7 TREATMENT OF SPECIFIC HEMORRHAGES

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All statements identified as recommendations are consensus based, as denoted by CB.

7.1 | Introduction

- The primary clinical hallmarks of hemophilia are prolonged spontaneous and/or traumatic hemorrhages, most commonly within the musculoskeletal system and predominantly intra-articular bleeding into the large synovial joints, i.e., the ankles, knees, and elbows, and frequently into the shoulder, wrist, and hip joints. Hemophilic bleeding is also common in muscle and mucosal soft tissues, and less common in other soft tissues, the brain, and internal organs. Without adequate treatment, such internal bleeds may lead to serious complications and even become life-threatening.
- Bleeding symptoms and tendencies depend on the patient's hemophilia severity and clotting factor level.
- People with mild hemophilia may not necessarily have abnormal or prolonged bleeding problems requiring clotting factor replacement therapy until they experience serious trauma or undergo surgery. Those with moderate hemophilia may experience occasional spontaneous bleeding and/or prolonged bleeding with minor trauma or surgery. (See Chapter 2: Comprehensive Care of Hemophilia – Table 2-1: Relationship of bleeding severity to clotting factor level.)
- In general, the main treatment for bleeding episodes in patients with severe hemophilia is prompt clotting factor replacement therapy and rehabilitation. However, different types of bleeds and bleeding at particular anatomical sites may require more specific management with additional measures. It is important to consult the appropriate specialists for the management of bleeds related to specific sites. (For discussion and recommendations on muscle hemorrhages and acute and chronic complications related to musculoskeletal bleeding, see Chapter 10: Musculoskeletal Complications – Muscle hemorrhage.)
- The aim of management of specific hemorrhages is not only to treat the bleed, but also to prevent bleed recurrence, limit complications, and restore tissue and/or organ function to a pre-bleed state.
- Diagnosing a specific bleed correctly is the first step and may require a combination of clinical evaluation, laboratory assessment, and imaging investigations.
- In most instances in hemophilia care, therapeutic intervention may precede diagnostic workup of the patient. The objective of early intervention is to limit the extent of bleeding and to reduce bleeding complications.
- The amount of hemostatic agent used for bleed treatment and duration of treatment depends on the site and severity of bleeding.
- More and more hemophilia A patients are being treated with emicizumab prophylaxis; this therapy is not intended for treatment of acute bleeding episodes and breakthrough bleeding (bleeding that occurs between prophylactic doses).

- For breakthrough bleeding in patients without inhibitors on emicizumab, factor VIII (FVIII) infusion at doses expected to achieve hemostasis should be used. To date, no cases of thrombosis or thrombotic microangiopathy have been reported in this setting.[1]
- Patients with inhibitors on emicizumab experiencing acute bleeds should be treated with recombinant activated factor VIIa (rFVIIa) at doses expected to achieve hemostasis. The use of activated prothrombin complex concentrate (aPCC) should be avoided in inhibitor patients on emicizumab experiencing breakthrough bleeding. If the use of aPCC is not avoidable, lower doses of aPCC can be used with close monitoring of the patient for development of thrombosis and/or thrombotic microangiopathy.[2]
- For inhibitor patients not on emicizumab, standard doses of rFVIIa or aPCC should be used.

Patient/caregiver education

- Since most bleeds in hemophilia occur outside of hemophilia treatment centres, ongoing patient/family caregiver education is an essential component of bleed management.
- It is important for healthcare providers to educate patients and caregivers on bleed recognition and treatment, on hemophilia self-care and self-management, and on potential bleeding risks and complications associated with different circumstances and at different stages of development. (See Chapter 2: Comprehensive Care of Hemophilia – Home therapy – Self-management.)
- Patient and caregiver education should include instruction on the limitations and potential side effects of hemostatic agents and on when to consult healthcare providers for guidance and further intervention.

7.2 | Joint hemorrhage

- The onset of bleeding into a joint is often experienced by patients as a sensation "aura",[3] described as a tingling sensation and tightness within the joint that precedes the appearance of clinical signs. A joint hemorrhage (hemarthrosis) is defined as an episode characterized by a combination of any of the following[3]:
  - increasing swelling or warmth of the skin over the joint;
  - increasing pain; or
  - progressive loss of range of motion or difficulty in using the limb as compared with baseline.
- The loss of range of motion associated with joint hemorrhage limits both flexion and extension.

