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SUPPLEMENT ARTICLE

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WFH Guidelines for the Management of Hemophilia, 3rd edition

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Summary

This new edition of the World Federation of Hemophilia (WFH) guidelines for the management of hemophilia comes at an exciting time in the evolution of the diagnosis and treatment of this condition. Since the publication of the second edition in 2012, tremendous advances have been made in several aspects of the management of hemophilia. These include genetic assessment as well as therapy with many innovative therapeutic products including extended half-life factor VIII (FVIII) and factor IX (FIX) products, a bi-specific antibody, and hemostasis rebalancing drugs now in clinical development. All of these allow for more effective hemostasis than was possible in the past. Laboratory monitoring of therapies is better defined and prophylaxis is accepted as the only way to change the natural history of bleeding. There are highly effective therapies for patients with inhibitors. Outcome assessment with validated clinimetric instruments is widely advocated and practiced. All these advances are reflected in this third edition of the WFH guidelines, with new chapters devoted to several of these topics along with a new chapter on principles of care that aims to provide a framework for development of a comprehensive healthcare system for hemophilia including advocacy and empowerment for people with hemophilia (PWH). The recommendations in this edition were all developed through a formal evidence-informed and consensus-based methodology involving multidisciplinary healthcare professionals (HCPs) and well-informed PWH. While directed primarily at HCPs, these guidelines should also be very useful for PWH as well as advocacy organizations.

KEYWORDS

bleeding disorders, hemophilia, management guidelines, novel hemostasis products, outcomes, treatment

This third edition of the WFH Guidelines for the Management of Hemophilia has been endorsed by the Asian-Pacific Society on Thrombosis and Hemostasis, European Haemophilia Consortium, and National Hemophilia Foundation (USA).

WFH Guidelines Disclaimer

The World Federation of Hemophilia (WFH) does not endorse any particular treatment product or manufacturer; any reference to a product name is not an endorsement by the WFH. The WFH does not engage in the practice of medicine and under no circumstances recommends particular treatments for specific individuals. Guidelines are intended for general information only and are based on population level research, not for the care or treatment of any particular individual. Guidelines do not replace professional medical care and physician advice and/or product insert information, but should be used to educate and inform shared decision-making between patients, caregivers, and healthcare providers.

Furthermore, guidelines may not be complete or accurate because new research studies may have been published or treatments, devices, or indications approved after the cut-off date for inclusion in these guidelines. Through a comprehensive and systematic literature review, WFH evidence-informed clinical practice guidelines incorporate data from the existing peer-reviewed literature. Although this literature met the pre-specified inclusion criteria for the guideline, and the WFH considered this scientific content to be the best evidence available for general clinical information purposes at the time the guidelines were developed, this evidence is of varying quality and varying methodological rigor.

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With more than one million print and online distributions in six languages and more than 1000 citations in peer-reviewed articles since its publication in 2012, the World Federation of Hemophilia (WFH) clinical practice resource, *Guidelines for the Management of Hemophilia, 2nd edition*, has served the community of hemophilia care providers and people with hemophilia extensively. Endorsed by the International Society on Thrombosis and Haemostasis (ISTH), the WFH guidelines were also the first hemophilia management guidelines to be accepted by the National Guideline Clearinghouse (NGC), formerly run by the Agency for Healthcare Research and Quality (AHRQ) of the United States Department of Health and Human Services (https://www.ahrq.gov/gam/index.html).

Over the past five years, unprecedented progress has been made not only in the development of newer therapeutics for hemophilia, but major paradigm shifts have also occurred in many of the principles governing the planning and philosophy of hemophilia treatment. Given the progress in genetic analysis technologies, in addition to much wider access, their applications in hemophilia have moved from the research arena to an increasingly greater role in the management of patients and their families. The advent of newer clotting factor concentrates (CFCs) with extended half-life has not only led to decreased burden of care for patients; more importantly, extended half-life CFCs have made it possible to maintain significantly higher factor trough levels on regular replacement therapy than has been possible with standard half-life CFCs. The bar of hemostatic safety was raised even higher with the introduction of non-CFC hemostatic agents such as the novel bispecific monoclonal antibody. This agent achieves hemostasis equivalent to approximately 15% FVIII levels, with subcutaneous administration and substantially less frequent dosing compared to CFCs. People with hemophilia treated with these newer therapies are now able to participate in many more activities than ever before without fear of bleeding. In addition, structured outcome assessment has been a relatively unevolved aspect of the management of hemophilia. With greater emphasis over the past few years on its significance in routine management of hemophilia, several clinimetric instruments are now being used for the standardized assessment and documentation of both hemostatic and musculoskeletal outcomes.

To acknowledge these advances and establish them more firmly in clinical practice, several modifications have been made in the third edition of these guidelines. New chapters have been added to provide the required detail to the following topics: genetic assessment; prophylaxis with hemostatic agents to prevent bleeding; management of inhibitors; and assessment of outcomes. An additional chapter defines the principles of management of hemophilia to provide aspirational benchmarks during the evolution of these services, within the local contexts of countries around the world.

Certain semantic changes introduced in this edition should be mentioned. The term “episodic” rather than “on demand” has been used to describe any hemostasis therapy after bleeding, as this term better reflects the concept of this practice. In keeping with the definition provided by the Scientific Standardization Committee of the ISTH, the term “exposure day” has been replaced with “exposure” to encompass all CFC replacement doses administered within 24 hours.

To ensure that bias was avoided as much as possible, a rigorous consensus-based methodology was adopted for formulating the final recommendations in these guidelines. An independent methods and process expert, unrelated to the field, was appointed alongside the content lead. All recommendations were informed by a comprehensive and systematic review of the relevant scientific literature and developed through an anonymous modified Delphi process resulting in evidence-informed consensus-based recommendations. Importantly, in addition to the experts in hemophilia care and related clinical disciplines, the Delphi panels included well-informed patients who also had the opportunity to review the manuscripts and the literature, and vote on the recommendations. All these steps are described in detail in the Methodology chapter.

It is also important to note that the final chapter drafts were reviewed internally both by the full panel and within the WFH, as well as by external subject experts prior to submission for publication. All these reviewers have been acknowledged at the end of the guidelines along with many others whose contributions have been invaluable to their development. A final round of independent peer review was also conducted by the journal before publication. It is also important to note that these guidelines have been endorsed by the Asian-Pacific Society on Thrombosis and Hemostasis, European Haemophilia Consortium, and National Hemophilia Foundation (USA).

As a result of all these modifications, the guidelines have become more comprehensive than the previous edition. However, to preserve their easy readability, the text remains structured using short sentences in bullet points. Detailed mechanistic explanations or descriptions of the original data underlying recommendations have been avoided. However, all relevant references have been cited and are listed at the end of each chapter.

It is hoped that the clinical care community, for whom these guidelines are primarily intended, will find them even more useful

than the previous editions. These guidelines may also serve as a resource to support education, advocacy, and decision-making related to hemophilia treatment and the delivery of care. In addition, they should help identify gaps in evidence upon which the recommendations have been formulated to help direct appropriate clinical research in these areas. As in the past, the electronic version of these guidelines is available on the WFH website (http://www.wfh.org). These guidelines will be updated, added to, or modified as significant new data or evidence justifying change become available. This will keep the guideline content current and cognizant of the advances that are expected in the coming years, particularly in the area of gene therapy for hemophilia, which will need to be included in more detail once the ongoing clinical trials are over and products are registered.

Chapter 1: Principles of Care

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Introduction

- These principles of care aim to provide globally relevant guidance based on current science and best practices in hemophilia diagnosis and treatment, as identified by the guidelines panel of the World Federation of Hemophilia (WFH). They include core concepts, requirements, and priorities in the delivery and management of hemophilia care, which together constitute a framework for implementing and advancing hemophilia treatment programs.
- The principles build on the original tenets set out by the WFH and the World Health Organization (WHO) in 1990[1] and the updated guidelines and recommendations developed collaboratively by the WFH, WHO, and International Society on Thrombosis and Haemostasis (ISTH) in 2002.[2]
- The principles integrate core components of principled integrated care[3] and primary health care, including: meeting people's lifetime health needs through comprehensive preventive, curative, and rehabilitative services as well as palliative care; addressing the broader determinants of health through multisectoral policy and action that engages relevant stakeholders and enables local communities to strengthen primary health care; and empowering individuals, families, and communities to take charge of their own health.[4]
- In addition, they align with the chronic care model's emphasis on the need to shift from acute, episodic, and reactive care towards care that embraces longitudinal, preventive, community-based, and integrated approaches.[5]
- In addition to guiding clinical practice, principles of care can also serve as a common foundation of understanding for patient organizations, healthcare providers, healthcare administrators, and policymakers; this in turn enables better discussion and collaboration on decisions surrounding allocation of resources for hemophilia programs, and priorities for achieving the best standards possible within the available resources.
- Principles of care aim for ideal hemophilia management to ensure that patients have access to appropriate, sustained, and high-quality medical services and comprehensive care; however, it should also be recognized that the priorities and capabilities in each country determine what is practical at any point in time.

1.1 | Principle 1: National coordination and delivery of hemophilia care

- A coordinated hemophilia care program, administered through a designated agency and integrated within the existing healthcare system, improves outcomes for people with hemophilia.[2,6-8]
- Optimal hemophilia care within such a program requires the following key components[2]:
  - comprehensive hemophilia care provided by a multidisciplinary team of specialists;
  - a national or regional network of hemophilia treatment centres (HTCs);
  - a national registry of patients with hemophilia;
  - robust processes for the procurement and distribution of safe and effective therapies, particularly clotting factor concentrates (CFCs) and other types of hemostasis products used in hemophilia treatment;
  - equitable access to these services and therapeutic products[9]; and
  - recognition of the socioeconomic and cultural diversities within any given community, region, or country.

Comprehensive hemophilia care

- Treatment centres based on the multidisciplinary comprehensive care model should be established to ensure that people with

hemophilia have access to the full range of clinical specialties and appropriate laboratory services.[6]
- See Principle 7: Multidisciplinary care for hemophilia and Chapter 2: Comprehensive Care of Hemophilia.

Network of hemophilia treatment centres

- Hemophilia care is best provided through designated diagnostic and treatment centres with clearly defined treatment protocols, standards of care, and quality and audit activities.[2]
- Hospitals providing clinical care for people with hemophilia and related disorders are strongly encouraged to seek formal designation as a hemophilia treatment centre (HTC) or hemophilia comprehensive care centre (HCCC), as applicable, by the local health authorities[6,9] (see Table 1-1).
- Such centres can also serve the needs of patients with other congenital bleeding disorders.

National patient registry

- Each country should have a national registry of patients with hemophilia, with standardized data collection by all hemophilia centres and centralized administration by a nationally mandated authority, or participate in a multinational or international registry.[10-13]
- The WFH's World Bleeding Disorders Registry (WBDR) provides an online platform for a network of HTCs around the world to collect uniform and standardized data to track treatment and management of patients, monitor patient outcomes, and guide clinical practice.[13] The WBDR can be used as a patient registry for some or all HTCs within a country.
- Patient registries are used to collect accurate data on people with hemophilia in terms of their treatment and outcomes including disease severity, type of treatment, bleeding episodes, adverse events, joint status, inhibitor status, comorbidities, and quality of life.
- Registry data allow analysis of standards of care and can be used as a tool for auditing clinical and laboratory services; this in turn can support the development of better quality of care and facilitate resource planning and allocation.[6]
- Patient registries can help to advance understanding of the variations in hemophilia treatment; describe care patterns, including appropriateness and disparities in the delivery and quality of care; indicate factors that influence prognosis and quality of life; and provide evidence on resource utilization.[14]
- Adequate provision must be made for data privacy, confidentiality, and respect for human rights[10] in compliance with national regulations and best ethical practices.[6]
- It is important to ensure that the patient and/or the parent or legal guardian (in the case of minors) understands a registry's purpose and uses and provides informed written consent for the collection and sharing of data related to the patient's care.[10,15]
- See Chapter 2: Comprehensive Care of Hemophilia and Chapter 11: Outcome Assessment.

National or regional procurement of hemophilia therapies

- Sustained availability of CFCs in sufficient quantities is strongly correlated with better outcomes for people with hemophilia.[16] To ensure that people with hemophilia have reliable access to safe and effective CFCs and other hemostasis products, countries must establish a rigorous national or regional system for the procurement and distribution of hemophilia therapies.[2]
- Hemophilia treatment relies on essential life-saving medicines that are relatively expensive compared to medications for other conditions.
- Setting up a national tender system or collaborating in a multinational system for the purchase of CFCs can help ensure that optimal products are selected at the best price.[17]
- The decision-making process for such tenders under the contracting authority (typically the Ministry of Health or other health authority) should include both well-informed hemophilia clinicians and patient representatives.[9]
- The WFH's *Guide to National Tenders for the Purchase of Clotting Factor Concentrates* describes tender and procurement systems around the world and explains how to set up a national procurement system and carry out tenders.[17]
- See Chapter 2: Comprehensive Care of Hemophilia and Chapter 5: Hemostatic Agents.

1.2 | Principle 2: Access to safe CFCs, other hemostasis products, and curative therapies

Safe and effective CFCs

- People with hemophilia must have access to safe and effective treatment with optimal efficacy in the prevention of bleeding and treatment of any spontaneous, breakthrough, or trauma-related bleeding. For many, this involves treatment with specific CFCs or other hemostasis products.
- Both virus-inactivated plasma-derived and recombinant CFCs, as well as other hemostasis products when appropriate, can be used for treatment of bleeding and prophylaxis in people with hemophilia.[16]
- Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia, or for those with another congenital bleeding disorder that is associated with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding.

TABLE 1-1 Roles of hemophilia comprehensive care centres and hemophilia treatment centres[6]

Hemophilia comprehensive care centre (HCCC)	Hemophilia treatment centre (HTC)
• Provide 24-hour service with experienced staff	• Provide 24-hour, appropriate hematological cover
• Provide inhibitor care and immune tolerance services	• Operate inhibitor care and immune tolerance services in cooperation with a HCCC
• Provide safe and effective CFCs and other hemostasis products	• Provide safe and effective CFCs and other hemostasis products
• Provide community liaison, including school and home visits	• Provide access to nursing staff, physical therapy services, social workers, and obstetric and gynecological services
• Offer laboratory services with 24-hour assay cover	• Provide preliminary genetic counselling followed by referral to a HCCC for full review
• Provide access to hospital-based nursing staff, physical therapy services, social workers, dental services, obstetric and gynecological services, and psychosocial support	• Provide access to HIV and hepatitis C care, through a HCCC, if necessary
• Provide HIV and hepatitis C care	• Offer regular follow-up and home treatment in cooperation with a HCCC
• Provide access to a genetics laboratory and genetic counselling	• Provide prophylaxis in cooperation with a HCCC
• Provide home treatment	• Keep reliable records
• Keep reliable records	• Undertake medical education
• Undertake medical education	• Collaborate with other HTCs in research and exchange of best practices
• Initiate and participate in research	

Abbreviations: CFC, clotting factor concentrate; HCCC, hemophilia comprehensive care centre; HIV, human immunodeficiency virus; HTC, hemophilia treatment centre.

- Episodic CFC replacement should not be considered a long-term option for the management of hemophilia as it does not alter its natural history of spontaneous bleeding and related complications.[18,19]
- The WFH's *Guide for the Assessment of Clotting Factor Concentrates* should be carefully reviewed in the context of the healthcare system in each country and incorporated into tender processes for procurement of hemophilia therapies.[16]
- The *WFH Online Registry of Clotting Factor Concentrates* lists all currently available plasma-derived and recombinant CFCs and their product details.[20]
- See Chapter 5: Hemostatic Agents and Chapter 6: Prophylaxis in Hemophilia.

Emerging therapies and potential cures

- Emerging therapies in development with alternative modes of delivery (e.g., subcutaneous injection) and novel targets may overcome the limitations of standard CFC replacement therapy (i.e., need for intravenous administration, short half-life, risk of inhibitor formation). These emerging therapies offer markedly improved pharmacokinetic (PK) profiles with a very low burden of administration (e.g., up to monthly dosing); therefore, they may help reduce treatment burden and increase compliance. These therapies are discussed in Chapter 5: Hemostatic Agents, Chapter 6: Prophylaxis in Hemophilia, and Chapter 8: Inhibitors to Clotting Factor.
- The development of gene therapies for hemophilia has advanced significantly, with product registration likely in the near future. Several clinical trials in both people with hemophilia A and B have demonstrated success with a favourable safety profile to date.[21,22]
- Gene therapy should make it possible for some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies. This will require evaluation through long-term follow-up as part of clinical trials and registries.
- Given the ongoing advances transforming the hemophilia treatment landscape, it is important to establish systems to constantly monitor developments in emerging and gene therapies for hemophilia and make them available as soon as possible following approval by regulatory authorities.
- See Chapter 5: Hemostatic Agents, Chapter 6: Prophylaxis in Hemophilia, and Chapter 8: Inhibitors to Clotting Factor.

1.3 | Principle 3: Laboratory services and genetic diagnosis of hemophilia

Laboratory diagnosis and testing

- The diagnosis and treatment of hemophilia require access to laboratory facilities that are equipped with appropriate resources and expertise to accurately perform factor assays and other coagulation tests.

- Screening and testing for inhibitor development, now the most serious complication in hemophilia, is vital for any comprehensive hemophilia treatment program to be able to provide medical treatment and eradication of inhibitors[23]; however, most centres around the world do not have inhibitor testing capacities.
- In many resource-constrained countries, centres and hospitals lack the appropriate technologies and capabilities for diagnosing hemophilia. Therefore, developing or enhancing existing laboratories with the capacity to perform coagulation tests with assured quality is an important priority in these countries.[8]
- Coagulation laboratories must have well-trained laboratory staff and appropriate resources, including suitable and readily available reagents.
- Ideally, coagulation laboratories should be able to provide 24-hour services for coagulation tests and factor assays and be able to perform inhibitor assays in a timely manner.[6]
- It is essential to have good communication between the laboratory and the clinical team ordering the tests to ensure that the appropriate assays are carried out and that the results reported are correctly evaluated and well understood.[24]
- All coagulation laboratories should include quality assurance programs and be subject to external quality assessment.
- See Chapter 3: Laboratory Diagnosis and Monitoring – Quality assurance.

Genetic assessment of hemophilia

- Genetic assessment of hemophilia is important to define disease biology, establish diagnosis in difficult cases, predict risk of inhibitor development, and provide prenatal diagnosis if desired. Wherever possible, genotype analysis should be offered to all patients with hemophilia.[9] (See Chapter 2: Comprehensive Care of Hemophilia and Chapter 3: Laboratory Diagnosis and Monitoring.)
- Genetic testing will not always identify the underlying variant associated with the phenotype. Genetic counselling of the person with hemophilia referred for genetic testing should highlight this possibility.
- The opportunity for discussion of the genetic analysis results between the clinical and the laboratory teams involved is an essential aspect of the genetic diagnostic service.
- Advances in molecular genetic technologies are becoming routinely integrated into many genetic diagnostic laboratories. Full *F8* or *F9* gene screening is performed by polymerase chain reaction (PCR) and Sanger sequencing, or next-generation sequencing.[25-29] Use of these techniques is evolving and increasing internationally. The approach and use of a specific technique depend on the available technical expertise and resources. Genetic counselling must include comprehensive discussion about the possibility of incidental findings in genes other than *F8* or *F9*, depending on the methods being used for the assessment.
- See Chapter 2: Comprehensive Care of Hemophilia, Chapter 3: Laboratory Diagnosis and Monitoring, Chapter 4: Genetic Assessment, Chapter 8: Inhibitors to Clotting Factor, and Chapter 9: Specific Management Issues.

1.4 | Principle 4: Education and training in hemophilia care

Recruitment of medical specialists

- As hemophilia is a rare disorder in which the availability of specialized care is a critical determinant of burden of disease,[30] recruitment and training of medical specialists in hemophilia management are key to establishing, maintaining, and advancing standards of care to reduce morbidity and mortality among people with hemophilia in well-resourced and resource-constrained countries alike.
- Recruitment of physicians, hematologists, and scientists in the area of thrombosis and hemostasis to the field of hemophilia is essential to ensure sustained, high-quality medical care, together with recruitment of medical laboratory specialists, nurses, physical therapists, occupational therapists, and other musculoskeletal specialists (e.g., orthopedic surgeons, rheumatologists, and physiatrists), dentists, and psychosocial counsellors. All are integral to multidisciplinary comprehensive care for hemophilia and require ongoing specialist education and development for practice in this field.
- Hemophilia education for allied specialists needed to help address specific medical and health-related issues that may arise in some patients is also important.
- Mentorship and fellowship opportunities are valuable and effective means to attract and retain new healthcare providers to the field of hemophilia.
- A coordinated approach to advancing clinical expertise in hemophilia (i.e., continued education, training, and fellowship programs) based on local, regional, and/or national needs and priorities will provide the foundation for sustaining and improving standards of care.
- Collaboration between hemophilia centres in resource-constrained and well-resourced countries and support from established expert bodies are effective avenues for advancing hemophilia knowledge, expertise, and standards of care.[8]
- The WFH works in many countries around the world to help develop and expand local, regional, and national capacities in laboratory diagnosis and treatment of hemophilia through its medical twinning program, humanitarian aid program,[31] and multidisciplinary education and training workshops for healthcare providers.[32]
- See Principle 7: Multidisciplinary care for hemophilia and Chapter 2: Comprehensive Care of Hemophilia.

1.5 | Principle 5: Clinical and epidemiological research

- Evidence-based research in hemophilia is greatly needed, but it is hampered by significant challenges due to the small size of the patient population.
- As most aspects of clinical management of hemophilia are empirical and lack high-level evidence, well-designed studies to generate the necessary evidence to evaluate current practices are needed.[8] A mutual basic scheme, such as the WHO's International Classification of Functioning, Disability and Health (ICF), ensures that disciplines are connected by the same model.
- Given the differences in priorities in practice around the world, it is important to promote locally relevant clinical research.
- Standardization of outcome assessment will permit meaningful comparison across studies.[33]
- Priority areas for clinical research in hemophilia include optimization of clotting factor replacement therapy; better understanding and prevention of inhibitor formation; and clinical data collection on existing hemophilia therapies and clinical practices, newer therapies such as extended half-life CFCs and non-factor hemostasis products, and potential gene therapies.
- Patient registries, with national and international collaboration between centres and countries, are an effective way to pool data to achieve the required sample size to conduct clinical research on rare disorders such as hemophilia.
- The WFH's World Bleeding Disorders Registry allows researchers to address important questions around patient care, compare country-specific levels of care, and use the evidence to advocate for better hemophilia care.[13]
- See Chapter 5: Hemostatic Agents, Chapter 6: Prophylaxis in Hemophilia, Chapter 8: Inhibitors to Clotting Factor, and Chapter 11: Outcome Assessment.

1.6 | Principle 6: Acute and emergency care for bleeds

- In critical situations, people with hemophilia need immediate access to emergency medicines and treatment as well as to specialist care at hospital emergency departments.[6] Lack of experience and knowledge of hemophilia management among medical professionals, particularly in emergency departments, may lead to serious treatment-related complications.[8,34]
- Therefore, it is essential to establish systems that are accessible around the clock for the management of acute life- or limb-threatening complications of hemophilia.[8]
- Treatment centres should develop protocols for emergency care for people with hemophilia, including those with inhibitors, that include management of serious acute complications such as intracranial hemorrhage (ICH) and other types of major internal hemorrhage and trauma.[8] (See Principle 9: Management of patients with inhibitors.)
- People with hemophilia should not be kept waiting in emergency departments and should be assessed immediately, even for less serious complications which can deteriorate while waiting. Prompt intervention is mandatory.[8]
- Primary physicians and HTC staff must be prepared to attend to emergency situations and provide advice and specialist support without delay.[6]
- The use of national online databases or the WBDR to capture treatment and health-related patient data allows for better acute and long-term management of people with hemophilia, and the use of digital mobile devices allows patients to record their bleeds and transmit their information to their HTC in real time.[8]
- See Principle 7: Multidisciplinary care for hemophilia and Chapter 2: Comprehensive Care of Hemophilia.

1.7 | Principle 7: Multidisciplinary care for hemophilia

- Optimal care of people with hemophilia, especially those with severe forms of the disorder, requires treatment and comprehensive care provided by a multidisciplinary team of specialists.
- Priorities in treatment and care to ensure the best health and quality-of-life outcomes for people with hemophilia include[6,8]:
  - prevention of bleeding and joint damage;
  - prompt management of bleeding episodes including follow-up physical therapy and rehabilitation;
  - appropriate emergency care;
  - appropriate pain management;
  - management of musculoskeletal complications and inhibitor development;
  - management of comorbidities;
  - regular psychosocial assessment and support as needed; and
  - ongoing education on treatment and self-care for people and families living with hemophilia.

Patient self-management and empowerment

- Self-management, i.e., the ability of patients to undertake daily management of their health and health care,[5] is essential in hemophilia. People with hemophilia must be competent in controlling bleeding symptoms to preserve their health, joint integrity, and functional independence.[2] Self-management allows them to minimize the short- and long-term consequences of the disorder and can help provide a sense of normalcy and control.[35]
- Key components of self-management in hemophilia include[35]:
  - bleed recognition;
  - record-keeping of bleeds and treatment;
  - self-administration of CFCs or other hemostasis products;

- self-care (i.e., nutrition and physical fitness) and medicines management (i.e., record-keeping, treatment routines, maintenance of adequate treatment supply, proper storage, reconstitution, and administration of treatment products);
- pain management;
- risk management; and
- participation in outcome reporting and documentation.

- Patient advocacy organizations have played an important role in advancing hemophilia care around the world. Such organizations should therefore be encouraged and supported to cover those aspects of care which are not covered by the healthcare system, including emphasis on patient empowerment and working with other agencies to advance care.
- See Chapter 2: Comprehensive Care of Hemophilia, Chapter 7: Treatment of Specific Hemorrhages, Chapter 8: Inhibitors to Clotting Factor, Chapter 9: Specific Management Issues, and Chapter 10: Musculoskeletal Complications.

Transition from pediatric to adult care

- The transition from pediatric to adult care, during which adolescents and young adults with hemophilia gradually assume responsibility for their own health and hemophilia management, can be a challenge for patients and their families.[36]
- Treatment adherence is a key challenge at two transition points: when young people with hemophilia switch to self-infusion, and again when they move away from home and assume the full responsibility of self-care.[37]
- Comprehensive hemophilia care should therefore include a conscientious approach to transition of care that starts in early adolescence[38] and supports the development of young people's self-efficacy and self-management skills, including psychosocial coping.[37]
- Both pediatric and adult healthcare providers must be engaged in considering the individual needs of patients and families to ensure a smooth transition and to ensure the best care possible during this time.[36]
- Engagement of adolescents and their caregivers early in the transition process allows time for acceptance and better understanding of the transition from the pediatric to the adult model of care as well as the associated reallocation of health management and medical decision-making responsibilities.[39]
- See Chapter 2: Comprehensive Care of Hemophilia – Transition from pediatric to adult care and Chapter 9: Specific Management Issues – Psychosocial issues.

1.8 | Principle 8: Regular replacement therapy (prophylaxis)

- The standard of care for all patients with severe hemophilia is regular replacement therapy (prophylaxis) with CFCs, or other hemostasis products to prevent bleeding, started early in life (before age 3) to prevent musculoskeletal complications from recurrent joint and muscle bleeds.[40]
- Episodic ("on demand") clotting factor replacement therapy should no longer be considered to be a long-term treatment option.
- Implementation of home-based prophylaxis programs increases compliance and allows people with hemophilia to live relatively normal lives. These programs should be accompanied by education of patients, families, and healthcare providers on the benefits of prophylaxis and the importance of adherence to treatment regimens.[35,37,41]
- Prophylaxis in young children may be the best way for a country to begin implementing universal prophylaxis for people with hemophilia.[8]
- See Chapter 6: Prophylaxis in Hemophilia and Chapter 10: Musculoskeletal Complications.

1.9 | Principle 9: Management of patients with inhibitors

- Systematic surveillance for inhibitors and comprehensive management of inhibitors should be implemented for people with hemophilia A,[23] particularly when patients are at highest risk during their first 20 exposures to CFCs (with one exposure defined as all CFCs administered within a 24-hour period[8,42]), and thereafter up to 75 exposures.[43]
- Eradication of inhibitors is currently best achieved through immune tolerance induction (ITI) therapy.
- Patients who develop inhibitors should have access to ITI and to suitable hemostatic agents for control of bleeding as well as surgical interventions, if needed, at specialized centres with relevant experience.[9,23]
- Bypassing agents and other suitable treatment products should be available for patients who do not respond to enhanced factor dosages or ITI.[23,40,44]
- Given the costs and other limitations of current treatment modalities, research and innovation in the prevention and treatment of inhibitors are required.[8]
- See Chapter 5: Hemostatic Agents and Chapter 8: Inhibitors to Clotting Factor.

1.10 | Principle 10: Management of musculoskeletal complications

- The prevention and treatment of musculoskeletal complications in people with hemophilia are important to their health, autonomy, and quality of life.
- In all cases of musculoskeletal bleeding, adequate treatment generally requires a combination of clotting factor replacement therapy and physical therapy with an experienced physical therapist to achieve complete functional recovery.[45]

- People with hemophilia should also have access to musculoskeletal specialists (i.e., physical therapist, occupational therapist, physiatrist, physical medicine/rehabilitation specialist, rheumatologist, orthopedist, orthopedic surgeon) with experience in hemophilia, with annual musculoskeletal assessments and longitudinal monitoring of their musculoskeletal outcomes and preventive or corrective measures as needed.
- Surgical interventions may become necessary for musculoskeletal complications if nonsurgical measures fail to provide satisfactory pain relief and improved function. Orthopedic surgeons should have specific training in surgical management of patients with hemophilia.
- See Chapter 2: Comprehensive Care of Hemophilia and Chapter 10: Musculoskeletal Complications.

1.11 | Principle 11: Management of specific conditions and comorbidities

- Specific complications and management issues may affect people with hemophilia and their families at different life stages. Treatment and care for these conditions should be established as part of national hemophilia programs.

Carriers of hemophilia

- Some carriers of hemophilia experience bleeding problems, including joint hemorrhages, similar to males; in addition, they may experience problems that are specific to women, such as prolonged or heavy menstrual bleeding.[46-49] Symptomatic carriers are considered to have mild or moderate hemophilia. It is therefore important to include a gynecologist in the comprehensive care team for the management of carriers.
- Carriers may experience a significant impact on various aspects of their lives and thus require specialist care specific to reproductive issues, including genetic counselling, genetic testing, prenatal diagnosis and planning, newborn testing, and psychosocial counselling.
- See Chapter 9: Specific Management Issues – Carriers.

Surgery and other invasive procedures

- Surgeries and other invasive procedures pose particular risks to patients with hemophilia; however, these procedures can be performed safely with the provision of adequate laboratory support, careful preoperative planning, appropriate hemostasis with sufficient quantities of CFCs and other hemostasis products during and after surgery, and optimal postoperative recovery and rehabilitation.
- Therefore, treatment centres and hospitals should establish protocols to ensure that people with hemophilia, with or without inhibitors, have ready access to these services, both in acute and elective surgery situations.
- See Chapter 9: Specific Management Issues – Surgery and invasive procedures.

Management of comorbidities

- Improved life expectancy in hemophilia has led to a greater interest in age-related disorders, with cardiovascular disease, hypertension, and other cardiovascular risk factors increasingly reported in adults with hemophilia.[50-54]
- The treatment of comorbidities, especially cardiovascular diseases, is one of the most important challenges.[50]
- Although most evidence suggests that hemophilia, at least the severe form, partially protects against myocardial infarction, stroke, and venous thromboembolism, typical cardiovascular risk factors may still be present and cause disease despite the clotting defect.[50,55]
- People with hemophilia are equally or even more prone to obesity, hypertension, and diabetes than the general population.[50]
- Preventive strategies are needed to identify people with hemophilia who are at higher risk of developing cardiovascular disease in adulthood.[56]
- See Chapter 9: Specific Management Issues – Comorbidities.

Medical issues with aging

- As they age, people with hemophilia require education and preventive strategies to reduce the risks and impacts of age-related morbidities.
- The hemophilia team should be closely involved in the planning and management of specialist care for people with hemophilia with comorbidities and any complications related to aging, to facilitate close consultation and agreement on treatment plans.
- Elderly patients with hemophilia should be managed in the same way as their peers in the general population, except for the necessary additional correction of impaired hemostasis with CFCs.[50]
- Specialist services should be well versed in bleed management and the specific treatment requirements of people with hemophilia.[8]
- See Chapter 9: Specific Management Issues – Medical issues with aging.

Management of transfusion-transmitted infections

- Transfusion-transmitted infections, particularly those with the human immunodeficiency and hepatitis C viruses, have been major complications in the treatment of hemophilia in the past.
- It is absolutely imperative to ensure that current replacement therapy products are well tested and virally inactivated to avoid any chance of such infections being transmitted.
- While the management of these conditions will not be covered further in these guidelines, given the effectiveness of current

anti-viral therapies for both these conditions, it is important that relevant services be universally accessible to all patients with hemophilia who need them.[57]

1.12 | Principle 12: Outcome assessment

- In the management of hemophilia, outcome assessment refers to the use of specific tools designed to monitor an individual's disease course and to measure the consequences of the disease and its treatment (i.e., effectiveness of hemostatic therapy and associated complications).[33]
- To ensure that all consequences of the disorder are evaluated, outcome assessment should follow the WHO's ICF model.[58,59]
- Standardized, validated outcome assessment is necessary for the clinical management of individual patients, to assess the quality of care provided, and for research or advocacy purposes.[33]
- The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.[6]
- In hemophilia care, the impact of bleeding on the musculoskeletal and other systems is measured across several domains, including body structure and function and activities and participation. All of these domains may be affected by contextual factors including environmental, personal, and economic factors.[33]
- Multiple clinical and radiological tools are used to assess the status of joints and specific muscle groups. Measurements of activities and participation are either self-reported or observed.[6,60]
- The ongoing development of hemophilia-specific measurement and assessment tools offers opportunities for clinicians and patients to better understand and evaluate the nature of the impairments and functional limitations associated with the condition.[8,60]
- Increasingly in recent years, health authorities, including health technology assessment bodies, are relying on patient-reported outcome data to evaluate the benefits of health interventions.[61]
- Despite the availability of numerous assessment options, a core set of measures for outcome assessment in hemophilia remains to be defined. Such a core set should ideally be applicable to the clinical and cultural realities of hemophilia management worldwide.[12,13]
- See Chapter 11: Outcome Assessment.

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SUPPORTING INFORMATION

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

Chapter 2: Comprehensive Care of Hemophilia

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

2.1 | Introduction

- Hemophilia is a rare X-linked congenital bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII), called hemophilia A, or factor IX (FIX), called hemophilia B. The factor deficiencies are the result of pathogenic variants in the *F8* and *F9* clotting factor genes.
- The best estimates of the prevalence of hemophilia, based on the most reliable national patient registry data available and recent World Federation of Hemophilia (WFH) annual global surveys, indicate that the expected number of males with hemophilia worldwide is 1,125,000, the majority of whom are undiagnosed, including an estimated 418,000 males with severe hemophilia.[1]

Hemophilia A and B

- Hemophilia A is much more common than hemophilia B. Hemophilia A is estimated to account for 80%-85% of all hemophilia cases; hemophilia B is estimated to account for 15%-20% of all hemophilia cases. Estimated prevalence at birth is 24.6 cases per 100 000 males for all severities of hemophilia A (9.5 cases for severe hemophilia A) and 5.0 cases per 100 000 males for all severities of hemophilia B (1.5 cases for severe hemophilia B).[1]
- Hemophilia is usually inherited through an X chromosome with an *F8* or *F9* gene mutation. However, both the *F8* and *F9* genes are prone to new mutations, and about 30% of all cases result from spontaneous genetic variants. Prospective studies report that over 50% of people newly diagnosed with severe hemophilia have no prior family history of hemophilia.[2,3]
- Hemophilia usually affects only males who inherit an affected maternal X chromosome. Females with hemophilia (FVIII or FIX <40 IU/dL) are rare; in such cases, both X chromosomes are affected or one is affected and the other is inactive. A female with one affected X chromosome is called a carrier of hemophilia.[4]
- Hemorrhages, musculoskeletal complications, and other sequelae of hemophilia typically occur in males with hemophilia but may also occur in a proportion of female carriers. Since the baseline factor levels in carriers may be normal or variably reduced, the symptoms and complications of hemophilia are less common in females and are often overlooked and underdiagnosed; joint bleeds in carriers often remain unrecognized, leading to poorer joint outcomes due to undiagnosed joint problems. Better diagnosis and management of bleeding problems in carriers are needed. (See Chapter 9: Specific Management Issues – Carriers.)

Clinical diagnosis

- Hemophilia should be suspected in individuals presenting with a history of any of these symptoms:
  - easy bruising;
  - "spontaneous" bleeding (i.e., bleeding for no apparent/known reason), particularly into the joints, muscles, and soft tissues;
  - excessive bleeding following trauma or surgery.

- Early symptoms of joint bleeds in children at a very young age are a key indicator of severe hemophilia.[5] (See also "Bleeding manifestations" below.)
- If hemophilia is suspected, the clinician should obtain the patient's bleeding history and family history of abnormal or unexplained bleeding experienced by any siblings or maternal male relatives (i.e., maternal cousin, uncle, or grandfather) to assess patterns of inheritance and assist with diagnosis.
- Accurate diagnosis of hemophilia is essential to inform appropriate management. A definitive hemophilia diagnosis is based on a factor assay to demonstrate deficiency of FVIII or FIX.
- See Chapter 3: Laboratory Diagnosis and Monitoring and Chapter 4: Genetic Assessment.

Bleeding manifestations

- The characteristic phenotype in hemophilia is the bleeding tendency. The severity of bleeding manifestations in hemophilia generally correlates with the degree of the clotting factor deficiency (see Table 2-1).
- People with mild hemophilia may not necessarily have abnormal or prolonged bleeding problems until they experience serious trauma or undergo surgery.
- People with severe hemophilia most commonly experience bleeds into the joints, muscles, and internal organs (see Tables 2-2 and 2-3).
- In newborns and children with severe hemophilia less than 2 years of age, common types of bleeding include[6,7]:
  - soft tissue and intramuscular bleeding;
  - bleeding associated with a medical procedure (e.g., venipuncture, central line placement, circumcision, neonatal heel prick);
  - mucocutaneous bleeding (e.g., oral, nasal);
  - extracranial bleeding.
- Some types of bleeds can be life-threatening and require immediate treatment and medical attention.
- See Table 2-2 and Chapter 7: Treatment of Specific Hemorrhages.

Patient/caregiver education

- People with hemophilia and family/primary caregivers must receive comprehensive education on hemophilia care, particularly on the prevention and treatment of bleeds and management of musculoskeletal complications, and training on essential skills for self-management, including bleed recognition, self-treatment, record-keeping, dental care, and risk management.[10,11] (See 2.5 Home therapy – Self-management, below.)

2.2 | Comprehensive care

- Comprehensive hemophilia care involves multidisciplinary medical services necessary for the diagnosis, treatment, and management of the condition and its complications. These services are typically delivered by a hemophilia treatment centre or hemophilia comprehensive care centre, as described in Chapter 1: Principles of Care – Principle 1: National coordination and delivery of hemophilia care. Comprehensive care promotes physical health, psychosocial well-being, and quality of life for people with hemophilia and reduces morbidity and mortality.[11-13] It should encompass family-centred care, particularly diagnosis and management of carriers.[11,14]

Key components of comprehensive care

- Hemophilia is a rare inherited disorder that is complex to diagnose and to manage. Optimal care, especially for people with severe forms of the disorder, requires more than treatment of acute bleeding.
- Priorities in hemophilia treatment and care include[10,11]:
  - prevention of bleeding and joint damage;
  - prompt management of bleeding episodes including physical therapy and rehabilitation after joint bleeds;
  - pain management;
  - management of musculoskeletal complications;
  - prevention and management of inhibitors;
  - management of comorbidities;
  - dental care;
  - quality-of-life assessments and psychosocial support;
  - genetic counselling and diagnosis;
  - ongoing patient/family caregiver education and support.
- Emergency care should be available at all times, with the following essential services and resources[10,11]:
  - coagulation laboratory services with the capacity to perform accurate and precise clotting factor assays and inhibitor testing;

TABLE 2-1 Relationship of bleeding severity to clotting factor level[8]

Severity	Clotting factor level	Bleeding episodes
Severe	<1 IU/dL (<0.01 IU/mL) or <1% of normal	• Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1-5 IU/dL (0.01-0.05 IU/mL) or 1-5% of normal	• Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5-40 IU/dL (0.05-0.40 IU/mL) or 5-<40% of normal	• Severe bleeding with major trauma or surgery; rare spontaneous bleeding

- provision of clotting factor concentrates (CFCs), either virus-inactivated plasma-derived or recombinant, as well as other hemostatic agents such as desmopressin (DDAVP) and antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid [EACA]) where available;
- provision of safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate if adequately screened, tested, and/or virus-inactivated where CFCs are not available;
- casting and/or splinting and mobility/support aids, as needed.

- See Chapter 5: Hemostatic Agents.

Comprehensive care team

- The wide-ranging needs of people with hemophilia and their families are best met by a multidisciplinary team of healthcare professionals with expertise and experience in hemophilia, in accordance with accepted protocols and practices and national standards of care, if available.[10,15,16]

Patient/healthcare provider partnership and decision-making

- People with hemophilia are regarded as distinct core members of the comprehensive care team who through day-to-day self-management become experts and partners in their own hemophilia care.
- It is important to involve patients (and their parents/caregivers) in decision-making; incorporate their particular preferences, values, and personal experiences;[17] and obtain their concurrence with short- and long-term treatment and management plans. All parties should engage in truly shared decision-making through educated discussions about available healthcare options and anticipated outcomes, including evidence-informed guideline recommendations, benefits and risks of the various choices, and expressed concerns and values of the patient and caregivers.[18] They should work together on the development and periodic updating of individualized treatment guidelines that the patient/caregiver can consult at will and share with others involved in care.
- Increasingly, patients are not only active members of their own healthcare team; they are becoming full partners in the healthcare team who are also involved in research, medical education, and student training in recognition of the value of their particular understanding and expertise.[17]

TABLE 2-2 Sites of bleeding in hemophilia[9]

Serious	• Joints (hemarthrosis) • Muscles, especially deep compartments (iliopsoas, calf, forearm) • Mucous membranes of the mouth, nose, and genitourinary tract
Life-threatening	• Intracranial • Neck/throat • Gastrointestinal

TABLE 2-3 Approximate frequency of bleeding at different sites

Site of bleeding	Approximate frequency
Joints • More common in hinged joints: ankles, knees, elbows • Less common in multi-axial joints: shoulders, wrists, hips	70-80%
Muscles	10-20%
Other sites (major bleeds)	5-10%
Central nervous system	<5%

Multidisciplinary team

- The core team typically consists of a medical director, nurse coordinator, physical therapist, laboratory specialist, and psychosocial counsellor; all of whom should be specifically trained in the field.
  - The medical director (normally a pediatric and/or adult hematologist or a physician with training and expertise in managing hemophilia and other bleeding disorders) oversees patient management including ordering diagnostic laboratory tests, prescribing treatment, and monitoring patient health and medical needs.
  - The nurse coordinator, who should have training in the management of patients with bleeding disorders, coordinates the provision of care by the multidisciplinary team, educates patients and their families, provides training for home therapy and other aspects of care, and assesses patients and institutes initial care where appropriate.
  - The physical therapist plays an important role in educating people with hemophilia and their caregivers on preventive measures, facilitating complete functional recovery after each bleed, and counselling individuals about preserving musculoskeletal health.[19] Other musculoskeletal specialists (i.e., occupational therapist, physiatrist, physical medicine/rehabilitation specialist, rheumatologist, orthopedist, orthopedic surgeon) provide treatment for specific musculoskeletal conditions.
  - The laboratory specialist performs specialized blood tests to establish the diagnosis and monitor therapy, including blood coagulation tests, factor assays, and inhibitor assays.
  - The psychosocial counsellor (preferably a social worker or psychologist) conducts psychosocial assessments and provides counselling and/or referrals to community resources.
- The roles assumed by core team members may differ at different centres, depending on the availability and expertise of trained staff and the organization of services within the centre.
- The comprehensive care team should also include or have access to dentists with hemophilia experience, and other specialists as

needed to address specific medical and health-related issues that some people with hemophilia and carriers may encounter, including:
  - chronic pain specialist;
  - pharmacist;
  - geneticist;
  - hepatologist;
  - infectious disease specialist;
  - immunologist;
  - gynecologist/obstetrician;
  - vocational counsellor.
- Other medical specialists may be needed to address comorbid conditions related to age, lifestyle, or other circumstances. (See Chapter 9: Specific Management Issues – Comorbidities.)
- Detailed clinical management protocols are essential to ensure continuity of care in the event of personnel changes within the comprehensive care team.[10,15,16]
- To foster the necessary expertise and experience in hemophilia, mentorships and fellowships can offer opportunities for recruiting medical professionals to the field and advancing clinical knowledge.

Recommendation 2.2.1:

- **For people with hemophilia, the WFH recommends coordinated delivery of comprehensive care by a multidisciplinary team of healthcare professionals with expertise and experience in hemophilia.**
- **Remark: The core members of the comprehensive care team should consist of a medical director, nurse coordinator, musculoskeletal specialists, medical laboratory specialist, psychosocial specialist, and the patient and family caregivers. The roles assumed by the core team members may differ at different centres depending on the availability and expertise of trained staff and the organization of services within the centre.** CB

Recommendation 2.2.2:

- **For people with hemophilia, the WFH recommends availability of and access to:**
  - **appropriate emergency care at all times;**
  - **a coagulation laboratory capable of performing clotting factor assays and inhibitor testing;**
  - **appropriate clotting factor concentrates (CFCs), either plasma-derived or recombinant, as well as other hemostatic agents such as desmopressin (DDAVP), emicizumab, and antifibrinolytics;**
  - **safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate that have been adequately screened, tested, and/or virus-inactivated if CFCs are not available;**
  - **casting and/or splinting for immobilization and mobility/support aids, as needed;**
  - **other specialists to address specific medical and health-related issues that some individuals may encounter, as needed.** CB

Recommendation 2.2.3:

- **For all patients with hemophilia, the WFH suggests the preparation of written clinical management protocols to ensure continuity of care in the event of changes in clinic personnel.** CB

Functions of a comprehensive care program

- A comprehensive care program helps put into operation the key principles of comprehensive care for hemophilia. The core functions are described here.

Coordination and provision of care

- A comprehensive care program enables centralized coordination of care from across multidisciplinary specialities, services, and facilities, and the provision of inpatient care (hospital stays) and outpatient care (checkups and other clinic visits) to patients and their families.
- People with hemophilia require periodic monitoring and assessment of their condition and circumstances. They should be evaluated at least once per year; those with mild or moderate hemophilia may require less frequent monitoring.[20]
- Referrals to other services (e.g., dentistry, surgery, obstetrics/gynecology) including communication of the care management plan to all treaters and care facilities are arranged through the program, which helps ensure that patients receive optimal care from specialists with appropriate hemophilia expertise. Planning and coordination of procedures must involve patients/family caregivers in consultation with all specialists required (e.g., for surgery, the anesthesiologist, surgeon, and surgical staff including nurses).[20-22]
- Ongoing collaboration with patients and family caregivers to develop, audit, and refine the comprehensive care management plan is essential.

Recommendation 2.2.4:

- **For people with hemophilia, the WFH recommends a multidisciplinary checkup including hematologic, musculoskeletal, and quality-of-life assessments by the core comprehensive care team members at least yearly (every 6 months for children).**
- **Remark: Smaller centres and family physicians can provide primary care and management of some complications of hemophilia, in frequent consultation with the hemophilia comprehensive care centre, especially for patients who live a long distance from the nearest hemophilia treatment centre.**

Patient registry and data collection

- The comprehensive care program facilitates centralized patient data collection on sites of bleeds, types and doses of treatment administered, complications of treatment, and assessment of long-term musculoskeletal and other health outcomes and patient-reported outcomes (e.g., bleed-related activities, acute and chronic pain, days missed from school or work, impact

of hemophilia on activities of daily living). The WFH's World Bleeding Disorders Registry (WBDR) is an online platform for use by hemophilia treatment centres around the world to collect such data to monitor patient outcomes and guide clinical practice.[23]

- Patient records should be maintained in accordance with confidentiality laws and other national regulations, ideally in a computerized patient registry that is updated regularly by designated clinic staff with direct or indirect patient input.
- Systematic data collection also serves to facilitate the auditing of services provided by the hemophilia treatment centre with the goal of improving care delivery and to help the patient better manage their health condition.
- See Chapter 9: Specific Management Issues, Chapter 10: Musculoskeletal Complications, and Chapter 11: Outcome Assessment.

Recommendation 2.2.5:

- **For all patients with hemophilia, the WFH recommends systematic data collection in patient registries, where possible, to inform allocation of resources, support improvement of care delivery services, and promote collaboration among centres in sharing data and conducting research.** CB

Clinical research

- Basic and clinical hemophilia research should be conducted where possible. Since the number of patients with hemophilia at individual centres may be limited, clinical research is best conducted in collaboration with other hemophilia centres and national hemophilia patient groups such as national member organizations (NMOs) of the WFH.

Patient/caregiver education and support

- Education and training on home therapy should be provided where available and should ideally include supervision of adherence to treatment.
- Ongoing support should be provided to families and caregivers including identifying resources and/or developing strategies to enable them to adapt to living with hemophilia.
- Potential challenges that patients and family members may encounter in everyday living, particularly those related to the management of bleeding, include:
  - changes associated with different stages of growth and development (especially adolescence and aging);
  - adherence to a complex medical regimen requiring frequent IV infusions in the midst of other competing family needs[24];
  - issues with schooling and/or employment;
  - psychosocial and mental health issues;
  - bleeding problems and reproductive issues in carriers.
- In collaboration with hemophilia patient organizations, a comprehensive care program helps promote and/or facilitate hemophilia support groups, educational workshops, and recreational activities such as hemophilia camps.
- See 2.5 Home therapy and 2.8 Transition from pediatric to adult care, below, and Chapter 9: Specific Management Issues.

Recommendation 2.2.6:

- **The WFH recommends that adequate education be provided to people with hemophilia, their family members, and other caregivers to enable self-management and sufficient understanding of the disease for prevention of bleeds and related complications and for life planning.** CB

Recommendation 2.2.7:

- **For people with hemophilia and their families, the WFH recommends promotion and/or facilitation of educational and recreational activities in collaboration with patient organizations, to provide them with opportunities to discover new interests and capabilities and build a support network with diverse members of the hemophilia community.** CB

2.3 | Fitness and physical activity

- Physical activity is important to promote normal neuromuscular development and physical fitness.[19]
- People with hemophilia may have an increased risk of low bone mineral density compared to the general population due to risk factors including hemophilia severity and hemophilic arthropathy and resulting immobility.[25] Ways to promote bone health include preventing hemarthrosis, regular exercise, and adequate vitamin D and calcium intake.[26,27]
- For those 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.[26]
- The choice of activities should reflect the individual's preferences/interests, physical condition and ability, local contexts, and available resources.
- Non-contact sports such as swimming, walking, jogging, golf, badminton, archery, cycling, rowing, sailing, and table tennis should be encouraged.
- High-contact and collision sports such as soccer, hockey, rugby, boxing, and wrestling, and high-velocity activities such as motocross racing and skiing are not advised due to the potential for life-threatening injuries, unless the individual is on adequate prophylaxis to cover such activities and is well educated on the potential risks.
- Custom-made dental mouthguards should be used by individuals with hemophilia for all contact sports to prevent trauma and injury to teeth and oral soft tissues.[28]
- Organized sports programs should be encouraged over unstructured sports activities where protective equipment and supervision may be lacking.
- Ideally, individuals with hemophilia (or their family caregivers) should consult a physical therapist before engaging in new sports

and physical activities to discuss their appropriateness, required protective gear, prophylaxis (factor coverage and other measures), and required physical skills prior to beginning the activity. This is particularly important if the individual has any joint with recurrent bleeding (i.e., target joint).[29]

- Ongoing patient/caregiver education on the physical implications of a given activity in relation to hemophilia (i.e., joint flexion, joint or muscle trauma) is important so that they can make informed choices, adapt their self-management accordingly, and responsibly manage the way they participate in sports and physical activities.
- Target joints can be protected with braces or splints during physical activity, especially in the absence of factor coverage.[30,31]
- See Chapter 7: Treatment of Specific Hemorrhages and Chapter 10: Musculoskeletal Complications.

Recommendation 2.3.1:

- **For people with hemophilia, the WFH recommends promotion of regular physical activity and fitness, with special attention on bone health maintenance, muscle strengthening, coordination, physical functioning, healthy body weight, and positive self-esteem.** CB

Recommendation 2.3.2:

- **For people with hemophilia, the WFH recommends promotion of non-contact sports. High-contact and collision sports and high-velocity activities should be avoided unless the individual is on a prophylactic regimen that is adequate to cover such activities and is properly educated on the potential risks and other required protective measures.**
- **Remark: The choice of sports activities should take into consideration the individual's physical condition and ability, preferences and interests, local customs, and available resources.** CB

Recommendation 2.3.3:

- **For people with hemophilia, the WFH recommends consultation with a physical therapist or other musculoskeletal specialist before engaging in sports and physical activities to discuss their appropriateness specific to the individual's condition and their requirement for particular physical skills and/or protective gear.** CB

2.4 | Adjunctive management

- Adjunctive therapies are important in the treatment of bleeds, particularly where coagulation therapies and hemostatic agents are limited (or unavailable), and may lessen the amount of treatment product required.
- First-aid measures are a key component of adjunctive management. In addition to CFCs to raise factor levels (or DDAVP in mild hemophilia A), the PRICE principles—protection, rest, ice, compression, and elevation—based on the conventional rest, ice, compression, and elevation (RICE) protocol for injuries, may be used for joint and muscle bleeds. Another approach, POLICE (protection, optimum loading, ice, compression, and elevation), replaces "rest" with "optimum loading" to focus attention on the need to balance rest with early mobilization and gradual weight-bearing to prevent complications associated with immobilization.[32] It is important to consider the appropriateness of each of these measures for the particular situation.
- In recent years, there has been debate on the application of ice, which is believed to help manage acute pain from joint bleeding and reduce blood flow to the injured tissue.[33] One study suggested that the cooling effect of ice may interfere with coagulation and slow the hemostasis process.[34] However, counter viewpoints note that many people with hemophilia appreciate ice for pain relief and that, for those without access to treatment products, ice for acute and chronic pain may be their only "treatment" option.[35-37]
- See Chapter 7: Treatment of Specific Hemorrhages – Joint hemorrhage – Adjunctive care.
- Physical therapy and rehabilitation are particularly important for functional improvement and recovery after musculoskeletal bleeds and for those with established hemophilic arthropathy.[38,39]
- See Chapter 7: Treatment of Specific Hemorrhages – Joint hemorrhage – Physical therapy and rehabilitation and Chapter 10: Musculoskeletal Complications – Hemophilic arthropathy and joint contractures – Physical therapy for hemophilic arthropathy.
- Antifibrinolytic drugs are effective as adjunctive treatment for mucosal bleeds and invasive dental procedures. (See 2.7 Dental care and management, below, and Chapter 5: Hemostatic Agents – Other pharmacological options.)
- Certain selective COX-2 inhibitors may be used for joint inflammation after an acute bleed and for chronic arthritis.[40] (See 2.6 Pain management, below.)
- Complementary techniques for pain management (e.g., meditation, distraction, mindfulness, or music therapy) may also be helpful for those with chronic hemophilic arthropathy. (See 2.6 Pain management, below.)

