong of APTT, and the levels of both factors are lower than normal. These tests should be performed by a specialist at a hemophilia/bleeding disorders treatment centre.

Treatment

- Fresh frozen plasma (FFP) in a dose of 15-20 ml/kg IV may add to it either VIII concentrate or desmopressine.

  Excessive menstrual bleeding in women with combined factor V and factor VIII deficiency may be controlled with hormonal contraceptives (birth control pills), intra-uterine devices (IUDs), or antifibrinolytic drugs.

9.5 Factor VII deficiency

Factor VII deficiency is an autosomal recessive disorder. Factor VII deficiency may be inherited with other factor deficiencies (Combined deficiency of vitamin K-dependent clotting factors). It can also be acquired later in life as a result of liver disease, vitamin K deficiency, or certain medications such as the blood-thinning drug Coumadin®.

Symptoms

The symptoms of factor VII deficiency are different for everyone. As a general rule, the less factor VII a person has in his/her blood, the more frequent and/or severe the symptoms.

Common symptoms:

- Epistaxis.
- Easy bruising.

- Menorrhagia.
- Bleeding in the mouth, particularly after dental surgery
- Bleeding in the head (newborns), characteristically, these newborns are liable for repeated intracranial bleeding.
- Heavy bleeding at circumcision.
- Hemarthrosis.
- Umbilical cord bleeding
- GI bleeding.

Diagnosis

Factor VII deficiency is diagnosed by markedly prolonged prothrombin time and normal aPTT, with low level of factor VII. Normal value of factor VII is 0.5 mg /ml. And its half-life is 3-6 hours.

Treatment

There are several treatments available for factor VII deficiency.

- Recombinant VIIa concentrate (rFVIIa) ,The recommended dose range for treatment of bleeding episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures is 15-30 mcg per kg body weight every 4 to 6 hours until haemostasis is achived. Dose and frequency of injections should be adapted to each individual.
- Prothrombin complex concentrate (PCC) containing factor VII.

Indications of recombinant factor VII (rFVIIa) administrations:

1. Congenital factor VII deficiency: for hemorrhagic episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures a dose of 15–30 mcg/kg every 4–6 hours until hemostasis achieved. Dose and frequency of injections should be adapted to each individual. Development of antibodies to factor VII reported rarely in patients with congenital factor VII deficiency receiving rFVIIa. Consider possibility that antibodies to factor VII may have developed if therapeutic response or expected factor VII levels are not achieved with calculated dosages.
2. HemophiliaA or B with Inhibitors with >5 Bethesda units:
   - Mild to moderate bleeding: two to three injections of 90mcg/kg administered at 3 hours intervals. If further treatment is required, one additional dose can be administered.
   - For serious bleeding episodes: initial dose of 90mcg/kg administered .The following dose varies according to the type and severity of the haemorrhage. Dose frequency should be every 2 hours until clinical improvement is observed. If continued therapy is indicated, the dose interval can be increased successively to every

4, 6, 8 or 12 hours for as long as treatment is needed. A major bleeding episode may be treated for 2-3 weeks or more as clinically indicated.

- For invasive procedure/surgery: Minor surgery: an initial dose of 90 mcg/kg immediately prior to procedure; repeats after 2 hours and then at 2-3 hour interval for the first 24-48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2-4 hours interval for 6-7 days. Then the dose interval may be increased to 6-8 hours for another 2 weeks .

3. Acquired Hemophilia: for control of bleeding or prevention of bleeding episodes with surgery IV 90 mcg/kg, further injections may be given if required. The duration of treatment and interval between injections will vary with the severity of the hemorrhage, and the procedure being performed. The initial dose interval should be 2-3 hours. Once haemostasis has been achieved, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is indicated.
4. Glanzmann‘s Thrombasthenia: First line of treatment is platelet transfusion, if the patient develops platelet refractriness, the second line of therapy is rVIIa. For control of bleeding or prevention of bleeding episodes with surgery a dose of 90 mcg (range 80–120) mcg/kg every 2 hours until hemostasis achieved.

9.6 Factor X deficiency

Factor X deficiency is an autosomal recessive disorder. It may also be inherited with other factor deficiencies (Combined deficiency of vitamin K-dependent clotting factors).