Clotting factor replacement therapy

- The goal in the treatment of acute hemarthrosis is to stop the bleeding as soon as possible. Treatment should ideally be given as soon as the patient suspects a bleed and before the onset of overt swelling, loss of joint function, and pain.[4]
- Clotting factor concentrate (CFC) should be administered immediately at a dose sufficient to raise the patient's factor level high enough to stop the bleeding.[5-8] (See Table 7-2.)
- In the acute setting, bleeding evaluation should include bleeding history assessment, physical examination, and pain assessment. Ultrasound may be a useful tool to aid in the assessment of early hemarthrosis.[5]
- Response to treatment is demonstrated by a decrease in pain and swelling, and an increase in range of motion of the joint. The definitions listed in Table 7-1 are recommended for the assessment of response to treatment of an acute hemarthrosis.[3]

RECOMMENDATION 7.2.1:

- **Hemophilia patients with severe hemarthrosis should be treated immediately with intravenous clotting factor concentrate replacement infusion(s) until there is bleed resolution.** CB

RECOMMENDATION 7.2.2:

- **Hemophilia patients with moderate or mild joint bleeding should be given 1 intravenous infusion of clotting factor concentrate, repeated if clinically indicated, depending on the resolution of the bleed.** CB

- If bleeding continues over the next 6-12 hours, a revised plan of assessment including further diagnostic assessment (i.e., factor assays) and/or intensification of factor replacement therapy should be adopted.
- Depending on the response to the first dose of treatment, a further dose(s) 12 hours after the initial loading dose for hemophilia A (if using standard half-life FVIII) or after 24 hours for hemophilia B (if using standard half-life factor IX [FIX]) may be required to achieve full resolution.[7] (See Table 7-2.)
- The need for a further dose of extended half-life FVIII or FIX will also depend on the product half-life.
- After an initial moderate to excellent response to hemostatic treatment, a new bleed is defined as a bleed occurring over 72 hours after stopping treatment for the original bleed for which treatment was initiated.[3]

TABLE 7-1 Definitions of response to treatment

Excellent	• Complete pain relief and/or complete resolution of signs of continuing bleeding after the initial infusion within 8 h and not requiring any further factor replacement therapy within 72 h after onset of bleeding
Good	• Significant pain relief and/or improvement in signs of bleeding within approximately 8 h after a single infusion but requiring more than 1 dose of factor replacement therapy within 72 h for complete resolution
Moderate	• Modest pain relief and/or improvement in signs of bleeding within approximately 8 h after the initial infusion and requiring more than 1 infusion within 72 h but without complete resolution
None	• No or minimal improvement, or condition worsens, within approximately 8 h after the initial infusion

Notes: The above definitions of response to treatment of an acute hemarthrosis refer to treatment with standard half-life products in inhibitor-negative individuals with hemophilia. These definitions may require modification for inhibitor patients receiving bypassing agents as hemostatic coverage and patients who receive extended half-life clotting factor concentrates. Modifications may be required for studies where patients receive *a priori* multidose clotting factor concentrate infusions for treatment of acute joint/muscle bleeds as part of an enhanced episodic treatment program. Adapted from Blanchette et al. (2014).[3]

- A target joint is a single joint in which three or more spontaneous bleeds have occurred within a consecutive 6-month period.[3]
- If symptoms and signs of bleeding persist despite normally appropriate and adequate interventions, the presence of inhibitors or alternative diagnoses such as septic arthritis or fracture should be considered. (See Chapter 8: Inhibitors to Clotting Factor.)

Pain management

- Acute hemarthrosis may be extremely painful, and prompt administration of clotting factor replacement and effective analgesia are key aspects of pain management.
- Analgesics for use in people with hemophilia include paracetamol/acetaminophen, selective COX-2 inhibitors (but not other NSAIDs), tramadol, or opioids.[9-11] (See Chapter 2: Comprehensive Care of Hemophilia – Pain management.)
- Many patients may require opioid analgesia; any usage of opioids should be under the guidance of a pain specialist, as even well-intentioned efforts may lead to medication addiction.
- Long-term use of opioid analgesics should be carefully monitored but preferably avoided because of the chronic nature of bleeding episodes in people with severe hemophilia and the risks of medication addiction.
- See Chapter 2: Comprehensive Care of Hemophilia – Pain management.