Recommendation 2.4.1:

- **For people with hemophilia with a muscle or joint bleed, the WFH recommends following the PRICE principles (protection, rest, ice, compression, and elevation) in addition to increasing factor level.** CB

Recommendation 2.4.2:

- **For people with hemophilia recovering from a joint or muscle bleed, the WFH recommends gradual re-initiation of physical activities under the supervision of a physical therapist with experience in hemophilia to assess resumption of normal motor development and coordination.**
- **Remark: For children with hemophilia recovering from a joint or muscle bleed, the physical therapist and family caregiver should**

remain in close contact to discuss and decide on the appropriate sports and activities for the child's progressive rehabilitation. CB

Recommendation 2.4.3:

- **For people with hemophilia with established hemophilic arthropathy or after recovery from musculoskeletal bleeding, the WFH recommends physical therapy and rehabilitation activities.** CB

Recommendation 2.4.4:

- **For people with hemophilia, the WFH recommends the use of antifibrinolytic drugs (e.g., tranexamic acid, epsilon aminocaproic acid [EACA]) alone or as adjuvant treatment, particularly in controlling mucosal bleeds and for invasive dental procedures.** CB

2.5 | Home therapy

- Home therapy gives people with hemophilia immediate access to CFCs or other coagulation therapies and hemostatic agents (e.g., emicizumab, DDAVP, antifibrinolytics) and hence enables optimal early treatment, resulting in less pain, dysfunction, and long-term disability, and significantly reduced hospitalization rates for hemophilic bleeding complications, especially for those on prophylaxis compared to episodic therapy.[41-43]
- Home therapy also offers people with hemophilia substantially improved quality of life including less school/work absenteeism, the ability to safely participate in a larger variety of sports and physical activities, greater employment stability, and greater freedom to travel.[44]
- Home therapy must be supervised closely by the comprehensive care team and should only be initiated after comprehensive patient/caregiver education and training.[41,42]
- Education should focus on instilling essential knowledge of hemophilia and the basics of home therapy, including:
  - recognition of bleeds and common complications;
  - first-aid measures;
  - dosage calculation;
  - storage, preparation, and administration of CFCs and/or other treatment products;
  - aseptic techniques;
  - venipuncture (or access through a central venous catheter) and self-infusion/self-injection;
  - record-keeping;
  - proper storage and disposal of needles/sharps;
  - handling of blood spills.
- A patient/caregiver home therapy certification program is helpful for acknowledging and ensuring readiness to begin home therapy.
- Treatment adherence, level of education, and understanding of episodic and prophylactic treatment, infusion/injection techniques, and bleed records should be reviewed and evaluated with patients and family caregivers at clinic checkups.
- See also "Self-management" below.

Clotting factor replacement therapy

- Home therapy with CFCs should ideally be achieved with products that are safe and are easily reconstituted. CFCs can be stored at room temperature or in a domestic refrigerator, depending on the product. People with hemophilia must be skilled in self-infusion to minimize time to treatment and improve their joint health outcomes.[45]
- Home therapy with CFCs can be started with young children with adequate venous access and motivated family caregivers who have undergone comprehensive training. Older children and teenagers can learn self-infusion with education and training from the hemophilia nurse coordinator (or home infusion nurse, where available) and family support.
- See "Self-management" below and Chapter 6: Prophylaxis in Hemophilia.

New coagulation therapies

- The use of new innovative therapies administered via different routes requires carefully planned patient/caregiver education, training, and supervision including specific training for those transitioning to another type of therapy (e.g., from intravenous factor replacement therapy to subcutaneous factor substitution therapy with emicizumab).
- Patients and their caregivers should understand the differences, benefits, and any risks associated with a particular treatment. Importantly, they should be taught how to monitor treatment and response, and under which circumstances they should contact their healthcare provider and/or hemophilia treatment centre (e.g., breakthrough bleeding, upcoming surgery).

Emicizumab

- People with hemophilia A on prophylaxis with emicizumab may begin home therapy after proper training in subcutaneous injection technique.[46]
- Emicizumab and those non-factor agents in development differ from conventional types of prophylaxis as they do not replace the missing coagulation factor, are administered subcutaneously and, in some cases, can be administered as infrequently as once or twice monthly.[47] Additionally, these agents are not associated with the peak and trough curves of protection that are now seen with factor prophylaxis regimens.
- Emicizumab's subcutaneous route of administration is already making it easier to start pediatric patients on prophylaxis at very young ages and without the need for central venous access devices (CVADs). Emicizumab makes it feasible to initiate prophylaxis at birth to provide protection of newborns and infants newly diagnosed with severe hemophilia A; however, further research in infants less than 1 year of age is required.[48]
- Emicizumab is not intended to treat acute bleeding episodes. Breakthrough bleeding is treated with doses of CFCs (or

bypassing agents in the case of patients with inhibitors) that are sufficient to achieve hemostasis. Caution is required when treating breakthrough bleeding episodes while on emicizumab as several patients have developed either venous thromboembolism or thrombotic microangiopathy with concomitant administration of activated prothrombin complex concentrate (aPCC).[49] Consult the individual product inserts for precautions and risk management guidance.

- See Chapter 5: Hemostatic Agents, Chapter 6: Prophylaxis in Hemophilia, and Chapter 8: Inhibitors to Clotting Factor.

Self-management

- Self-management focuses on patient empowerment and refers to a patient's ability to acquire the necessary skills and knowledge to become competent in their own care and apply it in their daily activities to keep their condition under control and minimize its impacts on their physical and psychological health.[45] For people with hemophilia, self-management requires concrete knowledge of bleeding mechanisms and treatment strategies (when and how to treat and what dose to give).[45]
- The key self-management skills required for people with hemophilia include[45]:
  - bleed recognition;
  - self-infusion/self-treatment skills;
  - self-care (i.e., nutrition and physical fitness) and medicines management (i.e., record-keeping, treatment routines, maintenance of adequate treatment supply, skills in storage, reconstitution, and administration of treatment products);
  - pain management; and
  - risk management and conceptualizing preventive therapy.
- Knowledge of appropriate adjunctive therapies (e.g., antifibrinolytics, pain medications) and adjunctive management (e.g., the PRICE principles) are also important to self-management.
- See 2.3 Fitness and physical activity, 2.4 Adjunctive management, and 2.5 Home therapy, above, and 2.6 Pain management, below.

Bleed recognition

- Bleed recognition, especially of joint and muscle bleeds, is an essential part of self-management so that prompt treatment can be initiated to minimize the short- and long-term impacts of bleeds. In hemophilia, a wait-and-see approach for potential bleeds or missed doses may result in the onset and progression of bleeding symptoms that are not only painful but ultimately lead to joint damage.
- It is important for family members/caregivers to be able to recognize subtle signs of bleeds in young children with hemophilia; in infants and young children, reluctance to use a limb may be indicative of a joint/muscle bleed.[50] The signs and symptoms of common types of hemorrhage in hemophilia[50] are described in Chapter 7: Treatment of Specific Hemorrhages and Chapter 11: Outcome Assessment.
- For those on prophylaxis with new types of coagulation therapy, it is important to monitor and assess the ability of patients/caregivers to recognize breakthrough bleeds and initiate prompt episodic treatment with CFCs or appropriate hemostatic agents.

Self-infusion/self-treatment

- In young children, injections or infusions are normally given by the parents and/or caregivers until the child is old enough to switch to self-treatment.[51]
- Children with hemophilia typically learn to self-infuse or self-inject in late childhood or early adolescence. Self-infusion requires skill and expertise developed through trial and error as well as education and support.[45] Becoming sufficient at self-infusion is complex as it requires a one-handed technique to perform all steps; however, most children self-infuse at least part of the time by 12 years of age.[45]
- Establishing routines, such as self-infusing at the same time every day, can help significantly with treatment adherence.[45]

Recommendation 2.5.1:

- **Patients (or caregivers of children) with hemophilia should be taught how to manage their care at home and be able to demonstrate understanding of how to recognize bleeds and the ability to infuse or self-infuse, with monitoring of venous access skills over the patient's lifetime.** **CB**

Self-care and medicines management

- Because people with hemophilia self-manage largely at home, healthcare providers have to depend on the patient/caregiver to inform them of their type of bleed episodes, bleeding frequency, and usage of treatment products.[52]
- Therefore, it is important for patients/caregivers to keep accurate bleed treatment records (paper or electronic) that include the date and site of bleeding, the dosage and lot number of the product used, any adverse effects, bleed-related activities, and other outcomes to be reported as required.
- Hemophilia treatment centres now have the option to use electronic diaries (e-diaries) in the form of smartphone applications, handheld wireless monitoring systems, and online platforms that allow real-time entries and direct data analysis. With these tools, healthcare providers no longer need to rely on patient visits to the hemophilia treatment centre to review paper diaries.[53-56]
- Studies on e-diaries have demonstrated that their use increases the amount of information provided as well as the completeness of data reporting.[53] Remote patient record management may also improve treatment compliance, increase patient quality of life, support healthcare providers in modifying treatment regimens, and improve communication with the healthcare team.[54-56]

Recommendation 2.5.2:

- **For patients with hemophilia, a detailed record of all treatments administered (reason, batch number, number of units, etc.) should be documented and used to personalize treatment plans.** CB

Risk management and conceptualizing preventative therapy

- Risk management requires the ability to judge and balance chances and risks encountered in daily life, including controlling and navigating risks that arise and distinguishing between negative risk-taking and positive risk management.[45] In addition, it requires being able to self-advocate for appropriate hemophilia care with support from the hemophilia treatment centre such as emergency care, surgical management, or dental treatment. (See 2.3 Fitness and physical activity, above, 2.7 Dental care and management, below, and Chapter 9: Specific Management Issues.)
- In addition, healthcare providers can educate and guide people with hemophilia in planning their daily lives to reduce bleeding risk. Strategies may include adapting the treatment regimen to fit within other priorities (e.g., school and sports), routines, activities, and events in their lives.[45]

Central venous access devices

- An implanted central venous access device can enable stable, long-lasting venous access to make infusions easier and may be required for administering prophylaxis or immune tolerance induction (ITI) therapy in young children with problematic venous access.[57,58]
- The complications and risks associated with surgical implantation of CVADs (i.e., hospitalization, bleeding, catheter infection, thrombosis, breakage, and/or malfunction) need to be weighed against the advantages of early initiation of intensive prophylaxis.[59-61] Many pediatricians and hemophilia treaters are shifting from the use of CVADs to peripheral venous access for early initiation of prophylaxis, starting with once-weekly prophylaxis then gradually escalating infusion frequency,[62] together with more intensive caregiver training.
- Alternatively, the use of emicizumab obviates the need for CVADs, and it is increasingly among the treatment options for people with hemophilia A in many countries. (See Chapter 6: Prophylaxis in Hemophilia.)
- The protocol used for device care (using aseptic precautions), quality of patient/caregiver education, and user compliance may affect frequency of infections; therefore, careful guidelines and surveillance protocols are important to reduce the risk of complications.[59]
- Parents and caregivers must be taught to keep CVADs scrupulously clean and to flush out the catheter properly after each therapy administration to prevent CVAD infection and clot formation.[59] Fibrinolytic agents may be helpful for preventing clotting and infections.[60]
- It is essential to ensure that parents and caregivers have a thorough understanding of all aspects of home therapy and are prepared and able to handle the issues and challenges that commonly arise in children with hemophilia at each development stage. (See 2.8 Transition from pediatric to adult care, below.)
- For patients in whom venous access is problematic, non-factor replacement therapy that can be administered subcutaneously (i.e., emicizumab) should be considered. (See Chapter 6: Prophylaxis in Hemophilia – Non-factor replacement therapy.)

Recommendation 2.5.3:

- **For children with hemophilia, central venous access devices could be considered to facilitate early access to bleed treatment and prophylaxis.** CB

2.6 | Pain management

- Acute and chronic pain are common in people with hemophilia. Proper assessment of the cause of pain is essential.[63]
- See also Chapter 7: Treatment of Specific Hemorrhages.

Recommendation 2.6.1:

- **For people with hemophilia with acute or chronic pain, the WFH recommends the use of age-appropriate pain assessment tools to determine the cause and guide appropriate management.** CB

Pain caused by venous access

- In general, no pain medication is given. If required, application of a local anesthetic spray or cream at the site of venous access may be helpful.[64-66]

Recommendation 2.6.2:

- **For people with hemophilia with venous access pain, discomfort or anxiety, the WFH recommends the application of a local anesthetic spray or cream at the site of venous access.** CB

Pain caused by joint or muscle bleeding

- While hemostatic treatment should be administered as soon as possible to stop bleeding, additional medications are often needed for pain control (see Table 2-4).
- Other adjunctive measures may be required.[40]
- See also Chapter 10: Musculoskeletal Complications.

Recommendation 2.6.3:

- **For people with hemophilia with acute pain due to a joint or muscle bleed, the WFH recommends immediate administration of clotting factor concentrates to stop bleeding, pain medication, and adjunctive measures such as immobilization, compression, and splinting to minimize pain, if appropriate.** CB

TABLE 2-4 Pain management strategies for people with hemophilia

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

Note: If for any reason medications have been stopped for a period of time, individuals who have been taking and tolerating high-dose narcotic drugs should restart the drug at a lower dose, or use a less powerful painkiller, under the supervision of a physician.

[a]COX-2 inhibitors should be used with caution by people with hemophilia with hypertension and renal dysfunction.

Postoperative pain

- Intramuscular injection of analgesics should be avoided.
- Postoperative pain management should be coordinated with the anesthesiologist or pain specialist.
- Initially, narcotic analgesics can be given, followed by an oral opioid.
- When pain decreases, paracetamol/acetaminophen may be used.

Recommendation 2.6.4:

- **For patients with hemophilia and postoperative pain, the WFH advises proportionate management of postoperative pain in coordination with the anesthesiologist or pain specialist. CB**

Recommendation 2.6.5:

- **For patients with hemophilia and postoperative pain, the WFH recommends analgesia similar to that used in patients without hemophilia including, as appropriate, the use of intravenous morphine or other narcotic analgesics, followed by an oral opioid (e.g., tramadol, codeine, hydrocodone, etc.) and paracetamol/acetaminophen as pain decreases.**
- **Remark: With the exception of selective COX-2 inhibitors, NSAIDs should not be used in patients with hemophilia.**
- **Remark: The intramuscular route for administration of analgesia is not advised. CB**

Pain due to chronic hemophilic arthropathy

- Chronic hemophilic arthropathy develops in individuals who have not had adequate treatment and follow-up physical therapy and rehabilitation for joint and muscle bleeds.
- Pain management for chronic hemophilic arthropathy should include functional training and adaptation, and appropriate analgesics as detailed in Table 2-4.[19,67-69]
- Pain medications that may be used by people with hemophilia for chronic hemophilic arthropathy include paracetamol/acetaminophen, selective COX-2 inhibitors, tramadol, and opioid analgesics.[70,71] Other NSAIDs should be avoided in people with hemophilia.[72] Codeine should not be administered to children under 12 years of age.
- For individuals with disabling chronic pain due to hemophilic arthropathy, orthopedic surgery may be indicated.[73]
- See Chapter 10: Musculoskeletal Complications – Hemophilic arthropathy.

Recommendation 2.6.6:

- **For people with hemophilia and chronic hemophilic arthropathy in need of pain management, the WFH recommends functional training and adaptations alongside appropriate analgesics. CB**

Recommendation 2.6.7:

- **For people with hemophilia and chronic hemophilic arthropathy, the WFH recommends education on pain management including the use of complementary pain management techniques (e.g., meditation, distraction, mindfulness, or music therapy). CB**

Recommendation 2.6.8:

- **For children and adults with hemophilia with pain due to chronic hemophilic arthropathy, the WFH recommends the use of paracetamol/acetaminophen, selective COX-2 inhibitors, tramadol, or morphine, and avoidance of other NSAIDs. Codeine may be used for children over 12 years of age but is contraindicated in younger children.**
- **Remark: Prolonged use of these medications may have risks of dependence or addiction, as well as organ damage, and must be carefully monitored.**
- **Remark: People with persistent pain should be referred to a specialized pain management team. CB**

Recommendation 2.6.9:

- **For patients with hemophilia with disabling pain from chronic hemophilic arthropathy, the WFH recommends referral to an orthopedic specialist for consideration of orthopedic surgery. CB**

Dental pain

- People with hemophilia experiencing dental pain should always be referred for a professional dental consultation. Proportionate pain management measures should be applied (see Table 2-4).

Recommendation 2.6.10:

- **For children and adults with hemophilia, the WFH recommends interim management of dental or orofacial pain according to a**

proportionate approach for pain relief and referral to a dental care professional for assessment. CB

2.7 | Dental care and management

- Maintaining good oral health and preventing dental problems is of great importance in people with hemophilia to prevent oral diseases and conditions such as gingivitis, dental caries, and periodontal diseases which may cause serious gum bleeding, especially in those with severe/moderate hemophilia,[74] and to avoid the need for major dental surgery.[75]
- Since prolonged bleeding after dental treatment can cause severe or even life-threatening complications, people with hemophilia are a priority group for preventive dental and oral health care.[74]
- It is important to ensure that people with hemophilia have access to dental treatment and regular preventive dental care at a designated dental care centre with expertise in the management of people with hemophilia according to evidence-based dental protocols.[75-77]
- See also Chapter 7: Treatment of Specific Hemorrhages – Oral hemorrhage.

Recommendation 2.7.1:

- **For children and adults with hemophilia, the WFH recommends provisions for access to regular preventive dental and oral health care as part of comprehensive hemophilia care.** CB

Recommendation 2.7.2:

- **For children with hemophilia, the WFH recommends referral to a designated dental care centre at the time of the first tooth eruption (around 6 months of age) or by age 1 in order to reduce the complications, morbidity, costs, and health and psychosocial impacts associated with oral diseases in people with hemophilia.** CB

Recommendation 2.7.3:

- **For adults with hemophilia, the WFH recommends facilitating access to appropriate adult dental services and procedures, with regular dental assessments throughout their lives to monitor and safeguard oral health using evidence-based and personalized preventive dental protocols.** CB

Recommendation 2.7.4:

- **For people with hemophilia, the WFH recommends preventive dental and oral care as a priority to ensure optimal oral health and hygiene to prevent periodontal disease and dental caries, which predispose to gum bleeding, dental pain, tooth loss, chewing difficulties, and social impacts.** CB

Oral care

- Optimal oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding, dental pain, tooth loss, chewing difficulties, and social impacts (e.g., halitosis and low self-esteem).[76,78] This involves the use of oral hygiene products and toothbrushes which can be adapted based on individual needs.[79]
- Dental pain occurring spontaneously or with facial swelling usually indicates the presence of advanced stages of oral disease and/or infection and should trigger a professional dental consultation. Short-term pain control should be achieved as described (see 2.6 Pain management, above), with paracetamol/acetaminophen as the drug of choice to manage toothache in children.[77]

Recommendation 2.7.5:

- **For all people with hemophilia, the WFH recommends education on the importance of good oral hygiene to prevent dental problems and complications, including instructions for twice-daily brushing of the teeth using a soft- or medium-texture toothbrush and fluoridated toothpaste to remove plaque deposits; the toothpaste should not be rinsed away but rather retained ("spit, but don't rinse") after brushing to maximize fluoride benefit.**
- **Remark: The use of dental floss or interdental brushes should be encouraged to ensure complete plaque removal.**
- **Remark: Individuals with elbow or shoulder restrictions may benefit from modified or electric toothbrushes and flossing aids.** CB

Recommendation 2.7.6:

- **For children with hemophilia 6 years of age and younger, the WFH recommends parental/caregiver supervision of toothbrushing.** CB

Dental surgery and invasive procedures

- Before any dental surgery or other invasive procedure within the oral cavity, hemostasis management should be individually planned under the advisement of a hematologist.[80]
- Systemic or topical antifibrinolytics (i.e., tranexamic acid or EACA) are effective as adjunct treatment in the management of dental interventions pre- and postoperatively and have the potential to reduce the need for factor replacement therapy.[76,81,82]
- Antibiotics should only be prescribed if clinically indicated for management of infection.
- Local hemostatic measures such as wound suture, topical antifibrinolytics, oxidized cellulose, and fibrin sealant should be used as appropriate whenever possible following a dental extraction.[82,83]
- Patients must be advised to immediately report any prolonged bleeding and/or difficulty speaking, swallowing, or breathing following dental surgery to the hematologist/dental surgeon as this can be life-threatening. Those who are not in hospital must report to the nearest emergency centre without delay.
- For many dental procedures, adequate local anesthesia is necessary, and most dental injections can be delivered safely.[84,85]
- Higher-risk intramuscular oral injections may require systemic hemostatic measures. These measures should be established preoperatively under advisement of a hematologist.[80]

- Alternative low-risk routes of delivery such as intraligamentary single-tooth anesthesia (STA) or buccal infiltration injections are effective alternatives to inferior alveolar nerve blocks (IDB).[84,86]
- Other nonsurgical dental procedures carry variable levels of bleeding risk. Most restorative dental procedures such as dental fillings are low risk and can be carried out without the need for factor replacement therapy.
- Minimally invasive buccal infiltration or intraligamentary injections and techniques to protect soft tissues should be used, and standard local measures to aid mucosal hemostasis should be applied as appropriate.
- Professional dental cleanings can be provided with the use of antifibrinolytic agents, if necessary.[82]

Recommendation 2.7.7:

- **For patients with hemophilia, the WFH recommends that dental extraction or other invasive procedures within the oral cavity (e.g., dental implantation, periodontal surgery, or gum biopsy) be performed only with a personalized plan for hemostasis management in consultation with a hematologist. CB**

Recommendation 2.7.8:

- **For patients with hemophilia, the WFH recommends the use of systemic or topical tranexamic acid or epsilon aminocaproic acid (EACA) as adjunct treatment in the management of dental interventions pre- and postoperatively, to reduce the need for factor replacement therapy. CB**

Recommendation 2.7.9:

- **For patients with hemophilia requiring dental extractions, the WFH recommends local hemostatic measures. Typical procedures include wound suture, topical use of antifibrinolytics, oxidized cellulose, and fibrin sealant, applied as appropriate.**
- **Remark: Patients should be advised to maintain a soft diet and undertake careful brushing around the wound site for a minimum of 3-5 days postoperatively to avoid disturbing the clot and wound healing within the tooth socket. CB**

Recommendation 2.7.10:

- **For patients with hemophilia, the WFH recommends appropriate local anesthesia for dental treatments as an essential part of pain and anxiety management. Most dental injections pose a low risk for patients with hemophilia when delivered by a dental care professional using local anesthesia with a vasoconstrictor, and when the agent is delivered slowly with a single-use fine-gauge needle. CB**

Recommendation 2.7.11:

- **For patients with hemophilia requiring higher-risk intramuscular oral injections commonly associated with the provision of surgical dentistry (such as inferior alveolar dental block [IDB], superior alveolar nerve block, or injections in the floor of the mouth or vascular lingual tissues), the WFH recommends systemic hemostatic measures preoperatively to avoid the risk of hematoma. These measures should be established in consultation with the hematologist.**
- **Remark: The availability and effectiveness of alternative low-risk routes of local anesthetic delivery (such as intraligamentary single-tooth anesthesia, or buccal infiltration injections with 4% articaine) are effective alternatives to IDB and permit dental procedures in primary and permanent mandibular molar teeth. CB**

Recommendation 2.7.12:

- **For patients with hemophilia, the WFH recommends the use of antifibrinolytic agents as effective adjunct treatment in the management of dental hygiene therapies that facilitates access to regular dental care delivered by a dental hygienist. CB**

Recommendation 2.7.13:

- **In patients with hemophilia, the WFH asserts that the presence of blood-borne infections does not affect the safety of dental treatment as stringent universal cross-infection procedures are now mandatory across all disciplines of dentistry and recommends the provision of full dental services regardless of infectivity or immunological status. CB**

2.8 | Transition from pediatric to adult care

- At different life stages, people with hemophilia and their caregivers go through transitions that involve transfer of care beyond the family, such as when a young person with hemophilia starts school, a new sport or leisure activities, and adolescence, and when moving from pediatric to adult medical care, moving away from home, starting new relationships, and making career choices.[51]
- Parents and/or caregivers typically assume primary responsibility for the management of care for children and adolescents with hemophilia; in particular, for administering treatment and maintaining adherence to therapeutic regimens.[51]
- Two transition periods are particularly challenging for treatment adherence: when adolescents switch to self-treatment; and when young adults move away from home and assume full responsibility for self-care.[51] Many children and adolescents with hemophilia on prophylaxis who receive excellent comprehensive care do not experience the serious sequelae of their disorder, which may result in complacency in young adulthood.[87]
- Ideally, young people with hemophilia should obtain the necessary knowledge and skills for self-management before transitioning to adult care; however, many young people still require parental assistance with hemophilia care even in their later teenage years.[87]
- Adherence to prophylaxis has been found to be suboptimal in many adolescents (13-17 years of age) and young adults (18-30 years of age) with hemophilia.[51]
- In general, the main barriers to adherence to prophylaxis include high perceived burden of treatment; no or low burden of bleeds

and symptoms; venous access difficulties; and viewing prophylaxis as complicated and time-consuming.[51]

- In adolescents and young adults with hemophilia in particular, barriers to treatment adherence include[51]:
  - low symptom burden;
  - forgetfulness and lack of basic self-management skills such as treatment routines;
  - lack of knowledge about hemophilia, including low perceived benefit of prophylaxis;
  - inability to identify and act on bleeds;
  - disease denial;
  - the desire to be "normal";
  - perceived negative impact on activities and social participation;
  - lack of transition planning;
  - difficulties with self-treatment; and
  - challenges communicating with a hemophilia treatment centre to receive optimal care.
- The transition to adulthood, with increased independence in living situations (e.g., living alone or away at college/university) and financial responsibilities, may be particularly challenging for young adults with hemophilia.[88]
- Hemophilia treatment centres and healthcare providers can play an important role in helping young people with hemophilia maintain treatment adherence as they make the transition to adulthood, by ensuring that patient education encompasses knowledge and technical skills and development of self-efficacy and self-management skills including psychosocial coping.[51]
- As no definitive systematic approach to transition from pediatric to adult care has yet been defined, the comprehensive care team should continuously assess and follow up on individual needs, preferences, and barriers to treatment adherence with age-appropriate, tailored support.[51,89]
- Key components of transition strategies include[51]:
  - development of a structured transition plan;
  - monitoring with systematic assessments of a patient's readiness;
  - individualized support; and
  - added support when switching to self-treatment or moving away from home.
- In addition, readiness self-assessment tools, such as the *HEMO-Milestones* tool, may be useful for promoting a standardized approach to assess self-management competency.[90]
- Outcome indicators for assessing the effectiveness of transition from pediatric to adult hemophilia care include:
  - measurement of adherence;
  - any change in bleeding rate;
  - self-efficacy skills;
  - hemophilia knowledge;
  - patient and caregiver satisfaction;
  - time gap between last pediatric and first adult clinic visit; and
  - number of emergency room or hospital admissions.[91]
- Self-management programs available on the Internet may also help to support young people with hemophilia in their transition to adult care.[87]
- See Chapter 6: Prophylaxis in Hemophilia and Chapter 11: Outcome Assessment.

Recommendation 2.8.1:

- **Children and adolescents with hemophilia should be supported with ongoing education and skills development, including the ability to self-infuse and other self-efficacy skills, to gain necessary hemophilia knowledge for self-management of their condition before they make the transition from pediatric to adult care.**
- **Remark: The comprehensive care team should support young patients and their families through the transition period. When possible, the first visit should be performed by both the pediatric and adult hematologists.** CB

Recommendation 2.8.2:

- **For adolescents with hemophilia on prophylaxis, the WFH recommends individual education and training, ideally from a hemophilia nurse coordinator, to ensure adequate knowledge of hemophilia, and to support prophylaxis adherence and self-care management. This should include understanding measurements of adherence, as well as factors and risks that can lead to changes in bleeding rates.** CB

Recommendation 2.8.3:

- **For adolescents 12-18 years of age with hemophilia, the WFH recommends age-specific hemophilia camps to foster peer group support and develop their self-infusion skills and understanding of the importance of adherence to treatment.** CB

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SUPPORTING INFORMATION

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

Chapter 3: Laboratory Diagnosis and Monitoring

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

3.1 | Introduction

- Different bleeding disorders may have very similar symptoms; therefore, a correct diagnosis is essential to ensure that a patient receives the appropriate treatment.
- An accurate diagnosis can only be made with the support of a comprehensive and reliable laboratory service. This is dependent on the laboratory following strict protocols and procedures, which require:
  - knowledge and expertise in coagulation laboratory testing;
  - use of the correct equipment and reagents; and
  - quality assurance (QA).
- For detailed information on technical aspects and specific instructions on screening tests and factor assays, please consult *Diagnosis of Hemophilia and Other Bleeding Disorders: A Laboratory Manual*, current edition, published by the World Federation of Hemophilia (WFH).[1]

Recommendation 3.1.1:

- **The WFH recommends that testing for diagnosis and monitoring of hemophilia must be carried out by staff with knowledge and experience in coagulation laboratory testing using equipment and reagents that have been validated for this specific purpose.**
- **Remark: Details of laboratory tests for the diagnosis and monitoring of hemophilia are described in the WFH laboratory manual. CB**

3.2 | Coagulation laboratory testing

Principles of diagnosis

- Diagnosis of hemophilia is based on the following three principles:
  - understanding the clinical features of hemophilia and the appropriateness of the clinical diagnosis;
  - using screening tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) or platelet function tests to identify the potential cause of bleeding (keeping in mind that normal screening test results do not exclude the possibility of a clinically relevant bleeding disorder being present); and
  - confirming the diagnosis by factor assays and other appropriate specific investigations.

Technical aspects

Preparation of the patient prior to taking a blood sample

- Fasting is not necessary before collection of blood for investigation of possible bleeding disorders.
- Whenever possible, patients should avoid medications that can affect test results such as acetylsalicylic acid (ASA), which can severely affect platelet function for 7-10 days.
- Levels of factor VIII (FVIII) and von Willebrand factor (VWF) may be temporarily elevated by strenuous exercise,[2] stress,[3] or inflammation enough to affect the accuracy of diagnosis. Factor VIII/VWF levels increase during pregnancy.[4]

Recommendation 3.2.1:

- **In preparation for collection of a blood sample for determination of prothrombin time (PT), activated partial thromboplastin time (APTT), or FVIII/FIX activity, the WFH advises that patients with hemophilia may maintain their regular diet—overnight fasting is not necessary prior to blood draw.**
- **Remark: High levels of lipid in the plasma may affect the determination of clotting times when using coagulometers with optical systems. CB**

Recommendation 3.2.2:

- **In preparation for collection of a blood sample for determination of APTT or FVIII/FIX activity, the WFH recommends that patients with hemophilia avoid strenuous exercise prior to blood draw.**
- **Remark: Strenuous exercise or stress can temporarily elevate FVIII activity of patients with mild hemophilia A into the reference range; therefore, patients should be rested for a few minutes prior to venipuncture. CB**

Sample collection

- The blood sample should be collected as per standard guidelines.[5]
- The sample should preferably be collected near the laboratory to ensure quick transport, and it should remain capped during transport.
- Results of tests can change according to the interval between collection and testing and according to sample storage conditions.[6-8] Higher temperatures (>25°C) lead to loss of FVIII activity over time,[9] whereas cold storage (2-8°C) may lead to cold activation of several proteolytic systems.[7,10] Storage of blood samples before processing at 2-8°C can lead to loss of FVIII and VWF sufficient to cause unaffected patients to be misdiagnosed with von Willebrand disease (VWD).[11]
- Specific guidance is available in relation to sample collection.[10] Venipuncture must be aseptic, and the sample must be collected within 1 minute of tourniquet application without prolonged venous stasis.
- Blood should be withdrawn into a plastic syringe or an evacuated collection system. The needle should be 19-21 gauge for adults and 22-23 gauge for small children. Collection through peripheral venous catheters or non-heparinized central venous catheters can be successful for many hemostasis tests.[10,12]
- Blood from an indwelling catheter should be avoided for some coagulation tests, particularly if platelet aggregation testing is being performed.
- Frothing of the blood sample should also be avoided. It is only necessary to discard the first 2 mL of blood collected if blood is collected through a catheter.[10]
- The sample should be collected in citrate tubes containing 0.105M-0.109M (c3.2%) aqueous trisodium citrate dihydrate, maintaining the proportion of blood to citrate at a 9:1 ratio. If the tube contains less than 90% of the target volume, results may be adversely affected, and prolongation of PT and APTT is expected when tubes contain less than 80% of target volume.[10]
- Patients with an elevated hematocrit above 55% have a reduced plasma volume leading to an exponential increase in PT and APTT with increasing hematocrit, which can be avoided by adjusting the ratio of blood to anticoagulant.[13,14]
- Results of some PT and APTT tests are different if samples are collected into 3.8% trisodium citrate.[10] The sample should be mixed promptly and adequately with citrate solution by gentle inversion 3 or 4 times.[10]
- If platelet-poor plasma (PPP) is frozen for future testing, the storage conditions affect the stability of the frozen material.[7] If the sample is frozen at −70°C, it may be stored for up to six months.[7,15] Storage at −20°C is usually inadequate.
- Frozen samples must be thawed rapidly in a water bath for 4-5 minutes at 37°C to avoid formation of cryoprecipitate.

Preparation of platelet-poor plasma (PPP)

- Most coagulation tests require the use of PPP.
- PPP should be prepared as per standard guidelines.[5,7]
- The residual platelet count in PPP depends on the centrifugation conditions including adverse effects on platelet function testing if refrigerated centrifuges are used since cold can activate platelets.[7,10]
- PPP may be kept at room temperature (20-25°C) prior to testing.
- Plasma that has been hemolyzed during collection and processing should not be used for platelet function testing, APTT testing, or related testing, irrespective of which method and instrument are used for analysis.[7,16,17] PT and fibrinogen testing are less affected, and only gross in vitro hemolysis may be relevant.[10,16] Adding hemolysate to plasma in vitro may give misleading results.[16,18]
- Sample acceptance criteria should take into account the risks from rejection (and delayed or missing test results) against the risks of acceptance and testing (and the degree to which sample artefacts may or may not influence clinical management).

Recommendation 3.2.3:

- **For the diagnosis and monitoring of hemophilia A and B, the WFH recommends that blood samples be labelled immediately with the patient's first and last name, an identification number or date of birth, and the date and time of specimen collection. This should be done before leaving the side of the patient.**
- **Remark: There is no consensus on whether the tube should be labeled immediately before or immediately after blood collection. CB**

Recommendation 3.2.4:

- **The WFH recommends that blood samples for determination of PT, APTT, or FVIII/FIX activity be collected in citrate tubes containing 0.105-0.109M (around 3.2%) aqueous trisodium citrate dihydrate, capped during processing, and kept at 18-25°C during transport and storage. Blood samples should be centrifuged at ambient temperature for a minimum of 1700 g for at least 10 minutes, and either be analyzed within 8 hours of collection (4 hours for FVIII:C) or stored deep frozen at −35°C or lower.**

- **Remark: Storage of citrated whole blood samples at 2-8°C should be avoided as this may result in loss of FVIII activity.**
- **Remark: Platelet poor plasma (PPP) samples can be stored at −35°C for up to 3 months and at −70°C for up to 6 months prior to determination of FVIII/FIX activity. Storage of PPP at −20°C is usually inadequate. Freezers with auto-defrost should not be used to store PPP prior to determination of PT, APTT, or FVIII/FIX activity.** CB

Recommendation 3.2.5:

- **The WFH recommends that blood samples for determination of PT, APTT, or FVIII/FIX activity should be rejected and replaced if the collection tube contains less than 80% of the target fill volume.**
- **Remark: If the collection tube contains between 80% and 90% of its target fill volume, the results obtained using certain methods may have minor artefactual prolongation of PT and APTT and minor artefactual reduction in FVIII/FIX activity.** CB

Recommendation 3.2.6:

- **The WFH recommends that blood samples for determination of APTT or FVIII/FIX activity should be rejected and replaced if in vitro hemolysis or clotting have occurred during the collection and processing of the sample.**
- **Remark: The impact of in vitro hemolysis on PT is insufficient to affect patient management.**
- **Remark: Samples from patients with in vivo hemolysis that have been collected for determination of PT, APTT, or FVIII/FIX activity can be accepted and tested.** CB

Endpoint detection

- Many laboratories now have some form of semi- or fully automated coagulation analyzers. Accurately detecting the clotting endpoint using a manual technique requires considerable expertise, particularly if clotting time is prolonged or if fibrinogen concentration is low, and the clot is thin and wispy.
- For manual testing, the tube should be tilted 3 times every 5 seconds through an angle of approximately 90° during observation. The tube should be immersed in a water bath at 37°C between tilting.

Screening tests

- Platelet count, PT, and APTT may be used to screen a patient suspected of having a bleeding disorder.[19]
- The sensitivity of both PT[20] and APTT tests[21,22] to factor deficiencies are influenced by the type of reagents used to perform the test.

Recommendation 3.2.7:

- **For laboratory investigation of patients being assessed due to clinical suspicion of hemophilia A, the WFH recommends that prothrombin time testing also be performed using a laboratory reagent containing human tissue factor.**
- **Remark: Hemophilia A is sometimes excluded despite clinical suspicion of its presence. Such cases may have other factor deficiencies. Some patients with certain FVII defects may have symptoms similar to mild hemophilia but may display normal PT and FVII activity if the laboratory reagent contains non-human tissue factor so that the diagnosis would be missed.** CB

Recommendation 3.2.8:

- **For laboratory investigation of patients being assessed due to clinical suspicion of hemophilia, the WFH recommends that an APTT result within the reference range not be used to rule out the presence of mild hemophilia A or B.**
- **Remark: In some cases of mild hemophilia A or B, APTT may be within the normal range.** CB

- Bleeding time testing lacks sensitivity and specificity, and it is also prone to performance-related errors. Therefore, other tests of platelet function such as platelet aggregometry are preferred when available.[23,24]
- Based on the results of these tests, the category of bleeding disorder may be partially characterized to guide subsequent analysis (see Table 3-1).
- These screening tests may not detect abnormalities in patients with mild bleeding disorders, including some variants of VWD, some cases of genetically confirmed mild hemophilia A or B, defects of platelet function, FXIII deficiency, and those rare defects of fibrinolysis which may be associated with a bleeding tendency.

Correction studies

- Abnormal screening tests may be further investigated using correction or mixing studies.
- Correction or mixing studies using pooled normal plasma (PNP) may help to define whether prolonged coagulation times are due to factor deficiency or circulating anticoagulants or inhibitors.
- The APTT of a patient/normal plasma mix may initially be normal and then progressively prolonged on incubation in the presence of a time-dependent inhibitor (e.g., many acquired autoantibodies against FVIII), although this pattern can be variable in cases with complex kinetics.

TABLE 3-1 Interpretation of screening tests

Possible diagnosis	PT	APTT	Platelet count
Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Prolonged[a]	Normal
VWD	Normal	Normal or prolonged[a]	Normal or reduced
Platelet defect	Normal	Normal	Normal or reduced

Abbreviations: APTT, activated partial thromboplastin time; PT, prothrombin time; VWD, von Willebrand disease.

[a]The same pattern can occur in the presence of FXI, FXII, prekallikrein, or high molecular weight kininogen deficiencies.

- Correction studies with FVIII/FIX-deficient plasma may be used to identify the particular deficiency if a factor assay is not available.

Recommendation 3.2.9:

- **The WFH recommends that an APTT result within the normal range obtained in a sample containing an equal volume mixture of patient and pooled normal plasma that was analyzed immediately after preparation of that mixture should not be used to rule out the possible presence of an FVIII inhibitor.**
- **Remark: The APTT of an equal volume mixture of patient and pooled normal plasma becomes substantially prolonged over a period of 1 to 2 hours of incubation at 37°C if the patient sample contains a neutralizing anti-FVIII inhibitor.** CB

Factor assays

- Several types of FVIII assay including chromogenic and fluorogenic clotting assays are available.[25-30] One-stage clotting assays based on APTT are the most commonly used techniques in most regions.[26,27]
- FVIII- and FIX-deficient plasma must completely lack FVIII and FIX, respectively, i.e., it must contain < 1 IU/dL and have normal levels of other clotting factors.[1]
- The level of clotting factors in pooled normal plasma varies substantially between pools,[31,32] therefore, a system of international units (IUs) has been established for continuity and traceability.[31,33] Factor levels are reported in international units, either per mL or per decilitre (IU/dL). If IU/dL is used, then results are not interchangeable with percentage (%) of pooled normal plasma.[34]
- Use of a single test plasma dilution leads to assay inaccuracy in the presence of some inhibitors, including lupus anticoagulants (LA),[35] specific high-responding factor inhibitors, and some anticoagulant drugs,[36] and leads to assay imprecision.
- Assay calibration method can affect the quality of results.[37,38] When assaying test samples from patients with moderate or severe hemophilia, an extended or separate calibration curve may be needed. It is not acceptable to simply extend the calibration curve by extrapolation without analyzing additional dilutions of the calibration plasma.
- Some cases of genetically confirmed mild hemophilia A show normal FVIII activity when a one-stage assay is used for diagnosis but reduced activity in chromogenic and two-stage clotting assays.[39-46] The reverse can also occur.[40,47,48] This means that more than one type of FVIII assay is needed to detect all forms of mild hemophilia A.
- All patients with reduced FVIII activity and a possible diagnosis of hemophilia A should have a full laboratory assessment to rule out VWD. This is especially important to differentiate VWD Normandy from mild hemophilia A since both have a normal level of VWF antigen usually associated with a reduced FVIII activity.[49]
- Chromogenic FIX assays are becoming more available,[50-54] and one study has reported that a chromogenic FIX assay may correlate better with the clinical picture than a one-stage assay in some hemophilia B cases.[53]
- Thrombin generation tests have been used in characterizing hemophilia[55-57] but are not in widespread use.

Recommendation 3.2.10:

- **For laboratory investigation of patients being assessed due to clinical suspicion of hemophilia A, the WFH recommends the use of both the one-stage FVIII assay and the chromogenic FVIII:C assay in the initial diagnostic workup.**
- **Remark: Both assays should be performed even if the result of one of the two assays shows FVIII activity within the normal range.**
- **Remark: The one-stage FVIII assay requires the use of FVIII-deficient plasma containing less than 1 IU/dL (<1%) FVIII activity and normal levels of other clotting factors that can influence APTT (fibrinogen, FII, FV, FIX, FX, FXI, FXII, prekallikrein, and HMWK).** CB

Recommendation 3.2.11:

- **For laboratory investigation of patients being assessed due to clinical suspicion of hemophilia B, the WFH recommends the use of the one-stage FIX assay in the initial diagnostic workup.**
- **Remark: Data are currently insufficient to make recommendations on the role of the chromogenic FIX assay in the initial diagnostic workup of hemophilia B.**
- **Remark: The one-stage FIX assay requires the use of FIX-deficient plasma containing less than 1 IU/dL (<1%) FIX activity and normal levels of other clotting factors that can influence APTT (fibrinogen, FII, FV, FVIII, FX, FXI, FXII, prekallikrein, and HMWK).** CB

Recommendation 3.2.12:

- **For one-stage or chromogenic FVIII/FIX assays, the reference/standard plasma used for calibration, whether commercially or locally prepared, must be traceable to a WHO international standard, and results should be reported in international units (IUs).**
- **Remark: Results should be reported as IU/mL or IU/dL.**
- **Remark: In principle, percentage is the appropriate unit of activity only when the assay is performed using pooled normal plasma as the reference plasma whose activity is not traceable back to a WHO international standard.** CB

Recommendation 3.2.13:

- **For laboratory investigation due to clinical suspicion of hemophilia using one-stage FVIII/FIX assays, the WFH recommends analysis using 3 different dilutions of test plasma samples.**
- **Remark: The results of the test and standard plasma dilutions should be compared by parallel-line analysis. One way to assess this is to calculate the coefficient of variation (CV) of the 3 results using the equation CV = ([standard deviation/mean] × 100). If the CV of the 3 results is less than 15%, then the average of the 3 results should be reported. If the CV is greater than 15%, the results should be scrutinized. Presence of pathological inhibitors against specific clotting factors or lupus**

anticoagulants can interfere with some one-stage FVIII and FIX assays. Some therapeutic anticoagulants can also show this interference effect. In all of these settings, factor activity increases in the assay as the plasma is increasingly diluted. Factor activity is underestimated when the plasma is diluted less, and a more accurate activity result is obtained when the test plasma is diluted more. CB

Recommendation 3.2.14:

- **In populations where lupus anticoagulant occurs, the WFH recommends the use of an APTT reagent insensitive to lupus anticoagulant to perform one-stage FVIII/FIX assays.** CB

Recommendation 3.2.15:

- **For all one-stage FVIII/FIX assays, only the clotting times of test sample dilutions that are within the range covered by the calibration curve should be used to calculate FVIII/FIX activity in the test sample.**
- **Remark: When assaying test samples from patients with moderate or severe hemophilia A or B, an extended or additional calibration curve may be needed. It is not acceptable to extend the calibration curve by extrapolation without analyzing additional dilutions of the reference/calibration plasma.** CB

Recommendation 3.2.16:

- **For all types of FVIII and FIX assays, an internal quality control (IQC) sample should be included with each batch of test samples analyzed. Results should only be released for patient management purposes after confirmation that the IQC result is within the target range for that material.**
- **Remark: A description of how to set target ranges for IQC materials and handle out-of-range IQC results is available in the WFH laboratory manual.** CB

Recommendation 3.2.17:

- **For internal quality control samples with FVIII/FIX activity in the range of 50-150 IU/dL, the between-assay coefficient of variation should be less than 10%.**
- **Remark: Some studies have shown use of a stored calibration curve to be associated with higher between-assay CVs than use of a new calibration curve generated alongside patient samples.** CB

Post-FVIII/FIX infusion monitoring

- Lower than expected recovery and/or reduced half-life of infused clotting factor concentrates (CFCs) may be an early indicator of the presence of inhibitors.
- For samples containing FVIII or FIX CFCs, results of FVIII or FIX assays may vary according to whether a one-stage or chromogenic assay is used for analysis and sometimes according to the specific reagents or kits used in the assay.
- If factor assays are used to confirm efficacy of treatment or to make dose adjustments, bear in mind that some assays are unsuitable for monitoring some products.[58]
- Using an assay that markedly overestimates activity compared to the expected results from the labelled potency of the concentrate could lead to undertreatment and clinical risk.
- A full consensus on the tolerable degree of difference in results from different assays before patient management is adversely affected has not been established at the time of this writing; in the meantime, assays that give results that differ by more than 25-30% from the labelled potency of the concentrate vial are best avoided or, in any case, should not be used without taking account of such differences.
- Routine in-house assays can be used for post-infusion monitoring, provided that the local assay system (method and reference/calibrator) is included in the manufacturer's guidance.[59] Any local assay should be verified for use with the specific CFC being used.[60]
- A number of articles have reviewed the published evidence related to use of specific assays for monitoring specific extended half-life (EHL) and unmodified CFCs.[58,60,61]
- One-stage assays used to monitor the single-chain recombinant FVIII molecule lonoctocog alfa (Afstyla®) underestimated relative potency by 45% whereas chromogenic assay recovered the expected values[62] which led to a recommendation that chromogenic assay is preferred, and that one-stage assay results should be multiplied by a conversion factor of 2 to determine the patient's FVIII activity level.[63] Such an approach did not fully correct for reagent differences,[64] and some experts have specifically recommended against using an assay known to give discrepant values and multiplying the result by a correction factor in this way.[65] Since there may be lot-to-lot variation in reagents used for factor assays, any such conversion factor should be verified for the lot numbers in use.
- There are numerous published assay studies comparing results in samples containing CFCs including EHL FVIII and FIX concentrates. Despite this, there are a number of one-stage and chromogenic assay reagents that have not been studied for use with some CFCs at the time of this writing. The reader is referred to the references in Table 3-2 (FVIII) and Table 3-3 (FIX) to see the evidence supporting the recommendations below.

Recommendation 3.2.18:

- **For monitoring replacement therapy with FVIII or FIX concentrates, the WFH recommends that laboratories use a FVIII/FIX assay that has been validated for use with the specific concentrate used for treatment.**
- **Remark: This recommendation is particularly important for modified molecular forms of FVIII and FIX.** CB

Recommendation 3.2.19:

- **For monitoring replacement therapy with plasma-derived FVIII concentrates, the WFH recommends use of a one-stage or chromogenic FVIII assay calibrated with a plasma standard traceable to a WHO international standard.** CB

TABLE 3-2 Publications with data related to the use of different FVIII assays in the presence of recombinant and modified factor VIII concentrates

Product type	Brand name	International non-proprietary name	References
Full-length recombinant	Advate®, Kogenate® FS, Kovaltry®	Octocog alfa	Church (2018)[66], Kitchen (2016)[67], Kitchen (2016)[68], Turecek (2016)[69]
BDD FVIII	NovoEight®	Turoctocog alfa	Viuff (2011)[70]
BDD FVIII	ReFacto AF®	Moroctocog alfa	Kitchen (2016)[68], Jacquemin (2018)[71], Cauchie (2013)[72], Morfini (2003)[73], Ingerslev (2004)[74], Santoro (2009)[75]
BDD FVIII fused to Fc portion of IgG1	Elocta®/Eloctate®	Efmoroctocog alfa	Powell (2012)[76], McCue (2015)[77], Sommer (2014)[78], Kitchen (2019)[79]
B-domain-truncated FVIII with site-specific 40 kDa polyethylene glycol moiety	Esperoct®	Turoctocog alfa pegol	Hillarp (2017)[80], Pickering (2016)[81], Persson (2019)[82], Ezban (2019)[83], Hegemann (2019)[84], Tiefenbacher (2019)[85]
BDD FVIII with site-specific 60 kDa polyethylene glycol	Jivi®	Damoctocog alfa pegol	Church (2018)[66], Gu (2014)[86]
Full-length recombinant FVIII with non-site-specific 20 kDa pegylation	Adynovate®/Adynovi®	Rurioctocog alfa pegol	Turecek (2016)[69], Bulla (2017)[87], Weber (2017)[88]
Single-chain recombinant FVIII	Afstyla®	Lonoctocog alfa	St Ledger (2018)[62], Bowyer (2017)[64]
Recombinant BDD porcine FVIII	Obizur®	Susoctocog alfa	Turecek (2016)[69], Vanguru (2018)[89]

Note: Therapeutic products are denoted by both their international non-proprietary name and their brand name because of the latter's more common usage and recognition by the community.

Abbreviations: BDD, B-domain-deleted; FVIII, factor VIII; kDA, kilodalton.

TABLE 3-3 Publications with data related to the use of different FIX assays in the presence of recombinant and modified factor IX concentrates

Product type	Brand name	International non-proprietary name	References
Recombinant	Not identified	Not identified	Wilmot (2014)[90]
Recombinant FIX fused to Fc portion of IgG1	Alprolix®	Eftrenonacog alfa	Kershaw (2018)[54], Sommer (2014)[91], Bowyer (2019)[92]
Recombinant fusion protein linking FIX to albumin	Idelvion®	Albutrepenonacog alfa	Horn (2019)[51], Bowyer (2019)[92]
Recombinant FIX with site-directed 40 kDa pegylation	Refixia®/Rebinyn®	Nonacog beta pegol	Bowyer (2016)[52], Rosen (2016)[93], Tiefenbacher (2017)[94], Ezban (2019)[95]

Note: Therapeutic products are denoted by both their international non-proprietary names and their brand names because of the latter's more common usage and recognition by the community.

Abbreviations: FIX, factor IX; IgG1, immunoglobulin G1; kDA, kilodalton.

