



# Guidelines for the management of haemophilia in Australia

A joint project between  
Australian Haemophilia Centre Directors' Organisation,  
and the National Blood Authority, Australia

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#### **Disclaimer**

This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement and patient's preferences in each individual case. It is designed to provide information to assist decision making. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time.

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# Guidelines for the management of haemophilia in Australia

The Australian Haemophilia Centre Directors' Organisation (AHCDO) wishes to acknowledge and thank the World Federation of Hemophilia (WFH) for allowing AHCDO to review and adapt the *Guidelines for the management of hemophilia (2nd edition)* for the Australian setting.

Clinical experts from the following organisations reviewed the WFH's *Guidelines for the management of hemophilia (2nd edition)* and adapted the content for the Australian setting.

Alfred Health

Australasian College of Phlebology

Australasian Society for Infectious Diseases

Australasian Society of Thrombosis and Haemostasis

Australia and New Zealand College of Anaesthetists

Australia/New Zealand Haemophilia Social Workers' and Counsellors' Group

Australian and New Zealand Society of Nephrology

Australian Haemophilia Nurses' Group

Australian Physiotherapy Association

Haematology Society of Australia and New Zealand – Nurses Group

Haemophilia Foundation Australia

Human Genetics Society of Australasia

New South Wales Haemophilia Advisory Committee

Royal Australasian College of Dental Surgeons

Royal Australasian College of Physicians

Royal Australasian College of Surgeons

Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Royal Australian and New Zealand College of Ophthalmologists

Royal College of Pathologists of Australasia

Royal Prince Alfred Hospital

World Federation of Hemophilia



NATIONAL BLOOD AUTHORITY  
AUSTRALIA

The development of the *Guidelines for the management of haemophilia in Australia* was a joint project between AHCDO and the National Blood Authority, Australia (NBA). The NBA provided project management oversight and managed the procurement of all goods and services associated with the development of these guidelines.

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## General care and management of haemophilia

No.	PRACTICE POINT
PP 1.1	Haemophilia is an X-linked inherited bleeding disorder that should be suspected in individuals presenting with joint or muscle bleeding.
PP 1.2	Laboratory testing is required to confirm the diagnosis of haemophilia.
PP 1.3	Prompt treatment of bleeding complications is required in patients with haemophilia.
PP 1.4	Patients should carry with them details of their diagnosis and treatment, to expedite prompt and appropriate therapy.
PP 1.5	A comprehensive care model improves outcomes in patients with haemophilia.
PP 1.6	Essential members of a comprehensive care team include a medical director, a dedicated haemophilia nurse, musculoskeletal experts (including a dedicated expert physiotherapist), a specialised coagulation laboratory scientist and a psychosocial worker.
PP 1.7	The Australian Bleeding Disorders Registry is a key tool for communication between team members and for documenting care plans.
PP 1.8	Haemophilia treatment centres should offer advice regarding physical activity to patients with bleeding disorders.
PP 1.9	Prophylaxis is the standard of care in all children with severe haemophilia. Decisions regarding the timing of commencement, dosing regimen and continuation of prophylaxis into adulthood will be influenced by the bleeding phenotype of the individual patient.
PP 1.10	Home therapy should be made available to all patients in whom the bleed frequency makes this desirable.
PP 1.11	Regular review of patients with haemophilia and documentation of key clinical outcomes is essential. The frequency of review will be determined by the age of the patient and the severity of the haemophilia.
PP 1.12	Chronic pain is a common feature in patients with haemophilia and may require the input of a specialist pain service.
PP 1.13	COX-2 inhibitors are the preferred agent (in preference to nonselective nonsteroidal anti-inflammatory drugs) if second-line analgesia is required in patients with haemophilia.
PP 1.14	Clotting factor replacement is required to minimise the risk of perioperative bleeding. Dosing, particularly for major surgery, should be determined and coordinated by a haemophilia treatment centre.
PP 1.15	Regular dental assessment is an important component of care of patients with haemophilia.

## Special management issues

No.	Practice point
PP 2.1	Women who are carriers of the haemophilia gene may have reduced clotting factor levels and an increased risk of bleeding. Such women should have their clotting factor level documented.
PP 2.2	Active intervention may be required to reduce bleeding risk in haemophilia carriers with reduced clotting factor levels, particularly around invasive procedures.
PP 2.3	Genetic counselling should be offered to all individuals with haemophilia, carriers and their partners as part of routine care.
PP 2.4	Genetic testing may also help in assessing individual risk of inhibitor development.
PP 2.5	Delivery of infants with known or suspected haemophilia should be atraumatic, and forceps delivery or vacuum extraction should be avoided. Ideally, delivery should occur in hospitals with a 'high-risk' obstetric service, in close liaison with a haemophilia treatment centre.
PP 2.6	Social work review is a central component of haemophilia management.
PP 2.7	Individuals with haemophilia are at risk of common age-related diseases. Monitoring and appropriate treatment of these conditions in liaison with the patient's general practitioner is an important component of clinical care.

## Laboratory diagnosis

No.	Practice point
PP 3.1	A correct diagnosis is essential in all patients with bleeding disorders, to ensure appropriate treatment, because different bleeding disorders may have similar symptoms.
PP 3.2	Accurate diagnosis can only be made with the support of a comprehensive and accurate laboratory service. This depends on the laboratory following strict protocols and procedures, which require: <ul style="list-style-type: none"> <li>▪ knowledge and expertise in coagulation laboratory testing</li> <li>▪ use of the correct equipment and reagents</li> <li>▪ quality assurance.</li> </ul>
PP 3.3	Laboratories are strongly advised to participate in an external quality assessment scheme to audit the effectiveness of the internal quality control systems in place. The minimum National Association of Testing Authorities requirement is one external quality assessment scheme.
PP 3.4	The Royal College of Pathologists of Australasia runs a comprehensive program for haemophilia, von Willebrand disease and other haemostatic disorders. All laboratories involved in the diagnosis of bleeding disorders should participate in this program.
PP 3.5	Other national and international quality assessment schemes are also available; for example, the External Quality Control of Diagnostic Assays and Tests (ECAT) Foundation, and the National External Quality Assessment Service. Most laboratories associated with haemophilia treatment centres should participate in an international external quality assessment scheme.
PP 3.6	It is suggested that a chromogenic factor VIII assay be performed on diagnostic samples where a diagnosis of mild haemophilia is suspected.
PP 3.7	The Nijmegen modification of the factor VIII inhibitor assay offers improved specificity and sensitivity over the original Bethesda assay.
PP 3.8	Detailed information on technical aspects and specific instructions on screening tests and factor assays is available from the World Federation of Hemophilia <i>Diagnosis of hemophilia and other bleeding disorders: a laboratory manual, Second edition</i> <sup>1</sup> and other reference documents. <sup>2-3</sup>



## Haemostatic agents

No.	Practice point
PP 4.1	Where recombinant clotting factor concentrates are available, they should be used in preference to plasma-derived products.
PP 4.2	In Australia, recombinant clotting factor concentrates are available for the treatment of haemophilia A and haemophilia B. Plasma-derived products should only be used in these patient groups for urgent treatment in cases where recombinant products are not available. Plasma-derived factor VIII may occasionally be indicated for use in patients with factor VIII inhibitors undergoing tolerisation – the management of such patients should be discussed with the Australian Haemophilia Centre Directors' Organisation Tolerisation Advisory Committee.
PP 4.3	The use of adjuvant therapy such as desmopressin and tranexamic acid should always be considered in responsive patients. Desmopressin should be considered as first-line therapy in patients with mild haemophilia, provided the individual response has been demonstrated to be adequate to cover the haemostatic challenge being treated.

## Treatment of specific haemorrhages

No.	Practice point
PP 5.1	Bleeding in patients with haemophilia can occur at different sites, each of which require specific management.
PP 5.2	It is important that individuals with bleeding disorders and their families be educated about the symptoms and signs of bleeding disorders, and understand the benefit of prompt treatment.
PP 5.3	All patients with bleeding disorders should have a management plan documented, to be followed in the event of bleeding. Ideally, the plan should be documented on a treatment card generated from the Australian Bleeding Disorders Registry (see Section 1.2).
PP 5.4	As a general principle, in case of large internal haemorrhage or repeated intermittent bleeding, haemoglobin should be checked and corrected while other measures are being planned. Measures of haemodynamic stability, such as pulse and blood pressure, should be monitored as indicated.
PP 5.5	Appropriate rehabilitation is an important component of care following joint and muscle haemorrhage, and ideally should be guided by a physiotherapist familiar with the management of bleeding disorder patients.

## Complications of haemophilia

No.	Practice point
PP 6.1	Musculoskeletal complications are common in patients with haemophilia, and are best managed through a multidisciplinary approach that includes input from physiotherapy and musculoskeletal experts (including rheumatology or orthopaedics specialists, or both).
PP 6.2	Acute synovitis should be managed aggressively to reduce the risk of the development of chronic complication. Adequate factor replacement, pain control and physiotherapy input are important. Other interventions require further investigation.
PP 6.3	Chronic arthropathy management requires a multimodal approach. Strategies to delay the time to joint replacement are important.
PP 6.4	Inhibitor management is often complex. Management of new patients with inhibitors, including tolerisation, should be referred to the Australian Haemophilia Centre Directors' Organisation Tolerisation Advisory Committee for discussion.
PP 6.5	Transfusion-related infection with HIV and the hepatitis viruses has been an important cause of morbidity and mortality in the haemophilia community. The ongoing treatment and monitoring for complications of these conditions in liaison with other speciality teams (including infectious disease and hepatology) is an important role of haemophilia treatment centres.

## Plasma factor level and duration of administration

No.	Practice point
PP 7.1	Factor replacement may be <i>episodic</i> for the management of acute bleeding or surgery, or <i>prophylactic</i> to limit or prevent haemophilic arthropathy.
PP 7.2	Standard doses for prophylaxis in the Australian setting range from 25 to 40 IU/kg three times per week or on alternate days.
PP 7.3	Further research is required to define the optimal prophylaxis regimen and the long-term effectiveness of current dosing regimens.
PP 7.4	The duration and dosing of episodic therapy will depend on the severity of the haemophilia and the nature of the bleed or surgical procedure being managed.
PP 7.5	Dosing according to individual pharmacokinetic profile should be considered, particularly in patients undergoing major surgery.
PP 7.6	The presence of an inhibitor should be excluded in patients undergoing surgery. Follow-up inhibitor testing is also recommended 6–8 weeks after intense factor VIII exposure in patients with mild or moderate haemophilia A.

## Introduction

Haemophilia is a sex-linked inherited bleeding disorder that is characterised by a deficiency of either factor VIII (FVIII) (haemophilia A) or factor IX (FIX) (haemophilia B). Although haemophilia mainly affects males, women carrying a haemophilia mutation can also have a clinically significant bleeding disorder. Recent data suggest that there are about 2700 individuals with haemophilia living in Australia, of whom about 25% have severe disease with residual clotting factor activity of less than 1% of normal.

The best outcomes for patients with haemophilia are achieved through a comprehensive care model, within which members of a dedicated team manage not only the direct bleeding complications of haemophilia but also other aspects of care, such as complications that may have arisen from treatment. Collaboration among all clinical team members, the patient population and the funders of haemophilia care is central to good clinical management and efficient use of resources. Guidelines offer an important framework to guide both clinical decision-making and policy regarding resource allocation.

Guidance for the management of haemophilia in Australia is needed because:

- there are currently no guidelines available that provide multidisciplinary guidance on the management of the patients with haemophilia relevant to the Australian setting
- guidelines will help to standardise management of haemophilia in treatment centres throughout Australia
- the Australian *Evidence-based clinical practice guidelines for the use of recombinant and plasma-derived FVIII and FIX products*<sup>4</sup> are due for revision
- the World Federation of Hemophilia's (WFH) *Guidelines for the management of hemophilia (2nd edition)*<sup>5</sup> provide a good basis upon which to develop Australian guidance
- Australia's *National safety and quality health service standards*<sup>6</sup> requires that blood product policies, procedures or protocols be consistent with national evidence-based guidelines for pretransfusion practices, prescribing and clinical use.

These guidelines are based on the WFH's *Guidelines for the management of hemophilia (2nd edition)*<sup>5</sup> but have been adapted for the Australian setting. All significant changes from the WFH document are listed at the beginning of each chapter. Further details of the process of adapting the WFH guidelines for the Australian setting can be found at Appendix B. An additional chapter – Chapter 8 – has been included in the guidelines to describe the supply of clotting factor products and the management of information systems and data in Australia.

In line with the WFH guidelines, this document contains several practice statements regarding the clinical management of people with haemophilia. All statements given in bold font are evidence-based. Further details on the systematic review methodology are given in Appendix C. Some guidance fell outside the selection for practice statements, and where relevant, references for this guidance have been included; these references have not been graded.

These guidelines offer practical advice on the diagnosis and general management of haemophilia, and on the management of complications such as musculoskeletal issues, inhibitors and transfusion-transmitted infections. By adapting the WFH guidelines for the Australian setting, the Australian Haemophilia Centre Directors' Organisation (AHCDO) aims to:

- assist health-care providers seeking to initiate or maintain haemophilia care programs
- encourage harmonisation of practices
- where adequate evidence is lacking, stimulate appropriate studies.



# 1

## General care and management of haemophilia

## GENERAL CARE AND MANAGEMENT OF HAEMOPHILIA

No.	PRACTICE POINT
PP 1.1	Haemophilia is an X-linked inherited bleeding disorder that should be suspected in individuals presenting with joint or muscle bleeding.
PP 1.2	Laboratory testing is required to confirm the diagnosis of haemophilia.
PP 1.3	Prompt treatment of bleeding complications is required in patients with haemophilia.
PP 1.4	Patients should carry with them details of their diagnosis and treatment, to expedite prompt and appropriate therapy.
PP 1.5	A comprehensive care model improves outcomes in patients with haemophilia.
PP 1.6	Essential members of a comprehensive care team include a medical director, a dedicated haemophilia nurse, musculoskeletal experts (including a dedicated expert physiotherapist), a specialised coagulation laboratory scientist and a psychosocial worker.
PP 1.7	The Australian Bleeding Disorders Registry is a key tool for communication between team members and for documenting care plans.
PP 1.8	Haemophilia treatment centres should offer advice regarding physical activity to patients with bleeding disorders.
PP 1.9	Prophylaxis is the standard of care in all children with severe haemophilia. Decisions regarding the timing of commencement, dosing regimen and continuation of prophylaxis into adulthood will be influenced by the bleeding phenotype of the individual patient.
PP 1.10	Home therapy should be made available to all patients in whom the bleed frequency makes this desirable.
PP 1.11	Regular review of patients with haemophilia and documentation of key clinical outcomes is essential. The frequency of review will be determined by the age of the patient and the severity of the haemophilia.
PP 1.12	Chronic pain is a common feature in patients with haemophilia and may require the input of a specialist pain service.
PP 1.13	COX-2 inhibitors are the preferred agent (in preference to nonselective nonsteroidal anti-inflammatory drugs) if second-line analgesia is required in patients with haemophilia.
PP 1.14	Clotting factor replacement is required to minimise the risk of perioperative bleeding. Dosing, particularly for major surgery, should be determined and coordinated by a haemophilia treatment centre.
PP 1.15	Regular dental assessment is an important component of care of patients with haemophilia.

## Significant changes from the original World Federation of Hemophilia guidelines

- a) The Australian Bleeding Disorders Registry (ABDR) is highlighted as the central point for the documentation of treatment plans, treatment administered and outcome measures. Essential and desirable data to be recorded in the ABDR are documented.
- b) Primary prophylaxis is the standard of care in patients with severe haemophilia in Australia.
- c) Long-acting clotting factor concentrates have been demonstrated to be as efficacious as concentrates with a shorter half-life.
- d) The results of a systematic review regarding the efficacy and safety of selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are summarised.
- e) Changes have been made to recommendations regarding analgesia selection, based on local guidelines.
- f) The important role of mutation testing in assessing inhibitor risk in patients with mild and moderate haemophilia A is emphasised.

## 1.1 What is haemophilia?

- 1.1.1 Haemophilia is an X-linked congenital bleeding disorder caused by a deficiency of the coagulation factors FVIII (in haemophilia A) or FIX (in haemophilia B). The deficiency is the result of mutations of the respective clotting factor genes.
- 1.1.2 The reported incidence of haemophilia A ranges from 6.6 to 12.8 per 100 000 males, and for haemophilia B from 1.2 to 2.7 per 100 000 males, with the reported incidence being higher in developed countries. In Australia, the reported incidence is 11.5 per 100 000 for haemophilia A and B combined.
- 1.1.3 Estimations based on the WFH's annual global surveys indicate that the number of people with haemophilia in the world is about 400 000.<sup>7</sup> The prevalence of haemophilia A and B combined in Australia is about 13 per 100 000 individuals.<sup>8</sup>
- 1.1.4 Haemophilia A is more common than haemophilia B, representing 80–85% of the total haemophilia population.
- 1.1.5 Haemophilia generally affects males on the maternal side; however, women who carry a F8 gene mutation may also have reduced FVIII levels and may therefore be classified as having haemophilia. Both F8 and F9 genes are prone to new mutations, and as many as one-third of all cases are the result of spontaneous mutation where there is no prior family history.
- 1.1.6 Accurate diagnosis of haemophilia is essential to inform appropriate management. Haemophilia should be suspected in patients presenting with a history of:
  - easy bruising in early childhood
  - 'spontaneous' bleeding (i.e. bleeding for no apparent or known reason, or due to minor trauma not identified by the patient), particularly into the joints, muscles and soft tissues
  - excessive bleeding following trauma or surgery
  - primary menorrhagia and postpartum bleeding (in affected females).

- 1.1.7 A family history of bleeding is present in about two-thirds of all patients with haemophilia.
- 1.1.8 A definitive diagnosis depends on a laboratory assay result that demonstrates a deficiency of FVIII or FIX.

## Bleeding manifestations

- 1.1.9 The characteristic phenotype in haemophilia is the bleeding tendency.
- 1.1.10 Although the history of bleeding is usually life long, some infants and children with severe haemophilia may not have bleeding symptoms until they begin walking or running.
- 1.1.11 Patients with mild haemophilia may not bleed excessively until they experience trauma or surgery.
- 1.1.12 The severity of bleeding in haemophilia is generally correlated with clotting factor level, as shown in Table 1-1.
- 1.1.13 Most bleeding occurs internally, into the joints or muscles (see Table 1-2 and Table 1-3).
- 1.1.14 Some bleeds can be life-threatening and require immediate treatment (see Section 5).

**Table 1-1 Relationship of bleeding severity to clotting factor level<sup>9</sup>**

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 haemostatic 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% to <40% of normal	Severe bleeding with major trauma or surgery; spontaneous bleeding is rare

**Table 1-2 Sites of bleeding in haemophilia<sup>10</sup>**

Severity	Site of bleeding
Serious	<ul style="list-style-type: none"> <li>▪ Joints (haemarthrosis)</li> <li>▪ Muscles, especially deep compartments (iliopsoas, calf and forearm)</li> <li>▪ Mucous membranes in the mouth, gums, nose and genitourinary tract</li> </ul>
Life-threatening	<ul style="list-style-type: none"> <li>▪ Intracranial</li> <li>▪ Neck or throat</li> <li>▪ Gastrointestinal</li> </ul>



Table 1-3 Approximate frequency in bleeding at different sites

Site of bleeding	Approximate frequency (%)
Haemarthrosis <ul style="list-style-type: none"> <li>more common into hinged joints (i.e. ankles, knees and elbows)</li> <li>less common into multiaxial joints (i.e. shoulders, wrists and hips)</li> </ul>	70–80
Muscle	10–20
Other major bleeds	5–10
Central nervous system	5

## 1.2 Principles of care

- 1.2.1 The primary aim of care is to prevent and treat bleeding caused by the deficient clotting factor, either by replacing the clotting factor or by other methods.
- 1.2.2 Whenever possible, specific factor deficiency should be treated with specific factor concentrate.
- 1.2.3 People with haemophilia are best managed in a comprehensive care setting (see Section 1.3 and Chapter 8).
- 1.2.4 **Acute bleeds should be treated as quickly as possible (preferably within 2 hours), either at home or in the hospital; treatment should be not delayed by the performance of diagnostic investigations. If in doubt, treat.**<sup>11</sup>
- 1.2.5 Patients usually recognise early symptoms of bleeding even before the manifestation of physical signs. The early symptoms are often described as a tingling sensation or ‘aura’.
- 1.2.6 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.
- 1.2.7 In severe bleeding episodes that are potentially life-threatening – especially in the head, neck, chest and gastrointestinal (GI) tract – treatment with factor should be initiated immediately, even before diagnostic assessment is completed.
- 1.2.8 **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 both severe traumatic or spontaneous bleeds and of minor bleeding events, and contact information of the treating physician or clinic.**<sup>12</sup> Hard plastic emergency treatment cards (also known as patient cards) that contain this information are available to all patients registered on the ABDR.
- 1.2.9 **Administration of desmopressin (DDAVP)<sup>a</sup> can raise FVIII level adequately (three to six times baseline levels) to control bleeding in patients with mild, and possibly moderate, haemophilia A. Testing for a desmopressin response in individual patients is appropriate.**<sup>13-14</sup>
- 1.2.10 Veins must be treated with care; they are the lifelines for a person with haemophilia.
  - 23-gauge or 25-gauge butterfly needles are recommended.