RECOMMENDATION 7.2.3:

- **In hemophilia patients with hemarthrosis, severity of pain should be graded and monitored according to the World Health Organization (WHO) pain scale.** CB

RECOMMENDATION 7.2.4:

- **Hemophilia patients with pain due to hemarthrosis should be given analgesic medication according to the severity of the pain.** CB

RECOMMENDATION 7.2.5:

- **In hemophilia patients with severe pain, management of such pain should include opioids based on clinical symptoms to an extent that the patient is comfortable to weight bear or use the joint as much as possible without any pain.** CB

Adjunctive care

- A key element of managing the symptoms of hemarthrosis is RICE (rest, ice, compression, elevation). In hemophilia care, immobilization is also considered to be an aspect of this approach; therefore, PRICE, which includes the concept of "protection" of the injured area, is often recommended. Compression may help to reduce the risk of rebleeding. However, as prolonged rest can negatively affect joint function through reduction in muscle strength, the acronym POLICE, which replaces "rest" with "optimal loading", has been put forward to encourage clinicians to establish a balance between rest, early mobilization, and weight-bearing to prevent unwanted complications associated with immobilization, while minimizing rebleeding leading to synovitis and cartilage damage.[12]
- The application of ice has been shown to reduce acute hemarthrosis-related pain; however, it has been suggested that a decrease in intra-articular temperature could interfere with coagulation in the presence of acute tissue lesions.[13,14] The use of ice without direct skin contact for short periods of 15-20 minutes soon after bleeding occurs is considered

acceptable but should not exceed 6 hours.[13] (See Chapter 2: Comprehensive Care of Hemophilia – Adjunctive management.)
- During a joint bleed, semi-flexion is usually the most comfortable position, and any attempt to change this position often exacerbates pain.[15]
- Depending on the site of the joint bleed, elevating the affected joint, if tolerated and comfortable, may help reduce hemarthrosis-related swelling.[13]
- Rest, in the case of a hip, knee, or ankle bleed, or the use of a sling for an elbow, shoulder, or wrist bleed, is advisable to immobilize a joint with severe bleeding until pain resolves.
- As soon as the pain and swelling begin to subside, the patient can change the position of the affected joint from a position of rest to a position of function, gently and gradually increasing mobilization of the joint.
- Patients with hip, knee, or ankle joint bleeds should be restricted from weight-bearing until complete pre-bleed joint range of motion and function are restored and acute pain and inflammation symptoms have dissipated. It is advisable to avoid weight-bearing for 1 week, with the use of walking aids (e.g., crutches, walker) to assist progressive weight-bearing under the guidance of a member of the comprehensive care team with experience in musculoskeletal rehabilitation after a bleed.[13] Pain can also be used to guide resumption of weight-bearing.
- These adjunctive measures will not stop joint bleeding but can help manage and reduce symptoms of pain and inflammation.[7]
- See also Chapter 2: Comprehensive Care of Hemophilia – Adjunctive management.

RECOMMENDATION 7.2.6:
- **Hemophilia patients with hemarthrosis should be managed using the RICE approach (Rest, Ice, Compression, and Elevation) in addition to clotting factor concentrate replacement.**
- **REMARK: The WFH recognizes that in some regions of the world, RICE may be the only initial treatment available or the best treatment available in the absence of an adequate supply of CFCs or other hemostatic agents. CB.**

RECOMMENDATION 7.2.7:
- **In hemophilia patients with hemarthrosis, weight-bearing should be avoided until the symptoms improve to an extent that the patient is comfortable to weight bear without significant pain. CB**

RECOMMENDATION 7.2.8:
- **In hemophilia patients, use of opioid analgesia in managing pain should be limited in duration, as much as possible. CB**

Physical therapy and rehabilitation
- Physical therapy and rehabilitation for the management of patients with hemophilia refers to the use of flexibility and strength training, proprioceptive/sensorimotor retraining, and balance and functional exercises to restore or preserve joint and muscle function.[16]
- Thorough assessment of acute joint bleeding followed by physical therapy tailored to the individual's clinical situation is essential to achieve a significant degree of success.[16]
- Ideally, physical therapy should be undertaken under adequate factor or hemostatic coverage. If hemostatic coverage is not available, physical therapy should be applied cautiously and exercises should be initiated judiciously.
- It is important to carefully monitor the affected joint throughout physical therapy and assess whether hemostatic treatment is needed to prevent recurrence of bleeding.[7,17]
- Rehabilitation should include both active and passive range of motion exercises.
- The patient should continue active exercises and proprioceptive training until complete pre-bleed joint range of motion and functioning are restored and signs of acute synovitis have dissipated.[18]