Symptoms

As a general rule, the less factor X a person has in his/her blood, the more frequent and/or severe the symptoms. People with severe factor X deficiency can have serious bleeding episodes.

Common symptoms:

- Epistaxis.
- Easy bruising.
- Gastrointestinal hemorrhage.
- Hemarthrosis.
- Muscle bleeds.
- Beeding from the umbilical cord stump at birth.
- Bleeding from the mouth, particularly after dental surgery.
- Bleeding during or after surgery or injury.

Diagnosis

Expect PT and aPTT to be prolonged.

Blood level of factor X is low.

Treatment

There are two treatments available for

factor X deficiency. Both are derived from human plasma.

- Prothrombin complex concentrate (PCC) containing factor X.
- Fresh frozen plasma (FFP).

Excessive menstrual bleeding in women with factor X deficiency may be controlled with hormonal contraceptives (birth control pills), intra-uterine devices (IUDs), or antifibrinolytic drugs.

9.7 Factor XI deficiency

Factor XI deficiency is also called hemophilia C. It differs from hemophilia A or B in that there is no bleeding into joints and muscles. Factor XI deficiency is the most common of the rare bleeding disorders and the second most common bleeding disorder affecting women (after von Willebrand disease).it is an autosomal recessive disorder.

Symptoms

Most people with factor XI deficiency will have little or no symptoms at all. The relationship between the amount of factor XI in a person's blood and the severity of his/her symptoms is unclear; people with only a mild deficiency in factor XI can have serious bleeding episodes. Symptoms of factor XI deficiency vary widely, even among family members, which can make it difficult to diagnose.

Common symptoms:

- Epistaxis.
- Easy bruising.
- Menorrhagia.
- Abnormal bleeding during or after surgery, injury, or childbirth.

Diagnosis

Factor XI deficiency is diagnosed by a prolonged APTT and low level of factor XI.normal value is 5mcg /ml. Its half-life is 52 hours.

Treatment

There are several treatments available to help control bleeding in people with factor XI deficiency.

- Factor XI concentrate
- Antifibrinolytic drugs
- Fibrin glue
- Fresh frozen plasma (FFP)

9.8 Factor XIII deficiency.

Factor XIII deficiency is an autosomal recessive disorder.

Symptoms

Most people with factor XIII deficiency experience symptoms from birth, often bleeding from the umbilical cord stump. Symptoms tend to continue throughout life. As a general rule, the less factor XIII a person has in his/her blood, the more frequent and/or severe the symptoms.

Common symptoms:

- Bleeding from the umbilical cord stump at birth.
- Epistaxis.

- Easy bruising.
- Hemarthrosis.
- Bleeding in the central nervous system.
- Bleeding in the mouth, particularly after dental surgery.
- Poor wound healing and abnormal scar formation.
- Bleeding in soft tissue.
- Problems during pregnancy (including recurrent miscarriages).
- Bleeding after circumcision.
- Abnormal bleeding during or after injury or surgery.

Diagnosis

Factor XIII deficiency is difficult to diagnose. There will be low factor XIII level (normal value is 60-130 U/dl).

PT, aPTT and bleeding time at normal references.

Positive test for clot solubility in 5M urea.

Treatment

There are several treatments available to help control bleeding in people with factor XIII deficiency.

- Factor XIII concentrate.
- Cryoprecipitate.
- Fresh frozen plasma (FFP).

Excessive menstrual bleeding in women with factor XIII deficiency may be controlled with hormonal contraceptives (birth control pills), intra-uterine devices (IUDs), or antifibrinolytic drugs.

9.9 Thrombosthenia Glanzmann thrombasthenia

9.9.1 Glanzmann thrombasthenia?

Glanzmann thrombasthenia is a platelet function disorder that is caused by an abnormality in the genes for glycoproteins IIb/IIIa. These genes code for a group of linked proteins normally found on the surface of platelets, the glycoprotein IIb/IIIa receptor (also called the fibrinogen receptor). Because this receptor is absent or is not working properly, platelets do not stick to each other at the site of injury and it is difficult for the normal blood clot to form. Glanzmann thrombasthenia is an autosomal recessive disorder.