<sup>a</sup> 1-deamino-8-D-arginine vasopressin



- Never cut down into a vein, except in an emergency.
  - Apply pressure for 3–5 minutes after venipuncture.
  - Avoid venous access devices whenever possible, although such devices may be required in some children.
- 1.2.11 Adjunctive therapies can be used to control bleeding, particularly in the absence of clotting factor concentrates, and may decrease the need for such concentrates (see Section 1.5).
- 1.2.12 If bleeding does not resolve despite adequate treatment, clotting factor levels should be measured. Inhibitor testing should be performed if the factor level is unexpectedly low or if the clinical response to replacement therapy is inadequate (see Section 6.2).
- 1.2.13 Prevention of bleeding can be achieved by prophylactic factor replacement (see Section 1.6).
- 1.2.14 Home therapy can be used to manage mild or moderate bleeding episodes (see Section 1.7).
- 1.2.15 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 Section 1.4).
- 1.2.16 Patients should avoid activities likely to cause trauma (see Section 1.4).
- 1.2.17 Regular monitoring of health status and assessment of outcomes are key components of care (see Section 1.8).
- 1.2.18 Drugs that affect platelet function, particularly acetylsalicylic acid and NSAIDs, except certain COX-2 inhibitors, should be avoided. Paracetamol or acetaminophen is a safe alternative for analgesia (see Section 1.9).
- 1.2.19 Factor levels should be raised to appropriate levels before any invasive procedure (see Section 1.10).
- 1.2.20 Good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding (see Section 1.11).

## 1.3 Comprehensive care

- 1.3.1 **Comprehensive care promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality.**<sup>15-16</sup>
- 1.3.2 Haemophilia is a rare disorder that is complex to diagnose and to manage. Optimal care of patients with haemophilia, especially those with severe forms of the disease, is more complex than simply treating acute bleeding.
- 1.3.3 Priorities in the improvement of health and quality of life of people with haemophilia include:
- prevention of bleeding and joint damage
  - prompt management of bleeding
  - management of complications such as:
    - joint and muscle damage and other sequelae of bleeding
    - inhibitor development
  - viral infection(s) transmitted through blood products
  - attention to psychosocial health.
- 1.3.4 Benchmarking of practice and available resources across haemophilia treatment centres is an important tool to help standardise and improve care (see Chapter 8).

## Comprehensive care team

- 1.3.5 **The wide-ranging needs of people with haemophilia 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 with national treatment guidelines, if available.**<sup>17-18</sup>
- 1.3.6 The comprehensive care team should be multidisciplinary in nature, with the expertise and experience to attend to the physical and psychosocial health of patients and their families.
- 1.3.7 The following members are essential to the care team:
- a medical director (preferably a paediatric or adult haematologist, or a physician with interest and expertise in haemostasis)
  - a nurse coordinator who:
    - specialises in the management of bleeding disorders
    - 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
  - musculoskeletal experts (including a physiotherapist, orthopaedic specialist or rheumatologist) who can address prevention as well as treatment
  - a specialist coagulation medical scientist
  - a psychosocial expert (preferably a social worker or a psychologist) familiar with available community resources.
- 1.3.8 The roles assumed by core team members will depend on the availability and expertise of trained staff and the organisation of services within the centre.
- 1.3.9 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.
- 1.3.10 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 haemostatic agents such as desmopressin and tranexamic acid, where possible
  - access to casting or splinting for immobilisation, and to mobility or support aids, as needed.
- 1.3.11 The comprehensive care team should also include or have access to the following:
- pain specialist with expertise in the management of both acute and chronic pain
  - dentist
  - geneticist or genetic counsellor
  - hepatologist
  - infectious disease specialist
  - immunologist
  - gynaecologist or obstetrician
  - vocational counsellor.

- 1.3.12 Written management protocols are required to ensure continuity of care if there are changes in clinic personnel.
- 1.3.13 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 ageing)
  - issues regarding schooling and employment
  - risk of having another affected child and the options available.
- 1.3.14 Establishing a long-term relationship between patients and their families, and members of the comprehensive care team, promotes compliance.

## Functions of a comprehensive care centre

- 1.3.15 A comprehensive care centre provides or coordinates inpatient (i.e. during hospital stays) and outpatient (i.e. clinic and other visits) care and services to patients and their family.
- Patients should be seen by all core team members at least yearly (every 6 months for children and for patients with severe bleeding disorders) for clinical review, and to develop, audit and refine an individual's comprehensive management plan. A comprehensive musculoskeletal and psychosocial assessment should be performed annually. Referrals for other services can also be given during these visits.**<sup>19-20</sup>
- 1.3.16 The management plan should be developed with the patient, and communicated to all treaters and care facilities. All changes in treatment plan should be recorded on the ABDR.
- 1.3.17 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 with mild disease who live a long distance from the nearest haemophilia treatment centre).
- 1.3.18 To initiate, provide training for and supervise home therapy with clotting factor concentrates where available.
- 1.3.19 To educate patients, family members and other caregivers to ensure that the needs of the patient are met.
- 1.3.20 To collect data on sites of bleeds, types and doses of treatment given, assessment of long-term outcomes (particularly with reference to musculoskeletal function), complications from treatment and surgical procedures. This information is best recorded on the ABDR; it should be updated regularly by an ABDR data manager or other designated person, and maintained in accordance with confidentiality laws and other national regulations. Particular emphasis should be placed on recording of:
- all bleeding events (both by haemophilia treatment centre staff through the ABDR, and by patients using MyABDR – an electronic tool available as an app and online for the recording of bleeding events)
  - clotting factor administration (again both through the ABDR and MyABDR)
  - joint outcome using the Haemophilia Joint Health Score<sup>b</sup> (HJHS) and an appropriate quality of life measure.
- Systematic collection of data will:
- facilitate the auditing of services provided by the haemophilia treatment centre and support improvements to care delivery
  - be useful in allocating resources
  - promote collaboration between centres in sharing and publishing data.

<sup>b</sup> <http://www.wfh.org/en/page.aspx?pid=885>

- 1.3.21 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 haemophilia centres.

## 1.4 Fitness and physical activity

- 1.4.1 **Physical activity should be encouraged, to promote physical fitness and normal neuro-muscular development, with attention paid to muscle strengthening, coordination, balance, general fitness, physical functioning, healthy body weight and self-esteem.**<sup>21</sup>
- 1.4.2 Bone density may be decreased in people with haemophilia.<sup>22-23</sup>
- 1.4.3 **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.**<sup>22</sup>
- 1.4.4 The choice of activities should reflect an individual's preference or interests, ability, physical condition, local customs and resources.
- 1.4.5 Noncontact sports should be encouraged in preference to contact sports.
- 1.4.6 Decisions to participate in high contact and collision sports (e.g. soccer, Australian rules football, hockey, rugby, boxing and wrestling) and high-velocity activities (e.g. motocross racing and skiing) are best made after discussion with the haemophilia treatment centre team. Such decisions should take into account the age of the individual, and the severity and type of their bleeding disorder. Because of the potential for life-threatening injuries, any individual who decides to participate in such activities should have adequate prophylaxis cover. It is again emphasised that noncontact sport is preferred.
- 1.4.7 Organised sports programs should be encouraged as opposed to unstructured activities, which may lack protective equipment and supervision.
- 1.4.8 Before beginning a particular physical activity, the patient should consult with a musculoskeletal physiotherapist familiar with haemophilia, to discuss the activity's appropriateness, protective gear, prophylaxis (factor and other measures) and physical skills required. This is particularly important if the patient has any problem or target joints (a target joint is a joint in which three or more bleeds without apparent cause have occurred within a consecutive 6-month period).<sup>24</sup>
- 1.4.9 **Target joints can be protected with braces or splints during activity.**<sup>25-26</sup>
- 1.4.10 Activities should be re-initiated gradually after a bleed has fully resolved, to minimise the chance of a re-bleed.

## 1.5 Adjunctive management

- 1.5.1 Adjunctive therapies are important, particularly where clotting factor concentrates are limited or not available, and such therapies may lessen the amount of treatment product required.
- 1.5.2 In addition to increasing factor level with clotting factor concentrates (or desmopressin in mild haemophilia A), adjunctive management for bleeding in muscles and joints can include first aid measures such as protection (splint), rest, ice, compression and elevation (PRICE).
- 1.5.3 Physiotherapy or rehabilitation is particularly important for functional improvement and recovery after musculoskeletal bleeds, and for those with established haemophilic arthropathy (see Section 6.1).

- 1.5.4 Antifibrinolytic drugs (e.g. tranexamic acid) are effective as adjunctive treatment for mucosal bleeds and dental extractions.
- 1.5.5 Certain COX-2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis (see Section 1.9).

## 1.6 Prophylactic factor replacement therapy

- 1.6.1 Prophylaxis is the treatment by intravenous injection of factor concentrate in order to prevent anticipated bleeding (see Table 1-4).
- 1.6.2 Prophylaxis was conceived from the observation that patients with moderate haemophilia with clotting factor level above 1 international unit (IU)/dl seldom experience spontaneous bleeding and have much better preservation of joint function than those with a lower level of clotting factor.<sup>27-28</sup>
- 1.6.3 **Prophylaxis prevents bleeding and joint destruction, and should be the goal of therapy, to preserve normal musculoskeletal function.**<sup>28-29</sup>
- 1.6.4 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.<sup>29-31</sup>
- 1.6.5 It is unclear whether all patients should remain on prophylaxis indefinitely as they transition into adulthood. Some data suggest that a proportion of young adults can do well without prophylaxis;<sup>32</sup> however, more studies are needed before a clear recommendation can be made.<sup>33</sup>
- 1.6.6 **In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for 4–8 weeks can be used to interrupt the bleeding cycle. This prophylaxis may be combined with intensive physiotherapy or synoviorthesis.**<sup>34-35</sup>
- 1.6.7 Prophylaxis does not reverse established joint damage; however, it does decrease frequency of bleeding, and it may slow progression of joint disease and improve quality of life.
- 1.6.8 Cost–efficacy studies designed to identify minimum dosage are needed, to allow access to prophylaxis in more areas of the world.

**Table 1-4 Definitions of factor replacement therapy protocols<sup>36</sup>**

Protocol	Definition
Episodic ('on demand') treatment	Treatment given at the time of clinically evident bleeding
Continuous prophylaxis	Regular continuous <sup>a</sup> treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination or imaging studies (or both), and started before the second clinically evident large joint bleed and age 3 years <sup>b</sup>
Primary prophylaxis	
Secondary prophylaxis	Regular continuous <sup>a</sup> treatment started after two or more bleeds into large joints, <sup>b</sup> and before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	Regular continuous <sup>a</sup> 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

<sup>a</sup> '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.

<sup>b</sup> 'Large joints' are ankles, knees, hips, elbows and shoulders.

## Administration and dosing schedules

- 1.6.9 Long-term data are available for two of the prophylaxis protocols currently in use:
- the *Malmö protocol*: 25–40 IU/kg per dose administered three times a week for those with haemophilia A, and twice a week for those with haemophilia B
  - the *Utrecht protocol*: 15–30 IU/kg per dose administered three times a week for those with haemophilia A, and twice a week for those with haemophilia B.
- 1.6.10 However, many different protocols are followed for prophylaxis, even within the same country, and the optimal regimen remains to be defined.
- 1.6.11 New long-acting factor concentrates are likely to become available during the lifetime of these guidelines. Data suggest that prophylactic treatment with these agents, using a reduced frequency of administration, results in a similar reduction in annual bleeding rates to that seen with conventional prophylactic regimens using normal half-life factor concentrates.
- 1.6.12 The protocol should be individualised as much as possible, based on age, venous access, bleeding phenotype, pharmacokinetics, activity and availability of clotting factor concentrates.
- 1.6.13 An alternative option for the treatment of very young children (e.g. <12 months) is to start prophylaxis once a week, and escalate as necessary, depending on bleeding and venous access.
- 1.6.14 Prophylaxis is best given in the morning, to cover periods of activity.
- 1.6.15 **Prophylactic administration of clotting factor concentrates is advisable before engaging in activities with higher risk of injury.**<sup>24; 35; 37</sup>

## 1.7 Home therapy

- 1.7.1 Where appropriate and possible, people with haemophilia should be managed in a home therapy setting. The decision to provide product for home therapy should take into account the likely frequency of administration of clotting factor and the likelihood of product expiry, regardless of severity of the haemophilia.
- 1.7.2 **Home therapy allows immediate access to clotting factor and hence to optimal early treatment; this results in decreased pain, dysfunction and long-term disability, and significantly decreased hospital admissions for complications.**<sup>38-39</sup>
- 1.7.3 Further improvements in quality of life include greater freedom to travel and participate in physical activities, less absenteeism and greater employment stability.<sup>40</sup>
- 1.7.4 Home therapy is ideally achieved with clotting factor concentrates or other lyophilised products that are safe, can be stored in a domestic fridge and are easily reconstituted.
- 1.7.5 **Home treatment must be supervised closely by the comprehensive care team, and should only be initiated after adequate education and training.**<sup>38-39</sup>
- 1.7.6 Teaching should focus on general knowledge of haemophilia; recognition of bleeds and common complications; first aid measures; dosage calculation; preparation, storage and administration of clotting factor concentrates; aseptic techniques; performance of venipuncture (or access of central venous catheter); record keeping; proper storage and disposal of needles or sharps; and handling of blood spills. A certification program is helpful.

- 1.7.7 Patients or parents should keep bleed records using MyABDR; such records should include date and site of bleeding, dosage and lot number of product used, and any adverse effects.
- 1.7.8 Infusion technique and bleed records should be reviewed and monitored at follow-up visits.
- 1.7.9 Home care can be started with young children with adequate venous access, provided that family members are motivated and have undergone adequate training. Older children and teenagers can learn self-infusion with family support.
- 1.7.10 **An implanted venous access device (Port-A-Cath) can make injections much easier, and may be required for administering prophylaxis in younger children.**<sup>41-42</sup>
- 1.7.11 **The risks of surgery, local infection, and thrombosis associated with venous access devices need to be weighed against the advantages of starting intensive prophylaxis early.**<sup>43-44</sup>
- 1.7.12 The venous access device must be kept scrupulously clean and be adequately flushed after each administration to prevent clot formation.<sup>43</sup>

## 1.8 Monitoring health status and outcome

- 1.8.1 **Regular standardised 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.**<sup>20; 30; 45</sup>
- 1.8.2 Patients should be seen by the multidisciplinary care team after every severe bleeding episode.
- 1.8.3 The following should be evaluated and education should be reviewed and reinforced:
- issues related to venous access
  - issues related to haemostasis (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 Section 6.1)
  - transfusion-transmitted infections – commonly human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV), and others if indicated (see Section 6.3)
  - development of inhibitors (see Section 6.2)
  - overall psychosocial status
  - dental or oral health.

- 1.8.4 Several haemophilia-specific scores are available to measure joint impairment and function, including activities and participation; they include:
- impairment:
    - clinical scores – WFH Physical Examination Score<sup>c</sup> (also known as the Gilbert Score) and the HJHS
    - radiological scores – Pettersson Score, magnetic resonance imaging (MRI) and ultrasound scores
    - activity scores – Haemophilia Activities List<sup>d</sup> (HAL), Paediatric Haemophilia Activities List<sup>e</sup> (PedHAL) and Functional Independence Score in Haemophilia<sup>f</sup> (FISH)
  - health-related quality of life scores – Haem-A-QOL for adults, HemoQol<sup>g</sup> for children and adolescents, and Canadian Hemophilia Outcomes: Kids' Life Assessment Tool<sup>h</sup> (CHO-KLAT) for children.
- 1.8.5 Outcome measures to be recorded in the Australian Bleeding Disorders Registry (ABDR) are outlined in Table 1-5.

**Table 1-5 Outcome measures to be recorded in the ABDR**

Essential	Desirable
Annualised bleeding rate	Pharmacokinetic measures
Haemophilia Joint Health Score (HJHS)	Adverse events other than bleeds
All administered clotting factor concentrate – combined with weight this will allow calculation of the benchmarking parameter of usage, summarised as IU/kg/year	Details of immune tolerance treatment other than factor administration
Weight (recorded at least every 6 months for paediatric patients and at least every 2 years for adult patients)	Radiological measures
	Quality of life measures (Haem-A-QOL for adult patients and CHO-KLAT for paediatric patients)

## 1.9 Pain management

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

### Pain caused by venous access

- 1.9.2 In general, no pain medication is given.
- 1.9.3 In some children, application of a local anaesthetic spray or cream at the site of venous access, or use of nitrous oxide gas, may be helpful.

<sup>c</sup> <http://www.wfh.org/en/page.aspx?pid=883>

<sup>d</sup> <http://www.wfh.org/en/page.aspx?pid=875>

<sup>e</sup> <http://www.wfh.org/en/page.aspx?pid=886>

<sup>f</sup> <http://www.wfh.org/en/page.aspx?pid=884>

<sup>g</sup> <http://www.haemoqol.de>

<sup>h</sup> <http://www.flintbox.com/public/project/3008/>



## Pain caused by joint or muscle bleeding

- 1.9.4 Clotting factor concentrates should be administered as quickly as possible to stop bleeding; however, additional drugs are often needed for pain control (see Table 1-6).
- 1.9.5 Other measures include cold packs, immobilization, splints, compression bandages and crutches.<sup>46</sup>

## Postoperative pain

- 1.9.6 Intramuscular injection of analgesia should be avoided.
- 1.9.7 Postoperative pain should be managed in coordination with specialist acute pain services.
- 1.9.8 If intravenous opioids are required, fentanyl, morphine and other opioids may be used. Oxycodone and tramadol should be used when pain is less severe and oral intake is possible. Codeine should be used with caution, because there is significant individual variation in its rate of metabolism to morphine.
- 1.9.9 Regular early use of paracetamol is recommended as part of all analgesic regimens.

## Pain due to chronic haemophilic arthropathy

- 1.9.10 Chronic haemophilic arthropathy develops in patients (including those with inhibitor development) who have not been adequately treated with clotting factor concentrates for joint bleeding.
- 1.9.11 **Treatment includes functional training, adaptations and adequate analgesia, as suggested in Table 1-6.**<sup>21; 47</sup>
- 1.9.12 **COX-2 inhibitors have a greater role in this situation.**<sup>48-49</sup>

A systematic review was performed to evaluate the efficacy and safety of COX-2 inhibitors in patients with haemophilia, with and without pre-existing haemophilic arthropathy (Appendix C). The following conclusions were made after available evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria:

- a) In patients with haemophilia and haemophilic arthropathy, COX-2 inhibitors probably lead to little or no difference in bleeding episodes compared with no COX-2 inhibitors.
- b) In patients with haemophilia and haemophilic arthropathy, COX-2 inhibition probably improves pain compared with no use of COX-2 inhibitors.
- c) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the impact of COX-2 inhibitors on recurrent haemarthrosis.
- d) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the impact of COX-2 inhibitors on development of a target joint.
- e) In patients with haemophilia, no studies were found that evaluated the impact of COX-2 inhibitors on cardiovascular events.
- f) In patients with haemophilia, no studies were found that evaluated the impact of COX-2 inhibitors on the presence and severity of arthropathy.

### 1.9.13 NSAIDs other than COX-2 inhibitors should be avoided.<sup>50</sup>

A systematic review was performed to evaluate the efficacy and safety of nonselective NSAIDs in patients with haemophilia, with and without pre-existing haemophilic arthropathy (Appendix C). The following conclusions were made after available evidence was assessed using the GRADE criteria:

- a) In patients with mild or moderate haemophilia, medium-term ibuprofen (i.e. taken for up to 8 weeks) may lead to little or no difference in the occurrence of bleeding episodes compared with no ibuprofen.
- b) In patients with haemophilia, the use of NSAIDs probably leads to little or no difference in the occurrence of upper GI bleeding compared with no NSAIDs.
- c) In patients with moderate or severe haemophilia and arthropathy, it is uncertain whether ibuprofen improves arthropathy symptoms.
- d) In patients with haemophilia, no studies were found that evaluated the impact of NSAIDs on cardiovascular events.
- e) In patients with haemophilia, with or without arthropathy, ibuprofen may lead to little or no difference in bleeding time compared with no ibuprofen.
- f) In patients with haemophilia, ibuprofen may improve pain compared with no ibuprofen.
- g) In patients with haemophilia, ibuprofen may lead to little or no difference in joint restriction.
- h) In patients with haemophilia and arthropathy, ibuprofen probably decreases the duration of morning stiffness compared with no ibuprofen.

As the level of evidence for the benefit of NSAIDs is low, and it is biologically plausible that COX-2 inhibitors may be associated with less bleeding risk than nonselective NSAID use, COX-2 inhibitors are the preferred agents in patients with haemophilia.

### 1.9.14 When pain is disabling, orthopaedic surgery may be indicated.<sup>51</sup>

1.9.15 Patients with persisting pain should be referred to a specialised pain management team.

**Table 1-6 Strategies for pain management in patients with haemophilia**

No.	Strategy
1	Paracetamol or acetaminophen <i>If not effective, see Strategy 2</i>
2	COX-2 inhibitor (e.g. celecoxib, meloxicam and others) OR Paracetamol or acetaminophen plus tramadol (3–4 times/day). <i>If not effective, see Strategy 3</i>
3	Opiate analgesia: use a slow-release product such as controlled-release oxycodone, tramadol SR, tapentadol SR or controlled-release morphine

**Notes:**

- If for any reason medications have been stopped for a 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.
- Patients with chronic pain requiring long-term narcotic analgesia should be managed in liaison with a specialist pain service, with clear communication with their primary care provider.