Recommendation 3.2.20:

- **For monitoring replacement therapy with clotting factor concentrates containing full-length recombinant FVIII, the WFH recommends use of a one-stage or chromogenic FVIII assay calibrated with a plasma standard traceable to a WHO international standard.** CB

Recommendation 3.2.21:

- **For monitoring replacement therapy with efmoroctocog alfa (recombinant FVIII fused with human immunoglobulin G1 [rFVIIIFc]; Elocta®/Eloctate®), the WFH recommends use of a one-stage or chromogenic FVIII assay calibrated with a plasma standard traceable to a WHO international standard.** CB

Recommendation 3.2.22:

- **For monitoring replacement therapy with turoctocog alfa pegol (recombinant B-domain-truncated FVIII with a site-specific 40-kDa polyethylene glycol group [N8-GP]; Esperoct®), the WFH recommends use of a chromogenic FVIII assay or APTT-based one-stage FVIII assay with validated reagents, including some ellagic acid activator reagents (Actin®, Actin® FS, SynthAFax™, DG Synth™) and some silica activator reagents (Pathromtin® SL, SynthASil™), calibrated with a plasma standard traceable to a WHO international standard.**
- **Remark: One-stage FVIII assays with APTT-SP™, STA®-PTT Automate, or TriniCLOT™ APTT HS reagents significantly**

underestimate true FVIII activity of N8-GP and should not be used. CB

Recommendation 3.2.23:

- For monitoring replacement therapy with damoctocog alfa pegol (recombinant B-domain-deleted FVIII with a site-specific 60 kDa branched polyethylene glycol group [BDD-rFVIII]; Jivi®), the WFH recommends use of a chromogenic FVIII assay or APTT-based one-stage FVIII assay with validated reagents, including the ellagic acid activator reagent Actin® FSL and some silica activator reagents (Pathromtin® SL, SynthASil™), calibrated with a plasma standard traceable to a WHO international standard.
- Remark: One-stage FVIII assays with the ellagic acid activator reagent Actin® FS or the kaolin activator reagent C.K. Prest® significantly overestimate true FVIII activity and should not be used. One-stage FVIII assays with APTT-SP™ and STA®-PTT Automate reagents significantly underestimate true FVIII activity and should not be used. CB

Recommendation 3.2.24:

- For monitoring replacement therapy with rurioctocog alfa pegol (full-length recombinant FVIII with non-site-specific 20-kDa polyethylene glycol; Adynovate®/Adynovi®), the WFH advises that more laboratory assay studies are required to inform recommendations about laboratory monitoring.
- Remark: There are conflicting findings in the literature assessing the use of one-stage and chromogenic FVIII assays in samples containing rurioctocog alfa pegol. CB

Recommendation 3.2.25:

- For monitoring replacement therapy with lonoctocog alfa (single-chain recombinant FVIII [rVIII-SingleChain]; Afstyla®), the WFH recommends use of a chromogenic FVIII assay calibrated with a plasma standard traceable to a WHO international standard.
- Remark: The summary of product characteristics recommends chromogenic assays. It also states that the one-stage FVIII assay result underestimates the FVIII activity level by approximately 45% compared to the chromogenic assay result, and suggests that if the one-stage assay is used, the result should be multiplied by a factor of 2. CB

Recommendation 3.2.26:

- For monitoring replacement therapy with plasma-derived FIX concentrates, the WFH recommends use of a one-stage or chromogenic FIX assay calibrated with a plasma standard traceable to a WHO international standard. CB

Recommendation 3.2.27:

- For monitoring replacement therapy with clotting factor concentrates containing unmodified recombinant FIX, the WFH recommends use of a one-stage FIX assay calibrated with a plasma standard traceable to a WHO international standard.
- Remark: Chromogenic FIX assays have been reported to underestimate the FIX activity of recombinant FIX concentrate. CB

Recommendation 3.2.28:

- For monitoring replacement therapy with eftrenonacog alfa (recombinant FIX fused with human immunoglobulin G1 [rFIXFc]; Alprolix®), the WFH recommends use of a chromogenic FIX assay or APTT-based one-stage FIX assay with validated reagents, including some ellagic acid activator reagents (Actin®, Actin® FS, Actin® FSL), some silica activator reagents (Pathromtin® SL, SynthASil™), and a polyphenol activator reagent (Cephascreen®), calibrated with a plasma standard traceable to a WHO international standard.
- Remark: One-stage FIX assays with STA®-PTT Automate or kaolin activator (C.K. Prest®) reagents significantly underestimate true rFIXFc (Alprolix®) activity and should not be used. CB

Recommendation 3.2.29:

- For monitoring replacement therapy with albutrepenonacog alfa (recombinant FIX fused with recombinant human albumin [rFIX-RFP]; Idelvion®), the WFH recommends use of an APTT-based one-stage FIX assay with validated reagents, including some silica activator reagents (Pathromtin® SL, SynthASil™), calibrated with a plasma standard traceable to a WHO international standard.
- Remark: One-stage FIX assays with the ellagic acid activator reagent Actin® FS or the kaolin activator reagent C.K. Prest® significantly underestimate true rFIX-RFP (Idelvion®) activity and should not be used. One-stage assays with the ellagic acid activator SynthAFax™ reagent or chromogenic FIX assays significantly overestimate true rFIX-RFP (Idelvion®) activity and should not be used. CB

Recommendation 3.2.30:

- For monitoring replacement therapy with nonacog beta pegol (recombinant FIX with a 40-kDa polyethylene glycol moiety [N9-GP]; Refixia®/Rebinyn®), the WFH recommends use of a chromogenic FIX assay or APTT-based one-stage FIX assay with validated reagents, including the ellagic acid activator reagent SynthAFax™ or the polyphenol activator Cephascreen®, calibrated with a plasma standard traceable to a WHO international standard.
- Remark: Most one-stage FIX assays significantly overestimate or underestimate true FIX activity of N9-GP and should not be used. One-stage assays using the ellagic acid activator reagent SynthAFax™ or the polyphenol activator reagent Cephascreen®, are suitable for monitoring therapy with N9-GP. CB

Emicizumab

- Emicizumab is an engineered bispecific antibody that binds both human FIX/FIXa and FX/FXa and which is not regulated by the mechanisms that regulate FVIII but which acts as a FVIII mimetic.[96,97]

- The APTT is considerably shortened by emicizumab to within or below the reference range irrespective of reagents used, which means that emicizumab affects all APTT-based laboratory tests and assays.[98-100]
- Emicizumab significantly interferes in chromogenic FVIII assays utilizing human FIXa and FX but not those using FIXa and FX of bovine origin. Local verification is needed for chromogenic kits containing bovine FX and human FIXa.[98,99]
- Emicizumab can be measured and reported in μg/mL using a modified one-stage assay with higher test sample dilution (in assay buffer) and calibrated with emicizumab-specific calibrators.[99]

Recommendation 3.2.31:

- **For patients receiving emicizumab in whom confirmation of expected emicizumab levels is required, the WFH recommends use of a modified one-stage assay including an additional pre-dilution step of test plasma and assay calibration with specific emicizumab calibrators.**
- **Remark: Even at subtherapeutic levels of emicizumab, APTT may be normal or subnormal in patients with severe hemophilia A with or without inhibitors.** CB

Recommendation 3.2.32:

- **For determination of FVIII activity in patients with hemophilia A receiving emicizumab, the WFH recommends use of a chromogenic FVIII assay containing bovine FX.**
- **Remark: At therapeutic levels, emicizumab affects any chromogenic FVIII assay containing FX of human origin. Emicizumab may also affect chromogenic FVIII assays containing FIXa of human and FX of bovine origin but only at emicizumab levels higher than those expected in patients receiving recommended doses.** CB

Recommendation 3.2.33:

- **For determination of FVIII inhibitor levels in patients receiving emicizumab, the WFH recommends use of a chromogenic FVIII assay containing bovine FX.** CB

Recommendation 3.2.34:

- **For patients with a suspected neutralizing anti-emicizumab antibody, the WFH recommends measuring emicizumab levels using a modified one-stage assay including an additional pre-dilution step of test plasma and assay calibration with specific emicizumab calibrators.**
- **Remark: Validated anti-drug antibody assays may also be used for this purpose, if available.** CB

Inhibitor testing

- The most frequently encountered functional inhibitors of hemostasis are lupus anticoagulants, which are not directed against specific clotting factors and whose presence should be excluded prior to specific factor inhibitor testing.
- Results of APTT testing on mixtures of test and normal plasma can be difficult to interpret, particularly since in acquired hemophilia there may initially be a full correction of APTT even in the presence of a potent specific anti-FVIII antibody. If anti-FVIII antibody is present, the APTT of this mixture will be prolonged with incubation.
- Most FVIII inhibitors that develop secondary to replacement therapy in patients with hemophilia A show a characteristic pattern: the APTT of a patient/PNP mixture is intermediate, i.e., between the APTTs of the two materials, and it is further prolonged when the mixture is incubated at 37°C for 1-2 hours.
- Confirmation that an inhibitor is directed against a specific clotting factor requires a specific inhibitor assay.
- Quantification of the inhibitor titer is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay for FVIII inhibitor testing,[1] because this modification offers improved specificity and sensitivity over the original Bethesda assay.[101-109]
- The results of Bethesda inhibitor assays can be affected by the use of different dilutions of test sample before those dilutions are mixed with normal plasma.[110]
- For patients treated with FVIII or FIX, washout is no longer necessary if a heat neutralization modification of the Nijmegen-Bethesda assay is used, which inactivates FVIII/FIX in the sample to allow detection of the inhibitor.[109,111-113] This is not required if FVIII/FIX is <5 IU/dL in the test sample since this low level will not have a significant effect on inhibitor titer calculations.
- Different types of FVIII assays can be used to determine the FVIII during the Nijmegen-Bethesda inhibitor assay.[114-118] The protocol for the US national inhibitor program requires a chromogenic assay to be used when positive FVIII inhibitor results below 2.0 BU are observed.[108] If there is suspicion of lupus anticoagulant or if the sample contains therapeutic anticoagulants such as heparin or direct FXa or FIIa inhibitors, it may be useful to confirm inhibitor presence using a chromogenic assay to measure residual factor activity (instead of a one-stage assay).
- An inhibitor titer of ≥ 0.6 BU/mL should be considered clinically significant.[119,120]
- Some non-neutralizing anti-FVIII antibodies which are not detected by the Nijmegen-Bethesda assay may be clinically relevant because they may increase the clearance of FVIII and can be measured by ELISA.[121-128]

Recommendation 3.2.35:

- **For determination of anti-FVIII inhibitors in a sample containing greater than 5 IU/dL FVIII activity, the WFH recommends that prior to testing, the sample be heated to 56°C for 30 minutes and centrifuged at ambient temperature for a minimum of 1700 g for at least 5 minutes.**
- **Remark: The quantification limit of the Nijmegen-Bethesda FVIII inhibitor assay is around 0.6 BU/mL.**
- **Remark: The Nijmegen-Bethesda FVIII inhibitor assay requires use of buffered pooled normal plasma as a source of FVIII, which is then mixed with an equal volume of FVIII-deficient plasma to prepare the control mixture.** CB

Recommendation 3.2.36:

- **For determination of anti-FIX inhibitors in a sample containing greater than 5 IU/dL FIX activity, the WFH recommends that prior to testing, the sample be heated at 56°C for 30 minutes and centrifuged at ambient temperature for a minimum of 1700 g for at least 5 minutes.** CB

Recommendation 3.2.37:

- **For quantification of anti-FVIII inhibitors, the WFH recommends that the Nijmegen-Bethesda assay be used.**
- **Remark: Bethesda assays detect neutralizing antibodies. A small proportion of anti-FVIII antibodies are non-neutralizing, shorten the half-life of infused FVIII, and are not detected by Bethesda assays.**
- **Remark: The Nijmegen modification describes a specific method for buffering pooled normal plasma; other buffering methods may be suitable.** CB

Recommendation 3.2.38:

- **For quantification of FVIII and FIX inhibitors, the WFH recommends that only residual FVIII/FIX activity between 25% and 75% of the FVIII/FIX in the control mixture be used to calculate inhibitor concentrations.**
- **Remark: The most accurate inhibitor results are obtained when the residual FVIII/FIX activity is close to 50% of the level in the control mixture.** CB

Recommendation 3.2.39:

- **For quantification of low-titer anti-FVIII inhibitors (<2 BU/mL), the WFH recommends use of a chromogenic Nijmegen-Bethesda FVIII assay to measure residual FVIII activity.**
- **Remark: Use of a chromogenic Nijmegen-Bethesda FVIII assay instead of a one-stage FVIII assay provides greater specificity and reduces possible variability in measurement of residual FVIII leading to underestimation to the extent that a false positive inhibitor is reported when no inhibitor is present.**

Gene therapy

- Discrepancies between results of one-stage and chromogenic assays have been reported after both FVIII and FIX gene therapy.
- Results of one-stage FVIII assays were approximately 1.65-fold higher[129] and 1.5-fold higher[130] than chromogenic assays for two different therapies with B-domain–deleted (BDD) FVIII, which is in contrast to CFC-containing BDD FVIII where chromogenic results are higher than one-stage assay results.[58,75]
- Results of one-stage FIX assays varied according to reagents used but were higher than results obtained in chromogenic FIX assays in patients who had received FIX gene therapy with a high specific activity FIX Padua variant.[131]

Recommendation 3.2.40:

- **For quantification of FVIII activity in recipients of gene transfer, the WFH advises that more research is necessary to determine the relative accuracy of chromogenic and one-stage assays in predicting hemostatic protection.**
- **Remark: The one-stage assay appears to consistently produce FVIII activity results that are approximately 1.6-fold greater than those obtained with the chromogenic assay for multiple FVIII transgene products. Correlation with both plasma and recombinant FVIII-specific activity and clinical response may be needed for accurate determination of FVIII activity in recipients.** CB

Recommendation 3.2.41:

- **For quantification of FIX activity in recipients of gene transfer, the WFH advises that more research is necessary to determine the relative accuracy of chromogenic and one-stage assays in predicting hemostatic protection.**
- **Remark: FIX Padua (R338L) has been utilized for FIX gene therapy because it has a higher specific activity than native FIX. The one-stage assay appears to consistently produce FIX Padua activity results that are approximately 1.6-fold greater than those obtained with the chromogenic assay. Correlation with both plasma and recombinant FIX-specific activity is needed for accurate determination of FIX Padua activity in recipients.** CB

Trained personnel

- A laboratory scientist/technologist with an interest in coagulation must have an in-depth understanding of the tests in order to achieve accurate results.
- In some cases, it may be beneficial to have a laboratory scientist/technologist who has had further training in a specialist centre.

3.3 | Use of correct equipment and reagents

Equipment

- The basic laboratory equipment requirements include a 37°C ± 0.5°C water bath for rapid thawing of frozen samples and for performing manual tests on any samples where automated analysis has failed, and calibrated automated pipettes.
- Plastic and glass consumables used in coagulation testing should not be re-used.
- Automated coagulometers offer significant advantages over manual methods of some semi-automates including improved accuracy precision, repertoire and in some cases automatic detection of pre-analytical problems.

Selection of coagulometers

- Important considerations in the selection of coagulometers include:
  - test repertoire;
  - operational requirements including service and breakdown response;

- throughput;
- comparability between the results on the primary analyzer and any back-up methods;
- compatibility with blood sample tubes and plasma storage containers in local use; and
- safety.

- Information is required in relation to the performance characteristics of the system. This can be obtained from a variety of sources including the published literature and manufacturers' data, but it may also require some form of local assessment. Detailed guidance on selection and assessment of analyzers is available.[132,133]

Reagents

- It is good practice to ensure continuity of the supply of a chosen reagent, with attention paid to continuity of batches and long shelf life. This may be achieved by asking the supplier to batch hold for the laboratory, if possible.
- Different reagent brands may have different sensitivities and should not be run side by side, unless this is done for a specific purpose.
- A normal reference range should be defined for all methods. Practical guidance on this is published,[1] and for APTT must take into account the sample collection and processing conditions used locally.

3.4 | Quality assurance

- Quality assurance covers all aspects of the diagnosis process from sample taking, separation and analysis, and internal quality control (IQC) through to reporting of the result and ensuring that it reaches the appropriate clinician within an appropriate time.

Internal quality control

- Internal quality control is used to establish whether a series of techniques and procedures is being performed consistently over a period of time.
- IQC measures are taken to ensure that the results of laboratory investigations are reliable enough to assist clinical decision-making, monitor therapy, and diagnose hemostatic abnormalities.
- Graphical display of quality control results, for example in the form of Levey-Jennings charts, may facilitate review of trends in IQC results.

External quality assessment

- External quality assessment (EQA) helps to identify the degree of agreement between the local laboratory results and those obtained by other centres.
- The WFH International External Quality Assessment Scheme (IEQAS) is specifically designed to meet the needs of hemophilia treatment centres worldwide. This scheme includes analyses relevant to the diagnosis and management of bleeding disorders. Details of this scheme, which is operated in conjunction with the U.K. National External Quality Assessment Service (UK NEQAS) for Blood Coagulation in Sheffield, U.K., can be obtained from the WFH.[134]
- In order for a laboratory to attain a high level of testing reliability and to participate successfully in an external quality assessment program, the laboratory must have access to appropriate reagents and techniques and an appropriate number of adequately trained staff.

Recommendation 3.4.1:

- **The WFH strongly recommends that coagulation laboratories implement quality assurance programs for all laboratory systems to ensure quality adherence and the reliability of laboratory blood testing procedures and reporting for the diagnosis and treatment of hemophilia.** CB

Recommendation 3.4.2:

- **For hemostasis screening tests, the WFH recommends performing internal quality controls with at least two levels of internal quality control samples (normal and abnormal plasma samples) for all test batches at least daily.** CB

Recommendation 3.4.3:

- **The WFH strongly recommends that clinical laboratories routinely participate in external quality assessment for each assay used for the diagnosis and treatment of hemophilia.**
- **Remark: Participation in the WFH International External Quality Assessment Scheme (IEQAS) enables laboratories to improve and standardize laboratory testing for hemophilia.** CB

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SUPPORTING INFORMATION

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

Chapter 4: Genetic Assessment

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

4.1 | Introduction

- Genetic assessment of hemophilia is important in defining disease biology, establishing diagnosis in difficult cases, predicting risk of inhibitor development, identifying female carriers, and providing prenatal diagnosis, if desired.[1]
- Genotype analysis should be offered to all people with hemophilia and their "at-risk" female family members.
- Genetic testing strategies are led by the phenotypic parameters measured by the coagulation laboratory in addition to the family pedigree. Therefore, it is essential that the data are made available to the genetic testing laboratory. An accurate interpretation of the underlying variant(s) detected is dependent on the supporting phenotypic data and family history for the patient.[2–5]
- Genetic counselling for people with hemophilia and their families is an essential requirement prior to genetic testing. This includes obtaining informed consent from the patient, parent, or legal guardian, requiring both permission to carry out testing as well as education to ensure that they fully understand the testing procedure, the benefits and limitations of the test, and possible consequences of the test results.[6,7]
- Genetic counselling should also provide information and advice about prenatal diagnosis (PND), management of pregnancy and delivery in hemophilia carriers, and pre-implantation genetic diagnosis (PGD). It is important to be aware of and follow the relevant laws governing such procedures in the country where the service is being provided.
- Genetic testing will not always identify the underlying variant associated with the hemophilia phenotype. Genetic counselling should highlight this possibility to the individual referred for genetic testing. (See Chapter 9: Specific Management Issues – Carriers – Genetic counselling – Psychosocial support.)
- Genetic diagnostic laboratories should adhere to strict protocols and procedures, which require:
  - knowledge and expertise in genetic laboratory testing;
  - use of the correct investigative platforms;
  - knowledge and expertise in the interpretation of the genetic variants identified in association with hemophilia;
  - use of the correct interpretative platforms for investigation of variants;
  - use of the correct nomenclature for description of variants and the correct classification systems for determining pathogenicity of variants;
  - internal quality control procedures;
  - participation in periodic accreditation, where available; and
  - participation in external quality assessment schemes (EQAS), where available.
- The interpretation of the results of genetic testing should be performed by scientists who have knowledge and expertise in hemophilia genetics.
- The opportunity for discussion of the genetic results between the ordering clinician and reporting scientist is an essential provision of the genetic diagnostic service.

Recommendation 4.1.1:

- **For people with hemophilia, the WFH recommends that genetic testing be offered to identify the specific underlying genetic variant associated with their disorder. CB**

Recommendation 4.1.2:

- **For obligate carriers of hemophilia and "at-risk" female relatives of people with hemophilia or potential carriers of hemophilia, the WFH recommends that genetic testing be offered for the previously identified genetic variant in the *F8* or *F9* gene. CB**

Recommendation 4.1.3:

- **For females with low phenotypic coagulation FVIII or FIX levels, the WFH recommends that investigation of the genetic/epigenetic basis of the phenotype be offered. CB**

Recommendation 4.1.4:

- **For obligate carriers of hemophilia and "at-risk" female relatives of people with hemophilia or potential carriers of hemophilia, the WFH recommends the inclusion of a detailed family pedigree to support the genetic testing referral.** CB

Recommendation 4.1.5:

- **For individuals with suspected hemophilia and potential carriers of hemophilia, the WFH strongly recommends that phenotypic screening for FVIII or FIX levels, von Willebrand factor (VWF) antigen, and VWF activity testing be performed prior to referral for genetic testing.** CB

Recommendation 4.1.6:

- **For people with hemophilia, obligate carriers of hemophilia, "at-risk" female relatives, or individuals with low coagulation factor levels, the WFH strongly recommends detailed genetic counselling prior to offering genetic testing.**
- **Remark: Genetic counselling should include a discussion of the experimental limits of the molecular results according to the availability of practical approaches.**
- **Remark: Genetic counselling should include a discussion of the possibility of incidental findings in genes other than *F8* or *F9*, if the methodology used by the investigating laboratory (e.g., next generation sequencing [NGS]) may detect such genetic variations.**
- **Remark: Genetic counselling should be performed by a genetic counsellor when available. If no genetic counsellor is available, a medical professional with knowledge of genetics in hemophilia can provide genetic counselling.** CB

Recommendation 4.1.7:

- **For all patients referred for genetic testing, the WFH strongly recommends that informed consent be obtained from the patient, parent, or legal guardian. This requires both permission to carry out testing and education to ensure that they fully understand the testing procedure, the benefits and limitations of the test, and possible consequences of the test results.**
- **Remark: Written informed consent may need to be obtained and documented by the clinician or genetic counsellor in compliance with local policies and practices.** CB

4.2 | Indications for genetic assessment

- Genetic testing is generally sought in all affected cases (probands) and "at-risk" female relatives within the family.
- Ideally, the disease-causing variant should first be identified in the proband or the obligate carrier. All other potential carriers may subsequently be screened for this variant to confirm or exclude the carrier status.
- If neither the proband nor the obligate carrier are available for testing, the genetic assessment may still be performed in potential carriers; however, when a disease-causing variant is not detected, it should be clearly mentioned in the report that failure to detect genetic variants with the existing techniques does not exclude the carrier status.
- Carriers of hemophilia exhibit a wide range of factor levels, with approximately 30% having levels <40 IU/dL.[8] Women and girls with low or borderline levels can experience a range of bleeding symptoms, usually consistent with mild hemophilia, but hemarthrosis and more severe bleeding symptoms can occur.[9,10]
- Besides the heterozygosity for the disease-causing variant, low factor levels in carriers of hemophilia may be attributed to other epigenetic factors such as X-chromosome inactivation (XCI)[11,12] or the ABO blood group system.[13]
- Pregnant women who are confirmed carriers of an *F8* or *F9* variant may be offered non-invasive testing to determine the sex of the fetus they are carrying in order to inform subsequent options for prenatal diagnosis in a male fetus. This is achieved through analysis of cell-free fetal DNA in the maternal plasma.[14–16]
- Prenatal diagnosis may be offered to all confirmed carriers of an *F8* or *F9* variant who are carrying a male fetus in early pregnancy by chorionic villus sampling or in late pregnancy by late-gestation amniocentesis, in order to guide the management of the delivery or to terminate the pregnancy in case of an affected fetus.[17–20] Genetic counselling should include a discussion of the risk of the PND procedure to the pregnancy.
- Pre-implantation genetic diagnosis may be offered to confirmed carriers of an *F8* or *F9* variant in order to select an embryo that will not result in the birth of a male with hemophilia.[21,22]
- It is important to be aware of and follow the relevant laws governing genetic counselling and pre-implantation genetic diagnosis in the country where the services are being provided.
- Among all the genetic risk factors, the nature of disease-causing variants in both *F8* and *F9* has been found to be the strongest risk factors for inhibitor development. Null variants, i.e., variants which result in total absence of the protein (large deletions, duplications, insertions, inversions, nonsense mutations, and splice-site variants), have shown the strongest association with inhibitors as compared to other variants (small in-frame deletions, duplications, insertions, missense mutations).[23–33] The response to immune tolerance induction (ITI) therapy has also been reported to be associated with the disease-causing variants with the latter group showing good response to ITI as compared to patients carrying null variants.[34]
- Some of the gene manipulation techniques (e.g., nonsense mutation suppression and gene editing) may require prior information of the disease-causing variants.
- Genetic assessment may be offered to:
  - all cases with clinically suspected hemophilia or hemophilia cases with confirmed laboratory diagnosis;
  - all obligate carriers to identify the molecular variant for possible future prenatal diagnosis;

- all at-risk female family members to establish carrier status, which is critical for optimal prenatal counselling and testing if indicated, or to offer pre-implantation genetic diagnosis;
- all symptomatic females (with low FVIII or FIX levels) with no family history;
- predict the risk of inhibitor development in individuals with hemophilia;
- predict the response to ITI therapy;
- ascertain the feasibility of some gene manipulation techniques.

- See Chapter 3: Laboratory Diagnosis and Monitoring.

Recommendation 4.2.1:

- **For people with suspected or established hemophilia undergoing genetic testing, the WFH recommends that the index case (proband) be genotyped to identify the underlying genetic variant.** CB

Recommendation 4.2.2:

- **For obligate carriers of hemophilia and "at-risk" female relatives of the affected proband or potential carrier of hemophilia, the WFH recommends genetic counselling about their risk of being a carrier.** CB

Recommendation 4.2.3:

- **For all obligate carriers of hemophilia and "at-risk" female relatives of people with hemophilia or potential carriers of hemophilia, the WFH recommends that phenotypic coagulation factor levels be measured.** CB

Recommendation 4.2.4:

- **For all obligate carriers of hemophilia and "at-risk" female relatives of people with hemophilia, the WFH recommends that genetic testing be offered for the previously identified genetic variant in the *F8* or *F9* gene.** CB

Recommendation 4.2.5:

- **For females with low phenotypic coagulation FVIII or FIX levels, the WFH recommends that investigation of the genetic/epigenetic basis of the phenotype be offered.** CB

Recommendation 4.2.6:

- **For pregnant females who are carriers of an *F8* or *F9* variant and are carrying a male fetus, the WFH recommends that prenatal diagnosis (PND) be offered to determine the hemophilia status of the fetus.**
- **Remark: Genetic counselling should include a discussion of the risk of the PND procedure to the pregnancy.**
- **Remark: It is important to be aware of and follow the relevant laws governing such procedures in the country where the service is being provided.** CB

Recommendation 4.2.7:

- **For families who wish to be prepared for a child with hemophilia before birth or who wish to terminate an affected fetus, the WFH recommends that prenatal diagnosis (PND) by chorionic villus sampling or amniocentesis be offered.**
- **Remark: It is important to be aware of and follow the relevant laws governing such procedures in the country where the service is being provided.**
- **Remark: PND may be offered in early pregnancy or in late pregnancy by late-gestation amniocentesis in order to guide the management of the delivery of an affected child.** CB

Recommendation 4.2.8:

- **For people with suspected or established hemophilia, the WFH recommends that genetic testing be performed; knowledge of the genetic variant may help predict the risk of inhibitor development, response to immune tolerance induction (ITI), and depth of phenotype severity, as well as determine the availability of gene manipulation techniques.** CB

4.3 | Strategy for genetic testing of probands

- Worldwide, approximately 30-45% of patients with severe hemophilia A show an unusual type of structural variant (SV), a large DNA inversion affecting the *F8* intron 22 (i.e., the intron 22 inversion, Inv22).[35,36]
- The *F8* intron 22 inversion originates almost exclusively from male germ cells[37] by an event of homologous recombination between large inverted repeated sequences.[38] Reported evidence in the literature supports the fact that almost all mothers of patients with the Inv22 are carriers[39] and that the Inv22 is the most prevalent cause for severe hemophilia A worldwide.[40–44]
- A second recurrent inversion event causing approximately 2% of severe hemophilia A phenotypes worldwide is the *F8* intron 1 inversion (Inv1).[45]
- The remaining patients with severe, moderate, or mild hemophilia A (i.e., uninformative for the common *F8* inversions), as well as all patients with hemophilia B, generally have small variants in *F8* or *F9*, such as single nucleotide substitutions, small insertions, duplications or deletions, or, less frequently, large copy number variations (CNVs).
- Information about *F8* and *F9* variants is compiled in internationally accessible databases, such as those developed by the Centers for Disease Control and Prevention (CDC), named CDC Hemophilia A Mutation Project (CHAMP) and CDC Hemophilia B Mutation Project (CHBMP; http://www.cdc.gov/ncbddd/hemophilia/champs.html), and by the European Association for Haemophilia and Allied Disorders (EAHAD) for *F8* and *F9*.

Recommendation 4.3.1:

- **For male probands, the WFH recommends that genetic testing be directed by the proband's baseline phenotypic coagulation factor level, which indicates the severity of the disorder.**
  - **In patients with severe hemophilia A (FVIII:C <1 IU/dL) or moderate hemophilia A with lower-borderline factor**

activity levels (FVIII:C 1-3 IU/dL), analysis of the *F8* intron 22 inversion and the *F8* intron 1 inversion should be performed first.

- **Patients with severe hemophilia A in whom recurrent inversions (i.e., *F8* intron 22 and intron 1 inversions) cannot be detected should undergo screening and characterization of small variants, including single nucleotide variants (SNV) and small insertion, duplication, or deletion variants covering the essential regions of *F8* including the 26 exons, exon/intron boundaries, and 5′ and 3′ untranslated regions. If these tests are still uninformative, patients should be screened for copy number variants (CNV) including large *F8* deletions, duplications, or complex rearrangements.**
- **In patients with moderate (FVIII:C 1-5 IU/dL) or mild (FVIII:C 5-40 IU/dL) hemophilia A, screening and characterization of small variants (i.e., SNV and small insertions, duplications, or deletions) covering the essential regions of *F8* including the 26 exons, exon/intron boundaries, and 5′ and 3′ untranslated regions should be performed first. If these tests are still uninformative, patients should be screened for *F8* CNV.**
- **In all patients with hemophilia B (i.e., patients with severe [FIX:C <1 IU/dL], moderate [FIX:C 1-5 IU/dL], and mild [FIX:C 5-40 IU/dL] hemophilia B), screening and characterization of small variants (i.e., SNV and small insertions, duplications, or deletions) covering the essential regions of *F9* including the 8 exons, exon/intron boundaries, and 5′ and 3′ untranslated regions should be performed first. If these tests are still uninformative, patients should be screened for *F9* CNV.** CB

4.4 | Techniques for genetic assessment

- The *F8* gene is localized to the long arm of the X chromosome at Xq28. *F8* spans 187 kb of genomic DNA and consists of 26 exons encoding a mRNA of 9.0 kb. The mature FVIII protein has 2,332 amino acids.
- The *F9* gene is localized to the long arm of the X chromosome at Xq27. *F9* spans 33 kb of DNA and comprises 8 exons. *F9* mRNA is 2.8 kb and encodes a pre-pro-protein of 461 amino acids that is post-translationally processed to yield a mature protein of 415 amino acids.
- Different techniques (e.g., Southern blot, long-range and inverse-shifting polymerase chain reaction [PCR]) can be used for detection of the recurrent *F8* intron 22 inversion.[35,46–55] The recurrent *F8* intron 1 inversion can be detected by double PCR[56] or by inverse-shifting PCR.[50] The approach and use of a specific technique depend on the available technical expertise and resources. All results should be confirmed by repeat analytical testing of the DNA sample.
- Depending on the availability of resources, full *F8* or *F9* gene screening is performed by PCR and Sanger sequencing, or next-generation sequencing (NGS), for the detection of missense, nonsense, splice-site, small and large deletions, duplications, and insertions.[46,57–61] Where resources are limited, laboratories may choose a cost-effective screening approach prior to Sanger sequencing,[62] e.g., by heteroduplex analysis using conformation sensitive gel electrophoresis (CSGE).
- When choosing an analytical technique, laboratories must be aware of the sensitivity and specificity of the approach used and the turn-around time for producing an interpretive report. All results should be confirmed by repeat analytical testing of the DNA sample.
- The presence of a variant should be confirmed in both 5′ (forward) and 3′ (reverse) directions, specifically in heterozygous carriers, when analyzing variants detected using Sanger sequencing.
- In case of no amplification in a particular exon or in a contiguous stretch during PCR, a large DNA deletion may be suspected. This should be confirmed by standard approaches such as gap-PCR or techniques which can detect gene dosage or CNVs such as multiplex ligation-dependent probe amplification (MLPA) or quantitative real-time PCR on the deleted region.[63–71] The conventional Sanger sequencing techniques are not sensitive to pick up CNVs in the case of carriers.
- When a disease-causing variant is not detected, large duplications or insertions may be suspected. These can be detected by applying the same methods as those employed for identifying large deletions, as described above.
- The technical approach for CNV analysis may depend on the resources available to the laboratory. According to the practical limitations of the technique, results should be provided with an estimation of error, if applicable.
- High-throughput sequencing techniques, e.g., NGS, should only be used after it is established that structural variants can be detected by the technique.[72]
- All results of genetic testing should be confirmed by independent testing of the DNA sample. This may be accomplished either through a repeat of the original assay or by using a different methodology, e.g., using Sanger sequencing to confirm an NGS result.
- During the technical process of taking a sample for prenatal diagnosis, the fetal sample may get contaminated with maternal blood which can lead to misdiagnosis. Different techniques can be used for maternal cell contamination testing depending on the available technical expertise and resources. For example, multiple autosomal short tandem repeat (STR) markers may be used.[73–76] When choosing an analytical technique, laboratories must be aware of the sensitivity and specificity of the approach used and the turn-around time for producing an interpretive report.

Recommendation 4.4.1:

- **For people with severe hemophilia A, or moderate hemophilia A with lower-borderline factor activity levels (FVIII:C 1-3 IU/dL), the WFH recommends testing for the *F8* intron 22 inversion and *F8* intron 1 inversion in the first line of genetic testing.**
- **Remark: Different techniques can be used for detection of the *F8* intron 22 inversion and intron 1 inversion depending on the available technical expertise and resources.**

- **Remark: All results should be confirmed by independent analytical testing of the DNA sample.** CB

Recommendation 4.4.2:

- **For people with severe hemophilia A who are negative for the common *F8* intron 22 inversion and *F8* intron 1 inversion variants, the WFH recommends full gene screening of the essential regions of *F8*, including the 26 exons, splice boundaries, promoter, and 5′ and 3′ untranslated regions.**
- **Remark: For example, depending on the availability of resources, full *F8* gene screening may take the form of polymerase chain reaction (PCR) and Sanger sequencing or next generation sequencing (NGS). Where resources are limited, laboratories may choose a cost-effective screening approach prior to Sanger sequencing.**
- **Remark: When choosing an analytical technique, laboratories must be aware of the sensitivity and specificity of the approach used and the turn-around time for producing an interpretive report.**
- **Remark: The presence of a variant should be confirmed in both 5′ (forward) and 3′ (reverse) directions, specifically in heterozygous carriers, when analyzing variants detected using Sanger sequencing.**
- **Remark: All results should be confirmed by independent analytical testing of the DNA sample.** CB

Recommendation 4.4.3:

- **For people with hemophilia B, the WFH recommends full gene screening of the essential regions of *F9*, including the 8 exons, splice boundaries, promoter, and 5′ and 3′ untranslated regions.**
- **Remark: For example, depending on the availability of resources, full *F9* gene screening may take the form of polymerase chain reaction (PCR) and Sanger sequencing or next generation sequencing (NGS). Where resources are limited, laboratories may choose a cost-effective screening approach prior to Sanger sequencing.**
- **Remark: When choosing an analytical technique, laboratories must be aware of the sensitivity and specificity of the approach used and the turn-around time for producing an interpretive report.**
- **Remark: The presence of a variant should be confirmed in both 5′ (forward) and 3′ (reverse) directions, specifically in heterozygous carriers, when analyzing variants detected using Sanger sequencing.**
- **Remark: All results should be confirmed by independent analytical testing of the DNA sample.** CB

Recommendation 4.4.4:

- **For people with hemophilia A or B in whom no variant is detectable on inversion analysis or full gene sequencing, the WFH recommends that a large deletion or duplication event be investigated.**
- **Remark: Copy number variation (CNV) analysis may be performed using various validated techniques dependent on the resources available to the laboratory. According to the practical limitations of the technique, results should be provided with an estimation of error, if applicable.**
- **Remark: All results should be confirmed by independent analytical testing of the DNA sample.** CB

Recommendation 4.4.5:

- **For prenatal testing, the WFH recommends maternal cell contamination testing of the fetal sample.**
- **Remark: Different techniques can be used for maternal cell contamination testing depending on the available technical expertise and resources. For example, multiple autosomal short tandem repeat (STR) markers may be used.**
- **Remark: When choosing an analytical technique, laboratories must be aware of the sensitivity and specificity of the approach used and the turn-around time for producing an interpretive report.** CB

4.5 | Classification and description of variants

- The American College of Medical Genetics and Genomics (ACMG) guidelines were developed to provide a standardized approach and terminology for classification of genetic variants in Mendelian disorders.[77] When applied across laboratories, they provide clinicians with useful information on the likelihood that the variant impacts gene function.[6]
- Genetic diagnostics are critically dependent on accurate and standardized descriptions and sharing of genetic variants. The Human Genome Variation Society (HGVS) maintains a sequence variant nomenclature system for this purpose (http://www.HGVS.org/varnomen).[78] Providing corresponding *F8* or *F9* legacy nomenclature can be helpful to the clinician for comparison to prior patient or family clinical reports.

Recommendation 4.5.1:

- **The WFH recommends that variants be classified per the American College of Medical Genetics and Genomics (ACMG) guidelines.**
- **Remark: ClinGen, a U.S. National Institutes of Health-funded resource dedicated to building a central resource that defines the clinical relevance of genes and variants, has assembled an international expert committee to apply ACMG recommendations to *F8* and *F9* variants, which should produce more hemophilia-specific recommendations.** CB

Recommendation 4.5.2:

- **The WFH recommends that variants be described using the Human Genome Variation Society (HGVS) nomenclature.** CB

4.6 | Interpretive reports

- Clinical laboratory reports should include information to allow correct identification of the patient and specimen, report the variant using standardized nomenclature with a genome reference,

note limitations of the assay, and provide an interpretation of the findings in a manner that will be helpful to the ordering clinician.[6,79,80]

Recommendation 4.6.1:

- **The WFH recommends that interpretive reports contain:**
  - **patient information including patient name, date of birth, ordering clinician, date of specimen collection, diagnosis, baseline factor level, and family pedigree;**
  - **description of the assay(s), references to the literature (if applicable), limitations of the test, and the genome reference sequence used for analysis;**
  - **results including DNA variant(s) in Human Genome Variation Society (HGVS) nomenclature and American College of Medical Genetic and Genomics (ACMG) variant classification; and**
  - **interpretation of test results in a format useful to the ordering clinician, including recommendations for follow-up testing if indicated, implications of test results for patients and family members, and the role of genetic counselling.** CB

Recommendation 4.6.2:

- **For all interpretive reports for all individuals undergoing genetic testing for hemophilia, the WFH recommends that the ordering clinician and reporting scientist be available to discuss the potential phenotypic consequences of the reported genotype, as required.** CB

4.7 | Strategies if causative variant is not detected

- Approximately 0.6% of patients with severe hemophilia A and 2.9% of patients with moderate or mild hemophilia A will have no identifiable genetic variant in *F8* genomic DNA using current diagnostic methods, i.e., covering all coding and regulatory regions of *F8* but not deep intronic sequences.[67]
- Approximately 1.1% of patients with moderate or mild hemophilia B will have no identifiable genetic variant in *F9* genomic DNA using current diagnostic methods that exclude the screening of deep intronic sequences.[67]
- In patients with a clear diagnosis of hemophilia A and no pathogenic variant identified in the *F8* coding sequences, analysis of intronic regions by sequencing or targeted massively parallel sequencing (MPS) to the whole *F8* is an option to detect and analyze deep intronic variants involved in splicing defects, which are suspected to account for most of these patients' phenotypes.[81–86] Deep intronic variants should be interpreted with caution, and functional analysis of these variants would be desirable to demonstrate their pathogenicity.
- NGS platforms have been designed to cover different needs. Among them, the My Life, Our Future platform (https://www.mylifeourfuture.org) simultaneously analyzes all small variants and the prevalent inversions causing hemophilia A and B[72]; the ThromboGenomics platform (http://thrombo.cambridgednadiagnosis.org.uk) analyzes 63 genes associated with thrombotic, coagulation, and platelet disorders[87]; and the 23-gene NGS panel for inherited bleeding coagulation disorders analyzes 23 genes known to be associated with inherited bleeding disorders.[88] The latter two approaches complement the variant screening with a separate testing of *F8* inversions. Due to the wide range of genes under analysis, the latter two platforms are particularly useful to investigate the hidden cause of bleeding in a patient lacking a proper diagnosis.
- Whole-genome sequencing (WGS) can be considered noting any limitations in detecting structural variation. Linkage analysis may be considered for family studies.[89]
- Complex genomic rearrangements may be considered in some individuals who present with an atypical phenotype. These patients, in whom a large genomic deletion including part or all of *F8* or *F9* is suspected, should be referred to a geneticist to evaluate the possible utility of a pangenomic study. The presence of a contiguous gene syndrome can be analyzed by cytogenetic microarray analysis.[90–93]
- In patients with a confirmed diagnosis of hemophilia A and no *F8* exonic or intronic pathogenic variant detected, identification of specific micro-RNA expression imbalances, either by ncRNA microarrays or RNA-seq (MPS-based transcriptome), may represent the cause for *F8* downregulation and hemophilia A expression.[94–96] However, further research is still necessary to determine the actual role of microRNAs in the pathogenesis of hemophilia A.
- Germline and somatic mosaicism may complicate any genetic assessment in hemophilia.[97,98]
- In some cases, when testing for the familial variant in the mother of a patient with hemophilia, the variant will not be detected. In this instance, the possibility of mosaicism should be considered.
- In hemophilia A-affected probands where the mode of inheritance is not conclusive, or in low-level female probands, other potential diagnoses that need to be investigated include:
  - type 2N VWD if only low FVIII:C level on the phenotypic screen has been assessed;
  - combined FV and FVIII deficiency caused by pathogenic variants affecting *LMAN1* or *MCFD2* genes[99];
  - other types of VWD.[100]
- See Chapter 3: Laboratory Diagnosis and Monitoring.
- As X-chromosome-linked recessive disorders, hemophilia A and B affect hemizygous males while heterozygous females (carriers) do not typically express hemophilia symptoms. However, in cases of symptomatic carriers, abundant evidence has indicated that non-random and extremely skewed X-chromosome inactivation plays central roles in hemophilia pathogenesis.[11,101] Furthermore, hemophilia expression in female heterozygous carriers is caused by the phase of the X-chromosome inactivation skewing, preferentially silencing the normal *F8* allele.[12]

Recommendation 4.7.1:

- **For people in whom a strong diagnosis of hemophilia is certain but no *F8* or *F9* variant is detected using current diagnostic**

genetic testing, the WFH recommends that other genetic causes be considered (e.g., deep intronic variants).

- **Remark: Current testing techniques are expected to evolve in the near future to include next generation sequencing (NGS) and whole genome sequencing (WGS).**
- **Remark: NGS and WGS techniques should only be used after it is established that structural variants can be detected by the technique.** CB

Recommendation 4.7.2:

- **For "at-risk" female relatives of people with hemophilia in whom the familial variant is not detected using standard diagnostic genetic testing, particularly in females with one affected child, the WFH recommends that the possibility of mosaicism be considered and discussed during genetic counselling.** CB

Recommendation 4.7.3:

- **For people with hemophilia A in whom the mode of inheritance is not conclusive, and in whom no inversion or variant is detected by current diagnostic testing, the WFH recommends that other potential diagnoses be investigated, including type 2N von Willebrand disease (VWD), combined FV and FVIII deficiency, or other types of VWD.** CB

Recommendation 4.7.4:

- **For symptomatic females with low phenotypic coagulation FVIII or FIX levels in whom just one pathogenic variant is found, the WFH recommends performing investigative tests for an X-chromosome inactivation pattern, if locally available.** CB

4.8 | Quality assurance

- Quality assurance (QA), as described in Chapter 3: Laboratory Diagnosis and Monitoring – Quality assurance, is an umbrella term used to describe all measures taken to ensure the reliability of laboratory testing and reporting. In genetic testing, this covers all aspects of the diagnostic process from nucleic acid extraction and genetic analysis, to the description and classification of the variant(s) detected, and the production of an interpretive report to the ordering clinician.
- Internal Quality Control (IQC) of genetic tests should routinely be performed to ensure the validity of any variant(s) detected.
- Genetics laboratories are strongly advised to participate in External Quality Assessment Schemes (EQAS) to ensure that the quality of their results identified, classified, and interpreted, are in agreement with those obtained by other laboratories. This may be by a formal EQAS or an informal sample exchange between laboratories. Formal EQAS for genomics are provided by, for example, Genomics Quality Assessment (GenQA), and specifically for hemophilia genetic assessment by the U.K. National External Quality Assessment Service (UK NEQAS) for Blood Coagulation.
- Genetic diagnostic laboratories should undergo periodic accreditation, if available, by an approved body. Accreditation assesses the laboratory against internationally agreed standards to ensure high-quality provision of the genetic diagnostic service.
- The formation of Genetics Laboratory Networks for those providing genetic assessment of hemophilia, either within countries or between those in regions of the world, enables an opportunity for sharing of good practice and expertise.

Recommendation 4.8.1:

- **The WFH recommends that genetic diagnostic laboratories should undergo periodic accreditation, if available, by an approved body.** CB

Recommendation 4.8.2:

- **The WFH recommends that internal quality control (IQC) of genetic tests be performed and recorded routinely within the laboratory.** CB

Recommendation 4.8.3:

- **The WFH recommends that laboratories participate in external quality assessment schemes (EQAS) for the genetic tests they provide.**
- **Remark: Participation in an EQAS ensures the provision of a test that is robust and reliable. This may be through participation in a formal EQAS or an informal sample exchange between laboratories.** CB

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SUPPORTING INFORMATION

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

Chapter 5: Hemostatic Agents

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

5.1 | Introduction

- Different types of hemostatic agents and coagulation therapies are available for the management of hemophilia. The wide range of product classes and types in use around the world reflects the evolution of hemophilia treatment products and the variations in local healthcare resources and capacities.
- Clotting factor concentrates (CFCs) are the treatment of choice for people with hemophilia as they are very safe and effective for treating and preventing bleeds. There are two main types of CFCs: virally inactivated plasma-derived products made from plasma donated by human blood donors; and recombinant products manufactured using genetically engineered cells and recombinant technology.
- The development of non-factor replacement therapies such as emicizumab has recently begun to offer an alternative treatment approach as such products become available in clinical practice.
- However, access to CFCs and emicizumab is limited in many parts of the world; in some countries, healthcare providers often rely on locally produced blood products such as cryoprecipitate and fresh frozen plasma (FFP) for hemophilia treatment. However, these blood products are less effective than CFCs and may contain viral and bacterial pathogens.[1,2] For this reason, where available, viral-inactivated plasma-derived or recombinant CFCs are preferred over cryoprecipitate and FFP.
- Although advances have been made in the safety of such blood products, the WFH's position is that the products of choice for hemophilia treatment are industrially manufactured CFCs where they fulfill the requirements for pharmaceutical Good Manufacturing Practice (GMP).[2]
- The comprehensive *WFH Guide for the Assessment of Clotting Factor Concentrates* describes the key elements that affect the quality, safety, efficacy, licensing, and regulation of factor products and the important principles involved in selecting suitable products for the treatment of hemophilia.[2]
- The WFH also publishes and regularly updates the *WFH Online Registry of Clotting Factor Concentrates*, which lists all currently available products and their manufacturing details.[3]

Recommendation 5.1.1:

- **For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived clotting factor concentrates.**
- **Remark: The choice between these classes of product must be made according to local criteria including availability, cost, and patient preferences. CB**

5.2 | Product selection

- Product selection should evaluate key requirements including product safety and quality, purity, viral inactivation, and efficacy.[2]

Safety and quality

- Currently manufactured plasma-derived CFCs produced to GMP standards have an exemplary safety record with respect to

lipid-enveloped viruses, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV).

- Product safety is the result of comprehensive measures and improvements in several areas including:
  - donor selection (exclusion of at-risk donors);
  - screening of donations, including nucleic acid testing (NAT);
  - a number of in-process viral inactivation and/or removal steps, notably solvent-detergent and heat treatment, and nanofiltration for the removal of some non-enveloped viruses and prions; and
  - post-marketing surveillance.[2]
- As new information evolves in this field, decision-makers need to always be aware of current scientific recommendations regarding choice of CFCs for people with hemophilia.
- When selecting plasma-derived CFCs, both plasma quality and the manufacturing process need to be considered. The WFH emphasizes the importance of assessment by the official agencies responsible for protecting and promoting public health (i.e., national regulatory authorities, health agencies, or ministries of health) to ensure the quality, safety, and efficacy of plasma-derived treatment products for hemophilia.[2]
- Two issues require special consideration:
  - purity of product; and
  - viral inactivation/elimination.

Purity

- Purity of CFCs refers to the percentage of the desired ingredient (i.e., factor VIII [FVIII] or factor IX [FIX]) relative to the other ingredients in the product.
- There is no universally accepted classification of products based on purity, and CFCs on the market vary widely in their purity. Their "specific activity" may be expressed in international units (IU) per milligram (mg) and, for example, can range from 10 to >100 IU/mg for FVIII.[4]
- Some products have high or very high purity at one stage in the production process but are subsequently stabilized by albumin, which decreases their final purity.
- In rare cases, lower-purity CFCs may give rise to adverse or allergic reactions.[5,6] Patients who experience repeated allergic reactions with a particular product may benefit from the administration of an antihistamine immediately prior to infusion or from the use of a higher-purity CFC.
- Plasma-derived FVIII CFCs may contain variable amounts of von Willebrand factor (VWF). Therefore, it is important to ascertain a product's VWF content (as most commonly measured by VWF activity assay) if it is used for the treatment of von Willebrand disease (VWD) and not hemophilia A.[7]
- For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates (PCCs). PCCs also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture and may predispose the patient to thromboembolism. Current PCCs are considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z.[8,9] Nevertheless, with intensive treatment (e.g., during perioperative management), prothrombotic clotting factors may accumulate in the plasma and increase the risk for thromboembolic complications.
- The viral safety of CFCs is not related to their purity, provided that adequate viral elimination measures are in place.

Viral inactivation/elimination

- In-process viral inactivation is the single largest contributor to the safety of plasma-derived CFCs.[10]
- Typically, two complementary or orthogonal-specific viral reduction steps are incorporated into the CFC manufacturing process. These measures should follow the regulations set by official regulatory agencies.
- Solvent-detergent treatment is highly effective against lipid-enveloped viruses such as hepatitis B virus (HBV), HCV, and HIV, but this treatment does not inactivate non-lipid-enveloped viruses such as hepatitis A virus (HAV) and human parvovirus B19.
- Heat treatment is generally effective against a broad range of viruses, both with and without a lipid envelope, including HAV and human parvovirus B19. However, the degree of inactivation is dependent upon the temperature, time, and whether heating occurs in the dry or wet state.
- As non-enveloped viruses currently pose a greater challenge than enveloped viruses to viral elimination during the manufacturing process,[11] any viral reduction/inactivation process should ideally inactivate both lipid-enveloped and non-lipid-enveloped viruses.
- Inactivation of prions in plasma-derived CFCs is not possible because the necessary techniques denature coagulation factors; nor is there a reliable screening test for variant Creutzfeldt–Jakob disease (vCJD). The risk of prion-mediated disease through plasma-derived products is currently being addressed by exclusion of at-risk donors, leukoreduction of donations, and plasma fractionation manufacturing steps including precipitation, chromatography, and filtration.[10]

Recommendation 5.2.1:

- **For people with hemophilia, the WFH recommends the use of products that have been accepted by the official regulatory agencies responsible for protecting and promoting public health with consideration given to the plasma quality (i.e., purity of the product) and the manufacturing process (i.e., viral inactivation/elimination).**
- **Remark: A plasma-derived 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. If only one step is used, this step should preferably inactivate viruses with and without lipid envelopes. Most recently, licensed products use two orthogonal viral inactivation/elimination steps.**
- **Remark: Current prothrombin complex concentrates should be considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z.** CB

Efficacy

- Product potency (the biological activity in terms of the concentration or amount of the drug required to produce a defined effect) and efficacy (the ability of a drug to produce a desired therapeutic effect in patients) are also important features for consideration in product selection.[2]
- Plasma-derived and conventional recombinant FVIII and FIX CFCs with standard half-life (SHL) have been proven to have similarly high clinical efficacy.[2]
- Recombinant CFCs with extended half-life (EHL) are engineered to provide longer-lasting therapy than SHL CFCs. (See "Extended half-life products" below.)

5.3 | Clotting factor concentrates (CFCs)

- The main treatment for severe hemophilia is CFC replacement therapy with plasma-derived or recombinant CFCs as they provide convenient high doses of clotting factor for the treatment and prevention of bleeds.
- See also Chapter 2: Comprehensive Care of Hemophilia, Chapter 6: Prophylaxis in Hemophilia, Chapter 7: Treatment of Specific Hemorrhages, and Chapter 9: Specific Management Issues.

FVIII CFCs

- All currently marketed plasma-derived and recombinant FVIII products are listed in the *WFH Online Registry of Clotting Factor Concentrates*.[3] Consult the individual product inserts for details.

Dosage/administration

- FVIII CFCs are available in vials labelled with the product potency expressed in IU, ranging from approximately 250-3000 IU per vial.
- In the absence of an inhibitor, each IU of plasma-derived or recombinant SHL FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level by approximately 2 IU/dL.[12] This raise (also called recovery) is dependent on several individual factors; most importantly, the body mass index (BMI). It is higher in patients with a high BMI and lower in those with a low BMI.[13]
- The half-life of SHL FVIII is approximately 12 hours in adults; its half-life is shorter in younger children and increases with age.
- To calculate dosage, multiply the patient's weight in kilograms by the FVIII level in IU/dL desired, then multiply by 0.5.
  - Example: 50 kg × 40 (IU/dL level desired) × 0.5 = 1000 IU of FVIII.
- See Chapter 7: Treatment of Specific Hemorrhages and refer to Table 7-2 for CFC replacement for different types of hemorrhage.
- FVIII CFCs should be infused slowly over several minutes as specified in the product insert.[14] The patient's peak factor level should be measured 15-30 minutes after the infusion to verify the expected FVIII activity level of the dose given.[12]
- For patients undergoing surgery or those with severe bleeds that require frequent infusions, laboratory monitoring of FVIII levels is necessary, including measurement of FVIII trough level to aid in the calculation of subsequent doses. (See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays, and Chapter 9: Specific Management Issues – Surgery and invasive procedures.)
- Subsequent doses should ideally be based on the FVIII half-life and on the factor recovery in the individual patient for a particular product. However, the half-life in individual patients cannot be predicted simply from patient characteristics such as age and body weight and typically requires empiric determination.
- Guidelines for pharmacokinetic (PK) studies on new FVIII CFCs include 10-11 blood samplings taken over a period of 32-48 hours (additional samplings over up to 96 hours or longer for EHL FVIII). However, for dose tailoring in routine practice, useful PK parameters can be estimated from population PK models which enable Bayesian estimation of individual PK from limited samples.[15]
- See Chapter 6: Prophylaxis in Hemophilia and Chapter 7: Treatment of Specific Hemorrhages.

