

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.
 - excessive bleeding following trauma or surgery
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 80-85% 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
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 <ul style="list-style-type: none"> ▪ 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 non-steroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors, should be avoided. Paracetamol/acetaminophen is a safe alternative for analgesia (see 'Pain management', 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]**
 - joint and muscle damage and other sequelae of bleeding
 - inhibitor development
 - viral infection(s) transmitted through blood products
 - attention to psychosocial health
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:

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 health-care 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 concentrates, either plasma-derived or recombinant, as well as other adjunct hemostatic agents such as desmopressin (DDAVP) and tranexamic acid where possible.
 - Where clotting factor concentrates are not available, access to safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate.
 - Access to casting and/or splinting for immobilization and mobility/support aids, as needed.
7. The comprehensive care team should also include or have access to, among others:
 - chronic pain specialist
 - dentist
 - geneticist
 - hepatologist
 - infectious disease specialist
 - immunologist
 - gynecologist/obstetrician
 - vocational 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 musculo-skeletal 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. Non-contact sports such as swimming, walking, golf, badminton, archery, cycling, rowing, sailing, and table tennis should be encouraged.
6. High contact and collision sports such as soccer, hockey, rugby, boxing, and wrestling, as well as high-velocity activities such as motocross racing and skiing, are best avoided because of the potential for life-threatening injuries, unless the individual is on good prophylaxis to cover such activities.
7. Organized sports programs should be encouraged as opposed to unstructured activities, where protective equipment and supervision may be lacking.
8. The patient should consult with a musculoskeletal professional before engaging in physical activities to discuss their appropriateness, protective gear, prophylaxis (factor and other measures), and physical skills required prior to beginning the activity. This is particularly important if the patient has any problem/target joints [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.

1.5 Adjunctive management

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

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

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]**

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.

1.9 Pain 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.
2. Post-operative pain should be managed in coordination with the anesthesiologist.
3. Initially, intravenous morphine or other narcotic analgesics can be given, followed by an oral opioid such as tramadol, codeine, hydrocodone, and others.

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.
4. When pain is decreasing, paracetamol/acetaminophen may be used.

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].

Post-operative pain

1. Intramuscular injection of analgesia should be avoided.
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.

Pain due to chronic hemophilic arthropathy

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 post-operatively for the length of time required for healing and/or rehabilitation.
9. If clotting factor concentrates are not available, adequate blood bank support for plasma components is needed.
10. The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed (see Tables 7-1 and 7-2).

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

Excellent	<p>Intra-operative and post-operative blood loss similar (within 10%) to the non-hemophilic patient.</p> <ul style="list-style-type: none"> ▪ No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND ▪ Blood component transfusions required are similar to non-hemophilic patient
Good	<p>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.</p> <ul style="list-style-type: none"> ▪ No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND ▪ Blood component transfusions required are similar to the non-hemophilic patient
Fair	<p>Intra-operative and/or post-operative blood loss increased over expectation (25-50%) for the non-hemophilic patient and additional treatment is needed.</p> <ul style="list-style-type: none"> ▪ Extra (unplanned) dose of FVIII/FIX/bypassing agents needed OR ▪ Increased blood component (within 2 fold) of the anticipated transfusion requirement
Poor/none	<p>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</p> <ul style="list-style-type: none"> ▪ 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 re-screened 4–12 weeks post-operatively. (Level 4) [54]**
13. Careful monitoring for inhibitors is also advisable in patients with non-severe hemophilia A receiving continuous 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.

1.11 Dental care and management

1. For persons with hemophilia, good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding [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 (20-40%) 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. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin must be avoided.
17. An appropriate dose of paracetamol/acetaminophen every six hours for two to three days will help prevent pain following an extraction.
18. The presence of blood-borne infections should not affect the availability of dental treatment.
19. Prevention of bleeding at the time of dental procedures in patients with inhibitors to FVIII or FIX requires careful planning [61].

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