## 1.10 Surgery and invasive procedures

- 1.10.1 Surgery may be required for haemophilia-related complications or unrelated diseases. The following issues are of primary importance when performing surgery on patients with haemophilia.
- 1.10.2 Surgery for patients with haemophilia will require additional planning and interaction with the health-care team compared with what is required for other patients. Appropriate surgical intervention should be available for all patients with haemophilia, regardless of the underlying severity of their bleeding disorder.
- 1.10.3 **A haemophilia patient requiring surgery is best managed at or in consultation with a comprehensive haemophilia treatment centre.<sup>52-53</sup> Emergency surgical procedures may need to be conducted in nonhaemophilia treatment centres; in such cases, they should be performed in close consultation with the staff of haemophilia treatment centres. It is recommended that major surgery be performed at a haemophilia treatment centre.**
- 1.10.4 The anaesthetist should have experience in treating patients with bleeding disorders.
- 1.10.5 Adequate laboratory support is required for reliable monitoring of clotting factor level and inhibitor testing.
- 1.10.6 **Preoperative assessment should include inhibitor screening and inhibitor assay, and possibly pharmacokinetic assessment, particularly if the recovery of the replaced factor is significantly less than expected.<sup>54-55</sup>**
- 1.10.7 Surgery should be scheduled early in the week and early in the day, to ensure optimal laboratory and blood bank support, if needed.
- 1.10.8 Adequate quantities of clotting factor concentrates should be available for the surgery itself and to maintain adequate coverage postoperatively for the length of time required for healing and rehabilitation.
- 1.10.9 In exceptional circumstances, if clotting factor concentrates are not available, blood bank support for the provision of alternative plasma components may be needed.
- 1.10.10 The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed (see Table 7-1).
- 1.10.11 Effectiveness of haemostasis for surgical procedures may be judged as per criteria defined by the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) (see Table 1-7).<sup>36</sup>
- 1.10.12 **Patients with mild or moderate haemophilia A, particularly those receiving intensive factor replacement for the first time, are at risk of inhibitor development and should be re-screened 4–12 weeks postoperatively.<sup>56</sup>**
- 1.10.13 **Mutation testing may be used to further assess the risk of inhibitor formation in the postoperative period in patients with mild to moderate haemophilia. Ideally, mutation analysis should be performed before major invasive procedures.**
- 1.10.14 Careful monitoring for inhibitors is also advisable in patients with non-severe haemophilia A receiving continuous infusion after surgery, particularly in individuals with high-risk mutations.<sup>57</sup>
- 1.10.15 Infusion of factor concentrates or haemostatic agents is necessary before invasive diagnostic procedures such as lumbar puncture, arterial blood gas determination or any endoscopy with biopsy.

Table 1-7 Definition of adequacy of haemostasis for surgical procedures<sup>36</sup>

Excellent	Intraoperative and postoperative blood loss similar (within 10%) to the nonhaemophilic patient, with: <ul style="list-style-type: none"> <li>no extra (unplanned) doses of FVIII, FIX or bypassing agents needed AND</li> <li>blood component transfusions required are similar to those for the nonhaemophilic patient.</li> </ul>
Good	Intraoperative and/or postoperative blood loss slightly increased over expectation for the nonhaemophilic patient (between 10% and 25% of expected), but the difference is judged by the involved surgeon or anaesthetist to be clinically insignificant, as evidenced by: <ul style="list-style-type: none"> <li>no extra (unplanned) doses of FVIII, FIX or bypassing agents needed AND</li> <li>blood component transfusions required are similar to those for the nonhaemophilic patient.</li> </ul>
Fair	Intraoperative and/or postoperative blood loss are increased over expectation (25–50%) for the nonhaemophilic patient and additional treatment is needed; for example: <ul style="list-style-type: none"> <li>extra (unplanned) dose of FVIII, FIX or bypassing agents OR</li> <li>increased blood component use (within twofold) of the anticipated transfusion requirement.</li> </ul>
Poor or none	Significant intraoperative and/or postoperative blood loss that is substantially increased over expectation (>50%) for the nonhaemophilic patient, requires intervention, and is not explained by a surgical or medical issue other than haemophilia: <ul style="list-style-type: none"> <li>unexpected hypotension or unexpected transfer to intensive care unit due to bleeding OR</li> <li>substantially increased blood component use (more than twofold of the anticipated transfusion requirement).</li> </ul>

## Notes:

- Apart from estimates of blood loss during surgery, data on preoperative and postoperative haemoglobin levels and the number of packed red blood cell units transfused may also be used, if relevant, to estimate surgical blood loss.
- Surgical haemostasis should be assessed by an involved surgeon or anaesthetist (or both) 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 haemostatic support for periods exceeding 5 consecutive days.

## 1.11 Dental care and management

- 1.11.1 For people with haemophilia, good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding.<sup>58</sup>
- 1.11.2 Dental examinations should be conducted regularly, starting at the time the baby teeth start to erupt.
- 1.11.3 Teeth should be brushed twice a day with a medium-texture brush to remove plaque deposits.
- 1.11.4 Dental floss or interdental brushes should be used wherever possible.
- 1.11.5 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.
- 1.11.6 An orthodontic assessment should be recommended for all patients between the ages of 10–14 years, to determine whether there are any problems associated with overcrowding, which can result in periodontal disease if left untreated.
- 1.11.7 Close liaison between the dental surgeon and the haemophilia team is essential to provide good, comprehensive dental care.

- 1.11.8 **Treatment can be safely carried out under local anaesthesia using the full range of techniques available to dental surgeons. Infiltration, intrapapillary and intraligamentary injections are often done under factor cover (20–40%), although dental surgeons with adequate experience may be able to administer these injections without such cover.**<sup>59-60</sup>
- 1.11.9 Treatment from the haemophilia unit may be required before an inferior alveolar nerve block or lingual infiltration.
- 1.11.10 **Dental extraction or surgical procedures carried out within the oral cavity should be done with a plan for haemostasis management, in consultation with a haematologist.**<sup>53</sup>
- 1.11.11 **Tranexamic acid is often used to cover dental procedures, to reduce the need for replacement therapy.**<sup>61-62</sup>
- 1.11.12 Oral antibiotics should only be prescribed if clinically necessary.
- 1.11.13 Local haemostatic measures should also be used whenever possible following a dental extraction. Typical products include oxidised cellulose and fibrin glue.
- 1.11.14 Following a tooth extraction, the patient should be advised to avoid hot food and drinks until normal feeling has returned. Smoking should be avoided because it 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 5–7 days or until the mouth has healed.
- 1.11.15 Prolonged bleeding or difficulty in speaking, swallowing or breathing following dental manipulation should be reported to the haematologist or dental surgeon immediately.
- 1.11.16 NSAIDs and aspirin must be avoided.
- 1.11.17 An appropriate dose of paracetamol every 6 hours for 2–3 days will help to prevent pain following an extraction.
- 1.11.18 The presence of bloodborne infections should not affect the availability of dental treatment. Patients with bloodborne viral infections can be at increased risk of periodontal complications and may require closer monitoring.
- 1.11.19 Careful planning is required to prevent bleeding at the time of dental procedures in patients with inhibitors to FVIII or FIX.<sup>63</sup>



# 2

## Special management issues

## SPECIAL MANAGEMENT ISSUES

No.	PRACTICE POINT
PP 2.1	Women who are carriers of the haemophilia gene may have reduced clotting factor levels and an increased risk of bleeding. Such women should have their clotting factor level documented.
PP 2.2	Active intervention may be required to reduce bleeding risk in haemophilia carriers with reduced clotting factor levels, particularly around invasive procedures.
PP 2.3	Genetic counselling should be offered to all individuals with haemophilia, carriers and their partners as part of routine care.
PP 2.4	Genetic testing may also help in assessing individual risk of inhibitor development.
PP 2.5	Delivery of infants with known or suspected haemophilia should be atraumatic, and forceps delivery or vacuum extraction should be avoided. Ideally, delivery should occur in hospitals with a 'high-risk' obstetric service, in close liaison with a haemophilia treatment centre.
PP 2.6	Social work review is a central component of haemophilia management.
PP 2.7	Individuals with haemophilia are at risk of common age-related diseases. Monitoring and appropriate treatment of these conditions in liaison with the patient's general practitioner is an important component of clinical care.



## Significant changes from the original World Federation of Hemophilia guidelines

- g) It is emphasised that genetic testing should be offered to all at-risk female family members to facilitate genetic counselling.
- h) The likely future role of noninvasive methods to determine fetal gender are highlighted.
- i) The recommended age for chorionic villus sampling (CVS) is altered, to be consistent with local guidelines.
- j) Delivery of haemophilia carriers should ideally occur in hospitals with a 'high-risk' obstetric service, a paediatric unit and a haemophilia treatment centre. This is particularly the case if the offspring may have a severe bleeding disorder.
- k) Dosing of obese patients should be based on ideal body weight.

## 2.1 Carriers

- 2.1.1 Haemophilia is an X-linked disorder that typically affects males, whereas females are normally classified as carriers. However, affected males will pass on the haemophilia gene to their daughters, and women carrying a F8 or F9 gene mutation may have reduced factor levels and should therefore be classified as having haemophilia.
- 2.1.2 Obligate carriers are any of the following:
- daughters of a male with haemophilia
  - mothers of one son with haemophilia, and who have at least one other family member with haemophilia
  - mothers of one son with haemophilia, and who have a family member who is a known carrier of the haemophilia gene
  - mothers of two or more sons with haemophilia.
- 2.1.3 The expected mean clotting factor level in carriers of haemophilia is 50% of the levels found in the healthy population.<sup>64-65</sup>
- 2.1.4 Most carriers are asymptomatic.
- 2.1.5 Carriers with clotting factor levels of 40–60% of normal may have an increased bleeding tendency, although this may not correlate well with factor level.<sup>66</sup>
- 2.1.6 Some carriers may have clotting factor levels in the range seen in males with haemophilia – mostly in the mild category (5–40%) – however, in rare instances, carriers can be in the moderate or severe range due to extreme lyonisation.
- 2.1.7 Carriers with clotting factor levels in the haemophilia range may be symptomatic, with bleeding manifestations commensurate with their degree of clotting factor deficiency, particularly during trauma and surgery.<sup>66</sup>
- 2.1.8 Menorrhagia and bleeding after medical interventions are the most common bleeding manifestations among women with significantly low factor levels.<sup>66</sup>
- 2.1.9 **Carriers with low clotting factor levels should be categorised as having haemophilia of appropriate severity, and should be managed accordingly.**



- 2.1.10 Use of the oral contraceptive pill and tranexamic acid may be useful in controlling symptoms of menorrhagia. In women in whom menorrhagia persists despite these measures, consideration should be given to use of the Mirena intrauterine device. Use of desmopressin may also be beneficial in some women.
- 2.1.11 Levels of FVIII increase significantly in pregnancy, but levels of FIX do not usually change significantly.<sup>67</sup>
- 2.1.12 **Immediate female relatives (mother, sisters and daughters) of a person with haemophilia should have their clotting factor level checked, especially before any invasive intervention or childbirth, or if bleeding symptoms occur.**<sup>66, 68</sup>

## 2.2 Genetic testing and counselling, and prenatal diagnosis

- 2.2.1 **Genetic testing for carrier status should be offered to at-risk female family members of people with haemophilia to facilitate genetic counselling and, if desired by the family, for prenatal diagnosis.**<sup>69</sup> **Mutation analysis is best performed on an affected male in the first instance. Cascade carrier testing should be offered to female first-degree relatives. If the female is a carrier, then clotting studies including FVIII should be undertaken. Ideally, management advice and genetic counselling in carriers should be provided through a centre with experience in managing haemophilia A.**
- 2.2.2 DNA-based mutation analysis to identify the specific mutation responsible for haemophilia in a particular family is becoming technically easier and more widely available. Such analysis facilitates identification of women carrying a F8 or F9 gene mutation, and prenatal diagnosis for male fetuses.
- 2.2.3 Genetic counselling is key to helping people with haemophilia, carriers and their families to make more informed choices.
- 2.2.4 Genetic testing may be helpful to determine risk of inhibitor formation in individuals with haemophilia, particularly in those with mild or moderate disease.
- 2.2.5 Prenatal diagnosis is usually offered when termination of the pregnancy would be considered if an affected fetus were to be identified. However, it may also be done to help the family prepare and to plan delivery. Assisted delivery is best avoided in an affected fetus.
- 2.2.6 Fetal gender can be determined using Y chromosome-specific polymerase chain reaction (PCR) in maternal plasma or serum after 7–9 weeks of gestation,<sup>70-71</sup> or by ultrasonography at the beginning of week 11 of gestation.<sup>72</sup> Noninvasive prenatal techniques using maternal blood sampling to determine gender are likely to replace the above methods in the near future.
- 2.2.7 **CVS, or biopsy, is the main method of prenatal diagnosis, and is best done between 11 and 14 weeks of gestation. Biopsy carried out earlier may be associated with increased complications including fetal limb abnormalities.**<sup>73-76</sup>
- 2.2.8 Amniocentesis can be done at 15–17 weeks of gestation.<sup>74</sup>
- 2.2.9 The above procedures should be performed by an appropriately medically registered practitioner.
- 2.2.10 For women with low clotting factor levels, haemostatic support may be required to prevent maternal bleeding during prenatal diagnosis procedures.
- 2.2.11 **All invasive methods used for prenatal diagnosis may cause feto-maternal haemorrhage. Anti-D immunoglobulin should be given if the mother is RhD negative.**<sup>77</sup>
- 2.2.12 In vitro fertilisation (IVF) with preimplantation genetic diagnosis allows selection of embryos without a specific known mutation, for transfer into the uterus.<sup>78</sup>

## 2.3 Delivery of infants with known or suspected haemophilia

- 2.3.1 FVIII levels usually rise into the normal range during the second and third trimesters; hence, they should be measured in carriers during the early third trimester of pregnancy, to inform decisions about factor coverage during delivery.<sup>67</sup>
- 2.3.2 In women with significantly low factor levels (<50 IU/dl), clotting factor replacement is necessary for surgical or invasive procedures, including delivery.<sup>67</sup>
- 2.3.3 The need for clotting factor replacement should be discussed and planned for in the prenatal period.
- 2.3.4 Ideally, delivery should occur in hospitals with a 'high-risk' obstetric service, a paediatric unit and a haemophilia treatment centre. This is particularly the case if the offspring may have a severe bleeding disorder.
- 2.3.5 Route of delivery in carriers with a normal fetus should be as per obstetric indications.
- 2.3.6 **Delivery of infants with known or suspected haemophilia should be atraumatic, regardless of whether delivery is vaginal or caesarean, to decrease the risk of bleeding.**<sup>67</sup>
- 2.3.7 Forceps and vacuum extraction **should be avoided** in vaginal delivery, as should invasive procedures to the fetus, such as fetal scalp blood sampling and internal fetal scalp electrodes.<sup>79</sup>

## 2.4 Vaccinations

- 2.4.1 **Individuals with bleeding disorders should be vaccinated, but should preferably receive the vaccine subcutaneously rather than intramuscularly or intradermally, unless the procedure is covered by infusion of clotting factor concentrates.**<sup>80</sup>
- 2.4.2 If intramuscular injection is to be given, it is best done as soon as possible after a dose of factor replacement therapy.
- An ice pack can be applied to the injection area for 5 minutes before the injection.
  - The smallest gauge needle available (usually 25–27 gauge) should be used.
  - Pressure should be applied to the injection site for at least 5 minutes. The site should not be rubbed.<sup>81</sup>
  - The subcutaneous route could be considered as an alternative in a person with haemophilia; however, the intramuscular route is preferred if that is the usual recommended mode of vaccine administration – if this is the case, seek expert advice. If a vaccine is administered subcutaneously, there may be diminished immune response (e.g. requirement to check antibodies to hepatitis B surface antigen, anti-HBs) and additional vaccine doses may be required.<sup>82</sup>
- 2.4.3 Vaccination in individuals with HIV should be performed as described in the Australian immunisation handbook.<sup>82</sup>
- 2.4.4 **Immunisation to hepatitis A and B is important for all people with haemophilia. These immunisations may not be fully effective in those with HIV infection.**<sup>82-84</sup>

## 2.5 Psychosocial issues

- 2.5.1 Patients and their families should be provided with psychological and social support.<sup>85-86</sup>
- 2.5.2 Haemophilia can be a financial burden that places restrictions on several aspects of normal living.<sup>87</sup>
- 2.5.3 The social worker or other members of the comprehensive care team should:
- provide as much information as possible about the physical, psychological, emotional and economic dimensions of haemophilia, in terms the patient or parents can understand
  - be open and honest about all aspects of care
  - allow the patient or parents to work through their emotions and ask questions
  - provide care and support in a patient manner
  - talk to affected children, not just their parents – children can often understand a great deal about their illness, and can work with the physician if properly informed and educated
  - remind parents not to ignore siblings that are healthy
  - be able to recognise warning signs of burnout and depression (which are common in chronic illness), and provide suggestions for coping
  - recognise that cultural background and religious beliefs may affect patients' views of illness and treatment
  - encourage patients to engage in productive activities and in leisure activities, both at work and at home
  - work in partnership with the patient organisation to advocate for haemophilia care, and to provide education to families and members of the community
  - where social workers are unavailable, enlist the assistance of local groups and organisations
  - involve the school in the care of the patient – to avoid discrimination against or bullying of individuals with bleeding disorders
  - promote participation in programs sponsored by Haemophilia Foundation Australia (HFA)
  - promote uptake of use of the MyABDR as an effective means of communication with the haemophilia treatment centre.

## 2.6 Sexuality

- 2.6.1 Patients with haemophilia can have normal sexual intercourse.<sup>88</sup>
- 2.6.2 Muscle bleedings (e.g. iliopsoas) may sometimes result from sexual activity.
- 2.6.3 Complications of haemophilia can be accompanied by sexual dysfunction (e.g. lack of libido or impotence).
- 2.6.4 Pain or fear of pain may affect sexual desire, and haemophilic arthropathy may place limitations on sexual intercourse.
- 2.6.5 Sexuality is also affected by chronic HCV and HIV infection, age-related diseases such as hypertension and diabetes mellitus, and certain medications.

- 2.6.6 In some cases, oral phosphodiesterase-5 inhibitors (e.g. sildenafil and tadalafil) may be helpful in the treatment of erectile dysfunction. These medications mildly inhibit platelet aggregation in vitro, and may cause epistaxis due to nasal congestion.

## 2.7 Ageing haemophilia patients

- 2.7.1 Ageing patients with haemophilia will inevitably suffer from age-related diseases.<sup>88-89</sup>
- 2.7.2 Comorbidities in ageing haemophilia patients should be managed appropriately, because they may accentuate problems associated with haemophilia and thus affect the patient's physical and psychosocial health, which in turn will affect quality of life. Liaison between the haemophilia treatment centre and geriatric specialist services is encouraged where appropriate.

### Osteoporosis

- 2.7.3 Bone mineral density (BMD) is decreased in people with haemophilia.<sup>22-23</sup>
- 2.7.4 Various factors are associated with a lower BMD; for example, increased number of arthropathic joints, loss of joint movement and muscle atrophy, leading to inactivity.<sup>23</sup> BMD should be routinely checked in individuals, in a manner consistent with local guidelines.
- 2.7.5 Weight-bearing activities (suitable sports) that promote development and maintenance of good BMD should be encouraged if joint health permits.
- 2.7.6 Calcium and vitamin D supplementation should be administered only when dietary and normal activities result in inadequate levels. Bisphosphonate therapy may be required in some individuals; however, a dental evaluation is advisable before initiating therapy.<sup>90-91</sup>

### Obesity

- 2.7.7 The prevalence of overweight (body mass index [BMI] 25–30 kg/m<sup>2</sup>) and obesity (BMI >30 kg/m<sup>2</sup>) is increasing.<sup>92</sup>
- 2.7.8 Lack of activity may contribute to an increase in BMI and in body weight.
- 2.7.9 A high BMI has been associated with:
  - a significant limitation in range of motion<sup>93</sup>
  - increased arthropathic pain
  - increased risk of developing target joints<sup>94</sup>
  - increased risk of diabetes mellitus, atherosclerosis and cardiovascular disease, which may further damage arthropathic joints.
- 2.7.10 Regular physical activity should be advised.
- 2.7.11 If functional limitations restrict daily activities, a physiotherapist familiar with haemophilia may be able to suggest appropriate alternatives.
- 2.7.12 In some cases, referral to a dietician may be indicated.
- 2.7.13 Dosing of FVIII in obese patients should be based on ideal body weight.<sup>95</sup>

## Hypertension

- 2.7.14 Haemophilia patients have a higher mean blood pressure, are twice as likely to have hypertension, and use more antihypertensive medication than the general population.<sup>96-97</sup>
- 2.7.15 In view of increased risk of bleeding, hypertensive patients with haemophilia should be treated adequately and should have their blood pressure checked as part of routine clinical review.
- 2.7.16 In the absence of other cardiovascular risk factors, a systolic blood pressure of  $\leq 140$  mmHg and a diastolic pressure of  $\leq 90$  mmHg should be maintained.

## Diabetes mellitus

- 2.7.17 The prevalence of diabetes mellitus in haemophilia is not well documented, but was observed to be higher in a cohort of patients with mild haemophilia.<sup>98</sup>
- 2.7.18 In ageing patients with haemophilia, especially among those who are overweight, glucose levels should be checked annually.
- 2.7.19 **If treatment with insulin is indicated, subcutaneous injections can be administered without bleeding complications.**<sup>88</sup>

## Hypercholesterolemia

- 2.7.20 Mean cholesterol levels in patients with haemophilia have been reported to be lower than those in the general population.<sup>99</sup>
- 2.7.21 As part of annual review, cholesterol levels – total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fraction – should be measured in ageing haemophilia patients at risk of cardiovascular disease.
- 2.7.22 Treatment is indicated if cholesterol levels are high, as per current Australian guidelines.<sup>100</sup>

## Cardiovascular disease

- 2.7.23 Haemophilia patients appear to have a reduced risk of mortality from ischaemic cardiovascular disease, but the number of deaths from this cause is increasing.<sup>97, 101-102</sup>
- 2.7.24 A possible association between the occurrence of myocardial infarction and previous administration of clotting factor concentrates has been described.<sup>103-104</sup>
- 2.7.25 Haemophilia patients with cardiovascular disease should receive routine care that has been adapted to the individual situation in discussion with a cardiologist.<sup>105-106</sup>
- 2.7.26 For acute coronary syndromes requiring percutaneous cardiac intervention (PCI), the following should be taken into account:
- **Adequate correction with clotting factor concentrates before PCI and until 48 hours after PCI is required.**<sup>104-105; 107</sup>
  - High factor levels should be avoided in order to prevent occlusive thrombi.  
During complete correction:
    - heparin can be administered according to standard cardiologic treatment protocols
    - glycoprotein IIb/IIIa inhibitors (e.g. abciximab and tirofiban) used in PCI with stenting can be administered.