Recommendation 5.3.1:

- **For people with hemophilia receiving FVIII concentrates who would benefit from optimization of prophylaxis, the WFH recommends individualized pharmacokinetic monitoring.**
- **Remark: Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 32-96 hours), or with limited sampling in combination with population PK estimates.** CB

- Continuous infusion of CFCs avoids peaks and troughs and may be advantageous and more convenient in certain clinical situations (e.g., major surgery or severe bleeding episodes in patients with low-responding inhibitors). However, the use of specifically designated pumps and knowledge of the stability of the particular CFC after reconstitution within the infusion device are required.[16]
- Continuous infusion may allow a reduction in factor clearance, dosage, and the total quantity of CFCs used.[17] It can potentially be more cost-effective for patients with severe hemophilia, depending on the doses used for continuous and intermittent bolus infusions.[18] However, caution should be exercised if considering continuous infusion for patients with mild hemophilia as this has been associated with an increased risk of the development of inhibitors,[19,20] although the contribution of continuous infusion alone may be confounded by the presence of high-risk pathogenic variants in mild hemophilia A.
- Doses for continuous infusion should be adjusted based on frequent factor assays (usually once a day) and calculation of clearance, noting that clearance of factor may be increased immediately after surgery or with severe bleeding (e.g., blood loss of >500 mL), whereby additional boluses of CFCs may be required to maintain effective levels. For some CFCs, stability can be demonstrated for up to 12 hours after preparing the solution; thus, continuous infusion over several hours is possible.[21]

Recommendation 5.3.2:

- **For patients with hemophilia receiving FVIII concentrates where steady-state hemostatic correction is necessary for a prolonged period of time (e.g., perioperative management or in the case of a severe bleeding episode in a patient with a low-responding inhibitor), the WFH recommends consideration for use of continuous infusion.**
- **Remark: Continuous infusion may lead to a reduction in the total quantity of clotting factor concentrates used and can be more cost-effective in patients with severe hemophilia. However, this cost-effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions.**
- **Remark: Continuous infusion requires the use of specifically designated pumps and knowledge of the stability of the particular clotting factor concentrate after reconstitution within the infusion device, and patients must be monitored frequently for pump failure.** CB

FIX CFCs

- All currently marketed plasma-derived and recombinant FIX products are listed in the *WFH Online Registry of Clotting Factor Concentrates*.[3] Consult the individual product inserts for details.
- FIX CFCs are categorized into two classes:
  - Pure FIX CFCs, which may be plasma-derived or recombinant (see below for information on EHL FIX CFCs);
  - FIX CFCs that also contain factors II, VII, IX, and X, known as prothrombin complex concentrates (PCCs), which are nowadays only rarely used.
- Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B[8,9] as they are associated with a reduced risk of thrombosis and disseminated intravascular coagulation compared to PCCs, particularly in the following instances:
  - surgery;
  - liver disease;
  - intensive exposure, i.e., prolonged therapy at high doses;
  - previous thrombosis or known thrombotic tendency;
  - concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents.
- See Chapter 9: Specific Management Issues – Surgery and invasive procedures.

Recommendation 5.3.3:

- **For treatment of FIX deficiency in patients with hemophilia B, the WFH recommends a product containing only FIX rather than prothrombin complex concentrates (PCCs), which also contain other clotting factors, such as factors II, VII, and X, some of which may become activated during manufacture and may predispose the patient to thromboembolism.**
- **Remark: Pure FIX products have reduced risk of thrombosis or disseminated intravascular coagulation, compared to what was observed with large doses of older-generation PCCs.**
- **Remark: Current PCCs are considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. Nevertheless, in cases of intensive treatment (e.g., perioperative management), prothrombotic clotting factors may accumulate in plasma and may increase the risk for thromboembolic complications. When PCCs are used in high doses in order to normalize FIX levels, thromboprophylaxis should be considered.** CB

Recommendation 5.3.4:

- **For hemophilia B patients requiring prolonged therapy at high doses, the use of pure FIX concentrates is recommended over prothrombin complex concentrates.** CB

Recommendation 5.3.5:

- **For hemophilia B patients undergoing surgery, the use of pure FIX concentrates is recommended over prothrombin complex concentrates.** CB

Recommendation 5.3.6:

- **For hemophilia B patients with liver disease, the use of pure FIX concentrates is recommended over prothrombin complex concentrates.** CB

Recommendation 5.3.7:

- **For hemophilia B patients with previous thrombosis or known thrombotic tendency, the use of pure FIX concentrates is recommended over prothrombin complex concentrates.** CB

Recommendation 5.3.8:

- **For hemophilia B patients concomitantly using drugs known to have thrombogenic potential, including antifibrinolytic agents, the use of pure FIX concentrates is recommended over prothrombin complex concentrates.** CB

Dosage/administration

- FIX CFCs are available in vials labelled with the product potency, ranging from approximately 250-4000 IU per vial.
- In the absence of an inhibitor, each IU of plasma-derived or recombinant SHL FIX per kilogram of body weight infused intravenously will raise the plasma FIX level by approximately 1 IU/dL.[12]
- The half-life of SHL FIX is approximately 18-24 hours. Guidelines for PK studies on FIX CFCs include at least 8 blood samplings taken over a period of 72 hours (additional samplings over up to 2 weeks for EHL FIX). However, for dose tailoring in routine practice, useful PK parameters can be estimated from population PK models which enable Bayesian estimation of individual PK from limited samples.[15]

Recommendation 5.3.9:

- **For patients with hemophilia B receiving FIX concentrates who would benefit from optimization of prophylaxis, the WFH recommends pharmacokinetic monitoring.**

- **Remark: Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 1-2 weeks), or with limited sampling in combination with population PK estimates.** CB

- Unmodified recombinant FIX (rFIX) CFCs have a lower recovery than plasma-derived FIX CFCs, such that each unit of FIX infused per kilogram of body weight will raise FIX activity by approximately 0.8 IU/dL in adults and 0.7 IU/dL in children under 15 years of age.[22]
- To calculate dosage, multiply the patient's weight in kilograms by the FIX level in IU/dL desired.
  - Example: 50 kg body weight × 40 (IU/dL level desired) = 2000 IU of plasma-derived FIX.
  - For rFIX, the dose is calculated as 2000 IU ÷ 0.8 (or 2000 IU × 1.25) = 2500 IU for adults, and 2000 IU ÷ 0.7 (or 2000 IU × 1.43) = 2860 IU for children.
- See Chapter 7: Treatment of Specific Hemorrhages and refer to Table 7-2 for practice patterns with CFCs for different types of hemorrhage.
- FIX CFCs should be infused slowly over several minutes as specified in the product insert.[14] The patient's peak FIX level should be measured approximately 15-30 minutes after infusion to verify the expected FIX activity of the dose given.[12]
- For patients undergoing surgery or those with severe bleeds that require frequent infusions, laboratory monitoring of FIX levels is required including measurement of FIX trough level to aid in the calculation of subsequent doses. (See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays, and Chapter 9: Specific Management Issues – Surgery and invasive procedures.)
- Purified FIX CFCs may also be administered by continuous infusion (as with FVIII CFCs).
- Allergic reactions may occur with infusions of both recombinant and plasma-derived FIX CFCs (in approximately 2%-4% of cases). These are often associated with anti-FIX inhibitors.

Extended half-life products

Rationale for development of EHL CFCs

- The frequency of infusions using SHL CFCs is associated with an increased burden of treatment and often leads to poor adherence to prophylaxis regimens.[23] Annualized bleeding rates (ABRs) are not always zero with prophylaxis with SHL CFCs, and joint disease can still appear in young adults.[24,25] EHL products were developed to address the need to reduce the treatment burden of prophylaxis and to maintain higher factor trough levels to improve bleed prevention.

Mechanisms of half-life extension

- Fusion technologies and PEGylation are successful half-life extension strategies in hemophilia.[26]
- Fusion technologies rescue endocytosed proteins from intracellular degradation pathways through interaction with the neonatal Fc receptor.
- PEGylation reduces interaction with clearance receptors.
- All currently marketed EHL products are listed in the *WFH Online Registry of Clotting Factor Concentrates*.[3] Consult the individual product inserts for details.
- Different types of recombinant and modified forms of FVIII and FIX are summarized in Chapter 3: Laboratory Diagnosis and Monitoring – Tables 3-2 and 3-3.
- The WFH recommendations on EHL products were structured accordingly:
  - The emphasis was on the absence of "clinical safety issues" and not on preclinical observations from animal models with unclear implications.
  - The WFH recognizes that evaluation of both clinical and preclinical observations of EHL products has led to divergence in regulatory approval for some PEGylated products, which has impacted their licensing for prophylaxis and pediatric application in some geographies.
  - Regarding allergic reactions, these are, albeit rarely, observed for all infusion treatment products and have been observed with fusion proteins as well.[27]
  - Regarding anti-PEG antibodies, there is no published evidence to support that these have clinical safety implications in patients with hemophilia.[28]

Recommendation 5.3.10:

- **For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the half-life of clotting factor concentrates.** CB

Pharmacokinetic properties of EHL products

- For EHL FVIII products, half-life extension has been limited to 1.4- to 1.6-fold (or approximately 19 hours) that of SHL FVIII products. EHL FIX products have a much longer half-life at 3- to over 5-fold that of SHL FIX products.
- The prolonged half-life of EHL products translates to dosing twice per week or every 3 days in most cases for FVIII, and once every 7-14 days for FIX.
- Clearance of EHL products in adolescents and adults is similar, as was observed for SHL products, and half-life is shorter in pediatric populations.[29]
- EHL FIX products do not demonstrate the lower factor recovery observed with standard rFIX products. Some EHL FIX products show much higher recovery, suggesting extravascular distribution of a lower proportion of EHL FIX.[30,31] Accordingly, clinical assessment of efficacy should supplement assessment of plasma PK measurements.
- Modification of these molecules has introduced variations in their activity measurements in routine coagulation assays. Thus,

clinicians should follow the recommendations accompanying a product's regulatory approval regarding the optimal assays to be used for laboratory monitoring. (See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays.)

Safety and efficacy of EHL products

- All registered EHL products have been shown to be efficacious in the prevention and treatment of bleeds in children, adolescents, and adults. Over 90% of bleeds were successfully treated with a single administration, and the efficacy in bleed prevention resulted in ABRs <4-5 across all EHL products. Hemostatic efficacy was demonstrated in a variety of minor and major surgeries.[32]
- In previously treated children, adolescents, and adults, no increased risk of new inhibitor development has been observed in those receiving EHL FVIII/FIX products; all clinical trials in previously treated patients (PTPs) have demonstrated either no inhibitor development or very low incidence rates that were within regulatory safety limits.
- EHL products have been given to previously untreated patients (PUPs), either as part of clinical PUP studies or outside of studies. Although inhibitor development has been reported in such settings, no substantial difference in levels of inhibitor development has been observed with EHL compared to SHL products. However, no completed trial in PUPs has yet been published in full.

Approaches to dosing with EHL products

- Although EHL CFCs extend the time until patients reach the minimum trough levels required to avoid spontaneous bleeds, there is significant interpatient variability related to age, body mass, blood group, VWF level, bleeding phenotype, physical activity level, joint status, and compliance. Accordingly, there is no consensus on standardized dosing with EHL CFCs nor management of patients receiving EHL products.[23,33]
- Each of the following approaches has established efficacy in clinical trials with EHL CFCs:
  - fixed programmatic prophylaxis (fixed dose and interval, e.g., once weekly for FIX, twice weekly for FVIII);
  - PK-tailored prophylaxis (dose tailored to target trough level, given at fixed intervals);
  - phenotypic-tailored prophylaxis (variable dose and interval tailored according to bleeding pattern and activity);
  - dose/frequency-tailored prophylaxis (dose and/or frequency tailored according to target trough level and interval, e.g., higher dose and longer interval).
- To transition from SHL to EHL factor replacement therapy, dose frequency is typically lowered from 3 to 2 times weekly for FVIII, and from twice weekly to once every 7-10 days for FIX.
- PK-driven dosing allows more individualized prophylaxis. Population PK tools are in development to aid the implementation of individualized prophylaxis in clinical practice. Once an individual's PK profile is generated, the dose and treatment frequency required to obtain a desired trough level can be estimated. The target trough level needs to be customized to the needs of the individual patient within their healthcare system's parameters and flexibilities.
- See Chapter 6: Prophylaxis in Hemophilia – Extended half-life factor prophylaxis.

Recommendation 5.3.11:

- **Patients with hemophilia who are transitioning from standard half-life clotting factor concentrates to extended half-life clotting factor concentrates would typically require decreased dose frequencies, but EHL products may also be used to maintain higher trough levels to optimize prophylaxis.**
- **Remark: Pharmacokinetic-guided dosing as per Recommendations 5.3.1 and 5.3.9 provides for more individualized prophylaxis.** CB

5.4 | Bypassing agents

- Bypassing agents are used for the treatment and prevention of bleeding complications in patients with hemophilia A or B who develop FVIII or FIX alloantibodies (called inhibitors) that typically neutralize the function of infused CFCs.[34] These agents are based on different mechanisms of action to achieve hemostasis, thereby bypassing the need for FVIII or FIX replacement to treat and prevent bleeds.[35]

Recombinant activated factor VIIa (rFVIIa)

- Recombinant activated factor VIIa (rFVIIa) is a bypassing agent that promotes coagulation through tissue factor-dependent and independent pathways.[35] rFVIIa binds to tissue factor to activate FX and FIX and allows the coagulation cascade to resume.[36,37]

Activated prothrombin complex concentrate (aPCC)

- Activated prothrombin complex concentrate (aPCC) is used to treat patients with hemophilia A with inhibitors. aPCC contains mainly non-activated FII (prothrombin), FIX, FX, and mainly activated FVII.[38-40]
- See Chapter 8: Inhibitors to Clotting Factor for more information on bleed management for patients with inhibitors.

Recommendation 5.4.1:

- **For people with hemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, the WFH recommends that a bypassing agent be used.**
- **Remark: Bypassing agents include recombinant activated factor VIIa or activated prothrombin complex concentrate.** CB

Recommendation 5.4.2:

- **For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used.** CB

Recommendation 5.4.3:

- **The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events.** CB

- In addition to bypassing agents, non-factor replacement therapies (e.g., emicizumab) are becoming available that offer new treatment paradigms including for the treatment of inhibitors.
- See 5.7 Non-factor replacement therapies, below; and Chapter 6: Prophylaxis in Hemophilia – Prophylaxis using non-factor replacement therapies.

5.5 | Other plasma products

- Cryoprecipitate and FFP are not normally subjected to viral inactivation procedures (such as heat or solvent-detergent treatment) and consequently carry an increased risk of transmission of viral pathogens, which is significant with repeated infusions.[1,41] However, the WFH recognizes the necessity of the continued use of cryoprecipitate and FFP in some parts of the world where they are the only available or affordable treatment options.[1,2]
- Certain steps can be taken to minimize the risk of transmission of viral pathogens. These include:
  - quarantining plasma until the donor has been tested or even retested for antibodies to HIV, HCV, and the surface antigens of the hepatitis B virus (HBsAg)—a practice that is difficult to implement in countries where the proportion of repeat donors is low;
  - NAT testing to detect viruses—a technology that has a potentially much greater relevance for the production of cryoprecipitate than for CFCs, as the latter are subjected to viral inactivation steps.[42]
- Allergic reactions are more common following infusion of cryoprecipitate than CFC.[41] (For use of antihistamine prophylaxis, see "Safety and quality" above.)

Recommendation 5.5.1:

- **For patients with hemophilia, the WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant clotting factor concentrates in preference to cryoprecipitate or fresh frozen plasma.**
- **Remark: The WFH supports the use of CFCs in preference to cryoprecipitate or FFP due to concerns about quality, safety, and efficacy. However, the WFH recognizes the reality that they are still widely used in countries around the world where they are the only available or affordable treatment options.** CB

Fresh frozen plasma (FFP)

- As fresh frozen plasma contains all coagulation factors, it is sometimes used to treat coagulation factor deficiencies.
- Cryoprecipitate is preferable to FFP for the treatment of hemophilia A.[43] However, as FFP and cryo-poor plasma contain FIX, albeit in low concentrations, they can be used for the treatment of hemophilia B in countries unable to afford plasma-derived FIX CFCs.

Recommendation 5.5.2:

- **For patients with hemophilia, fresh frozen plasma is not recommended due to concerns about the safety and quality.**
- **Remark: However, the WFH recognizes the as yet unavoidable reality of their continued use in some parts of the world where it is the only available or affordable treatment option.** CB

- It is possible to apply some forms of virucidal treatment to packs of FFP (including solvent-detergent treatment). The use of treated packs is recommended; however, virucidal treatment may have some impact on coagulation factors. The large-scale preparation of pooled solvent-detergent–treated plasma has also been shown to reduce the proportion of the largest multimers of VWF,[44,45] which is important for VWD, but is irrelevant for treatment of hemophilia A.

Dosage/administration

- One mL of FFP contains 1 unit of factor activity.
- It is generally difficult to achieve FVIII levels higher than 30 IU/dL with FFP alone.
- FIX levels above 25 IU/dL are difficult to achieve. A starting FFP dose of 15-20 mL/kg is acceptable.[43]

Cryoprecipitate

- Cryoprecipitate is the insoluble concentrate of high molecular weight plasma proteins that precipitate when frozen plasma is slowly thawed at 1-60°C.
- Cryoprecipitate contains significant quantities of FVIII (about 3-10 IU/mL), VWF, fibrinogen, and FXIII but not FIX nor FXI. The resultant supernatant is called cryo-poor plasma and contains other coagulation factors such as factors VII, IX, X, and XI.
- The use of viral inactivation procedures is strongly encouraged.[1,43,46,47]
- The manufacture of small pool, viral-inactivated (solvent-detergent–treated) cryoprecipitate has been described, although this provides safety only for lipid-enveloped viruses.[47]

Recommendation 5.5.3:

- **For patients with hemophilia, cryoprecipitate is not recommended due to concerns about the safety and quality.**

- **Remark: The use of cryoprecipitate can only be justified in situations where clotting factor concentrates are not available as there is no proven advantage for their use over CFCs. It is strongly encouraged that viral-inactivation procedures be used, if available.** CB

Dosage/administration

- A bag of cryoprecipitate made from 1 unit of FFP (200-250 mL) may contain 70-80 units of FVIII in a volume of 30-40 mL.

5.6 | Other pharmacological options

- In addition to CFCs, other agents can be of great value in a significant proportion of cases. These include:
  - desmopressin (DDAVP);
  - tranexamic acid; and
  - epsilon aminocaproic acid (EACA).
- See also Chapter 2: Comprehensive Care of Hemophilia, Chapter 7: Treatment of Specific Hemorrhages, and Chapter 9: Specific Management Issues.

Desmopressin (DDAVP)

- Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) is a synthetic analogue of vasopressin that boosts plasma levels of FVIII and VWF.[48]
- DDAVP may be the treatment of choice for patients with mild or moderate hemophilia A when FVIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using CFC including the risk of FVIII inhibitor development.[48-51]
- DDAVP does not affect FIX levels and is of no value in hemophilia B.
- There are significant differences in individual patient response to DDAVP. The response to intranasal DDAVP is more variable and therefore less predictable.[48,49]
- DDAVP is particularly useful in the treatment and prevention of bleeding in carriers of hemophilia A.[52]
- DDAVP is not licensed for use in pregnancy, but it has been used with caution in pregnant carriers during labour and delivery. Its use should be avoided in preeclampsia and eclampsia because of the already high levels of VWF.[53,54] (See Chapter 9: Specific Management Issues – Carriers.)
- The decision to use DDAVP must be based on both the patient's baseline FVIII activity, the increment achieved, and the duration of treatment required.

Dosage/administration

- Though DDAVP may be given subcutaneously, it is primarily administered by intravenous infusion or nasal spray. It is important to choose the correct preparation of DDAVP because some lower-dose preparations are used for other medical purposes.
- Appropriate preparations include:
  - 4 μg/mL for intravenous use;
  - 15 μg/mL for intravenous and subcutaneous use;
  - 150 μg per metered dose as nasal spray.
- A single dose of 0.3 μg/kg body weight, either via intravenous or subcutaneous administration, can be expected to boost the FVIII level 3- to 6-fold.[48,55]
- For intravenous use, DDAVP is usually diluted in at least 50-100 mL of physiological saline and given by slow infusion over 20-30 minutes.
- The peak response is seen approximately 60 minutes after either intravenous or subcutaneous administration.
- Children should generally not be given DDAVP more than once per day; in adults under close supervision, twice-daily dosing may be considered. With subsequent dosing, therapeutic response decreases (tachyphylaxis) and the risk of complications rises; thus, in general, DDAVP should not be used for more than 3 consecutive days.
- CFCs may be needed when higher factor levels are required for a prolonged period.[56]
- Rapid DDAVP infusion may result in tachycardia, flushing, tremor, and abdominal discomfort.
- A single metered intranasal DDAVP spray of 1.5 mg/mL in each nostril is appropriate for an adult. For patients with a body weight of less than 40 kg, a single dose in one nostril is sufficient.[57,58]
- Some patients may find the intranasal preparation of DDAVP difficult to use, and it may be less efficacious than DDAVP given subcutaneously.
- Because DDAVP is an antidiuretic agent, water retention, hyponatremia, and even seizures may occur in patients receiving large amounts of hypotonic intravenous or oral fluids, necessitating fluid restriction during DDAVP treatment.[59] This is especially important in the context of home treatment of minor bleeding episodes and peri-operatively, when large quantities of infusions are used—patients/caregivers should be instructed to restrict fluids after DDAVP use.[59]
- DDAVP should be used with caution in young children, and it is contraindicated in children under 2 years of age. For young pediatric inpatients (i.e., postoperative patients), hypotonic intravenous fluids should be avoided and total fluid intake should be reduced to 75% of maintenance requirements in the 24 hours after use of DDAVP.[59] Plasma osmolality and sodium levels should be measured before and after DDAVP use in young children, especially if more than one dose is used over a 24-hour period.[48,59-61]
- Hyponatremia is uncommon in most adults treated with DDAVP. However, hypotension is commonly observed in both children and adults, and children under 2 years of age have an increased risk of seizures secondary to cerebral edema caused by water retention/hyponatremia.[61,62] Other side effects of DDAVP include headache, flushing, fatigue, and tachycardia. Given the vasoactive effect of DDAVP, caution should be exercised if it is used in patients with hypertension that is not completely controlled by therapy. These side effects may occur more often after intravenous administration.[63,64]

- There are case reports of thrombosis (including myocardial infarction) after infusion of DDAVP. It should be used with caution in patients with a history or risk of cardiovascular disease.[55]

Recommendation 5.6.1:

- **For patients with mild or moderate hemophilia A and carriers of hemophilia A, the WFH recommends considering desmopressin (DDAVP) as an option for treatment.**
- **Remark: The WFH recommends testing DDAVP prior to therapeutic use to evaluate the individual FVIII response. The decision to use DDAVP must be based on the patient's baseline FVIII activity, the increment achieved, and the duration of treatment required.**
- **Remark: In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion, and are mostly mild and transient. However, hypotension and/or severe hyponatremia can also occur.**
- **Remark: For pregnant women during labour and delivery, the WFH recommends caution in the use of DDAVP, and it should be avoided in pre-eclampsia and eclampsia.**
- **Remark: With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period.** CB

Recommendation 5.6.2:

- **For adults, the WFH recommends DDAVP not be used for more than 3 consecutive days and only under close supervision. If DDAVP is administered twice in a single day, subsequent daily dosing should be limited to once per day.**
- **Remark: In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion. However, hypotension and/or hyponatremia can also occur.**
- **Remark: With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period.** CB

Recommendation 5.6.3:

- **For children, the WFH recommends using no more than 1 dose of DDAVP per day for no more than 3 consecutive days.**
- **Remark: In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion. However, hypotension and/or hyponatremia can also occur.**
- **Remark: With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period.** CB

Recommendation 5.6.4:

- **For children under 2 years of age, the WFH alerts that DDAVP is contraindicated due to increased risk of seizures as consequences of water retention and hyponatremia.** CB

Recommendation 5.6.5:

- **For patients at risk of cardiovascular disease or thrombosis, the WFH recommends that DDAVP should be used with caution due to the risk of thromboembolism and myocardial infarction.** CB

Tranexamic acid

- Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin. It promotes clot stability and is useful as adjunctive therapy for some types of hemophilic bleeding.[65]
- Treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia.[65]
- Tranexamic acid is useful for treating superficial soft tissue and mucosal bleeds (e.g., oral bleeding, epistaxis, and menorrhagia).[66-68]
- 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.[67,69]
- See also Chapter 2: Comprehensive Care of Hemophilia and Chapter 7: Treatment of Specific Hemorrhages.

Dosage/administration

- Tranexamic acid is usually given as oral tablets (25 mg/kg/dose) 3-4 times daily. It can also be given by intravenous infusion (10 mg/kg/dose) 2-3 times daily. It is also available as an oral rinse.
- Gastrointestinal upset (nausea, vomiting, or diarrhea) may rarely occur as a side effect of tranexamic acid, but these symptoms usually resolve if the dosage is reduced. When administered intravenously, tranexamic acid must be infused slowly as rapid injection may result in dizziness and hypotension.
- A syrup formulation of tranexamic acid is also available for pediatric use. If this is not obtainable, a tablet can be crushed finely and dissolved in clean water for topical use on bleeding mucosal lesions.
- Tranexamic acid is commonly prescribed for 7 days following dental extractions to prevent postoperative bleeding.
- Tranexamic acid is excreted by the kidneys, and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.
- The use of tranexamic acid is contraindicated for the treatment of hematuria as its use may prevent dissolution of clots in the ureter, leading to serious obstructive uropathy and potentially permanent loss of renal function.
- Tranexamic acid is also contraindicated in the setting of thoracic surgery where it may result in the development of insoluble hematomas.

- Tranexamic acid may be given alone or together with standard doses of CFCs including bypassing agents such as aPCC and rFVIIa.[70-72]
- Tranexamic acid is contraindicated in patients with hemophilia B receiving PCCs, as it increases the risk of thromboembolism.[73]

Recommendation 5.6.6:

- **For patients with hemophilia, the WFH recommends that antifibrinolytics are a valuable alternative to use alone or as adjuvant treatment, particularly in controlling mucocutaneous bleeding (e.g., epistaxis, oral and gastrointestinal bleeding, and menorrhagia) and for dental surgery and eruption or shedding of teeth.**
- **Remark: Antifibrinolytics can be used with standard doses of clotting factor concentrates, including bypassing agents. However, they should not be used with prothrombin complex concentrates due to the increased risk of thromboembolism. CB**

Recommendation 5.6.7:

- **For patients with hematuria, the WFH recommends against the use of antifibrinolytics, as it is contraindicated in these patients due to increased risk of obstructive uropathy. CB**

Recommendation 5.6.8:

- **For patients with renal impairment, the WFH recommends reduced dosing of antifibrinolytics and close monitoring. CB**

Epsilon aminocaproic acid

- Epsilon aminocaproic acid is similar to tranexamic acid but is less widely used as it has a shorter plasma half-life, lower potency, and higher toxicity.[65]
- See also Chapter 2: Comprehensive Care of Hemophilia and Chapter 7: Treatment of Specific Hemorrhages.

Dosage/administration

- In adults, EACA is typically administered orally (100 mg/kg/dose up to a maximum of 2 g/dose) or intravenously (100 mg/kg/dose up to a maximum of 4 g/dose) every 4-6 hours up to a maximum of 24 g/day.
- A 250 mg/mL syrup formulation of EACA is also available.
- Gastrointestinal upset is a common complication with EACA use; reducing the dose often alleviates this side effect.
- Myopathy is a rare adverse reaction specifically reported in association with EACA therapy (but not tranexamic acid) and typically occurs after administration of high doses for several weeks.
- The myopathy associated with EACA use is often painful and associated with elevated levels of creatine kinase and even myoglobinuria. Full resolution may be expected once EACA treatment is stopped.

5.7 | Non-factor replacement therapies

- For the past five decades, the focus of hemophilia therapies has been on replacing the missing clotting factor protein; however, recombinant technology combined with improved basic understanding of coagulation biochemistry is currently shifting the treatment paradigm.

Rationale and mechanisms of action

- New and emerging innovative therapeutics have been developed with alternative modes of delivery (e.g., subcutaneous), targets that overcome the limitations of current clotting factor replacement therapy (i.e., intravenous administration, short half-life, risk of inhibitor formation), and markedly improved PK profiles with a very low burden of administration (e.g., up to monthly dosing), which may increase compliance.

Substitution therapy

- Substitution therapy differs from factor replacement therapy in that it is based on the use of an alternative hemostatic agent to substitute for clotting factor. The factor mimetic, emicizumab, is the first and only licensed substitution therapy at the time of this publication.
- Emicizumab is a chimeric bispecific antibody directed against the enzyme FIXa and the zymogen FX that mimics the cofactor function of FVIII in patients with hemophilia A, with or without inhibitors. Emicizumab binds to FIX, FIXa, FX, and FXa; however, it is its affinity to FIXa and FX that promotes FIXa-catalyzed FX activation and tenase formation.[74,75]
- The key benefits of emicizumab are its subcutaneous route of administration, long half-life, high efficacy in bleed prevention, and reduction of the frequency of bleeding episodes in patients with or without FVIII inhibitors.
- As emicizumab differs biochemically from FVIII, many questions remain regarding its long-term impact on joint pathology and immunogenicity in non-inhibitor patients.
- Emicizumab is not intended to treat acute bleeding episodes. Caution is required when treating breakthrough bleeding episodes while on emicizumab as several patients have developed either venous thromboembolism or thrombotic microangiopathy with concomitant administration of aPCC.[76] Consult the hemophilia treatment centre and risk management guidance.

Recommendation 5.7.1:

- **For patients with hemophilia A with an inhibitor, the WFH recommends that emicizumab should be used for regular prophylaxis.**
- **Remark: For patients with hemophilia A with no inhibitor, the WFH recommends that emicizumab can be used for regular prophylaxis. CB**

Hemostatic rebalancing agents

- The hemostatic system regulates the balance between procoagulants (e.g., clotting factors) and natural anticoagulants (e.g., antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C). Bleeding disorders result from a deficiency of the procoagulants, whereas deficiencies of the natural anticoagulants are associated with increased thrombotic risk.
- Hemophilia has typically been treated by replacing the missing procoagulant protein or with bypassing agents (i.e., when inhibitors are present). However, inhibiting the natural anticoagulants can also restore hemostasis. This has been observed naturally as co-inheritance of thrombophilic risk factors can moderate the clinical phenotype of severe hemophilia A. In addition, thrombin generation is increased with co-inheritance of hemophilia with some forms of thrombophilia (e.g., protein C deficiency).
- Fitusiran is an RNA interference therapy that specifically targets antithrombin messenger RNA to suppress the production of antithrombin in the liver.[77] This therapy has the advantage of subcutaneous administration, prolonged duration of action and, due to its mechanism of action, it could be used in both hemophilia A and B patients with or without inhibitors.
- For prevention of bleeding, suppression of antithrombin by 75% is most effective. Breakthrough bleeding can be treated with FVIII/FIX replacement or with bypassing agents, but lower doses must be used to minimize the risk of excessive procoagulant activity.
- Anti-TFPI antibodies represent another modality in clinical trials. Different anti-TFPI antibodies are currently in development, all of which bind to the K2 domain or to both the K1 and K2 domains of TFPI, thus rescuing FXa and FVIIa from inhibition.[78] These therapies may also be administered subcutaneously and restore hemostasis in both hemophilia A and B patients with or without inhibitors, but their duration of action is limited by target-mediated drug disposition. The use of fitusiran requires close monitoring to minimize risk of thrombosis. Two anti-TFPI clinical programs are ongoing, while two others have seen evidence of thrombotic complications. One clinical program has been stopped and one halted due to these adverse events.
- See also Chapter 2: Comprehensive Care of Hemophilia, Chapter 6: Prophylaxis in Hemophilia, Chapter 8: Inhibitors to Clotting Factor, and Chapter 9: Specific Management Issues.

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SUPPORTING INFORMATION

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

Chapter 6: Prophylaxis in Hemophilia

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This chapter discusses prophylaxis for people with hemophilia in the absence of inhibitors to factor VIII or IX. For prophylaxis for patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.

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

6.1 | Introduction

- Prophylaxis in hemophilia consists of regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding, especially joint hemorrhages, which would lead to arthropathy and disability. Prophylaxis should enable people with hemophilia to lead healthy and active lives including participation in most physical and social activities (at home, school, work, and in the community), similar to the non-hemophilic population.
- Prophylaxis with clotting factor concentrates (CFCs) is referred to as regular replacement therapy; it stands in contrast to episodic replacement therapy (also known as on-demand therapy), which is defined as the administration of CFCs only at the time of a bleed.[1] Episodic therapy, regardless of the doses used, while essential in reducing the pain and debilitating impact of individual bleeds, does not alter the bleeding profile significantly and hence does not change the natural history of hemophilia leading to musculoskeletal damage and other complications due to bleeding.
- Therefore, the use of prophylaxis is always recommended over episodic therapy. In countries with healthcare constraints and for patients with limited access to CFCs, less intensive prophylaxis regimens may be used. (See 6.9 Health economics of prophylaxis.) Still, in all countries the ideal is for patients to not experience any bleeds (i.e., achieve "zero" bleeds).
- With the advent of innovative non-factor replacement therapies, which for the most part can be administered subcutaneously, prophylaxis is being redefined as the regular administration (intravenously, subcutaneously, or otherwise) of a hemostatic agent/agents to enhance hemostasis and effectively prevent bleeding in people with hemophilia.[2,3]

Recommendation 6.1.1:

- **For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.**
- **Remark: Individualizing prophylaxis means that if patients continue to experience bleeds, their prophylaxis regimen should be escalated (in dose/frequency or both) to prevent bleeding.**
- **Remark: In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used. CB**

- See 6.9 Health economics of prophylaxis and 6.10 Low-dose prophylaxis for patients with limited access to CFCs.

Standard half-life factor replacement therapy

- Prophylaxis has conventionally been defined as the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A and factor IX (FIX) in people with hemophilia B, given in order to increase the FVIII/FIX level with the intent to prevent bleeding.[1] The focus of this conventional definition of prophylaxis has been on preventing joint bleeds and maintaining musculoskeletal health.
- The objective of prophylaxis has been to convert a person with severe hemophilia (baseline FVIII/FIX level <1 IU/dL [1%]) to a bleeding phenotype typical of moderate or mild hemophilia by maintaining factor levels above 1 IU/dL (1%) at all times.[4]
- This was based on the observation that people with moderate hemophilia seldom experienced spontaneous bleeding and had much better preservation of joint function.
- However, there has been increasing recognition and evidence that factor trough levels of 1-3 IU/dL (1%-3%) are insufficient to totally prevent bleeds in all people with hemophilia and allow occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan.[5]
- In general, the higher the factor levels at all times, the less the bleeding. For every 1% increase in baseline factor levels (in people with hemophilia not on prophylaxis), there is a decrease in bleeding frequency, and when baseline FVIII:C levels are above 15 IU/dL (15%), spontaneous bleeding is uncommon.[6-8] The same is thought to apply with FIX:C levels, although this has been less well studied. Similarly, it has been shown that the more time spent with FVIII levels below 1 IU/dL (1%), the higher the rate of breakthrough bleeds during prophylaxis.[6]

Extended half-life factor replacement therapy

- The use of extended half-life (EHL) CFCs fits within the definition of conventional factor prophylaxis but allows for more ambitious prophylaxis than simply converting an individual from a severe to a moderate phenotype.
- This is particularly the case with some EHL FIX products which allow individuals to have FIX levels in a non-hemophilic range (>40 IU/dL [40%]) for a substantial proportion of time and levels in the mild hemophilia range (5-40 IU/dL [5%-40%]) just prior to the next infusion.[9]
- While prophylaxis with CFCs has been the mainstay of hemophilia treatment for many decades, the treatment landscape is changing with the development of new types of therapies.

Non-factor replacement therapy

- Non-factor replacement therapy differs from clotting factor replacement therapy in that it provides hemostasis through a different mechanism than FVIII/FIX replacement. The first, and at the time of this publication, the only licensed non-factor replacement therapy for hemophilia A is emicizumab.[10] Emicizumab mimics the cofactor activity of FVIII. It is administered subcutaneously once weekly, and in some cases can be administered as infrequently as once every 2 or 4 weeks.[11] (See 6.5 Prophylaxis with non-factor replacement therapy.)

Basic definitions and concepts in prophylaxis with CFCs

- Prophylaxis has been characterized according to when it is initiated and according to its intensity. These definitions apply to both hemophilia A and B. (See Tables 6-1 and 6-2.)

Initiation of prophylaxis: timing and approach

- Age at initiation of prophylaxis has been a strong predictor of long-term clinical outcomes.
- People with hemophilia initiated on early prophylaxis (i.e., primary or secondary prophylaxis) have shown the best long-term outcomes.[12] (See Table 6-1 for prophylaxis definitions.) Furthermore, early initiation of prophylaxis also reduces the risk and incidence of intracranial hemorrhage (ICH), which is highest in very young children.[13]
- Long-term cohort studies have shown that a small number of joint bleeds occurring early in life prior to the start of prophylaxis may (in some patients) ultimately result in hemophilic arthropathy.[14-16]
- Regular prophylaxis begun at a young age and given in appropriate doses should therefore be considered the standard of care to treat hemophilia until an alternate long-term therapy such as gene therapy is available.
- There have been various approaches regarding how to initiate conventional prophylaxis with IV factor replacement therapy. The two main ways (high-dose prophylaxis and low-dose escalating prophylaxis) are mainly differentiated in the frequency of CFC administration and less so in the doses used.[17]
- Escalating frequency prophylaxis, which starts with less intense prophylaxis (e.g., once-weekly infusions), followed by an increase in frequency, has enabled young children and their families to gradually adapt to the burdens of prophylaxis (e.g., peripheral venous infusion).[18,19] Young children commenced on low-dose escalating prophylaxis need to be followed closely, and strong consideration should be given to escalating prophylaxis quickly (either all patients or according to bleeding symptoms) in order to prevent bleeding and resulting morbidity.
- Starting with less intense prophylaxis and then gradually escalating may improve family acceptance of starting prophylaxis early and may improve adherence to prophylaxis. This approach also appears to result in less need for placement of central venous access devices (CVADs). However, patients on less intense

TABLE 6-1 Conventional factor prophylaxis for hemophilia A and B defined according to when prophylaxis is initiated[1]

Primary prophylaxis	• Regular continuous prophylaxis started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and 3 years of age
Secondary prophylaxis	• Regular continuous prophylaxis initiated after 2 or more joint bleeds but before the onset of joint disease; this is usually at 3 or more years of age
Tertiary prophylaxis	• Regular continuous prophylaxis initiated after the onset of documented joint disease. Tertiary prophylaxis typically applies to prophylaxis commenced in adulthood

TABLE 6-2 Conventional factor prophylaxis with standard half-life clotting factor defined according to its intensity

Prophylaxis intensity	Hemophilia A	Hemophilia B
• High-dose prophylaxis[4]	• 25-40 IU FVIII/kg every 2 days (>4000 IU/kg per year)	• 40-60 IU FIX/kg twice per week (>4000 IU/kg per year)
• Intermediate-dose prophylaxis	• 15-25 IU FVIII/kg 3 days per week (1500-4000 IU/kg per year)	• 20-40 IU FIX/kg twice per week (2000-4000 IU/kg per year)
• Low-dose prophylaxis (with escalation of dose intensity, as needed)[a]	• 10-15 IU FVIII/kg 2-3 days per week (1000-1500 IU/kg per year)	• 10-15 IU FIX/kg 2 days per week (1000-1500 IU/kg per year)

Abbreviations: FIX, factor IX; FVIII, factor VIII; IU, international unit; kg, kilogram.

[a]Should only be taken as the starting point of replacement therapy to be tailored, as possible, to prevent bleeding.

prophylaxis are at a higher risk of bleeding until escalation of prophylaxis occurs.[20,21]

- For people with hemophilia A, starting with small doses of FVIII CFC therapy may have the additional (unproven) benefit of decreasing inhibitor development, as large and frequent doses of FVIII early on have been associated with an increase in the rate of inhibitor development.[22]
- People with severe/moderate hemophilia who have had a life-threatening bleed in early childhood should, however, not be placed on escalating dose prophylaxis but instead be started immediately on high-dose prophylaxis.
- How to start and when to start prophylaxis with either standard half-life (SHL) or extended half-life (EHL) CFCs is not significantly different. In both cases, prophylaxis should be commenced early by starting with a high-dose/high-frequency approach or a low-frequency approach, followed by escalation of frequency.
- With EHL CFCs, less frequent infusions (e.g., once weekly) may be sufficient for many individuals, particularly those with severe hemophilia B receiving EHL FIX CFCs. As EHL CFCs must still be given intravenously, they remain difficult to administer in very young children with poor peripheral venous access.[17]
- Time to initiation of prophylaxis with non-factor replacement agents has not been well studied. Since emicizumab is administered subcutaneously, challenges of venous access are mitigated. It may be started at a similar time as CFC prophylaxis initiation, or perhaps earlier, although data are still very limited.[23] Further research on initiation of emicizumab in newborns is needed.[24]
- See Tables 6-1 and 6-2, above, and Chapter 3: Laboratory Diagnosis and Monitoring – Inhibitor testing.

Recommendation 6.1.2:

- **For pediatric patients with severe hemophilia A or B, the WFH recommends early initiation of prophylaxis with clotting factor concentrates (standard or extended half-life FVIII/FIX) or other hemostatic agent(s) prior to the onset of joint disease and ideally before age 3, in order to prevent spontaneous and breakthrough bleeding including hemarthroses which can lead to joint disease.** CB

Recommendation 6.1.3:

- **For adolescents and adults with hemophilia who show evidence of joint damage and have not as yet been on prophylaxis, the WFH recommends commencing tertiary prophylaxis in order to reduce the number of hemarthroses, spontaneous and breakthrough bleeding, and slow down the progression of hemophilic arthropathy.** CB

Intensity of prophylaxis

- Although intensity of prophylaxis has generally been referred to as high, intermediate, and low dose, it should be appreciated that intensity is a function of both dose and frequency and that high dose usually refers to a combination of both high doses and high frequencies, while low dose usually refers to a combination of lower doses and lower frequencies, although not always.
- See 6.6 Fixed/non-tailored factor prophylaxis regimens, below, and 6.7 Tailored factor prophylaxis regimens, below.

6.2 | Benefits of prophylaxis

Prophylaxis using clotting factor concentrates

- All forms of prophylaxis (high/intermediate/low dose with CFCs or prophylaxis with non-factor replacement agents, e.g.,

emicizumab) provide superior benefits over episodic therapy. Conventional high-dose and intermediate-dose prophylaxis, initiated early in life, have been associated with over 90% reduction in joint bleeding rates, annualized joint bleeding rates (AJBRs) below 3 per year, and a significant reduction in joint deterioration and degenerative joint disease.[12,25]

- Prophylaxis also provides protection from other types of hemorrhages in hemophilia, including preventing or substantially reducing the risk of intracranial hemorrhage.[13]
- Longer-term benefits include reduction of chronic musculoskeletal pain, functional limitations and disability, need for orthopedic surgery, hospitalization, emergency room visits, and reduced length of hospital stays; all of this leads to greater participation (i.e., regular attendance) in educational, recreational, and professional activities, with improved quality of life.[26]
- Because of these benefits, the World Health Organization (WHO), the World Federation of Hemophilia (WFH), and many national and international hemophilia organizations have endorsed early prophylaxis as the standard of care for children with a severe phenotype hemophilia[27] and recommend that prophylaxis be continued lifelong. Additionally, adults with severe phenotype hemophilia (if not already on prophylaxis) should initiate prophylaxis as well.[22]

Prophylaxis using non-factor replacement therapies

- Emicizumab prophylaxis in a number of clinical trials has been shown to be associated with very low rates of bleeding (an annualized bleeding rate [ABR] of 1.5) and ABRs lower than what patients previously reported while on prophylaxis with CFCs.[2] More research is needed regarding long-term outcomes with emicizumab. Data on the use of other non-factor therapies for prophylaxis are at present much more limited.

Recommendation 6.2.1:

- **For patients with severe phenotype hemophilia A or B, especially children, the WFH recommends regular long-term prophylaxis as the standard of care to prevent hemarthrosis and other spontaneous and breakthrough bleeding, maintain musculoskeletal health, and promote quality of life. When prophylaxis is not feasible, episodic therapy is essential treatment for acute hemorrhages, but it will not prevent long-term joint damage.**
- **Remark: In the long term, early and regular prophylaxis for children reduces hemarthrosis and other hemophilic bleeding, produces better health and joint outcomes, reduces the number of hospital visits and admissions, and may avert the need for orthopedic interventions, including surgery, in the future.** CB

6.3 | Standard half-life factor prophylaxis

- All SHL CFCs (i.e., plasma-derived and recombinant) have essentially similar pharmacokinetic properties. The short half-life of SHL CFCs results in the need for frequent venipunctures for prophylaxis (3-4 times per week for FVIII and 2-3 times per week for FIX); this often leads to the need for CVADs in young children and to reduced adherence in older children/adults.[28]
- With SHL CFCs, it is difficult to achieve factor trough levels much higher than 1 IU/dL (1%); to do so would require very frequent infusions (possibly daily) that many patients are likely unwilling or unable to do.
- Individual factor levels in people with hemophilia on prophylaxis are determined by:
  - the prophylaxis regimen (dose and frequency) that individuals are on;
  - their individual pharmacokinetic (PK) handling of factor (factor recovery and half-life/clearance); and
  - the PK characteristics of the CFC product used. (See Table 6-3.)

Recommendation 6.3.1:

- **For patients with severe phenotype hemophilia A or B, prophylaxis with clotting factor concentrates (either standard or extended half-life) is recommended at a dose and dosing interval (dependent on the pharmacokinetic [PK] properties of the clotting factor concentrate) that allow them to at all times have sufficient circulating factor to prevent hemarthrosis, and spontaneous and breakthrough bleeding, based on their individual needs and lifestyles and preserve musculoskeletal function.**
- **Remark: In the past, a trough factor level of 1 IU/dL (1%) was deemed an adequate goal. Now recognizing that with a 1% trough level, patients remain at risk of bleeding, most clinicians would prefer to target higher trough levels (>3%-5%, or higher). Recent studies show that such trough levels achieve less bleeding. However, the trade-off is that higher trough levels may require higher doses or more frequent infusions of clotting factor concentrates. This should therefore be personalized based on the individual's activities, lifestyle, and PK handling of factor.** CB

Time of day dosing for SHL CFCs

- Timing of prophylactic doses is important particularly for conventional CFCs with shorter half-lives (i.e., SHL FVIII/FIX). Due to the short half-life of SHL CFCs, conventional prophylaxis produces a sinusoidal curve of factor peaks and troughs, corresponding to times when patients can safely be more active and times when they cannot.
- As people are more likely to be active during the day, it makes logical sense for most to infuse SHL CFCs in the mornings rather than in the evenings.

Recommendation 6.3.2:

- **For patients who are adherent to their prescribed prophylaxis regimen but still experience breakthrough bleeds, the WFH recommends escalation of prophylaxis with measurement of trough levels and, if required, orthopedic interventions as appropriate.**

- **Remark: Any patient who fails to respond to adequate factor replacement therapy after past responsiveness should be tested for inhibitor development prior to escalation of therapy.** CB

6.4 | Extended half-life factor prophylaxis

- The limitations of prophylaxis with SHL CFCs led to the recent development, introduction, and increasing use of EHL CFCs.

Half-life/clearance

- Current EHL FVIII CFCs show modest improvement (1.4- to 1.6-fold) in half-life/clearance in comparison to SHL FVIII CFCs, with no significant differences in PK properties between these EHL FVIIIs. (Note that there is one EHL FVIII still in clinical trials [BIVV001] that shows a 3- to 4-fold half-life extension.) By contrast, EHL FIX CFCs show greatly improved half-lives (3- to 5-fold longer) in comparison to SHL FIX, but unlike with EHL FVIIIs, there are significant differences in the PK properties between EHL FIX CFCs.[9,30-32]

Dose

- It is not as yet determined what constitutes high-, intermediate-, and low-dose prophylaxis with EHL CFCs and whether these definitions should be revised, given that much higher factor trough levels can be obtained with EHL CFCs, particularly with EHL FIXs. For the most part, EHL FVIIIs have similar recoveries as SHL FVIIIs, and hence doses used for prophylaxis will be similar. Certain EHL FIX products show higher recoveries on the basis of less extravascular distribution than SHL FIX; for these products, lower doses might be used for prophylaxis.[9,31] It has been hypothesized that differences in extravascular distribution of FIX between various EHL and SHL FIX CFCs may be important in the protective effect that these CFCs deliver.[33,34] Further research into this is necessary.

Frequency of dosing

- Overall, EHL CFCs allow people with hemophilia to reduce the number of infusions needed to still achieve levels of protection similar to SHL CFCs, or allow them to increase their factor trough levels and achieve higher levels of bleed protection with a similar number of infusions, or a combination of both. Modest reductions in infusion frequency or modest increases in factor trough levels (likely not both) may be accomplished with EHL FVIII concentrates.
- Some (but not all) EHL FIX concentrates permit patients to infuse much less frequently (e.g., once every 7-14 days) and still maintain FIX trough levels of ≥10%-20%[9,31,32,35] or infuse weekly or more frequently and achieve FIX trough levels of 20%, 30%, or potentially higher levels. The only caveat to this is that differences in extravascular distribution of FIX may be important in the protective effect of FIX.[36]

Time of day dosing for EHL CFCs

- The longer the half-life of a product, the less critical the timing of infusions. This is particularly the case with some EHL FIX concentrates.[37-39] (See Table 6-4.)

Recommendation 6.4.1:

- **For patients with severe phenotype hemophilia A or B using EHL FVIII or FIX concentrates, the WFH recommends prophylaxis with EHL clotting factor concentrates at sufficient doses and**

TABLE 6-3 Variables that affect factor levels (applies to both SHL and EHL clotting factors) in people with hemophilia

Variables	Impacts on factor levels
Most important	
Frequency of dosing[a]	• Doubling frequency of infusions (without changing the dose/infusion) provides on average 5 half-lives of additional coverage
Half-life/clearance[b]	• Doubling half-life provides on average 5 half-lives of additional coverage
Least important	
Dose	• Doubling dose provides 1 half-life of additional coverage
Recovery	• Doubling recovery provides 1 half-life of additional coverage

Note: This table is adapted from Carcao (2015).[29]

Abbreviations: CFC, clotting factor concentrate; EHL, extended half-life; FIX, factor IX; SHL, standard half-life.

[a]Frequent small doses of CFC are generally much more efficient than infrequent large doses. Daily prophylaxis would be the most efficient prophylaxis regimen with SHL CFCs, as it would allow for use of relatively small doses of CFC and yet permit high factor levels to be maintained. However, such a regimen may be very difficult to adhere to, particularly for younger patients.

[b]Known variables that impact half-life/clearance of FVIII include blood group (O vs non-O) and von Willebrand factor levels; less is known as to what contributes to individual differences in pharmacokinetic handling of FIX. For the most part, individual factor recovery and half-lives increase with age. This may result in older patients needing a lower dose per infusion to maintain similar factor trough levels.

TABLE 6-4 Documented benefits of EHL CFCs

Benefits of lower infusion frequency	Benefits of higher factor trough levels
• Fewer clinic visits or home care nurse visits when commencing patients on prophylaxis, possibly leading to earlier start of prophylaxis	• More effective prophylaxis—higher level of prevention of bleeds (both clinically evident and subclinical microbleeds) while maintaining similar dosing schedules
• Less need for CVADs leading to some cost savings and reduced morbidity	• Potentially greater level of sports participation (possibly including sports that have traditionally been discouraged) without incurring a substantially increased risk of bleeding
• Less burdensome infusion schedules (dosing days and times): ◦ fewer morning infusions ◦ fewer infusions on work/school days	
• Increased uptake of prophylaxis among patients not currently on prophylaxis	

Note: This table is adapted from Carcao (2015).[29]

Abbreviations: CFC, clotting factor concentrate; CVADs, central venous access devices; EHL, extended half-life.

dosing intervals to prevent hemarthroses and spontaneous and breakthrough bleeding and preserve joint function. CB

6.5 | Prophylaxis with non-factor replacement therapy

- Note: Emicizumab is the only licensed non-factor replacement product available at the time of publication.
- The development of new non-factor hemostatic therapies in hemophilia is causing a reconsideration of the concepts and definitions of prophylaxis. These new non-factor therapies include emicizumab, a FVIII mimetic already in clinical use for hemophilia A,[10] and others still in development including agents that inhibit natural endogenous anticoagulants (antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C).
- Emicizumab and those non-factor agents in development differ from conventional types of prophylaxis as they do not replace the missing coagulation factor, are administered subcutaneously, and in some cases can be administered as infrequently as once every 2 or 4 weeks.[11] Additionally, these agents are not associated with the peak and trough curves of protection that we now see with factor prophylaxis regimens.
- There have already been extensive clinical trials of emicizumab in patients with hemophilia A with and without inhibitors that attest to the safety and bleed protection with this agent.[2,32,40] (For emicizumab use in patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.)
- Emicizumab is already making it easier to start patients on prophylaxis at an earlier age and without the need for CVADs. This may cause a re-evaluation of what constitutes primary prophylaxis (see Table 6-1), as perhaps prophylaxis can be commenced much earlier than usual. This could reduce the risk of bleeding that now occurs in very young children (ages 6-12 months) prior to the usual commencement of prophylaxis.[12,30,41] Further research on the safety of emicizumab in this very young population is required.[24]
- Non-factor products should allow for less burdensome prophylaxis, which might improve adherence and might lead to increased uptake of prophylaxis among patients not currently on prophylaxis (including those with moderate hemophilia), permitting them increased participation in social and sports activities. The above is already demonstrated by the increasing uptake and usage of emicizumab.
- All of these developments are transforming the concepts of prophylactic intensity. No longer can one refer to high-dose prophylaxis as prophylaxis that results in factor trough levels of 1%-3%.[3]

Recommendation 6.5.1:

- **For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.**
- **Remark: The WFH however notes that there are very little long-term data on patient outcomes with such an approach and recommends that such data be obtained.** CB

- See also Chapter 5: Hemostatic Agents and Chapter 8: Inhibitors to Clotting Factor.