RECOMMENDATION 7.2.9:
- **In hemophilia patients with hemarthrosis, physical therapy exercises performed under clotting factor coverage should begin as soon as the pain symptoms stop. CB**

RECOMMENDATION 7.2.10:
- **In hemophilia patients with hemarthrosis, the aim of physical therapy should be to return joint function to the pre-bleed state. CB**

Arthrocentesis
- Arthrocentesis (removal of blood from a joint) may be considered for patients with hemophilia experiencing prolonged or worsening bleeding symptoms including:
  - tense, painful hemarthrosis that shows no improvement within 24 hours of the initial infusion (this is particularly the case for bleeding into the hip joint due to the particular anatomy of the hip joint); or
  - clinical suspicion of infection/septic arthritis.[7,19,20]

- Inhibitors should be considered as a possible reason for persistent bleeding despite adequate factor replacement therapy, and the presence of inhibitors should be assessed before arthrocentesis is attempted.
- For hemophilia patients with inhibitors, other appropriate hemostatic agents should be used to provide hemostatic coverage for the procedure, as needed.[7] (See "Management of bleeding" in Chapter 8: Inhibitors to Clotting Factor.)
- Arthrocentesis should always be done under strictly aseptic conditions to avoid introducing intra-articular infections.
- When necessary, arthrocentesis should only be performed under factor coverage, with factor activity levels of at least 30-50 IU/dL maintained for 48-72 hours. Arthrocentesis should not be done in circumstances where such factor coverage (or equivalent coverage with other hemostatic agents) is not available.[21]
- A large-bore needle, at least 16 gauge, should be used. The joint should be immobilized with mild compression following arthrocentesis, and weight-bearing should be restricted until the remaining blood is absorbed or absence of pain permits mobilization.
- Arthrocentesis should be followed by carefully supervised physical therapy and rehabilitation.
- See also Chapter 10: Musculoskeletal Complications.

RECOMMENDATION 7.2.11:

- **For hemophilia patients without inhibitors on factor replacement therapy presenting with joint hemorrhage and persistent pain, arthrocentesis is recommended only if there is a tense, painful hemarthrosis or suspicion of infection. Routine arthrocentesis is not advised.**
- **REMARK: In many healthcare settings, arthrocentesis is not common practice because of fear of introducing intra-articular infection.** CB

7.3 | Central nervous system and intracranial hemorrhage

- All head injuries, confirmed or suspected, significant headaches including headaches lasting for several hours, and somnolence in some instances, must be treated as possible intracranial bleeds. Sudden severe back pain may be a symptom of bleeding around the spinal cord.
- In the event of significant head trauma or clinical suspicion of central nervous system and/or intracranial hemorrhage, immediate treatment with CFC infusion is required without waiting for further symptoms to develop or for laboratory or radiologic evaluation.

RECOMMENDATION 7.3.1:

- **In hemophilia patients presenting with suspected central nervous system bleeds or bleed-related symptoms, clotting factor replacement therapy should be administered immediately before investigations are performed.** CB

- Immediately administer appropriate clotting factor replacement therapy as soon as significant trauma or symptoms occur, before any other intervention, and maintain factor level until etiology is defined. If a bleed is confirmed, maintain the appropriate factor level for 10-14 days.[22,23] (See Table 7-2.)
- Immediate medical evaluation and hospitalization are required, including a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain and neurological consultation as soon as possible.[24,25] Ultrasound examination may be considered in children.

RECOMMENDATION 7.3.2:

- **In patients with hemophilia presenting with suspected central nervous system bleeding that could be life-threatening, clotting factor replacement therapy should be administered immediately before investigations are performed and continued until the bleed resolves.**
- **REMARK: In patients with hemophilia who have been treated for central nervous system bleeding, secondary prophylaxis is recommended to prevent bleed recurrence.** CB

- Intracranial hemorrhage may be an indication for secondary prophylaxis (short-term prophylaxis for 3-6 months or even lifelong), especially where a relatively high risk of bleed recurrence has been observed (e.g., in the presence of human immunodeficiency virus [HIV] infection).[22,26,27]

7.4 | Throat and neck hemorrhage

- Bleeding into the throat or neck may be due to local pathology, trauma, or severe coughing, and may present with swelling or pain. This is a medical emergency because it can lead to airway obstruction. If indicated, gently elevate the head to help reduce airway obstruction due to the hemorrhage.
- Treat immediately with CFC to raise the patient's factor level when significant trauma or bleeding symptoms occur in the throat and neck area, without any delay that could occur while awaiting full evaluation. (See Table 7-2.)