- **A radial artery access site, if technically possible, is preferred over a femoral access site, to minimise retroperitoneal or groin bleeds.**<sup>104-105; 107</sup>
- Factor concentrates should be given for the duration of dual antiplatelet therapy (i.e. for about 2 weeks), aiming at trough levels of 30 IU/dl.<sup>105</sup>
- Prolonged use of aspirin is not recommended in severe haemophilia. Its use in patients on regular intensive prophylaxis is possible, although the data available are inadequate.<sup>105</sup> It is generally accepted that antiplatelet therapy is acceptable in patients with mild bleeding disorders; however, such patients should be closely observed for changes in bleeding phenotype.

## Psychosocial impact

- 2.7.27 In the ageing patient, the presence of crippling, painful arthropathy can affect quality of life and may lead to loss of independence.<sup>108</sup>
- 2.7.28 Patients may be confronted with unexpected emotional problems due to memories of negative experiences related to haemophilia (e.g. hospitalisation) during their youth.
- 2.7.29 Adaptations at home or at work and an adequate pain schedule are indicated to improve quality of life and preserve independence.
- 2.7.30 Active psychosocial support should be provided by a social worker, haemophilia nurse, physician or psychologist.

## 2.8 von Willebrand disease and rare bleeding disorders

- 2.8.1 These guidelines are intended for the treatment of haemophilia. Recent publications that address the principles of diagnosis and treatment of von Willebrand disease (VWD) and rare bleeding disorders include:
- *Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization*<sup>109</sup>
  - *The diagnosis, evaluation and management of von Willebrand disease*<sup>110</sup>
  - *Von Willebrand disease: an introduction for the primary care physician*<sup>111</sup>
  - *Rare bleeding disorders*<sup>112</sup>
  - *The rare coagulation disorders*.<sup>113</sup>





# 3

## Laboratory diagnosis



## LABORATORY DIAGNOSIS

No.	PRACTICE POINT
PP 3.1	A correct diagnosis is essential in all patients with bleeding disorders, to ensure appropriate treatment, because different bleeding disorders may have similar symptoms.
PP 3.2	Accurate diagnosis can only be made with the support of a comprehensive and accurate laboratory service. This depends on the laboratory following strict protocols and procedures, which require: <ul style="list-style-type: none"> <li>▪ knowledge and expertise in coagulation laboratory testing</li> <li>▪ use of the correct equipment and reagents</li> <li>▪ quality assurance.</li> </ul>
PP 3.3	Laboratories are strongly advised to participate in an external quality assessment scheme to audit the effectiveness of the internal quality control systems in place. The minimum National Association of Testing Authorities requirement is one external quality assessment scheme.
PP 3.4	The Royal College of Pathologists of Australasia runs a comprehensive program for haemophilia, von Willebrand disease and other haemostatic disorders. All laboratories involved in the diagnosis of bleeding disorders should participate in this program.
PP 3.5	Other national and international quality assessment schemes are also available; for example, the External Quality Control of Diagnostic Assays and Tests (ECAT) Foundation, and the National External Quality Assessment Service. Most laboratories associated with haemophilia treatment centres should participate in an international external quality assessment scheme.
PP 3.6	It is suggested that a chromogenic factor VIII assay be performed on diagnostic samples where a diagnosis of mild haemophilia is suspected.
PP 3.7	The Nijmegen modification of the factor VIII inhibitor assay offers improved specificity and sensitivity over the original Bethesda assay.
PP 3.8	Detailed information on technical aspects and specific instructions on screening tests and factor assays is available from the World Federation of Hemophilia <i>Diagnosis of hemophilia and other bleeding disorders: a laboratory manual, Second edition</i> <sup>1</sup> and other reference documents. <sup>2-3</sup>

### **Significant change from the original World Federation of Hemophilia guidelines**

- l) Extensive governance structures overseen by the Royal College of Pathologists of Australasia (RCPA) are in place regarding the quality of diagnostic services in Australia. It was felt that extensive guidance regarding preanalytical and analytical aspects of the diagnosis were not required as part of these guidelines. A separate collaborative document in conjunction with the RCPA is, however, seen as a future priority.





# 4

## Haemostatic agents

## HAEMOSTATIC AGENTS

No.	PRACTICE POINT
PP 4.1	Where recombinant clotting factor concentrates are available, they should be used in preference to plasma-derived products.
PP 4.2	In Australia, recombinant clotting factor concentrates are available for the treatment of haemophilia A and haemophilia B. Plasma-derived products should only be used in these patient groups for urgent treatment in cases where recombinant products are not available. Plasma-derived factor VIII may occasionally be indicated for use in patients with factor VIII inhibitors undergoing tolerisation – the management of such patients should be discussed with the Australian Haemophilia Centre Directors' Organisation Tolerisation Advisory Committee.
PP 4.3	The use of adjuvant therapy such as desmopressin and tranexamic acid should always be considered in responsive patients. Desmopressin should be considered as first-line therapy in patients with mild haemophilia, provided the individual response has been demonstrated to be adequate to cover the haemostatic challenge being treated.

## Significant changes from the original World Federation of Hemophilia guidelines

- m) Recombinant clotting factor concentrates are the treatment of choice for haemophilia A and haemophilia B in Australia.
- n) Where recombinant or specific plasma-derived factor concentrates are available, cryoprecipitate or fresh frozen plasma (FFP) should not be used.
- o) Intranasal desmopressin is not available for the treatment of bleeding disorders in Australia.

## 4.1 Clotting factor concentrates

- 4.1.1 **The WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate or FFP for the treatment of haemophilia and other inherited bleeding disorders.**<sup>114-115</sup>
- 4.1.2 The comprehensive WFH *Guide for the assessment of clotting factor concentrates* reviews factors affecting the quality, safety, licensing and assessment of plasma-derived products, and the important principles involved in selecting suitable products for the treatment of haemophilia.<sup>115</sup>
- 4.1.3 The WFH also publishes and regularly updates a *Registry of clotting factor concentrates*, which lists all currently available products and their manufacturing details.<sup>116</sup>
- 4.1.4 Currently, manufactured plasma-derived concentrates produced to good manufacturing practice standards have an exemplary safety record with respect to lipid-coated viruses, such as HIV and HCV.
- 4.1.5 Product safety is the result of efforts in several areas:
- improved donor selection (exclusion of at-risk donors)
  - improved screening tests of donations, including nucleic acid testing (NAT)
  - type and number of in-process viral inactivation or removal steps.
- 4.1.6 The risk of prion-mediated disease through plasma-derived products exists. In the absence of a reliable screening test for variant Creutzfeldt–Jakob disease (vCJD), and with no established manufacturing steps to inactivate the vCJD prion, this problem is currently being handled by excluding plasma from all donors perceived to be at risk. As new information evolves in this field, constant awareness of current scientific recommendations is needed for those involved in making decisions about choice of clotting factor concentrate for people with haemophilia.
- 4.1.7 The above measures mean that the use of the current commercially available plasma-derived products is associated with a very low risk of transmission of infection; nevertheless, it is recommended that Australian patients with bleeding disorders receive recombinant factor concentrates, where suitable products are available.

### Product selection

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



## Purity

- 4.1.9 Purity of concentrates refers to the percentage of the desired ingredient (e.g. FVIII), relative to other ingredients present.
- 4.1.10 There is no universally agreed classification of products based on purity.
- 4.1.11 Concentrates on the market vary widely in their purity.
- 4.1.12 Some products have high or very high purity at one stage of the production process, but are subsequently stabilised by albumin, which lowers their final purity. In general, products with higher purity tend to be associated with low manufacturing yields and are therefore costlier than products of lower purity.
- 4.1.13 Concentrates of lower purity may give rise to allergic reactions.<sup>117-118</sup> Patients who experience such reactions repeatedly with a particular product may benefit from the administration of an antihistamine immediately before infusion, or from use of a higher purity concentrate.
- 4.1.14 Plasma-derived FVIII concentrates may contain variable amounts of von Willebrand factor (VWF). It is therefore important to ascertain the VWF content (as measured by ristocetin cofactor activity) of products to be used for the treatment of VWD.<sup>119</sup>
- 4.1.15 **For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates (PCCs), which also contain other clotting factors (e.g. factors II, VII and X), some of which may become activated during manufacture. Products containing activated clotting factors may predispose to thromboembolism. Recombinant FIX (rFIX) is available in Australia for the management of FIX deficiency, and is the preferred product to be used in this patient population. PCCs should be used only in emergency situations where recombinant product is not available.**<sup>120-121</sup>
- 4.1.16 The viral safety of products is not related to purity, provided that adequate viral elimination measures are in place.

## Viral inactivation or elimination

- 4.1.17 In-process viral inactivation is the single largest contributor to the safety of plasma-derived concentrates.<sup>122</sup>
- 4.1.18 There is a growing tendency to incorporate two specific viral-reducing steps in the manufacturing process of concentrates:
- heat treatment is generally effective against a broad range of viruses, both with and without a lipid envelope, including HIV, hepatitis A virus (HAV), HBV and HCV
  - solvent or detergent treatment is effective against HBV, HCV and HIV, but does not inactivate viruses without a lipid envelope, such as HAV.
- 4.1.19 Some viruses (e.g. human parvovirus B19) are relatively resistant to both types of process. None of the current methods can inactivate prions.
- 4.1.20 Nano (ultra) filtration can be used to remove small viruses such as parvovirus, but the filtration techniques currently in use do not eliminate the risk of transmission.<sup>123</sup>
- 4.1.21 A product created by a process that incorporates two viral reduction steps should not automatically be considered better than one that only has one specific viral inactivation step.
- 4.1.22 If only one step is used, this step should preferably inactivate viruses both with and without lipid envelopes.

## FVIII concentrates

- 4.1.23 **Recombinant FVIII (rFVIII) concentrates are the treatment of choice for haemophilia A in the Australian setting.**
- 4.1.24 All plasma-derived products currently in the market are listed in the WFH *Registry of clotting factor concentrates*.<sup>116</sup> Consult the product insert for specific details.

### Dosage and administration

- 4.1.25 Vials of factor concentrates are available in dosages ranging from about 250 to 3000 units each.
- 4.1.26 **In the absence of an inhibitor, each unit of FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level by about 2 IU/dl.**<sup>124</sup>
- 4.1.27 The half-life of FVIII is about 8–12 hours.
- 4.1.28 **Where clinically indicated, the patient's factor level should be measured about 15 minutes after the infusion, to verify the calculated dose.**<sup>124</sup>
- 4.1.29 The dose is calculated by multiplying the patient's weight in kilograms by the factor level in IU/dl desired, multiplied by 0.5.
- Example: 50 kg × 40 (IU/dl level desired) × 0.5 = 1000 units of FVIII.*
- See Table 7-1 for suggested factor level and duration of administration based on type of haemorrhage.*
- 4.1.30 **FVIII should be infused by slow intravenous injection at a rate not greater than 3 ml/minute in adults or as specified in the product information leaflet.**<sup>125</sup>
- 4.1.31 Subsequent doses should ideally be based on the half-life of FVIII and on the recovery in an individual patient for a particular product.
- 4.1.32 It is best to use the entire vial of FVIII once reconstituted, by rounding up the dose to the nearest vial size, although many products have been shown to have extended stability after reconstitution.
- 4.1.33 **Continuous infusion avoids peaks and troughs and is considered by some to be advantageous and more convenient. However, patients receiving continuous infusion must be monitored frequently for pump failure.**<sup>52; 126</sup>
- 4.1.34 Continuous infusion may lead to a reduction in the total quantity of clotting factor concentrates used, and thus can be more cost-effective in patients with severe haemophilia.<sup>127</sup> However, whether continuous infusion is more cost-effective depends on the doses used for continuous and intermittent bolus infusions.<sup>54</sup>
- 4.1.35 Dose for continuous infusion is adjusted based on frequent factor assays and calculation of clearance. Since FVIII concentrates of very high purity are stable in intravenous solutions for at least 24–48 hours at room temperature (<10% loss of potency), continuous infusion for a similar number of hours is possible.

## FIX concentrates

- 4.1.36 **rFIX concentrates are the treatment of choice for haemophilia B.**
- 4.1.37 All plasma-derived products currently in the market are listed in the WFH *Registry of clotting factor concentrates*.<sup>116</sup> The product information guide will provide specific details.



4.1.38 FIX concentrates fall into two classes:

- pure FIX concentrates, which may be plasma derived or recombinant
- FIX concentrates that also contain factors II, VII, IX and X (i.e. PCC).

4.1.39 **The use of a pure FIX concentrate is preferable to the use of PCC for the treatment of haemophilia B.**<sup>120-121</sup> Prothrombinex HT, the only PCC currently available in Australia, should only be used for the treatment of haemophilia B where emergency replacement of FIX is required and a pure FIX concentrate is not available.

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

#### Dosage and administration

4.1.41 Vials of FIX concentrates are available in doses ranging from about 250 to 3000 units each.

4.1.42 **In the absence of an inhibitor, each unit of FIX per kilogram of body weight infused intravenously will raise the plasma FIX level by about 1 IU/dl.**<sup>124</sup>

4.1.43 The half-life is about 18–24 hours.

4.1.44 **Where clinically indicated, the patient's FIX level should be measured about 15 minutes after infusion to verify calculated doses.**<sup>124</sup>

4.1.45 rFIX has a lower recovery than plasma-derived products, such that each unit of rFIX per kilogram of body weight infused will raise the FIX activity by about 0.8 IU/dl in adults and 0.7 IU/dl in children under 15 years of age. The reason for the lower recovery of rFIX is not entirely clear.<sup>128</sup>

4.1.46 The dose is calculated by multiplying the patient's weight in kilograms by the factor level desired.

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

*For rFIX, the dosage will be 2000 ÷ 0.8 (or 2000 × 1.25) = 2500 units for adults, and 2000 ÷ 0.7 (or 2000 × 1.43) = 2860 units for children.*

*See Table 7-1 for suggested factor level and duration of administration based on type of haemorrhage.*

4.1.47 **FIX concentrates should be infused by slow intravenous injection at a rate not greater than 3 ml/minute in adults, or as recommended in the product information leaflet.**<sup>125</sup>

4.1.48 **If used, PCCs should generally be infused at half this rate. Consult the product information leaflet for instructions.**<sup>129</sup>

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

4.1.50 Allergic reactions may occur with infusions of FIX concentrates in patients with anti-FIX inhibitors. In such patients, infusions may need to be covered with hydrocortisone.<sup>130</sup> Changing the brand of clotting factor concentrate sometimes reduces symptoms.

## 4.2 Other plasma products

4.2.1 The WFH supports the use of coagulation factor concentrates in preference to cryoprecipitate or FFP, because of concerns about the quality and safety of the latter. Where recombinant or specific plasma-derived factor concentrates are available, cryoprecipitate or FFP should not be used.<sup>114-115</sup>

- 4.2.2 Cryoprecipitate and FFP are not subjected to viral inactivation procedures (e.g. heat or treatment with solvent or detergent), leading to an increased risk of transmission of viral pathogens, which is significant with repeated infusions.<sup>114</sup>
- 4.2.3 Certain steps have been taken to minimise the risk of transmission of viral pathogens. Such steps include the use of NAT to detect viruses—a technology that potentially has much greater relevance for the production of cryoprecipitate than for factor concentrates, because the latter are subjected to viral inactivation steps.<sup>131</sup>
- 4.2.4 Allergic reactions are more common following infusion of cryoprecipitate than of concentrate.<sup>132</sup>

## Fresh frozen plasma

- 4.2.5 Because FFP contains all the coagulation factors, it is sometimes used to treat coagulation factor deficiencies.
- 4.2.6 **Cryoprecipitate is preferable to FFP for the treatment of haemophilia A.**<sup>133</sup>
- 4.2.7 **Due to concerns about the safety and quality of FFP, its use for treatment of haemophilia A is not recommended, and alternatives should be used if possible.**<sup>134</sup> However, because FFP and cryo-poor plasma (see point 4.2.13) contain FIX, they can be used for the treatment of haemophilia B.
- 4.2.8 In Australia, it is possible to apply some forms of virucidal treatment to packs of FFP (including solvent or detergent treatment) and the use of treated packs is recommended. However, virucidal treatment may have some impact on coagulation factors. The large-scale preparation of pooled solvent or detergent-treated plasma has also been shown to reduce the proportion of the largest multimers of VWF.<sup>135–136</sup>

### Dosage and administration

- 4.2.9 One ml of FFP contains one unit of factor activity.
- 4.2.10 It is generally difficult to achieve FVIII levels higher than 30 IU/dl with FFP alone.
- 4.2.11 FIX levels above 25 IU/dl are difficult to achieve. **An acceptable starting dose is 15–20 ml/kg.**<sup>133</sup>

## Cryoprecipitate

- 4.2.12 Cryoprecipitate is prepared by slow thawing of FFP at 4°C for 10–24 hours. It appears as an insoluble precipitate and is separated by centrifugation.
- 4.2.13 Cryoprecipitate contains significant quantities of FVIII (about 3–5 IU/ml), VWF, fibrinogen and factor XIII, *but not factors IX or XI*. The resultant supernatant is called ‘cryo-poor plasma’, and it contains other coagulation factors such as factors VII, IX, X and XI.
- 4.2.14 **Due to concerns about the safety and quality of cryoprecipitate, its use in the treatment of congenital bleeding disorders is not recommended; such use can only be justified in situations where clotting factor concentrates are not available.**<sup>114; 133; 137</sup>

### Dosage and administration

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

## 4.3 Other pharmacological options

4.3.1 In addition to conventional coagulation factor concentrates, other agents can be of great value in a significant proportion of cases. These include desmopressin and tranexamic acid.

### Desmopressin

4.3.2 Desmopressin is a synthetic analogue of vasopressin that boosts plasma levels of FVIII and VWF.<sup>138</sup>

4.3.3 **Desmopressin may be the treatment of choice for patients with mild or moderate haemophilia A when FVIII can be raised to an appropriate therapeutic level, because it avoids the expense and potential hazards of using a clotting factor concentrate, and it lowers the risk of inhibitor formation.**<sup>62; 138</sup>

4.3.4 Desmopressin *does not affect FIX levels* and is therefore of no value in haemophilia B.

4.3.5 **Each patient's response should be tested before therapeutic use of desmopressin, because there are significant differences between individuals.**<sup>62; 138</sup>

4.3.6 **Desmopressin is particularly useful in the treatment or prevention of bleeding in carriers of haemophilia.**<sup>139</sup>

4.3.7 **Although desmopressin is not licensed for use in pregnancy, there is evidence that it can be safely used during delivery and in the postpartum period in an otherwise normal pregnancy. Its use should be avoided in pre-eclampsia and eclampsia because of the already high levels of VWF.**<sup>140-141</sup>

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

4.3.9 Desmopressin may also be useful to control bleeding and reduce the prolongation of bleeding time associated with disorders of haemostasis, including some congenital platelet disorders.

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

#### Dosage and administration

4.3.11 Although desmopressin is given subcutaneously in most patients, it can also be administered by intravenous infusion. It is important to choose the correct preparation of desmopressin because some lower dose preparations are used for other medical purposes. Intranasal preparations of DDAVP are not available at adequate concentration for use for this indication in Australia.

4.3.12 Appropriate preparations of desmopressin available in Australia include:

- 4 µg/ml for intravenous use
- 15 µg/ml for intravenous and subcutaneous use.

4.3.13 **A single dose of 0.3 µg/kg body weight, either by intravenous or subcutaneous route, can be expected to boost the level of FVIII between threefold and sixfold.**<sup>138; 142</sup>

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

4.3.15 The peak response is seen about 60 minutes after administration, whether given intravenously or subcutaneously.

- 4.3.16 **Closely spaced repetitive use of desmopressin over several days may result in decreased response (tachyphylaxis). Factor concentrates may be needed when higher factor levels are required for a prolonged period.**<sup>143</sup>
- 4.3.17 Rapid infusion of desmopressin may result in tachycardia, flushing, tremor and abdominal discomfort.
- 4.3.18 **As a result of the antidiuretic activity of desmopressin, water retention and hyponatraemia can be a problem. When repeated doses are given, the plasma osmolality or sodium concentration should be measured.**<sup>138; 144</sup>
- 4.3.19 Careful, regular assessment is needed in the postoperative setting to avoid potentially life-threatening hyponatraemia, although this is uncommon in most adults.
- 4.3.20 **Due to water retention, desmopressin should be used with caution in young children and is contraindicated in children under 2 years of age, who are at particular risk of seizures secondary to cerebral oedema due to water retention.**<sup>145-146</sup>
- 4.3.21 **There are case reports of thrombosis (including myocardial infarction) after infusion of desmopressin. It should be used with caution in patients with a history, or who are at risk, of cardiovascular disease, particularly the elderly.**<sup>142</sup>

## Tranexamic acid

- 4.3.22 Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin.
- 4.3.23 Tranexamic acid promotes clot stability, and is useful as adjunctive therapy in haemophilia and some other bleeding disorders.<sup>147</sup>
- 4.3.24 **Regular treatment with tranexamic acid alone is of no value in the prevention of haemarthrosis in haemophilia.**<sup>147</sup>
- 4.3.25 **Tranexamic acid is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g. oral bleeding, epistaxis and menorrhagia).**<sup>59; 61; 148</sup>
- 4.3.26 **Tranexamic acid is particularly valuable in the setting of dental surgery, and may be used to control oral bleeding associated with eruption or shedding of teeth.**<sup>59; 149</sup>

### Dosage and administration

- 4.3.27 Tranexamic acid is usually given as an oral tablet, 25 mg/kg or up to 1.5 g in adults, three to four times daily. It can also be given by intravenous infusion two to three times daily, and is also available as a mouthwash.
- 4.3.28 GI upset (nausea, vomiting or diarrhoea) may occur as a side effect, but this is rare, and the symptoms usually resolve if the dosage is reduced. When administered intravenously, tranexamic acid must be infused slowly because rapid injection may result in dizziness and hypotension.
- 4.3.29 Tranexamic acid can be constituted as a suspension for topical use on bleeding mucosal lesions, particularly in the oral cavity.
- 4.3.30 Tranexamic acid is commonly prescribed for 7 days following dental extractions, to prevent postoperative bleeding.
- 4.3.31 Tranexamic acid is excreted by the kidneys and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.

