Clinical Practice Guidelines

Hemophilia

Program Update: 08/31/2014

Approved by:
Andrew Krueger, MD
Alice Ma, MD
Cathy G. Rosenfield, MD

These World and National Guidelines replace Accordant's Clinical Practice Guidelines for Hemophilia

WFH 50 YEARS OF ADVANCING TREATMENT FOR ALL

WORLD FEDERATION OF HEMOPHILIA
Fédération mondiale de l'hémophilie
Federación Mundial de Hemofilia

GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA

2nd edition

These guidelines were originally published by Blackwell Publishing in *Haemophilia*; Epub 6 JUL 2012. DOI: 10.1111/j.1365-2516.2012.02909.x. They are reprinted with their permission.

This publication is accessible from the World Federation of Hemophilia's website at www.wfh.org.

Additional copies are also available from the WFH at:

World Federation of Hemophilia
1425, boul. René-Lévesque O., bureau 1010
Montréal, Québec
H3G 1T7 Canada
Tel.: (514) 875-7944
Fax: (514) 875-8916
E-mail: wfh@wfh.org
www.wfh.org

GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA

2nd edition

Prepared by the Treatment Guidelines Working Group, on behalf of the World Federation of Hemophilia (WFH)

Dr. Alok Srivastava (Chair)
Department of Hematology, Christian Medical College, Vellore, Tamil Nadu, India

Dr. Andrew K. Brewer
Department of Oral Surgery, The Royal Infirmary, Glasgow, Scotland

Dr. Eveline P. Mauser-Bunschoten,
Van Creveldkliniek and Department of Hematology, University Medical Center Utrecht, Utrecht, the Netherlands

Dr. Nigel S. Key
Department of Medicine, University of North Carolina, Chapel Hill, NC, U.S.A.

Dr. Steve Kitchen
Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK

Dr. Adolfo Llinas
Department of Orthopaedics and Traumatology, Fundación Santa Fe University Hospital Fundación Cosme y Damián and Universidad de los Andes and Universidad del Rosario, Bogotá, Colombia

Dr. Christopher A. Ludlam
Comprehensive Care Haemophilia and Thrombosis Centre, Royal Infirmary, Edinburgh, U.K.

Dr. Johnny N. Mahlangu
Haemophiia Comprehensive Care Centre, Johannesburg Hospital and Department of Molecular Medicine and Haematology, Faculty of Health Sciences, National Health Laboratory Services and University of the Witwatersrand, Johannesburg, South Africa

Kathy Mulder
Bleeding Disorders Clinic, Health Sciences Center
Winnipeg, Canada

Dr. Man-Chiu Poon
Departments of Medicine, Pediatrics and Oncology, and Southern Alberta Rare Blood and Bleeding Disorders Comprehensive Care Program, University of Calgary, Foothills Hospital and Calgary Health Region, Alberta, Canada

Dr. Alison Street
Department of Haematology, Alfred Hospital
Melbourne, Australia

Acknowledgements

A professional agency was engaged to assist with the literature search and to grade the evidence. In addition, given the fact that many recommendations are based on expert opinion, a draft version of these guidelines was circulated to many others involved in hemophilia care outside of the writing group. The authors are grateful to those who provided detailed comments. Finally, we would like to acknowledge the extraordinary effort from WFH staff, Jennifer Laliberté, and also Elizabeth Myles, in completing this work.

Disclaimer

The World Federation of Hemophilia (WFH) does not endorse particular treatment products or manufacturers. Any reference to a product name is not an endorsement by the WFH. The WFH does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimens are continually revised and new side-effects recognized. These guidelines are intended to help develop basic standards of care for the management of hemophilia. They do not replace the advice of a medical advisor and/or product insert information. Any treatment must be designed according to the needs of the individual and the resources available.

CONTENTS

TABLES AND FIGURES

Summary

Hemophilia is a rare disorder that is complex to diagnose and to manage. These evidence-based guidelines offer practical recommendations on the diagnosis and general management of hemophilia, as well as the management of complications including musculoskeletal issues, inhibitors, and transfusion-transmitted infections. By compiling these guidelines, the World Federation of Hemophilia (WFH) aims to assist healthcare providers seeking to initiate and/or maintain hemophilia care programs, encourage practice harmonization around the world and, where recommendations lack adequate evidence, stimulate appropriate studies.

Introduction

The first edition of these guidelines, published in 2005 by the WFH, served its purpose of being a useful document for those looking for basic information on the comprehensive management of hemophilia. The need for revision has arisen for several reasons. The most significant of these was to incorporate the best existing evidence on which recommendations were based. There is recent high quality data from randomized controlled trials establishing the efficacy and superiority of prophylactic factor replacement over episodic treatment—though the optimal dose and schedule for prophylaxis continue to be subjects of further research. There is also greater recognition of the need for better assessment of outcomes of hemophilia care using newly developed, validated, disease-specific clini-metric instruments. This revised version addresses these issues in addition to updating all sections.

These guidelines contain several recommendations regarding the clinical management of people with hemophilia (**practice statements**, in **bold).** All such statements are supported by the best available evidence in the literature, which were graded as per the 2011 Oxford Centre for Evidence-Based Medicine (see Appendix I). Where possible, references for recommendations that fell outside the selection for practice statements were also included. These references have not been graded.

A question often raised when developing a guideline document such as this is 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 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, these guidelines continue to include a dual set of dose recommendations for CFC replacement therapy. These are based on published literature and practices in major centres 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 data and greater availability of CFC.

One of the reasons for the wide acceptance of the first edition of these guidelines was its easy reading format. While enhancing the content and scope of the document, we have ensured that the format has remained the same. We hope that it will continue to be useful to those initiating and maintaining hemophilia care programs. Furthermore, the extensive review of the literature and the wide consensus on which practice statements have been made may encourage practice harmonization around the world. More importantly, in areas where practice recommendations lack adequate evidence, we hope that this document will stimulate appropriate studies.

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 has an estimated frequency of approximately one in 10,000 births.
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% to 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 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.
7. A family history of bleeding is obtained in about two-thirds of all patients.
8. 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 (see Section 5).

TABLE 1-1: RELATIONSHIP OF BLEEDING SEVERITY TO CLOTTING FACTOR LEVEL [62]

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 [63]

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 (see “Comprehensive care,” on page 9).

4. **Acute bleeds should be treated as quickly as possible, preferably within two hours. If in doubt, treat. (Level 4) [2]**

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 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. (Level 5) [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. (Level 3) [4-6]

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" on page 12).

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" on page 32 and "Inhibitors" on page 59).

13. Prevention of bleeding can be achieved by prophylactic factor replacement (see "Prophylactic factor replacement therapy" on page 12).

14. Home therapy can be used to manage mild/moderate bleeding episodes (see "Home therapy" on page 13).

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" on page 11).

16. Patients should avoid activities likely to cause trauma (see "Fitness and physical activity" on page 11).

17. Regular monitoring of health status and assessment of outcomes are key components of care (see "Monitoring health status and outcome" on page 14).

18. Drugs that affect platelet function, particularly acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors, should be avoided. Paracetamol/acetaminophen is a safe alternative for analgesia (see "Pain management" on page 15).

19. Factor levels should be raised to appropriate levels prior to any invasive procedure (see "Surgery and invasive procedures" on page 16).

20. Good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding (see "Dental care and management" on page 17).

1.3 Comprehensive care

1. **Comprehensive care promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality. (Level 3) [7-9]**

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:
- prevention of bleeding and joint damage
- prompt management of bleeding

- management of complications including:
  - joint and muscle damage and other sequelae of bleeding
  - inhibitor development
  - viral infection(s) transmitted through blood products
- attention to psychosocial health

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. (Level 5) [10-12]

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, physiatrist, orthopedist, rheumatologist) who can address prevention as well as treatment
   - a laboratory specialist
   - a psychosocial expert (preferably a social worker, or a psychologist) familiar with available community resources

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 centre.

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 concetrates, 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 counsellor

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 patient's 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. (Level 5) [13,14]
   - The management plan should be developed with the patient and communicated to all treaters and care facilities. Communication among treaters is important.
   - Smaller centres and personal physicians can provide primary care and management of some complications, in frequent consultation with the comprehensive care centre (particularly for patients who live a long distance from the nearest hemophilia treatment centre).

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 centre and support improvements to care delivery.
   - help inform allocation of resources.
   - promote collaboration between centres in sharing and publishing data.

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

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. (Level 2) [15]

2. Bone density may be decreased in people with hemophilia [16, 17].

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. (Level 3) [16]

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

5. Noncontact 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 [18].

9. Target joints can be protected with braces or splints during activity, especially when there is no clotting factor coverage. (Level 4) [19,20]

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

1.5Adjunctive 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.

3. Physiotherapy/rehabilitation is particularly important for functional improvement and recovery after musculoskeletal bleeds and for those with established hemophilic arthropathy (see "Principles of physiotherapy/Physical medicine in hemophilia" on page 57).

4. Antifibrinolytic drugs (e.g., tranexamic acid, epsilon aminocaproic acid) are effective as adjunctive treatment for mucosal bleeds and dental extractions (see "Tranexamic acid" on page 42 and "Epsilon aminocaproic acid" on page 43).

5. Certain COX-2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis (see "Pain management" on page 15).

1.6 Prophylactic factor replacement therapy

1. Prophylaxis is the treatment by intravenous injection of factor concentrate in order to prevent anticipated bleeding (see Table 1-4).

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 [21-24].

3. Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. (Level 2) [24-29]

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. [26, 29, 30]

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 studies, 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

5. It is unclear whether all patients should remain on prophylaxis indefinitely as they transition into adulthood. Although some data suggest that a proportion of young adults can do well off prophylaxis [31], more studies are needed before a clear recommendation can be made [32].

6. 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. (Level 3) [33, 34]

7. 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.

8. Prophylaxis as currently practiced in countries where there are no significant resource constraints is an expensive treatment and is only possible if significant resources are allocated to hemophilia care. However, it is cost-effective in the long-term because it eliminates the high cost associated with subsequent management of damaged joints and improves quality of life.

9. In countries with significant resource constraints, lower doses of prophylaxis given more frequently may be an effective option.

10. Cost-efficacy studies designed to identify minimum dosage are necessary to allow access to prophylaxis in more of the world.

Administration and dosing schedules

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

- The Malmö protocol: 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 Utrecht protocol: 15-30 IU/kg per dose administered three 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.

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.

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. (Level 4) [18, 34, 35]

1.7 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. (Level 3) [36, 37]

3. Further improvements in quality of life include greater freedom to travel and participate in physical activities, less absenteeism, and greater employment stability [38].

4. Home therapy is ideally achieved with clotting factor concentrates or other lyophilized products that are safe, can be stored in a domestic fridge, and are reconstituted easily.

5. Home treatment must be supervised closely by the comprehensive care team and should only be initiated after adequate education and training. (Level 3) [36, 37]

6. Teaching should focus on general knowledge of hemophilia; recognition of bleeds and common complications; first aid measures; dosage calculation; preparation, storage, and administration of clotting factor concentrates; aseptic techniques; performing venipuncture (or access of central venous catheter); record keeping; proper storage and disposal of needles/sharps; and handling of blood spills. A certification program is helpful.

7. Patients or parents should keep bleed records (paper or electronic) that include date and site of bleeding, dosage and lot number of product used, and adverse effects.

8. Infusion technique and bleed records should be reviewed and monitored at follow-up visits.

9. Home care can be started with young children with adequate venous access and motivated family members who have undergone adequate training. Older children and teenagers can learn self-infusion with family support.

10. An implanted venous access device (Port-A-Cath) can make injections much easier and may be required for administering prophylaxis in younger children. (Level 2) [39, 40]

11. However, the risks of surgery, local infection, and thrombosis associated with such devices need to be weighed against the advantages of starting intensive prophylaxis early. (Level 2) [41, 42]

12. The venous access device must be kept scrupulously clean and be adequately flushed after each administration to prevent clot formation [41].

1.8 Monitoring health status and outcome

1. Regular standardized evaluation at least every 12 months allows longitudinal assessment for individual patients and can identify new or potential problems in their early stages so that treatment plans can be modified. (Level 3) [14, 26, 43]

2. Patients should be seen by the multidisciplinary care team after every severe bleeding episode.

3. The following should be evaluated and education should be reviewed and reinforced:
- issues related to venous access
- issues related to hemostasis (bleed record)
- use of products for replacement therapy and the response to them
- musculoskeletal status: impairment and function through clinical assessment of joints and muscles, and radiological evaluation annually or as indicated (see "Musculoskeletal complications" on page 55)
- transfusion-transmitted infections: commonly HIV, HCV, and HBV, and others if indicated (see "Transfusion-transmitted and other infection-related complications" on page 61)
- development of inhibitors (see "Inhibitors" on page 59)
- overall psychosocial status
- dental/oral health

4. Several hemophilia-specific scores are available to measure joint impairment and function, including activities and participation. These include:
- Impairment:
  - Clinical: WFH Physical Examination Score (aka Gilbert score), Hemophilia Joint Health Score (HJHS)
  - Radiological: Pettersson score, MRI, and ultrasound scores
  - Activity: Haemophilia Activities List (HAL), Paediatric Haemophilia Activities List (PedHAL), Functional Independence Score in Hemophilia (FISH)
- Health-related quality of life: (HaemoQol, Canadian Hemophilia Outcomes: Kids' Life Assessment Tool [CHO-KLAT])

5. For more information on available functional and physical examination scores, see the WFH's Compendium of Assessment Tools at: www.wfh.org/assessment_tools.

1.9Pain management

1. 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

1. While clotting factor concentrates should be administered as quickly as possible to stop bleeding, additional drugs are often needed for pain control (see Table 1-5: Strategies for pain management in patients with hemophilia).