- Immediate hospitalization and medical evaluation by a specialist otolaryngologist is required.[28]
- Protective factor levels should be maintained until symptoms resolve.[28-30] (See Table 7-2.)

RECOMMENDATION 7.4.1:

- **In hemophilia patients with throat and neck bleeding, clotting factor replacement therapy should be administered immediately and critical care evaluation sought.** CB

RECOMMENDATION 7.4.2:

- **In hemophilia patients with throat and neck bleeding, including injury of the tongue, clotting factor replacement therapy should continue until the bleeding symptoms have resolved.** CB

- To prevent oral hemorrhage in patients with severe tonsillitis, prophylaxis with CFCs, desmopressin (DDAVP; for those with mild or moderate hemophilia A), or antifibrinolytics (epsilon aminocaproic acid [EACA] and tranexamic acid) are advised in addition to bacterial culture and treatment with appropriate antibiotics.

RECOMMENDATION 7.4.3:

- **In hemophilia patients with throat and neck bleeding and local infection, antifibrinolytics should be started to treat the bleed and antibiotics to treat the infection.** CB

7.5 Gastrointestinal/abdominal hemorrhage

- Acute gastrointestinal (GI) hemorrhage may present as hematemesis, hematochezia (rectal passage of fresh blood), or melena.
- In a patient with liver disease, the first sign of GI bleeding may be hepatic encephalopathy, as the failing liver cannot process the high protein load of GI bleeding.
- Any sign of GI bleeding and/or acute hemorrhage in the abdomen requires immediate medical evaluation. All patients with GI bleeds should be hospitalized.

RECOMMENDATION 7.5.1:

- **In hemophilia patients with gastrointestinal bleeding, factor levels should be raised immediately and the underlying etiology of the bleed identified and treated.** CB
- GI bleeds must be treated as soon as possible following injury and/or the onset of the earliest symptoms with clotting factor replacement therapy to raise the patient's factor level, with factor levels maintained until hemorrhaging has stopped and the etiology of the hemorrhage is defined.[31,32] (See Table 7-2.)

RECOMMENDATION 7.5.2:

- **Hemophilia patients with gastrointestinal bleeding should be prescribed antifibrinolytics.** CB

- Antifibrinolytics are often effective adjunctive therapy for both patients with hemophilia A and hemophilia B. Concurrent use with aPCC or prothrombin complex concentrate (PCC) may be used with caution in some patients.
- Treat the origin of the hemorrhage as indicated.
- Monitor hemoglobin levels regularly and treat anemia or shock as needed. Perform endoscopy, if clinically indicated, in any patient with dropping hemoglobin levels. In GI bleeding, the investigation of choice is endoscopy.
- In patients with advanced liver disease, ammonia levels should be monitored, and treatment to prevent clinical encephalopathy with lactulose or a similar agent should be initiated.

RECOMMENDATION 7.5.3:

- **In hemophilia patients with gastrointestinal bleeding, endoscopic and radiologic imaging should be performed to identify all sites of bleeding.** CB

RECOMMENDATION 7.5.4:

- **In hemophilia patients with gastrointestinal bleeding, hemoglobin levels should be monitored regularly.** CB

- 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.
- Abdominal bleeds must be treated immediately to raise and maintain the patient's factor levels until the etiology can be defined.
- Perform a clinical assessment of the patient with a physical examination, pain assessment, and history taking including bleed history. An ultrasound and/or CT scan can identify the site and extent of abdominal bleeding.
- Determine appropriate treatment in consultation with a specialist.[28-30] (See Table 7-2.)

7.6 | Renal hemorrhage

- Bleeding in the kidneys (renal hemorrhage) can occur spontaneously or following injury.
- Urinary tract bleeding may be the first sign of malignancy in the bladder, particularly in older patients.
- Symptoms may include abdominal pain and swelling, severe flank and back pain, and hematuria.
- Patients with mild painless hematuria can be treated with complete bed rest and vigorous hydration (3 L/ m^2 body surface area/ day), with or without clotting factor replacement as feasible, for 48 hours unless there is concurrent renal or cardiac impairment. Avoid DDAVP when hydrating intensively.[33]
- All renal bleeding should be treated as urgent.