6.6 | Fixed/non-tailored factor prophylaxis regimens

- Many factor prophylaxis regimens have been developed and promulgated by different groups. These regimens can, in general, be categorized as non-tailored/fixed-dose ("one size fits all") or tailored prophylaxis regimens.

"One size fits all" SHL factor prophylaxis regimens

High-dose and intermediate-dose prophylaxis

- The high-dose prophylaxis approach involves the administration of usually 25-40 IU/kg per dose given every other day or 3 times per week (for SHL FVIII concentrates) or twice per week (for SHL FIX concentrates) in order to ensure protection from spontaneous

TABLE 6-5 Advantages and disadvantages of fixed "one size fits all" SHL factor prophylaxis regimens

Regimen	Advantages	Disadvantages
High dose/high frequency	• Ensures that, on average, patients with hemophilia will have at all times measurable FVIII/FIX levels; i.e., levels above 1 IU/dL (1%) • Ensures that virtually all individuals receive enough treatment to prevent virtually all bleeds • Achieves lowest AJBRs and best long-term joint outcomes • Offers benefits for very active individuals	• May be associated with adherence and convenience issues due to increased infusion demands on patients • Is associated with highest factor utilization and consequently highest cost • Results in high need for CVADs or AVFs • May overtreat some individuals who have a milder phenotype which may negatively impact adherence • Is not ideal for resource-constrained countries
Intermediate dose/ intermediate frequency	• Reduces AJBRs by approximately 90% to <1 per year • Is less expensive than high-dose prophylaxis and consequently affordable in more countries • Provides quality of life and activity participation rates comparable to high-dose prophylaxis • Might be best for adolescents and adults	• Results in undertreatment of some patients • Leads to slightly worse long-term MSK outcomes
Low dose/low frequency	• Is the least expensive of the fixed regimens and consequently affordable in more countries • Reduces the incidence of bleeding by ~80% or more in comparison to episodic therapy and can achieve AJBRs of around <3 per year[20]	• Has unknown long-term effect on MSK outcomes which are likely worse than those achieved with intermediate-/high-dose regimens

Note: This table is adapted from Carcao (2015).[29]

Abbreviations: AJBR, annual joint bleeding rate; AVF, arteriovenous fistula; CVAD, central venous access device; FIX, factor IX; FVIII, factor VIII; MSK, musculoskeletal; SHL, standard half-life.

and breakthrough bleeds. Intermediate-dose prophylaxis is differentiated from high-dose prophylaxis mainly in that lower doses are used (15-25 IU/kg) but generally at similar or almost similar infusion frequencies. (See Tables 6-2 and 6-5.)

- High-dose regimens are associated with a higher need for CVADs in children. These can empower parents to be able to manage their child's hemophilia at home such that they no longer rely on regular trips to the hospital. They also make treatment less stressful for young patients, potentially improving adherence. However, there is expense and discomfort associated with the insertion of CVADs, and there is an appreciable frequency of complications (i.e., infection, thrombosis, and mechanical device failure) which often lead to hospitalization and CVAD replacement.[28,42] Consequently, CVADs should be viewed as a temporary aid and kept in place only for the minimum time possible to transition to using peripheral veins.
- As a result of a greater appreciation of CVAD complications, there has been a shift away from starting high-dose prophylaxis immediately in young children. More and more young children with severe phenotype hemophilia have been commenced on escalating prophylaxis regimens that start with once-weekly prophylaxis and then gradually escalate frequency of infusions regardless of bleeding phenotype.[22]
- In patients who have experienced a life-threatening bleed, doses of CFC or non-factor therapy used for prophylaxis should be adequate to prevent further bleeding; however, optimal doses to achieve this goal remain to be defined.

Recommendation 6.6.1:

- **For patients with moderate/severe hemophilia A or B, especially those who have experienced a life-threatening bleed (e.g., intracranial hemorrhage [ICH]), the WFH recommends prophylaxis with FVIII or FIX concentrates or with a non-factor therapy (e.g., emicizumab for hemophilia A) in order to prevent a recurrent life-threatening bleed. This is particularly important during the first 3-6 months following an ICH as the risk of recurrence is highest during this period.**
- **Remark: As inhibitor development is associated with intense exposure as would occur in the setting of an ICH, such patients require good clinical monitoring of treatment response and frequent laboratory testing for inhibitors.** CB

Recommendation 6.6.2:

- **For patients with hemophilia and venous access difficulties that impede regular clotting factor concentrate infusions, the WFH recommends insertion of a central venous access device (CVAD) to facilitate prophylactic clotting factor concentrate infusions. Another currently available option is the use of emicizumab while in the future there may be other subcutaneous non-factor therapies that become available.** CB

Low-dose prophylaxis

- Low-dose prophylaxis involves the administration of factor replacement therapy at either less frequent intervals (generally

once-weekly or twice-weekly prophylaxis) or using lower doses or a combination of both.
- In well-resourced countries, low-dose prophylaxis tends to be low-frequency prophylaxis with usual doses. This often is used as a way of initiating prophylaxis and is then followed by escalation of frequency to a higher degree of protection.
- Some centres choose to escalate only those patients who demonstrate breakthrough bleeds on less intense prophylaxis (escalation tailored to bleeding phenotype approach); other centres choose to escalate all patients rapidly to more intense prophylaxis regardless of bleeding phenotype (escalation regardless of bleeding phenotype approach) to provide greater protection.
- In resource-constrained countries, low-dose prophylaxis tends to focus on the use of smaller doses. This is a way for patients in these countries to start receiving prophylaxis but at lower cost. To minimize cost, the focus tends to be on minimizing the doses used while keeping infusion frequencies similar.[20,43-46]
- This allows replacement therapy with annual consumption similar to episodic treatment but with a much lower rate of spontaneous bleeds.
- Advantages and disadvantages of fixed "one size fits all" SHL factor prophylaxis regimens are shown in Table 6-5.

6.7 | Tailored factor prophylaxis regimens

- Tailored prophylaxis regimens are individualized to the needs of each patient; this means that individuals get a prophylaxis regimen tailored to their needs rather than a generic regimen received by all. Ideally, this allows for the "right amount of prophylaxis to be given to the right patient." This has the potential to more efficiently allocate CFCs such that they will not be "wasted" on patients who may not require as much and yet not be denied to patients who require more. (See 6.9 Health economics of prophylaxis, below.)
- Prophylaxis can be tailored in different ways. This applies to both hemophilia A and B. (See Tables 6-2 and 6-6).
- Differences in disease phenotype as well as differences in individual PK handling of factor form the basis of the rationale for tailoring prophylaxis to the individual.
- Advantages and disadvantages of both fixed prophylaxis regimens and tailored prophylaxis regimens are shown in Table 6-5 (fixed-dose regimens) and Table 6-6 (tailored regimens). There is likely no one regimen that is best for all patients and for all economies.
- The ultimate goal of all prophylaxis therapy should be the same—to have no spontaneous bleeding.
- See Chapter 11: Outcome Assessment.

Variables that affect bleeding phenotype

- People with hemophilia exhibit significant phenotypic heterogeneity in bleeding; this inter-individual variability is seen even among people with severe hemophilia with comparable baseline factor levels.[6,17,30]
- The bleeding phenotype results from the combined effect of the individual patient's genotypic profile (including hemophilia genotype, genetic profiles for all other hemostatic factors, and other genetic traits), joint health status, and behavioral characteristics. (See Table 6-7.)
- It has been noted that people with hemophilia who suffer recurrent bleeds at a young age and develop joint damage (target joints) will usually require much higher factor trough levels to prevent bleeding in the future.
- Inter-individual differences in the balance between positive and negative regulators of coagulation lead to differential bleeding risks.[49]
- Furthermore, activity levels can vary greatly over a person's lifetime. Young children may be constantly and unpredictably active while older children and adults may be much less active and when active may engage in planned physical activities less likely to cause bleeding.
- Consequently, a patient's prophylaxis regimen may need to change over time, particularly with changes in activity levels. Hence, prophylaxis may be individualized over a person's lifetime.
- Some of this individualization might have to do with individual lifestyle; some people who tend to be more sedentary may opt for fewer infusions leading to a lower degree of protection, while more active individuals may opt for more frequent infusions and a higher level of protection. This leads to increased inter-patient and intra-patient individualization of prophylaxis as patients age.
- All of the factors described above contribute to the wide variability in clinical phenotype among people with hemophilia. This variability in inherent bleeding phenotype is demonstrated in the wide range of ages at which children experience their first joint bleed, which may vary from <1 year to about 6 years with a median of around 2 years of age.[50] Age at first joint bleed has been shown in several studies to predict bleeding phenotype in later years as reflected in subsequent annual clotting factor utilization and arthropathy rates, wherein patients who had their first joint bleed at a later age required less treatment and developed less arthropathy.[50-53]

6.8 | Adherence and patient/caregiver education

- Despite the benefits of prophylaxis, adherence has traditionally been a significant problem. There are many reasons for reduced adherence to prophylaxis. The main reason is likely the burden of administering CFCs both intravenously and frequently. This results in venous access difficulties (particularly in young children but also in older adults with significant arthropathy and potentially extinguished veins) and child/family resistance to the time-consuming nature of conventional prophylaxis.
- Another reason for reduced adherence stems from the fact that prophylaxis is designed mainly to prevent long-term complications

TABLE 6-6 Tailoring prophylaxis to patient needs

Tailoring approach	Advantages	Disadvantages
Pharmacokinetics • Involves undertaking at least a minimal PK evaluation of patients and then adjusting the dose/frequency of factor infusions in order to achieve in each patient a predetermined factor trough level. • Can be estimated with population PK modeling (e.g., WAPPS-Hemo)[a] using Bayesian analysis	• Recognizes that hemophilia patients have different PK handling of factor which will impact on prophylaxis needs. • Matches the amount of CFCs given to a patient with their PK perceived needs, ensuring that every patient is receiving a sufficient amount of treatment to attain similar factor levels. • Does not force patients to experience bleeds in order to declare their prophylaxis needs. • May result in substantial savings in factor consumption as patients would receive targeted amounts needed to achieve certain factor trough levels. • Allows for individualizing prophylaxis with aging as PKs change with patient age. PK assessments will require repeating with aging[48]	• Requires patients to undergo at least a minimal PK evaluation. • Requires expertise in interpreting results of PK. • Focuses solely on one attribute that contributes to bleeding (PK handling of factor) and ignores other differences between patients, including physical activity levels. Sports participation may be better supported by attention to factor levels at the time of participation rather than by factor trough levels alone. • May lead to overtreatment in some patients who might do well with lower factor trough levels, and may lead to undertreatment of some patients (e.g., very active patients) who might need higher factor trough levels
Clinical factors (bleeding phenotype and physical activity patterns) • Involves selection of a starting regimen, which can be of any frequency, and patients are carefully monitored for bleeding. Dose and frequency are adjusted (escalated or de-escalated) as needed to suppress excessive clinical bleeding with the minimum intensity of prophylaxis	• Recognizes that patients with hemophilia are heterogeneous, not just in PK handling of factor but in many other aspects (some unknown) that contribute to bleeding and MSK outcomes. • Better matches the amount of prophylaxis to the needs of the patient, potentially saving at a population level a certain amount of CFCs. • Suited to transitional stages in life, e.g., escalating prophylaxis in early childhood; de-escalating prophylaxis in adulthood. • Allows very young children to become accustomed to receiving IV infusions when escalating prophylaxis and might allow the avoidance of CVADs	• Forces patients to experience bleeds to declare their bleeding phenotype and prophylaxis needs • Depends heavily on the bleeding criteria used to adjust treatment. Although some patients may tolerate some bleeds without long-term joint damage, other patients (particularly young children) are much more susceptible; in these patients, even one or a few bleeds might contribute to long-term joint damage. • Puts patients at risk of a serious bleed (e.g., ICH) while escalating prophylaxis. • Requires constant adaptation of prophylaxis to physical activity patterns which may be difficult if physical activity patterns are frequently changing

Note: This table is adapted from Carcao (2015).[29]

Abbreviations: CFC, clotting factor concentrate; CVADs, central venous access devices; ICH, intracranial hemorrhage; IV, intravenous; MSK, musculoskeletal; PK, pharmacokinetic.

[a]Available at: http://www.wapps-hemo.org.[47]

from hemophilia. There may be a lack of comprehension on the part of the patient/caregiver of the long-term complications of hemophilia that can occur if prophylaxis is not commenced at a young age and a lack of appreciation of the benefits of prophylaxis.[54] (See Chapter 2: Comprehensive Care of Hemophilia – Transition from pediatric to adult care.)

- The consequences of reduced adherence are reduced effectiveness of prophylaxis; in the extreme, reduced adherence leads to cessation of prophylaxis and places the patient at significant risk of bleeding. This problem of reduced adherence is seen in both well-resourced countries as well as in countries with more constrained resources.
- With SHL CFCs, missed or delayed prophylaxis doses immediately increase the bleeding risk; thus missed/delayed doses account for a substantial proportion of breakthrough bleeds.[6] With EHL CFCs, the consequences of a missed dose may be even greater; however, there is much more margin for a dose to be simply delayed rather than missed.
- EHL CFCs may improve adherence by allowing treatment to be administered less often and at less burdensome times (evenings rather than mornings and weekends rather than weekdays). This is particularly the case with some EHL FIX CFCs.
- Emicizumab, which may be administered weekly, biweekly, or every 4 weeks, should improve adherence even further; this needs to be studied. The impact of other non-factor therapies, if they are found to be effective and safe and become clinically available, will also need to be studied.
- Prophylaxis is a team effort that relies on ongoing patient/caregiver education and consultation. The hemophilia treatment centre care team plays a key role in teaching the patient/family about prophylaxis, about the importance of maintaining a paper or electronic diary of bleeding episodes and amount of CFC or

TABLE 6-7 Factors that affect bleeding phenotype and contribute to inter-patient phenotypic variability

Genetic differences	Non-genetic differences
• Hemophilic variants	• Levels and patterns of activity
• Levels of other procoagulant and anticoagulant proteins	• Functional ability and physical coordination (i.e., strength, flexibility, balance, stability, mobility)
• Inflammatory responses that might impact a person's susceptibility to joint damage from bleeding	• Risk-taking behaviors
	• Body build (i.e., muscle status)
	• Presence or absence of existing target joints or established hemophilic arthropathy
	• Occurrence of trauma

TABLE 6-8 Basic requirements for effective prophylaxis

• Reliable, uninterrupted supply of prophylactic treatments (clotting factor concentrates and/or non-factor therapies)
• Consistent, expert monitoring (clinical and laboratory) of prophylaxis and its effectiveness
• Home therapy, preferably administered by the patient/caregiver
• Good patient understanding of the value of prophylaxis
• Good patient adherence to prophylaxis

other therapy administered, and about the importance of adhering to the treatment plan.

- A key component of prophylaxis has been teaching patients/families how to infuse intravenous therapies at home; this is referred to as home therapy. (See Chapter 2: Comprehensive Care of Hemophilia – Home therapy.)
- Regular checkups throughout a lifetime at the hemophilia treatment centre are important to review the prophylaxis plan together, including the type of therapy, dosage, and frequency, with adjustments according to the patient's body weight, bleeding patterns, or other factors.
- The above are integral requirements for effective prophylaxis. Other requirements for effective prophylaxis are noted in Table 6-8.

Recommendation 6.8.1:

- **For patients with severe phenotype hemophilia A or B on prophylaxis, the WFH recommends that patients/caregivers be taught to maintain timely and accurate records of bleeding episodes and treatment and be followed in hemophilia treatment centres.**

6.9 | Health economics of prophylaxis

- CFCs have generally been quite expensive and have usually accounted for over 90% of the cost of hemophilia care. This has historically led to prophylaxis in the short term being considerably more expensive than episodic factor replacement therapy.
- Cost of prophylaxis is very sensitive to the cost of CFCs and to the intensity (frequency and dose) of prophylaxis. In the long term, some of the cost of early and routine prophylaxis may be mitigated by decreased healthcare costs in adulthood due to better joint health outcomes which may diminish hemarthroses and other hemophilic bleeding and therefore reduce the number of hospital visits and admissions over the years as well as diminish or eliminate the need for costly orthopedic surgery in the future.
- By contrast, the direct costs of episodic therapy increase over time because numerous joint bleeds lead to joint damage and greater susceptibility to bleeding, often resulting in greater need for episodic CFC infusions and for orthopedic surgery in later years.
- There are considerable long-term personal and societal indirect costs stemming from people with hemophilia not being on prophylaxis, including absenteeism from school or work and limitations in vocational opportunities for adults with hemophilic arthropathy.
- The development of new therapies for hemophilia will likely have considerable economic ramifications. Historically, when new therapies are introduced, they tend to be more expensive than existing available "older therapies."
- However, they often lead to a drop in the price of "older therapies." This may lead to the increased uptake of prophylaxis (and possibly high-dose prophylaxis) with older CFCs where their reduced prices may make conventional prophylaxis much more affordable and more widely available.
- Furthermore, many countries have achieved substantial decreases in CFC prices through national and regional tenders.[55]

6.10 | Low-dose prophylaxis for patients with limited access to CFCs

- For over two decades, prophylaxis has been the standard of care in most well-resourced countries but was seldom undertaken in resource-constrained countries as it was deemed to not be affordable at the doses conventionally used.[56] In the early 2000s, a number of observational studies showed the benefits of low-dose factor prophylaxis (i.e., reduced bleeds and better preservation of joint health) over episodic factor replacement therapy, without a dramatic increase in cost.[20,57] Consequently, it became recognized that low-dose factor prophylaxis should also be the preferred way of managing patients even in resource-constrained countries.

- Showing the benefits of low-dose prophylaxis regimens over episodic therapy can be an important step in convincing stakeholders in resource-constrained countries to gradually transition patients with hemophilia from episodic therapy to prophylaxis.[20,43-46,58,59]
- For those countries with healthcare constraints where prophylaxis may potentially be instituted gradually, the WFH's position is that it is most essential to initiate prophylaxis in young children since prevention of target joint development may offer marked long-term joint health benefits.

Recommendation 6.10.1:

- **For patients with severe phenotype hemophilia A or B in countries with healthcare constraints, the WFH still strongly recommends prophylaxis (even when the only option is using lower factor doses) over episodic factor therapy to reduce hemarthroses and other spontaneous and breakthrough bleeding and better preserve joint function.**

6.11 | New definitions of prophylaxis

- With emicizumab and potentially with other non-factor therapies in the future, as well as with EHL CFCs (particularly EHL FIX), new definitions for prophylaxis are required. Modern prophylaxis definitions will need to be inclusive of a wide variety of hemostatic agents with diverse mechanisms of action and modes of administration.
- The WFH proposes the following as a new definition of prophylaxis based on outcomes rather than doses of therapeutic products or time for initiation of the treatment regimen: the regular administration of a hemostatic agent/agents with the goal of preventing bleeding in people with hemophilia while allowing them to lead active lives and achieve quality of life comparable to non-hemophilic individuals.

6.12 | Future research questions to be addressed

- Prophylaxis in the future will create new challenges and need for research studies, including:
  - how to assess the pharmacodynamic effects and pharmacokinetics of new therapies, considering that monitoring is more complex than simply measuring FVIII or FIX levels;
  - how to assess the intensity of prophylaxis with emicizumab and potentially other non-factor therapies, especially given current challenges in monitoring such therapies;
  - how to manage breakthrough bleeds and surgical procedures in patients on prophylaxis with emicizumab and potentially other non-factor therapies;
  - how best to monitor short- and long-term clinical outcomes and adverse events with these new products as they may be associated with outcomes and adverse events not previously encountered;
  - how to approach inhibitor development (traditionally the greatest threat to managing hemophilia) and inhibitor eradication in the face of emicizumab and potentially other non-factor therapies;
  - how best to select a hemostatic therapy or a combination of therapies tailored to an individual patient.

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SUPPORTING INFORMATION

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

Chapter 7: Treatment of Specific Hemorrhages

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

7.1 | Introduction

- The primary clinical hallmarks of hemophilia are prolonged spontaneous and/or traumatic hemorrhages, most commonly within the musculoskeletal system and predominantly intra-articular bleeding into the large synovial joints, i.e., the ankles, knees, and elbows, and frequently into the shoulder, wrist, and hip joints. Hemophilic bleeding is also common in muscle and mucosal soft tissues, and less common in other soft tissues, the brain, and internal organs. Without adequate treatment, such internal bleeds may lead to serious complications and even become life-threatening.
- Bleeding symptoms and tendencies depend on the patient's hemophilia severity and clotting factor level.
- People with mild hemophilia may not necessarily have abnormal or prolonged bleeding problems requiring clotting factor replacement therapy until they experience serious trauma or undergo surgery. Those with moderate hemophilia may experience occasional spontaneous bleeding and/or prolonged bleeding with minor trauma or surgery. (See Chapter 2: Comprehensive Care of Hemophilia – Table 2-1: Relationship of bleeding severity to clotting factor level.)
- In general, the main treatment for bleeding episodes in patients with severe hemophilia is prompt clotting factor replacement therapy and rehabilitation. However, different types of bleeds and bleeding at particular anatomical sites may require more specific management with additional measures. It is important to consult the appropriate specialists for the management of bleeds related to specific sites. (For discussion and recommendations on muscle hemorrhages and acute and chronic complications related to musculoskeletal bleeding, see Chapter 10: Musculoskeletal Complications – Muscle hemorrhage.)
- The aim of management of specific hemorrhages is not only to treat the bleed, but also to prevent bleed recurrence, limit complications, and restore tissue and/or organ function to a pre-bleed state.
- Diagnosing a specific bleed correctly is the first step and may require a combination of clinical evaluation, laboratory assessment, and imaging investigations.
- In most instances in hemophilia care, therapeutic intervention may precede diagnostic workup of the patient. The objective of early intervention is to limit the extent of bleeding and to reduce bleeding complications.
- The amount of hemostatic agent used for bleed treatment and duration of treatment depends on the site and severity of bleeding.
- More and more hemophilia A patients are being treated with emicizumab prophylaxis; this therapy is not intended for treatment of acute bleeding episodes and breakthrough bleeding (bleeding that occurs between prophylactic doses).
- For breakthrough bleeding in patients without inhibitors on emicizumab, factor VIII (FVIII) infusion at doses expected to achieve hemostasis should be used. To date, no cases of thrombosis or thrombotic microangiopathy have been reported in this setting.[1]
- Patients with inhibitors on emicizumab experiencing acute bleeds should be treated with recombinant activated factor VIIa (rFVIIa) at doses expected to achieve hemostasis. The use of activated prothrombin complex concentrate (aPCC) should be avoided in inhibitor patients on emicizumab experiencing breakthrough bleeding. If the use of aPCC is not avoidable, lower doses of aPCC can be used with close monitoring of the patient for development of thrombosis and/or thrombotic microangiopathy.[2]
- For inhibitor patients not on emicizumab, standard doses of rFVIIa or aPCC should be used.

Patient/caregiver education

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

7.2 | Joint hemorrhage

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

Clotting factor replacement therapy

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

Recommendation 7.2.1:

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

Recommendation 7.2.2:

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

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

TABLE 7-1 Definitions of response to treatment

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

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

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

Pain management

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

Recommendation 7.2.3:

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

Recommendation 7.2.4:

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

Recommendation 7.2.5:

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

Adjunctive care

- A key element of managing the symptoms of hemarthrosis is RICE (rest, ice, compression, elevation). In hemophilia care, immobilization is also considered to be an aspect of this approach; therefore, PRICE, which includes the concept of "protection" of the injured area, is often recommended. Compression may help to reduce the risk of rebleeding. However, as prolonged rest can negatively affect joint function through reduction in muscle strength, the acronym POLICE, which replaces "rest" with "optimal loading", has been put forward to encourage clinicians to establish a balance between rest, early mobilization, and weight-bearing to prevent unwanted complications associated with immobilization, while minimizing rebleeding leading to synovitis and cartilage damage.[12]
- The application of ice has been shown to reduce acute hemarthrosis-related pain; however, it has been suggested that a decrease in intra-articular temperature could interfere with coagulation in the presence of acute tissue lesions.[13,14] The use of ice without direct skin contact for short periods of 15-20 minutes soon after bleeding occurs is considered acceptable but should not exceed 6 hours.[13] (See Chapter 2: Comprehensive Care of Hemophilia – Adjunctive management.)
- During a joint bleed, semi-flexion is usually the most comfortable position, and any attempt to change this position often exacerbates pain.[15]
- Depending on the site of the joint bleed, elevating the affected joint, if tolerated and comfortable, may help reduce hemarthrosis-related swelling.[13]
- Rest, in the case of a hip, knee, or ankle bleed, or the use of a sling for an elbow, shoulder, or wrist bleed, is advisable to immobilize a joint with severe bleeding until pain resolves.
- As soon as the pain and swelling begin to subside, the patient can change the position of the affected joint from a position of rest to a position of function, gently and gradually increasing mobilization of the joint.
- Patients with hip, knee, or ankle joint bleeds should be restricted from weight-bearing until complete pre-bleed joint range of motion and function are restored and acute pain and inflammation symptoms have dissipated. It is advisable to avoid weight-bearing for 1 week, with the use of walking aids (e.g., crutches, walker) to assist progressive weight-bearing under the guidance of a member of the comprehensive care team with experience in musculoskeletal rehabilitation after a bleed.[13] Pain can also be used to guide resumption of weight-bearing.
- These adjunctive measures will not stop joint bleeding but can help manage and reduce symptoms of pain and inflammation.[7]
- See also Chapter 2: Comprehensive Care of Hemophilia – Adjunctive management.

Recommendation 7.2.6:

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

Recommendation 7.2.7:

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

Recommendation 7.2.8:

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

Physical therapy and rehabilitation

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

Recommendation 7.2.9:

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

Recommendation 7.2.10:

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

Arthrocentesis

- Arthrocentesis (removal of blood from a joint) may be considered for patients with hemophilia experiencing prolonged or worsening bleeding symptoms including:
  - tense, painful hemarthrosis that shows no improvement within 24 hours of the initial infusion (this is particularly the case for bleeding into the hip joint due to the particular anatomy of the hip joint); or
  - clinical suspicion of infection/septic arthritis.[7,19,20]
- Inhibitors should be considered as a possible reason for persistent bleeding despite adequate factor replacement therapy, and the presence of inhibitors should be assessed before arthrocentesis is attempted.
- For hemophilia patients with inhibitors, other appropriate hemostatic agents should be used to provide hemostatic coverage for the procedure, as needed.[7] (See "Management of bleeding" in Chapter 8: Inhibitors to Clotting Factor.)
- Arthrocentesis should always be done under strictly aseptic conditions to avoid introducing intra-articular infections.
- When necessary, arthrocentesis should only be performed under factor coverage, with factor activity levels of at least 30-50 IU/dL maintained for 48-72 hours. Arthrocentesis should not be done in circumstances where such factor coverage (or equivalent coverage with other hemostatic agents) is not available.[21]
- A large-bore needle, at least 16 gauge, should be used. The joint should be immobilized with mild compression following arthrocentesis, and weight-bearing should be restricted until the remaining blood is absorbed or absence of pain permits mobilization.
- Arthrocentesis should be followed by carefully supervised physical therapy and rehabilitation.
- See also Chapter 10: Musculoskeletal Complications.

Recommendation 7.2.11:

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

7.3 | Central nervous system and intracranial hemorrhage

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

Recommendation 7.3.1:

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

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

Recommendation 7.3.2:

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

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

7.4 | Throat and neck hemorrhage

- Bleeding into the throat or neck may be due to local pathology, trauma, or severe coughing, and may present with swelling or pain. This is a medical emergency because it can lead to airway obstruction. If indicated, gently elevate the head to help reduce airway obstruction due to the hemorrhage.
- Treat immediately with CFC to raise the patient's factor level when significant trauma or bleeding symptoms occur in the throat and neck area, without any delay that could occur while awaiting full evaluation. (See Table 7-2.)
- Immediate hospitalization and medical evaluation by a specialist otolaryngologist is required.[28]
- Protective factor levels should be maintained until symptoms resolve.[28-30] (See Table 7-2.)

Recommendation 7.4.1:

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

Recommendation 7.4.2:

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

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

Recommendation 7.4.3:

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

7.5 | Gastrointestinal/abdominal hemorrhage

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

Recommendation 7.5.1:

- **In hemophilia patients with gastrointestinal bleeding, factor levels should be raised immediately and the underlying etiology of the bleed identified and treated. CB**

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

Recommendation 7.5.2:

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

- Antifibrinolytics are often effective adjunctive therapy for both patients with hemophilia A and hemophilia B. Concurrent use with aPCC or prothrombin complex concentrate (PCC) may be used with caution in some patients.
- Treat the origin of the hemorrhage as indicated.
- Monitor hemoglobin levels regularly and treat anemia or shock as needed. Perform endoscopy, if clinically indicated, in any patient with dropping hemoglobin levels. In GI bleeding, the investigation of choice is endoscopy.

- In patients with advanced liver disease, ammonia levels should be monitored, and treatment to prevent clinical encephalopathy with lactulose or a similar agent should be initiated.

Recommendation 7.5.3:

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

Recommendation 7.5.4:

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

- An acute abdominal (including retroperitoneal) hemorrhage can present with abdominal pain and distension and can be mistaken for a number of infectious or surgical conditions. It may also present as a paralytic ileus.
- Abdominal bleeds must be treated immediately to raise and maintain the patient's factor levels until the etiology can be defined.
- Perform a clinical assessment of the patient with a physical examination, pain assessment, and history taking including bleed history. An ultrasound and/or CT scan can identify the site and extent of abdominal bleeding.
- Determine appropriate treatment in consultation with a specialist.[28-30] (See Table 7-2.)

7.6 | Renal hemorrhage

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

Recommendation 7.6.1:

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

Recommendation 7.6.2:

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

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

Recommendation 7.6.3:

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

Recommendation 7.6.4:

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

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

7.7 | Ophthalmic hemorrhage

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

Recommendation 7.7.1:

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

Recommendation 7.7.2:

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

Recommendation 7.7.3:

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

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

7.8 | Oral hemorrhage

- The most common causes of bleeding in the mouth (oral hemorrhage) are dental extraction, gingival bleeding (often due to poor oral hygiene), and trauma.

- Gum bleeding is a sign of inflammatory gum disease (gingivitis) and is preventable and treatable in people with hemophilia. It is not caused by the underlying congenital bleeding disorder itself.
- Early referral to a dental professional for assessment and appropriate periodontal treatment and advice will reduce bleeding after brushing, prevent progression of gum disease, and reduce the likelihood of early tooth loss and risk of associated systemic effects.
- Other less common causes of bleeding from the mouth may include: self-injury, shedding of deciduous (baby) teeth, and recent dental surgery without appropriate hemostatic measures in place.
- Bleeding following loss of baby teeth is not usually prolonged if recognized and treated early. Direct pressure should be applied on the tooth socket using a damp gauze swab and maintained for at least 15-30 minutes. Parents/caregivers should be advised that if bleeding persists for longer than 6 hours, they should consult their hemophilia treatment centre for additional support.
- A carefully planned preoperative hemostatic care plan is advised for patients with hemophilia about to undergo oral surgery or invasive dental procedures to avoid postoperative bleeding.

Recommendation 7.8.1:

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

Recommendation 7.8.2:

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

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

Recommendation 7.8.3:

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

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

7.9 | Epistaxis

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

Recommendation 7.9.1:

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

Recommendation 7.9.2:

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

Recommendation 7.9.3:

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

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

Recommendation 7.9.4:

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

Recommendation 7.9.5:

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

7.10 | Lacerations and abrasions

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

Recommendation 7.10.1:

- **In hemophilia patients with lacerations and abrasions, clotting factor replacement therapy should be administered and the wound sutured immediately, if appropriate, in consultation with appropriate surgeons.** CB
- Hemostatic coverage should be considered for suture removal, if the risk of bleeding is considered high.

7.11 | Soft tissue hemorrhage

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

7.12 | Practice patterns in CFC replacement

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

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

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

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

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

[a]May be longer if response is inadequate.

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

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

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

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SUPPORTING INFORMATION

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

Chapter 8: Inhibitors to Clotting Factor

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

This chapter describes inhibitor formation, one of the most serious complications in hemophilia treatment, and provides key definitions and guidance on inhibitor screening, testing, and treatment. The management of hemophilia A inhibitors and hemophilia B inhibitors is discussed separately given the differences in inhibitor incidence and treatment.

All recommendations on product use in this chapter are made under the assumption that a specific product is available in a particular country, region, or healthcare system.

8.1 | Introduction

- "Inhibitors" in hemophilia are IgG alloantibodies to exogenous clotting factor VIII (FVIII) or factor IX (FIX) that neutralize the function of infused clotting factor concentrates (CFCs).[1] Inhibitors are detected and quantified by the Nijmegen-modified Bethesda assay.
- The presence of a new inhibitor should be suspected in any patient with hemophilia who fails to respond clinically to CFC replacement therapy, particularly in previously responsive patients. (See 8.2 Inhibitor screening, below.)
- Inhibitors are more frequently encountered in patients with severe disease than in those with moderate or mild hemophilia, and more commonly in patients with hemophilia A than in those with hemophilia B. Controlling bleeds is a greater challenge in hemophilia patients with inhibitors than in those without inhibitors. Inhibitors to FVIII or FIX are associated with a higher disease burden, including increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges, all of which may impact a patient's physical functioning, capacity for physical activities, and quality of life.
- In addition, the immune response to FVIII and FIX products is poorly understood and, in the absence of evidence, there remain areas of evolving and sometimes ambiguous or conflicting information on inhibitor management.
- Furthermore, while new therapies and strategies for inhibitor treatment and eradication are emerging that may offer benefits, the long-term clinical outcomes remain unknown.
- Significant differences exist between hemophilia A and hemophilia B regarding inhibitor incidence, management, and response to immune tolerance induction (ITI) and alternative hemostatic agents. Therefore, in this chapter, hemophilia A inhibitors and hemophilia B inhibitors are discussed separately.

Patient/caregiver education

- Ongoing patient and family caregiver education and psychosocial support are essential components of the management of hemophilia patients with inhibitors given the complexity and challenges of this serious complication. It is vital for clinicians, patients, caregivers, and the hemophilia treatment centre team to maintain good communication through a well-coordinated plan of care.

8.2 | Inhibitor screening

- Inhibitors are measured by the Bethesda assay or the Nijmegen-modified Bethesda assay.[2,3]
- The definition of a positive inhibitor is a Bethesda titer of >0.6 Bethesda units (BU) for FVIII and ≥0.3 BU for FIX.[1,4]
- Inhibitor measurement may be performed during replacement therapy by assays utilizing heat treatment techniques.[5] (See Chapter 3: Laboratory Diagnosis and Monitoring – Coagulation laboratory testing – Inhibitor testing.)
- A low-responding inhibitor is an inhibitor <5.0 BU, whereas a high-responding inhibitor is an inhibitor ≥5.0 BU.
- Low-responding inhibitors tend to be transient; a transient inhibitor is defined as a positive inhibitor that drops below the definition threshold within 6 months of initial documentation without any change in treatment regimen and despite antigenic challenge with CFCs.[1] A suspected inhibitor should be confirmed by repeat laboratory testing, documenting poor factor recovery and/or shortened half-life ($t_{½}$) of less than 6 hours in hemophilia A (in the case of standard half-life FVIII CFCs[6]) and 9 hours in hemophilia B (in the case of standard half-life FIX CFCs).[7]
- High-responding inhibitors tend to be persistent and may fall or become undetectable after a long period without CFC exposure; however, they increase 3-5 days after re-challenge with CFCs (anamnestic response).[8]
- It is critical to detect inhibitors early to ensure appropriate treatment. At least half of inhibitor cases are detected by routine inhibitor screening after initial exposures to CFCs, while the rest are detected after there is poor clinical response to CFC replacement therapy (i.e., when factor recovery and/or half-life are not as expected) when treating or preventing a bleed.[9]
- Inhibitor testing should be performed before major surgery and if there is suboptimal response to CFC replacement therapy in the post-operative period[7,10,11]; and in any patient who fails to respond to adequate CFC replacement therapy after past responsiveness.[7,12-14] (See Table 8-1.)

TABLE 8-1 Indications for inhibitor testing

• After initial factor exposure
• After intensive factor exposure, e.g., daily exposure for more than 5 days[7,15]
• For recurrent bleeds or target joint bleeds, despite adequate CFC replacement therapy[7,12-14]
• For failure to respond to adequate CFC replacement therapy[7,12,14]
• For lower than expected factor recovery or half-life after CFC replacement therapy[7,12-14]
• For suboptimal clinical or laboratory response to CFC replacement therapy[9]
• Before surgery[1,7,11]
• For suboptimal post-operative response to CFC replacement therapy[7,12-14]

Abbreviation: CFC, clotting factor concentrate.

- It is particularly important to perform routine inhibitor screening during the time of greatest risk for inhibitor development, at least every 6-12 months after CFC replacement therapy is initiated, and annually thereafter. While some advocate more frequent screening,[8] this remains controversial with few data to support the benefit of this approach.
- Screening should be performed in any patient, regardless of age or disease severity, who is intensively treated (i.e., for more than 5 consecutive days)[7,15] and within 4 weeks of the last infusion.
- See also 8.3 Hemophilia A and FVIII inhibitors – Inhibitor incidence and 8.4 Hemophilia B and FIX inhibitors – Inhibitor incidence, below; and Chapter 3: Laboratory Diagnosis and Monitoring – Coagulation laboratory testing – Inhibitor testing.

Recommendation 8.2.1:

- **For patients with newly diagnosed hemophilia A, the WFH recommends regular inhibitor screening at least every 6-12 months, and then annually.**
- **Remark: In general, more frequent screening should be considered for recurrent bleeds or target joints that occur despite standard factor replacement.**
- **Remark: This recommendation places greater value on early inhibitor diagnosis in patients with severe hemophilia and late diagnosis in adulthood in patients with less severe disease, such as after intensive exposure to clotting factor concentrate, for example after surgery.**
- **Remark: The requirement for frequent blood draws was considered in relationship to the potential morbidity of uncontrolled or life-threatening bleeds.** CB

Recommendation 8.2.2:

- **For patients with hemophilia A who receive clotting factor concentrate for more than 5 consecutive days, the WFH suggests inhibitor screening within 4 weeks of the last infusion.** CB

Recommendation 8.2.3:

- **For patients with hemophilia A who have poor or no response to adequate clotting factor replacement therapy, or who have lower than expected factor recovery or half-life, the WFH suggests inhibitor screening.** CB

Recommendation 8.2.4:

- **For patients with hemophilia A who undergo surgery, the WFH suggests inhibitor screening preoperatively in order to determine if an inhibitor is present which, if present, may require non-FVIII-containing therapy.** CB

Recommendation 8.2.5:

- **For patients with newly diagnosed hemophilia B, the WFH recommends regular inhibitor screening at least every 6-12 months, and then annually.**

- **Remark: In general, more frequent inhibitor screening should be considered when recurrent bleeds or target joints occur despite adequate factor replacement.**
- **Remark: Because inhibitor incidence is much lower in hemophilia B than in hemophilia A, experience and evidence are limited.**
- **Remark: This recommendation places greater value on early inhibitor diagnosis to avoid uncontrolled bleeds and bleeding complications. The requirement for frequent blood draws was considered in relationship to the potential morbidity of uncontrolled or life-threatening bleeds.** CB

Recommendation 8.2.6:

- **For patients with hemophilia B who are treated with clotting factor concentrate for more than 5 consecutive days, the WFH suggests inhibitor screening within 4 weeks of the last infusion.** CB

Recommendation 8.2.7:

- **For patients with hemophilia B who fail to respond to adequate clotting factor replacement therapy or who have lower than expected factor recovery or half-life, the WFH suggests inhibitor screening.** CB

Recommendation 8.2.8:

- **For patients with hemophilia B who develop an allergic reaction to FIX therapy, including anaphylaxis or nephrotic syndrome, the WFH suggests inhibitor screening to determine if an inhibitor is present.** CB

Recommendation 8.2.9:

- **For patients with severe hemophilia B who undergo major surgery, the WFH suggests preoperative inhibitor screening.** CB

8.3 | Hemophilia A and FVIII inhibitors

Genetic and environmental risk factors

- Inhibitors are more frequently encountered in persons with severe hemophilia A than in those with moderate or mild forms of the disease.
- Other risk factors for inhibitor formation in hemophilia A include family history of inhibitors, black African ancestry, Hispanic ancestry, genetic variants such as type of mutation and polymorphic immune regulatory genes, and high-intensity factor exposure (e.g., intensive CFC replacement therapy for a severe early bleed, central nervous system bleed, surgery, or trauma).[6,9,10,12,14-20] (See Table 8-2.)
- Product type (i.e., plasma-derived FVIII CFCs with or without von Willebrand factor or recombinant FVIII CFCs) may contribute to inhibitor risk in hemophilia A patients; however, this is not well understood and remains controversial.[6,16,21]

Inhibitor incidence

- Inhibitory antibodies develop with a cumulative incidence of approximately 30% among previously untreated patients with hemophilia A,[16,22] of which 79% occur within the first 20 exposures and the remainder, 21%, within the first 75 exposures.[22] An exposure is defined as any 24-hour period in which a FVIII/FIX-containing product is given.[1,22]
- Inhibitor rates vary by study and may be underestimated in studies in which not all subjects are previously untreated patients (PUPs) and in whom follow-up is incomplete.[6]
- The incidence of inhibitors in mild and moderate hemophilia A patients is 5%-10%, lower than in those with severe hemophilia. These inhibitors typically occur at an older age and often after intensive FVIII exposure, e.g., for surgery or severe bleeds.[12,23] In most cases, these are low-responding inhibitors; high-responding inhibitors are less common in such patients.[24]
- Most cases of mild and moderate hemophilia A are caused by missense mutations, which in general are associated with a low rate of inhibitor development, although there are a few exceptions.[25]

Disease burden

- Children and adults with persistent FVIII inhibitors typically have higher rates of hospitalization,[25] greater treatment costs,[19] and higher mortality rates than those without inhibitors.[26] Development of new non-factor replacement therapies may reduce this burden in the future.
- Bleeding manifestations in mild and moderate hemophilia A patients with inhibitors are predominantly mucocutaneous, urogenital, and gastrointestinal bleeding, reminiscent of bleeding symptoms in patients with acquired hemophilia A (due to autoantibodies to FVIII).[19] Consequently, the risk of severe complications or even death from serious bleeding may still be significant in these patients. The mortality rate among mild and moderate hemophilia A patients with inhibitors is reported to be five times greater than among those without inhibitors.[26]
- Despite the availability of non-factor replacement therapies for hemophilia patients who develop inhibitors, there has been a consensus that patients with inhibitors should undergo a trial of ITI, when possible, in order to eradicate the inhibitor.[27]

TABLE 8-2 Potential risk factors for inhibitors

• Race[9,10,15]
• Family history[9,10,15]
• Genotype, immune regulatory genes[9,16,17,20,25]
• Hemophilia severity[9,10,12,14,19,25]
• CFC replacement intensity[9,12,14-16,18,20]
• CFC type[6,16,21]

Abbreviation: CFC, clotting factor concentrate.

- The availability of non-factor replacement therapies (e.g., emicizumab) that are effective in bleed prevention in patients with FVIII inhibitors has raised questions about whether such agents should be used before, during, after, or in place of ITI. This remains controversial, however, as there are insufficient data to resolve this question.

Management of bleeding

- Management of bleeding in hemophilia patients with inhibitors must be carried out in consultation with a hemophilia treatment centre and staff experienced in inhibitor treatment.[7,28] (See Table 8-3.)
- Choice of treatment product should be based on inhibitor titer, clinical response to the product, site and nature of the bleed,[7,29] and product availability by country.

Recommendation 8.3.1:

- **For patients with hemophilia A and FVIII inhibitors who develop an acute bleed, the WFH recommends that treatment be based on whether the inhibitor is low-responding or high-responding.** CB

Therapeutic options for FVIII inhibitor patients

CFC replacement therapy

- For low-responding inhibitors, FVIII CFC replacement therapy is preferred for acute bleeds if measurable factor levels are achieved.[7,29,30] Careful monitoring for clinical efficacy is needed, as higher doses may be required to achieve hemostasis.
- In the absence of a rational and validated dosing algorithm, the following formula is used to estimate the amount of FVIII needed as a loading dose to neutralize the inhibitor[31]:
  - [body weight (kg) × 80 × [(1 − hematocrit) × antibody titer (BU)]
- An additional 50 IU/kg above the calculated loading dose is added to achieve a measurable FVIII activity.[31]
- FVIII levels should be measured 15 minutes after completion of the bolus, and adjustment to reach target levels is necessary because there is substantial individual variation.[31]
- For high-responding inhibitors, bypass agent therapy (recombinant activated factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) or porcine FVIII should be used to treat bleeds.

Recommendation 8.3.2:

- **For patients with hemophilia A and inhibitors who have acute bleeds, the WFH recommends FVIII concentrate for those with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors.**
- **Remark: In those receiving non-factor therapy for prophylaxis (e.g., emicizumab), the WFH prefers rFVIIa over aPCC because of the risk of thrombotic microangiopathy when aPCC is used with emicizumab.**
- **Remark: In patients receiving emicizumab who receive FVIII concentrate, the WFH recommends bovine reagent chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-ST segment elevation myocardial infarction (non-STEMI) and pulmonary embolism.** CB

- For patients with high-responding inhibitors whose titers have fallen to undetectable or low levels, standard FVIII CFC replacement may be used in an emergency for up to 3-5 days, at more frequent dosing due to the shorter half-life, until an anamnestic response occurs. When the latter occurs, further treatment with FVIII CFCs is typically no longer effective,[7,29] and bypass agent therapy is needed. This underscores the need for close FVIII monitoring.
- The factor substitution therapy, emicizumab, is increasingly used to prevent hemorrhage in FVIII inhibitor patients.[32,33] This agent is effective for *preventing* bleeds (prophylaxis) in hemophilia A inhibitor patients but is not indicated for *treating* bleeds. Thus, breakthrough bleeds require treatment with FVIII CFCs (for low-responding inhibitors) as described above, or hemostatic bypassing agents (for

TABLE 8-3 Treatment of acute bleeds in hemophilia A patients with inhibitors

Hemophilia A	Low-responding inhibitors	High-responding inhibitors
Agent	• FVIII[31,a]	• rFVIIa or aPCC[33,40,47,b] or FVIII[39,c]
Monitoring	• FVIII activity (FVIII:C) assay	• Thromboelastography or thrombin generation assay[46,d]

Abbreviations: aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; FVIII:C, FVIII activity; rFVIIa, recombinant activated factor VIIa.

[a]Will require higher, more frequent dosing if half-life is shortened.

[b]In patients on emicizumab prophylaxis, aPCC should be avoided or used with caution at lower doses because of the thrombotic microangiopathy risk (black box warning). Caution is also urged when rFVIIa is used in patients on emicizumab who have risk factors for thrombosis because of risk of myocardial infarction or pulmonary embolism.

[c]In patients with high-responding inhibitors with a currently low inhibitor titer, FVIII may be considered, with close monitoring for an anamnestic response.

[d]The thrombin generation assay is not state-of-the-art monitoring and is unavailable in most laboratories, but increasingly being used to assess response.

high-responding inhibitors), as described below. Conventional bypassing agents include rFVIIa and aPCC, which have been shown to be effective as prophylaxis[34,35] and for treatment of bleeds.

Conventional hemostatic bypassing agents

- Treatment with bypassing agents typically consists of one dose of aPCC or two doses of rFVIIa. The efficacy of two doses of rFVIIa (90-270 μg/kg) or one dose of aPCC (75-85 unit/kg) is comparable in the management of joint bleeding.[36] Notably, however, some patients may respond better to one agent than the other, highlighting the need to individualize therapy.[30,36] (See Table 8-3.)
- However, if hemostasis is unsatisfactory with rFVIIa or aPCC as single agents, each may be alternated every 6 hours.[37,38] (See Table 8-4.)
- Combination/sequential bypass agent treatment should be used only in treatment centres with extensive experience in managing hemophilia patients with inhibitors; close monitoring for thrombosis and disseminated intravascular coagulation is required.
- It is estimated that aPCC leads to an anamnestic response in approximately 30% of patients with FVIII inhibitors due to the presence of FVIII in aPCC.[39]
- While rFVIIa or aPCC may be used to treat bleeds in both hemophilia A and B patients with inhibitors, there has been concern about using aPCC, which contains FIX, in patients with FIX inhibitors who manifest anaphylaxis to FIX. This, however, is not an issue for patients with FVIII inhibitors.
- ***Caution*:** Thrombosis or thrombotic microangiopathy may occur in patients receiving emicizumab who are also receiving aPCC.[33,40] Thus, aPCC should be avoided in patients on emicizumab except in patients unresponsive to rFVIIa or when rFVIIa is unavailable, and with aPCC dosing not above 50 IU/kg and no more than 100 IU/kg total per day.

Recommendation 8.3.3:

- **For patients with hemophilia A and low-responding inhibitors who develop an acute bleed, the WFH recommends a FVIII-containing product or, if the hemostatic response is poor, the WFH recommends rFVIIa or aPCC. For those receiving emicizumab prophylaxis who develop an acute bleed, the WFH prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.**
- **Remark: The WFH recommends bovine reagent-based chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels.** CB

TABLE 8-4 Sequential bypass agent therapy alternating rFVIIa and aPCC[37]

6:00 AM	90 μg/kg rFVIIa
9:00 AM	50 U/kg aPCC
12:00 PM	90 μg/kg rFVIIa
3:00 PM	50 U/kg aPCC
6:00 PM	90 μg/kg rFVIIa
9:00 PM	50 U/kg aPCC
12:00 AM	90 μg/kg rFVIIa
3:00 AM	50 U/kg aPCC
6:00 AM	90 μg/kg rFVIIa

Abbreviations: aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

Recommendation 8.3.4:

- **For patients with hemophilia A and high-responding FVIII inhibitors receiving emicizumab who develop an acute bleed, the WFH prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of arterial thromboembolism, e.g., acute non-STEMI and pulmonary embolism.**
- **Remark: The WFH recommends bovine reagent-based chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels.** CB

Emicizumab

- The factor substitution therapy, emicizumab, a bispecific monoclonal antibody and FVIII mimic, has been licensed for bleed prevention in patients with hemophilia A with and without inhibitors. Patients on emicizumab who experience breakthrough bleeds require episodic treatment with FVIII CFCs or with hemostatic bypassing agents, as described above.
- Several phase 3 clinical trials and post-marketing experience have shown that emicizumab is effective prophylaxis in adults and children with inhibitors.[33,41–43] As emicizumab is injected subcutaneously every 1, 2, or 4 weeks, the burden of prophylaxis is much less than with bypassing agents. Emicizumab reduces morbidity, complications, and hospitalization, and is cost-effective.[41]
- Prophylaxis dosing with emicizumab consists of an induction period of 3.0 mg/kg/week for 4 weeks by subcutaneous injection. This is followed thereafter by 1.5 mg/kg/week or alternative dosing schedules including 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks.[41–44]
- As emicizumab interferes with the measurement of FVIII:C and FVIII inhibitors using the one-stage FVIII assay, a specific chromogenic assay using bovine reagents is used to detect inhibitors to FVIII.[45,46]

Recommendation 8.3.5:

- **For patients with hemophilia A and inhibitors who receive emicizumab, the WFH recommends bovine chromogenic assays (bovine FX in kit reagent) to monitor inhibitor levels.** CB

- Close monitoring of clinical response to emicizumab and laboratory monitoring of inhibitor titer level is advised with a chromogenic Bethesda assay using bovine reagents.
- In patients receiving emicizumab who have risk factors for thrombosis, e.g., past venous thromboembolism, obesity, smoking, chronic infection, or inflammation, rFVIIa should be used with caution due to the potential risk of acute non-STEMI and pulmonary embolism.[47]

Recommendation 8.3.6:

- **For patients with hemophilia A and inhibitors receiving emicizumab, the WFH recommends close clinical monitoring for thrombosis, adverse reactions, and thrombotic microangiopathy.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. CB**

Recommendation 8.3.7:

- **As emicizumab is used to prevent, but not treat, acute bleeds in patients with hemophilia A and inhibitors, the WFH recommends clotting factor replacement therapy for acute bleeds. CB**

Recommendation 8.3.8:

- **For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH recommends clotting factor replacement therapy including FVIII for those with low-responding inhibitors; the WFH prefers rFVIIa over aPCC for those with high-responding FVIII inhibitors due to the risk of thrombotic microangiopathy.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. CB**

Recommendation 8.3.9:

- **For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH prefers rFVIIa over aPCC, because of the risk of thrombotic microangiopathy.**
- **Remark: The WFH suggests following black box warnings for emicizumab and maintaining vigilance as new evidence develops.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. Thrombotic risks may last for up to 6 months during which plasma levels of emicizumab may persist. CB**

Therapies in clinical trials

- Extended half-life rFVIIa may have a role in the management of bleeds in hemophilia patients with inhibitors, although investigations have been in vitro and early-phase clinical trials.[48,49]
- Non-factor therapies such as fitusiran, an investigational RNA interference agent that targets antithrombin (siRNA-AT),[50] and tissue factor pathway inhibitors (anti-TFPI),[51] are in clinical trials on bleed prevention in patients with inhibitors. These are not expected to be effective in episodic treatment of bleeds.

Surgery and invasive procedures

- Inhibitor testing of patients with hemophilia of all types of severity is advised prior to surgery and invasive procedures. Special precautions must be taken in hemophilia patients with inhibitors undergoing surgery: factor coverage, bypass agent treatment, and follow-up must be determined and planned in advance.
- Close monitoring of clinical response to bypass agent therapy is required, specifically monitoring for safety, i.e., thrombosis or consumptive coagulopathy.
- Once hemostasis is achieved and maintained on a selected regimen for 3-5 days, these agents may be tapered over 1-3 weeks. However, it is recognized that the dose and taper schedule must be individualized for each patient, as variability exists in individual response to bypass agent therapy.
- Adjusted-dose continuous infusion is another option in surgery and invasive procedures, for which clearance should be calculated every day with dose adjustment accordingly.[52]
- Combination/sequential bypass agent treatment should be considered in those with poor response to one bypassing agent. Sequential use (i.e., alternating rFVIIa and aPCC every 3 hours) has been shown to improve efficacy over single bypass agent therapy and allows for lower total daily dose of aPCC,[37,38] potentially reducing thrombotic risk. Sequential regimens should be used only in treatment centres with extensive experience in managing hemophilia patients with inhibitors, with close monitoring for thrombosis and disseminated intravascular coagulation. (See Table 8-4.)