2. Other measures include cold packs, immobilization, splints, and crutches [44].

Postoperative pain

1. Intramuscular injection of analgesia should be avoided.

2. Postoperative 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. (Level 2) [15, 45]

3. COX-2 inhibitors have a greater role in this situation. (Level 2) [46, 47]

4. Other NSAIDs should be avoided. (Level 2) [48]

5. When pain is disabling, orthopedic surgery may be indicated. (Level 5) [49]

6. Patients with persisting pain should be referred to a specialized pain management team.

TABLE 1-5: STRATEGIES FOR PAIN MANAGEMENT IN PATIENTS WITH HEMOPHILIA

1	Paracetamol/acetaminophen *If not effective* ↓
2	COX-2 inhibitor (e.g. celecoxib, meloxicam, nimesulide, and others) OR Paracetamol/acetaminophen plus codeine (3-4 times/day) OR Paracetamol/acetaminophen plus tramadol (3-4 times/day)
3	Morphine: use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more than 4 times/day

Notes:

- If for any reason medications have been stopped for a period of time, patients who have been taking and tolerating high-dose narcotic drugs should re-start the drug at a lower dose, or use a less powerful painkiller, under the supervision of a physician.
- COX-2 inhibitors should be used with caution in patients with hypertension and renal dysfunction.

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 centre. (Level 3) [50, 51]

4. The anesthesiologist should have experience treating patients with bleeding disorders.

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. (Level 4) [52, 53]

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 postoperatively 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 (see Tables 7-1 and 7-2).

TABLE 1-6: DEFINITION OF ADEQUACY OF HEMOSTASIS FOR SURGICAL PROCEDURES [64]

Excellent	Intra-operative and post-operative blood loss similar (within 10%) to the non-hemophilic patient. ▪ No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND ▪ Blood component transfusions required are similar to non-hemophilic patient
Good	Intra-operative and/or post-operative blood loss slightly increased over expectation for the non-hemophilic patient (between 10-25% of expected), but the difference is judged by the involved surgeon/anaesthetist to be clinically insignificant. ▪ No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND ▪ Blood component transfusions required are similar to the non-hemophilic patient
Fair	Intra-operative and/or post-operative blood loss increased over expectation (25-50%) for the non-hemophilic patient and additional treatment is needed. ▪ Extra (unplanned) dose of FVIII/FIX/bypassing agents needed OR ▪ Increased blood component (within 2 fold) of the anticipated transfusion requirement
Poor/none	Significant intra-operative and/or post-operative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia ▪ Unexpected hypotension or unexpected transfer to ICU due to bleeding OR ▪ Substantially increased blood component (> 2 fold) of the anticipated transfusion requirement

Notes:
- Apart from estimates of blood loss during surgery, data on pre- and post-operative hemoglobin levels and the number of packed red blood cell units transfused may also be used, if relevant, to estimate surgical blood loss.
- Surgical hemostasis should be assessed by an involved surgeon and/or anaesthetist and records should be completed within 72 hours following surgery.
- Surgical procedures may be classified as major or minor. A major surgical procedure is defined as one that requires hemostatic support for periods exceeding 5 consecutive days.

11.Effectiveness of hemostasis for surgical procedures may be judged as per criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (see Table 1-6) [64].

12. 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 rescreened 4–12 weeks post-operatively. (Level 4) [54]

13. Careful monitoring for inhibitors is also advisable in patients with nonsevere hemophilia A receiving continous infusion after surgery [55].

14. 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.

1.11Dental 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 [56].

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, intra-papillary, and intra-ligamentary injections are often done under factor cover (20% to 40%) though it may be possible for those with adequate experience to administer these injections without it. (Level 4) [57,58]

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. (Level 3) [51]

11. Tranexamic acid or epsilon aminocaproic acid (EACA) is often used after dental procedures to reduce the need for replacement therapy. (Level 4) [59,60]

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 mouthwashes (a teaspoon 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. Nonsteroidal 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 [61].

References

1. Stonebraker JS, Bolton-Maggs PH, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia* 2010;16(1):20-32.
2. Ingram GI, Dykes SR, Creese AL, Mellor P, Swan AV, Kaufert JK, Rizza CR, Spooner RJ, Biggs R. Home treatment in haemophilia: clinical, social and economic advantages. *Clin Lab Haematol* 1979;1(1):13-27.
3. Singleton T, Kruse-Jarres R, Leissinger C. Emergency department care for patients with haemophilia and von Willebrand disease. *J Emerg Med* 2010;39(2):158-65.
4.Castaman G, Mancuso ME, Giacomelli SH, et al. Molecular and phenotypic determinants of the response to desmopressin in adult patients with mild hemophilia A. *J Thromb Haemost* 2009;7(11):1824-31.
5. Franchini M, Zaffanello M, Lippi G. The use of desmopressin in mild hemophilia A. *Blood Coagul Fibrinolysis* 2010;21(7):615-9.
6. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first twenty years. *Haemophilia* 2000;6(Suppl 1):60-67.
7.Berntorp E, Boulyzenkov V, Brettler D, et al. Modern treatment of haemophilia. *Bull WHO* 1995;73:691-701.
8. Kasper CK, Mannucci PM, Boulyzenkov V, et al. Haemophilia in the 1990s: Principles of treatment and improved access to care. *Semin Thrombosis Haemostas* 1992;18:1-10.
9.Soucie JM, Nuss R, Evatt B, Abdelhak A, Cowan L, Hill H, Kolakoski M, Wilber N; Hemophilia Surveillance System Project Investigators. Mortality among males with hemophilia: relations with source of medical care. *Blood* 2000;96:437–42.
10.Colvin BT, Astermark J, Fischer K, Gringeri A, Lassila R, Schramm W, Thomas A, Ingerslev J; Inter Disciplinary Working Group. European principles of haemophilia care. *Haemophilia* 2008;14(2):361-74.
11. Evatt BL. The natural evolution of haemophilia care: developing and sustaining comprehensive care globally. *Haemophilia* 2006;12(Suppl 3):13-21.
12. Evatt BL, Black C, Batorova A, Street A, Srivastava A. Comprehensive care for haemophilia around the world. *Haemophilia* 2004;10(Suppl 4):9-13.
13. Canadian Hemophilia Standards Group. Canadian Comprehensive Care Standards for Hemophilia and Other Inherited Bleeding Disorders, First Edition, June 2007. http://www.ahcdc.ca/documents/CanadianHemophiliaStandardsFirstEdition070612_1.pdf (Accessed September 4, 2011).
14.de Moerloose P, Fischer K, Lambert T, Windyga J, Batorova A, Lavigne-Lissalde G, Rocino A, Astermark J, Hermans C. Recommendations for assessment, monitoring and follow-up of patients with haemophilia. *Haemophilia* 2012 May;18(3):319-25.
15. Gomis M, Querol F, Gallach JE, Gonzalez LM, Aznar JA. Exercise and sport in the treatment of haemophilic patients: a systematic review. *Haemophilia* 2009;15(1):43-54.
16.Iorio A, Fabbriciani G, Marcucci M, Brozzetti M, Filipponi P. Bone mineral density in haemophilia patients: a meta-analysis. *Thromb Haemost* 2010;103(3):596-603.
17. Wallny TA, Scholz DT, Oldenburg J, et al. Osteoporosis in haemophilia - an underestimated comorbidity? *Haemophilia* 2007;13(1):79-84.
18. Seuser A, Boehm P, Kurme A, Schumpe G, Kurnik K. Orthopaedic issues in sports for persons with haemophilia. *Haemophilia* 2007;13(Suppl 2):47–52.
19. Philpott J, Houghton K, Luke A. Physical activity recommendations for children with specific chronic health conditions: Juvenile idiopathic arthritis, hemophilia, asthma and cystic fibrosis. *Paediatr Child Health* 2010;15(4):213-25.
20. Querol F, Aznar JA, Haya S, Cid A. Orthoses in haemophilia. *Haemophilia* 2002;8(3):407-12.
21. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; 7: 446-52.
22.Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients: a long-term follow-up. *J Intern Med* 1997;241:395-400.
23. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992;232(1):25-32.
24. Aronstam A, Arblaster PG, Rainsford SG, Turk P, Slattery M, Alderson MR, et al. Prophylaxis in haemophilia: a double-blind controlled trial. *Br J Haematol* 1976;33(1):81-90.
25. Astermark J, Petrini P, Tengborn L, et al. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *Br J Haematol* 1999;105:1109-13.
26. Feldman BM, Pai M, Rivard GE, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost* 2006; 4(6):1228-36.

27. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, et al. Effects of postponing prophylactic treatment on long-term outcome in patients with severe haemophilia. *Blood* 2002;99:2337-41.
28. Gringeri A, Lundin B, Mackensen SV, et al; ESPRIT Study Group. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study*). J Thromb Haemost* 2011;9(4):700-10.
29.Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *NEJM* 2007;357(6):535-44.
30. Petrini P. What factors should influence the dosage and interval of prophylactic treatment in patients with severe haemophilia A and B? *Haemophilia* 2001;7(1):99-102.
31. Fischer K, Van Der Bom JG, Prejs R, et al. Discontinuation of prophylactic therapy in severe haemophilia: incidence and effects on outcome. *Haemophilia* 2001;7(6):544-50.
32. Hay CR. Prophylaxis in adults with haemophilia. *Haemophilia* 2007;13(Suppl 2):10-5.
33.Kavakli K, Aydogdu S, Taner M, et al. Radioisotope synovectomy with rhenium186 in haemophilic synovitis for elbows, ankles and shoulders. *Haemophilia* 2008;14(3):518-23.
34. Luchtman-Jones L, Valentino LA, Manno C; Recombinant Therapy Workshop Participants. Considerations in the evaluation of haemophilia patients for short-term prophylactic therapy: a paediatric and adult case study. *Haemophilia* 2006;12(1):82-6.
35. Petrini P, Seuser A. Haemophilia care in adolescents—compliance and lifestyle issues. *Haemophilia* 2009; 15 Suppl 1:15-9.
36.Soucie JM, Symons J, Evatt B, Brettler D, Huszti H, Linden J; Hemophilia Surveillance System Project Investigators. Home-based factor infusion therapy and hospitalization for bleeding complications among males with haemophilia. *Haemophilia* 2001;7:198-206.
37.Teitel JM, Barnard D, Israels S, Lillicrap D, Poon MC, Sek J. Home management of haemophilia. *Haemophilia* 2004;10(2):118-33.
38. Szucs TD, Offner A, Kroner B, et al; European socioeconomic study group. Resource utilization in haemophiliacs treated in Europe: results from the European study on socioeconomic aspects of haemophilia care. *Haemophilia* 1998;4(4):498-501.
39. Neunert CE, Miller KL, Journeycake JM, et al. Implantable central venous access device procedures in haemophilia patients without an inhibitor: systematic review of the literature and institutional experience. *Haemophilia* 2008;14(2):260-70.
40. Valentino LA, Ewenstein B, Navickis RJ, Wilkes MM. Central venous access devices in haemophilia. *Haemophilia* 2004;10(2):134-46.
41. Ljung R.The risk associated with indwelling catheters in children with haemophilia. *Br J Haematol* 2007;138(5):580-6.
42. Ragni MV, Journeycake JM, Brambilla DJ. Tissue plasminogen activator to prevent central venous access device infections: a systematic review of central venous access catheter thrombosis, infection and thromboprophylaxis. *Haemophilia* 2008;14(1):30-8.
43.Su Y, Wong WY, Lail A, Donfield SM, Konzal S, Gomperts E; Hemophilia Growth And Development Study. Long-term major joint outcomes in young adults with haemophilia: interim data from the HGDS. *Haemophilia* 2007;13(4):387-90.
44.Hermans C, de Moerloose P, Fischer K, Holstein K, Klamroth R, Lambert T, et al; European Haemophilia Therapy Standardisation Board. Management of acute haemarthrosis in haemophilia A without inhibitors: literature review, European survey and recommendations. *Haemophilia* 2011;17(3):383-92.
45. Vallejo L, Pardo A, Gomis M, et al. Influence of aquatic training on the motor performance of patients with haemophilic arthropathy. *Haemophilia* 2010;16(1):155-61.
46. Rattray B, Nugent DJ, Young G. Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia. *Haemophilia* 2006;12(5):514-7.
47.Tsoukas C, Eyster ME, Shingo S, et al. Evaluation of the efficacy and safety of etoricoxib in the treatment of hemophilic arthropathy. *Blood* 2006;107(5):1785-90.
48.Eyster ME, Asaad SM, Gold BD, Cohn SE, Goedert JJ; Second Multicenter Hemophilia Study Group. Upper gastrointestinal bleeding in haemophiliacs: incidence and relation to use of non-steroidal anti-inflammatory drugs. *Haemophilia* 2007;13(3):279-86.
49. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. *HSSJ* 2010;6:37-42.
50. Batorova A, Martinowitz U. Intermittent injections vs. continuous infusion of factor VIII in haemophilia patients undergoing major surgery. *Br J Haematol* 2000;110(3):715-20.
51. Hermans C, Altisent C, Batorova A, et al.; European Haemophilia Therapy Standardisation Board. Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations. *Haemophilia* 2009;15(3):639-58.
52.Mathews V, Viswabandya A, Baidya S, George B, Nair S, Chandy M, Srivastava A. Surgery for hemophilia in developing countries. *Semin Thromb Hemost* 2005;31(5):538-43.
53. Teitel JM, Carcao M, Lillicrap D, et al. Orthopaedic surgery in haemophilia patients with inhibitors: a practical guide to haemostatic, surgical and rehabilitative care. *Haemophilia* 2009;15(1):227-39.
54. Kempton CL, Soucie JM, Miller CH, et al. In non-severe hemophilia A the risk of inhibitor after intensive factor treatment is greater in older patients: a case-control study. *J Thromb Haemost* 2010;8(10):2224-31.
55.Eckhardt CL, Van der Bom JG, Van der Naald M, Peters M, Kamphuisen PW and Fijnvandraat K. Surgery and inhibitor development in hemophilia A: a systematic review. *J Thromb Haemost* 2011;9:1948–1958.
56. Friedman M, White B, Dougall AJ. An audit of the protocol for the management of patients with hereditary bleeding disorders undergoing dental treatment. *J Disab Oral Health* 2009;10(4):151-55.
57.Frachon X, Pommereuil M, Berthier AM, et al. Management options for dental extraction in hemophiliacs: a study of 55 extractions (2000-2002). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;99(3):270-5.
58. Hewson I, Makhmalbaf P, Street A, et al. Dental surgery with minimal factor support in the inherited bleeding disorder population at the Alfred Hospital. *Haemophilia* 2011;17(1):e185-8.