RECOMMENDATION 7.6.1:

- **For hemophilia patients with urinary tract hemorrhage, the site of bleeding should be identified and clotting factor replacement therapy should be administered immediately.** CB

RECOMMENDATION 7.6.2:

- **Hemophilia patients with renal bleeding should be given adequate hydration and prescribed bed rest until bleeding stops.** CB

- If there is pain or persistent gross hematuria, it is important to watch for clots and urinary obstruction.[33,34] Avoid use of antifibrinolytic agents.[33]

RECOMMENDATION 7.6.3:

- **In hemophilia patients with renal bleeding, antifibrinolytics should not be administered.** CB

RECOMMENDATION 7.6.4:

- **In hemophilia patients with renal bleeding, clotting factor replacement therapy should continue until the bleeding is resolved.** CB

- Refer the patient to a urologist for evaluation of a local cause if hematuria (gross/macroscopic or microscopic hematuria) persists or if there are repeated episodes. (See Table 7-2.)

7.7 | Ophthalmic hemorrhage

- Bleeding in the eye (ophthalmic hemorrhage) is uncommon unless associated with trauma or infection of the eye.
- Eye bleeds should be treated immediately to raise the patient's factor level, with factor levels maintained until the etiology of the bleed can be defined, followed by appropriate treatment in consultation with a specialist.[28-30]

RECOMMENDATION 7.7.1:

- **In hemophilia patients with ophthalmic bleeding, clotting factor levels should be raised immediately and the patient evaluated by an ophthalmologist.** CB

RECOMMENDATION 7.7.2:

- **In hemophilia patients with ophthalmic bleeding, regular physical examination should be carried out every 6-8 hours for the duration of the ophthalmic bleed.**
- **REMARK: Imaging may be included as clinically indicated.** CB.

RECOMMENDATION 7.7.3:

- **In hemophilia patients with ophthalmic bleeding, treatment and monitoring should be continued until the bleeding is resolved.** CB

- Refer the patient for evaluation by an ophthalmologist as soon as possible. (See Table 7-2.)

7.8 | Oral hemorrhage

- The most common causes of bleeding in the mouth (oral hemorrhage) are dental extraction, gingival bleeding (often due to poor oral hygiene), and trauma.
- Gum bleeding is a sign of inflammatory gum disease (gingivitis) and is preventable and treatable in people with hemophilia. It is not caused by the underlying congenital bleeding disorder itself.
- Early referral to a dental professional for assessment and appropriate periodontal treatment and advice will reduce bleeding after brushing, prevent progression of gum disease, and reduce the likelihood of early tooth loss and risk of associated systemic effects.
- Other less common causes of bleeding from the mouth may include: self-injury, shedding of deciduous (baby) teeth, and recent dental surgery without appropriate hemostatic measures in place.

- Bleeding following loss of baby teeth is not usually prolonged if recognized and treated early. Direct pressure should be applied on the tooth socket using a damp gauze swab and maintained for at least 15-30 minutes. Parents/caregivers should be advised that if bleeding persists for longer than 6 hours, they should consult their hemophilia treatment centre for additional support.
- A carefully planned preoperative hemostatic care plan is advised for patients with hemophilia about to undergo oral surgery or invasive dental procedures to avoid postoperative bleeding.

RECOMMENDATION 7.8.1:

- **In hemophilia patients with oral bleeding, the site of bleeding should be identified and direct pressure and/or sutures applied, if possible.** CB

RECOMMENDATION 7.8.2:

- **In hemophilia patients with oral bleeding, antifibrinolytics should be prescribed and administered at appropriate dosages.** CB

- Antifibrinolytic agents should be used with caution in patients with hemophilia B who are being treated with large doses of PCC or in patients with inhibitors being treated with aPCC.[35,36]

RECOMMENDATION 7.8.3:

- **In hemophilia patients with persistent oral bleeding, clotting factor replacement therapy should be administered along with local measures such as sutures and topical adrenaline application to stop the bleeding.** CB