- 4.3.32 The use of tranexamic acid is contraindicated for the treatment of haematuria because its use may prevent dissolution of clots in the ureters, leading to serious obstructive uropathy and potential permanent loss of renal function.
- 4.3.33 Similarly, tranexamic acid is contraindicated in the setting of thoracic surgery, where it may result in the development of insoluble haematomas.
- 4.3.34 **Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrates.**<sup>150</sup>
- 4.3.35 **Tranexamic acid should *not* be given to patients with FIX deficiency receiving PCC, because this will exacerbate the risk of thromboembolism.**<sup>151</sup>
- 4.3.36 **If treatment with both PCC and tranexamic acid is deemed necessary, it is recommended that at least 12 hours elapse between the last dose of activated PCC (APCC) and the administration of tranexamic acid.**<sup>151</sup>
- 4.3.37 **In contrast, thromboembolism is less likely when tranexamic acid is used in combination with recombinant activated factor VII (rFVIIa) to enhance haemostasis.**<sup>152</sup>



# 5

## Treatment of **specific** haemorrhages

## TREATMENT OF SPECIFIC HAEMORRHAGES

No.	PRACTICE POINT
PP 5.1	Bleeding in patients with haemophilia can occur at different sites, each of which require specific management.
PP 5.2	It is important that individuals with bleeding disorders and their families be educated about the symptoms and signs of bleeding disorders, and understand the benefit of prompt treatment.
PP 5.3	All patients with bleeding disorders should have a management plan documented, to be followed in the event of bleeding. Ideally, the plan should be documented on a treatment card generated from the Australian Bleeding Disorders Registry (see Section 1.2).
PP 5.4	As a general principle, in case of large internal haemorrhage or repeated intermittent bleeding, haemoglobin should be checked and corrected while other measures are being planned. Measures of haemodynamic stability, such as pulse and blood pressure, should be monitored as indicated.
PP 5.5	Appropriate rehabilitation is an important component of care following joint and muscle haemorrhage, and ideally should be guided by a physiotherapist familiar with the management of bleeding disorder patients.



## Significant change from the original World Federation of Hemophilia guidelines

- p) A summary of the findings of a systematic review evaluating the efficacy and safety of selective and nonselective nonsteroidal anti-inflammatory medications, and joint aspiration in acute joint haemorrhage are incorporated.

### 5.1 Joint haemorrhage (haemarthrosis)

- 5.1.1 A haemarthrosis (*joint bleed*) is defined as an episode of bleeding that is typically associated with loss of range of motion, pain or unusual sensation in the joint, swelling and warmth of the overlying skin.
- 5.1.2 The onset of bleeding in joints is frequently described by patients as a tingling sensation and tightness within the joint. This 'aura' precedes the appearance of clinical signs. In infants and babies the onset can be nonverbal; for example, 'favouring a limb', refusing to bear weight, irritability and crying.
- 5.1.3 The earliest clinical signs of a joint bleed are increased warmth over the area and discomfort with movement, particularly at the ends of range.
- 5.1.4 Later symptoms and signs include pain at rest, swelling, tenderness and extreme loss of motion.
- 5.1.5 A *re-bleed* is defined as worsening of the condition either on treatment or within 72 hours of stopping treatment.<sup>36</sup>
- 5.1.6 A *target joint* is a joint in which three or more bleeds without apparent cause have occurred within a consecutive 6-month period.
- 5.1.7 Following a joint bleed, flexion is usually the most comfortable position, and any attempt to change this position causes more pain.
- 5.1.8 Secondary muscle spasm follows as the patient tries to prevent motion and the joint appears 'frozen'.
- 5.1.9 The goal of treatment of acute haemarthrosis is to stop the bleeding as soon as possible. Ideally, this should occur as soon as the patient recognises the 'aura' or it is recognised that the child is not moving the joint or the limb, rather than after the onset of overt swelling and pain.
- 5.1.10 The patient should be evaluated clinically. Usually, X-rays are not indicated unless a history suggests significant trauma. In the absence of trauma, ultrasound examination may assist in distinguishing between an acute bleed and alternative causes of pain such as synovitis.
- 5.1.11 **An appropriate dose of factor concentrate should be administered, to raise the patient's factor level to a suitable level (see Table 7-1).**<sup>46; 54; 153-154</sup>
- 5.1.12 The definitions listed in Table 5-1 are recommended for the assessment of response to treatment of an acute haemarthrosis.<sup>36</sup>
- 5.1.13 **The patient should be instructed to avoid weight bearing, apply compression and elevate the affected joint.**<sup>46</sup>
- 5.1.14 **Appropriate analgesia may also be prescribed. Paracetamol-containing medications are recommended as first-line therapy, with rapid escalation of analgesia if required (see Section 1.9). Nonselective NSAIDs should be avoided (see Section 1.9.13).**
- 5.1.15 Consider immobilising the joint with a splint or casting until pain resolves.



- 5.1.16 Ice or cold packs may be applied around the joint for 15–20 minutes every 2–4 hours for pain relief, if found beneficial. Ice should not be applied in direct contact with skin.<sup>155</sup>
- 5.1.17 **If bleeding does not stop, a second infusion may be required. If so, half the initial loading dose should be repeated in 12 hours (haemophilia A) or 24 hours (haemophilia B).**<sup>46</sup>
- 5.1.18 Further evaluation is necessary if the patient's symptoms continue despite appropriate factor therapy. The presence of inhibitors, septic arthritis or fracture should be considered if symptoms and findings persist.
- 5.1.19 **Rehabilitation must be stressed as an active part of the management of acute joint bleeding episodes.**<sup>21; 46; 156</sup>
- As soon as the pain and swelling begin to subside, the patient should be encouraged to change the position of the affected joint from one of comfort to one of function, gradually decreasing the flexion of the joint and striving for complete extension.
  - This should be done as much as possible through active muscle contractions. Gentle supervised passive assistance may be used initially, but with caution if muscle inhibition is present.
  - Joint loading should be minimised during the initial 7–10 days after the bleed.
  - Early active muscle control must be encouraged, to minimise muscle atrophy and prevent chronic loss of joint motion.
  - Active exercises and proprioceptive training must be continued until the prebleed range of motion and functioning of joints are completely restored, and signs of acute synovitis have dissipated.<sup>157</sup> Physiotherapy supervision of rehabilitation is recommended.
  - If exercises are progressed judiciously, factor replacement is not necessarily required before exercising.

**Table 5-1 Definition of response to treatment of acute haemarthrosis**<sup>36</sup>

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

Note: The above definitions of response to treatment of an acute haemarthrosis relate to inhibitor-negative individuals with haemophilia. These definitions may require modification for inhibitor-positive patients receiving bypassing agents as haemostatic cover, or patients who receive factor concentrates with extended half-lives.

## Arthrocentesis

- 5.1.20 **Arthrocentesis (removal of blood from a joint) may be considered in the following situations:**<sup>46; 158-159</sup>
- a bleeding, tense and painful joint that shows no improvement 24 hours after conservative treatment
  - joint pain that cannot be alleviated
  - evidence of neurovascular compromise of the limb
  - unusual increase in local or systemic temperature, and other evidence of infection (septic arthritis).

- 5.1.21 Inhibitors should be considered as a reason if bleeding persists despite adequate factor replacement. The presence of inhibitors must be ruled out before arthrocentesis is attempted.
- 5.1.22 The early removal of blood should theoretically reduce its damaging effects on the articular cartilage.<sup>159</sup> If there is a large accumulation of blood, it will also decrease pain.
- 5.1.23 Arthrocentesis is best done soon after a bleed, and must be done under strictly aseptic conditions.
- 5.1.24 **When necessary, arthrocentesis should be performed under factor levels of at least 30–50 IU/dl for 48–72 hours. Arthrocentesis should not be done in circumstances where such factor replacement is not available. In the presence of inhibitors, other appropriate haemostatic agents should be used for the procedure, as needed.**<sup>46</sup>
- 5.1.25 A 19–21 gauge needle should be used.<sup>272</sup>
- 5.1.26 The joint should be immobilised with mild compression.
- 5.1.27 Weight bearing should be avoided for 24–48 hours.
- 5.1.28 Physiotherapy should be initiated as described above.

In patients with acute haemarthrosis, the routine use of joint aspiration (with or without administration of intra-articular steroids) to limit active synovitis and reduce the risk of recurrent bleeding is unclear. A systematic review was performed to evaluate the efficacy of joint aspiration and intra-articular steroid injection in patients with haemophilia with and without pre-existing haemophilic arthropathy or synovitis (Appendix C). The following conclusions were made after the available evidence was assessed using the GRADE criteria:

- a) In patients with haemophilia A and haemarthrosis of the knee, it is uncertain whether joint aspiration leads to bleeding episodes compared with no joint aspiration because the certainty of the evidence is very low.
- b) In patients with haemophilia A and acute, tense knee haemarthrosis, it is uncertain whether early joint aspiration (performed in the first 24 hours after the onset of symptoms) leads to better resolution of acute knee haemarthroses compared with no joint aspiration.
- c) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of joint aspiration on recurrent haemarthrosis.
- d) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of joint aspiration on development of a target joint.
- e) In patients with haemophilia A and haemarthrosis of the knee, it is uncertain whether joint aspiration (performed in the first 48 hours after the onset of symptoms) improves range of movement compared with no joint aspiration, because the certainty of the evidence is very low.
- f) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid on recurrent haemarthrosis.
- g) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid on development of a target joint.
- h) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid on bleeding rates or events.
- i) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid on development of or change in arthropathy.

Further research is therefore required to evaluate the routine use of joint aspiration (with or without the administration of intra-articular steroids) in the management of acute haemarthrosis.

## 5.2 Muscle haemorrhage

- 5.2.1 Muscle bleeds can occur in any muscle of the body, usually from a direct blow or a sudden stretch.
- 5.2.2 A muscle bleed is defined as an episode of bleeding into a muscle, determined clinically or by imaging studies, generally associated with pain or swelling and functional impairment; for example, a limp associated with a calf bleed.<sup>36</sup>
- 5.2.3 Early identification and proper management of muscle bleeds are important to prevent permanent contracture, re-bleeding and formation of pseudotumours.
- 5.2.4 Sites of muscle bleeding that are associated with neurovascular compromise (e.g. the deep flexor muscle groups of the limbs) require immediate management to prevent permanent damage and loss of function. These groups include:
- the iliopsoas muscle (risk of femorocutaneous, crural and femoral nerve palsy)
  - the superior-posterior and deep posterior compartments of the lower leg (risk of posterior tibial and deep peroneal nerve injury)
  - the flexor group of forearm muscles (risk of Volkmann's ischaemic contracture).
- 5.2.5 Bleeding can also occur in more superficial muscles such as the biceps brachii, hamstrings (triceps surae), gastrocnemius, quadriceps and the gluteal muscles.
- 5.2.6 Symptoms of muscle bleeds are:
- aching in the muscle
  - maintenance of the limb in a position of comfort
  - severe pain if the muscle is stretched
  - pain if the muscle is made to actively contract
  - tension and tenderness upon palpation and possible swelling.
- 5.2.7 **In the event of a muscle bleed, the patient's factor level should be raised as soon as possible, ideally when the patient recognises the first signs of discomfort or after trauma. If there is neurovascular compromise, the levels should be maintained for 5–7 days or longer, depending on resolution of symptoms (see Table 7-1).**<sup>160-162</sup>
- 5.2.8 Rest the injured part and elevate the limb.
- 5.2.9 Splint the muscle in a position of comfort and adjust to a position of function as pain allows.
- 5.2.10 Ice or cold packs may be applied around the muscle for 15–20 minutes every 4–6 hours for pain relief if found beneficial. Ice should not be applied in direct contact with skin.
- 5.2.11 **Repeat infusions are often required for 2–3 days, or much longer in the case of bleeds at critical sites causing compartment syndromes, or if extensive rehabilitation is required.**<sup>12; 51</sup>
- 5.2.12 **The patient should be monitored continuously for neurovascular compromise; fasciotomy may be required in some such cases.**<sup>163-164</sup>
- 5.2.13 The haemoglobin level should be checked and corrected if necessary, because muscle bleeds can result in significant blood loss.
- 5.2.14 **Physiotherapy should begin as soon as pain subsides and should be progressed gradually to restore full muscle length, strength and function.**<sup>161; 165</sup>
- 5.2.15 Factor coverage during this process is prudent, unless the physiotherapist is experienced with haemophilia management. Serial casting or splinting may be required. Supportive bracing will be required if there has been nerve damage.

- 5.2.16 Increasing pain during physical therapy can suggest re-bleeding and should be evaluated regularly.<sup>166</sup>

### Iliopsoas haemorrhage

- 5.2.17 Iliopsoas muscle haemorrhage has a unique presentation. Signs can include pain in the lower abdomen, groin or lower back, and pain on extension (but not on rotation) of the hip joint. There may be paraesthesia in the medial aspect of the thigh, or other signs of femoral nerve compression such as loss of patellar reflex and quadriceps weakness. The symptoms may mimic acute appendicitis, including a positive Blumberg's sign.
- 5.2.18 **When iliopsoas muscle haemorrhage occurs, the patient's factor level should *immediately* be raised, then maintained for 5–7 days or longer, as symptoms indicate (see Table 7-1).**<sup>167-169</sup>
- 5.2.19 **Hospitalisation should be considered for observation and control of pain, and *strict* bed rest should be maintained. Ambulation with crutches is *not* permitted, because ambulation requires contraction of the muscle.**<sup>167-169</sup>
- 5.2.20 **It is useful to confirm the diagnosis by medical imaging; that is, by ultrasonography, computed tomography (CT) scan or MRI. If clinically indicated, imaging may be required to monitor recovery.**<sup>167-169</sup>
- 5.2.21 **The patient's activity should be limited until pain resolves and hip extension improves. A carefully supervised program of physiotherapy is key to restoring full activity and function, and preventing re-bleeding. Restoration of complete hip extension before returning to full activity is recommended.**<sup>167-169</sup> **During the subacute recovery phase, progression of mobility using crutches can begin, using crutches as pain-free movement improves.**
- 5.2.22 If residual neuromuscular deficits persist, further orthotic support may be necessary.

## 5.3 Central nervous system haemorrhage or head trauma

- 5.3.1 **A central nervous system haemorrhage or head trauma is a medical emergency. It must first be treated, then investigated with relevant scans and blood tests.**
- 5.3.2 All post-traumatic head injuries (confirmed or suspected) and significant headaches (with or without vomiting) must be treated as intracranial bleeds. Sudden severe pain in the back may be associated with bleeding around the spinal cord. Do not wait for further symptoms to develop, or for laboratory or radiologic evaluation.
- 5.3.3 **When significant trauma or early symptoms occur, the patient's factor level should *immediately* be raised. Further doses will depend on imaging results. The factor level should be maintained until the aetiology has been defined. If a bleed is confirmed, the appropriate factor level should be maintained for 10–14 days (see Table 7-1).**<sup>170-171</sup>
- 5.3.4 **Intracranial haemorrhage may be an indication for prolonged secondary prophylaxis (3–6 months), especially where a relatively high risk of recurrence has been observed (e.g. in the presence of HIV infection).**<sup>170; 172-173</sup>
- 5.3.5 **Immediate medical evaluation and hospitalisation is required. A CT scan or MRI of the brain should be performed. Neurosurgical consultation should be sought as soon as possible.**<sup>174-175</sup>
- 5.3.6 Severe headache may also be a manifestation of meningitis in immunocompromised patients.

## 5.4 Throat and neck haemorrhage

- 5.4.1 Throat and neck haemorrhage is a medical emergency because it can lead to airway obstruction; the haemorrhage must first be treated, then evaluated.
- 5.4.2 When significant trauma or symptoms occur, the patient's factor level should *immediately* be raised, then maintained until symptoms resolve (see Table 7-1).<sup>12; 176-177</sup>
- 5.4.3 Hospitalisation and evaluation by a specialist is essential.<sup>12</sup>
- 5.4.4 To prevent haemorrhage in patients with severe tonsillitis, treatment with factor may be indicated, in addition to bacterial culture and treatment with appropriate antibiotics.

## 5.5 Acute gastrointestinal haemorrhage

- 5.5.1 In acute GI haemorrhage, the patient's factor levels should *immediately* be raised, then maintained until haemorrhage has stopped and the aetiology has been defined (see Table 7-1).<sup>178-179</sup>
- 5.5.2 Acute GI haemorrhage may present as haematemesis, haematochezia or melena.
- 5.5.3 For signs of GI bleeding or acute haemorrhage (or both) in the abdomen, medical evaluation and possibly hospitalisation are required.
- 5.5.4 **If shock is present it should be treated.** Haemoglobin levels should be checked and appropriate transfusion support given, with ongoing monitoring of haemoglobin if bleeding persists.
- 5.5.5 Investigation to identify and treat the origin of haemorrhage should be initiated, as indicated.
- 5.5.6 Tranexamic acid may be used as adjunctive therapy.

## 5.6 Acute abdominal haemorrhage

- 5.6.1 An acute abdominal (including retroperitoneal) haemorrhage can present with abdominal pain and distension, and can be mistaken for a number of infectious or surgical conditions. Such a haemorrhage may also present as a paralytic ileus. Appropriate radiologic studies may be necessary.
- 5.6.2 ***Immediately* raise the patient's factor levels. Maintain the factor levels (see Table 7-1) until the etiology can be defined, then treat appropriately in consultation with a specialist.**<sup>12; 176-177</sup>
- 5.6.3 **If shock is present it should be treated.** Haemoglobin levels should be checked, and appropriate transfusion support given, with ongoing monitoring of haemoglobin if bleeding persists.

## 5.7 Ophthalmic haemorrhage

- 5.7.1 Ophthalmic haemorrhage is uncommon unless associated with trauma or infection.
- 5.7.2 ***Immediately* raise the patient's factor level. Maintain the factor level as indicated (see Table 7-1).**<sup>12; 176-177</sup>
- 5.7.3 Have the patient evaluated by an ophthalmologist as soon as possible.

## 5.8 Renal haemorrhage

- 5.8.1 Painless haematuria should be treated with complete bed rest and vigorous hydration (3 litres/m<sup>2</sup> body surface area) for 48 hours. Desmopressin should be avoided when hydrating intensively.<sup>180</sup>
- 5.8.2 The patient's factor levels should be raised (see Table 7-1) if there is pain or persistent gross haematuria, and the patient should be monitored for clots and urinary obstruction.<sup>180-181</sup>
- 5.8.3 Antifibrinolytic agents must not be used in renal haemorrhage.<sup>180</sup>
- 5.8.4 Evaluation by a urologist is essential for evaluation of a local cause if haematuria (gross or microscopic) persists or if there are repeated episodes. A child with haematuria should be seen by a paediatrician, and an ultrasound of the kidneys and a urine microscopy and culture should be performed.

## 5.9 Oral haemorrhage

- 5.9.1 In oral haemorrhage with significant bleeding, early consultation with a dentist or an appropriate surgical specialist is recommended, to determine the source of bleeding. The most common causes are:
- dental extraction
  - gingival bleeding often due to poor oral hygiene
  - trauma.
- 5.9.2 Local treatments must be considered to treat the haemorrhage. These may include:
- direct pressure on the area using a damp gauze swab, maintained for at least 15 minutes
  - sutures to close the wound
  - application of local haemostatic agents
  - antibiotics, especially in gingival bleeding due to poor oral hygiene
  - use of tranexamic acid – an adult dose of 1 g three to four times per day, and a paediatric dose of 25 mg/kg three to four times per day are recommended; a standard mouthwash solution of 500 mg crushed and dissolved in 10 ml of saline may also be used
  - young children may be offered ice to suck (e.g. an icy pole).
- 5.9.3 An appropriate dose of regular paracetamol will help to control the pain.
- 5.9.4 Antifibrinolytic agents should not be used systemically in patients with FVIII inhibitors receiving APCC (e.g. factor eight inhibitor bypassing activity, FEIBA).<sup>147, 182</sup>
- 5.9.5 Factor replacement may be required, as directed by the haemophilia centre.
- 5.9.6 The patient should be advised to eat a soft diet for a few days.
- 5.9.7 If significant bleeding occurs, the patient should be evaluated and treated for anaemia as indicated.

## 5.10 Epistaxis

- 5.10.1 In the case of epistaxis, the patient's head should be placed in a forward position to avoid swallowing blood. Firm pressure with gauze soaked in ice water should be applied to the anterior, softer part of the nose for 10–20 minutes.
- 5.10.2 Factor replacement therapy is often not necessary unless there is ongoing evidence of continued bleeding or unless recurrent bleeding occurs.<sup>12; 176</sup>
- 5.10.3 Antihistamines and decongestant drugs are useful for bleeds specifically related to allergies, upper respiratory infections or seasonal changes. Topical steroids can also be helpful.
- 5.10.4 If bleeding is prolonged or occurs frequently, the patient should be evaluated for anaemia and treated appropriately.
- 5.10.5 Tranexamic acid applied locally in a soaked gauze may be helpful.
- 5.10.6 If bleeding is persistent or recurrent, an ear, nose and throat surgeon should be consulted. Anterior or posterior nasal packing may be needed to control bleeding.
- 5.10.7 Epistaxis can often be prevented by increasing the humidity of the environment, applying gels (e.g. Vaseline, or saline drops or gel) to the nasal mucosa to preserve moisture, or administering saline spray.

## 5.11 Soft tissue haemorrhage

- 5.11.1 Symptoms of soft tissue haemorrhage will depend on the site of the haemorrhage.
- 5.11.2 Factor replacement therapy is not necessary for most superficial soft tissue bleeding. The application of firm pressure and ice may be helpful.<sup>12; 176</sup>
- 5.11.3 The patient should be evaluated for severity of haemorrhage and possible muscular or neurovascular involvement. Also, it is important to rule out possible trauma to spaces containing vital organs, such as the head or abdomen.
- 5.11.4 Open compartmental haemorrhage – for example, in the retroperitoneal space, scrotum, buttocks or thighs – can result in extensive blood loss. If this situation is suspected, the haemorrhage should be immediately treated with factor.
- 5.11.5 Haemoglobin levels and vital signs should be regularly monitored if bleeding is in an open compartment.

