

6 COMPLICATIONS OF HEMOPHILIA

6.1 Musculoskeletal complications

1. The most common sites of bleeding are the joints and muscles of the extremities.
2. Depending on the severity of the disease, bleeding episodes may be frequent and without apparent cause (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].
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.

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.
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
- 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.

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.
- ### *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.

6.2 Inhibitors

1. "Inhibitors" in hemophilia refer to IgG antibodies that neutralize clotting factors.
2. In the current era in which clotting factor concentrates have been subjected to appropriate viral inactivation, inhibitors to FVIII or FIX are considered to be the most severe treatment-related complication in hemophilia.
3. The presence of a new inhibitor should be suspected in any patient who fails to respond clinically to clotting factors, particularly if he has been previously responsive. In this situation, the expected recovery and half-life of the transfused clotting factor are severely diminished.
4. Inhibitors are more frequently encountered in persons with severe hemophilia compared to those with moderate or mild hemophilia.
5. The cumulative incidence (i.e. lifetime risk) of inhibitor development in severe hemophilia A is in the range of 20-30% and approximately 5-10% in moderate or mild disease [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.
20. **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]**
21. **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]**
22. **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]**
23. Porcine factor VIII prepared from the plasma of pigs has been effective in halting bleeding in some patients. The plasma-derived preparation is being superseded by a recombinant porcine factor VIII concentrate currently in clinical trials.
24. With an inhibitor level ≥ 5 BU, the likelihood is low that specific factor replacement will be effective in overwhelming the inhibitor without ultra high dose continuous infusion therapy.
25. Alternative agents include bypassing agents such as recombinant factor VIIa (rFVIIa) and prothrombin complex concentrates (PCC), including the activated forms (APCC).
26. **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].**
27. **Notably, however, some patients respond better to one agent than the other, highlighting the need to individualize therapy. (Level 2) [69,70]**
28. 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.
29. On the other hand, the risk of anamnesis in patients with hemophilia A and an inhibitor treated with a(n) (activated) prothrombin

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. 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].

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