59. Coetzee MJ. The use of topical crushed tranexamic acid tablets to control bleeding after dental surgery and from skin ulcers in haemophilia. *Haemophilia* 2007;13(4):443-4.
60. Franchini M, Rossetti G, Tagliaferri A, et al. Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers. *Haemophilia* 2005;11:504–9.
61. Brewer A. *Dental Management of Patients with Inhibitors to Factor VIII or Factor IX*. Treatment of Hemophilia monograph no 45. Montreal: World Federation of Hemophilia, 2008.
62.White GC 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001;85(3):560.
63. Aronstam A, Rainsford SG, Painter MJ. Patterns of bleeding in adolescents with severe haemophilia A. *Br Med J* 1979;1(6161):469-70.
64. Definitions in hemophilia. Recommendations of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *JTH* 2012 (in press).

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 [1, 2].

4. Most carriers are asymptomatic.

5. Carriers with clotting factor levels of 40-60% of normal may have an increased bleeding tendency [3].

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 lyonization (see Table 1-1).

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 [3].

8. Menorrhagia and bleeding after medical interventions are the most common manifestations among carriers with significantly low factor levels [3].

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 [4].

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. (Level 3) [3, 5]

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 counselling, and if desired by the family, prenatal diagnosis. (Level 4) [6]

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 counselling 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 using Y chromosome-specific PCR in maternal plasma/serum after 7 to 9 weeks of gestation [7,8] or by ultrasonography beginning week 11 of gestation [9].

6. Chorionic villus sampling (CVS), or biopsy, is the main method of prenatal diagnosis and is best done between 9 to 14 weeks of gestation. Biopsy carried out earlier may be associated with increased complications including fetal limb abnormalities. (Level 1) [10-13]

7. Amniocentesis can be done at 15 to 17 weeks of gestation [11].

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 RhD negative. (Level 3) [14]

11. Pre-implantation genetic diagnosis allows selection of embryos without specific mutation to be implanted into the uterus [15].

2.3 Delivery of infants with known or suspected hemophilia

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. (Level 3) [4]

2. In carriers with significantly low factor levels (< 50 IU/dl), clotting factor replacement is necessary for surgical or invasive procedures including delivery. (Level 3) [4]

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. (Level 3) [4]

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 [16].

2.4Vaccinations

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. (Level 4) [17]

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 (usually 25-27 gauge) should be used.
- Pressure should be applied to the injection site for at least five minutes [18].

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. (Level 4) [19, 20]

2.5 Psychosocial issues

1. Patients and their families should be provided with psychological and social support [21, 22].

2. Hemophilia is also a financial burden that places restrictions on several aspects of normal living [23].

3. The social worker and/or other members of the comprehensive care team should:
- provide as much information as possible about the physical, psychological, emotional, and economic dimensions of hemophilia, in terms the patient/parents can understand.
- be open and honest about all aspects of care.
- allow the patient/parents to work through their emotions and ask questions. Provide care and support patiently.
- talk to affected children, not just their parents. Children can often understand a good deal about their illness and can work with the physician if properly informed and educated.
- remind parents not to ignore siblings that are healthy.
- be able to recognize warning signs of burnout and depression, which are common with chronic illness, and provide suggestions for coping.
- recognize that cultural background may affect patients' views of illness.
- encourage patients to engage in productive and leisure activities at home and in the workplace.
- work in partnership with the patient organization to advocate for hemophilia care and to provide education to families and members of the community.
- enlist the assistance of local groups and organizations where social workers are unavailable.

2.6 Sexuality

1. Patients with hemophilia can have normal sexual intercourse [24].

2. Muscle bleedings (for e.g., iliopsoas) may sometimes be the result of sexual activity.

3. Complications of hemophilia can be accompanied by sexual dysfunction, which may include lack of libido or impotence.

4. Pain or fear of pain may affect sexual desire, and hemophilic arthropathy may place limitations on sexual intercourse.

5. Sexuality is also affected by chronic HCV and HIV infection, age-related diseases like hypertension and diabetes mellitus, and certain medications.

6. In some cases, oral phosphodiesterase-5 inhibitors (sildenafil, tadalafil) may be helpful. These medications mildly inhibit platelet aggregation *in vitro*, and may cause epistaxis due to nasal congestion.

2.7Ageing hemophilia patients

1. Ageing patients with hemophilia will inevitably suffer from age-related diseases [24, 25].

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 [26, 27].

2. An increased number of arthropathic joints, loss of joint movement, and muscle atrophy leading to inactivity are associated with a lower BMD [27].

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 [28, 29].

Obesity

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

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) [31]
- increased arthropathic pain
- increased risk of developing target joints [32]
- 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 [33, 34].

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 ≤140 mmHg and a diastolic pressure ≤90 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 [35].

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. (Level 5) [24]

Hypercholesterolemia

1. Mean cholesterol levels in patients with hemophilia have been reported to be lower than in the general population [36].

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 [34, 37, 38].

2. A possible association between the occurrence of myocardial infarction and previous administration of clotting factor concentrates has been described [39, 40].

3. Hemophilia patients with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist [41, 42].

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. (Level 4) [40,41,43]
- 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/IIIa inhibitors (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. (Level 4) [40,41,43]
- Factor concentrates should be given for the duration of dual antiplatelet therapy, usually about two weeks, aiming at trough levels of 30 IU/dl [41].
- 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 [41].

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 [44].

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.

2.8 Von Willebrand disease and rare bleeding disorders

1. The WFH is committed to providing support and information to patients, families, and clinicians on other hereditary bleeding disorders and many such patients are cared for in hemophilia treatment centres.

2. These guidelines are intended for the treatment of hemophilia. Recent publications that address the principles of diagnosis and treatment of von Willebrand disease (VWD) and rare bleeding disorders include:

- Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2004;10(3):218.231.
- The Diagnosis, Evaluation and Management of von Willebrand Disease. US Dept of Health and Human Services, National Heart, Lung and Blood Institute NIH Publication no. 08-5832, December 2007. www.nhlbi.nih.gov
- Von Willebrand Disease: An Introduction for the Primary Care Physician. David Lillicrap and Paula James, World Federation of Hemophilia Treatment of Hemophilia monograph No 47, January 2009. www.wfh.org
- Rare Bleeding Disorders. Peyvandi F, Kaufman R, Selighson U et al. *Haemophilia* 2006 Jul; 12 Suppl: 137-42.
- The Rare Coagulation Disorders. Paula Bolton-Maggs, World Federation of Hemophilia Treatment of Hemophilia No 39, April 2006. www.wfh.org

References

1. Lee CA, Chi C, Pavord SR, Bolton-Maggs PH, Pollard D, Hinchcliffe-Wood A, Kadir RA; UK Haemophilia Centre Doctors' Organization. The obstetric and gynaecological management of women with inherited bleeding disorders--review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2006 Jul;12(4):301-36.
2. Rizza CR, Rhymes IL, Austen DE, Kernoff PB, Aroni SA. Detection of carriers of haemophilia: a "blind' study. *Br J Haematol* 1975;30(4):447-56.
3. Plug I, Mauser-Bunschoten EP, Brocker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood* 2006;108(1):52-6.
4. Chi C, Lee CA, Shiltagh N, Khan A, Pollard D, Kadir RA. Pregnancy in carriers of hemophilia. *Haemophilia* 2008;14(1):56-64.
5. Ljung R, Tedgård U. Genetic counseling of hemophilia carriers. *Semin Thromb Hemost* 2003;29(1):31-6.
6. Dunn NF, Miller R, Griffioen A, Lee CA. Carrier testing in haemophilia A and B: adult carriers' and their partners' experiences and their views on the testing of young females. *Haemophilia* 2008;14(3):584-92.
7. Mortarino M, Garagiola I, Lotta LA, Siboni SM, Semprini AE, Peyvandi F. Non-invasive tool for foetal sex determination in early gestational age. *Haemophilia* 2011 Nov;17(6):952-6**.**
8. Rijnders RJ, van der Luijt RB, Peters ED, Goeree JK, Van Der Schoot CE, Ploos Van Amstel JK, Christiaens GC. Earliest gestational age for fetal sexing in cell-free maternal plasma. *Prenat Diagn* 2003;23(13):1042-4.
9. Chi C, Hyett JA, Finning KM, Lee CA, Kadir RA. Non-invasive first trimester determination of fetal gender: a new approach of prenatal diagnosis of haemophilia. *BJOG* 2006;113(2):239-42.
10. Evans MI, Andriole S. Chorionic villus sampling and amniocentesis in 2008. *Curr Opin Obstet Gynecol* 2008;20(2):164-8.
11. Jauniaux E, Pahal GS, Rodeck CH. What invasive procedure to use in early pregnancy? *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;14(4):651-62.
12. Tabor A, Alfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. *Fetal Diagn Ther* 2010;27(1):1-7.
13. Wapner RJ.Invasive prenatal diagnostic techniques. *Semin Perinatol* 2005;29(6):401-4.
14. Katiyar R, Kriplani A, Agarwal N, Bhatla N, Kabra M. Detection of fetomaternal hemorrhage following chorionic villus sampling by Kleihauer Betke test and rise in maternal serum alpha feto protein. *Prenat Diagn* 2007;27(2):139-42.
15. Lavery S. Preimplantation genetic diagnosis of haemophilia. *Br J Haematol* 2009;144:303-307.
16. Kletzel M, Miller CH, Becton DL, Chadduck WM, Elser JM. Postdelivery head bleeding in hemophilic neonates: Causes and management. *Am J Dis Child* 1989;143:1107-10.
17. Kulkarni R, Lusher J. Perinatal management of newborns with haemophilia. *Br J Haematol* 2001 Feb;112(2):264-74.
18. Evans DI, Shaw A. Safety of intramuscular injection of hepatitis B vaccine in haemophiliacs. *BMJ* 1990;300:1694–95.
19. Miller EJ, Lee CA, Karayiannis P, Holmes S, Thomas HC, Kernoff PB. Immune response of patients with congenital coagulation disorders to hepatitis B vaccine: suboptimal response and human immunodeficiency virus infection. *J Med Virol* 1989;28:96–100.
20. Steele M, Cochrane A, Wakefield C, et al. Hepatitis A and B immunization for individuals with inherited bleeding disorders.

Haemophilia 2009;15(2):437-47.
21. Cassis F. Psychosocial care for people with hemophilia. Treatment of Hemophilia monograph no 44. Montreal: World Federation of Hemophilia, 2007.
22. Miller R. Counselling about diagnosis and inheritance of genetic bleeding disorders: haemophilia A and B. *Haemophilia* 1999;5(2):77-83.
23. Bullinger M, von Mackensen S. Psychosocial determinants of quality of life in children and adolescents with haemophilia: a cross-cultural approach. *Clin Psychol Psychother* 2008;15(3):164-72.
24. Mauser-Bunschoten EP, Fransen Van De Putte DE, Schutgens RE. Co-morbidity in the ageing haemophilia patient: the down side of increased life expectancy. *Haemophilia* 2009 Jul;15(4):853-63.
25. Siboni SM, Mannucci PM, Gringeri A, et al. Health status and quality of life of elderly persons with severe haemophilia born before the advent of modern replacement therapy. *J Thromb Haemost* 2009;7(5):780-6.
26. Iorio A, Fabbriciani G, Marcucci M, Brozzetti M, Filipponi P. Bone mineral density in haemophilia patients: A meta-analysis. *Thromb Haemost* 2010 Mar;103(3):596-603.
27. Wallny TA, Scholz DT, Oldenburg J, et al. Osteoporosis in haemophilia - an underestimated comorbidity? *Haemophilia* 2007;13(1):79-84.
28. Kovacs CS. Hemophilia, low bone mass, and osteopenia/osteoporosis. *Transfus Apher Sci* 2008;38(1):33-40.
29. Scottish Dental Clinical Effectiveness Programme, Oral Health Management of Patients Prescribed Bisphosphonates: Dental Clinical Guidance. Dundee: Scottish Dental Clinical Effectiveness Programme, April 2011.
30. Hofstede FG, Fijnvandraat K, Plug I, Kamphuisen PW, Rosendaal FR, Peters M. Obesity: a new disaster for haemophilic patients? A nationwide survey. *Haemophilia* 2008;14(5):1035-38.
31. Soucie JM, Cianfrini C, Janco RL, et al. Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. *Blood* 2004;103(7):2467-73.
32. Carpenter SL, Chrisco M, Johnson E. The effect of overweight and obesity on joint damage in patients with moderate to severe hemophilia. *Blood* 2006;108:ASH Annual Meeting Abstracts 4064.
33. Biere-Rafi S, Baarslag MA, Peters M, Kruip MJ, Kraaijenhagen RA, Den Heijer M, Büller HR, Kamphuisen PW. Cardiovascular risk assessment in haemophilia patients. *Thromb Haemost* 2011 Feb 1;105(2):274-8.
34. Lim MY, Pruthi RK. Cardiovascular disease risk factors: prevalence and management in adult hemophilia patients. *Blood Coagul Fibrinolysis* 2011 Jul;22(5):402-6.
35. Walsh M, Macgregor D, Stuckless S, Barrett B, Kawaja M, Scully MF. Health-related quality of life in a cohort of adult patients with mild hemophilia A. *J Thromb Haemost* 2008;6(5):755-61.
36. Rosendaal FR, Briet E, Stibbe J, van Herpen G, Leuven JA, Hofman A, Vandenbroucke JP. Haemophilia protects against ischaemic heart disease: a study of risk factors. *Br J Haematol* 1990;75(4):525-30.
37. Kulkarni R, Soucie JM, Evatt BL; Hemophilia Surveillance System Project Investigators. Prevalence and risk factors for heart disease among males with hemophilia. *Am J Hematol* 2005;79(1):36-42.
38. Ragni MV, Moore CG. Atherosclerotic heart disease: prevalence and risk factors in hospitalized men with haemophilia A. *Haemophilia* 2011 Nov;17(6):867-71.
39. Girolami A, Ruzzon E, Fabris F, Varvarikis C, Sartori R, Girolami B. Myocardial infarction and other arterial occlusions in hemophilia A patients: a cardiological evaluation of all 42 cases reported in the literature. *Acta Haematol* 2006;116(2):120-5.
40. Schutgens RE, Tuinenburg A, Roosendaal G, Guyomi SH, Mauser-Bunschoten EP. Treatment of ischaemic heart disease in haemophilia patients: an institutional guideline. *Haemophilia* 2009;15(4):952-58.
41. Mannucci PM, Schutgens RE, Santagostino E, Mauser-Bunschoten EP. How I treat age-related morbidities in elderly patients with hemophilia. *Blood* 2009;114 (26):5256-63.
42. Tuinenburg A, Mauser-Bunschoten EP, Verhaar MC, Biesma DH, Schutgens RE. Cardiovascular disease in patients with hemophilia. *J Thromb Haemost* 2009;7(2):247-54.
43. Coppola A, Tagliaferri A, Franchini M. The management of cardiovascular diseases in patients with hemophilia. *Semin Thromb Hemost* 2010;36(1):91-102.
44.Street A, Hill K, Sussex B, Warner M, Scully MF. Haemophilia and ageing. *Haemophilia* 2006;12(Suppl 3): 8-12.