Recommendation 8.3.10:

- **For patients with hemophilia A and low-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH suggests higher, more frequent FVIII product dosing than usual due to the short half-life of FVIII.**
- **Remark: The WFH also recognizes adjusted-dose FVIII continuous infusion as an option. CB**

Recommendation 8.3.11:

- **For patients with hemophilia A and high-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH recommends bypass agent therapy (rFVIIa or aPCC) at the discretion of the clinician. If single-agent bypass fails, sequential bypass agent treatment, i.e., rFVIIa alternating with aPCC, is another therapeutic approach. The WFH also recommends close clinical monitoring for thrombosis. CB**

Recommendation 8.3.12:

- **For patients with hemophilia A and inhibitors receiving emicizumab who undergo major surgery or an invasive procedure, the WFH recommends a FVIII-containing product for those with low-responding inhibitors. The WFH prefers rFVIIa over aPCC for those with high-responding inhibitors due to the risk of thrombotic microangiopathy. The WFH makes no recommendations on specific dose, frequency, or duration as there are insufficient data.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.** CB

Recommendation 8.3.13:

- **For patients with hemophilia A and inhibitors receiving emicizumab who undergo minor surgery or an invasive procedure, the WFH recommends either low-dose or no clotting factor replacement therapy.**
- **Remark: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.** CB

Recommendation 8.3.14:

- **For patients with hemophilia A and inhibitors receiving emicizumab who undergo major surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis, consumptive coagulopathy, or thrombotic microangiopathy.** CB

Recommendation 8.3.15:

- **For patients with hemophilia A and inhibitors who use bypass agent therapy, the WFH recommends clinical monitoring and consideration for laboratory monitoring with thrombin generation and other coagulation tests, but more data are needed to recommend the latter.** CB

Immune tolerance induction

- Inhibitor eradication by immune tolerance induction therapy is successful in 70%-80% of patients with severe hemophilia A.[53-55]
- Response to ITI may be less favourable in patients with moderate/mild hemophilia A.[7,17]

Recommendation 8.3.16:

- **For patients with hemophilia A who develop persistent low-responding inhibitors, the WFH suggests that immune tolerance induction (ITI) be considered.** CB
- Successful ITI is defined as a persistently negative Bethesda titer, accompanied by normal pharmacokinetics, including factor recovery >66% and half-life >6 hours for standard FVIII CFCs. Once successful ITI is achieved, FVIII prophylaxis may be initiated or resumed.
- There is general consensus that failure of ITI is the inability to achieve successful tolerance within 2-3 years of initiation of an ITI regimen.[27]

Recommendation 8.3.17:

- **For patients with hemophilia A and persistent inhibitors who fail immune tolerance induction (ITI) or never underwent ITI, the WFH recommends emicizumab prophylaxis over bypass agent prophylaxis (rFVIIa or aPCC), as emicizumab is more effective in bleed prevention and simpler to administer, as it is given weekly and subcutaneously.** CB

- When to initiate ITI has been a topic of debate. Registry data from the 1990s and 2000s showed success was highest when ITI was begun in patients with low inhibitor titers (<10 BU). Thus, clinicians adopted a policy of waiting to start ITI until inhibitor titers had fallen to <10 BU; however, more recently, clinicians have begun to initiate ITI immediately after inhibitor detection no matter the titer, with good response.[56]
- The optimal regimen (product or dose) for ITI remains to be defined. In the International ITI Trial, there was no difference in efficacy between a low-dose/low-frequency regimen (50 IU/kg FVIII 3 times weekly) and a high-dose/high-frequency regimen (200 IU/kg daily), but the low-dose/low-frequency regimen required a longer time to achieve tolerance and more bleeds occurred during that period, particularly in the first 3-6 months of ITI. For this reason, the trial was stopped early,[57] with subsequent clinician preference for the high-dose/high-frequency regimen.
- While on ITI, if patients experience frequent bleeding, bypass agent prophylaxis (rFVIIa, aPCC) or emicizumab prophylaxis may be instituted. Emicizumab prophylaxis has been associated with a significantly greater reduction in bleeding rates than bypass agent prophylaxis.[33]
- It may be possible to delay or avoid ITI altogether with emicizumab prophylaxis, given the very low bleeding rates seen with this agent, but controversy continues and data are scarce. (See "Therapeutic options for FVIII inhibitor patients – Emicizumab" above.)
- Few data exist on the use of extended half-life factor therapies or ancillary non-factor therapies for ITI. Preliminary data from small case series and observational studies have shown that extended half-life CFCs are effective in some patients with inhibitors, including those with high-responding inhibitors and those who have previously failed ITI with standard half-life CFCs or were never tolerized, and may shorten duration of ITI.[17,59,60] Data from a small case series found FVIII 100 IU/kg three times weekly plus emicizumab prophylaxis is safe and associated with a decline in

inhibitor titer.[61] Larger, randomized studies are needed to confirm these findings.

- Because ITI requires frequent infusions (up to once daily), it generally requires good venous access. In young children with small veins and/or poor access, a central venous access device (CVAD) is usually required for ITI. However, CVAD use is associated with complications such as infection and/or thrombosis. For this reason, emicizumab, which is administered subcutaneously and requires no IV access, has been considered a simpler option than standard ITI and, it may allow for lower dose/lower frequency FVIII CFC infusions when used with ITI or instead of ITI, although this is unproven. This remains controversial as there are no data regarding inhibitor risk if episodic CFC replacement therapy is required for breakthrough bleeds during emicizumab prophylaxis.
- Whether emicizumab should be initiated before, during, after, or instead of ITI is unknown,[62] and answering this question will require clinical trials. As emicizumab differs biochemically from FVIII, many questions remain regarding its long-term impact on joint pathology, immunogenicity, and cost-effectiveness in non-inhibitor patients.
- Although there has been interest in the use of immunosuppressive and immunomodulatory therapies in hemophilia patients with inhibitors, the role of these agents is not yet defined, and as there is no consensus regarding these agents in the management of inhibitor patients, clinical trials are needed.

FVIII prophylaxis after immune tolerance induction

- After successful ITI in hemophilia A patients with inhibitors, FVIII prophylaxis with close monitoring of clinical response should be initiated.
- At least one extended half-life CFC, rFVIIIFc, has been evaluated for its tolerogenic potential in the prevention of inhibitor formation and in the induction of immune tolerance. At this time, data on the impact of extended half-life therapies are limited.[58,60,63]

Product switching

- While there is controversy regarding inhibitor development in those switching CFC products, including rare case reports, data from large studies indicate there is no evidence supporting increased risk.[64-66]

Recommendation 8.3.18:

- **For patients with hemophilia A who switch to another type or brand of factor product, the WFH has no preference for the choice of specific type of therapy, as current evidence indicates product switching does not increase risk of inhibitor development.**
- **Remark: The WFH encourages product choice based on potential advantages, such as simpler administration, safety, efficacy, and personal preferences.**
- **Remark: The WFH supports prospective data collection on inhibitor formation by product, particularly before and after switching products.** CB

Recommendation 8.3.19:

- **For patients with severe hemophilia A and inhibitors, the WFH recommends emicizumab over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis.** CB

8.4 | Hemophilia B and FIX inhibitors

Genetic and environmental risk factors

- FIX inhibitors are almost exclusively seen in patients with severe hemophilia B and very rarely in the milder forms.[67]
- Inhibitors in patients with severe hemophilia B are rare and occur most commonly in those with null variants, in which no endogenous clotting factor is produced, in most cases due to large deletion, frame-shift, and nonsense variants.[67,68] There is no known ancestral predilection to inhibitor development in hemophilia B.
- Inhibitor formation in hemophilia B is not thought to be related to type of FIX CFC, and it has been reported in those receiving plasma-derived and recombinant FIX CFCs alike.

Inhibitor incidence

- Inhibitor formation in patients with hemophilia B occurs infrequently, with a cumulative incidence of up to 5%.[69,70]
- The development of an FIX inhibitor is considered the most serious complication in patients with hemophilia B,[9] due not only to loss of response to FIX replacement, but also to the associated risks of anaphylaxis and nephrotic syndrome.[67]
- Inhibitor detection in hemophilia B is similar to that in hemophilia A, with most inhibitors occurring after a median of 9-11 exposures, and before 20 exposures, typically before 2 years of age.[18]
- Treatment strategies for FIX inhibitors are similar to those for FVIII inhibitors; specifically, they focus on controlling hemostasis and eradicating the inhibitor.
- It is recommended that because of the severity of complications, patients with hemophilia B should be followed closely and screened for inhibitors every 6-12 months after initiating CFC replacement therapy, and annually thereafter.

Disease burden

Anaphylaxis to FIX

- Inhibitor formation in patients with hemophilia B is overall associated with a similar disease burden as in hemophilia A but may also be associated with allergic reaction to FIX CFCs. Anaphylaxis

occurs in 50% of hemophilia B patients with inhibitors,[20] and more frequently in those with null mutations. Such reactions may be the first symptom of FIX inhibitor development.[67]

- Newly diagnosed severe hemophilia B patients, particularly those with a family history of severe hemophilia B with inhibitors and/or with genetic variants predisposing to inhibitor development, should be treated in a clinic or hospital setting capable of managing severe allergic reactions for the initial 10-20 exposures to FIX CFCs, with emergency equipment available to treat anaphylaxis.[67] Reactions may also occur later but may be less severe.[20,71]

Recommendation 8.4.1:

- **For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for an inhibitor to FIX, as an allergic reaction may be the first sign of inhibitor development.** CB

Recommendation 8.4.2:

- **For patients with hemophilia B and a family history of inhibitors or risk factors for inhibitor development, the WFH recommends monitoring initial infusions in a clinic or hospital setting capable of managing severe allergic reactions.** CB

Recommendation 8.4.3:

- **For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for nephrotic syndrome, as it is more common in FIX inhibitor patients with allergic reactions to FIX.** CB

Recommendation 8.4.4:

- **For patients with hemophilia B and inhibitors and an allergic reaction/anaphylaxis to FIX therapy, the WFH recommends rFVIIa to treat acute bleeds but is against use of aPCC as it contains FIX and may cause or worsen an allergic reaction.**
- **Remark: For patients with hemophilia B and inhibitors and allergic reaction to FIX therapy, the WFH indicates there are insufficient data to recommend desensitization by small, repeated doses of FIX, intravenously or subcutaneously, and recognizes that in some, this approach may worsen an allergic reaction or cause anaphylaxis. If undertaken, FIX desensitization should be performed with caution and under close supervision by experts only.** CB

Recommendation 8.4.5:

- **For patients with hemophilia B and inhibitors who develop anaphylaxis to FIX therapy, the WFH recommends bypass therapy with rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction.** CB

Management of bleeding

- Management of bleeding in hemophilia patients with inhibitors must be carried out in consultation with a hemophilia treatment centre and staff experienced in inhibitor treatment.[7,28]
- Treatment of bleeding in hemophilia B patients with inhibitors should be individualized.[67] Choice of treatment product should be based on inhibitor titer, clinical response to the product, previous infusion reactions, site and nature of the bleed,[7,29] and product availability by country.

Recommendation 8.4.6:

- **For patients with hemophilia B and inhibitors who develop an acute bleed, the WFH recommends treatment based on whether the inhibitor is low-responding or high-responding and whether there is a history of allergic reactions.** CB

Therapeutic options for patients with FIX inhibitors

CFC replacement therapy

- For those with low-responding inhibitors, specific FIX CFC replacement therapy may be used if there is adequate inhibitor neutralization to control bleeding. Because allergic reactions and anaphylaxis may occur in up to 50% of hemophilia B patients with inhibitors,[20] close monitoring is essential.

Recommendation 8.4.7:

- **For patients with hemophilia B and low-responding FIX inhibitors, the WFH recommends use of a FIX-containing product to treat acute bleeds, as long as there is no allergic reaction to FIX.** CB

- For hemophilia B patients with high-responding inhibitors or those with low-responding inhibitors who develop allergic reactions or anaphylaxis, the bypassing agent rFVIIa may be used to control bleeding. As aPCC contains FIX, it may trigger or worsen an allergic or anaphylactic response; for that reason, aPCC should be avoided in hemophilia B patients. However, in the absence of such a reaction, aPCC has shown similar efficacy in controlling acute bleeding.[27]

Recommendation 8.4.8:

- **For patients with hemophilia B and high-responding FIX inhibitors, the WFH prefers rFVIIa over aPCC to treat acute bleeds, as aPCC contains FIX and may cause or worsen an allergic reaction.** CB

Conventional hemostatic bypassing agents

- Alternative hemostatic agents for prevention of spontaneous or traumatic bleeds (prophylaxis) in hemophilia B inhibitor patients include rFVIIa, or, in the absence of an allergic/anaphylactic reaction to FIX, aPCC.[34,47,60,72,73]
- Bypass agent prophylaxis in inhibitor patients is not as effective nor as convenient as standard factor prophylaxis is in patients without inhibitors.[72]
- For hemostasis, bypass agent therapy with rFVIIa constitutes the standard approach. In general, aPCC may increase risk of

anaphylaxis because of FIX content and should be avoided in those with hemophilia B inhibitors (see above). Both agents are effective in treating 90% of musculoskeletal bleeds and can be used in major and minor prophylaxis.[34,72] (See Table 8-5.)

- As there are no reliable laboratory assays to monitor bypass agent therapy, careful monitoring of hemoglobin levels, blood loss, wound healing, and clinical response to treatment is advised, including patient-reported outcomes and subjective patient feedback.

Recommendation 8.4.9:

- **For patients with hemophilia B and inhibitors who use bypass agent therapy, the WFH recommends clinical monitoring and consideration for laboratory monitoring with thrombin generation and other coagulation tests, although more data are needed to recommend the latter.** CB

Therapies in clinical trials

- Several emerging non-factor therapies are in clinical trials for bleed prevention in hemophilia B patients with inhibitors, including fitusiran (siRNA-AT3)[50] and anti-TFPI.[51,74] These therapies may provide a less invasive route and/or lower frequency of dosing and, if safe and effective, may be adopted into use.
- An extended half-life rFVIIa with in vitro hemostasis[48] is in early clinical trials for bleed prevention in patients with hemophilia B and inhibitors.[49] This therapy may reduce the frequency of dosing and, if safe and effective, may be adopted into use.[49]

Immune tolerance induction

- Because inhibitor prevalence is low in hemophilia B, experience with ITI is limited. The principles of treatment are similar to those in hemophilia A, but the success rate is lower, especially in patients with an allergic reaction to FIX. The latter may require FIX desensitization before attempting ITI, although few data are available regarding the efficacy or safety of this approach.
- Hemophilia B inhibitor patients with a history of severe allergic reactions to FIX may develop nephrotic syndrome, which may be irreversible. In some patients undergoing ITI, nephrotic syndrome may develop; close monitoring is required even after ITI is completed, as nephrotic syndrome may persist.
- There is little evidence regarding when or whether to initiate ITI in hemophilia B patients after inhibitor detection; however, some have initiated a high-dose/high-frequency FIX regimen until tolerance is achieved, i.e., the inhibitor titer is persistently negative and factor recovery and half-life return to normal. However, there is no supporting evidence, and this approach is based on experience with hemophilia A inhibitor management. Clinical and laboratory monitoring is important, especially for development of allergic reactions or nephrotic syndrome.
- Little is known about the role of immunosuppressive agents in hemophilia B patients with inhibitors, as few data are available; thus, there is no consensus regarding their use in these patients.

Recommendation 8.4.10:

- **For patients with hemophilia B and inhibitors, the WFH is unable to make a recommendation on the use of immune tolerance induction, as experience with ITI in hemophilia B is limited.**
- **Remark: In patients with hemophilia B and inhibitors in whom ITI is attempted, high-dose factor replacement protocols should be followed similar to what is recommended for hemophilia A, with strong consideration for the use of immunosuppression. It should be noted the risk of nephrotic syndrome may increase with high-dose ITI.** CB

FIX prophylaxis after immune tolerance induction

- After successful immune tolerization in hemophilia B patients with inhibitors (defined as the return to a persistently negative inhibitor titer), FIX prophylaxis with close monitoring of clinical response should be initiated.[7]

Surgery and invasive procedures

- Inhibitor testing is advised in patients with hemophilia B prior to surgery and invasive procedures. Special precautions, as noted above in the "Management of bleeding" section, must be taken in hemophilia B patients with inhibitors, including monitoring for allergic reactions and nephrotic syndrome.
- In those with low-responding inhibitors, standard FIX CFC coverage may be considered if high enough levels are achieved. In

TABLE 8-5 Treatment of acute bleeds in hemophilia B patients with inhibitors

Hemophilia B	Low-responding inhibitors	High-responding inhibitors
Agents	• FIX[20,a]	• rFVIIa or aPCC[27,b] or porcine FVIII
Monitoring	• FIX activity (FIX:C) assay	• Thromboelastography or thrombin generation assay[46,c]

Abbreviations: aPCC, activated prothrombin complex concentrate; FIX, factor IX; FVIII, factor VIII; rFVIIa, recombinant activated factor VIIa.

[a]Will require higher, more frequent dosing if half-life is shortened.

[b]In patients with FIX inhibitors, there is high risk for allergic reaction and nephrotic syndrome with FIX-containing products, e.g., aPCC, and caution is urged; however, in those with an allergic reaction or nephrotic syndrome with FIX-containing products, aPCC should be avoided since it contains FIX.

[c]The thrombin generation assay is not state-of-the-art monitoring and is unavailable in most laboratories, but increasingly being used to assess response.

those with high-responding inhibitors or in those with a history of allergic reactions to FIX CFCs, treatment with the bypassing agent rFVIIa is advised, recognizing the risk of an allergic reaction or worsening of such a reaction in those who experience allergic reactions to FIX when treated with aPCC due to its FIX content.

- If hemostasis is unsatisfactory with rFVIIa or aPCC used as single agents, these agents may be alternated,[37] recognizing this is based on a small observational study and also recognizing the risk for allergic reaction or worsening of an allergic reaction with aPCC due to FIX content.
- Close perioperative monitoring of clinical response to bypass agent therapy is required, particularly for thrombosis or consumptive coagulopathy. (See Recommendation 8.4.9 on clinical monitoring of bypass agent therapy, above.)
- Once hemostasis is achieved and maintained on a bypass agent regimen for 3-5 days, use of these agents may be tapered over a week or more.

Recommendation 8.4.11:

- **For patients with hemophilia B and low-responding FIX inhibitors who undergo surgery, the WFH has no preference for type of FIX products, but recommends more frequent dosing due to the short FIX half-life.** CB

Recommendation 8.4.12:

- **For patients with hemophilia B and FIX inhibitors who undergo surgery, the WFH recommends rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction.** CB

Recommendation 8.4.13:

- **For patients with hemophilia B and inhibitors and an allergic reaction to FIX who undergo surgery, the WFH prefers rFVIIa over aPCC as aPCC contains FIX and may cause or worsen an allergic reaction.** CB

Recommendation 8.4.14:

- **For patients with hemophilia B and inhibitors who undergo surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis or consumptive coagulopathy.** CB

Product switching

- While there is controversy regarding risk of inhibitor development in patients with hemophilia B switching FIX CFC products, including rare case reports, there is a lack of evidence supporting this risk.[64]

Recommendation 8.4.15:

- **For patients with hemophilia B who switch to another type or brand of factor product, the WFH has no preference in the choice of specific type of therapy, as current evidence indicates product switching does not increase the risk of inhibitor development, but rigorous controlled trials are lacking.** CB

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SUPPORTING INFORMATION

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

Chapter 9: Specific Management Issues

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

9.1 | Introduction

- People with hemophilia and their families may experience a number of health- or hemophilia-related conditions or management issues over the course of their lives. These include bleeding and reproductive complications that may affect carriers, specific requirements for surgery and other invasive procedures, psychosocial matters, a range of comorbidities due to lifestyle and aging, and other issues.
- As the management of these conditions can sometimes be complex, education aimed at preventing and/or appropriately treating the issues discussed in this chapter should be a primary and ongoing focus of collaboration between people and family members affected by hemophilia and their multidisciplinary healthcare team.

9.2 | Carriers

- The most severe forms of hemophilia typically affect males; females have conventionally been designated as "carriers."
- Carriers often do not show symptoms of hemophilia because, although they have an abnormal *F8* or *F9* gene on one X chromosome, their other X chromosome contains a normal *F8* or *F9* gene that generally works as normal to produce factor levels in the lower limit of the normal range.
- A proportion of carriers have low factor VIII (FVIII) or factor IX (FIX) activity due to lyonization (the random suppression of one of the two X chromosomes; also called X inactivation), which can result in mild, moderate, or even severe hemophilia in rare instances. Symptomatic females should be designated as having hemophilia of a specified severity, like males with hemophilia.

Inheritance of hemophilia

- A female who has an *F8* or *F9* pathogenic variant is called an obligate carrier of hemophilia. Obligate carriers can be identified as having a hemophilia gene based on analysis of their family history of hemophilia.
- Obligate carriers include:
  - any biological daughter of a father with hemophilia;
  - any biological mother of a child with hemophilia who also has at least one other family member with hemophilia (i.e., her brother, maternal grandfather, uncle, nephew, or male cousin) or who is a known carrier of hemophilia (i.e., her mother, sister, maternal grandmother, aunt, niece, or female cousin);
  - any biological mother of two or more children with hemophilia.
- Potential carriers include:
  - any biological daughter, sister, mother, maternal grandmother, aunt, niece, or female cousin of a carrier of hemophilia;
  - a biological mother of a child with hemophilia and no known family history of hemophilia or carriers of hemophilia.

Factor levels in carriers

- Carriers with FVIII/FIX levels in the normal range may never require factor replacement therapy. However, some carriers with factor levels in the lower range of normal (i.e., below 50 IU/dL)

experience bleeding problems similar to males with mild hemophilia (e.g., hemorrhaging after dental extraction, surgery, or trauma) as well as problems that are specific to women, such as prolonged or heavy menstrual bleeding.[1]
- Carriers who exhibit a greater bleeding tendency than would be predicted by their factor level, as in males, may have a second coagulation defect, such as a von Willebrand factor (VWF) gene variant or a congenital platelet defect.

Recommendation 9.2.1:

- **Carriers of hemophilia, irrespective of factor level, should be registered at a hemophilia treatment centre. CB**

Recommendation 9.2.2:

- **Carriers of hemophilia with low factor levels should be treated and managed the same as males with hemophilia. CB**

Carrier factor level testing

- All immediate female relatives (mother, sister, or daughter) of a person with hemophilia should have their factor levels measured, especially prior to any invasive procedure, childbirth, or as soon as any abnormal bleeding symptoms occur.[1,2]
- In potential carriers, the diagnosis should be confirmed by genetic testing, if available, as factor levels may be above 50 IU/dL.[3,4]
- In some carriers, levels consistent with moderate or even severe hemophilia may be found on factor level testing as a result of lyonization.[5] (See Chapter 2: Comprehensive Care of Hemophilia – Table 2-1.)

Recommendation 9.2.3:

- **All potential and obligate carriers of hemophilia should have their FVIII/FIX levels measured to establish their baseline levels prior to major procedures, surgery, or pregnancy. CB**

Bleeding symptoms

- The most common manifestations among symptomatic carriers include[1]:
  - menorrhagia (heavy menstrual bleeding);
  - dysmenorrhea (pain during menstrual bleeding);
  - postpartum hemorrhage;
  - perimenopausal bleeding (abnormal bleeding during the pre-menopause transition);
  - abnormal bleeding alone, following trauma, or after medical interventions (e.g., dental extraction or surgery).
- Hormonal therapy is useful in managing heavy menstrual bleeding.[6,7] Options include:
  - oral, subcutaneous, or transdermal formulations containing estrogen/progesterone/progestin;
  - the levonorgestrel intrauterine device (IUD).
- Oral antifibrinolytics, e.g., tranexamic acid (15-25 mg/kg every 6-8 hours), may also be helpful in managing heavy menstrual bleeding.[8]

Genetic counselling

- Genetic counselling is an essential but complex component of comprehensive care for individuals and families with a diagnosis of hemophilia and for those at risk.[9]
- While the scope and availability of services vary among countries[10] and individual hemophilia treatment centres,[11] comprehensive genetic counselling generally involves[9]:
  - collection and analysis of family and medical histories to assess the chance of disease occurrence;
  - education about inheritance, genetic testing, treatment, prevention, and available resources; and
  - counselling to promote informed choices and adaptation to the risk or condition.
- Genetic counselling should take into account the individual's experiences and perceptions, as well as the social, cultural, and religious factors and contexts that may influence decisions and options related to their genetic status.
- Genetic counsellors can help both obligate and potential carriers of hemophilia understand their bleeding and genetic risks and adapt to the medical, psychological, familial, and reproductive implications and consequences of their genetic status.[9]
- The primary role of genetic counsellors is to educate individuals on the natural history of hemophilia, establish their family tree/pedigree, perform risk assessments related to the inheritance of hemophilia, facilitate genetic testing, help them process and integrate genetic information, and discuss relevant reproductive options.[9]
- Where access to trained genetic counsellors is limited, the hemophilia treatment centre and the comprehensive care team members, specifically physicians, nurses, and/or psychosocial professionals,[9] often take responsibility for delivering important genetic information.[2]

Psychosocial support

- Ongoing psychosocial assessment and counselling should be integrated within case management and comprehensive care for carriers. Carriers may require referral to psychosocial professionals (e.g., psychologists) for further support to address psychological or emotional issues that may arise during the genetic counselling process or at different life stages.
- Collaboration between psychosocial professionals and genetic counsellors can enhance overall patient care.
- Carriers may experience a wide range of emotional and psychosocial impacts, including feelings of guilt, sorrow, and self-blame related to reproductive choices or consequences such as passing on their genetic variant.[12] Such feelings run across generations of

a family and may also be experienced by grandmothers who were carriers and fathers with hemophilia.[12]

- It is important for hemophilia treatment centres and healthcare providers (especially genetic counsellors and clinical geneticists), families, and patient organizations to be aware that the experience of being a hemophilia carrier may change with different life stages, and carriers may need genetic and/or psychosocial counselling more than once during their lifetime.[12]
- Comprehensive genetic counselling including a formalized system for the education, management, follow-up, and long-term medical and psychosocial support of carriers should be implemented.[10]

Genetic testing

- Genetic testing facilitates identification of carriers and prenatal diagnosis. Where available, formal genetic testing should be offered to potential carriers when they are mature enough to understand the consequences of the diagnosis and give consent.[13]
- It is important to be aware of and abide by the relevant laws governing genetic testing and prenatal diagnosis procedures in the country where the service is being provided.
- See also Chapter 4: Genetic Assessment.

Recommendation 9.2.4:

- **Carriers of hemophilia should be offered counselling that includes reproductive implications and choices.** CB

Prenatal diagnosis

- Prenatal diagnosis is usually offered to help with reproductive planning and risk assessment. Determination of whether a male fetus is affected by hemophilia assists parents and healthcare providers in making decisions regarding pregnancy management, such as caesarean delivery of a fetus with severe disease to reduce intracranial hemorrhage (ICH) and maternal anesthesia for childbirth. (See Chapter 4: Genetic Assessment.)

Pregnancy and prenatal planning

Management of care for all pregnant carriers should involve close cooperation between the hemophilia and obstetric teams. It is important to have a clear plan for delivery that is shared with the carrier and written in her medical file.

Factor levels during pregnancy

- During pregnancy, FVIII levels can increase significantly in carriers and may completely normalize in the later stages. Levels of FIX, however, do not usually change significantly.[14]
- Even with factor levels above 50 IU/dL in the third trimester, carriers may experience abnormal bleeding during childbirth; therefore, it is critical to obtain a carrier's bleeding history and score, family history of bleeding, and history of bleeding with past childbirth prior to delivery[15] and, if possible, prior to pregnancy.

Recommendation 9.2.5:

- **Pregnant carriers of hemophilia should have their FVIII/FIX levels assayed in the third trimester of pregnancy to assess their bleeding risk during delivery and in the postpartum period.** CB

Labour and delivery

- Regional block anesthesia (epidural) in carriers of hemophilia is not contraindicated if the coagulation screen is normal and the relevant factor level is above 50 IU/dL or raised to above 50 IU/dL by prophylactic treatment.[16] The anesthesia should be performed by an expert anesthetist, taking into account the carrier's coagulation parameters and factor levels, with arrangements for appropriate timing of treatment, if applicable.
- Factor replacement therapy, if required, should be administered to maintain factor levels above 50 IU/dL for labour and delivery and maintained in the normal range for at least 3 days after vaginal delivery and at least 5 days after caesarean delivery.[16,17] Route of delivery for carriers with a fetus without hemophilia should be as per obstetric indications. Some suggest caesarean delivery to prevent intracranial hemorrhage in an infant expected to be born with severe hemophilia.[18]
- Delivery of infants known or suspected to have hemophilia must be atraumatic, regardless of whether it is by vaginal or caesarean delivery, to decrease the risk of bleeding complications.[14]
- Forceps and vacuum extraction vaginal delivery as well as invasive procedures to the fetus such as fetal scalp blood sampling and internal fetal scalp electrodes should be avoided.[19]
- See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for major and minor surgery.

Recommendation 9.2.6:

- **For pregnant carriers of hemophilia, delivery should be in a hospital with access to hemophilia specialists where complications during labour and delivery can be dealt with promptly to maintain the safety of mother and child.** CB

Recommendation 9.2.7:

- **For pregnant carriers of hemophilia, the WFH recommends against instrumental delivery.** CB

Postpartum care

- Carrier FVIII and VWF levels fall off fairly rapidly after delivery,[5] usually returning to baseline levels in 7-10 days, but sometimes earlier.[20]

- It is important to monitor and maintain factor levels post-delivery as carriers are at increased risk of primary and secondary postpartum hemorrhage.[21] If postpartum hemorrhage occurs, factor replacement therapy, antifibrinolytics (tranexamic acid), and hormonal therapy are the first-line therapies for its management.[5]
- Prophylactic hormonal therapy may be started immediately after delivery and continued for one month in selected carriers deemed to be at higher risk of bleeding.[5]
- Desmopressin (DDAVP) is occasionally used in the postpartum period for hemophilia A.[5] (See Chapter 5: Hemostatic Agents – Other pharmacological options – Desmopressin [DDAVP].)
- Hemoglobin levels in carriers at risk of late postpartum hemorrhage should be checked before discharge from hospital.[22]
- Delayed bleeding up to 35 days postpartum is possible; carriers must be informed of this risk and should be seen 2 weeks postpartum. Follow-up to monitor postpartum bleeding for approximately 1-2 months may be appropriate.[22]

Recommendation 9.2.8:

- **Carriers of hemophilia should be monitored for both primary and secondary postpartum hemorrhage, which should be treated with appropriate hemostatic measures.** CB

Newborn testing

- Cord blood should be collected from all male newborn infants of carriers of hemophilia to assess clotting factor levels for early identification and management of hemophilia. The test results should be conveyed to the parents by an appropriate member of the hemophilia team.
- Normally in newborn and pre-term infants without hemophilia, FVIII levels at birth are within the normal adult range or mildly increased. Therefore, it is possible to diagnose most cases of hemophilia A at birth; the exception being in mild hemophilia A, wherein a FVIII result at the lower end of the normal range should be repeated when the infant is around 6 months of age.[23]
- In contrast to FVIII, FIX levels at birth are significantly lower than normal in newborns without hemophilia and even more so in preterm infants.[23] While it is usually possible to make a diagnosis of severe or moderate hemophilia B in the neonatal period, infants who may be mildly affected will require repeat screening at 3-6 months of age.

Recommendation 9.2.9:

- **Male babies born to known or potential carriers of hemophilia should have cord blood testing of activated partial thromboplastin time (APTT) or factor levels.** CB

Miscarriage management

- Miscarriage refers to a spontaneous abortion or pregnancy loss before 20 weeks of gestation[24,25] by complete or incomplete expulsion of the products of conception from the uterus, by failure of the embryo to develop, or by death of the fetus in utero.[25]
- Once the determination has been made that the pregnancy has ended because the embryo or fetus has died or because a miscarriage is in progress, the obstetrician will surgically evacuate the uterus or await spontaneous expulsion of the products of conception.
- Surgical management of spontaneous abortion is preferred in patients with a pre-existing hemostatic abnormality such as an inherited bleeding disorder.[24] In such cases, adequate hemostatic treatment is required in accordance with the recommended perioperative protocols. (See 9.5 Surgery and invasive procedures, below, and Chapter 7: Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for major and minor surgery.)
- Since bleeding in pregnancy is almost always attributed to obstetric bleeding, adequate obstetric management is required. In the case of bleeding in a pregnant carrier, appropriate hemostatic management may also be required.
- Hemostatic management consists of replacement of the deficient clotting factor or other treatment modalities in accordance with protocols for the management of bleeding complications in patients with hemophilia.

9.3 | Circumcision

- Circumcision is a widely practiced surgical procedure; up to 30% of the male population in the world are circumcised.[26,27]
- Medical benefits of circumcision include reduced risk of sexually transmitted diseases, reduced risk of carcinoma of the penis, and reduced risk of cervical cancer in sexual partners of circumcised males.[28]
- The accepted medical indications include treatment of phimosis, paraphimosis, recurrent balanitis, and recurrent balanoposthitis.[27,29] Non-medical reasons and indications may be social, cultural, personal, or religious.
- In hemophilia, circumcision is associated with a number of complications including prolonged bleeding, infection, delayed skin healing/increased morbidity, gangrene, human immunodeficiency virus (HIV) and hepatitis infection acquired through contaminated blood products to treat bleeding, risk of neonatal inhibitor development, psychosocial scarring, and risk of mortality.[29,30]
- The key considerations for circumcision in patients with hemophilia include individual patient factors such as inhibitor development, venous access, and wound care, as well as the expertise and resources at the hospital/treatment centre. Patients will invariably bleed when stitches are removed, and this should be managed with clotting factor replacement. (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for minor surgery.)

- A risk–benefit ratio assessment should be performed and discussed with family and other caregivers.

Recommendation 9.3.1:

- **In patients with hemophilia, the circumcision procedure should be performed electively by an experienced surgeon and hematology team in a resourced hematology treatment centre with access to clotting factor concentrates.** CB

Recommendation 9.3.2:

- **In patients with hemophilia, the plasma factor level should be raised to 80-100 IU/dL just prior to the procedure.** CB

Recommendation 9.3.3:

- **In patients with hemophilia undergoing circumcision, intraoperative care should be taken to cauterize all bleeding vessels.** CB

Recommendation 9.3.4:

- **For patients with hemophilia undergoing circumcision, the WFH suggests use of topical fibrin sealant as an adjunctive therapy, using a product manufactured with robust viral reduction/inactivation processes if available, to minimize the risk of bloodborne pathogen transmission.** CB

Recommendation 9.3.5:

- **For patients with hemophilia undergoing circumcision, the WFH recommends adjusting clotting factor replacement to the clinical course of the procedure. If continued clotting factor replacement is required, the goal would be to maintain factor levels above 50 IU/dL for the first 3 days, and above 30 IU/dL for the subsequent 4-8 days.** CB

Recommendation 9.3.6:

- **In patients with hemophilia post-circumcision, inhibitor measurement should be repeated if there is intractable bleeding that is poorly responsive to replacement therapy and local hemostatic measures.** CB

Recommendation 9.3.7:

- **In patients with hemophilia post-circumcision, non-dissolvable stitches (if used) should be removed 10-14 days postsurgery; the inevitable bleeding should be managed with clotting factor replacement.** CB

Recommendation 9.3.8:

- **In hemophilia patients with intractable bleeding post-circumcision, all angles should be considered, including blood vessel bleeding, clotting factor deficiency, and platelet abnormalities.** CB

Recommendation 9.3.9:

- **In hemophilia patients with intractable bleeding post-circumcision, adjunct and supportive therapy should be used; this includes transfusion and local hemostatic measures, such as the application of topical agents.** CB

9.4 | Vaccinations

- Vaccination against communicable diseases is crucial for disease prevention. People with hemophilia should receive all immunizations recommended for their age group.
- Challenges associated with vaccinations include:
  - route of vaccine administration; and
  - vaccination of patients with compromised immunity (e.g., HIV infection).
- Live virus vaccines may be contraindicated in those with weakened immunity.
- There has been no evidence that vaccinations result in inhibitor development.[31]

Recommendation 9.4.1:

- **Children and adults with hemophilia should be administered the same routine vaccines as the general population; however, they should preferably receive the vaccines subcutaneously rather than intramuscularly or intradermally, as it is as safe and effective as the latter and does not require clotting factor infusion.**
- **Remark: If intramuscular injection must be the route of administration, a dose of clotting factor concentrate should be given, and the smallest gauge needle available (25-27 gauge) should be used.**
- **Remark: Additionally, an ice pack should be applied to the injection site for 5 minutes before injection of the vaccine, and pressure should be applied to the site for at least 10 minutes to reduce bleeding and swelling.** CB

Recommendation 9.4.2:

- **In children and adults with hemophilia and human immunodeficiency virus (HIV) infection, the WFH recommends standard immunizations, including pneumococcal and influenza vaccines and hepatitis A and B immunization.** CB

Recommendation 9.4.3:

- **In children and adults with hemophilia and HIV infection, the WFH recommends that live virus vaccines (such as chickenpox, yellow fever, rotavirus, oral polio, and combined measles, mumps, and rubella [MMR] vaccines) should be avoided.** CB

9.5 | Surgery and invasive procedures

- Surgery may be required for hemophilia-related complications or unrelated diseases. The issues discussed here are of prime importance when performing surgery on patients with hemophilia.
- Surgery for patients with hemophilia requires additional planning and interaction with the healthcare team compared to what is required for other patients.

- The anesthesiologist should have experience treating patients with bleeding disorders.
- Neuraxial anesthesia requires factor levels above 50 IU/dL to avoid bleeding and ensuing neurological complications.[32]
- Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.
- Adequate quantities of CFCs (or bypassing agents for patients with inhibitors) should be available for the surgery itself and to maintain adequate coverage postoperatively for the length of time required for healing and/or rehabilitation. (For patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor – Surgery and invasive procedures.)
- If CFCs or bypassing agents are not available, adequate blood bank support for plasma components is needed.
- The dosage and duration of CFC or other hemostatic coverage depend on the type of surgery performed. (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for major and minor surgery.)
- Effectiveness of hemostasis for surgical procedures may be assessed as per criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (see Table 9-1).[33]
- Treatment with CFCs or other hemostatic agents should be considered before invasive diagnostic procedures such as lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy.
- DDAVP may be useful hemostatic treatment for surgery and other invasive procedures in responsive patients with mild hemophilia A (without medical contraindications) for minor bleeding or surgery.[34] Limitations of DDAVP include water retention, hyponatremia, and tachyphylaxis. Tachyphylaxis occurs when repeated dosages of DDAVP are given within short time intervals (12-24 hours), with approximately 30% decrease in FVIII activity response from the second dose onwards in the case of a 24-hour interval. Due to possible tachyphylaxis, DDAVP may not be a good option for those patients who require adequate hemostasis for longer periods of time, e.g., following major surgery.[35]
- Combined administration of DDAVP and FVIII concentrate may be able to overcome several of the drawbacks of these separate treatment options; however, there is a lack of experience and knowledge with regard to the efficacy and safety of combination treatment.[35]
- When needed, or if CFCs are not available, DDAVP and antifibrinolytics (tranexamic acid or epsilon-aminocaproic acid) are therapeutic options as hemostatic support to the initial replacement treatment.[36] More potent and better tolerated among antifibrinolytics is tranexamic acid. This compound is particularly effective and useful in cases of mucosal bleeds.
- See Chapter 5: Hemostatic Agents – Other pharmacological options – Desmopressin (DDAVP).
- Inhibitors should be assessed prior to surgery and when there is suboptimal response to treatment in the postoperative period. (See Chapter 8: Inhibitors to Clotting Factor – Surgery and invasive procedures.)

Recommendation 9.5.1:

- **Patients with hemophilia A and B should have ready access to and be evaluated for acute and elective surgical procedures that could enhance their well-being or quality of life.** CB

Recommendation 9.5.2:

- **The WFH recommends patients with hemophilia requiring surgery should be managed at or in consultation with a comprehensive hemophilia treatment centre.** CB

TABLE 9-1 Definition of adequacy of hemostasis for surgical procedures[33]

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

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

Abbreviations: FIX, factor IX; FVIII, factor VIII; ICU, intensive care unit.

Recommendation 9.5.3:

- **For patients with hemophilia requiring surgery, sufficient quantities of clotting factor concentrates must be available for the surgery itself and to maintain adequate coverage post-operatively for the duration required for recovery and/or rehabilitation. CB**

Recommendation 9.5.4:

- **The WFH recommends centres providing surgery for patients with hemophilia should have adequate laboratory support for reliable monitoring of clotting factor levels in the perioperative period. CB**

Recommendation 9.5.5:

- **For patients with mild hemophilia A undergoing surgery, the WFH recommends the use of DDAVP for hemostasis if the patient shows good therapeutic response to DDAVP in pre-surgery testing.**
- **Remark: DDAVP is not recommended for surgical hemostasis in those patients with mild hemophilia A in whom the response to DDAVP (increase of plasma FVIII activity levels) is unsatisfactory or in whom DDAVP is contraindicated (e.g., in those with significant cardiovascular disease).**
- **Remark: Due to the risk of tachyphylaxis, DDAVP should not be given for more than 3-5 days unless the patient can be monitored closely and switched to clotting factor concentrate if this occurs. Therefore, if the anticipated treatment duration will be longer than 3-5 days (e.g., after major surgery), providers may choose to avoid the use of DDAVP from the outset.**
- **Remark: DDAVP is the first choice for patients with mild hemophilia A to avoid the cost of CFCs and exposure to FVIII concentrates and the potential risk of inhibitor development, which increases with the number of exposures.**
- **Remark: Given the need for close monitoring, an experienced hematology team should manage these patients. CB**

Recommendation 9.5.6:

- **For patients with hemophilia undergoing surgery, antifibrinolytics and topical hemostatic agents should be considered if ancillary therapies are required beyond factor replacement. CB**

Recommendation 9.5.7:

- **Pre- and postoperative assessment of all patients with hemophilia A and B should include inhibitor screening and inhibitor assay. CB**

Recommendation 9.5.8:

- **For patients with hemophilia undergoing surgery, the WFH advises against neuraxial anesthesia. If neuraxial anesthesia is required, it should be performed only under adequate clotting factor coverage as the safety of neuraxial procedures has not been established in patients with hemophilia.**
- **Remark: It is recognized that in some centres, neuraxial anesthesia is acceptable after restoring hemostasis in patients with hemophilia, whereas in other centres this procedure is discouraged and general anesthesia is preferred. CB**

Recommendation 9.5.9:

- **Patients with mild hemophilia A and all patients with hemophilia receiving intensive factor replacement for the first time are at particular risk of inhibitor development, and therefore should be rescreened for inhibitor presence 4-12 weeks post-operatively. CB**

Recommendation 9.5.10:

- **In surgical patients with hemophilia B requiring intensive replacement therapy, the WFH recommends against use of prothrombin complex concentrate (PCC) due to risk of accumulation of clotting factors II, VII, and X, which can be associated with higher risk of thrombotic complications. CB**

Recommendation 9.5.11:

- **The WFH recommends replacement therapy for a duration of at least 3 days for minor surgical procedures, and at least 7-10 days for major surgical procedures. CB**

Recommendation 9.5.12:

- **For patients with hemophilia A and B undergoing major surgery, the WFH recommends against routine use of pharmacologic thromboprophylaxis. CB**

9.6 | Sexuality

- People with hemophilia are able to have entirely normal sexual lives.[37] Although sexual health has generally been inadequately assessed in routine care of people with hemophilia, recent studies have shown that the prevalence of difficulty with sexual activity is significantly higher compared to the general population.[38]
- Complications of hemophilia can be accompanied by sexual dysfunction, such as lack of libido or impotence. Pain, fear of pain, or analgesia may affect sexual desire, and hemophilic arthropathy may place physical limitations on sexual intercourse.
- Older age, joint bleeding, and joint status contribute to poor sexual health; in addition, poor sexual health is strongly associated with worse general health status.[38]
- People with hemophilia have reported experiencing joint stiffness that affected their sexual life (53%), joint pain from sexual activity (53%), and not having adequate information regarding sexual activity.[39]
- Muscle bleeding (e.g., iliopsoas) may sometimes arise from sexual activity, and this may require active management or specific counselling to reduce recurrence.[40] (See Chapter 10: Musculoskeletal Complications.)

- Sexuality may also be affected by viral complications such as chronic hepatitis C virus (HCV) and HIV infection.[40]
- Age-related diseases such as hypertension and diabetes mellitus may also result in sexuality issues, as well as certain medications to treat comorbidities.
- In some cases, oral phosphodiesterase-5 inhibitors (sildenafil, tadalafil) may be helpful. Note that these medications mildly inhibit platelet aggregation in vitro and may cause epistaxis due to nasal congestion.
- In addition to the physical effects on sexuality, people with hemophilia may experience social and psychological issues surrounding sexual health. Worries about having a bleed due to sexual activity, lack of desire, body image issues, fear of rejection, medication side effects, pain, and tiredness have all been reported to affect the sexual lives of people with hemophilia.[40]
- Cultural influences may play a role in a person's decision about whether to discuss sexual health issues with their healthcare provider. As some individuals may be reluctant to have such discussions, all members of the comprehensive care team should be proficient in initiating and engaging patients in a conversation about their sexual health and quality of life, and this approach should be integrated into routine care.[40]
- Hematospermia (defined as the macroscopic presence of blood in the semen) is not uncommon in people with hemophilia and may cause considerable anxiety in some individuals and their partners.
- Hematospermia is rarely linked to serious dysfunctions; nevertheless, a more serious pathology may be underlying, consequently requiring further investigations.

Recommendation 9.6.1:

- **Adult patients with hemophilia should be assessed for sexual health issues as part of routine care to address possible impacts related to age, joint bleeding, joint pain and stiffness, and muscle bleeding (e.g., iliopsoas), which can sometimes arise during sexual activity.** CB

Recommendation 9.6.2:

- **For patients with hemophilia with comorbidities who may experience complications of hemophilia accompanied by sexual dysfunction, the WFH recommends that healthcare providers at hemophilia treatment centres provide a multipronged psychosocial approach that includes communicating openly about sexual activity and quality of life in a consistent and comprehensive manner.** CB

9.7 | Psychosocial issues

- Severe hemophilia is associated with major psychological and economic burdens for people with hemophilia and their caregivers.[41] As hemophilia can impact many aspects of daily living and family life, psychological and social support are important components of comprehensive care for hemophilia.[42]
- Psychosocial care is an important aspect of healthcare services for individuals and families living with hemophilia and related complications.
- The hemophilia treatment centre social worker and/or other members of the comprehensive care team typically fulfill this role. Key functions include:
  - Provide as much information as possible about all aspects of care, including the physical, psychological, emotional, and economic dimensions of living with hemophilia, in terms the patient/family members can understand.
  - Provide psychosocial support and counselling to patients, their parents, and other family members (including unaffected siblings).
  - Interact and speak directly with children with hemophilia about their treatment, not just with their parents.
  - Assess and address issues related to adherence.
  - Help patients understand and deal with issues and challenges related to school or employment.
  - Encourage patients and family members to build a support network (e.g., by forming or joining support groups at their hemophilia treatment centre and patient organization).
  - Work in partnership with the patient organization to provide education to patients, families, and healthcare providers, and advocate for hemophilia care.
  - Enlist the assistance of local healthcare organizations where social workers are unavailable.
  - Encourage patients, family members and caregivers to discuss issues or challenges with regards to mental health such as depression or anxiety.
  - Recognize warning signs of burnout and depression, which are common with chronic illness, and provide suggestions and resources for coping.
  - Encourage patients to engage in productive and fulfilling activities at home and in the workplace.
- See 9.9 Medical issues with aging – Psychosocial issues with aging, below.

Recommendation 9.7.1:

- **For patients with severe hemophilia, the WFH recommends the provision of psychological and social support as part of comprehensive hemophilia care, with enlistment of assistance from local healthcare organizations wherever psychologists or social workers are unavailable.** CB

Recommendation 9.7.2:

- **For patients with hemophilia, the WFH recommends that hemophilia treatment centres assist patients and families in forming and joining support groups or networks, and encourage participation in their patient organizations.** CB

Recommendation 9.7.3:

- **For patients with hemophilia, the WFH recommends appropriate programming at hemophilia treatment centres and patient**

organizations to assist in successful aging through assessment of their developmental progression, assessment and prevention of comorbidities and functional impairments, assessment of cognitive and emotional function, identification of depression and referral for treatment, and reinforcement of social connectedness. CB

9.8 | Comorbidities

- The increase in life expectancy for people with hemophilia—due to major advances in hemophilia care, including the availability of safe and effective CFCs—is accompanied by a range of new challenges. An increasing number of people with hemophilia develop significant comorbidities, such as cardiovascular and metabolic diseases, renal disease, and cancer/malignancies.[43]
- As a result, hemophilia treatment centres increasingly require the expertise of specialists rarely needed before, such as cardiologists, endocrinologists, and oncologists.[44]
- In general, the comorbidities occurring in older patients with hemophilia should be treated in consultation with relevant specialists as they would in the unaffected population of the same age, but treatment should be adapted when the risk of bleeding is increased by the use of invasive procedures or medications that may cause bleeding.[44]

Cancer/malignancy

- The risk of developing cancer increases with age, and the same holds true in aging patients with hemophilia.[45]
- It has been well documented that older patients with hemophilia have a higher incidence of virus-related malignancies caused by HIV (e.g., non-Hodgkin lymphoma, basal cell carcinoma, Kaposi sarcoma) and HCV (e.g., hepatocellular carcinoma) infection.[46-48]
- It is unclear whether hemophilia exerts an impact on the prevalence of other cancers among people with hemophilia, and it is unclear whether hemophilia exerts an impact on the clinical course of malignancy.[49-51]
- More recent analyses suggest that, with the exception of hepatocellular carcinoma due to chronic hepatitis infection, mortality rates from cancer are essentially the same among people with hemophilia and the general population.[52]
- The risk of bleeding in people with hemophilia and cancer is exacerbated by factors including[44]:
  - use of invasive diagnostic and therapeutic procedures;
  - thrombocytopenia induced by chemotherapy and/or radiotherapy.
- Therefore, hemostatic therapy should be provided not only episodically at the time of invasive procedures, but also in the form of ongoing prophylaxis in cases of severe thrombocytopenia due to chemotherapy and/or radiotherapy.[44]
- It is unknown which platelet count is safe in patients with hemophilia and malignancy. Some experts advise considering prophylaxis with replacement of the deficient clotting factor when platelet count is less than 30 G/L apart from management of thrombocytopenia,[44] although previous studies have suggested that prophylaxis should be instituted when platelet counts fall below 50 because of the risk of central nervous system (CNS) and other serious bleeds.[53] (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)
- Since thrombocytopenia is in itself not antithrombotic, antithrombotic prophylaxis should be considered in those types of malignancy that are associated with a high risk of thrombosis.[44]
- For patients with hemophilia who are diagnosed with cancer, which in the general population is accompanied by an increased risk for developing venous thromboembolism (VTE), thromboembolism prophylaxis may not be necessary as patients with clotting deficiencies are relatively protected from developing VTE.[53,54]

Recommendation 9.8.1:

- **In patients with hemophilia, the WFH recommends age-appropriate cancer screening.** CB

Recommendation 9.8.2:

- **For diagnosis and treatment of malignancy in patients with hemophilia, the WFH recommends the provision of adequate factor replacement as necessary to minimize bleeding risk.** CB

Recommendation 9.8.3:

- **In patients with hemophilia, if chemotherapy or radiotherapy is accompanied by severe long-lasting thrombocytopenia, the WFH recommends continuous prophylactic replacement therapy.** CB

Recommendation 9.8.4:

- **Antineoplastic treatments for patients with hemophilia diagnosed with cancer should be the same as recommended for the general population.** CB

Recommendation 9.8.5:

- **For hemophilia patients without inhibitors diagnosed with cancer, the WFH advises that venous thromboembolism prophylaxis management decisions should be based on evaluation of the individual patient's bleeding and thrombotic risk. If used in patients receiving factor concentrates, it must be carefully managed to maintain factor levels below the risk range for VTE.**
- **Remark: If pharmacologic thromboprophylaxis for hemophilia patients without inhibitors diagnosed with cancer is used, it should mimic what is recommended for the general population, provided that appropriate factor replacement therapy is administered, taking into account that factor replacement to high factor levels above normal is a potential risk factor for VTE.** CB

Cerebrovascular accident/stroke

- Patients with hemophilia are prone to hemorrhagic stroke, the most serious type of bleeding in this population; however,

ischemic/thrombotic strokes have also been reported.[55,56] (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)

Atrial fibrillation

- Non-valvular atrial fibrillation (AF) is the most common type of arrhythmia, and it is associated with a significant increase in the risk of embolic stroke. Its prevalence in the general population increases with age, ranging from <0.1% in patients less than 55 years of age to 3% in patients between 65 and 69 years of age, and up to 9% in patients over 80 years of age.[57-59]
- Results of recent studies indicate that the prevalence of atrial fibrillation in patients with hemophilia is similar to that reported in their peers in the general population.[60]
- There is no evidence to suggest that patients with hemophilia and atrial fibrillation are protected from thromboembolic complications.
- Management of non-valvular atrial fibrillation comprises rhythm control strategies such as cardioversion or ablation; however, these strategies do not always obviate the need for therapeutic anticoagulation.[54]
- The selection of patients with hemophilia who have a high chance of successful cardioversion should involve a cardiologist at a hemophilia treatment centre.[44]
- Left atrial appendage occlusion may be an option for patients with non-valvular atrial fibrillation at high risk of bleeding and cardioembolism.[61]
- In patients without bleeding diathesis, treatment decisions regarding anticoagulation in atrial fibrillation are determined by weighing an individual's stroke risk as calculated by the CHA_2DS_2-VASc score against an estimated bleeding risk occurring as a consequence of anticoagulation therapy (the risk of bleeding associated with anticoagulation for atrial fibrillation in the general population is calculated by the HAS-BLED score).[54]
- There is no evidence to support or reject the hypothesis that the CHA_2DS_2-VASc and HAS-BLED scores are equally useful in patients with hemophilia.[54,60]
- There are no evidence-based guidelines for the management of atrial fibrillation in patients with hemophilia.