## 5.12 Lacerations and abrasions

- 5.12.1 Superficial lacerations should be treated by cleaning the wound, then applying pressure and steri-strips.
- 5.12.2 **For deep lacerations, the factor level should be raised (see Table 7-1), and the lacerations then sutured.**<sup>12; 176-177</sup>
- 5.12.3 Sutures may be removed under cover of factor concentrate.



# 6

## Complications of haemophilia



## COMPLICATIONS OF HAEMOPHILIA

No.	PRACTICE POINT
PP 6.1	Musculoskeletal complications are common in patients with haemophilia, and are best managed through a multidisciplinary approach that includes input from physiotherapy and musculoskeletal experts (including rheumatology or orthopaedics specialists, or both).
PP 6.2	Acute synovitis should be managed aggressively to reduce the risk of the development of chronic complication. Adequate factor replacement, pain control and physiotherapy input are important. Other interventions require further investigation.
PP 6.3	Chronic arthropathy management requires a multimodal approach. Strategies to delay the time to joint replacement are important.
PP 6.4	Inhibitor management is often complex. Management of new patients with inhibitors, including tolerisation, should be referred to the Australian Haemophilia Centre Directors' Organisation Tolerisation Advisory Committee for discussion.
PP 6.5	Transfusion-related infection with HIV and the hepatitis viruses has been an important cause of morbidity and mortality in the haemophilia community. The ongoing treatment and monitoring for complications of these conditions in liaison with other speciality teams (including infectious disease and hepatology) is an important role of haemophilia treatment centres.

## Significant changes from the original World Federation of Hemophilia guidelines

- q) The results of a systematic review regarding the efficacy and safety of selective and nonselective NSAIDs and intra-articular steroid in the management of synovitis and chronic arthropathy are incorporated.
- r) Chemical synovectomy is not generally recommended.
- s) The role of the AHCCO Tolerisation Advisory Committee (TAC) as a resource to guide the management of patients with inhibitors is emphasised.
- t) The role of triple therapy in HCV management is added.

## 6.1 Musculoskeletal complications

- 6.1.1 The most common sites of bleeding are the joints and muscles of the extremities.
- 6.1.2 Depending on the severity of the disease, bleeding episodes may be frequent and without apparent cause (see Table 1-1).
- 6.1.3 In a child with severe haemophilia, the first haemarthrosis typically occurs when the child begins to crawl and walk; this is usually before 2 years of age, but occasionally later.
- 6.1.4 If haemophilia is 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.<sup>51; 183</sup>

### Synovitis

- 6.1.5 Following acute haemarthrosis, the synovium becomes inflamed, and is hyperaemic and extremely friable.
- 6.1.6 Failure to manage acute synovitis may result in repeated haemarthroses.<sup>51; 183</sup>
- 6.1.7 In patients who develop acute synovitis, developing joint protection through the use of a removable splint or compressive bandaging or appropriate gait aid should be considered.
- 6.1.8 Activities and weight bearing should be restricted until swelling and temperature of the joint return to baseline.
- 6.1.9 In some cases, COX-2 inhibitors may be useful.

A systematic review was performed to evaluate the efficacy and safety of COX-2 inhibitors in patients with haemophilia, with and without pre-existing haemophilic arthropathy or synovitis (Appendix C). The following conclusions were made after available evidence was assessed using the GRADE criteria:

- a) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the impact of COX-2 inhibitors on recurrent haemarthrosis.
- b) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the impact of COX-2 inhibitors on development of a target joint.
- c) Although COX-2 inhibitors are used in patients with acute synovitis, the impact of their use on the rate of further bleeding events or the development of a target joint is uncertain. Further evaluation in properly performed studies is warranted before routine use can be recommended.

- 6.1.10 Range of motion is preserved in the early stages of the disease. Differentiation between haemarthrosis and synovitis is difficult, particularly in patients who have established target joints. Expert rheumatology and physiotherapy review is critical.
- 6.1.11 The presence of synovial hypertrophy may be confirmed by MRI or ultrasonography. MRI will also assist in defining the extent of osteochondral changes.
- 6.1.12 Chronic synovitis occurs when repeated bleeding leads to the synovium becoming chronically inflamed and hypertrophied, and the joint appearing swollen (this swelling is usually not tender to touch). As above, expert rheumatology and physiotherapy review is recommended to ensure accurate diagnosis and appropriate treatment.
- 6.1.13 As the swelling continues to increase, articular damage, muscle atrophy and loss of motion will progress to chronic haemophilic arthropathy. A joint can have changes of chronic haemophilic arthropathy but still have episodes of bleeding with acute synovitis. In such cases, treatment of the acute synovitis is necessary because this, rather than the mechanical arthropathy, is usually the cause of pain and swelling.
- 6.1.14 **The goal of treatment is to deactivate the synovium as quickly as possible and preserve joint function.**<sup>159; 184</sup> Options include:
- **factor concentrate replacement, ideally given with the frequency and at a dose sufficient to prevent recurrent bleeding**<sup>28-30; 185</sup>
  - short treatment courses (6–8 weeks) of secondary prophylaxis with intensive clotting factor replacement
  - **physiotherapy**,<sup>21; 165</sup> including:
    - daily exercise to improve muscle strength and maintain joint motion
    - modalities to reduce secondary inflammation, if available<sup>186</sup>
    - functional training<sup>187</sup>
  - **a course of NSAIDs (COX-2 inhibitors), which may reduce inflammation (see point 6.1.9 above)**<sup>48-49</sup>
  - functional bracing, with physiotherapy oversight where possible, 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<sup>26</sup>
  - synovectomy.

The role of intra-articular steroids to limit active synovitis and reduce the risk of recurrent bleeding is unclear. A systematic review was performed to evaluate the efficacy of intra-articular steroid injection in patients with haemophilia, with and without pre-existing haemophilic arthropathy or synovitis (Appendix C). The following conclusions were made after available evidence was assessed using the GRADE criteria:

- a) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid injection on recurrent haemarthrosis.
- b) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid on development of a target joint.
- c) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid on bleeding rates or events.
- d) In patients with haemophilia and haemophilic arthropathy, no studies were found that evaluated the effect of intra-articular steroid on development of or change in arthropathy.
- e) Further studies to assess the efficacy and safety of intra-articular steroid injection in patients with haemophilia and acute synovitis are warranted.

## Synovectomy

- 6.1.15 **Synovectomy should be considered if chronic synovitis persists with frequent recurrent bleeding that is not controlled by other means. Options for synovectomy include radioisotopic synovectomy, and arthroscopic or open surgical synovectomy. Removal of the synovium should only be considered in haemophilia treatment centres that have experience with this procedure.**<sup>188-189</sup>
- 6.1.16 Nonsurgical synovectomy is the procedure of choice.
- 6.1.17 **Radioisotopic synovectomy (performed in Australia using yttrium-90) is highly effective, has few side effects and can be accomplished in an outpatient setting.**<sup>190-191</sup>
- 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.
- 6.1.18 Chemical synovectomy has a limited role in the Australian setting.
- 6.1.19 Surgical synovectomy, whether open or arthroscopic, requires cover with clotting factor for both surgery and the rehabilitation period. The procedure must be performed by an experienced team at a dedicated haemophilia treatment centre. It should be considered only when other less invasive procedures fail.

## Chronic haemophilic arthropathy

- 6.1.20 Chronic haemophilic arthropathy can develop at any time from the second decade of life (and sometimes earlier), depending on the severity of bleeding and its treatment. It is less common in Australia than elsewhere, because of the ready availability of clotting factor concentrate in Australia.
- 6.1.21 The process is set in motion by the immediate effects of blood on the articular cartilage during haemarthrosis;<sup>51; 183</sup> it is reinforced by persistent chronic synovitis and recurrent haemarthroses, resulting in irreversible damage.

- 6.1.22 With advancing cartilage loss, a progressive arthritic condition develops that includes:
- secondary soft tissue contractures
  - muscle atrophy
  - angular deformities.
- 6.1.23 Deformity can also be enhanced by contracture following muscle bleeds or neuropathy.
- 6.1.24 Loss of motion is common, with flexion contractures causing the most significant functional loss.
- 6.1.25 Joint motion and weight bearing can be extremely painful.
- 6.1.26 As the joint deteriorates, swelling usually subsides due to progressive fibrosis of the synovium and the capsule.
- 6.1.27 If the joint becomes ankylosed, pain may diminish or disappear.
- 6.1.28 The radiographic features of chronic haemophilic arthropathy depend on the stage of involvement:
- radiographs will show only late osteochondral changes<sup>192-193</sup>
  - ultrasound or MRI examination will show early soft tissue and osteochondral changes<sup>194-196</sup>
  - bony erosions and subchondral bone cysts will develop, causing collapse of articular surfaces, which can lead to angular deformities
  - fibrous or bony ankylosis may be present.<sup>197</sup>
- 6.1.29 The goals of treatment are to improve joint function, relieve pain and assist the patient to continue or resume normal activities of daily living.
- 6.1.30 Treatment options for chronic haemophilic arthropathy depend on:
- the stage of the condition
  - the patient's symptoms
  - the impact of the condition on the patient's lifestyle and functional abilities.
- Patients with chronic haemophilic arthropathy should ideally be reviewed by a multidisciplinary team that includes a physiotherapist and a musculoskeletal medical specialist.
- 6.1.31 **Pain should be controlled with appropriate analgesics. Certain COX-2 inhibitors may be used to relieve arthritic pain (see Section 1.9).**<sup>48-49</sup>
- 6.1.32 **Supervised physiotherapy aiming to preserve muscle strength and functional ability is an important part of management at this stage. Secondary prophylaxis may be necessary if recurrent bleeding occurs, and may be timed with physiotherapy to optimise outcomes.**<sup>21; 165</sup>
- 6.1.33 Other conservative management techniques include:
- serial casting to assist in correcting deformities<sup>198-199</sup>
  - bracing and orthotics to support painful and unstable joints<sup>26</sup>
  - 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.<sup>200</sup>
- 6.1.34 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
  - osteotomy to correct angular deformity
  - prosthetic joint replacement for severe disease involving a major joint (knee, hip, shoulder or elbow)<sup>201</sup>

- elbow synovectomy with radial head excision<sup>202</sup>
- 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 people with haemophilia in the future.<sup>203-204</sup>

Strategies should be developed to delay the time to first prosthetic joint replacement, because of the life expectancy of joint replacements and the increasing level of difficulty and complications with each subsequent replacement.

- 6.1.35 **Adequate resources – including sufficient factor concentrates and postoperative rehabilitation – must be available in order to proceed with any surgical procedure.**<sup>53-54; 205</sup>

## Principles of physiotherapy and physical medicine in haemophilia

- 6.1.36 Physiotherapists and occupational therapists should be part of the core haemophilia team. Their involvement with patients and their families should begin at the time of diagnosis, and they remain important to the patient throughout that person's lifespan.
- 6.1.37 The role of physiotherapists and occupational therapists in the management of the patient with haemophilia includes the following:<sup>46; 157; 165; 206</sup>
- assessment:
    - determining the site of an acute bleed
    - regular assessment throughout life
    - preoperative assessment
    - differential diagnosis of acute bleeds, acute or chronic synovitis, arthropathy and other musculoskeletal pathology
  - education:
    - of the patient and family regarding musculoskeletal complications and their prevention and management
    - 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
    - of other health-care providers as appropriate, and of work places and community groups such as sporting clubs
  - treatment of acute and subacute bleeds, chronic synovitis, chronic arthropathy and other musculoskeletal pathology
  - postbleed rehabilitation, including ongoing exercise programs for restoration of premorbid status, minimising re-bleed risk, and prevention of secondary musculoskeletal complications.
- 6.1.38 Podiatry input regarding the potential benefit of orthotics is also of benefit in targeted patients, particularly those with ankle arthropathy.

## Pseudotumours

- 6.1.39 Pseudotumour formation, although uncommon in Australia, is a potentially limb- and life-threatening condition unique to haemophilia. It occurs as a result of inadequately treated soft tissue bleeds, usually in muscle adjacent to bone, which can then be secondarily involved. It is most commonly seen in a long bone or the pelvis.
- 6.1.40 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.

- 6.1.41 Diagnosis is made by the physical finding of a localised mass.
- 6.1.42 Radiographic findings include a soft tissue mass with adjacent bone destruction.
- 6.1.43 A more detailed and accurate evaluation of a pseudotumour can be obtained with CT scan and MRI.
- 6.1.44 Management of pseudotumour depends on the site, size, rate of growth and effect on adjoining structures. Options include factor replacement and monitoring, aspiration and surgical ablation.
- **A 6-week course of treatment with factor is recommended, followed by repeat MRI. If the tumour is decreasing, factor should be continued and MRI repeated for three cycles.**<sup>207-208</sup>
  - If necessary, the patient should proceed to surgery, 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.**<sup>209-210</sup>
  - 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 haemophilia; surgery must only be performed by teams with experience in haemophilia.

## Fractures

- 6.1.45 Fractures are not frequent in people with haemophilia, possibly due to lower levels of ambulation and intensity of activities.<sup>211</sup> Nevertheless, with an increase in quality of life and life expectancy, fractures may become more common, particularly in patients of advanced age. A person with haemophilic arthropathy may be at risk for fractures around joints that have significant loss of motion and in bones that are osteoporotic.
- 6.1.46 **Treatment of a fracture requires immediate factor concentrate replacement.**<sup>211-213</sup>
- 6.1.47 **Clotting factor levels should be raised to at least 50% and maintained for 3–5 days.**<sup>159; 211-213</sup>
- 6.1.48 Lower levels may be maintained for 10–14 days while the fracture becomes stabilised and to prevent soft tissue bleeding.
- 6.1.49 The management plan should be appropriate for the specific fracture, including operative treatment under appropriate coverage of clotting factor concentrates.
- 6.1.50 **Circumferential plaster should be avoided; splints are preferred.**<sup>211</sup>
- 6.1.51 Compound or infected fractures may require external fixators.<sup>214</sup>
- 6.1.52 **Prolonged immobilisation, which can lead to significant limitation of range of movement in the adjacent joints, should be avoided.**<sup>211-212</sup>
- 6.1.53 Physiotherapy should be started as soon as the fracture is stabilised, to restore range of motion, muscle strength and function.<sup>206</sup>
- 6.1.54 Treatment should be in collaboration with a recognised haemophilia treatment centre.

## Principles of orthopaedic surgery in haemophilia

Section 1.10 outlines important considerations related to performing surgical procedures in people with haemophilia. Specific issues in relation to orthopaedic surgery include:

- 6.1.55 Orthopaedic surgeons should have undergone specific training in surgical management of people with haemophilia.<sup>159</sup>

- 6.1.56 **Performing multiple site elective surgery in a simultaneous or staggered fashion to use clotting factor concentrates judiciously should be considered.**<sup>215</sup>
- 6.1.57 **Local coagulation enhancers may be used. Fibrin glue is useful to control oozing when operating in extensive surgical fields.**<sup>53; 216-217</sup>
- 6.1.58 **Postoperative care in patients with haemophilia requires closer monitoring of pain and, often, higher doses of analgesics in the immediate postoperative period.**<sup>53</sup>
- 6.1.59 Good communication with the postoperative rehabilitation team is essential.<sup>206</sup> Knowledge of the details of the surgery performed and intraoperative joint status will facilitate planning of an appropriate rehabilitation program.
- 6.1.60 Postoperative rehabilitation should be carried out by a physiotherapist experienced in haemophilia management.
- 6.1.61 Rehabilitation may have to progress more slowly in people with haemophilia.
- 6.1.62 Adequate pain control is essential to allow appropriate exercise and mobilisation.
- 6.1.63 These principles also apply to fixation of fractures and excision of pseudotumours.

## 6.2 Inhibitors

- 6.2.1 In haemophilia, 'inhibitors' refer to immunoglobulin G (IgG) antibodies that neutralise clotting factors.
- 6.2.2 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 haemophilia.
- 6.2.3 The presence of a new inhibitor should be suspected in any patient who fails to respond clinically to clotting factors, particularly if the patient has been previously responsive. In this situation, the expected recovery and half-life of the transfused clotting factor are severely diminished.
- 6.2.4 Inhibitors are more frequently encountered in people with severe haemophilia than in those with moderate or mild haemophilia.
- 6.2.5 The cumulative incidence (i.e. lifetime risk) of inhibitor development in severe haemophilia A is about 20–30%, and in moderate or mild disease it is about 5–10%.<sup>218-219</sup>
- 6.2.6 In severe haemophilia A, the median age of inhibitor development is 3 years or less in developed countries. In moderate or mild haemophilia A, it is closer to 30 years of age, and is often seen in conjunction with intensive FVIII exposure with surgery.<sup>56; 220</sup>
- 6.2.7 In severe haemophilia, inhibitors do not change the site, frequency or severity of bleeding. In moderate or mild haemophilia, the inhibitor may neutralise endogenously synthesised FVIII, thereby effectively converting the patient's phenotype to 'severe'.
- 6.2.8 Bleeding manifestations in moderate or mild haemophilia complicated by an inhibitor are more frequently reminiscent of those seen in patients with acquired haemophilia A (due to autoantibodies to FVIII), with a greater predominance of mucocutaneous, urogenital and GI bleeding sites.<sup>221</sup> Consequently, the risk of severe complications or even death from bleeding may be significant in these patients.
- 6.2.9 Inhibitors are much less frequently encountered in haemophilia B, occurring in less than 5% of affected individuals.<sup>222</sup>



- 6.2.10 In all cases, inhibitors render treatment with replacement factor concentrates difficult. Patients on clotting factor therapy should therefore be screened for development of inhibitors.
- 6.2.11 **Confirmation of the presence of an inhibitor and quantification of the titre is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay.**
- 6.2.12 **For children, inhibitors should be screened once every 5 exposure days until 20 exposure days, then every 10 exposure days between 21 and 50 exposure days, and at least two times a year until 150 exposure days.**<sup>20</sup>
- 6.2.13 **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.**<sup>56; 223–225</sup>
- 6.2.14 **Inhibitors should also be assessed in all patients who have been intensively treated for more than 5 days, within 4 weeks of the last infusion.**<sup>224; 226</sup>
- 6.2.15 **Inhibitors should also be assessed before surgery or if recovery assays are not as expected, and when clinical response to treatment of bleeding is suboptimal in the postoperative period.**<sup>55; 218; 224</sup>
- 6.2.16 A low-responding inhibitor is defined as an inhibitor level that is persistently below 5 Bethesda units (BU)/ml, whereas a high-responding inhibitor is defined by a level of at least 5 BU/ml.
- 6.2.17 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 3–5 days when challenged again with specific factor products.
- 6.2.18 Some low-titre inhibitors may be transient, disappearing within 6 months of initial documentation, despite recent antigenic challenge with factor concentrate.
- 6.2.19 Very low titre inhibitors may not be detected by the Bethesda inhibitor assay, but by a poor recovery or shortened half-life ( $T-1/2$ ), or both, following infusions of clotting factor.

## Management of bleeding

- 6.2.20 **Management of bleeding in patients with inhibitors must be in consultation with a haemophilia treatment centre experienced in the management of such patients.**<sup>17; 224</sup>
- 6.2.21 **Choice of treatment product should be based on titre of inhibitor, records of clinical response to product, and site and nature of bleed.**<sup>224; 227</sup>
- 6.2.22 **Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralise the inhibitor with excess factor activity and stop bleeding.**<sup>224; 227</sup>
- 6.2.23 **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 3–5 days, precluding further treatment with concentrates that only contain the missing factor.**<sup>224; 227</sup>
- 6.2.24 With an inhibitor level of more than 5 BU, it is unlikely that specific factor replacement will be effective in overwhelming the inhibitor without ultra-high-dose continuous infusion therapy.
- 6.2.25 Alternative agents include bypassing agents such as rFVIIa and PCC, including APCC.
- 6.2.26 **The efficacy of two doses of rFVIIa and one dose of APCC for management of joint bleeding has been shown to be essentially equivalent.**<sup>228</sup>
- 6.2.27 **Some patients respond better to one agent than the other, highlighting the need to individualise therapy.**<sup>228–229</sup>

- 6.2.28 An anamnestic immune response should be expected in patients with haemophilia B and a FIX inhibitor treated with PCC – whether activated or not – since these concentrates all contain FIX.
- 6.2.29 On the other hand, the risk of anamnesis in patients with haemophilia A and an inhibitor treated with PCC or APCC 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 about 30% of FVIII inhibitor patients.
- 6.2.30 Although there has been interest in the use of immunosuppressive therapies in patients with inhibitors, their role has not yet been defined, and there is no consensus as to whether they have a place in the management of these patients.