- Patients who experience prolonged bleeding from the mouth should seek early consultation with their hemophilia team in association with the dentist or oral and maxillofacial surgeon to determine the source and severity of bleeding.
- If there has been unexpected bleeding following a carefully planned invasive dental procedure, laboratory tests should be performed alongside management of oral bleeding to identify possible causes, e.g., the presence of an inhibitor or platelet function defect due to medication.
- Persistent oral bleeding should be managed using staged local and/or systemic measures including:
  - direct pressure on the area using a damp gauze swab, maintained for at least 15-30 minutes;
  - local anesthesia with adrenaline/epinephrine to aid local vasoconstriction;
  - sutures for wound closure;
  - application of local hemostatic agents, e.g., oxidized cellulose, thrombin, fibrin sealant, or similar;
  - use of oral or topical antifibrinolytics as a mouthwash or paste[29,30];
  - systemic treatment of choice, e.g., CFC replacement, DDAVP, or antifibrinolytic therapy as directed by the hemophilia team; and
  - monitoring of vital signs and treatment for anemia, if required.
- Once hemostasis is achieved, stringent postoperative management will reduce risk of rebleeding.
- Patients with hemophilia should be advised to:
  - use systemic and/or topical antifibrinolytic agents for 5-7 days;
  - refrain from sports and intensive exercises for 3-5 days;
  - eat a soft diet with no vigorous mouth rinsing for 3-5 days;
  - refrain from or reduce smoking for at least 24 hours; and
  - consider use of a soft splint to protect the wound longer term, if required.
- See also Chapter 2: Comprehensive Care of Hemophilia – Dental care and management.

7.9 | Epistaxis

- Bleeding from the nose (epistaxis) can occur with injury or irritation to the nasal mucous membrane.
- People with hemophilia may experience frequent and prolonged nosebleeds which can be minor nuisances or major events that require medical attention in the hospital or emergency room.
- Clotting factor replacement therapy is often not necessary unless bleeding is severe or recurrent.[28,29]

RECOMMENDATION 7.9.1:

- **In hemophilia patients with epistaxis, the head should be elevated and cold compression applied to the Little's area of the nose.** CB

RECOMMENDATION 7.9.2:

- **In hemophilia patients with epistaxis, nasal packing should be avoided as it can cause bleeding when removed. However, in practice, nasal packing is used extensively.** CB

RECOMMENDATION 7.9.3:

- **In hemophilia patients with epistaxis, gauze soaked in an antifibrinolytic agent may be used in addition to clotting factor replacement therapy.** CB

- Patients with acute epistaxis must receive first aid treatment as follows:
  - Place the patient's head in a forward position to avoid swallowing of blood and have the patient gently blow out weak clots.
  - Apply firm continuous pressure with a gauze soaked in ice water to the anterior nasal septum, i.e., Little's area, for 5-10 minutes.
  - An antifibrinolytic agent applied locally using a soaked gauze is helpful.
- Nasal packing is contraindicated because the vascular endothelial lining is destroyed upon removal of the packing material, and hemostasis will be challenged. Cauterization is an effective alternative.
- For epistaxis specifically related to allergies, upper respiratory infections, or seasonal changes, administer antihistamines and decongestant medications if indicated.
- For epistaxis caused by infection, administer antibiotics if indicated.
- If epistaxis is prolonged or occurs frequently, evaluate for anemia and treat appropriately.
- For patients with severe and recurrent nosebleeds, specialist consultation and preventative measures are recommended. Consultation with an otolaryngologist is advisable if nosebleeds are persistent or recurrent.
- In severe or persistent cases, therapeutic occlusion of the arterial supply to the nose may be indicated.
- Preventive measures to reduce risk of epistaxis include:
  - 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;
  - adhering to prescribed medications such as antihistamines, decongestant medications, and antibiotics as directed.

RECOMMENDATION 7.9.4:

- **In hemophilia patients with persistent epistaxis, vital signs and hemoglobin levels should be monitored until the bleeding stops (usually within 24-48 hours).** CB

RECOMMENDATION 7.9.5:

- **In hemophilia patients with recurrent epistaxis, the underlying pathology should be identified immediately and treated. Decongestants and antihistamines should help if bleeding is related to allergy, and antibiotics should be administered if bleeding is related to infection.** CB

7.10 | Lacerations and abrasions

- Lacerations and abrasions are external bleeds caused by superficial or deep cuts or scrapes to the surface of the skin.
- Superficial lacerations should be treated with first aid.
- For deep lacerations, raise the patient's factor level, then suture the wound if appropriate.[28-30] (See Table 7-2.)

RECOMMENDATION 7.10.1:

- **In hemophilia patients with lacerations and abrasions, clotting factor replacement therapy should be administered and the wound sutured immediately, if appropriate, in consultation with appropriate surgeons.** CB

- Hemostatic coverage should be considered for suture removal, if the risk of bleeding is considered high.