Recommendation 9.8.6:

- **Patients with hemophilia and non-valvular atrial fibrillation should be treated by medical teams composed of experienced hematologists and cardiologists.** CB

Recommendation 9.8.7:

- **For patients with severe or moderate hemophilia and atrial fibrillation, the WFH recommends clinical management based on basal FVIII/FIX levels and stroke risk by weighing the patient's stroke risk as calculated by the CHA_2DS_2-VASc score against an estimated bleeding risk occurring as a consequence of anticoagulation therapy, and withholding anticoagulation if stroke risk is deemed to be lower than bleeding risk.** CB

Recommendation 9.8.8:

- **For patients with hemophilia and atrial fibrillation at high risk of bleeding and thromboembolism, the WFH recommends left atrial appendage occlusion, particularly if long-term replacement therapy with deficient clotting factor is not feasible.**
- **Remark: Left atrial appendage occlusion for patients with hemophilia and atrial fibrillation should be preceded by assessments of the individual's risk of bleeding and thromboembolism and implemented under the advisement of a cardiologist.** CB

Recommendation 9.8.9:

- **For patients with hemophilia in whom the risk of non-valvular atrial fibrillation-associated stroke is high or outweighs the risk of bleeding complications, the WFH recommends careful consideration of the use of anticoagulants.**
- **Remark: The choice between direct oral anticoagulants and vitamin K antagonists depends on the local protocols, availability of antidotes for reversal of anticoagulant activity, and feasibility of maintaining adequate trough levels of the deficient clotting factor.**
- **Remark: Despite the scarcity of evidence-based data for this indication in patients with hemophilia, most experts suggest maintaining trough levels of the deficient clotting factor in the individual patient at ≥15-30 IU/dL while on anticoagulant therapy for atrial fibrillation.**
- **Remark: Because treatment responses to DOACs and VKAs may vary, decisions on anticoagulant therapy should be based on the individual patient in consultation with a cardiologist.** CB

Recommendation 9.8.10:

- **In hemophilia patients with inhibitors, antithrombotic therapy is generally contraindicated.** CB

- More research is needed to better understand the safety of antithrombotic therapy in patients with hemophilia A complicated by FVIII inhibitors who are treated with emicizumab.

Venous thromboembolism/thrombosis

- Patients with hemophilia are considered to be protected against venous thromboembolism (VTE) by virtue of their coagulation factor deficiency.
- Spontaneous VTE is uncommon among patients with hemophilia, including those with inherited thrombophilia; however, VTE associated with surgical interventions (e.g., total knee or hip replacement or major abdominal surgery for cancer) has been reported. It has been postulated that in this clinical setting, the natural protection against VTE is mitigated by administration of high doses of concentrates of the deficient clotting factor.[62-64]
- Intensive replacement therapy with prothrombin complex concentrate (PCC) in patients with hemophilia B may result in accumulation of clotting factors II, VII, and X, which may be associated with a higher risk of VTE development.[65]

- Intensive therapy with bypassing agents may also be associated with a higher risk of VTE development.[54,65]
- Concomitant use of emicizumab and activated prothrombin complex concentrate (aPCC) may also result in thrombotic complications, including VTE and thrombotic microangiopathy.[66] (See Chapter 8: Inhibitors to Clotting Factor.)
- There is currently a lack of evidence-based consensus on how to manage VTE in patients with hemophilia. It has been suggested that therapeutic doses of anticoagulants may be administered when deficient clotting factor levels are maintained above 30 IU/dL[44] or above 15 IU/dL.[54]
- Hemostatic response to bypassing agents is often unpredictable; therefore, antithrombotics should only be used in patients with hemophilia and high-responding inhibitors who are at the highest risk of developing thromboses. In rare cases, the risk of untreated thrombosis may outweigh the risk of bleeding complications and therefore justify the use of antithrombotic agents. (For patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.)

Recommendation 9.8.11:

- **In patients with hemophilia undergoing surgical procedures who carry a high risk of developing venous thromboembolism (e.g., in cases of major orthopedic surgery, major abdominal surgery for cancer, or long post-surgery immobilization), the WFH recommends an assessment of individual risk of VTE.** CB

Recommendation 9.8.12:

- **For patients with hemophilia undergoing surgery associated with a high risk of venous thromboembolism and bleeding complications, the WFH recommends consideration of the use of mechanical methods for thromboprophylaxis.**
- **Remark: In contrast to pharmacological thromboprophylaxis, mechanical methods of thromboprophylaxis are not associated with the risk of bleeding complications.** CB

Recommendation 9.8.13:

- **For patients with hemophilia in whom the balance of the risk of bleeding compared to the risk of developing venous thromboembolism favours pharmacological thromboprophylaxis, the WFH recommends the same practice as that applied in the general population, provided that adequate replacement therapy is administered.**
- **Remark: Decisions on anticoagulant therapy in a patient with hemophilia should always be preceded by assessments of the individual's bleeding and thrombotic risk. In some patients with hemophilia, the risk of uncontrolled bleeding may outweigh the benefit of anticoagulation.** CB

Recommendation 9.8.14:

- **For patients with hemophilia without inhibitors, the WFH recommends the use of prophylactic doses of anticoagulants only after ensuring hemostatic control with adequate replacement therapy.**
- **Remark: If the risk of uncontrolled bleeding outweighs the benefit of anticoagulation, anticoagulants should not be used.**
- **Remark: This recommendation does not apply to patients with hemophilia and inhibitors in whom anticoagulants are generally contraindicated.** CB

Recommendation 9.8.15:

- **In hemophilia patients without inhibitors who experience an acute episode of venous thromboembolism, the WFH recommends the use of high-intensity anticoagulation for the minimal duration and under clotting factor replacement protection and close clinical and laboratory monitoring.**
- **Remark: This recommendation does not apply to hemophilia patients with inhibitors in whom anticoagulants are generally contraindicated.** CB

- More research is needed to better understand the safety of antithrombotic therapy in patients with hemophilia A complicated by FVIII inhibitors who are treated with emicizumab.

Metabolic syndrome

- Metabolic syndrome is associated with obesity and physical inactivity, both of which are common in older patients with hemophilia due to severe hemophilic arthropathy.[43]
- Obesity (body mass index [BMI] ≥30 kg/m^2) is a major health concern in developed countries in both the general population and in patients with hemophilia.[67] The number of patients with hemophilia who are overweight is also increasing.[68]
- Obesity impacts physical activity in both children[69] and adults.[70] Although few studies have assessed the effects of obesity on hemophilia-specific outcomes, there is evidence that excess weight has a significant impact on lower extremity joint range of motion and functional ability, as well as on joint pain, with potentially significant effects on overall quality of life.[71,72]
- Overweight and obesity can affect frequency of bleeding in different ways: some overweight/obese patients have reduced bleeding rates, but this may be due to lower levels of physical activity; conversely, obese patients with hemophilia tend to have more joint bleeds, compared to non-obese patients with hemophilia.[70]
- Venous access is more complex in obese patients with hemophilia, which may inhibit their ability to self-infuse and therefore result in lower compliance with their prophylaxis regimen.[73] Lower compliance with prophylaxis may result in more joint bleeding and ultimately worsen hemophilic arthropathy and osteoarthritis in obese patients with hemophilia.[70]
- Factor recovery is different in patients with hemophilia who are overweight or obese. A median FVIII recovery has been observed in obese children (2.65), compared to those with normal weight (1.94).[74,75]
- For some obese patients, lean body weight dosing may be effective while reducing cost of treatment based on body weight. However, each patient would have to be assessed by pharmacokinetic

studies, including trough and peak levels, and factor levels at additional timepoints to establish ideal dosing.
- Weight management should be offered as part of health promotion within hemophilia treatment centres for all patients. This should include:
  - nutritional education for parents of children as well as for adults with hemophilia;
  - weight management programs;
  - psychological support;
  - exercise programs (preferably monitored by the centre's physical therapist);
  - pharmacological therapy;
  - bariatric surgery; and
  - collaboration with or referral to obesity medical/surgical teams.
- Bariatric surgery is possible in morbidly obese people with hemophilia.[76]

Recommendation 9.8.16:

- **Patients with hemophilia should have regular height and weight measurements to monitor body mass index. CB**

Recommendation 9.8.17:

- **Patients with hemophilia who are overweight or obese should be referred for dietary advice and/or weight management. CB**

Recommendation 9.8.18:

- **Patients with hemophilia who are obese should have FVIII/FIX replacement therapy based on lean body weight after individual pharmacokinetic assessments. CB**

Diabetes mellitus

- Little is known about the prevalence of diabetes mellitus in people with hemophilia, but it has been found to be higher in the hemophilia population than in the general population.[43]
- If treatment with insulin is indicated, subcutaneous injections can be administered without bleeding and without the need for factor replacement.[37]
- Higher body weight/BMI is a major risk factor for not only the development of diabetes mellitus, but also for atherosclerosis, cardiovascular disease, and further damage to arthropathic joints. As a result, regular physical activity and physical therapy aimed at preventing further joint deterioration are advisable.[43]

Recommendation 9.8.19:

- **Patients with hemophilia should have the same screening for diabetes as the general population. CB**

Recommendation 9.8.20:

- **Patients with hemophilia and diabetes should have the same management strategies to control their diabetes as the general population; if treatment with insulin is indicated, subcutaneous injections can be administered without bleeding and without the need for factor replacement. CB**

Renal disease

- A higher incidence of renal disease has been reported in people with hemophilia, compared with the general population. In addition, the likelihood of death from renal failure is about 50 times higher among patients with hemophilia than in the general population.[45]
- The increasing frequency of renal disease in older patients with hemophilia is likely due to a number of concomitant risk factors including[44,45]:
  - older age;
  - non-white population;
  - hypertension;
  - history of renal bleeds and hematuria, potentially resulting in structural renal damage;
  - HIV infection and combined antiretroviral therapy;
  - use of antifibrinolytic amino acids.
- Therefore, the need for dialysis may be increasing in patients with hemophilia.[44]
- In those patients who require renal replacement therapy, the choice between peritoneal dialysis and hemodialysis depends on patient-specific factors, such as the increased risk of infection in patients with cirrhosis and/or ascites.[45]
- Theoretically, peritoneal dialysis is preferable to hemodialysis because it requires factor coverage only at the time of catheter insertion; however, the procedure is associated with a high risk of peritoneal infections, particularly in HCV- and HIV-infected patients. Thus, hemodialysis using heparin and a single dose of CFC before and after each procedure is often preferred.[44]
- If hemodialysis is selected, central venous access is mandatory. Before placement of the device, factor levels should be 80-100 IU/dL and then maintained between 50 and 70 IU/dL for 3 days after the procedure.[45,77]

Osteoporosis

- Bone mineral density (BMD) has been shown to be lower in people with hemophilia. An increased number of arthropathic joints, loss of joint movement, and muscle atrophy leading to inactivity are associated with a lower BMD.[78,79]
- It is not clear whether patients with hemophilia require routine monitoring of bone mass; it may be advisable in patients with high risk or multiple risk factors.
- Weight-bearing activities and suitable sports that promote development and maintenance of good bone density should be encouraged for younger patients, if their joint health permits, to build bone mass and reduce the risk of later osteoporosis.
- Calcium and vitamin D supplements or bisphosphonates should be considered for patients with demonstrated osteopenia, and a

dental evaluation should be carried out before initiating long-term bisphosphonate therapy.[80,81]

Degenerative joint disease

- Joint damage progresses with increasing age in a near-linear fashion not only in patients with severe hemophilia but also in moderate cases.[44]
- Contributing factors include osteoporosis and osteopenia, a sedentary lifestyle, overweight, and obesity.[44]
- Due to the increased rate of joint morbidity, preventive strategies are necessary. While secondary prophylaxis reduces the incidence of bleeding, its efficacy in improving orthopedic function has not been clearly established.[45]
- See also Chapter 10: Musculoskeletal Complications.

Recommendation 9.8.21:

- **All patients with hemophilia should be encouraged to engage in regular physical activity and to have adequate calcium and vitamin D intake.**
- **Remark: Hemophilia patients with musculoskeletal conditions and injuries should have physical therapy and rehabilitation supervised by a physical therapist with hemophilia experience.** CB

Recommendation 9.8.22:

- **Hemophilia patients with osteoporosis, fragility fractures, or who are at increased fracture risk should be treated with individually adjusted anti-osteoporotic medications.** CB

9.9 | Medical issues with aging

- See also 9.8 Comorbidities, above, for discussion of cancer/malignancy, cerebrovascular accident/stroke, atrial fibrillation, venous thromboembolism/thrombosis, metabolic syndrome, diabetes mellitus, renal disease, and degenerative joint disease.
- It is important to provide older patients with regular education and counselling on the importance of informing the hemophilia team of their health issues to ensure appropriate treatment.
- Aging patients with hemophilia require the same access as patients without hemophilia to health education and preventive strategies to reduce the risk or impact of age-related morbidity.
- The hemophilia team should be closely involved in managing aspects and complications of care related to aging, and ensure close consultation and agreement on treatment plans.
- Patients with mild hemophilia may require specific education and attention to highlight potential issues associated with hemophilia and other illnesses.

Recommendation 9.9.1:

- **The WFH recommends that aging patients with hemophilia be granted the same access to health education and preventive strategies to reduce the risks or impacts of age-related morbidities as the general population.** CB

Recommendation 9.9.2:

- **The WFH recommends the hemophilia team should be closely involved in managing aspects and complications of care related to aging and ensure close consultation and agreement on treatment plans.** CB

Hypertension

- Studies have shown that people with hemophilia have higher mean blood pressure, are twice as likely to have hypertension, and use more antihypertensive medications compared to the general population.[82,83]
- Hypertension is associated with the usual risk factors, such as older age, diabetes mellitus, dyslipidemia, or higher BMI and obesity; however, the causes of the increased prevalence of hypertension in patients with hemophilia remain unclear.[84,85]
- Hypertension is a well-established risk factor for cardiovascular diseases, renal diseases, and intracranial hemorrhage, all of which may pose significant challenges in the management of care for patients with hemophilia.[84]
- In view of the increased risk of bleeding, hypertensive patients with hemophilia should receive appropriate treatment and have their blood pressure checked regularly.
- In the absence of other cardiovascular risk factors, a systolic blood pressure ≤130 mm Hg and a diastolic blood pressure ≤80 mm Hg should be maintained.

Recommendation 9.9.3:

- **For all patients with hemophilia, the WFH recommends regular blood pressure measurements as part of their standard care.**
- **Remark: This recommendation is based on data indicating a higher prevalence of arterial hypertension among patients with hemophilia irrespective of age as compared with males in the general population.** CB

Recommendation 9.9.4:

- **For patients with hemophilia, the WFH recommends the same management of arterial hypertension as that applied in the general population.**
- **Remark: Patients with hemophilia diagnosed with hypertension may be treated in a hemophilia treatment centre or referred to primary care providers depending on the local healthcare system and practices.** CB

Coronary artery disease

- There is evidence that people with hemophilia develop atherosclerosis at similar rates to those in the general population.[86,87]

- By contrast, patients with hemophilia have lower cardiovascular mortality rates compared with the general population (most likely because of lower thrombin generation at the point of plaque rupture).[87,88]
- It is not known whether the increasing use of prophylaxis in aging patients with hemophilia will result in an increase in cardiovascular mortality.[89]
- Individuals with severe, moderate, and mild hemophilia may develop overt ischemic heart disease. The management of such cases should be individualized and requires close cooperation between the hemophilia and cardiology teams.
- Making a decision on antithrombotic therapy in a patient with innate bleeding tendency is particularly difficult; a recent study found that antiplatelet and anticoagulant medications increased severe bleeding in patients with hemophilia (odds ratio [OR] = 3.5).[90]
- When considering antithrombotic therapy in patients with hemophilia, the following aspects should be evaluated[54]:
  - patient bleeding phenotype;
  - intensity of the antithrombotic therapy;
  - duration of the planned therapy; and
  - characteristics of the antithrombotic agent.
- Healthcare providers working with patients with hemophilia should educate them on cardiovascular risk and encourage risk reduction (smoking, obesity, exercise) or optimization (hypertension, hyperlipidemia).[89]

Recommendation 9.9.5:

- **Patients with hemophilia should receive the same screening and management for individual cardiovascular disease risk factors as the general population. CB**

Recommendation 9.9.6:

- **Patients with hemophilia and cardiovascular disease should receive routine care adapted to their individual situation in consultation with a cardiologist. CB**

Recommendation 9.9.7:

- **For patients with hemophilia without inhibitors who have been diagnosed with cardiovascular disease, the WFH recommends similar management as that applied to the general population, except for the necessary additional correction of impaired hemostasis with clotting factor concentrates.**
- **Remark: Decisions on cardiovascular treatment strategy for patients with hemophilia should always be preceded by assessments of the individual's bleeding and thrombotic risks and cardiac disease severity and implemented under the advisement of a cardiologist. CB**

Recommendation 9.9.8:

- **Among patients with hemophilia and high-responding inhibitors, the WFH recommends limiting the use of antithrombotics to those patients in whom the risk of untreated thrombosis outweighs the risk of bleeding complications.**
- **Remark: This recommendation is based on the observation that hemostatic response to bypassing agents is often unpredictable.**
- **Remark: More research is needed to better understand the safety of antithrombotic therapy in patients treated with emicizumab. CB**

Recommendation 9.9.9:

- **Given the scarcity of published data on antiplatelet therapy in patients with hemophilia, the WFH recommends careful evaluation of an individual's bleeding and thrombotic risk.**
- **Remark: It has been suggested that the trough level of the deficient clotting factor be maintained at ≥15-30 IU/dL during dual antiplatelet therapy and at ≥1-5 IU/dL during single-agent antiplatelet therapy; however, treatment strategy should be tailored to the individual.**
- **Remark: The decision on use of antiplatelet therapy in a patient with hemophilia should always be made in consultation with a cardiologist. CB**

Recommendation 9.9.10:

- **Given the scarcity of published data on patients with hemophilia undergoing percutaneous coronary intervention, the WFH recommends careful evaluation of an individual's bleeding and thrombotic risk. CB**
- **Remark: It has been suggested that in patients with hemophilia without inhibitors who are undergoing PCI, the deficient clotting factor be maintained at the peak level of 80-100 IU/dL for as long as therapeutic doses of antithrombotics are used; however, treatment strategy should be tailored to the individual.**
- **Remark: The decision on use of antithrombotic therapy for this indication should always be made in consultation with a cardiologist. CB**

Recommendation 9.9.11:

- **Given the scarcity of published data on patients with hemophilia undergoing coronary artery bypass grafting, the WFH recommends careful evaluation of an individual's bleeding and thrombotic risk.**
- **Remark: It has been suggested that in patients with hemophilia without inhibitors who are undergoing CABG, similarly to other major surgical procedures, the deficient clotting factor be maintained at the peak level of 80-100 IU/dL before, during, and after CABG until sufficient wound healing has taken place; however, treatment strategy should be tailored to the individual.**
- **Remark: The decision on use of antithrombotic therapy for this indication should always be made in consultation with a cardiologist. CB**

Recommendation 9.9.12:

- **Given the scarcity of published data on patients with hemophilia and ST-elevation myocardial infarction in whom early percutaneous coronary intervention is not available, the WFH recommends careful evaluation of an individual's bleeding risk and cardiac disease severity.**

- **Remark: Use of fibrinolytic therapy may only be considered after complete correction of hemostasis with deficient clotting factor replacement.**
- **Remark: The decision on use of fibrinolytic therapy for this indication should always be made in consultation with a cardiologist. CB**

Recommendation 9.9.13:

- **When heart valve replacement is indicated in patients with hemophilia, a bioprosthetic valve should be the first choice to avoid the need for indefinite anticoagulation. CB**

Hypercholesterolemia

- Mean cholesterol levels in patients with hemophilia have been reported to be lower than in the general population.[91] Cholesterol levels (total cholesterol, HDL, and LDL fraction) should be measured in aging patients with hemophilia at risk of cardiovascular disease.
- Treatment is indicated if cholesterol levels are high. As a general rule, the total cholesterol/HDL ratio should not be higher than 8.

Recommendation 9.9.14:

- **In patients with hemophilia, the management of hypercholesterolemia should be the same as for the general population. CB**

Psychosocial issues with aging

- For aging patients with hemophilia, crippling, painful arthropathy can affect quality of life and may lead to loss of independence.[92]
- Aging patients may be confronted with unexpected emotional problems due to memories of negative experiences related to hemophilia (e.g., hospitalization) during their youth.[89]
- Adaptations at home or at work and an appropriate pain management regimen are indicated to improve quality of life and preserve independence.
- Active psychosocial support should be provided by a social worker, hemophilia nurse, physician, and/or psychologist.
- The patient's annual checkup at the hemophilia treatment centre is a good time to assess and address changing needs with age. Refer patients to appropriate services and resources as needed and as mutually agreed upon.

Recommendation 9.9.15:

- **As adults with hemophilia experience many personal and social changes with aging, the WFH recommends active psychosocial assessments and support for their changing needs. CB**

Quality of life assessment

- People with hemophilia may face a variety of psychosocial issues which may impact their well-being. Quality of life assessments can help to:
  - identify patient perceptions of their health status and needs;
  - gather evidence on clinical findings that can lead to improved quality of care;
  - serve as a rapid screening to identify individual patients or populations who might require more detailed assessment of their health and quality of life needs; and
  - identify individual and overall patient needs in terms of gaps in knowledge and/or education to facilitate better self-management.
- See also Chapter 11: Outcome Assessment.

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SUPPORTING INFORMATION

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

Chapter 10: Musculoskeletal Complications

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

10.1 | Introduction

- Hemophilia is characterized by acute bleeds, over 80% of which occur in specific joints (most commonly the ankle, knee, and elbow joints, and frequently the hip, shoulder, and wrist joints) and in particular muscles (iliopsoas and gastrocnemius).[1,2] Spontaneous bleeding may occur depending on the severity of the disease (see Chapter 2: Comprehensive Care of Hemophilia – Table 2-1), or breakthrough bleeding may occur depending on the prophylactic treatment approach.
- In children with severe hemophilia, the first joint and muscle bleeds typically occur when they begin to crawl and walk, usually between 1 and 2 years of age, but sometimes in later toddler years.[3]
- Recurrent joint bleeds cause progressive joint damage as a result of blood accumulation in the joint cavity and synovial inflammation. This leads to complications such as chronic synovitis and hemophilic arthropathy.[1,2] For discussion and recommendations on joint bleeds, see Chapter 7: Treatment of Specific Hemorrhages and Table 7-2.
- Inadequate treatment of intramuscular bleeds can lead to muscle contractures, especially in bi-articular muscles (e.g., calf and psoas muscles), often within the first decades of life.[1,2] Other more serious complications such as compartment syndrome and pseudotumours may also develop. (See "Clotting factor replacement therapy" and 10.5 Pseudotumours, below.)
- Prophylaxis to prevent bleeding episodes is considered the standard of care to the extent that resources permit.[4]
- Successful treatment to achieve complete functional recovery generally requires a combination of clotting factor concentrate (CFC) replacement therapy or other hemostatic coverage (e.g., bypassing agents for patients with inhibitors) and physical therapy.

Patient/caregiver education

- Patient education on musculoskeletal issues in hemophilia is critical and should encompass joint and muscle health, recognition and treatment of musculoskeletal bleeds, pain management, musculoskeletal complications, and the importance of physical therapy and rehabilitation. A multidisciplinary approach to addressing the bleed and its consequences is essential.[5] (See Chapter 2: Comprehensive Care of Hemophilia.)

10.2 | Synovitis

- Following acute hemarthrosis, the synovium becomes inflamed, hyperemic, and friable. This acute synovitis can take several weeks to resolve.[2,6,7]
- Failure to manage acute synovitis results in recurrent hemarthroses and subclinical bleeds[1,2]; the synovium becomes chronically inflamed and hypertrophic, and the joint becomes prone to further bleeding. A vicious cycle of bleeding, loss of joint motion, and inflammation can ensue which ultimately leads to irreversible cartilage[7,8] and bone damage and impaired joint function.[6]
- If this process exceeds 3 months, it is defined as chronic synovitis.
- Regular assessments are required until the joint and synovial condition are fully rehabilitated, and there is no evidence of residual

blood and/or associated synovitis.[9] Physical examination for joint changes (e.g., in joint circumference, muscle strength, joint effusion, joint angle, pain according to a visual analogue scale) should be conducted at all routine follow-ups. (See Chapter 11: Outcome Assessment.). However, in many cases, the synovium never returns to its original state.

- Given that clinical signs do not always adequately represent the actual situation, ultrasound evaluation is advised.[9,10] Magnetic resonance imaging (MRI), while currently the gold standard for imaging, is expensive technology, time-consuming, and is not feasible for very young children.[6]

Recommendation 10.2.1:

- **For people with hemophilia, the WFH recommends regular physical assessment of the synovial condition after every bleed, preferably using suitable imaging techniques such as ultrasound (when feasible) until the situation is controlled, as clinical assessment alone is inadequate to detect early synovitis. CB**

Treatment of chronic synovitis

- The goal of chronic synovitis treatment is to suppress synovial activation and reduce inflammation to preserve joint integrity and function.[11,12]
- Nonoperative options include prophylaxis for 6-8 weeks (for those not on regular prophylaxis), physical therapy, and selective COX-2 inhibitors to reduce inflammation.[13,14]

Recommendation 10.2.2:

- **For patients with hemophilia who have chronic synovitis and no access to regular prophylaxis, the WFH recommends nonsurgical treatment, including short-term prophylaxis for 6-8 weeks to control bleeding; physical therapy to improve muscle strength and joint function; and selective COX-2 inhibitors to reduce pain and inflammation.**
- **Remark: Physical therapy with individualized goals and exercises based on the patient's functional level should start slowly with increasing progression of weight-bearing activities.**
- **Remark: For patients with acute pain and recurrent bleeding, bracing may stabilize the affected joint and limit motion, but caution is advised as prolonged immobilization leads to muscle weakness, so isometric exercises even within bracing are advised.**
- **Remark: If unresponsive to nonsurgical interventions, treatment should be escalated to treat the synovitis directly, by the treatment intervention of the local expert. CB**

Recommendation 10.2.3:

- **For patients with hemophilia who have chronic synovitis (characterized only by minimal pain and loss of range of motion) the WFH recommends consultation with an experienced musculoskeletal specialist in a hemophilia treatment centre. CB**

Physical therapy for synovitis

- Physical therapy[15,16] under the direction of a hemophilia treatment centre is advised throughout the entire rehabilitation trajectory, with progressive exercises to build up to full weight bearing and complete functional recovery. This may include daily exercises to improve muscle strength and restore joint range of motion.[17]
- Functional training may commence based on practical goals for each individual.[18]
- Bracing may be appropriate to stabilize the affected joint and limit movement in order to prevent recurrent bleeding and synovial impingement during movement.[19] (See Chapter 7: Treatment of Specific Hemorrhages – Joint hemorrhage – Physical therapy and rehabilitation.)
- In chronic cases that no longer respond to nonoperative measures, synovectomy/synoviorthesis may be indicated.

Synovectomy/synoviorthesis

- Synovectomy should be considered if chronic synovitis persists with frequent recurrent bleeding not controlled by other means.
- The procedure can be performed in several ways: chemical or radioisotope intra-articular injection (synoviorthesis); arthroscopic synovectomy; or open surgical synovectomy.[20,21]
- Nonsurgical synovectomy should always be the first procedure of choice for all patients.
- Radiosynovectomy is indicated for synovitis (confirmed clinically or by point-of-care ultrasound) causing 2 or more bleeds in a particular joint over the last 6 months despite adequate treatment.[9]
- Radioisotope synovectomy using a pure beta emitter (phosphorus-32, yttrium-90, rhenium-186, or rhenium-188) is highly effective, has few side effects, and can be accomplished in a single outpatient procedure.[9,22-30]
- Choice and dose of radioisotope depend on the joint to be injected, the condition of its synovium, and available radioisotopes.
- Prophylaxis should be administered prior to radiosynovectomy; one dose of CFC is usually sufficient for a single injection of the radioisotope.
- Where possible, simultaneous administration of intra-articular steroids is recommended.[31]
- The joint should then be rested for at least 24-48 hours[31,32] in a splint or other immobilization device, after which rehabilitation can commence.
- Rehabilitation after radiosynovectomy is less intensive than after surgical synovectomy, but it is still required to help patients regain strength, proprioception, and functional use of the joint.[15] An individualized rehabilitation program for at least 3 weeks may be appropriate.[26] Intensive exercise and weight bearing should be avoided immediately following radiosynovectomy.[33]
- The aim of treatment is to reduce synovitis and the frequency of bleeds, thereby indirectly reducing pain. It has no effect on articular degeneration. With the improvement in pain and the reduction of bleeds, the patient may regain function through appropriate rehabilitation. Pain reduction typically occurs 1-3 weeks postinjection.[31,32]

- The minimum interval between repeated treatments in the same joint is 6 months.[31]
- If radioisotopes are not available, chemical synoviorthesis with either rifampicin or oxytetracycline chlorhydrate may be considered. Chemical synoviorthesis may be painful, and the sclerosant injection should be combined with an intra-articular local anesthetic to minimize pain, supplemented by oral analgesics (a combination of acetaminophen/paracetamol and an opioid) as required.[34-36]
- Frequent injections may be required; typically, 5-6 weekly injections are needed until the synovitis is controlled.[34-36]

Recommendation 10.2.4:

- **For patients with hemophilia who have unresolved chronic synovitis, the WFH recommends nonsurgical synovectomy as a first-line treatment option using radioisotope synovectomy with a pure beta emitter (phosphorus-32, yttrium-90, rhenium-186, or rhenium-188). One dose of CFC per dose of isotope should be used.**
- **Remark: Choice of isotope depends on the joint being injected and isotope availability.**
- **Remark: The joint should be immobilized for at least 24 hours, followed by progressive rehabilitation for restoration of strength and function.**
- **Remark: When radioisotopes are not available, chemical synoviorthesis with either rifampicin or oxytetracycline chlorhydrate (once weekly injection for 5-6 weeks) is an alternative, accompanied by one dose of CFC per treatment, a local anesthetic, and oral analgesics.** CB

- In cases where chronic synovitis is resistant to treatment with radiosynovectomy, selective embolization of the blood vessels that supply the synovium may be performed. This procedure is to be performed only in specialized medical imaging centres.[37]
- Surgical synovectomy may be considered when other less invasive procedures have failed or when an additional procedure is required that must be performed through arthroscopy[38] such as removal of a tibial anterior osteophyte of the ankle.
- Arthroscopic synovectomy is suggested over open synovectomy.[39]
- If surgical synovectomy (either open or arthroscopic) is necessary, ensure longer prophylaxis coverage with CFCs or other appropriate hemostatic agents sufficient for the procedure and postoperative rehabilitation. The procedure must be performed by an experienced team at a dedicated hemophilia treatment centre.

Recommendation 10.2.5:

- **For patients with hemophilia who have chronic synovitis that no longer responds to nonoperative interventions, the WFH recommends surgical synovectomy (preferably arthroscopic, not open) only by an experienced team in a hemophilia treatment centre.** CB

- See also Chapter 7: Treatment of Specific Hemorrhages – Table 7-2; Chapter 8: Inhibitors to Clotting Factor – Hemophilia A/Hemophilia B – Surgery and invasive procedures; and Chapter 9: Specific Management Issues – Surgery and invasive procedures.

10.3 | Hemophilic arthropathy

- Hemophilic arthropathy can result from a single bleed or recurrent bleeds. It generally evolves gradually from hemarthrosis to chronic synovitis and extended erosions of the articular surface, culminating in the final stage of joint destruction, chronic hemophilic arthropathy,[40] which often manifests during the second decade of life, particularly if prophylactic therapy is unavailable or inadequate.
- Muscle bleeds can result in joint deformity and contracture, particularly with bleeds within the psoas muscle or gastrocnemius. Fixed flexion contractures result in loss of motion and significant functional impairment and thus need to be prevented.
- As the arthropathy worsens, range of motion and swelling of the joint often subside due to progressive fibrosis of the synovium and capsule. As the joint becomes ankylosed (stiffened), pain may diminish or disappear.
- The appropriate radiographic technique for assessing chronic hemophilic arthropathy depends on the stage of progression.
- MRI is useful to assess early arthropathy and will show early soft tissue and osteochondral changes.[41-43]
- Ultrasound imaging is useful for assessing soft tissue and peripheral cartilage pathology in early hemophilic arthropathy.[44]
- Plain radiographs are insensitive to early change and are used to assess late arthropathic changes.[45,46]
- See Chapter 11: Outcome Assessment.

Treatment of chronic hemophilic arthropathy

- The goals of treatment are to reduce the incidence of hemarthroses, improve joint function, relieve pain, and help the patient continue or resume normal activities of daily living.
- Treatment options for chronic hemophilic arthropathy depend on many factors including:
  - the stage of the condition;
  - the patient's symptoms;
  - the patient's age;
  - the impacts on the patient's lifestyle and functional abilities;
  - the resources available.
- Pain should be controlled with appropriate analgesics.
- See Chapter 2: Comprehensive Care of Hemophilia – Pain management.

Physical therapy for hemophilic arthropathy

- Physical therapy aimed at preserving muscle strength and functional ability is an essential component of treatment of chronic hemophilic arthropathy.
- The intensity of physical therapy should be increased gradually and adapted according to prophylaxis coverage; physical therapy

should be less intense in patients with limited access to CFC replacement.

- In settings with limited resources and factor availability, physical therapy without factor coverage may be performed if the treatment is coordinated by an experienced multidisciplinary team with musculoskeletal expertise.[47]
- Intermittent prophylaxis coverage may be necessary if breakthrough bleeding occurs as a result of physical therapy.[16] Other modes of therapy such as exercise therapy, manual therapy, electrotherapy, and hydrotherapy have been used to complement physical therapy.[48]

Recommendation 10.3.1:

- **For the prevention and treatment of chronic hemophilic arthropathy in people with hemophilia, the WFH recommends a combination of regular replacement therapy to reduce frequency of bleeding and physical therapy aimed at preserving muscle strength and functional ability. Physical therapy may be done with or without factor coverage, depending on availability and the patient's response to therapy.** CB

- Other conservative management techniques include:
  - serial casting to correct deformities[49];
  - traction devices;
  - bracing and orthotics to support painful and unstable joints[19];
  - 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.[50]

Recommendation 10.3.2:

- **For the prevention and treatment of the sequelae of joint arthropathy in people with hemophilia, the WFH recommends nonsurgical measures such as bracing, orthotics, mobility aids, and serial casting and traction devices to aid in the correction of flexion contractures. This may be done with or without factor coverage.** CB

Surgical interventions

- If nonsurgical measures fail to provide satisfactory pain relief and improved function, surgical intervention may be necessary.
- Surgical procedures, depending on the specific condition, may include:
  - synovectomy and joint debridement, if required[38];
  - arthroscopy to release intra-articular adhesions and correct impingement, especially in the ankle or elbow joint[51];
  - extra-articular soft tissue release to treat contractures[52];
  - osteotomy to correct angular deformity;
  - external fixators to assist in deformity correction[53];
  - prosthetic joint replacement (knee, hip, shoulder, elbow, or ankle)[54];
  - radial head excision for select patients with radiocapitellar arthropathy[55];
  - arthrodesis for painful ankle joint arthropathy.
- Adequate resources, including prophylaxis (e.g., sufficient supply of CFCs) and postoperative rehabilitation, must be available to support and increase the likelihood of success of any surgical procedure.[56-58]

Recommendation 10.3.3:

- **For patients with hemophilia with chronic hemophilic arthropathy for whom nonsurgical measures have failed to provide satisfactory pain relief and improved function, the WFH recommends consultation with an orthopedic specialist on surgical intervention options which may include:**
  - **synovectomy and joint debridement;**
  - **arthroscopy to release intra-articular adhesions and correct impingement;**
  - **extra-articular soft tissue release to treat contractures;**
  - **osteotomy to correct angular deformity;**
  - **arthrodesis (of the ankle);**
  - **joint replacement in end-stage arthritis.**
- **Remark: Adequate resources including a sufficient supply of CFCs or other appropriate hemostatic agents (e.g., bypassing agents for patients with inhibitors) and postoperative rehabilitation services must be available to increase the likelihood of success for any surgical procedure.** CB

- See also Chapter 7: Treatment of Specific Hemorrhages – Joint hemorrhage and Table 7-2; Chapter 8: Inhibitors to Clotting Factor – Hemophilia A/Hemophilia B – Surgery and invasive procedures; and Chapter 9: Specific Management Issues – Surgery and invasive procedures.

10.4 | Muscle hemorrhage

- Bleeds may occur in any muscle of the body, often as a result of injury or a sudden stretch.
- A muscle bleed is defined as an episode of bleeding into a muscle, determined clinically and/or by imaging studies. It is generally associated with pain and/or swelling and functional impairment, e.g., a limp associated with a calf bleed.[59]
- Early identification and proper management of muscle bleeds are important to prevent permanent contracture, re-bleeding, and possible later formation of pseudotumours.[60]
- Symptoms of a muscle bleed include:
  - discomfort in the muscle and maintenance of the limb in a position of comfort;
  - severe pain if the muscle is actively contracted or stretched;
  - tension and tenderness upon palpation; and
  - swelling.
- Sites of muscle bleeding that are associated with neurovascular compromise, such as the deep flexor muscle groups of the limbs,

require immediate management to prevent permanent damage and loss of function. These groups include:
  - the iliopsoas muscle (risk of femoral nerve palsy);
  - the superficial and deep posterior compartments of the lower leg (risk of posterior tibial and deep peroneal nerve injury); and
  - the flexor group of forearm muscles (risk of Volkmann's ischemic contracture).
- Bleeding can also occur in more superficial muscles such as the biceps, hamstrings, quadriceps, and gluteal muscles.
- There is emerging evidence that suggests musculoskeletal ultrasound (MSKUS) may be useful in differentiating between muscle bleeds and other regional pain syndromes.[61,62] Nonetheless, if a patient or clinician suspects a muscle bleed or has difficulty assessing whether a bleed is in progress, hemostatic treatment is advised immediately before performing confirmatory investigations or awaiting such results.

Clotting factor replacement therapy

- An untreated muscle bleed can result in compartment syndrome (a deep muscle bleed within a closed space) with secondary neurovascular and tendon damage and muscle contracture and necrosis. In addition, an injured muscle that is not properly rehabilitated can exert secondary effects on the adjacent joints.[63]
- The best practice to achieve the best outcomes is to treat muscle bleeds with CFC immediately, ideally when the patient recognizes the first signs of discomfort or right after trauma, to raise the patient's factor level to stop the bleed. Factor replacement therapy should continue until bleeding symptoms and signs resolve, generally for 5-7 days or longer, if symptoms indicate recurrent bleeding or worsening neurovascular symptoms.[64-66] (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)
- Repeat infusions are often required, particularly if there is a potential risk of compartment syndrome and/or if extensive rehabilitation is required.[2,67]
- See Chapter 8: Inhibitors to Clotting Factor for the management of bleeds in patients with inhibitors.

Recommendation 10.4.1:

- **All hemophilia patients with muscle bleeds should be given clotting factor replacement therapy immediately and, where applicable, be observed for neurovascular complications associated with the bleed.** CB

Clinical monitoring and management

- It is important to monitor the patient continuously for possible compartment syndrome. Symptoms of possible compartment syndrome include increasing pain, loss of sensation, loss of function, and poor blood supply in the distal area. If in doubt, measure the compartment pressure.
- Pain should be assessed frequently and regularly, as it is an indirect measure of compartment pressure.
- Acute muscle bleeds may require escalating the analgesia protocol to obtain relief. (See Chapter 2: Comprehensive Care of Hemophilia – Pain management.)
- In addition to factor replacement therapy or other appropriate hemostatic therapy, clinicians may apply the following measures as adjunctive management of acute muscle bleeds:
  - Rest the injured muscle.
  - Where possible, elevate the affected area; this may help to reduce the associated swelling.[68]
  - If appropriate, splint the affected limb in a position of comfort and adjust to a position of function as pain subsides.
  - Apply ice/cold packs around the muscle for 15-20 minutes every 4-6 hours for pain relief. Do not apply the ice directly on the skin.
- See also "Physical therapy and rehabilitation for muscle bleeds" below.

Recommendation 10.4.2:

- **For all hemophilia patients with muscle bleeds, the WFH recommends detailed clinical assessment, grading, and monitoring of pain according to the WHO pain scale, as muscle bleed pain may be an early indicator of reversible neurovascular and tissue damage.**
- **Remark: While many pain assessment scales exist, use of the WHO pain scale is preferred because it is a simple and universal tool that permits uniform measurement of pain in people with hemophilia and generates comparable population-level outcome data important to advancing hemophilia treatment and research.**

Compartment syndrome

- Neurovascular compromise is a musculoskeletal emergency and requires direct, continuous observation and monitoring of the need for fasciotomy. Prophylaxis should be administered to raise and maintain factor levels for 5-7 days or longer as symptoms indicate, along with physical therapy and rehabilitation to restore baseline muscle function.[69-71] (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)
- If compartment syndrome is suspected on clinical grounds, measure the compartment pressure. If confirmed, fasciotomy should be performed within 12 hours of onset of the compartment syndrome.[72-74] Late fasciotomy has a very high incidence of complications and is contraindicated.[75]
- Earlier fasciotomy is associated with improved patient outcomes, including decreased muscle and nerve injury. Once a motor nerve deficit has occurred, patients rarely recover fully after fasciotomy.
- In patients with hemophilia, if there is uncertainty regarding the adequacy of hemostatic response, as may occur in patients with high-responding inhibitors, a longer observation period may be warranted to possibly avoid fasciotomy and the risk of

uncontrolled bleeding after the procedure. However, any delay in performing fasciotomy once compartment syndrome is established may lead to suboptimal outcomes in muscle recovery and subsequent loss of function.[76]

Recommendation 10.4.3:

- **In hemophilia patients with muscle bleeds with evidence of compartment syndrome and neurovascular compromise, a fasciotomy is required within 12 hours from the time of onset of symptoms before irreversible damage sets in due to tissue necrosis.** CB

Physical therapy and rehabilitation for muscle bleeds

- Physical therapy should begin as soon as pain subsides and should be progressed gradually to restore full muscle length, strength, and function.[15,73] Supervised physical therapy and rehabilitation directed by a physical therapist experienced in hemophilia management should be initiated:
  - Ensure appropriate prophylaxis coverage during physical therapy and rehabilitation. In settings with limited resources and factor availability, physical therapy without factor coverage may be performed during the rehabilitation period if the treatment is coordinated by an experienced multidisciplinary team with musculoskeletal expertise.[47]
  - Use serial casting or splinting as required to correct any contracture.
  - Use supportive bracing if there has been nerve damage.
  - Regularly evaluate the patient for pain during physical therapy, which may suggest re-bleeding.[77]

Iliopsoas hemorrhage

- Iliopsoas hemorrhages can potentially lead to musculoskeletal damage; therefore, early and effective factor replacement therapy or other appropriate hemostatic therapies are essential to minimize and prevent the related complications.[65]
- An iliopsoas hemorrhage has a particular presentation that can sometimes be misleading.[68] Signs may include pain in the lower abdomen, groin, and/or lower back, with inability to straighten or stand up from a seated position; and pain on extension, but not on rotation, of the hip joint.[64] The symptoms of iliopsoas hemorrhage may mimic those of acute appendicitis, including a positive Blumberg's sign (rebound tenderness).[9] It can also be mistaken for a hip joint bleed.
- There may be paresthesia in the medial aspect of the thigh or other signs of femoral nerve compression, such as loss of the patellar tendon reflex, quadriceps weakness, and ultimately muscle wasting.[9]
- Patients with an iliopsoas bleed may need to be hospitalized for observation and pain control.
- Strict bed rest may be indicated. Ambulation with crutches should be avoided as muscle contractions may exacerbate pain and bleeding.[64-66]
- It is useful to confirm the diagnosis and monitor patient recovery using imaging studies (ultrasound, CT scan,[59] or MRI[78]).[64-66]
- Physical activity should be restricted until pain resolves and hip extension improves. A carefully supervised program of physical therapy is essential to restore complete hip extension and full activity and function, and prevent re-bleeding.[64-66]
- If residual neuromuscular deficits persist, further orthotic support may be necessary, particularly to prevent flexion of the knee due to quadriceps weakness.
- See also Chapter 7: Treatment of Specific Hemorrhages – Table 7-2, and Chapter 8: Inhibitors to Clotting Factor.

10.5 | Pseudotumours

- A pseudotumour is a potentially limb- and life-threatening condition unique to hemophilia.
- It develops as a result of inadequately treated soft tissue bleeds, usually in muscle adjacent to bone, which can be secondarily involved.
- If untreated, a pseudotumour can become massive, causing pressure on the adjacent neurovascular structures and possibly resulting in pathologic fractures.
- A fistula can develop through the overlying skin.
- Pseudotumours may be assessed and serially followed up using ultrasound imaging.
- A more detailed and accurate evaluation of a pseudotumour can be obtained with a CT scan and MRI.

Recommendation 10.5.1:

- **For hemophilia patients with soft tissue bleeding and signs of a possible pseudotumour, the WFH recommends clinical assessment and radiological confirmation using X-ray, ultrasound, and magnetic resonance imaging, as appropriate.**
- **Remark: While ultrasound is useful for serial assessment of a soft tissue pseudotumour, MRI provides more detailed information prior to surgical intervention.**
- **Remark: A CT scan or CT angiogram may be indicated, especially for a large pseudotumour and/or pre-operative planning.** CB

- Management of a pseudotumour depends on its site, size, growth rate, and effect on adjoining structures. Options include factor replacement therapy and monitoring, aspiration, radiation, surgical excision, and surgical ablation.
- For small early pseudotumours, a short course (6-8 weeks) of factor replacement therapy can be attempted, and the pseudotumour can be monitored using serial ultrasound screening. If the pseudotumour is shown to be shrinking, continue factor replacement therapy in combination with repeat ultrasound

evaluation for 4-6 months.[79,80] (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)

Recommendation 10.5.2:

- **For patients with hemophilia who have developed small early pseudotumours (prior to acquiring a pseudocapsule) and have no access to regular prophylaxis, the WFH recommends a short course (6-8 weeks) of clotting factor replacement therapy with possible continuation of therapy if serial ultrasound evaluations indicate that the pseudotumour is shrinking, with repeat evaluation after 4-6 months.** CB

- The management of pseudotumours is complex and associated with a high rate of potential complications. Therapeutic alternatives include embolization, radiation, percutaneous management, surgical removal, and filling of the dead cavity.[9]
- Aspiration of the pseudotumour followed by injections of fibrin sealant, arterial embolization, or radiotherapy may heal some smaller lesions.[81,82]
- Surgical excision may be necessary for large pseudotumours. Removal of the pseudotumour with the pseudocapsule—rather than evacuation of the hematoma—is required.
- Surgical resection of large abdominal/pelvic pseudotumours, which present a special challenge in the surgical management of hemophilia, must only be performed by a surgical team with experience in hemophilia. Preoperative embolization has been found to be useful in excision of these large tumours.

Recommendation 10.5.3:

- **For patients with hemophilia who have developed large pseudotumours, the WFH recommends surgical excision of the pseudotumour with the pseudocapsule, performed only by a surgical team with experience in hemophilia, in a hemophilia treatment centre wherever possible, followed by close monitoring and long-term prophylaxis to prevent recurrence of bleeding.**
- **Remark: Fluctuations in factor levels during the first postoperative year may increase the likelihood of bleed recurrence. Therefore, close monitoring and optimal correction of factor levels are of paramount importance.** CB

- See also Chapter 7: Treatment of Specific Hemorrhages – Table 7-2; Chapter 8: Inhibitors to Clotting Factor – Hemophilia A/Hemophilia B – Surgery and invasive procedures; and Chapter 9: Specific Management Issues – Surgery and invasive procedures.

10.6 | Fractures

- Fractures are not frequent in patients with hemophilia despite a high incidence of osteopenia and osteoporosis, possibly due to lower levels of ambulation and intensity of activities.[83]
- However, a patient with hemophilic arthropathy may be at risk for fractures around a joint with significant loss of motion and in bones that are osteoporotic.
- Treatment of a fracture requires immediate factor replacement therapy.[83-85] Ideally, patients should be on continuous prophylaxis (e.g., high doses of CFC) and factor levels of at least 50 IU/dL should be maintained for at least a week.[11,83-85] Subsequently, lower levels may be maintained for 10-14 days while the fracture becomes stabilized and to prevent soft tissue bleeding. (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)

Recommendation 10.6.1:

- **For people with hemophilia who incur fractures, the WFH recommends immediate treatment with clotting factor concentrates or other hemostatic agents, and continued treatment to maintain sufficiently high factor levels for bleed control for a week or longer, depending on the likelihood of bleeding due to fracture site or stability. Subsequently, lower factor levels may be maintained for 10-14 days to prevent soft tissue bleeding while the fracture becomes stabilized. Clinical monitoring is paramount due to the risk of compartment syndrome.** CB

- The management plan should be devised for the specific fracture and include appropriate prophylaxis coverage if surgical procedures are necessary.
- Avoid full circumferential plaster and split casts if possible, especially in the early stages; splints are preferred.[83] Monitoring, especially of forearm fractures, is mandatory in order to avoid complications such as compartment syndrome.
- Consider external fixators for open/infected fractures.[86]
- Avoid prolonged immobilization if possible as it can lead to significant limitation of range of motion in the adjacent joints.[83,84]
- Arrange for physical therapy as soon as the fracture is stabilized to restore range of motion, muscle strength, and function.[33]

Recommendation 10.6.2:

- **For people with hemophilia who incur fractures, the WFH recommends splints over full casts to avoid compartment syndrome (especially in the early stages), and external fixators for open or infected fractures.** CB

Recommendation 10.6.3:

- **For people with hemophilia who incur fractures, the WFH recommends avoiding prolonged immobilization and advises supervised physical therapy and rehabilitation as soon as the fracture is stabilized to restore range of motion, muscle strength, and function.** CB

- See also Chapter 7: Treatment of Specific Hemorrhages – Table 7-2; Chapter 8: Inhibitors to Clotting Factor – Hemophilia A/Hemophilia B – Surgery and invasive procedures; and Chapter 9: Specific Management Issues – Surgery and invasive procedures.

10.7 | Orthopedic surgery in hemophilia

- For patients with hemophilia undergoing orthopedic surgery, best results are achieved in dedicated hemophilia centres where skillful multidisciplinary teams are prepared to manage these patients using tailored approaches.[5,11]
- Multiple-site elective surgery with simultaneous or staggered procedures may simultaneously allow for a more expedient recovery of gait and overall function, as well as for judicious use of factor replacement therapy[87] or other hemostatic agents. (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)
- Use of local coagulation enhancers may be appropriate. Wound infiltration with local anesthetic agents (lignocaine/lidocaine and/or bupivacaine) with an adrenaline and fibrin sealant/spray is useful to control oozing when operating in extensive surgical fields.[56,88,89]
- Postoperative care in patients with hemophilia requires, in addition to factor replacement therapy (continuous infusion preferred) or other prophylaxis, close monitoring of pain, and often higher doses of analgesics in the immediate postoperative period.[56]
- Good communication with the postoperative rehabilitation team is essential.[33] Knowledge of the details of the surgery performed and intra-operative joint status will facilitate planning of an appropriate rehabilitation program.
- As part of comprehensive care, both pre- and postoperative physical therapy is needed to achieve optimal functional outcome.[33]

Recommendation 10.7.1:

- **For patients with hemophilia requiring orthopedic surgery, especially in cases where oozing is present at closure as well as dead space or cavities, the WFH suggests the use of local coagulation enhancers and wound infiltration with local anesthetic agents (lignocaine/lidocaine and/or bupivacaine) with an adrenaline and fibrin sealant or spray to control blood oozing when operating in extensive surgical fields.** CB

Recommendation 10.7.2

- **For patients with hemophilia requiring orthopedic surgery, the WFH recommends factor replacement therapy and close pain control and monitoring, with higher doses of analgesics in the immediate postoperative period.** CB

Recommendation 10.7.3:

- **For patients with hemophilia in the postoperative period following orthopedic surgery, the WFH recommends gradual rehabilitation by a physical therapist experienced in hemophilia management.** CB

- See also Chapter 7: Treatment of Specific Hemorrhages – Table 7-2; Chapter 8: Inhibitors to Clotting Factor – Hemophilia A/Hemophilia B – Surgery and invasive procedures; and Chapter 9: Specific Management Issues – Surgery and invasive procedures.

10.8 | Joint replacement

- Joint replacement is indicated in cases of established hemophilic arthropathy with associated pain and functional impairment not responsive to nonsurgical or other surgical treatments.
- Joint replacement should be performed only in recognized hemophilia treatment centres with experienced orthopedic surgeons and appropriate hematological and laboratory support.
- Such centres will have a multidisciplinary team including a nurse, social worker, and physical therapist familiar with the requirements of hemophilia patients undergoing arthroplasty.[90]

Hemostasis during the perioperative period

- Meticulous hemostasis is critical for the success of the surgical procedure. The specific plasma factor levels needed during different phases of surgery are described in Chapter 7: Treatment of Specific Hemorrhages – Table 7-2. Some centres use continuous infusion of factor replacement therapy, particularly during the first 72 hours, which more consistently maintains a protective factor trough level.[91]
- The use of perioperative antifibrinolytics and fibrin sealants has been shown to reduce blood loss. However, there is no consensus on the duration of postoperative treatment.[92]
- There is usually no need for deep vein thrombosis prophylaxis in those undergoing arthroplasty under factor coverage unless very high plasma levels are maintained during the postoperative period.[93] (For venous thromboembolism and thromboprophylaxis considerations for surgery, see Chapter 9: Specific Management Issues – Surgery and invasive procedures.)