## Allergic reactions in patients with haemophilia B

- 6.2.31 Up to 50% of haemophilia B patients with inhibitors may have severe allergic reactions, including anaphylaxis, to FIX administration. Such reactions can be the first symptom of inhibitor development.
- 6.2.32 **Newly diagnosed haemophilia B patients, particularly those with a family history 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.**<sup>118; 230</sup>

## Immune tolerance induction

- 6.2.33 **Immune tolerance induction (ITI) is supported and monitored by the AHCDO Tolerisation Advisory Committee (TAC). It is recommended that all new cases of high titre inhibitors are referred to the TAC for discussion, and that AHCDO should have a central role in coordinating cases of ITI.**
- 6.2.34 **In patients with severe haemophilia A, eradication of inhibitors is often possible by ITI therapy.**<sup>230–231</sup>
- 6.2.35 **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 also develop an anamnestic response to the inactive FVIII molecules in APCC.**<sup>232</sup>
- 6.2.36 An optimal regimen (product or dose) for ITI has not yet been defined. An international trial comparing 50 IU/kg three times a week to 200 IU/kg daily was stopped recently due to safety concerns (a higher number of intercurrent bleeds in the low-dose arm), pending detailed analysis and interpretation of the data.<sup>233</sup> A typical regimen is 100 IU/kg/day rFVIII with review by the TAC, followed by reassessment every 3 months, with escalating treatment in difficult cases. Alternatively, cases that pose a particular high risk of failure (e.g. strong family history or multidomain gene deletion) may use either a higher dose or plasma-derived products.
- 6.2.37 Response to ITI may be less favourable in patients with moderate or mild haemophilia.<sup>224</sup> Optimal management of patients with mild and moderate haemophilia with inhibitors should be a focus of ongoing research.
- 6.2.38 Experience with ITI for haemophilia B patients with inhibitors is limited. The principles of treatment in these patients are similar, but the success rate is much lower, especially in those in whom the inhibitor is associated with an allergic diathesis.
- 6.2.39 Haemophilia B patients with inhibitors and 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, have been reported to be successful.<sup>234</sup>

## Patients switching to different concentrates

- 6.2.40 For the vast majority of patients, switching products does not lead to inhibitor development.
- 6.2.41 In rare instances, inhibitors in previously treated patients have occurred with the introduction of new FVIII concentrates.
- 6.2.42 In such patients, the inhibitor usually disappears after withdrawal of the new product.
- 6.2.43 **Patients switching to a new factor concentrate should be monitored for inhibitor development before and after switching product.**<sup>218</sup>

## 6.3 Transfusion-transmitted and other infection-related complications

- 6.3.1 In the 1980s and early 1990s, the emergence and transmission of HIV, HBV and HCV through clotting factor products resulted in high mortality of people with haemophilia.<sup>235-236</sup> Experience from a single centre in Australia suggests that up to 50% of people exposed to clotting factor during the 'at-risk' period may have a bloodborne viral infection, with this figure rising to >80% in individuals with severe haemophilia due to increased product exposure.<sup>237</sup>
- 6.3.2 Many studies conducted all over the world indicate that HIV, HBV and HCV transmission through factor concentrate has been almost completely eliminated.<sup>238-239</sup>
- 6.3.3 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 the development of more sensitive diagnostic technologies for detection of various pathogens.<sup>240</sup>
- 6.3.4 Recombinant factor concentrates have been adopted over the past two decades, particularly in developed countries. Recombinant products have contributed significantly to the reduction of infection risk.
- 6.3.5 The challenge of emerging and re-emerging infections remains, and many of these infections may not be amenable to current risk-reduction measures. These include the nonlipid enveloped viruses and prions, for which diagnosis and elimination methods are still a challenge.<sup>239; 241-242</sup>
- 6.3.6 New treatments are continually emerging in this rapidly changing field; hence, transfusion-transmitted infections in people with haemophilia are best managed by a specialist.

## Principles of management of HIV infection in haemophilia

- 6.3.7 Knowledge and expertise in the treatment of HIV-infected people with haemophilia is currently limited to case series and reports. HIV treatment in people with haemophilia is therefore largely informed by guidelines used in the nonhaemophilia population.
- 6.3.8 **As part of the haemovigilance program, all people with haemophilia 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.**<sup>114</sup>
- 6.3.9 **The diagnosis, counselling, initiation of treatment and monitoring of HIV, as well as the treatment of HIV-associated complications in infected people with haemophilia, should be the same as in the nonhaemophilic population.**<sup>243-244</sup>

- 6.3.10 **None of the currently available classes of anti-HIV drugs are contraindicated in people with haemophilia.**<sup>245-247</sup>

## Principles of management of HCV infection in haemophilia

- 6.3.11 Assessment of HCV in people with haemophilia should include:
- anti-HCV serology to determine exposure
  - HCV PCR in those who are anti-HCV positive
  - baseline viral load
  - HCV genotyping in those who are HCV PCR positive
  - liver function tests and noninvasive assessment of fibrosis and liver architecture, including through fibroscan.
- Diagnostic testing should be consistent with the Australian national policy.<sup>i</sup>
- 6.3.12 **The diagnosis, counselling, initiation of treatment and monitoring of HCV, and the treatment of HCV-associated complications in infected people with haemophilia, should be the same as in the nonhaemophilic population.**
- 6.3.13 New antiviral therapies – namely the direct-acting antiviral agents, usually given in combination – improve virologic response rates and are likely to be available in the lifetime of these guidelines.<sup>248</sup>
- 6.3.14 Where HCV eradication cannot be achieved, regular monitoring (every 6 months) for end-stage liver complication is recommended.<sup>249</sup> Clear communication is required between haemophilia treatment centre staff, hepatologists and other liver clinic staff, and the patient's general practitioner regarding planned monitoring and the delegation of responsibility for following up of results.

## Principles of management of HBV infection in haemophilia

- 6.3.15 **All people with haemophilia treated with plasma-derived products that are not adequately virus-inactivated should be screened for hepatitis B antigen and antihepatitis B at least every 6–12 months and whenever clinically indicated.**<sup>84</sup> Diagnostic testing should be consistent with the Australian national policy.<sup>i</sup>
- 6.3.16 Active HBV infection should be managed as per local infectious disease guidelines and protocols.
- 6.3.17 **Those without HBV immunity should be given the anti-HBV vaccine. Protective seroconversion should be rechecked following vaccination.**<sup>83-84; 250</sup>
- 6.3.18 **People with haemophilia who do not seroconvert should probably be revaccinated with double the dose of hepatitis B vaccine.**<sup>84; 251</sup>

## Principles of management of bacterial infection in haemophilia

- 6.3.19 The risk factors for bacterial infections in people with haemophilia are venous access catheter insertion, surgical arthroplasty and other surgical interventions.<sup>29; 252-253</sup>
- 6.3.20 In general, joint aspiration to treat haemarthrosis should be avoided, unless done early under appropriate cover of factor replacement and with strict aseptic precautions to prevent infection.<sup>254-255</sup>
- 6.3.21 Bleeding is likely to delay healing and worsen infection; therefore, it should be well controlled.<sup>256</sup>
- 6.3.22 Control of the source of infection is paramount in people with haemophilia.<sup>257-258</sup>

<sup>i</sup> <http://testingportal.ashm.org.au>





# 7

## Plasma factor level and duration of administration

## PLASMA FACTOR LEVEL AND DURATION OF ADMINISTRATION

No.	PRACTICE POINT
PP 7.1	Factor replacement may be <i>episodic</i> for the management of acute bleeding or surgery, or <i>prophylactic</i> to limit or prevent haemophilic arthropathy.
PP 7.2	Standard doses for prophylaxis in the Australian setting range from 25 to 40 IU/kg three times per week or on alternate days.
PP 7.3	Further research is required to define the optimal prophylaxis regimen and the long-term effectiveness of current dosing regimens.
PP 7.4	The duration and dosing of episodic therapy will depend on the severity of the haemophilia and the nature of the bleed or surgical procedure being managed.
PP 7.5	Dosing according to individual pharmacokinetic profile should be considered, particularly in patients undergoing major surgery.
PP 7.6	The presence of an inhibitor should be excluded in patients undergoing surgery. Follow-up inhibitor testing is also recommended 6–8 weeks after intense factor VIII exposure in patients with mild or moderate haemophilia A.



## Significant change from the original World Federation of Hemophilia guidelines

- u) Guidelines for factor concentrate dosing in a resource-constrained environment are removed.

## 7.1 Choice of factor replacement therapy protocols

- 7.1.1 The correlation shown in Figure 7-1 between possible factor replacement therapy protocols and overall outcome depicts the choices that need to be made when selecting doses and regimen of clotting factor concentrates.
- 7.1.2 Enabling a completely normal life should remain the ultimate goal of factor replacement therapy; however, this cannot be achieved immediately in people with haemophilia in all situations.
- 7.1.3 Table 7-1 presents commonly followed guidelines on plasma factor peak levels and duration of administration; the guidelines reflect the different practice in countries where there is no significant resource constraint.
- 7.1.4 The doses listed in Table 7-1 have been shown to avoid joint damage, but the optimal dose needed to achieve this has not yet been defined.
- 7.1.5 Observational studies documenting the musculoskeletal outcome of doses and protocols of factor replacement are extremely important in defining these issues.
- 7.1.6 Doses for prophylactic replacement of factor concentrates vary between different countries, and also among haemophilia treatment centres in the same country.
- 7.1.7 **A commonly used dosage for prophylactic factor replacement is 25–40 IU/kg three to four times weekly in countries with no significant resource constraints (see Section 1 for details).**<sup>185; 259-260</sup>

Figure 7-1 Strategies for clotting factor replacement at different ages and impact on outcomes

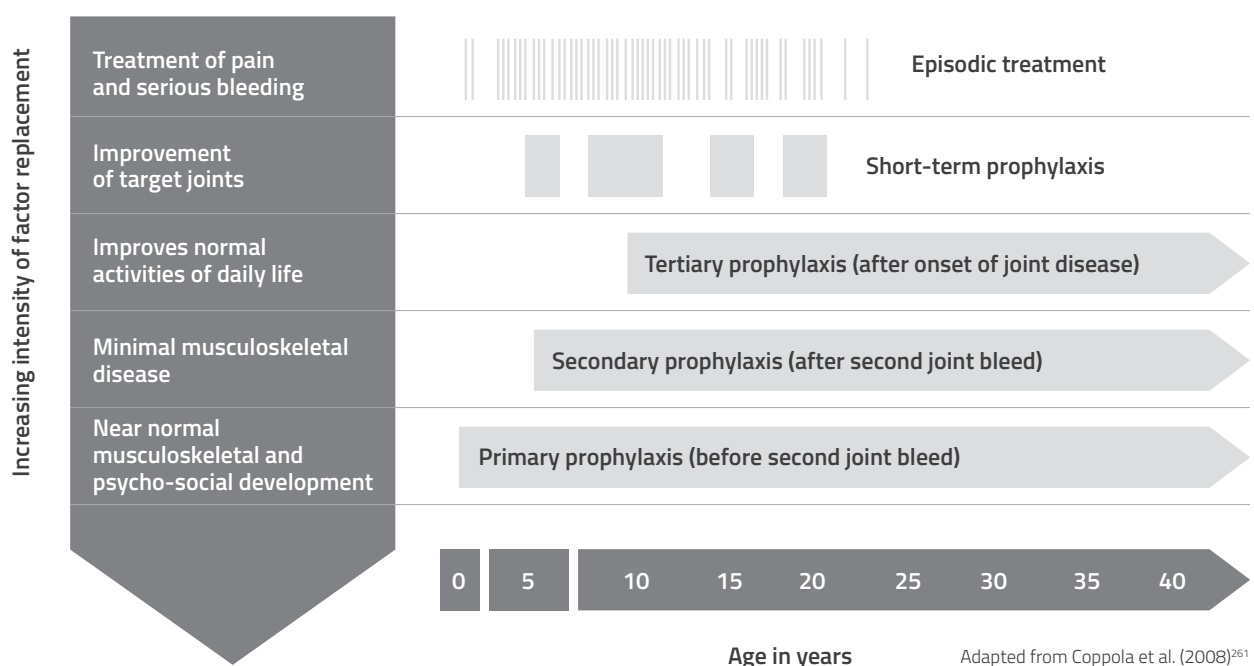





Table 7-1 Suggested plasma factor peak level and duration of administration (when there is no significant resource constraint)<sup>262</sup>

Type of haemorrhage	Haemophilia A		Haemophilia B	
	Desired level (IU/dl)	Duration (days)	Desired level (IU/dl)	Duration (days)
<b>Joint</b>	40–60	1–2, may be longer if response is inadequate	40–60	1–2, may be longer if response is inadequate
<b>Superficial muscle with no neurovascular compromise (except iliopsoas)</b>	40–60	2–3, may be longer if response is inadequate	40–60	2–3, may be longer if response is inadequate
<b>Iliopsoas and deep muscle with neurovascular injury, or substantial blood loss</b>				
▪ Initial	80–100	1	60–80	1–2
▪ Maintenance	30–60	3–5, may be longer owing to secondary prophylaxis during physiotherapy	30–60	3–5, may be longer owing to secondary prophylaxis during physiotherapy
<b>Central nervous system or head</b>				
▪ Initial	80–100	1–7	60–80	1–7
▪ Maintenance	50	8–21	30	8–21
<b>Throat and neck</b>				
▪ Initial	80–100	1–7	60–80	1–7
▪ Maintenance	50	8–14	30	8–14
<b>Gastrointestinal</b>				
▪ Initial	80–100	7–14	60–80	7–14
▪ Maintenance	50		30	
<b>Renal</b>	50	3–5	40	3–5
<b>Deep laceration</b>	50	5–7	40	5–7
<b>Surgery (major)</b>				
▪ Preoperative	80–100		60–80	
▪ Postoperative	60–80 40–60 30–50	1–3 4–6 7–14	40–60 30–50 20–40	1–3 4–6 7–14
<b>Surgery (minor)</b>				
▪ Preoperative	50–80		50–80	
▪ Postoperative	30–80	1–5, depending on type of procedure	30–80	1–5, depending on type of procedure



# 8

## The framework for management of bleeding disorders in Australia



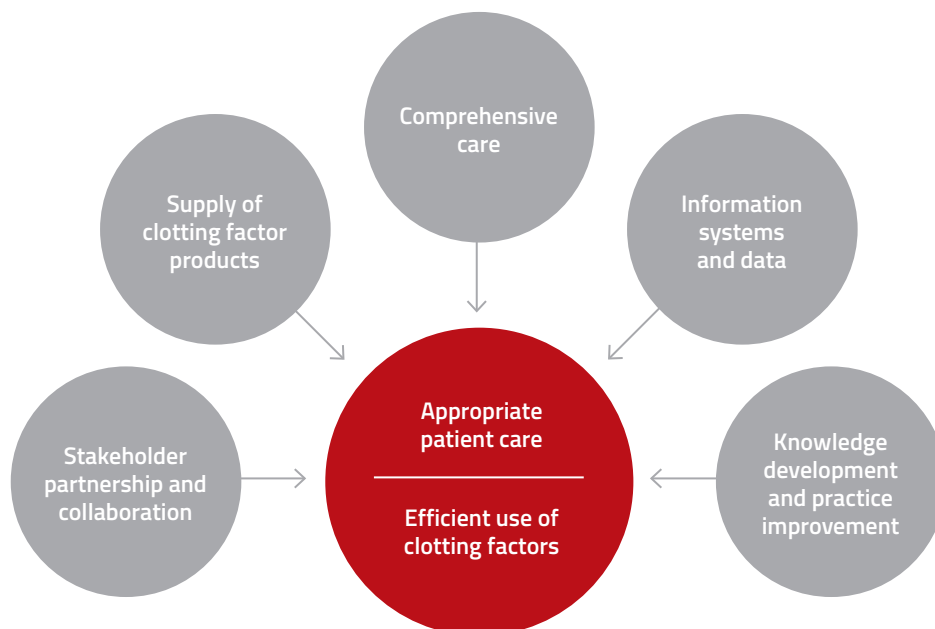
## 8.1 Introduction

Australia has a well-established framework of policy, funding, health service and stakeholder arrangements for the care of people with bleeding disorders.

Within this framework, five key elements (shown in Figure 8-1 and discussed below) contribute towards the following complementary objectives:

- ensuring an appropriate and high-quality standard of care for people with bleeding disorders
- ensuring an effective and efficient use of clotting factor products, which comprise a significant part of the treatment of many people with bleeding disorders.

Figure 8-1 Key elements of the Australian framework for management of bleeding disorders



## 8.2 Comprehensive care

Comprehensive care is a model of care that provides and coordinates hospital and outpatient care and associated services to people with bleeding disorders and their carers and families. The comprehensive care model seeks to ensure the coordinated management of all aspects of haemophilia by a multidisciplinary team with specialised expertise.

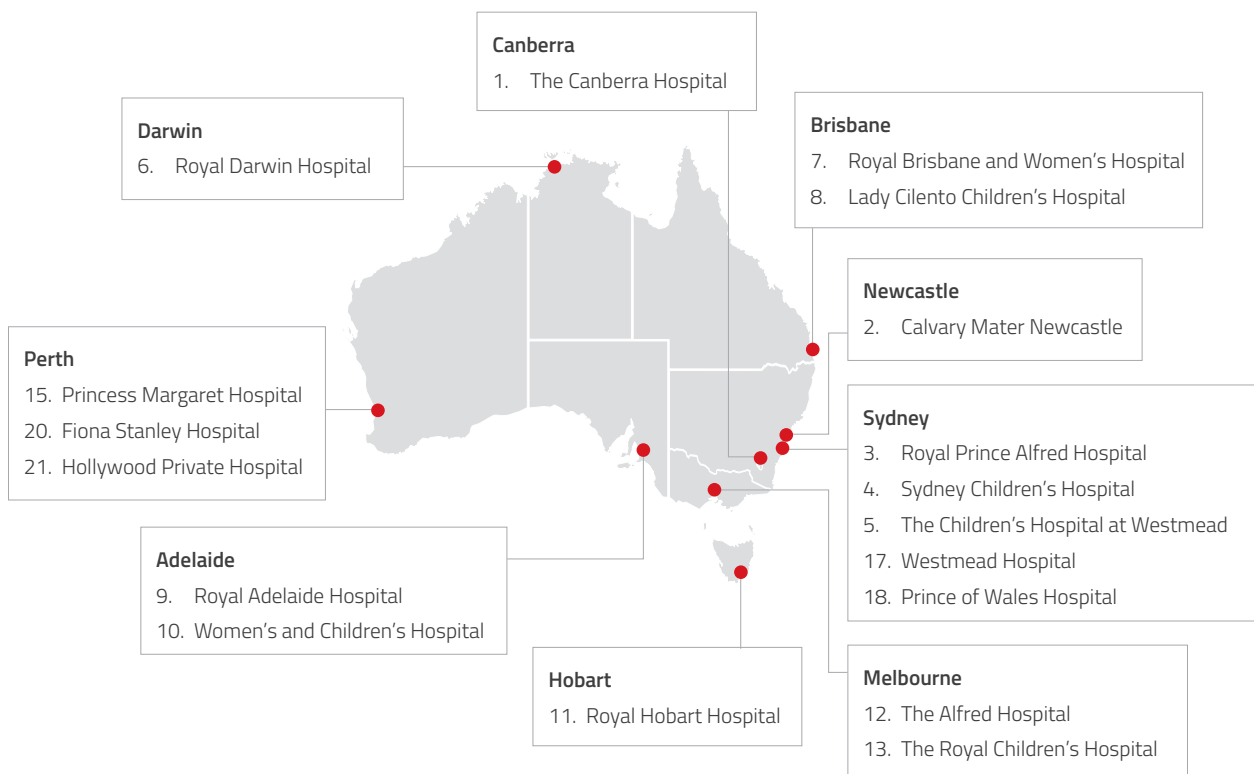
The identified benefits of comprehensive care include:

- reduced hospital days and treatment costs<sup>263</sup>
- reduced number of hospitalisation episodes, and decreases in school or work absences or unemployments<sup>264</sup>
- improved mortality and quality of life.<sup>16; 265</sup>

## Implementation of comprehensive care in Australia

In Australia, most people with haemophilia and other bleeding disorders receive care through specialist haemophilia treatment centres. Such centres were established following a decision by the Australian Health Ministers' Advisory Council in 1998, to provide a leadership role within their hospital, city and outlying areas to ensure optimal care and an equitable distribution of professional and therapeutic resources, together with responsible record keeping. The locations of these centres in Australia are shown in Figure 8-2.

**Figure 8-2** Location of haemophilia treatment centres



The operating concept of haemophilia treatment centres is to coordinate and, where possible, integrate patient care, research and education to provide the optimal use of expertise and resources within hospitals and the community. Specifically, the centres are intended to provide:

- coordination of the clinical management of patients with haemophilia and patients with other bleeding disorders; this includes:
  - access to specialist medical services, including haematology and nursing services
  - access to or coordination with other medical and allied health services including surgery, rheumatology, infectious diseases, dental and general practice services, and physiotherapy, social work and podiatry services
  - a counselling and advisory service for people with bleeding disorders and their families, including genetic counselling and family planning
  - a laboratory service able to carry out all investigations required for accurate diagnosis and effective management of bleeding disorders
  - a resource and potentially an outreach service for isolated patients with bleeding disorders and their treating clinicians.

- a single point of contact with responsibility for the coordination, allocation and distribution of therapeutic resources (i.e. coagulation products derived either from blood donors or recombinant technologies); this includes organisation and supervision of home therapy programs
- a system to record all relevant investigations, treatments, complications and adverse reactions, including data management resources (in Australia, this data should be recorded in the ABDR)
- the capability to participate in research, including clinical trials
- educational programs for medical staff and other personnel, and for people with bleeding disorders and their carers and families
- coordination and cooperation with patient groups supporting people with bleeding disorders and their carers and families.

The implementation of the model for haemophilia treatment centres varies between states and territories in relation to resourcing, availability of a relevant range of medical and allied health services, centralisation and organisation of services, and demographics of the patient population.

Some care for people with bleeding disorders is managed by clinicians or health services that are not associated with a haemophilia treatment centre. This may occur where a patient chooses to attend a private medical practitioner or health service, or where a bleeding disorder has not previously been identified and is initially diagnosed outside a centre, or becomes apparent as a complication of other medical treatment.

## 8.3 Supply of clotting factor products

A significant part of contemporary medical care of people with bleeding disorders is the use of clotting factor concentrates. These products are infused to replace the specific blood plasma protein that is not present or functional at adequate levels in that particular individual. The aim is to achieve sufficient levels of that blood plasma protein level to either avoid bleeding symptoms or to stop bleeding that has already occurred.

Clotting factors can be derived from human blood plasma through the plasma fractionation manufacturing process. Factors VIII, IX and VIIa are also able to be manufactured by commercial-scale expression from recombinant technology. Although current plasma-derived clotting factors have an excellent safety record, recombinant products, where available, are preferred by patients and clinicians due to the lower risk of transmission of diseases that are theoretically transmissible through human plasma. A number of manufacturers have new versions of recombinant clotting factor products in development.

Clotting factor products may be used to treat and manage bleeding disorders in a number of ways:

- 'on demand' treatment for specific bleed events
- short-term prophylaxis to cover a specific surgery or other high-risk interventions or activities
- immune tolerisation therapy, or bypass therapy, in cases where a patient has developed inhibitory antibodies to first-line clotting factor therapy
- routine prophylaxis to maintain functional trough levels of clotting factor sufficient to prevent bleeding occurring.