3 LABORATORY DIAGNOSIS

1. A correct diagnosis is essential to ensure that a patient gets the appropriate treatment. Different bleeding disorders may have very similar symptoms.

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

- knowledge and expertise in coagulation laboratory testing
- use of the correct equipment and reagents
- quality assurance

3. For detailed information on technical aspects and specific instructions on screening tests and factor assays, please consult the WFH's *Diagnosis of Hemophilia and Other Bleeding Disorders: A Laboratory Manual, Second edition* [1].

3.1Knowledge 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, prothrombin time (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].

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 (c3.2%) aqueous trisodium 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% trisodium 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].

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°C–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 37°C between tilting.

Screening tests

1. Platelet count, BT, PT, and APTT may be used to screen a patient suspected of having a bleeding disorder [4].

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 [5,6].

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.

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.

Correction studies

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 analysing 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 [7,8].

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. (Level 1) [9,10]**

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 [11].

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 centre.

3.2Use of the correct equipment and reagents

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

Equipment

1. A 37°C ± 0.5°C water bath.

2. A good light source placed near the water bath to accurately observe clot formation.

3. Stopwatches.

4. Automated pipettes (either fixed or variable volume) capable of delivering 0.1 ml and 0.2 ml accurately and precisely.

5. Clean soda glass test tubes (7.5 cm × 1.2 cm) for clotting tests. Reuse of any glassware consumables should be avoided whenever possible, unless it can be demonstrated that test results are unaffected by the process used. Plasticware used in coagulation analysers should not be re-used.

6. An increasingly large number of semi-automated and fully automated coagulometers are now available. In many cases this equipment has the following advantages:

- Accuracy of end-point reading.
- Improved precision of test results.
- Ability to perform multiple clot-based assays.
- Reduction of observation errors (the end-point of the reaction is typically measured electromechanically or photoelectrically).
- Use of polystyrene (clear) cuvettes instead of glass tubes.

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

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

8. Good results can be obtained using basic equipment and technology provided that good laboratory practice is observed. These skills can then be adapted to more automated technology.

Selection of coagulometers

1. Many coagulation analysers are provided as a package of instrument and reagent, and both components can influence the results obtained. This needs to be taken into account when evaluating and selecting a system. Other important issues to consider are:

- type of tests to be performed and the workload, as well as workflow, in the laboratory
- operational requirements (power, space, humidity, temperature, etc)
- service requirements and breakdown response
- throughput and test repertoire
- costs
- ability to combine with reagents from other manufacturers

- user-programmable testing
- comparability between results on primary analyser and any back-up methods
- compatibility with blood sample tubes and plasma storage containers in local use
- safety assessment (mechanical, electrical, microbiological)
- availability of suitable training

2. Information is required in relation to the performance characteristics of the system. This can be obtained from a variety of sources including the published literature and manufacturers' data, but may also require some form of local assessment. Aspects to consider include:

- precision of testing with a target of <3% of CV for screening tests and <5% for factor assays
- carry-over
- interfering substances
- reagent stability on board analyser
- comparability with other methods
- sample identification
- data handling, software, and quality control
- training required
- reliability

3. A number of published guidelines and recommendations describe the evaluation of coagulation analysers [12,13].

Reagents

1. It is good practice to ensure continuity of supply of a chosen reagent, with attention paid to continuity of batches and long shelf-life. This may be achieved by asking the supplier to batch hold for the laboratory, if possible.

2. Changing to a different source of material is not recommended unless there are supply problems or because of questionable results. Different brands may have completely different sensitivities and should not be run side by side.

3. Instructions supplied with the reagent should be followed.

4. Particular attention should be paid to reagent stability. Once a reagent is reconstituted or thawed for daily use, there is potential for deterioration over time depending on the conditions of storage and use.

5. Once an appropriate test and reagents have been decided upon, normal/reference ranges should ideally be defined, and must take account of the conditions used locally.

3.3Quality 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 centres worldwide. The scheme includes analyses relevant to the diagnosis and management of bleeding. Details 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 [14].

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.

References

1. Kitchen S, McCraw A, Echenagucia M. Diagnosis of Hemophilia and Other Bleeding Disorders: A Laboratory Manual, 2nd edition. Montreal: World Federation of Hemophilia, 2010.
2. Clinical and Laboratory Standards Institute. Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays: Approved Guideline–Fifth edition. CLSI H21-A5, Wayne PA, Clinical and Laboratory Standards Institute 2008.
3. Woodhams B, Girardot O, Blanco MJ, et al. Stability of coagulation proteins in frozen plasma. *Blood Coagul Fibrinolysis* 2001;12(4):229-36.
4. Clinical and Laboratory Standards Institute. One Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test: Approved Guideline–Second edition. CLSI H47-A2 Wayne PA, Clinical and Laboratory Standards Institute, 2008.
5. Bick RL. Laboratory evaluation of platelet dysfunction. *Clin Lab Med* 1995 Mar;15(1):1-38.
6. Rodgers RP, Levin J. Bleeding time revisited. *Blood* 1992 May 1;79(9):2495-7.
7. Duncan EM, Duncan BM, Tunbridge LJ, et al. Familial discrepancy between one stage and 2 stage factor VIII assay methods in a subgroup of patients with haemophilia A. *Br J Haematol* 1994:87(4);846-8.
8. Oldenburg J, Pavlova A. Discrepancy between one-stage and chromogenic FVIII activity assay results can lead to misdiagnosis of haemophilia A phenotype. *Haemostaseologie* 2010:30(4);207-11.
9. Meijer P, Verbruggen B. The between-laboratory variation of factor VIII inhibitor testing: the experience of the external quality assessment program of the ECAT foundation. *Semin Thromb Hemost* 2009;35(8):786-93.
10. Verbruggen B, van Heerde WL, Laros-van Gorkom BA. Improvements in factor VIII inhibitor detection: From Bethesda to Nijmegen. *Semin Thromb Hemost* 2009;35(8):752-9.
11.Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability. *Thromb Haemos* 1995; 73:247-251.
12. Clinical and Laboratory Standards Institute. Protocol for the Evaluation, Validation, and Implementation of Coagulometers: Approved Guideline. CLSI document H57-A, Vol.28 No.4. Wayne PA, Clinical and Laboratory Standards Institute 2008c.
13.Gardiner C, Kitchen S, Dauer RJ, et al. Recommendations for evaluation of coagulation analyzers. *Lab Hematol* 2006;12(1):32-8.
14. Jennings I, Kitchen DP, Woods TA, et al. Laboratory Performance in the World Federation of Hemophilia EQA programme, 2003-2008. *Haemophilia* 2009;15(1):571-7.

4 HEMOSTATIC AGENTS

4.1 Clotting factor concentrates

1. **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. (Level 5) [1,2]**

2. The comprehensive WFH *Guide for the Assessment of Clotting Factor Concentrates* reviews factors affecting the quality, safety, licensing, and assessment of plasma-derived products and the important principles involved in selecting suitable products for the treatment of hemophilia [2].

3. The WFH also publishes and regularly updates a *Registry of Clotting Factor Concentrates*, which lists all currently available products and their manufacturing details [3].

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

5. Currently manufactured plasma-derived concentrates produced to Good Manufacturing Practice (GMP) standards have an exemplary safety record with respect to lipid-coated viruses, such as HIV and HCV.

6. Product safety is the result of efforts in several areas:
- improved donor selection (exclusion of at-risk donors)
- improved screening tests of donations, including nucleic acid testing (NAT)
- type and number of in-process viral inactivation and/or removal steps

7. The risk of prion-mediated disease through plasma-derived products exists. In the absence of a reliable screening test for variant Creutzfeldt-Jakob disease (vCJD), and with no established manufacturing steps to inactivate the vCJD prion, this problem is currently being handled by excluding plasma from all donors perceived to be at risk. As new information evolves in this field, constant awareness of current scientific recommendations is needed for those involved in making decisions regarding choice of clotting factor concentrate for people with hemophilia.

Product selection

When selecting plasma-derived concentrates, consideration needs to be given to both the plasma quality and the manufacturing process. Two issues deserve special consideration:
- Purity of product
- Viral inactivation/elimination

Purity

1. Purity of concentrates refers to the percentage of the desired ingredient (e.g. FVIII), relative to other ingredients present.

2. There is no universally agreed classification of products based on purity.

3. Concentrates on the market vary widely in their purity.

4. Some products have high or very high purity at one stage of the production process but are subsequently stabilized by albumin, which lowers their final purity. Generally speaking, products with higher purity tend to

be associated with low manufacturing yields. These concentrates are, therefore, costlier.

5. Concentrates of lower purity may give rise to allergic reactions [4,5]. Patients who experience these repeatedly with a particular product may benefit from the administration of an antihistamine immediately prior to infusion or from use of a higher purity concentrate.

6. Plasma-derived FVIII concentrates may contain variable amounts of von Willebrand factor (VWF). It is therefore important to ascertain a product's VWF content (as measured by ristocetin cofactor activity) if it is used for the treatment of VWD [6].

7. **For treatment of FIX deficiency, 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. (Level 2) [7,8]**

8. The viral safety of products is not related to purity, as long as adequate viral elimination measures are in place.

Viral inactivation/elimination

1. In-process viral inactivation is the single largest contributor to the safety of plasma-derived concentrates [9].

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

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

3. Some viruses (such as human parvovirus B19) are relatively resistant to both types of process. None of the current methods can inactivate prions.

4. Nano (ultra) filtration can be used to remove small viruses such as parvovirus but filtration techniques currently in use do not eliminate the risk of transmission [10].

5. A product created by a process that incorporates two viral reduction steps should not automatically be considered better than one that only has one specific viral inactivation step.

6. If only one step is used, this step should preferably inactivate viruses with and without lipid envelopes.

FVIII concentrates

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

2. All plasma-derived products currently in the market are listed in the WFH *Registry of Clotting Factor Concentrates* [3]. Consult the product insert for specific details.

Dosage/administration

1. 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. (Level 4) [11]**

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. (Level 4) [11]**

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

Example: *50 kg × 40 (IU/dl level desired) × 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. (Level 5) [12]**

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. (Level 3) [13,14]**

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 [15]. However, this cost-effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions [16].

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. All plasma-derived products currently in the market are listed in the WFH *Registry of Clotting Factor Concentrates* [3]. Consult the product information guide for specific details.

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 (Level 2) [7,8],** 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. (Level 4) [11]**

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. (Level 4) [11]**

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 [17].

6. To calculate dosage, multiply the patient's weight in kilograms by the factor level desired.

Example: *50 kg × 40 (IU/dl level desired) = 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. (Level 5) [12]**

8. **If used, PCCs should generally be infused at half this rate. Consult the product information leaflet for instructions. (Level 2) [18]**

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 [19]. Changing the brand of clotting factor concentrate sometimes reduces symptoms.

4.2Other 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. (Level 5) [1,2]**

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 [1].

3. Certain steps can be taken to minimize the risk of transmission of viral pathogens. These include:
- Quarantining plasma until the donor has been tested or even retested for antibodies to HIV, hepatitis C, and HBsAg—a practice that is difficult to implement in countries where the proportion of repeat donors is low.
- Nucleic acid testing (NAT) to detect viruses—a technology that has a potentially much greater relevance for

the production of cryoprecipitate than for factor concentrates, as the latter are subjected to viral inactivation steps [20].