7.11 | Soft tissue hemorrhage

- A soft tissue hemorrhage (hematoma) occurs in muscles, ligaments, tendons, and subcutaneous spaces.
- Common soft tissue injuries are often caused by a sprain or strain, a blow resulting in a contusion, or overuse of a particular body part. Symptoms depend on the site of hemorrhage.
- Clotting factor replacement therapy may not be necessary for most superficial soft tissue bleeding. The application of firm pressure and ice may be helpful.
- Open compartmental hemorrhage, such as in the retroperitoneal space, scrotum, buttocks, or thighs, can result in extensive blood loss. If this situation is suspected, immediate clotting factor replacement therapy is required to decrease bleeding as well as ice and adjunct treatment to reduce pain, tissue metabolism, edema, and inflammation.[13]
- Evaluate the patient for severity of hemorrhage and possible distal neurovascular involvement. Rule out possible trauma to spaces containing vital organs, such as the head or abdomen.
- Continued evaluation should be considered to avoid compartment syndrome.[28,29]
- Monitor hemoglobin levels and vital signs regularly until bleeding has stopped and/or function is restored.
- See also Chapter 10: Musculoskeletal Complications.

TABLE 7-2 Practice patterns: peak plasma factor levels and duration of administration

	Hemophilia A				Hemophilia B			
	Lower-dose practice pattern		Higher-dose practice pattern		Lower-dose practice pattern		Higher-dose practice pattern	
Type of hemorrhage	Peak factor level (IU/dL)	Treatment duration (d)	Peak factor level (IU/dL)	Treatment duration (d)	Peak factor level (IU/dL)	Treatment duration (d)	Peak factor level (IU/dL)	Treatment duration (d)
Joint	10-20	1-2[a]	40-60	1-2[a]	10-20	1-2[a]	40-60	1-2[a]
Superficial muscle/ no NV compromise (except iliopsoas)	10-20	2-3[a]	40-60	2-3[a]	10-20	2-3[a]	40-60	2-3[a]
Iliopsoas or deep muscle with NV injury or substantial blood loss								
Initial	20-40	1-2	80-100	1-2	15-30	1-2	60-80	1-2
Maintenance	10-20	3-5[b]	30-60	3-5[b]	10-20	3-5[b]	30-60	3-5[b]
Intracranial								
Initial	50-80	1-3	80-100	1-7	50-80	1-3	60-80	1-7
Maintenance	20-40	8-14	50	8-21	20-40	8-14	30	8-21
	30-50	4-7	–	–	30-50	4-7	–	–
Throat and neck								
Initial	30-50	1-3	80-100	1-7	30-50	1-3	60-80	1-7
Maintenance	10-20	4-7	50	8-14	10-20	4-7	30	8-14
Gastrointestinal								
Initial	30-50	1-3	80-100	7-14	30-50	1-3	60-80	7-14
Maintenance	10-20	4-7	50		10-20	4-7	30	
Renal	20-40	3-5	50	3-5	15-30	3-5	40	3-5
Deep laceration	20-40	5-7	50	5-7	15-30	5-7	40	5-7
Surgery (major)								
Pre-op	60-80		80-100		50-70		60-80	
Post-op[c]	30-40	1-3	60-80	1-3	30-40	1-3	40-60	1-3
	20-30	4-6	40-60	4-6	20-30	4-6	30-50	4-6
	10-20	7-14	30-50	7-14	10-20	7-14	20-40	7-14
Surgery (minor)								
Pre-op	40-80		50-80		40-80		50-80	
Post-op[d]	20-50	1-5	30-80	1-5	20-50	1-5	30-80	1-5

Notes: In this table, the desired peak factor levels of CFC replacement shown for treatment of hemorrhages at different anatomical sites represent the ranges in global practice patterns depending on available resources. Importantly, it should be recognized that the goal of such treatment is effective control of bleeding and should be the same everywhere in the world. Lower CFC replacement levels require much closer observation for effectiveness of bleeding control, with a potentially greater chance of requiring additional CFC replacement to achieve the target plasma level as well as the hemostatic and musculoskeletal outcomes.

Abbreviations: CFC, clotting factor concentrate; NV, neurovascular.

[a]May be longer if response is inadequate.

[b]Sometimes longer as secondary prophylaxis during physical therapy.

[c]The duration of treatment refers to sequential days post-surgery. Type of CFC and patient's response to CFC should be taken into account.

[d]Depending on procedure; the number of doses would depend on the half-life of the CFC used.

7.12 Practice patterns in CFC replacement

- The desired peak plasma factor levels shown in Table 7-2 reflect the range of practice in the community and have been part of the WFH guidelines since 2005. Over this long period, they have helped guide clinical care as well as research, particularly for surgical hemostasis, without any reported safety concerns. More research is needed to critically evaluate these practices.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.