### Supply under national blood arrangements

Since 2003, clotting factor products have been supplied and funded in Australia through arrangements established under the National Blood Agreement. These arrangements provide an adequate, safe, secure and affordable supply of clotting factor products for the Australian health system. Products are supplied under these arrangements to meet clinical requirements in the scenarios above.

The National Blood Authority (NBA) conducts national tendering and contract negotiation for the supply of clotting factor products. The NBA manages the national contracts and makes payment for products supplied. Funding is provided to the NBA for this purpose by the Commonwealth and state and territory governments through the cost sharing arrangements under the National Blood Agreement. Successive tendering and negotiation rounds conducted by the NBA since 2003 have provided significant improvement in value for money for these products.

The national contracts managed by the NBA provide for supply of both plasma-derived and recombinant clotting factors (full access to which has been funded by Australian governments since 2005), from both Australian and imported sources. The NBA collaborates with AHCD0 and with state and territory representatives to undertake national supply planning, and to establish protocols for management of supply-risk scenarios that may eventuate. The National Blood Agreement also includes a process for evidence-based evaluation of proposals to add new or materially changed products into the national funding and supply arrangements.

In addition to a primary obligation to supply to meet orders, national supply contracts include obligations for holding of contingency supply reserves and other supplier obligations to ensure continuity of supply, as well as obligations to provide product support services and resources suitable for clinical personnel and (through a health-care provider) to patients. Suppliers are also required to provide services to support delivery of products direct to suitable patients, for home-based therapy under the supervision of a relevant haemophilia treatment centre.

In determining the specific requirements and approach for a national tendering round, the NBA seeks input from clinical and patient-group stakeholders and from industry, and obtains policy guidance from funding governments. Clinical and patient stakeholders are involved to provide expert or user input in the tender development and evaluation process.

For some products, the outcome of a tender process may involve a change in the specific brands of clotting factor products supplied under the national arrangements, and the NBA cooperates closely with clinical and patient stakeholders and with suppliers in planning and supporting the transition process between products.

## Other products

In addition to clotting factors, other pharmaceutical products, medical devices and therapeutic interventions may be important for the care of people with bleeding disorders. They may be supplied and funded outside the National Blood Agreement via hospital supply, or under the Pharmaceutical Benefits Scheme or Medicare Benefits Scheme. They include tranexamic acid, desmopressin, analgesia, antiviral therapy, immune modulating therapy, other fractionated blood products and mobility aids.

## 8.4 Stakeholder partnership and collaboration

The effective treatment and care of patients with bleeding disorders in Australia benefits from the involvement of a number of important clinical and patient stakeholder groups or organisations:

- **Haemophilia Foundation Australia (HFA)** and state and territory member bodies, which represent the Australian community of people with bleeding disorders and their carers and families. HFA is committed to improving treatment and care through representation and advocacy, education and the promotion of research.
- **Australian Haemophilia Centre Directors' Organisation (AHCD0)**, which is the national medical body for haemophilia and other bleeding disorders in Australia. The NBA provides funding to AHCD0 for a range of advice, services and management activities to support the effective management of bleeding disorders in Australia.



- A number of specialist health professional groups that are supported by HFA and facilitate professional expertise in a number of disciplines that support the comprehensive care of people with bleeding disorders, including:
  - **Australian Haemophilia Nurses' Group**
  - **Australia/New Zealand Haemophilia Social Workers' and Counsellors' Group**
  - **Australian and New Zealand Physiotherapy Haemophilia Group.**
- The **ABDR Data Managers' Group**, which is supported by AHCDO and coordinates the protocols for entry of data into the ABDR.

These groups collaborate through formal partnerships or informal processes to oversee key outcomes or undertake projects to support or improve haemophilia care. Some key examples include:

- Management of patients with inhibitors through the AHCDO Tolerisation Advisory Committee (TAC).
- Annual education meetings around topics on bleeding disorders.
- Redevelopment of the ABDR and development of the MyABDR patient recording application. The processes for detailed design, and for ongoing operation and enhancement of ABDR and MyABDR have been greatly assisted over an extended period by the involvement of representatives of all patient and clinical stakeholder groups. The ABDR Steering Committee, which oversees the development and operation of ABDR and MyABDR, is chaired by AHCDO and includes representatives of AHCDO, HFA, state and territory governments and the NBA. Under the oversight of this Steering Committee, the governance and management of ABDR and MyABDR is conducted as an effective partnership between the key patient and clinical groups and governments.
- Tender evaluation and associated consultation, reference group or transition committees that oversee major national procurement actions for clotting factors. Australia's national procurement arrangements realise the best product price and associated service arrangements available globally. This price increases affordability, and hence provision of effective haemophilia care.<sup>266</sup> The expertise and involvement of key clinical and patient stakeholder groups in these processes is of great value in achieving these outcomes.
- Clinical and stakeholder reference groups that oversee the development of supporting clinical guidelines, such as the current document. These clinical guidelines record an increasing level of national consensus on significant aspects of the care and management of bleeding disorders, and the key indicators to be used to guide future quality improvement.

## 8.5 Information systems and data

### Australian Bleeding Disorders Registry

The ABDR is a database that is designed to collect clinical information related to the treatment of people with inherited bleeding disorders. This includes information about patient diagnosis, viral status, treatment details, hospital admissions and administrative information, as well as details on ordering, supply and use of clotting factor products. Information is entered into the ABDR web-enabled software by staff at haemophilia treatment centres. Patients with haemophilia receiving treatment should be registered on the ABDR, and their product use recorded.

ABDR provides the following benefits:

- a single point of access to all relevant individual clinical data relating to the management of haemophilia for clinicians treating patients with bleeding disorders
- exchange of selected information between states and haemophilia treatment centres
- national demographic information (e.g. age and sex) of people with bleeding disorders
- national data on inhibitor incidence and outcomes of treatment
- allied health (physiotherapy and social work) interactions and outcomes



- recording of personal usage of factor replacement for clinical monitoring
- data for forward planning and funding of factor concentrates on a national basis.

The ABDR provides health-care teams and support staff with a record that enables them to monitor and manage treatment over time to improve patients' quality of life. De-identified information from the ABDR may be used for research purposes by authorised organisations, to understand and improve treatment for bleeding disorders. Considerations for the release of any information for research are made under specific governance arrangements. The ABDR also provides governments with information on total clotting factor product requirements, to inform supply planning to meet the needs of all Australians with bleeding disorders.

The ABDR is managed on a day-to-day basis by the NBA in accordance with the guidance and policy oversight provided by the ABDR Steering Committee. The committee comprises representatives of the key stakeholders involved in the clinical management, advocacy and funding of treatment for people with bleeding disorders.

A robust governance framework oversees the management and operation of the ABDR. An AHCD member chairs the Steering Committee tasked with these responsibilities. The Steering Committee also includes the Executive Director of HFA, to ensure that patient needs are met. Patient privacy and confidentiality are paramount to these arrangements, and individual patients are required to give consent for their data to be recorded in the ABDR.

In addition, stringent security protocols are embedded into the technical architecture of the ABDR. These effectively control access to personal data, ensuring that this information is only accessible to treating health professionals and authorised support staff.

## MyABDR

MyABDR is a secure app for use on smartphones or home computers, developed as a collaborative project by the NBA, AHCD and HFA on behalf of Australian governments (Commonwealth, and state and territory), for use by people with bleeding disorders or parents or carers. MyABDR can be used to record home treatments for both prophylaxis or bleeding episodes, and to manage treatment product stock. The MyABDR app and website link directly to the ABDR; thus, data entered are available to the patient's treating clinician. By enhancing the accurate recording of bleed frequency and factor usage, and making that information accessible to the clinician, MyABDR can aid decision-making regarding treatment regimens and optimise patient care. MyABDR is the preferred method of patient record keeping in Australia.

## Data reporting

Health professionals can use the data recorded in ABDR for the care and treatment of individual patients, and haemophilia treatment centres can use the data in managing the provision of comprehensive care services. It is planned that benchmarking data will be made available to individual centres to identify variation in management among centres, and to help identify areas in which differences can be examined, to assist in standardising practice.

In addition, a number of useful national level reports are produced from de-identified data in ABDR:

- annual reporting, including published reports and the above haemophilia treatment centre benchmarking reports
- adverse event reporting and recording as the Australian Haemophilia Safety Surveillance System (AUSHASS) reporting scheme
- national contributions to the WFH survey.

Individual centres are also able to submit data requests for summary data regarding their patient population, to enhance clinical management.

## 8.6 Knowledge development and practice improvement

The other elements of the national framework for management of bleeding disorders in Australia enable and support a range of activities that seek to evaluate, maintain and improve an appropriate and high-quality standard of patient treatment care, and the effective and efficient use of clotting factor products. These activities are summarised below:

- **Education and training** – members of AHCDO and other health-care professionals are regularly involved in educational activities, including registrar training events, the annual AHCDO education day, participation in national and international conferences, and contribution to patient education material in partnership with HFA.
- **Practice benchmarking, development and peer review** – forums for peer discussion of difficult clinical management decisions are provided by the AHCDO TAC and the complex patient advisory group. The planned provision of regular benchmarking data to individual centres will enable the examination of variation in practice and aid in the standardisation of management where appropriate.
- **Guidelines and consensus statements** – AHCDO is committed to the development of clinical guidelines such as these, to provide a framework to guide the management of patients with haemophilia. Ongoing activities – including detailed systematic review of clinical questions and the development of consensus statements in areas not covered by these guidelines – are planned.
- **Research and publications** – ethics approval for use of the ABDR for demographic research is a key component of examining national data to help answer key research questions (see Appendix D). AHCDO has a mechanism for providing funding for local research initiatives in collaboration with the NBA.





# Appendices

Appendix A	Acronyms and abbreviations
Appendix B	Development process
Appendix C	Systematic review methodology
Appendix D	Areas for further research
Appendix E	Patient information
Appendix F	Implementation and review of the Australian haemophilia guidelines
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## Appendix A – Acronyms and abbreviations

ABDR	Australian Bleeding Disorders Registry
AHCDO	Australian Haemophilia Centre Directors' Organisation
APCC	activated prothrombin complex concentrate
BMD	bone mineral density
BMI	body mass index
BU	Bethesda unit
CHO-KLAT	Canadian Hemophilia Outcomes: Kids' Life Assessment Tool
CT	computed tomography
CVS	chorionic villus sampling
DDAVP	desmopressin
DNA	deoxyribonucleic acid
FEIBA	factor eight inhibitor bypassing activity
FFP	fresh frozen plasma
FISH	Functional Independence Score in Haemophilia
FIX	factor IX
FVIII	factor VIII
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAL	Haemophilia Activities List
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HFA	Haemophilia Foundation Australia
HIV	human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
ITI	immune tolerance induction
IU	international unit
LDL	low-density lipoprotein
MRI	magnetic resonance imaging
NAT	nucleic acid testing
NBA	National Blood Authority
NSAIDs	nonsteroidal anti-inflammatory drugs
PCC	prothrombin complex concentrate
PCI	percutaneous cardiac intervention
PCR	polymerase chain reaction
PedHAL	Paediatric Haemophilia Activities List
PICO	population, intervention, comparator and outcome
PRICE	protection, rest, ice, compression and elevation
RCPA	Royal College of Pathologists of Australasia
RCT	randomised controlled trial
rFVIIa	recombinant activated factor VII
rFVIII	recombinant factor VIII
rFIX	recombinant factor IX
TAC	Tolerisation Advisory Committee (AHCDO)
vCJD	variant Creutzfeldt–Jakob disease
VWD	von Willebrand disease
VWF	von Willebrand factor
WFH	World Federation of Hemophilia

## Appendix B – Development process

In 2013, the National Blood Authority (NBA) and the Australian Haemophilia Centre Directors' Organisation (AHCDO) agreed that guidance for the management of haemophilia patients should be developed for the Australian setting for the following reasons:

- guidelines that provide multidisciplinary guidance on the management of the patients with haemophilia relevant to the Australian setting are not currently available
- it is suspected that there is variation in approaches to some aspects of the management of haemophilia in Australia
- the Australian *Evidence-based clinical practice guidelines for the use of recombinant and plasma-derived FVIII and FIX products*<sup>4</sup> are due for revision
- Australia's *National Safety and Quality Health Service Standards*<sup>5</sup> requires that blood product policies, procedures or protocols are consistent with national evidence-based guidelines for pretransfusion practices, prescribing and clinical use.

The NBA and AHCDO agreed that the World Federation of Hemophilia (WFH) *Guidelines for the management of hemophilia (2nd edition)*<sup>5</sup> provided a good basis upon which to develop Australian guidance. However, in order to maximise the opportunity of standardising haemophilia care in Australia, some adaptation of the WFH guidelines was required.

Each chapter of the WFH guidelines was reviewed by at least two AHCDO members, who were asked to appraise the chapter, assess the need for a systematic review and draft additional content. These reviewers were asked to be mindful of the Australian setting, the sustainability of products, the appropriateness of treatment regimens and the need for a consensus approach. An additional chapter on the framework for the management of bleeding disorders in Australia (Chapter 8) was also drafted for inclusion in the guidelines.

During the review of the WFH guidelines, AHCDO members identified a number of research areas requiring further consideration and possible systematic review. Following an initial scan of literature, AHCDO recommended that a systematic review should be conducted to address two research questions:

1. In patients with haemophilia what is the effect of anti-inflammatory medication (including aspirin) compared to no anti-inflammatory or a different type of anti-inflammatory medication on bleeding events?
2. In patients with haemophilia who have presented with an acute joint bleed or historical joint bleeds, what is the effect of therapy to reduce inflammation compared to no therapy on recurrent joint haemorrhage and subsequent arthropathy?

The findings were considered by AHCDO and incorporated into the guidelines. Further details of the systematic review can be found at Appendix C.

The revised chapters were then reviewed for consistency, consolidated and circulated to nominated clinical experts as well as to Haemophilia Foundation Australia in a 'critical friends' consultation process. Eight submissions were received. All comments received were considered to be not controversial and were incorporated into the draft guideline in preparation for the open public consultation process.

Public consultation was conducted for 6 weeks, from Wednesday 11 November 2015 to Wednesday 23 December 2015, during which time the draft guidelines were available on the AHCDO and NBA websites. Five submissions were received. AHCDO members considered all the public consultation submissions and, where necessary, revised the guidelines in accordance with the submissions.

During the development process, all AHCDO members and 'critical friends' were asked to declare any conflicts of interest before contributing to the development process. No conflicts were declared during the development process.



## Appendix C – Systematic review methodology

The WFH *Guidelines for the management of hemophilia (2nd edition)*<sup>5</sup> contain several recommendations for the management of haemophilia patients. In those guidelines, all statements in bold font were supported by the best practice evidence available at that time, and were graded using the 2011 Oxford Centre for Evidence-Based Medicine levels of evidence<sup>267</sup> (see Appendix G). The WFH guidelines also contain guidance that fell outside the selection criteria for practice statements. This guidance was included in the guidelines but not highlighted in bold font. The Australian Haemophilia Centre Directors' Organisation (AHCDO) and the NBA agreed to retain this method of presentation of the clinical guidance for the Australian guidelines.

During a review of the WFH's *Guidelines for the management of hemophilia (2nd edition)*,<sup>5</sup> AHCDO members identified a number of research areas requiring further consideration and possible systematic review. Following an initial scan of the literature, AHCDO recommended that a systematic review should be conducted to address two research questions:

1. In patients with haemophilia what is the effect of anti-inflammatory medication (including aspirin) compared to no anti-inflammatory or a different type of anti-inflammatory medication on bleeding events?
2. In patients with haemophilia who have presented with an acute joint bleed or historical joint bleeds, what is the effect of therapy to reduce inflammation compared to no therapy on recurrent joint haemorrhage and subsequent arthropathy?

The NBA engaged an expert systematic review team from HealthConsult, on behalf of AHCDO, to conduct a systematic review of the scientific literature using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.<sup>268</sup>

Electronic searches of EMBASE and the Cochrane Library were conducted using search terms related to the clinical questions. The search of EMBASE was conducted on 18 February 2015, and the search of the Cochrane Library on 19 February 2015. In addition to the database search, the reference lists of relevant primary studies were hand-searched to identify additional studies. Also, guideline websites (e.g. the National Guideline Clearinghouse and the Guidelines International Network) were searched on 24 February 2015. Identified guidelines were checked to ensure that all relevant studies had been identified. The literature searches resulted in the identification of a total of 773 citations for Question 1, and 54 citations for Question 2.

The eligibility criteria for inclusion in the systematic review were underpinned by the main components of the research question. Specifically, studies were excluded for the following reasons:

- (i) not a clinical study (excludes narrative reviews, editorials, surveys, individual case reports, animal studies and in vitro studies);
- (ii) wrong intervention;
- (iii) wrong indication; and
- (iv) wrong outcomes.

Studies were also excluded if they were not published in English or included duplicate data published in another included study. The study sample size was restricted to at least five subjects, because of the small number of studies available. In addition, study type was not restricted; due to the small number of Level II studies (randomised controlled trials [RCTs]) and Level III studies (cohort and case-control) available, Level IV studies (case series) were also eligible for inclusion.<sup>k</sup> The exclusion criteria were initially applied to the titles and abstracts of the identified citations. Full-text articles of the remaining citations were then retrieved, and the exclusion criteria were again applied. This resulted in 13 studies being included for Question 1 and seven studies being included for Question 2.

<sup>k</sup> Studies were assigned a level of evidence based on the NHMRC evidence hierarchy for intervention questions.



Study and patient characteristics for each included study, as well as the results of the selected outcomes, were extracted into data extraction tables. These tables also included a judgement on the quality of each included study, and a brief description of how this quality judgement was made. Quality assessment was performed using checklists related to specific study types (i.e. RCTs and cohort studies), which are based on quality criteria defined by the National Health and Medical Research Council (NHMRC) (2000)<sup>269</sup> and the Scottish Collegiate Guidelines Network.<sup>270</sup> Because they presented the lowest level of evidence, Level IV studies (case series) were not assessed for quality, and were automatically given a poor quality rating.

Results from each of the studies were brought together into evidence summary tables that were organised by outcome. The body of evidence for each comparison and outcome was then assessed using GRADE methodology.<sup>268</sup>

The overall quality of the body of evidence for each outcome was assessed using an evidence profile table, and scored based on the included study types and the gradings of the following criteria: limitations, inconsistency, indirectness, imprecision and publication bias. Systematic reviews are considered to provide the strongest evidence because they summarise one or more well-designed and well-executed RCTs, and yield consistent and directly applicable results.<sup>271</sup> In the GRADE methodology, systematic reviews and RCTs both start as high-quality evidence. However, the quality of RCT evidence can be downgraded to moderate, low or even very low, depending on the presence of one or more of the following five factors:

- (i) limitations in the design and implementation of available studies suggesting high likelihood of bias;
- (ii) unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- (iii) indirectness of evidence (indirect population, intervention, control and outcomes);
- (iv) imprecision of results (wide confidence intervals); and
- (v) high probability of publication bias.

The 'moderate strength' category is populated by RCTs with important limitations. Observational studies are generally graded as low-quality evidence. If, however, these studies yield large effects and there is no obvious bias explaining those effects, reviewers may rate the evidence as moderate or – if the effect is large enough – even high quality. The following three factors may lead to a study receiving a higher rating:

- (i) large magnitude of effect;
- (ii) all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect; and
- (iii) dose–response gradient.

Very low quality evidence also includes studies with critical problems and unsystematic clinical observations (e.g. case series or case reports).

Upon completion of the evidence profile tables, evidence statements were developed for each question and its associated comparisons and outcomes. To ensure consistency of the evidence statements across different questions and outcomes, a standard sentence format was applied in which the strength of the statement reflected the quality of the underlying evidence.

The findings of the systematic review were considered by AHCDO and incorporated into the guidelines.

## Appendix D – Areas for further research

The following areas were identified by AHCDO as priority areas for further research:

1. What is the optimal regimen when initiating primary prophylaxis in previously untreated patients?
2. What are the benefits of continuation of prophylaxis into adulthood?
3. What is the role of anti-inflammatory medication, in particular COX-2 inhibitors, in the management of acute joint bleeds, synovitis and chronic arthropathy?
4. What impact does joint aspiration, with or without intra-articular steroid injection, following acute haemarthrosis have on the development of haemophilia arthropathy?
5. How good are clinicians and patients at distinguishing acute bleeding events from other causes of joint pain, and should additional investigations be performed to aid diagnosis?
6. What frequency of inhibitor testing is optimal for patient outcomes?

## Appendix E – Patient information

Patient information designed for the Australian setting can be obtained from the website of Haemophilia Foundation Australia.<sup>1</sup>

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<sup>1</sup> [www.haemophilia.org.au](http://www.haemophilia.org.au)

## Appendix F – Implementation and review of the Australian haemophilia guidelines

The Australian haemophilia guidelines will be made available within the public domains of the NBA and AHCDO websites. The availability of the guidelines will be communicated with all AHCDO members, members of the Australian Haemophilia Nurses' Group, the Haemophilia Physiotherapist Group, and also more widely via other haematology professional groups including the Haematology Society of Australia and New Zealand, and the Australasian Society of Thrombosis and Haemostasis.

While the guidelines were specifically adapted from the WFH document to reflect current practice in Australia, ongoing projects to benchmark current practice and resourcing of haemophilia care against the standards outlined in the guidelines are planned for the year following publication.

The guidelines will be reviewed by AHCDO every 5 years, however may require modification or additional sections to be added within that timeframe, particularly with the advent of new therapeutic options. It is also anticipated that more detailed documents dealing with a specific aspect of haemophilia disorder management (e.g. inhibitor management) may be developed within the review time-period.

## Appendix G – Oxford Centre for Evidence-Based Medicine – 2011 levels of evidence

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

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

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

OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-Based Medicine. [http://www.cebm.net/index\\_aspx?o=5653](http://www.cebm.net/index_aspx?o=5653)

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