4. Allergic reactions are more common following infusion of cryoprecipitate than concentrate [21].

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. (Level 4) [22]**

3. **Due to concerns about the safety and quality of FFP, its use is not recommended, if avoidable (Level 4) [23].** 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.

4. It is possible to apply some forms of virucidal treatment to packs of FFP (including solvent/detergent treatment) and the use of treated packs is recommended. However, virucidal treatment may have some impact on coagulation factors. The large scale preparation of pooled solvent/detergent-treated plasma has also been shown to reduce the proportion of the largest multimers of VWF [24,25].

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. (Level 4) [22]**

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 supernatant is 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. (Level 4) [1,22,26]**

4. Although the manufacture of small pool, viral-inactivated cryoprecipitate has been described, it is uncertain whether it offers any advantage with respect to overall viral safety or cost benefit over conventionally manufactured large pool concentrates [27].

Dosage/administration
1. 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

1. 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 [28].

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. (Level 3) [28,29]**

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. (Level 3) [28,29]**

5. **DDAVP is particularly useful in the treatment or prevention of bleeding in carriers of hemophilia.** (**Level 3) [30]**

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. (Level 3) [31,32]**

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*Dosage/administration*

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

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. (Level 4) [28,33]**

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. (Level 3)**

[34]
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. (Level 4) [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. (Level 4) [28,37]**

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. (Level 4) [38,39]**

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**. **(Level 4) [33]**

Tranexamic acid
1. Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin.

2. It promotes clot stability and is useful as adjunctive therapy in hemophilia and some other bleeding disorders [40].

3. **Regular treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia. (Level 4) [40]**

4. **It is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g. oral bleeding, epistaxis, menorrhagia). (Level 2) [41-43]**

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. (Level 4) [42,44]**

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. (Level 4) [45]**

9. **Tranexamic acid should *not* be given to patients with FIX deficiency receiving prothrombin complex concentrates, as this will exacerbate the risk of thromboembolism. (Level 5) [46]**

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. (Level 5) [46]**

11. **In contrast, thromboembolism is less likely when tranexamic acid is used in combination with rFVIIa to enhance hemostasis. (Level 4) [47]**

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 [40].

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.

References

1. Evatt BL, Austin H, Leon G, Ruiz-Sáez A, de Bosch N. Haemophilia therapy: assessing the cumulative risk of HIV exposure by cryoprecipitate. *Haemophilia* 1999;5(5):295-300.
2. Farrugia A. Guide for the assessment of clotting factor concentrates, 2nd ed. Montreal: World Federation of Hemophilia, 2008.
3. Brooker M. Registry of Clotting Factor Concentrates, 9th edition. Facts and Figures monograph no 6. Montreal: World Federation of Hemophilia, 2012.
4.Brettler DB, Forsberg AD, Levine PH, Petillo J, Lamon K, Sullivan JL. Factor VIII:C concentrate purified from plasma using monoclonal antibodies: human studies. *Blood* 1989 May 15;73(7):1859-63.
5.Recht M, Pollmann H, Tagliaferri A, Musso R, Janco R, Neuman WR. A retrospective study to describe the incidence of moderate to severe allergic reactions to factor IX in subjects with haemophilia B. *Haemophilia* 2011 May;17(3):494-9.
6. Federici AB, Mannucci PM. Management of inherited von Willebrand disease in 2007. *Ann Med* 2007;39(5):346-58.
7. Kim HC, McMillan CW, White GC, et al. Purified factor IX using monoclonal immunoaffinity technique: clinical trials in hemophilia B and comparison to prothrombin complex concentrates. *Blood* 1992;79(3):568-75.
8. Lippi G, Franchini M. Pathogenesis of venous thromboembolism: when the cup runneth over. *Semin Thromb Hemost* 2008;34(8):747-61.
9. Giangrande PL. Blood products for hemophilia: past, present and future. *BioDrugs* 2004;18(4):225-34.
10. Burnouf T, Radosevich M. Nanofiltration of plasma-derived biopharmaceutical products. *Haemophilia* 2003 Jan;9(1):24-37.
11. Björkman S, Berntorp E. Pharmacokinetics of coagulation factors: clinical relevance for patients with haemophilia. *Clin*

Pharmacokinet 2001;40(11):815-32.
12. Hemophilia of Georgia. Protocols for the treatment of hemophilia and von willebrand disease. Hemophilia of Georgia, 2012. http://www.hog.org/publications/page/protocols-for-the-treatment-of-hemophilia-and-von-willebrand-disease-2 (Accessed June 6 2012).
13. Batorova A, Martinowitz U. Intermittent injections vs. continuous infusion of factor VIII in haemophilia patients undergoing major surgery. *Br J Haematol* 2000;110(3):715–20.
14. Martinowitz U, Luboshitz J, Bashari D, et al. Stability, efficacy, and safety of continuously infused sucrose-formulated recombinant factor VIII (rFVIII-FS) during surgery in patients with severe haemophilia. *Haemophilia* 2009;15(3):676-85.
15. Martinowitz U, Schulman S, Gitel S, et al. Adjusted dose continuous infusion of factor VIII in patients with haemophilia A. *Br J Haematol* 1992;82(4):729-34.
16. Mathews V, Viswabandya A, Baidya S, George B, Nair S, Chandy M, Srivastava A. Surgery for hemophilia in developing countries. *Semin Thromb Hemost* 2005 Nov;31(5):538-43.
17. Poon MC, Lillicrap D, Hensman C, Card R, Scully MF. Recombinant FIX recovery and inhibitor safety: A Canadian post-licensure surveillance study. *Thromb Hemost* 2002;87:431-5.
18. Ruiz-Sáez A, Hong A, Arguello A, Echenagucia M, Boadas A, Fabbrizzi F, Minichilli F, Bosch NB. Pharmacokinetics, thrombogenicity and safety of a double viral inactivated factor IX concentrate compared with a prothrombin complex concentrate. *Haemophilia* 2005;11(6):583-8.
19. Shibata M, Shima M, Misu H, et al. Management of haemophilia B inhibitor patients with anaphylactic reactions to FIX concentrates. *Haemophilia* 2003;9(3):269-71.
20. Chamberland ME. Surveillance for transfusion-transmitted viral infections in the United States. *Biologicals* 1998 Jun;26(2):85-8.
21. O'Shaughnesy DF, Atterbury C, Bolton Maggs P, et al. Guideline for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004;126(1):11-28.
22. Stanworth SJ. The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. *Hematology Am Soc Hematol Educ Program* 2007:179-86.
23. Kasper CK. Products for clotting factor replacement in developing countries. *Semin Thromb Hemost* 2005 Nov;31(5):507-12.
24. Budde U, Drewke E. Von Willebrand factor multimers in virus-inactivated plasmas and F VIII concentrates. *Beitr Infusionsther Transfusionsmed* 1994;32:408-14.
25. Chin S, Williams B, Gottlieb P, Margolis-Nunno H, Ben-Hur E, Hamman J, Jin R, Dubovi E, Horowitz B. Virucidal short wavelength ultraviolet light treatment of plasma and factor VIII concentrate: protection of proteins by antioxidants. *Blood* 1995 Dec 1;86(11):4331-6.
26. Chuansumrit A, Isarangkura P, Chantanakajornfung A, et al. The efficacy and safety of lyophilized cryoprecipitate in hemophilia A. *J Med Assoc Thai* 1999;82(Suppl 1):S69-73.
27.El-Ekiaby M, Sayed MA, Caron C, et al. Solvent-detergent filtered (S/D-F) fresh frozen plasma and cryoprecipitate minipools prepared in a newly designed integral disposable processing bag system. *Transfus Med* 2010;20:48-61.
28. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997;90(7):2515-21.
29. Franchini M, Rossetti G, Tagliaferri A, et al. Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers. *Haemophilia* 2005;11:504–9.
30.Leissinger C, Becton D, Cornell C Jr, Cox Gill J. High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A. *Haemophilia* 2001;7(3):258-66.
31. Mannucci PM. Use of desmopressin (DDAVP) during early pregnancy in factor VIII-deficient women. *Blood* 2005;105(8):3382.
32. Trigg DE, Stergiotou I, Peitsidis P, Kadir RA. A Systematic Review: The use of desmopressin for treatment and prophylaxis of bleeding disorders in pregnancy. *Haemophilia* 2012;18(1):25-33.
33. Castaman G. Desmopressin for the treatment of haemophilia. *Haemophilia* 2008;14(Suppl 1):15-20.
34. Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). *Br J Haematol* 1992;82(1):87-93.
35. Khair K, Baker K, Mathias M, et al. Intranasal desmopressin (Octim): a safe and efficacious treatment option for children with bleeding disorders. *Haemophilia* 2007;13(5):548-51.
36. Rose EH, Aledort LM. Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. *Ann Intern Med* 1991;114(7):563-8.
37. Sica DA, Gehr TWG. Desmopressin: safety considerations in patients with chronic renal disease. *Drug Safety* 2006;29:553–556.
38. Das P, Carcao M, Hitzler J. DDAVP-induced hyponatremia in young children. *J Pediatr Hematol Oncol* 2005;27(6):330-2.
39. Smith TJ, Gill JC, Ambruso DR, Hathaway WE. Hyponatremia and seizures in young children given DDAVP. *Am J Hematol* 1989;31(3):199-202.
40. Mannucci PM. Hemostatic drugs. *N Engl J Med* 1998 Jul 23;339(4):245-53.
41. Coetzee MJ. The use of topical crushed tranexamic acid tablets to control bleeding after dental surgery and from skin ulcers in haemophilia. *Haemophilia* 2007;13(4):443-4.
42. Frachon X, Pommereuil M, Berthier AM, et al. Management options for dental extraction in hemophiliacs: a study of 55 extractions (2000-2002). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;99(3):270-5.
43. Kouides PA, Byams VR, Philipp CS, et al. Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid. *Br J Haematol* 2009;145(2):212-20.

44. Franchini M, Zaffanello M, Lippi G. The use of desmopressin in mild hemophilia A. *Blood Coagul Fibrinolysis* 2010;21(7):615-9.
45. Hvas AM, Sorensen HT, Norengaard L, et al. Tranexamic acid combined with recombinant factor VIII increases clot resistance to accelerated fibrinolysis in severe hemophilia A. *J Thromb Haemost* 2007;5(12):2408-14.
46. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application. *Haemophilia* 2004 Sep;10 (Suppl 2):10-6.
47.Giangrande PL, Wilde JT, Madan B, et al. Consensus protocol for the use of recombinant activated factor VII in elective orthopaedic surgery in haemophilic patients with inhibitors. *Haemophilia* 2009;15(2):501-8.

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 [1].

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 [1].

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.

11. **Administer the appropriate dose of factor concentrate to raise the patient's factor level suitably (refer to Tables 7-1 and 7-2). (Level 2) [2-5]**

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

13. **Instruct the patient to avoid weight-bearing, apply compression, and elevate the affected joint. (Level 3) [4]**

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 [39].

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). (Level 3) [4]**

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 part of the management of acute joint bleeding episodes. (Level 2) [4,6,7]**

- 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 [8].
- 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) (Level 3) [4,9,10]**

2. Inhibitors should be considered as a reason for persistent bleeding despite adequate factor replacement. 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 [10]. If there is a large accumulation of blood, it 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. (Level 3) [4]

6. A large bore 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.

5.2Muscle 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 [1].

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 deep flexor 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 (refer to Tables 7-1 and 7-2). (Level 3) [11-13]**

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. (Level 5) [14,15]**

12. **The patient should be monitored continuously for neurovascular compromise; fasciotomy may be required in some such cases. (Level 5) [16,17]**

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. (Level 4) [12,18]**

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 [19].

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 (refer to Tables 7-1 and 7-2). (Level 4) [20-22]**

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. (Level 4) [20-22]**

4. **It is useful to confirm the diagnosis and monitor recovery with an imaging study (ultrasonography, CT scan, or MRI). (Level 4) [20-22]**

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. (Level 4) [20-22]**

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

5.3 Central nervous system hemorrhage/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 (refer to Tables 7-1 and 7-2). (Level 4) [23,24]**

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). (Level 3) [23,25,26]**

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. (Level 4) [27,28]

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

5.4Throat and neck hemorrhage

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 (refer to Tables 7-1 and 7-2). (Level 4) [15,29,30]**

3. **Hospitalization and evaluation by a specialist is essential. (Level 5) [15]**

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.

5.5 Acute gastrointestinal (GI) hemorrhage

1. ***Immediately*** **raise the patient's factor levels. Maintain the factor level until hemorrhage has stopped and etiology is defined (refer to Tables 7-1 and 7-2). (Level 4) [31,32]**

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.

5.6 Acute abdominal hemorrhage

1. An acute abdominal (including retroperitoneal) hemorrhage 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 (refer to Tables 7-1 and 7-2) until the etiology can be defined, then treat appropriately in consultation with a specialist. (Level 4) [15,29,30]**

5.7Ophthalmic 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 (refer to Tables 7-1 and 7-2). (Level 4) [15,29,30]**

3. Have the patient evaluated by an ophthalmologist as soon as possible.

5.8 Renal hemorrhage

1. **Treat painless hematuria with complete bed rest and vigorous hydration (3 litres/m2 body surface area) for 48 hours. Avoid DDAVP when hydrating intensively. (Level 4) [33]**

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. (Level 4) [33,34]**

3. **Do not use antifibrinolytic agents. (Level 4) [33]**

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.

5.9 Oral hemorrhage

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 due to poor oral hygiene
   - use of EACA or tranexamic acid as a mouthwash

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). (Level 4) [35,36]**

5. Factor replacement may be required as directed by the hemophilia centre.

6. **Oral EACA or tranexamic acid should be used if appropriate. (Level 4) [37,38]**

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.