Symptoms

Symptoms of Glanzmann thrombasthenia vary quite a bit from one individual to the next, from very mild to potentially life-threatening bleeding. Signs of the disorder are usually first noticed during childhood.

People with Glanzmann thrombasthenia may experience:

- Easy bruising
- Epistaxis
- Bleeding from gums
- Menorrhagia or postpartum haemorrhage
- Abnormal bleeding after surgery, circumcision, or dental intervention.
- Rarely gastrointestinal hemorrhage or bleeding into genito-urinary tract
- Glanzmann thrombasthenia often causes more problems for women than men because of menstruation and childbirth.

Diagnosis

- In people with Glanzmann thrombasthenia:
- The bleeding time is longer than normal. This test may be difficult to perform in young children, normal platelet count.
- The closure time is longer than normal by platelet function analyzer (PFA-100).
- Platelets do not clump together the way they should with several different chemicals in a laboratory test (platelet aggregation). But do aggregate with Ristocetin.
- GP IIb/IIIa is not detectable in blood samples (using a test called flow cytometry)

Note: Some of these tests may not be available in all centres.

Treatment

Most people with platelet function disorders only need treatment during surgical procedures (including dental work) and after injury or accidents. When needed, Glanzmann thrombasthenia may be treated with:

- Antifibrinolytic drugs.
- Fibrin sealants.

- Hormonal contraceptives (to control excessive menstrual bleeding).
- Iron replacement (if necessary to treat anemia caused by excessive or prolonged bleeding).
- Platelet transfusions (only if bleeding is severe).
- Recombinant factor VIIa in dose 90 mcg per kg body weight every 1.5 to 2.5 hours

People with inherited platelet function disorders should not take Aspirin®, nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen), and blood thinners, which can make their bleeding symptoms worse.

9.9.2 Bernard-Soulier syndrome

What is Bernard-Soulier syndrome?

Bernard-Soulier syndrome is a platelet function disorder caused by an abnormality in the genes for glycoprotein Ib/IX/V. These genes code for a group of linked proteins normally found on the surface of platelets, the glycoprotein Ib/IX/V receptor (also called the von Willebrand factor or VWF receptor). Because this receptor is absent or is not working properly, platelets do not stick to the injured blood vessel wall the way they should and it is difficult for the normal blood clot to form. Bernard-Soulier syndrome is an autosomal recessive disorder

Symptoms

Symptoms of Bernard-Soulier syndrome vary from one individual to the next. Signs of the disorder are usually first noticed during childhood.

People with Bernard-Soulier syndrome may experience:

- Easy bruising.
- Epistaxis.
- Bleeding from gums.
- Menorrhagia or postpartum hemorrhage.
- Abnormal bleeding after surgery, circumcision, or dental intervention.
- Rarely gastrointestinal hemorrhage.

Bernard-Soulier syndrome often causes more problems for women than men because of menstruation and childbirth.

Diagnosis.

In people with Bernard-Soulier syndrome:

- The bleeding time is longer than normal. This test may be difficult to perform in young children, normal platelet count.
- The closure time is longer than normal by platelet function analyzer (PFA-100).
- Platelets appear larger than normal under a microscope and fewer than nomal.

- Platelets do not clump together normally in the presence of ristocetin (a substance that normally promotes platelet aggregation)
- GPIb/IX/V is not detectable in blood samples (using a test called flow cytometry)

Note: Some tests are not available in all centres.

In children, Bernard-Soulier syndrome is sometimes misdiagnosed as immune thrombocytopenic purpura, Acquired type of bleeding problem in which there are also fewer platelets than normal.

Treatment

Most people with platelet function disorders only need treatment during surgical procedures (including dental work) and after injury or accidents. When needed, Bernard-Soulier syndrome may be treated with:

- Antifibrinolytic drugs
- Desmopressin
- Fibrin sealants
- Hormonal contraceptives (to control excessive menstrual bleeding)
- Iron replacement (if necessary to treat anemia caused by excessive or prolonged bleeding)
- Platelet transfusions (only if bleeding is severe)

People with inherited platelet function disorders should not take Aspirin, nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen), which can make their bleeding symptoms worse