5.10 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 [15,29].

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

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

5. EACA or 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.

5.11Soft tissue hemorrhage

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 [15,29].

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.

5.12 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 (refer to Tables 7-1 and 7-2), and then suture. (Level 4) [15,29,30]**

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

References

1. Definitions in hemophilia. Recommendations of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *JTH* 2012 (in press).
2.Aronstam A, Wassef M, Choudhury DP, Turk PM, McLellan DS. Double-blind controlled trial of three dosage regimens in treatment of haemarthroses in haemophilia A. *Lancet* 1980 Jan 26;1(8161):169-71.
3.Aronstam A, Wassef M, Hamad Z, Cartlidge J, McLellan D. A double-blind controlled trial of two dose levels of factor VIII in the treatment of high risk haemarthroses in haemophilia A. *Clin Lab Haematol* 1983;5(2):157-63.
4.Hermans C, de Moerloose P, Fischer K, Holstein K, Klamroth R, Lambert T, et al; European Haemophilia Therapy Standardisation Board. Management of acute haemarthrosis in haemophilia A without inhibitors: literature review, European survey and recommendations. *Haemophilia* 2011;17(3):383-92.
5.Mathews V, Viswabandya A, Baidya S, George B, Nair S, Chandy M, Srivastava A. Surgery for hemophilia in developing countries. *Semin Thromb Hemost* 2005 Nov;31(5):538-43.
6. Gomis M, Querol F, Gallach JE, Gonzalez LM, Aznar JA. Exercise and sport in the treatment of haemophilic patients: a systematic

review. *Haemophilia* 2009;15(1):43-54.
7. Mulder K. Exercises for People with Hemophilia. Montreal: World Federation of Hemophilia 2006.
8. Heijnen L, Buzzard BB. The role of physical therapy and rehabilitation in the management of hemophilia in developing countries. *Semin Thromb Hemost* 2005;31(5):513-7.
9. Ingram GI, Mathews JA, Bennett AE. Controlled trial of joint aspiration in acute haemophilic haemarthrosis. *Ann Rheum Dis* 1972;31:423.
10. Rodriguez-Merchan EC. Aspects of current management: orthopaedic surgery in haemophilia. *Haemophilia* 2012;18(1):8-16.
11. Aronstam A, Browne RS, Wassef M, Hamad Z. The clinical features of early bleeding into the muscles of the lower limb in severe haemophiliacs. *J Bone Joint Surgery* 1983;65-B(1):19-23.
12. Beyer R, Ingerslev J, Sørensen B. Current practice in the management of muscle haematomas in patients with severe haemophilia. *Haemophilia* 2010;16(6):926-31.
13. Railton GT, Aronstam A. Early bleeding into upper limb muscles in severe haemophilia clinical features and treatment. *J Bone Joint Surgery* 1987;69-B(1):100-102.
14. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. *HSSJ* 2010;6:37–42.
15. Singleton T, Kruse-Jarres R, Leissinger C. Emergency department care for patients with hemophilia and von Willebrand disease. *J Emerg Med* 2010 Aug;39(2):158-65.
16. Llinás A, Silva M, Pasta G, Luck JV, et al. Controversial subjects in musculoskeletal care of haemophilia: cross fire. *Haemophilia* 2010;16(Suppl 5):132-5.
17. Rodriguez-Merchan EC. Orthopedic management in hemophilia: a Spanish outlook. *Semin Hematol* 2008;45(2 Suppl 1):S58-63.
18.Blamey G, Forsyth A, Zourikian N, et al. Comprehensive elements of a physiotherapy exercise programme in haemophilia—a global perspective. *Haemophilia* 2010;16(Suppl 5):136-45.
19. Beeton K, Cornwell J, Alltree J. Rehabilitation of muscle dysfunction in hemophilia, 2nd edn. World Federation of Hemophilia Treatment of Hemophlia monograph 24. Montreal: World Federation of Hemophilia, 2012.
20. Ashrani AA, Osip J, Christie B, Key NS. Iliopsoas haemorrhage in patients with bleeding disorders--experience from one centre. *Haemophilia* 2003;9(6):721-6.
21. Balkan C, Kavakli K, Karapinar D. Iliopsoas haemorrhage in patients with haemophilia: results from one centre. *Haemophilia* 2005;11(5):463-7.
22. Fernandez-Palazzi F, Hernandez SR, De Bosch NB, De Saez AR. Hematomas within the iliopsoas muscles in hemophilic patients: the Latin American experience. *Clin Orthop Relat Res* 1996;(328):19-24.
23. Ljung RC. Intracranial haemorrhage in haemophilia A and B. *Br J Haematol* 2008;140(4):378-84.
24. Nakar C, Cooper DL, DiMichele D. Recombinant activated factor VII safety and efficacy in the treatment of cranial haemorrhage in patients with congenital haemophilia with inhibitors: an analysis of the Hemophilia and Thrombosis Research Society Registry (2004-2008). *Haemophilia* 2010;16(4):625-31.
25. Patiroglu T, Ozdemir MA, Unal E, Altuner Torun Y, Coskun A, Menku A, Mutlu FT, Karakukcu M. Intracranial hemorrhage in children with congenital factor deficiencies. *Childs Nerv Syst* 2011;27(11):1963-6.
26.Zanon E, Iorio A, Rocino A, Artoni A, Santoro R, Tagliaferri A, Coppola A, Castaman G, Mannucci PM; the Italian Association of Hemophilia Centers. Intracranial haemorrhage in the Italian population of haemophilia patients with and without inhibitors. *Haemophilia* 2012;18(1):39-45.
27. Traivaree C, Blanchette V, Armstrong D, et al. Intracranial bleeding in haemophilia beyond the neonatal period--the role of CT imageing in suspected intracranial bleeding. *Haemophilia* 2007;13(5):552-9.
28. Witmer CM, Manno CS, Butler RB, Raffini LJ. The clinical management of hemophilia and head trauma: a survey of current clinical practice among pediatric hematology/oncology physicians. *Pediatr Blood Cancer* 2009;53(3):406-10.
29.Bush MT, Roy N. Hemophilia emergencies. *J Emerg Nurs* 1995 Dec;21(6):531-8.
30.Guthrie TH Jr, Sacra JC. Emergency care of the hemophiliac patient. *Ann Emerg Med* 1980 Sep;9(9):476-9.
31. Kouides PA, Fogarty PF. How do we treat upper gastrointestinal bleeding in adults with haemophilia. *Haemophilia* 2010;16(2):360-2.
32. Mittal R, Spero JA, Lewis JH, Taylor F, Ragni MV, Bontempo FA, Van Thiel DH. Patterns of gastrointestinal hemorrhage in hemophilia. *Gastroenterology* 1985;88(2):515-22.
33. Quon DV, Konkle BA. How we treat haematuria in adults with haemophilia. *Haemophilia* 2010;16(4):683-5.
34. Ghosh K, Jijina F, Mohanty D. Haematuria and urolithiasis in patients with haemophilia. *Eur J Haematol* 2003;70(6):410-2.
35. Kane MJ, Silverman LR, Rand JH, Paciucci PA, Holland JF. Myonecrosis as a complication of the use of epsilon amino-caproic acid: a case report and review of the literature. *Am J Med* 1988 Dec;85(6):861-3.
36.Mannucci PM. Hemostatic drugs. *N Engl J Med* 1998 Jul 23;339(4):245-53.
37. Franchini M, Rossetti G, Tagliaferri A, et al. Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers. *Haemophilia* 2005;11:504–9.
38. Vinall C, Stassen LF. The dental patient with a congenital bleeding disorder. *J Ir Dent Assoc* 2008 Feb-Mar;54(1):24-8.
39. D'Young AI. Domiciliary application of CryoCuff in severe hemophilia: qualitative questionnaire and clinical audit. *Haemophilia* 2008; 14:823-7.

6 COMPLICATIONS OF HEMOPHILIA

6.1Musculoskeletal 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 (see Table 1-1).

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 [1,2].

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 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 (Level 5) [3,4].** Options include:

- **factor concentrate replacement, ideally given with the frequency and at dose levels sufficient to prevent recurrent bleeding (Level 2) [5-8]**
  - If concentrates are available in sufficient doses, short treatment courses (6-8 weeks) of secondary prophylaxis with intensive physiotherapy are beneficial.
- **physiotherapy (Level 2) [9,10],** including:
  - daily exercise to improve muscle strength and maintain joint motion
  - modalities to reduce secondary inflammation, if available [11]

    - functional training [12]
- **a course of NSAIDs (COX-2 inhibitors), which may reduce inflammation (Level 2) [13,14]**
- 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. (Level 4) [16,17]**

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. (Level 4) [18,19]**
- 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 [20,21].
- 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 [1,2] 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 [22,23].
- Ultrasound or MRI examination will show early soft tissue and osteochondral changes [24-26].
- 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 [27].

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', page 18). (Level 2) [13,14]**

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. (Level 2) [9,10]**

14. Other conservative management techniques include:
- serial casting to assist in correcting deformities [28,29].
- bracing and orthotics to support painful and unstable joints [15].
- 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 [30].

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 [31].
- osteotomy to correct angular deformity.
- prosthetic joint replacement for severe disease involving a major joint (knee, hip, shoulder, elbow) [32].
- elbow synovectomy with radial head excision [33].
- 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 [34,35].

16. **Adequate resources, including sufficient factor concentrates and post-operative rehabilitation, must be available in order to proceed with any surgical procedure. (Level 3) [36-38]**

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 [9,39-41]:

- 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 a localized 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 tumour is decreasing, continue with factor and repeat MRI for three cycles. (Level 4) [42,43]**
- Proceed to surgery if necessary, which will be much easier if the tumour has shrunk.
- **Aspiration of the pseudotumour followed by injections of fibrin glue, arterial embolization, or radiotherapy may heal some lesions. Surgery may be needed for others. (Level 4) [44,45]**
- 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 [46]. 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. (Level 4) [46-48]**

3. **Clotting factor levels should be raised to at least 50% and maintained for three to five days. (Level 4) [3,46-48]**

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. (Level 4) [46]**

7. Compound/infected fractures may require external fixators [49].

8. **Prolonged immobilization, which can lead to significant limitation of range of movement in the adjacent joints, should be avoided. (Level 4) [46,47]**

9. Physiotherapy should be started as soon as the fracture is stabilized to restore range of motion, muscle strength, and function [39].

Principles of orthopedic surgery in hemophilia

For important considerations related to performing surgical procedures in persons with hemophilia, please see "Surgery and invasive procedures", on page 16. Specific issues in relation to orthopedic surgery include:

1. Orthopedic surgeons should have had specific training in surgical management of persons with hemophilia [3].

2. **Performing multiple site elective surgery in a simultaneous or staggered fashion to use clotting factor concentrates judiciously should be considered. (Level 3) [50]**

3. **Local coagulation enhancers may be used. Fibrin glue is useful to control oozing when operating in extensive surgical fields. (Level 3) [36,51,52]**

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. (Level 5) [36]**

5. Good communication with the post-operative rehabilitation team is essential [39]. Knowledge of the details of the surgery performed and intra-operative 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.

6.2Inhibitors

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 [53-54].

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 [55,56].

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 gastrointestinal bleeding sites [57]. 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 [58].

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

11. **Confirmation of the presence of an inhibitor and quantification of the titre is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay (see "Inhibitor testing', on page 32). (Level 1) [59,60]**

12. **For children, inhibitors should be screened once every five exposure days until 20 exposure days, every 10 exposure days between 21 and 50 exposure days, and at least two times a year until 150 exposure days. (Level 5) [61]**

13. **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. (Level 3) [56,62-64]**

14. **Inhibitor measurement should also be done in all patients who have been intensively treated for more than five days, within four weeks of the last infusion. (Level 4) [63,65]**

15. **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. (Level 2) [53,63,66]**

16. 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.

17. 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.

18. 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. (Level 5) [63,67]**

2. **Choice of treatment product should be based on titre of inhibitor, records of clinical response to product, and site and nature of bleed. (Level 4) [63,68]**

3. **Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralize the inhibitor with excess factor activity and stop bleeding. (Level 4) [63,68]**

4. **Patients with a history of a high responding inhibitor but with low titres may be treated similarly in an emergency until an anamnestic response occurs, usually in three to five days, precluding further treatment with concentrates that only contain the missing factor. (Level 4) [63,68]**

5. Porcine factor VIII prepared from the plasma of pigs has been effective in halting bleeding in some patients. The plasma-derived preparation is being superceded by a recombinant porcine factor VIII concentrate currently in clinical trials.

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

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

8. **The efficacy of two doses of rFVIIa and one dose of APCC for management of joint bleeding has been shown to be essentially equivalent (Level 2) [69].**

9. **Notably, however, some patients respond better to one agent than the other, highlighting the need to individualize therapy.** (**Level 2) [69,70]**

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

11. 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.

12. 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. (Level 4) [71-72]**

Immune tolerance induction

1. **In patients with severe hemophilia A, eradication of inhibitors is often possible by immune tolerance induction (ITI) therapy. (Level 2) [73,74]**

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. (Level 2) [75]**

3. Optimal regimen (product or dose) for ITI remains to be defined. An international trial comparing 50 IU/kg three times a week to 200 IU/kg daily was recently stopped due to safety concerns (higher number of intercurrent bleeds) in the low-dose arm pending detailed analysis and interpretation of the data [76].

4. Response to ITI may be less favourable in patients with moderate/mild hemophilia [63].

5. Experience with ITI for hemophilia B inhibitor patients is limited. The principles of treatment in these patients are similar, but the success rate is much lower, especially in persons whose inhibitor is associated with an allergic diathesis.

6. Hemophilia B inhibitor patients with a history of severe allergic reactions to FIX may develop nephrotic syndrome during ITI, which is not always reversible upon cessation of ITI therapy. Alternative treatment schedules, including immunosuppressive therapies, are reported to be successful [77].

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. (Level 2) [53]**

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 hemophilia in the 1980s and early 1990s [78,79].

2. Many studies conducted all over the world indicate that HIV, HBV, and HCV transmission through factor concentrate has been almost completely eliminated [80,81].

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 [82].

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 [81,83,84].

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. (Level 4) [85]**

3. **The diagnosis, counselling, 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. (Level 2) [86,87]**

4. **None of the currently available classes of anti-HIV drugs are contraindicated in people with hemophilia. (Level 5) [88-90]**

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. (Level 1) [91-96]**

3. New antiviral therapies, in combination with these drugs, may improve sustained virologic response rates [97].

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. (Level 3) [98]**

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. (Level 4) [99]**

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 seroconversion should be rechecked following vaccination. (Level 4) [99-101]**

4. **People with hemophilia who do not seroconvert should be revaccinated with double the hepatitis B vaccine dose. (Level 4) [99,102]**

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 [103-105].

2. In general, joint aspiration to treat hemarthrosis should be avoided, unless done early under appropriate cover of factor replacement and with strict aseptic precautions to prevent infection [106,107].

3. Bleeding is likely to delay healing and worsen infection and should therefore be well controlled [108].

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

References

1. Llinás A. Haemophilic arthropathy. *Haemophilia* 2010 Jul;16(Suppl 5):121.
2. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. *HSSJ* 2010 Feb; 6(1): 37-42.
3. Rodriguez-Merchan EC. Aspects of current management: orthopaedic surgery in haemophilia. *Haemophilia* 2012;18(1):8-16.
4. Seuser A, Berdel P, Oldenburg J. Rehabilitation of synovitis in patients with haemophilia. *Haemophilia* 2007;13 Suppl 3:26-31.
5. Aronstam A, Arblaster PG, Rainsford SG, Turk P, Slattery M, Alderson MR, et al. Prophylaxis in haemophilia: a double-blind controlled trial. *Br J Haematol* 1976;33(1):81-90.
6. Feldman BM, Pai M, Rivard GE, Israels S, et al; Association of Hemophilia Clinic Directors of Canada Prophylaxis Study Group.Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost* 2006 Jun;4(6):1228-36.
7. Gringeri A, Lundin B, Mackensen SV, et al. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011;9(4):700-10.
8.Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007;357:535–544.
9. Blamey G, Forsyth A, Zourikian N, Short L, Jankovic N, De Kleijn P, Flannery T. Comprehensive elements of a physiotherapy exercise programme in haemophilia - a global perspective. *Haemophilia* 2010;16 Suppl 5:136-45.
10. Gomis M, Querol F, Gallach JE, Gonzalez LM, Aznar JA. Exercise and sport in the treatment of haemophilic patients: a systematic review. *Haemophilia* 2009;15(1):43-54.
11. Watson T. Current concepts in electrotherapy. *Haemophilia* 2002;8:413–418.
12.De Kleijn P, Gilbert M, Roosendaal G, Poonnose PM, Narayan PM, Tahir N. Functional recovery after bleeding episodes in haemophilia. *Haemophilia* 2004;10:157–160.
13. Rattray B, Nugent DJ, Young G. Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia. *Haemophilia* 2006;12(5):514-7.
14.Tsoukas C, Eyster ME, Shingo S, et al. Evaluation of the efficacy and safety of etoricoxib in the treatment of hemophilic arthropathy. *Blood* 2006;107(5):1785-90.
15. Querol F, Aznar JA, Haya S, Cid A. Orthoses in haemophilia. *Haemophilia* 2002;8(3):407-12.
16. Llinás A. The role of synovectomy in the management of a target joint. *Haemophilia* 2008;14 (Suppl 3):177-80.
17. Yoon KH, Bae DK, Kim HS, Song SJ. Arthroscopic synovectomy in haemophilic arthropathy of the knee. *Int Orthop* 2005;29(5):296-300.
18.Thomas S, Gabriel MB, Assi PE, Barboza M, Perri ML, Land MG, et al. Radioactive synovectomy with Yttrium90 citrate in haemophilic synovitis: Brazilian experience. *Haemophilia* 2011;17(1):e211-e216.
19. van Kasteren ME, Nováková IR, Boerbooms AM, Lemmens JA. Long term follow up of radiosynovectomy with yttrium-90 silicate in haemophilic haemarthrosis. *Ann Rheum Dis* 1993;52(7):548-50.
20.Bernal-Lagunas R, Aguilera-Soriano JL, Berges-Garcia A, Luna-Pizarro D, Perez-Hernandez E. Haemophilic arthropathy: the usefulness of intra-articular oxytetracycline (synoviorthesis) in the treatment of chronic synovitis in children. *Haemophilia* 2011 Mar;17(2):296-9.
21.Caviglia HA, Fernandez-Palazzi F, Galatro G, Perez-Bianco R. Chemical synoviorthesis with rifampicin in haemophilia. *Haemophilia* 2001 Jul;7 Suppl 2:26-30.
22. Arnold WD, Hilgartner MW. Hemophilic arthropathy. Current concepts of pathogenesis and management. *J Bone Joint Surg Am* 1977;59(3):287-305.
23. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res* 1980;(149):153-159.
24.Doria AS, Lundin B, Miller S, Kilcoyne R, Dunn A, Thomas S, Rivard G, Moineddin R, Babyn PS; Expert Imageing Working

Group of The International Prophylaxis Study Group. Reliability and construct validity of the compatible MRI scoring system for evaluation of elbows in haemophilic children. *Haemophilia* 2008 Mar;14(2):303-14.
25.Keshava S, Gibikote S, Mohanta A, Doria AS. Refinement of a sonographic protocol for assessment of haemophilic arthropathy. *Haemophilia* 2009 Sep;15(5):1168-71.
26. Zukotynski K, Jarrin J, Babyn PS, Carcao M, Pazmino-Canizares J, Stain AM, Doria AS. Sonography for assessment of haemophilic arthropathy in children: a systematic protocol. *Haemophilia* 2007 May;13(3):293-304.
27.Solimeno L, Goddard N, Pasta G, Mohanty S, Mortazavi S, Pacheco L, Sohail T, Luck J. Management of arthrofibrosis in haemophilic arthropathy. *Haemophilia* 2010 Jul;16 Suppl 5:115-20.
28. Fernandez-Palazzi F, Battistella LR. Non-operative treatment of flexion contracture of the knee in haemophilia. *Haemophilia* 1999 Mar;5(Suppl 1):20-4.
29. Gilbert MS, Radomisli TE. Management of fixed flexion contracture of the elbow in haemophilia. *Haemophilia* 1999 Mar;5(Suppl 1):39-42.
30. Spilsbury M. Models for psychosocial services in the developed and developing world. *Haemophilia* 2004 Oct;10(Suppl 4):25-9.
31.Wiedel JD. Arthroscopic synovectomy: state of the art. *Haemophilia* 2002; 8:372-4.
32. Goddard NJ, Mann HA, Lee CA. Total knee replacement in patients with end-stage haemophilic arthropathy: 25-year results. *J Bone Joint Surg Br* 2010 Aug;92(8):1085-9.
33. Silva M, Luck JV Jr. Radial head excision and synovectomy in patients with hemophilia. Surgical technique. *J Bone Joint Surg Am* 2008 Oct;90 Suppl 2 Pt 2:254-61.
34. Barg A, Elsner A, Hefti D, Hintermann B. Haemophilic arthropathy of the ankle treated by total ankle replacement: a case series. *Haemophilia* 2010;16(4):647-55.
35.Tsailas PG, Wiedel JD. Arthrodesis of the ankle and subtalar joints in patients with haemophilic arthropathy. *Haemophilia* 2010 Sep 1;16(5):822-31.
36. Hermans C, Altisent C, Batorova A, et al. Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations. *Haemophilia* 2009;15(3):639-58.
37. Lobet S, Pendeville E, Dalzell R, et al. The role of physiotherapy after total knee arthroplasty in patients with haemophilia. *Haemophilia* 2008;14(5):989-98.
38.Mathews V, Viswabandya A, Baidya S, George B, Nair S, Chandy M, Srivastava A. Surgery for hemophilia in developing countries. *Semin Thromb Hemost* 2005 Nov;31(5):538-43.
39.De Kleijn P, Blamey G, Zourikian N, Dalzell R, Lobet S. Physiotherapy following elective orthopaedic procedures. *Haemophilia* 2006;12 Suppl 3:108-12.
40. Heijnen L, Buzzard BB.The role of physical therapy and rehabilitation in the management of hemophilia in developing countries. *Semin Thromb Hemost* 2005;31(5):513-7.
41.Hermans C, de Moerloose P, Fischer K, et al; European Haemophilia Therapy Standardisation Board. Management of acute haemarthrosis in haemophilia A without inhibitors: literature review, European survey and recommendations. *Haemophilia* 2011 May;17(3):383-92.
42. D'Young AI. Conservative physiotherapeutic management of chronic haematomata and haemophilic pseudotumours: case study and comparison to historical management. *Haemophilia* 2009;15(1):253-60.
43. Rodriguez-Merchan EC. The haemophilic pseudotumour. *Int Orthop* 1995;19(4):255-60.
44. Alcalay M, Deplas A. Rheumatological management of patients with hemophilia. Part II: Muscle hematomas and pseudotumors. *Joint Bone Spine* 2002 Dec;69(6):556-9.
45. Espandar R, Heidari P, Rodriguez-Merchan EC. Management of haemophilic pseudotumours with special emphasis on radiotherapy and arterial embolization. *Haemophilia* 2009;15(2):448-57.
46.Rodriguez-Merchan EC. Bone fractures in the haemophilia patient. *Haemophilia* 2002; 8(2):104-11.
47.Lee VN, Srivastava A, Nithyananth M, Kumar P, Cherian VM, Viswabandya A, et al. Fracture neck of femur in haemophilia A - experience from a cohort of 11 patients from a tertiary centre in India. *Haemophilia* 2007;13(4):391-4.
48. Mortazavi SM, Heidari P. Retrograde intramedullary nailing of supracondylar femoral fractures in haemophilic patients. *Haemophilia* 2008;14(3):661-664.
49.Lee VN, Srivastava A, PalaniKumar C, Daniel AJ, Mathews V, Babu N, Chandy M, Sundararaj GD. External fixators in haemophilia. *Haemophilia* 2004;10(1):52-57.
50. Schild FJ, Mauser-Bunschoten EP, Verbout AJ, Van Rinsum AC, Roosendaal G. Total knee arthroplasty in hemophilic arthropathy: efficiency of clotting factor usage in multijoint procedures. *J Thromb Haemost* 2009;7(10):1741-3.
51. Kavakli K. Fibrin glue and clinical impact on haemophilia care. *Haemophilia* 1999;5(6):392-6.
52.Serban M, Poenaru D, Pop L, Schramm W, et al. Surgery--a challenge in haemophiliacs with inhibitors. *Hamostaseologie* 2009;29(Suppl 1):S39-41.
53. Astermark J, Altisent C, Batorova A, et al; European Haemophilia Therapy Standardisation Board. Non-genetic risk factors and the development of inhibitors in haemophilia: a comprehensive review and consensus report. *Haemophilia* 2010;16(5):747-66.
54. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia* 2003;9(4):418-35.
55.Eckhardt CL, Menke LA, Van Ommen CH, et al. Intensive peri-operative use of factor VIII and the Arg593 ->Cys mutation are risk factors for inhibitor development in mild/moderate hemophilia A. *J Thromb Haemost* 2009;7:930-37.
56. Kempton CL, Soucie JM, et al. In non-severe hemophilia A the risk of inhibitor after intensive factor treatment is greater in older patients: a case-control study. *JTH* 2010 Oct;8(10):2224-31.

57. Hay CR. Factor VIII inhibitors in mild and moderate-severity haemophilia A. *Haemophilia* 1998;4(4):558-63.
58. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet* 2003 May 24;361(9371):1801-9.
59. Meijer P, Verbruggen B. The between-laboratory variation of factor VIII inhibitor testing: the experience of the external quality assessment program of the ECAT foundation. *Semin Thromb Hemost* 2009;35(8):786-93.
60. Verbruggen B, van Heerde WL, Laros-van Gorkom BA. Improvements in factor VIII inhibitor detection: from Bethesda to Nijmegen. *Semin Thromb Hemost* 2009;35:752–9.
61.de Moerloose P, Fischer K, Lambert T, Windyga J, Batorova A, Lavigne-Lissalde G, Rocino A, Astermark J, Hermans C. Recommendations for assessment, monitoring and follow-up of patients with haemophilia. *Haemophilia* 2012 May; 18(3): 319-25.
62. Berntorp E, Collins P, D'Oiron R, et al. Identifying non-responsive bleeding episodes in patients with haemophilia and inhibitors: a consensus definition. *Haemophilia* 2011;17(1):e202-10.
63. Hay CR, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 2006;133:591–605.
64. McMillan CW, Shapiro SS, Whitehurst D, et al. The natural history of factor VIII:C inhibitors in patients with hemophilia A: a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors. *Blood* 1988;71(2):344-8.
65.Sharathkumar A, Lillicrap D, Blanchette VS, et al. Intensive exposure to factor VIII is a risk factor for inhibitor development in mild hemophilia A. *J Thromb Haemost* 2003;1(6):1228-36.
66. Teitel JM, Carcao M, Lillicrap D, et al. Orthopaedic surgery in haemophilia patients with inhibitors: a practical guide to haemostatic, surgical and rehabilitative care. *Haemophilia* 2009; 15(1):227-39.
67.Colvin BT, Astermark J, Fischer K, Gringeri A, Lassila R, Schramm W, Thomas A, Ingerslev J; Inter Disciplinary Working Group. European principles of haemophilia care. *Haemophilia* 2008;14(2):361-74.
68. Teitel JM, Berntorp E, Collins P, et al. A systematic approach to controlling problem bleeds in patients with severe congenital haemophilia A and high-titre inhibitors. *Haemophilia* 2007;13: 256–63.
69. Astermark J, Donfield SM, DiMichele DM, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA Novoseven Comparative (FENOC) Study. *Blood* 2007;109(2):546-51.
70.Berntorp E, Shapiro A, Astermark J, et al. Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. *Haemophilia* 2006;12(Suppl 6):1–7.
71. Chitlur M, Warrier I, Rajpurkar M, Lusher JM. Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006). *Haemophilia* 2009;15(5):1027-31.
72. Recht M, Pollmann H, Tagliaferri A, et al. A retrospective study to describe the incidence of moderate to severe allergic reactions to factor IX in subjects with haemophilia B. *Haemophilia* 2011;17(3):494-9.
73.Coppola A, Di Minno MN, Santagostino E. Optimizing management of immune tolerance induction in patients with severe haemophilia A and inhibitors: towards evidence-based approaches. *Br J Haematol* 2010;150(5):515-28.
74. DiMichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. *Haemophilia* 2007;13 Suppl 1:1-22.
75. DiMichele DM. Immune tolerance induction in haemophilia: evidence and the way forward. *J Thromb Haemost* 2011 Jul;9 Suppl 1:216-25.
76. Hay CR, Dimichele DM. The principal results of the International Immune Tolerance Study: a randomized dose comparison. *Blood* 2012;119:1335-1344.
77.Beutel K, Hauch H, Rischewski J, Kordes U, Schneppenheim J, Schneppenheim R. ITI with high-dose FIX and combined immunosuppressive therapy in a patient with severe haemophilia B and inhibitor. *Hamostaseologie* 2009 May;29(2):155-7.
78. Arnold DM, Julian JA, Walker IR, et al; Association of Hemophilia Clinic Directors of Canada. Mortality rates and causes of death among all HIV-positive individuals with hemophilia in Canada over 21 years of follow-up. *Blood* 2006;108(2):460-4.
79. Lee CA, Sabin CA, et al. Morbidity and mortality from transfusion-transmitted disease in haemophilia. *Lancet* 1995;345(8960):1309.
80.Farrugia A, Evers T, Falcou PF, Burnouf T, Amorim L, Thomas S. Plasma fractionation issues. *Biologicals* 2009 Apr;37(2):88-93.
81.Mauser-Bunschoten EP, Posthouwer D, Fischer K, van den Berg HM. Safety and efficacy of a plasma-derived monoclonal purified factor VIII concentrate during 10 years of follow-up. *Haemophilia* 2007 Nov;13(6):697-700.
82. Ludlam CA, Mannucci PM, Powderly WG; European Interdisciplinary Working Group. Addressing current challenges in haemophilia care: consensus recommendations of a European Interdisciplinary Working Group. *Haemophilia* 2005;11(5):433-7.
83. Farrugia A, Manno CS, Evatt BL. Emerging and receding risks of therapeutic regimens for haemophilia. *Haemophilia* 2004;10(Suppl 4):47-54.
84. Tapper ML. Emerging viral diseases and infectious disease risks. *Haemophilia* 2006;12(Suppl 1):3-7.
85. Evatt BL, Austin H, Leon G, Ruiz-Sáez A, de Bosch N. Haemophilia therapy: assessing the cumulative risk of HIV exposure by cryoprecipitate. *Haemophilia* 1999;5(5):295-300.
86. Mannucci PM, Gringeri A, Savidge G, et al; European-Australian Haemophilia Collaborative Study Group. Randomized double-blind, placebo-controlled trial of twice-daily zidovudine in asymptomatic haemophiliacs infected with the human immunodeficiency virus type 1. *Br J Haematol* 1994;86(1):174-9.
87. Ragni MV, Amato DA, LoFaro ML, et al. Randomized study of didanosine monotherapy and combination therapy with zidovudine in hemophilic and nonhemophilic subjects with asymptomatic human immunodeficiency virus-1 infection. *Blood* 1995;85(9):2337-46.
88. Humphreys EH, Chang LW, Harris J. Antiretroviral regimens for patients with HIV who fail first-line antiretroviral therapy. *Cochrane Database Syst Rev* 2010 Jun 16;(6):CD006517.

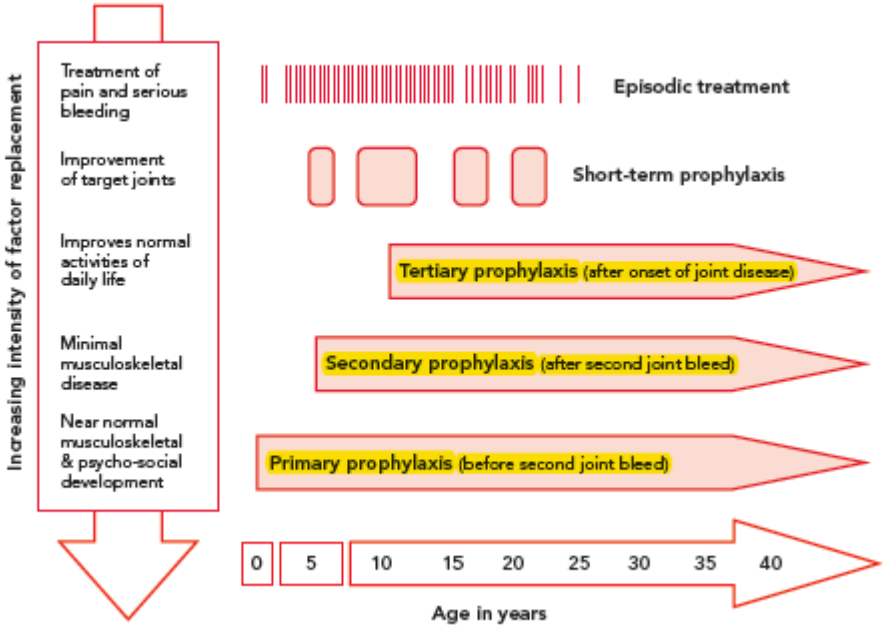
89.Spaulding A, Rutherford GW, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naïve individuals. *Cochrane Database Syst Rev* 2010 Oct 6;(10):CD008740.
90.Spaulding A, Rutherford GW, Siegfried N. Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naïve individuals. *Cochrane Database Syst Rev* 2010 Aug 4;(8):CD008651.
91. Denholm JT, Wright EJ, Street A, Sasadeusz JJ. HCV treatment with pegylated interferon and ribavirin in patients with haemophilia and HIV/HCV co-infection. *Haemophilia* 2009;15(2):538-543.
92. Franchini M, Mengoli C, Veneri D, Mazzi R, Lippi G, Cruciani M. Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis. *J Antimicrob Chemother* 2008;61(6):1191-200.
93.Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011 Apr;15(17):i-xii, 1-210.
94. Operskalski EA, Kovacs A. HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. *Curr HIV/AIDS Rep* 2011 Mar;8(1):12-22.
95.Posthouwer D, Mauser-Bunschoten EP, Fischer K, Makris M. Treatment of chronic hepatitis C in patients with haemophilia: a review of the literature. *Haemophilia* 2006;12(5):473-8.
96.Schulze Zur Wiesch J, Pieper D, et al. Sustained virological response after early antiviral treatment of acute hepatitis C virus and HIV coinfection. *Clin Infect Dis* 2009;49(3):466-72.
97.Lok AS, Gardiner DF, Lawitz E, et al. Preliminary Study of Two Antiviral Agents for Hepatitis C Genotype 1. *NEJM* 2012;366(3):216-224.
98. Santagostino E, Colombo M, Rivi M, et al. A 6-month versus a 12-month surveillance for hepatocellular carcinoma in 559 hemophiliacs infected with the hepatitis C virus. *Blood* 2003;102(1):78-82.
99.Steele M, Cochrane A, Wakefield C, Stain AM, Ling S, Blanchette V, et al. Hepatitis A and B immunization for individuals with inherited bleeding disorders. *Haemophilia* 2009;15:437–447.
100. Miller EJ, Lee CA, Karayiannis P, Holmes S, Thomas HC, Kernoff PB. Immune response of patients with congenital coagulation disorders to hepatitis B vaccine: suboptimal response and human immunodeficiency virus infection. *J Med Virol* 1989;28:96–100.
101. Pillay D, Pereira C, Sabin C, Powell L, Zuckerman AJ, Lee CA. A long-term follow-up of hepatitis B vaccination in patients with congenital clotting disorders. *Vaccine* 1994;12:978–83.
102.Mannucci PM, Gringeri A, Morfini M, et al. Immunogenicity of a recombinant hepatitis B vaccine in hemophiliacs. *Am J Hematol* 1988;29(4):211-4.
103. Buehrer JL, Weber DJ, Meyer AA, et al. Wound infection rates after invasive procedures in HIV-1 seropositive versus HIV-1 seronegative hemophiliacs. *Ann Surg* 1990;211(4):492-8.
104.Monch H, Kostering H, Schuff-Werner P, et al. Hemophilia A, idiopathic thrombocytopenia and HTLV-III-infection impressive remission after splenectomy: a case report. *Onkologie* 1986; 9(4):239-40.
105. Trieb K, Panotopoulos J, Wanivenhaus A. Risk of infection after total knee arthroplasty in HIV-positive hemophilic patients. *J Bone Joint Surg Am* 2003;85-A(5):969-70.
106.Ashrani AA, Key NS, Soucie JM, Duffy N, Forsyth A, Geraghty S; Universal Data Collection Project Investigators. Septic arthritis in males with haemophilia. *Haemophilia* 2008;14:494 –503.
107. Zuber TJ. Knee joint aspiration and injection. *Am Fam Physician* 2002;66(8):1497-500.
108. Tourbaf KD, Bettigole RE, Southard SA. Infection in hemophilia. Local bleeding and prophylactic treatment. *NY State J Med* 1976;76(12):2034-6.
109.Heyworth BE, Su EP, Figgie MP, Acharya SS, Sculco TP. Orthopedic management of hemophilia. *Am J Orthop* 2005 Oct;34(10):479-86.
110. Rodriguez-Merchan EC. Orthopaedic surgery of haemophilia in the 21st century: an overview. *Haemophilia* 2002 May;8(3):360-8.

7 PLASMA FACTOR LEVEL AND DURATION OF ADMINISTRATION

7.1 Choice of factor replacement therapy protocols

1. The correlation shown in Figure 7-1 between possible factor replacement therapy protocols and overall outcome depicts the choices that one needs to make when selecting doses and regimen of clotting factor concentrates.
2. While enabling a completely normal life should remain the ultimate goal of factor replacement therapy, this cannot be achieved immediately in people with hemophilia in all situations.
3. The availability of treatment products varies significantly around the world and there will therefore always be a range of doses with which people with hemophilia are treated. Lower doses may increase as the global availability of treatment products improves incrementally over time.

FIGURE 7-1: STRATEGIES FOR CLOTTING FACTOR REPLACEMENT AT DIFFERENT AGES AND IMPACT ON OUTCOMES



Adapted from Blood Transfus 2008 Sep;6 Suppl 2:s4-11

4.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).

5. 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.

6. 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.

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

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

9. **Commonly-used dosage for prophylactic factor replacement is 25-40 IU/kg 2-3 times weekly in countries with less resource constraints (see Section 1 for details). [1-3]**

10. **In situations where there are greater constraints on supply of factor concentrates, prophylaxis may be initiated with lower doses of 10-20 IU/kg 2-3 times per week. (Level 2) [4,5]**

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 (IU/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/no NV compromise (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
Deep laceration	50	5–7	40	5–7
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 (IU/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/no NV compromise (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	
▪ 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

NV; neurovascular

References

1. Astermark J, Petrini P, Tengborn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be in dividualized. *Br J Haematol* 1999 Jun;105(4):1109-13.
2. Blanchette VS. Prophylaxis in the haemophilia population. *Haemophilia* 2010;16(Suppl 5):181-8.
3. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM; ESPRIT Study Group. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011 Apr;9(4):700-10.
4. Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, Grobbee DE, van den Berg HM. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001 Sep;7(5):446-52.
5. Wu R, Luke KH, Poon MC, Wu X, Zhang N, Zhao L, Su Y, Zhang J. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China. *Haemophilia* 2011 Jan;17(1):70-4.
6. Rickard KA. Guidelines for therapy and optimal dosages of coagulation factors for treatment of bleeding and surgery in haemophilia. *Haemophilia* 1995;1(S1):8–13.

APPENDIX I: Oxford Centre for Evidence-Based Medicine, 2011 Levels of Evidence

QUESTION	STEP 1 (LEVEL 1*)	STEP 2 (LEVEL 2*)	STEP 3 (LEVEL 3*)	STEP 4 (LEVEL 4*)	STEP 5 (LEVEL 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/ follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/ follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine.
http://www.cebm.net/index.aspx?o=5653

NATIONAL HEMOPHILIA FOUNDATION
www.hemophilia.org

MASAC Document #225
(Replaces Document #218)

MASAC RECOMMENDATIONS CONCERNING PRODUCTS LICENSED FOR THE TREATMENT OF HEMOPHILIA AND OTHER BLEEDING DISORDERS
(Revised April 2014)

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on April 13, 2014, and adopted by the NHF Board of Directors on May 6, 2014.

Please follow the link below to read MASAC recommendations.

http://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/All-MASAC-Recommendations/Recommendations-Concerning-Products-Licensed-for-the-Treatment-of-Hemophilia-and-Other-Bleeding-Disorders