Surgical considerations

- In the knee, there is often an anteroposterior/medio-lateral mismatch, which should be anticipated. Occasionally, a custom implant may be required. Significant angular deformity, patellar subluxation, and posterior subluxation of the tibia are often encountered, all of which may require extensive soft tissue release.
- Bilateral simultaneous knee replacement has been recommended in some instances, and consideration should be given to undertaking additional procedures if indicated.[87]
- The principles of knee replacement are the same as in the general population. Most often, posterior-stabilized implants or implants with stems and augments for associated bony defects are used.
- Antibiotic-loaded cement should be used in all cases where cement fixation is performed.
- Wound closure should be meticulous.
- There is no consensus on the use of drains.
- There is no consensus on the best type of fixation for hip replacement.[94]

Postoperative physical therapy

- Physical therapy should be started as soon as possible, ideally on the day of the surgery. Therapy sessions need to focus on regaining body functions such as range of motion and muscle strength before increasing functional training and endurance.
- To prevent the formation of joint adhesions, early mobilization and dedicated work on regaining motion are critical.[95] During this phase, attention to delayed wound and tissue healing and risks for re-bleeds is also required. Functional rehabilitation should be the goal, but only when all possible body functions are restored.
- Physical therapists at the hemophilia treatment centre are generally the best resource for devising a safe and comprehensive outpatient program. Alternatively, the hemophilia physical therapist can contact a physical therapist in the patient's community to arrange for postoperative care.[57]

Recommendation 10.8.1:

- **For patients with hemophilia, the WFH recommends joint replacement only in cases of established hemophilic arthropathy that is not responsive to nonsurgical or other surgical treatments, and that is accompanied by associated pain, functional impairment, and loss of participation in activities of daily living.**
- **Remark: Perioperatively, tranexamic acid and fibrin sealants may be used to reduce blood loss.**
- **Remark: Physical therapy should ideally start on the day of surgery with early mobilization and appropriately progressive exercises to regain motion and muscle strength.** CB

Complications and long-term considerations

- Patients with hemophilia tend to have less favourable knee functional scores and more postoperative complications following knee replacement, compared to the general population. This is mainly due to complicating factors and multijoint involvement.[96-98]
- Knee surgery should not be delayed for too long, as preoperative flexion deformity has a significant effect on postoperative outcome. Knees with flexion deformity of more than 25 degrees have a higher risk of a poor outcome and of developing postoperative flexion deformities.[99]
- Historically, infection rates following arthroplasty in hemophilia patients were higher than those seen in the general population. However, these infection rates have decreased over the past decade. Today, they are reported to be almost the same as in the general population.[54]
- Patients with hemophilia are at a higher risk of contracting a delayed secondary infection.[100]
- Patients with HIV or HCV infection may have a higher risk for prosthetic joint infection.
- The long-term survival of joint replacement implants may be the same as in the general population, depending on the level of expertise of the hemophilia care team, the type of implant used, and the severity of musculoskeletal disease of the joint.[54,101]
- See also Chapter 8: Inhibitors to Clotting Factor – Hemophilia A/Hemophilia B – Surgery and invasive procedures, and Chapter 9: Specific Management Issues – Surgery and invasive procedures.

10.9 | Psychosocial impacts of musculoskeletal complications

- Despite great strides in hemophilia care in recent years, people with hemophilia continue to face psychosocial challenges with hemophilia-related musculoskeletal complications. In particular, this affects those who grew up prior to prophylaxis and those who do not have access to prophylaxis.[102]
- A study of people with moderate and severe hemophilia found that those with more significant arthropathy experienced a lower quality of life, especially in the physical domain.[103]
- Psychosocial limitations from hemophilic arthropathy may be compounded by[104]:
  - gait changes;
  - multiple joints being affected;
  - chronic pain.
- The psychosocial impacts of these compounding factors may result in[104]:
  - lost time from school or work;
  - limitations in sports participation;
  - decreased socialization and/or increased isolation;
  - negative self-perceptions related to body image, masculinity, and/or self-esteem;
  - lack of a sense of normalcy;
  - limited physical flexibility with sexual positioning;
  - challenges in personal relationships;
  - role loss and/or role changes;
  - increase in fatigue;
  - negative coping behaviours.
- In people with hemophilia, disability from joint disease frequently occurs at an earlier age than in the general population and may impair their ability to perform reliably in the workplace. This may cause individuals to retire earlier than planned, result in unwanted role loss or shifts in all aspects of life, and negatively impact finances.[104]
- Psychosocial interventions should be tailored to meet the specific circumstances and needs of each individual, including their physical, emotional, social, educational, and cultural needs.[105]
- Individual psychosocial intervention strategies may be aimed at helping individuals adapt to pain and functional impairment[105] and develop coping strategies such as:
  - identifying/recognizing stressors and strengths;
  - partializing concerns (i.e., setting goals and priorities and developing strategies to address issues one by one);
  - examining options;
  - seeking information;

- strengthening support systems;
- communicating effectively;
- reframing the situation;
- using distraction techniques;
- using coping self-statements.[106]

- Psychosocial intervention strengthens patient resilience by fostering self- and health efficacy, cognitive flexibility, hardiness, optimism, and self-advocacy.
- Peer mentoring and group learning opportunities help foster support, reduce isolation, enhance receptivity to information, and strengthen resilience.[107]

Recommendation 10.9.1:

- **For patients with hemophilia who have chronic musculoskeletal pain or functional limitations, the WFH recommends psychosocial interventions tailored to meet the specific needs of each individual based on their physical, emotional, social, educational, and cultural circumstances. CB**

Recommendation 10.9.2:

- **For patients with hemophilia who have chronic musculoskeletal pain or functional limitations, the WFH recommends specific individualized psychosocial assessments and intervention strategies aimed at achieving better quality of life, including psychosocial counselling, educational and employment counselling, and financial planning. CB**

Recommendation 10.9.3:

- **For patients with hemophilia who have chronic musculoskeletal pain or functional limitations, the WFH recommends the promotion of support networks, peer mentoring, and group educational opportunities to support their ability to cope with musculoskeletal complications, reduce social isolation, and strengthen resilience. CB**

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SUPPORTING INFORMATION

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

Chapter 11: Outcome Assessment

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

11.1 | Introduction

- In order to optimize treatment and make economically sound clinical decisions, objective evidence of both short- and long-term outcomes of treatment regimens is required.[1]
- Outcome refers to the condition of a patient that results from a disease or medical intervention. It is assessed by clinical evaluation including the use of generic and disease-specific health-related quality of life (HRQoL) assessment instruments, measures of patient-reported outcomes (PROs), and laboratory tests including imaging studies.[2-7] These instruments measure a variety of parameters including activities and participation, body structure and function, burden of disease, and subjective health status, as described later in this chapter.
- Both generic and hemophilia-specific assessment instruments make it possible to evaluate the nature of the physical impairments and functional limitations and their impacts on the lives of people with hemophilia and their families.[1]
- The increasing use of these instruments will standardize assessment and permit comparison of data between individuals and cohorts.[8-10]

Purposes of outcome assessment

- Outcome assessment may be used to follow an individual's disease course, obtain information to guide routine clinical care, measure response to therapy, and determine whether there is a need to modify therapy. Outcome assessment may also be used to quantify the health of a group of patients, measure quality of care, and advocate for resources.
- In addition, outcome assessment may be used for research purposes such as to document the natural history of the disease, test new therapies, or compare different therapies.
- Health outcome research may be used to inform decisions regarding expenditures on treatment.

11.2 | Outcome assessment in hemophilia

- Outcome assessment in hemophilia should cover two aspects: disease-related and therapy-related outcomes.
- Disease-related outcomes pertain to the effectiveness of hemostatic therapy and are reflected in outcomes such as:
  - frequency of bleeding; and
  - impact of bleeding on the musculoskeletal system and other systems in the short and long term, including the psychosocial impact of hemophilia.
- Therapy-related outcomes need to be monitored using a prospective and systematic plan and should include screening and testing of people with hemophilia treated with clotting factor concentrates (CFCs) for inhibitor development. (See Chapter 8: Inhibitors to Clotting Factor.)
- Other less common complications of CFC replacement therapy include thrombosis and allergic/anaphylactic reactions. (See Chapter 9: Specific Management Issues.)

Frequency of bleeding

- Frequency of bleeding (particularly joint and muscle bleeds) and response to treatment have been the most important indicators

of the effectiveness of hemostatic therapy and the best surrogate predictors of long-term musculoskeletal outcomes.

- All bleeds must be documented by patients/caregivers in real time as they occur using manual or electronic diaries or other reporting systems, and analyzed periodically (at least once a year) by their hemophilia treater using a standard protocol. (See Chapter 2: Comprehensive Care of Hemophilia – Home therapy – Self-management.)
- In particular, bleeding into the central nervous system (CNS) requires documentation because of its potential impact on neurological and musculoskeletal functions.
- Given the potential difficulties in clinical determination of joint and muscle bleeding and to bring consistency into documenting this important parameter, criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis should be followed.[11]
- A joint bleed is defined as an unusual sensation "aura" in the joint, in combination with any of the following[11]:
  - increasing swelling or warmth of the skin over the joint;
  - increasing pain; or
  - progressive loss of range of motion or difficulty in using the limb as compared with baseline.
- A muscle bleed is defined as an episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and loss of movement over baseline.[11]
- In infants and young children, reluctance to use the limb alone may be indicative of a joint or muscle bleed.[11]
- Definitions for effectiveness of hemostatic therapy for joint and muscle bleeds have been developed and should be used when documenting treatment outcomes. (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-1.)

Recommendation 11.2.1:

- **For providers of care for people with hemophilia, the WFH recommends ensuring that the frequency of all bleeds is documented in real time by patients/caregivers and reviewed together at least annually, with particular reference to intra-articular, intramuscular, and central nervous system bleeds, including their recovery status. Standard criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis should be used. CB**

Pain assessment in hemophilia

- Pain in hemophilia can be either acute (as in an acute bleed) or chronic (as a result of arthropathy), or both may occur concurrently.
- Hemophilia-related pain can be assessed using single-dimensional numerical or visual rating scales[12] such as the Wong-Baker FACES Scale,[13,14] or multi-dimensional pain questionnaires like the generic McGill Pain Questionnaire[15] or the Brief Pain Inventory (BPI),[16,17] or disease-specific instruments like the Multidimensional Haemophilia Pain Questionnaire (MHPQ).
- Pain can also be scored through subscales within quality-of-life questionnaires—both generic[18] and disease-specific[19] questionnaires—and also within specific joint assessment instruments such as the Gilbert Score[20] and the Hemophilia Joint Health Score (HJHS).[21]
- Pain is best assessed and addressed in the context of a comprehensive care setting.[16]

Domains to assess the impact of bleeding on the musculoskeletal and other systems

- In conditions like hemophilia, it is recommended that outcomes be assessed according to the domains in the International Classification of Functioning, Disability and Health (ICF) model of the World Health Organization (WHO).[22,23]
- According to the ICF, evaluation of disability and health[4,24] should focus on the impact of the disease on body structures and functions, activities, and participation.
- These domains can be affected by individual contextual factors, which represent a person's circumstances and background, and include both environmental and personal factors.
- Environmental factors comprise the physical, social, and attitudinal environments in which an individual lives and conducts day-to-day activities.
- Personal factors include aspects that are not necessarily part of an individual's health condition or health status, such as age, sex, and indigenous status.
- See Figure 11-1 for an overview of the ICF model and outcome assessment instruments by domain.
- The concept of quality of life (QoL) is complex and encompasses many characteristics of an individual's social, cultural, economic, and physical environments as well as physical and mental health state.[4,22]
- Health-related quality of life (HRQoL) is a synonym for self-reported health state; HRQoL measurements generally include several aspects of the ICF model.[25] To be meaningful, this is best not used in isolation but in addition to assessment of body structure, function, and activities.
- While most outcome assessment instruments have been validated for older children, there is a paucity of validated disease-specific instruments to assess outcomes in very young children with severe hemophilia (i.e., younger than 4 years of age) during the period when they are typically started on long-term prophylaxis and the chances of inhibitor development are at their highest.
- The ability of the instruments to detect subtle changes following treatment interventions in children with good joint status and low bleeding frequency is limited and needs further attention.[26]

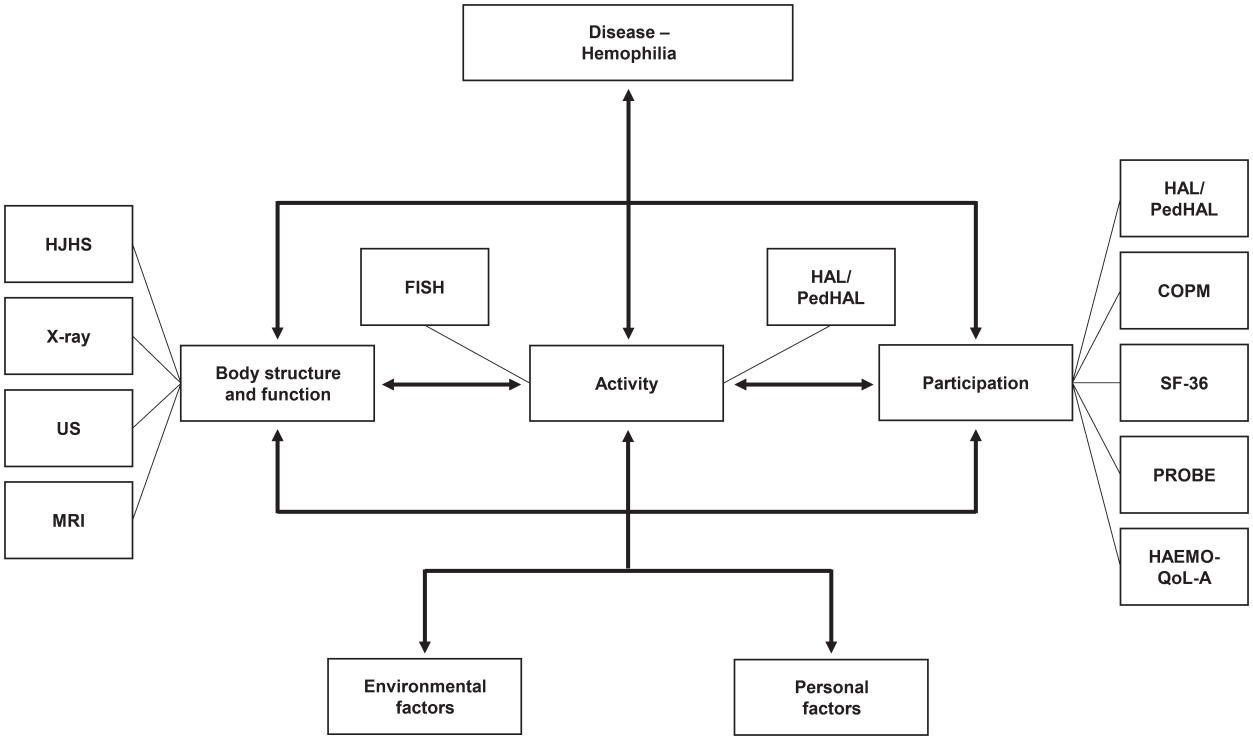

FIGURE 11-1 International Classification of Functioning and Health (ICF) model, with domain-related outcome assessment instruments. COPM, Canadian Occupational Performance Measure; FISH, Functional Independence Score in Hemophilia; HAEMO-QoL-A, hemophilia-specific quality-of-life questionnaire for adults; HAL, Haemophilia Activities List; HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; PaedHAL, Haemophilia Activities List for children; PROBE, Patient-Reported Outcomes, Burdens and Experiences; SF-36, 36-Item Short Form Survey Instrument; US, ultrasound

11.3 | Body structure and function

- Body structure refers to anatomical structures and bodily parts, such as organs, limbs, and their components.[22,24]
- Body function refers to the physiologic functions of these systems, such as range of motion, strength, and joint stability.
- In hemophilia, this refers to, for example, the status of joints and specific muscle groups, assessed both clinically and radiologically.

Recommended measures of body structure and function in hemophilia

- The Hemophilia Joint Health Score (HJHS) is the best studied of the physical examination instruments in both children and adults.[21,27,28] (See Figure 11-2.)
- The radiological Pettersson score[29] is the most widely used imaging measure of joint structure. This score is not sensitive to early changes; therefore, more sensitive instruments have been developed to assess arthropathy. (See Table 11-1.)
- Magnetic resonance imaging (MRI) is likely the most sensitive measure of joint structure. There are a number of scales that can be used to quantify arthropathy on MRI[30,31]; however, this modality is expensive, time consuming, and difficult to perform in small children. (See Table 11-2.)
- Ultrasound (US) scoring systems to assess hemophilic arthropathy are now available[32-35] and can detect joint effusion,[36] early joint disease,[37] and subclinical joint disease,[38] and promote medication adherence.[39] (See Table 11-3.)
- US scoring algorithms can be relatively subjective, but their reliability can be improved if the assessment is performed by a hemophilia provider trained in musculoskeletal US.[35]
- There is emerging evidence that suggests musculoskeletal ultrasound (MSKUS) may be useful in the clinical assessment and management of painful hemophilic arthropathy as it can differentiate between joint bleeds and joint inflammation and between muscle bleeds and other regional pain syndromes.[40,41] Nonetheless, in any circumstance, if a patient or clinician suspects an acute joint or muscle bleed or has difficulty assessing whether a bleed is in progress, hemostatic treatment is advised immediately before performing confirmatory investigations or awaiting such results.

11.4 | Activities and participation

- Activity refers to the execution of a task or action by an individual.[4] In the context of hemophilia, activity generally refers to instrumental activities of daily living (e.g., walking, climbing steps, brushing teeth, toileting).

Subject ID #:_____ **Name of Physiotherapist:**_____

Assessment #: _____ **Date:** _____
yyyy / mm / dd

Time: _____

Hemophilia Joint Health Score 2.1 - Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

Sum of Joint Totals + ☐

Global Gait Score ☐

(☐ NE included in Gait items)

HJHS Total Score = ☐

NE = Non-Evaluable

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = ≥ 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss

	Contralateral:	Normative Tables:
0	< 5°	within range
1	5° - 10°	1° - 4°
2	11° - 20°	5° - 10°
3	> 20°	> 10°

Extension loss (from hyperextension)

	Contralateral:	Normative tables:
0	< 5°	within range
1	5° - 10°	1° - 4°
2	11°- 20°	5° - 10°
3	> 20°	> 10°

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)
NE = Non-evaluable

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-evaluable

NOTE: There is an accompanying instruction manual and worksheets that are required when administering the HJHS

General Comments:

_____

_____

_____

_____

FIGURE 11-2 Hemophilia Joint Health Score 2.1 – Summary Score Sheet.[42] Available at: http://www1.wfh.org/docs/en/Publications/Assessment_Tools/HJHS_Summary_Score.pdf

TABLE 11-1 Radiological Pettersson score[29]

Radiologic change	Finding	Score[a] (points)
• Osteoporosis	Absent	0
	Present	1
• Enlargement of epiphysis	Absent	0
	Present	1
• Irregularity of subchondral surface	Absent	0
	Slight	1
	Pronounced	2
• Narrowing of joint space	Absent	0
	<50%	1
	>50%	2
• Subchondral cyst formation	Absent	0
	1 cyst	1
	>1 cyst	2
• Erosions at joint margin	Absent	0
	Present	1
• Incongruence between joint surfaces	Absent	0
	Slight	1
	Pronounced	2
• Deformity (angulation and/or displacement of articulating bones)	Absent	0
	Slight	1
	Pronounced	2

[a]Possible joint score: 0-13 points for each joint (total possible score, $6 \times 13 = 78$).

- Participation refers to involvement in life situations in the context of social interactions.
- It is often difficult to distinctly categorize items and outcome assessment instruments as belonging to only one of these two domains; therefore, the two domains are often combined in outcome assessment.
- In hemophilia, measurements of activities are defined as either self-reported or performance-based (i.e., observed).[22]

Recommended instruments for measuring activities and participation

- The Haemophilia Activities List (HAL)[15,44] is a disease-specific measurement instrument. It is the best-studied measure of self-reported activities for adults[45] and has been translated into many languages. The three subscores (upper extremity, basic lower extremity, and complex lower extremity) have been proven useful in the United States and the United Kingdom.[15,16,46] (See Table 11-4.)
- The Paediatric Haemophilia Activities List (PedHAL)[47] is derived from the HAL. It is a self-reported measure for children with hemophilia.[45] (See Table 11-5.)
- Both the HAL and PedHAL were developed by hemophilia treaters in the Netherlands; thus, they may not apply as well when used in other cultural settings.[48,49]
- The Functional Independence Score in Hemophilia (FISH)[48,50] is the best-studied observed performance measure for people with hemophilia,[45] with many reports of its use in different countries and age groups. (See Table 11-6.)
- The Patient-Reported Outcomes, Burdens and Experiences (PROBE) questionnaire also includes metrics that assess activities and participation, such as school/education, employment, family life, and impact on activities of daily living.[6,7] (See 11.8 Patient-reported outcomes, below.)
- The Canadian Occupational Performance Measure (COPM)[51] and the McMaster Toronto Patient Disability Questionnaire (MACTAR)[52] are generic instruments that have been used for day-to-day assessment of a person's perception of changes in the domains of activities and participation. They can be used for goal attainment scaling.

11.5 | Environmental and personal factors

Environmental factors

- While environmental factors are part of the ICF model, they are not often considered "outcomes" *per se* but can be the major intervention in the rehabilitation process.[4]
- Environmental factors that influence outcome include facilitators and barriers to treatment. These might include access to a comprehensive hemophilia care centre, availability of CFCs, medical understanding, medical insurance coverage,[53] and travel distance to a hemophilia treatment centre.[54]
- For children with hemophilia, family support and, if needed, additional psychosocial support and assessment provided by the hemophilia care team, may be an important facilitating factor.

Personal factors

- An individual's personal strengths and deficiencies may significantly influence treatment outcomes.
- Assessment of factors, such as the locus of control, and psychological characteristics, such as anger, depression, and optimism, can be used to guide and inform individual care or research.[55]
- Another important and measurable influence on treatment outcomes is patient/family treatment adherence.[56,57]

11.6 | Economic factors

- The costs and associated benefits of medical care can be quantified and used in research, program development, and advocacy.

TABLE 11-2 IPSG MRI Scale to Assess Hemophilic Arthropathy[43]

Soft tissue changes	Effusion/hemarthrosis	Small	(1)__
		Moderate	(2)__
		Large	(3)__
	Synovial hypertrophy	Small	(1)__
		Moderate	(2)__
		Large	(3)__
	Hemosiderin	Small	(1)__
		Moderate	(2)__
		Large	(3)__
Soft tissue changes subscore		Maximum 9 points	__
Osteochondral changes	Surface erosions involving subchondral cortex or joint margins	Any surface erosion	(1)__
		Half or more of the articular surface eroded in at least one bone	(1)__
	Subchondral cysts	At least one subchondral cyst	(1)__
		Subchondral cysts in at least two bones, or cystic changes involving a third or more of the articular surface in at least one bone	(1)__
	Cartilage degradation	Any loss of joint cartilage height	(1)__
		Loss of half or more of the total volume of joint cartilage in at least one bone	(1)__
		Full-thickness loss of joint cartilage in at least some area in at least one bone	(1)__
		Full-thickness loss of joint cartilage including at least one half of the joint surface in at least one bone	(1)__
Osteochondral changes subscore		Maximum 8 points	__

Abbreviations: IPSG, International Prophylaxis Study Group; MRI, magnetic resonance imaging.

Direct costs

- Direct costs include the cost of medical treatments, health services, and surgical and medical supplies.
- CFCs for patients with severe hemophilia usually account for more than 90% of treatment-related costs.[58]

Indirect costs

- Indirect costs arise from loss of work productivity of adult patients and of parents of pediatric patients due to the time they spend managing their child's hemophilia care.
- The costs that result from illness or seeking medical care are sometimes similar but often vary by country.[59]

11.7 | Health-related quality of life

- Health-related quality of life is a synonym for subjective (self- or family-reported) health status.[25]
- HRQoL measurements are usually questionnaires that aim to quantify a patient's health in a global way.
- Given their global nature, HRQoL measures are often more superficial in their scope than individual measures of the different domains listed above; therefore, they are best applied in combination with specific assessments of the ICF domains rather than in isolation.[60]
- An additional challenge in their use is that they must be validated in the language and social and cultural contexts of their application.

Instruments most used for measurement of health-related quality of life

- The EQ-5D[2,3] and SF-36[61,62] are widely used generic instruments for assessing QoL in hemophilia. (See Tables 11-7 and 11-8.)
- The PROBE questionnaire assesses QoL in addition to burden of disease in people with hemophilia.[6,63-65]
- For children with hemophilia, the Canadian Hemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT) has been extensively used.[4,66]
- For adults with hemophilia, the Hemophilia Well-Being Index[67] and the hemophilia-specific QoL questionnaire for adults (HAEMO-QoL-A) have been widely used.[4,5]

TABLE 11-3 HEAD-US Scoring Method[32]

Disease activity (synovitis)	Scale
Hypertrophic synovium	
0. Absent/minimal	0
1. Mild/moderate	1
2. Severe	2
Disease damage (articular surfaces)	
Cartilage	
0. Normal	0
1. Echotexture abnormalities, focal partial-/full-thickness loss of the articular cartilage involving <25% of the target surface[a]	1
2. Partial-/full-thickness loss of the articular cartilage involving ≤50% of the target surface[a]	2
3. Partial-/full-thickness loss of the articular cartilage involving >50% of the target surface[a]	3
4. Complete cartilage destruction or absent visualization of the articular cartilage on the target bony surface[a]	4
Bone	
1. Normal	0
2. Mild irregularities of the subchondral bone with/without initial osteophytes around the joint	1
3. Deranged subchondral bone with/without erosions and presence of prominent osteophytes around the joint	2

Abbreviations: HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound.

[a]Elbow, anterior aspect of the distal humeral epiphysis; knee, femoral trochlea; ankle, anterior aspect of the talar dome.

TABLE 11-4 Haemophilia Activities List (HAL) 2005[15]

	Items (n)
HAL overall	42
HAL domains	
Lying/sitting/kneeling/standing	8
Functions of the legs	9
Functions of the arms	4
Use of transportation	3
Self-care	5
Household tasks	6
Leisure activities and sports	7
HAL components	
Upper extremity (HAL_{upper})	9
Basic lower extremity (HAL_{lowbas})	6
Complex lower extremity (HAL_{lowcom})	9

Note: Available in multiple languages at: http://elearning.wfh.org/resource/hemophilia-activities-list-hal/

TABLE 11-5 Haemophilia Activities List—Pediatric (PedHAL) v.11[47]

	Items (n)
PedHAL overall	53
PedHAL domains	
Lying/sitting/kneeling/standing	10
Functions of the legs	11
Functions of the arms	6
Use of transportation	3
Self-care	9
Household tasks	3
Leisure activities and sports	11

Note: Available at: http://elearning.wfh.org/resource/haemophilia-activities-list-pediatric-pedhal/

TABLE 11-6 Functional Independence Score in Hemophilia (FISH)[48]

List of activities tested		
Self-care	**Transfers**	**Locomotion**
Eating	Chair transferring	Walking
Grooming	Squatting	Climbing stairs
Bathing		Running
Dressing		

Notes: Scores range from 1 to 4 for each activity depending on the degree of independence: 1, unable to perform; 2, requires the help of an assistant/aid; 3, able to perform the activity without an aid but not like a healthy subject; 4, able to perform the activity like other healthy subjects. Available at: http://elearning.wfh.org/resource/functional-independence-score-in-hemophilia-fish/.

TABLE 11-7 EQ-5D Instrument[68]

EQ-5D description system[a]	EQ-VAS
Mobility Self-care Usual activities Pain/discomfort Anxiety/depression	• Records the respondent's self-rated health on a vertical, visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state)

Abbreviations: EQ, EuroQoL; VAS, visual analogue scale.

[a]Three-item, five-item, and youth versions are available.

Recommendation 11.7.1:

- **The WFH recommends assessing and documenting the musculoskeletal and overall health of each patient at least annually. This should include an assessment of body structure and function, activity levels, participation and health-related quality of life as per the World Health Organization's International Classification of**

Functioning, Disability and Health (WHO ICF), as much as possible, in the right clinical context.

- **Remark: Standard definitions and validated tools should be used as much as possible, including the following:**
  - **For body structure and function, clinical assessment of joints is (most) commonly done using the Hemophilia Joint Health Score (HJHS) in both children and adolescents.**
  - **Under the same domain, early structural changes in joints are best assessed using ultrasound (US) or magnetic resonance imaging (MRI). Late osteochondral changes may be assessed on plain radiographs.**
  - **Functional activity levels should be assessed using the most appropriate option available for that individual, including the Haemophilia Activities List (HAL), the Haemophilia Activities List for children (PedHAL), or the Functional Independence Score in Hemophilia (FISH).**
  - **HRQoL is an important aspect of outcome measurement that may be assessed using either generic or disease-specific tools, but only in combination with the other domains of the WHO ICF.** CB

11.8 | Patient-reported outcomes

- Patient-reported outcomes (PROs) provide a report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.[70]
- It encompasses both single-dimensional and multi-dimensional measures of symptoms, HRQoL, health status, adherence to treatment, satisfaction with treatment, and other measures.[71]
- PROs include generic instruments such as EQ-5D-5L, Brief Pain Inventory v2 (BPI), International Physical Activity Questionnaire (IPAQ), Short Form 36 Health Survey v2 (SF-36v2), Patient-Reported Outcomes Measurement Information System (PROMIS),[71,72] and disease-specific instruments such as the HAL,[73] HRQoL measures such as CHO-KLAT,[66] HAEMO-QoL-A,[5] and burden of disease questionnaires such as PROBE.[6]

TABLE 11-8 36-Item Short Form Survey Instrument (SF-36)[69]

	Items (n)
SF-36 overall	36
SF-36 domains	
• Physical functioning	10
• Role limitations due to physical health problems	4
• Role limitations due to personal or emotional problems	3
• Energy/fatigue	4
• Emotional well-being	5
• Social functioning	2
• Pain	2
• General health	5

- While data generated by a PRO instrument can provide evidence of a treatment benefit from the patient perspective, the choice of instrument should be tailored to the study design or clinical need for specific outcome assessment, rather than just psychometric properties of the instrument.[74]

11.9 | Core set of measures for use in the clinic or research setting

- In health care, the focus is increasingly shifting from the volume of services delivered to the value created for patients. In this context, value is defined as outcomes achieved relative to costs.[75]
- While many outcome assessment options have been described here, in practice, hemophilia treatment centres and clinicians may select the instruments most appropriate for their patients. Outcome assessment instruments may be classified as mandatory, recommended, and optional.[1]
- To extract the potential of value-based health care, standardized outcome measures must be encouraged.
- This will mean committing to measuring a minimum sufficient set of outcomes for every major medical condition, with well-defined methods for their collection, which will then need to be applied universally.
- The WFH World Bleeding Disorders Registry (WBDR) provides a platform for hemophilia treatment centres to collect uniform and standardized patient data and outcomes globally to guide clinical practice (http://www.wfh.org/en/our-work-research-data/world-bleeding-disorders-registry).[8,9]
- Defining a standardized core set of outcome measures for specific clinical settings within which hemophilia is managed worldwide is key to advancing the clinical care of people with hemophilia and conducting further studies on treatment options.[1] A selection of outcome assessment instruments can be accessed at the WFH Compendium of Assessment Tools webpage (http://elearning.wfh.org/resource/compendium-of-assessment-tools/).[10]

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SUPPORTING INFORMATION

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

Chapter 12: Methodology

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12.1 | Background

The World Federation of Hemophilia (WFH) developed the first edition of the Guidelines for the Management of Hemophilia in 2005.[1] These guidelines were updated in 2012[2] and have since seen global print and online distribution of more than one million (including downloads from the *Haemophilia* journal and WFH websites, WFH print distributions, and WFH and National Member Organization translations). For this third edition, the WFH decided to adopt a different method for development, incorporating evidence-based and Trustworthy Consensus-Based Statement (TCBS)[3] approaches in conformance with established international standards for clinical practice guidelines.[4,5]

In rare diseases such as hemophilia,[6] there are limitations in developing evidence-based guidelines due to gaps in the evidence base related to small sample sizes and the paucity of methodologically rigorous data stemming from randomized controlled trials. The wide range of hemophilia treatments and practices used globally also contributes to the disparate research foci in the current state of hemophilia science. Quantitative analyses of the data for several aspects of management (e.g., direct meta-analyses or network meta-analyses) are not feasible under these circumstances.

When the evidence is not sufficiently evolved to support quantitative analyses for evidence-based recommendations, it is important to provide physicians and other healthcare providers, people with hemophilia, and advocates with advice they can trust.[4,7] The TCBS approach[3] produces unbiased, scientifically valid, and trustworthy recommendations through a transparent process that incorporates both the available evidence, identified using a systematic approach to reduce biases, and expert clinical advice.

This chapter describes the methodology used to develop the third edition of the WFH Guidelines for the Management of Hemophilia.

12.2 | Methodology

The TCBS process produces evidence-informed recommendations supported by a comprehensive and systematic search for relevant scientific literature, which is first screened based on predetermined inclusion/exclusion criteria, then followed by data extraction of the available and relevant evidence. The Delphi technique is a widely used and well-accepted process for soliciting feedback and achieving consensus.[8] There are several variations,[9-12] but the modified Delphi approach for guideline recommendations allows consideration of the evidence base as well as expert opinion while suppressing the introduction of group interaction bias. The WFH adopted the TCBS approach, already in use by several medical professional societies,[13,14] as this type of guideline brings thoroughness and transparency to the guideline development process for the expert panel's evidence-informed and consensus-based recommendations.[7] As with fully evidence-based guidelines, the TCBS approach includes a rigorous review of both methods and content by internal and external stakeholders of all types. This approach is based on five important pillars:

- confidence in the panel composition and screening;
- systematic and comprehensive evidence searches;
- formal consensus achievement;
- transparency of data and methods throughout; and
- rigorous review process.

Composition of the panels: structure and review

The WFH appointed an overall content lead (AS) and an assistant content lead (GP), both highly experienced in the field of hemophilia, and a methodology consultant (SZL) with extensive experience in developing guidelines and expertise in the TCBS approach. A WFH Guidelines Process Task Force (GPTF) was established to provide objective oversight of the process. The GPTF was composed of members of the WFH Education Committee, including patients and a hematologist not involved in the development of the guidelines.

The content lead and the previous WFH Vice President, Medical, offered initial invitations to the expert and representative panel to meet the criteria described below. An important goal, not always achieved by guideline and research organizations,[15] was to ensure that no serious topic-related conflicts of interest existed for the leads and to minimize the percentage of the panel with relevant conflicts.

This third edition of the WFH guidelines comprises an extensive revision of the existing seven chapters of the 2012 edition, as well as several new chapters. Each chapter was assigned to a panel composed of 7-10 members, including a chapter lead, healthcare professionals with clinical expertise, and patients/caregivers, with the latter making up at least 25% of each chapter panel. A total of 50 panelists were assigned to the 11 content chapters, with some panelists serving on more than one panel. The WFH drew upon its international volunteers and wide stakeholder network to recruit experts from diverse healthcare disciplines (hematologists, orthopedic surgeons and other musculoskeletal specialists, physical and occupational therapists, laboratory scientists, nurses, dentists, and psychosocial professionals). The panel also included a broad representation of people living with hemophilia including those with related complications such as inhibitors, musculoskeletal complications, and diverse comorbidities, as well as parents of children living with these conditions. Panelists were recruited from diverse demographic, geographic, and socioeconomic contexts to ensure the global relevance of these guidelines.

Process for panel workflow and oversight

The content and chapter leads guided the panels through the chapter development process and provided content expertise. The responsibilities of the chapter leads, with help from other healthcare professionals on their panels, included developing a comprehensive set of important subtopics per chapter, advising the medical librarians on relevant search terms, drafting initial recommendations, and developing the manuscripts including citation of important research. The responsibilities of the chapter leads also included ensuring that the patient/caregiver panelists' perspectives were solicited and addressed. Even though the vast majority of recommendations address the care and management of patients, rather than treatments, content and chapter leads also ensured that no specific products or brand names were mentioned; with the exception of the Laboratory Diagnosis and Monitoring chapter, wherein the therapeutic products may not be recognized by their international nonproprietary names (INN) by the community and brand names were included for all products, without which medical errors could inadvertently be made. For the diagnostic reagents, the specific brand names for which published evidence of assay validation is available were included within each category of the reagents.

All panelists were involved throughout topic organization, evidence generation, consensus achievement of recommendations, and manuscript drafting and reviews. Meetings, communications, and trainings were conducted via videoconferences, emails, and electronic surveys. Recordings and slides of training sessions and calls were made available to all members afterward. All panelists were afforded the opportunity to review all of the chapters before finalization and external reviews.

The equal status of all panelists (whether healthcare professional or patient/caregiver), the importance of each individual's expertise, and the imperative for all panelists to work together to solicit and validate all perspectives were emphasized in the trainings. Under the direction of the GPTF, a patient partner facilitator was hired to contribute training on the value that this approach adds to guideline development and the practicalities of its application, and assist with the implementation of this philosophy. The patient partner facilitator supported the patient/caregiver panelists throughout the guideline development process with monthly calls and guidance and non-financial support as needed.

Funding

The sole source of funding for these guidelines was the World Federation of Hemophilia.

12.3 | Evidence generation

A team of qualified and experienced medical librarians, screeners, methodologists, and data extractors was assembled to update the evidence base. Separate systematic reviews of the published literature were conducted on 10 of the 11 content chapters. A review of the literature was deemed not relevant for one chapter, Principles of Care, which focuses on ideal goals and aspirations given the current understanding of hemophilia and available science and technologies. Additional searches were developed specifically to target dental procedures, planned and emergent surgical and invasive procedures, and the emerging area of genetic assessment, resulting in a total of 11 reviews conducted. Details of the search strategies, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the extracted evidence are provided in the online supplemental materials.

Study eligibility criteria

Population, interventions, comparisons, and outcomes

For all chapters, studies that included patients with hemophilia A or B were retained. Additional population criteria were established

for each chapter. There were no exclusions based on sex or age. Eligibility of included studies was not restricted by interventions, comparisons, or outcomes for any content area.

Search strategies and information sources

All search strategies were developed by a medical librarian in collaboration with content experts involved in each of the chapters and the overall content lead. All searches were restricted to English language and human-only studies. No exclusions based on geography or type of care setting were implemented. Searches were run in PubMed, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE, covering the period from January 1, 2000, to the date of the search between May and November 2019. The complete search strategies can be found in the online supplemental materials.

No crawling or searching of reference lists of identified systematic reviews was conducted. One exception was made for the new review on Outcome Assessment, for which the reference list of one generally well-respected landmark paper was crawled. Chapter leads and panelists were invited to propose any directly relevant literature that was not identified through formal searching to be reviewed for inclusion.

Setting and study designs

Due to the volume of literature identified, post hoc restrictions on included studies (e.g., by publication year and study design) were applied without knowledge of the literature identified. Most studies selected for extractions were limited to publication dates after January 1, 2010 (preceding the search date limit for the previous edition of the guidelines), with the exception of the new chapter on Outcome Assessment, for which the inclusion date extended back to January 1, 2005. Additional papers and qualitative reviews were referenced when relevant, but data extraction was not performed. Study designs retained were randomized controlled trials, quasi-randomized controlled trials, and prospective comparative studies. In some cases, retrospective studies were included at the request of individual chapter leads. Some included studies were later confirmed as retrospective during extraction. These were retained in the evidence tables and marked as retrospective in the study design column. Cross-sectional studies were included in the evidence base for the Laboratory Diagnosis and Monitoring chapter. Systematic reviews were included for reference only.

Study selection

For each of the 11 search strategies, screening criteria were developed based on pre-specified criteria as defined during the chapter's search development calls and in collaboration with the chapter leads. Identified references were screened for chapter-specific eligibility using the reference management software Distiller SR®.

A team of seven trained reviewers screened titles and abstracts. Pilot testing was conducted prior to screening of each chapter, with all reviewers screening the same 50 references, followed by discussions and modifications to the screening forms when required for clarification. The remainder of title and abstract screening was completed by single review for all chapters. Dual screenings were not performed. For 8 of the 11 chapters, a secondary round of title and abstract screening of those studies deemed potentially eligible was conducted for two reasons. First, as the screening team became more familiar with the literature identified by the searches and through further discussions with the chapter and content leads, additional screening criteria were applied for subsequent rounds of review. Screening decisions were made without the panelists' knowledge of the identified literature to avoid biasing the results. Second, a secondary title and abstract screening allowed the team to efficiently eliminate irrelevant references, providing time- and cost-saving measures. References not eliminated during title and abstract screening were reviewed for eligibility at full-text screening.

For further details related to the flow of references in PRISMA diagrams, please see the online supplemental materials.

Data extraction and development of evidence tables

Evidence tables were created for each chapter. Relevant outcomes were determined with the help of the chapter leads.

A senior methodologist (TS) provided oversight and organization of the evidence tables. A team of 15 methodologists and data analysts extracted the relevant data from all included studies. Dual extractions were not performed. The evidence tables and the underlying research articles for each chapter were shared with the entire chapter panel and used by the chapter leads and healthcare professionals to inform the recommendations. The evidence tables are available in the online supplemental materials.

Risk of bias in individual studies

No formal quantitative analyses were conducted, and no critical assessments were made of individual study quality. It should be noted that hemophilia is classified[6] as a rare disease which results in inherent limitations of primary research studies; thus, most assessments would have resulted in low or very low levels of evidence. Other than the study design limitations placed on the literature search and screenings, no additional exclusions were made based on methodological quality of the research studies.

By design, no recommendations were graded as the vast majority of the evidence base in the field, given the barriers to clinical research and data collection in rare diseases, is insufficient to support meta-analyses. Grading is based on two components, the quality of the evidence and the balance of benefits to harms and/or risks. The former is an assessment of the quality of the evidence supporting the recommendations specific to each outcome. When low-level evidence is partitioned by outcomes, the remaining data are not feasible to support quantitative analyses. Attempting to grade such recommendations can be misleading to the target audience of healthcare providers.[16] The second component is not explicit in the absence of the quality assessments, so we did not assign a level of strength to the recommendations. Therefore, in the interest of transparency,

the WFH guideline recommendations were not graded but were clearly marked "CB" for consensus-based.

12.4 | Formal consensus achievement through Delphi techniques

A priori rules and processes

Following the drafting of the recommendations by the assigned healthcare professionals, each set of recommendations went through the modified Delphi consensus process.

Several *a priori* decisions guiding the modified Delphi process were determined by the GPTF:

- Up to three rounds of Delphi surveys were permitted to achieve consensus.
- The minimum response rate for each survey round was set at 75% of eligible voting panelists.
- The threshold for achieving consensus was 80% of the respondents indicating agreement or strong agreement.
- Statements achieving consensus in the first or second round were not subjected to subsequent rounds.
- No minority reports were permitted.

Drafted recommendations that did not achieve consensus after three rounds do not appear as recommendations in the final guidelines. However, the underlying topics may be included in the relevant chapter text, often with a call for additional research in these areas to help resolve some of the controversies.

Delphi surveys

The modified Delphi surveys were conducted using SurveyMonkey, with all responses remaining anonymous except to the independent administrator (MG) who created and managed the process. All panelists received two trainings on the TCBS approach, written reminders of the Delphi process and rules, and instructions on the first page of the surveys.

The initial recommendations were drafted by the healthcare professionals, as assigned by the chapter leads. Recommendations were based on the evidence provided in the evidence tables and articles, as well as on the experience and expertise of the panelists. Panelists were trained in writing recommendations. The consultant and editors provided advice and edited the recommendations to make them specific and actionable.

Before the modified Delphi process began, the entire chapter panel, including the patients/caregivers, convened via teleconference to discuss the evidence as a group and receive instructions on the Delphi process. They were not permitted to discuss the drafted recommendations so as to avoid the occurrence or even perception of group interaction bias. Panelists were permitted to suggest topics for additional recommendations that did not appear in the list. When new topics were suggested, the assigned healthcare professionals for that chapter's section were tasked with drafting new recommendations to address the identified gaps.

Panelists were encouraged to respond completely to all recommendations in every round of the surveys. The healthcare professionals were advised to base their level of agreement or disagreement on the evidence and their experience treating patients with hemophilia. The patient/caregiver panelists were asked to make similar judgments based on the evidence and their experience as hemophilia patients/family caregivers in the healthcare system. These guidelines benefitted from the experiences of patient/caregiver panelists. However, some expressed hesitation about being asked to vote on recommendations for which they did not have any expertise or experience. Therefore, if the recommendation addressed an area in which the patient/caregiver panelists were not familiar, they could opt out of the denominator by voting neutral and adding the phrase "No experience in this area" in the comments field. This signaled that their neutral vote should not be added to the denominator when the votes were tallied. Across all chapters, 53 of 344 recommendations (15%) achieved consensus with at least one patient/caregiver panelist selecting this option. These choices were made selectively by individual patient/caregiver panelists on a recommendation-by-recommendation basis and did not impact the votes of others.

For recommendations that did not achieve consensus in the first or second round, the chapter leads drafted revisions based on the comments provided by the respondents. The revised recommendations were submitted for the next round of voting. The topics of any recommendations that did not achieve consensus by the end of the third round could be noted in the manuscripts along with calls for future research in the respective areas. After all Delphi rounds were completed, consensus was not achieved for 13 (<4%) of the recommendations. Research funding agencies are encouraged to prioritize these areas to address knowledge gaps.

Survey tallies with the degree of consensus for each recommendation are available upon request (research@wfh.org).

Diversions from the process

There were a few diversions from the described process requiring additional surveys after the third round. One recommendation in the muscle hemorrhage section of the Treatment of Specific Hemorrhages chapter was resubmitted for voting because new evidence (albeit low level) was brought forth that raised doubts about the timeframe specified in the recommendation. Due to inadvertent group discussion of this recommendation, this section with all three recommendations was then moved to the Musculoskeletal Complications chapter, which was composed of different panelists, to avoid the introduction of group interaction bias. The panelists were informed of the full set of evidence, provided with the relevant papers and extracted data, and voting on the updated recommendation took place. During reviews for consistency and gaps, three additional recommendations (one from the Treatment of Specific Hemorrhages chapter and two from the Inhibitors to Clotting Factor

chapter) required additional revisions or the addition of remarks. One recommendation was inadvertently excluded from the original surveys for the Prophylaxis in Hemophilia chapter. All were rectified through additional survey rounds.

12.5 | Finalization of the recommendations and manuscript development

At the conclusion of the final round of the modified Delphi surveys, the chapter leads finalized the manuscripts for their assigned chapters. All recommendations that achieved consensus were incorporated within the relevant section of the manuscript, bolded, and numbered accordingly. All remarks are considered integral to the recommendations themselves and therefore included as part of the recommendations. *The WFH advises that as recommendations are uploaded into digital platforms, incorporated into separate lists, or otherwise removed from this full guideline publication, the remarks should always be kept with the rest of the recommendation as a single unit.*

These guidelines have an intrinsic navigation system for the chapters, sections, recommendations, and supplemental materials. The numbering system uses the chapter number as the initial number, followed by the section numbers. Recommendations are numbered according to the chapter and section in which they appear. This will help readers locate the background information that builds the case for the recommendations themselves. For example, a recommendation numbered 4.2.3 represents the third recommendation in Chapter 4, section 2.

Review and finalization

Each chapter manuscript underwent extensive review. Final manuscripts were reviewed by the chapter lead and panelists; the content lead and co-lead; the GPTF; key members of the WFH senior management team; followed by an external team of highly experienced healthcare professionals with expertise in the care of people with hemophilia, and well-informed expert people with hemophilia from around the world, ensuring a global perspective. Finally, the entirety of the guidelines was submitted to several organizations for their review and consideration for endorsement. Comments at each stage of review were considered by the chapter leads, and modifications were made when relevant. No editing or changes to the recommendations or remarks were permitted. A final independent peer review was also done through the *Haemophilia* journal and the extensive comments were addressed.

12.6 | Methodology limitations

As is common in guideline development, methodological processes have to be pragmatically adjusted to accommodate challenges with the available evidence, organizational matters, and other constraints. Similarly, with these guidelines, compromises were required in order to provide the best guidance possible in a clinical area with limitations in the evidence base.

The panels were organized by invitation and without a declared review of conflicts of interest (although current disclosures accompany this publication). All panelists were invited to participate in the scope of the chapter searches, which was accepted as a proxy for *a priori* established PICO (Population/Intervention/Comparators/Outcomes paradigm) questions.

Search strategies were then developed by highly experienced medical librarians based on the scope discussions and early drafts, although they were not peer-reviewed. Since the last guidelines were published in 2012, the searches were restricted to the years 2010-2019 for the chapters which are revisions from the previous edition. However, since that edition did not include a formal systematic review, future searches may have to be extended further back in time.

Studies identified as retrospective by the screeners were excluded, except where specified above. For a rare disease, especially for the more subjective topics, a more comprehensive and reliable evidence base would have included these reviews.

Due to the high yield of references from the searches for the Prophylaxis in Hemophilia chapter, references were limited to studies with a minimum sample size of 40. Sample size is not a proxy for quality, but alternative options to limit the number of studies to meet the timeframe did not exist.

Both single screening, rather than dual screening with adjudication, and single data extractions, rather than dual extractions with adjudication, were necessary compromises.

There were no critical appraisals of the quality of the evidence or assessments of the feasibility of quantitative analyses as these had been ruled out in advance due to previous efforts to conduct systematic reviews in this rare disease.

Considerable support was provided to reduce the burden on the volunteer panelists in the literature searches, screenings, data extractions, and drafting of the manuscripts. Like all multi-chapter guidelines, the level of consistency of writing varied across chapters, but the medical editors strove to reduce duplication and ensure standardization. This helped to ensure a final consistent format in these important guidelines for all users.

12.7 | Future plans for updates

With this third edition, the WFH Guidelines for the Management of Hemophilia have advanced considerably and comply with current standards for guideline development using the TCBS approach.[3] As additional research is conducted in the field of hemophilia, as methods standardize, and knowledge grows, published data should become more homogeneous and quantifiable, permitting more evidence-based guideline updates by the WFH in many of the content areas. This will also increase the methodological rigor and allow the evolving science to guide future recommendations, especially in

areas where the research is growing, such as diagnostic methods, hemostatic agents, regular replacement strategies, and management of inhibitors apart from curative treatments. Additional efforts will follow the advancing work of several international initiatives to provide recommendations for digital platforms and repositories and to increase implementation, especially at the point of care.

12.8 | Conclusion

Even though this third edition of the WFH Guidelines for the Management of Hemophilia is primarily intended for use by healthcare professionals, it will also be useful for people living with hemophilia and healthcare agencies and advocates around the world. These are trustworthy, reliable, evidence-informed, and expert-driven recommendations that should inform and empower medical professionals, patients and their caregivers so that they can be better informed and active participants in shared decision-making guiding hemophilia treatment and management plans.

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SUPPORTING INFORMATION

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

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Alok Srivastava served as the **Content Lead** for the overall guidelines project. He made substantial contributions to the design and conception, organization of the panel, and methodology decisions, and was the primary author of the Introduction and the Principles of Care chapter.

Glenn F. Pierce served as the **Co-Content Lead** for the overall guidelines project, panelist on three chapters, and performed extensive reviews of all chapters at multiple times in the process. He also contributed to the methodology decisions. H. Marijke van den Berg, as initial **Co-Content Lead**, helped design the project and panel, in addition to serving as a panelist on three chapters.

Chapter Leads served as the primary authors of their assigned chapters and most were also panelists on other chapters. All panelists voted in the Delphi rounds.

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The following individuals served as consultants or staff and did not vote in any Delphis:

- Sandra Zelman Lewis contributed the first draft of the Methodology chapter and consulted on guideline development, TCBS process, and methods. She helped review chapters and provided overall guidance on development and publication steps.
- Donna Coffin provided overall management of the guideline development and was responsible for specific sections of the Methodology chapter.
- Lucy T. Henry oversaw the library work and contributed to drafting sections of the Methodology chapter.
- Sonia O'Hara served as lead reviewer, advised on search, screening, and review strategies, and contributed to the Methodology chapter.
- Thomas J. Schofield served as lead methodologist for data extractions, advised on several library activities, and contributed to the Methodology chapter.
- Maura Sostack served as lead librarian developing and conducting all searches, and contributed to the Methodology chapter.
- Debbie Hum, lead medical editor and co-author of the Principles of Care chapter, led the review, editing, formatting, and reference implementation by the editorial team for all manuscripts, and contributed to the Methodology chapter.
- Melanie M. Golob served as the project manager, controlling and organizing all aspects of the project, including serving as the

independent administrator of the Delphi process. She also assisted with reviewing the Methodology chapter and other chapters.
- Fiona Robinson was the first manager of this process, coordinating the panel, processes, and chapter development, and contributed to the methods selection and the Methodology chapter.
- Mark Brooker assisted with panel composition and management, as well as methods selection and chapter development.
- Vincent Dumez served as the Guidelines Process Task Force chair, managing all taskforce activities, decisions, and content reviews.

All authors and contributors were involved in final approval of the submitted version.

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Acronyms and Abbreviations

AAV	adeno-associated virus
ABR	annualized bleeding rate
AJBR	annualized joint bleeding rate
ACMG	American College of Medical Genetics and Genomics
AF	atrial fibrillation
aPCC	activated prothrombin complex concentrate
APTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
AVF	arteriovenous fistula
BDD	B-domain–deleted
BMD	bone mineral density
BMI	body mass index
BPI	Brief Pain Inventory
BT	bleeding time
BU	Bethesda unit
CABG	coronary artery bypass grafting
CDC	Centers for Disease Control (U.S.)
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CFC	clotting factor concentrate
CHAMP	CDC Hemophilia A Mutation Project
CHBMP	CDC Hemophilia B Mutation Project
CHO-KLAT	Canadian Hemophilia Outcomes-Kids Life Assessment Tool
CNS	central nervous system
CNV	copy number variation
COPM	Canadian Occupational Performance Measure
COX-2	cyclooxygenase-2
CSGE	conformation sensitive gel electrophoresis
CT	computed tomography
CV	coefficient of variation
CVAD	central venous access device
DDAVP	1-deamino-8-D-arginine vasopressin, also known as desmopressin
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulant
EACA	epsilon aminocaproic acid
EAHAD	European Association for Haemophilia and Allied Disorders
EHL	extended half-life
EMA	European Medicines Agency
EQ	EuroQoL
EQA	external quality assessment
EQAS	external quality assessment scheme
EQ-VAS	EuroQoL Visual Analogue Scale
EQ-5D	EuroQoL 5 Dimensions
FDA	Food and Drug Administration (U.S.)
FFP	fresh frozen plasma
FII, FIIa	factor II, activated factor II
FISH	Functional Independence Score in Hemophilia
FIX, FIXa	factor IX, activated factor IX
FIX:C	factor IX activity
FV	factor V
FVII, FVIIa	factor VII, activated FVII
FVIII	factor VIII
FVIII:C	factor VIII activity
FX, FXa	factor X, activated factor X
FXI	factor XI
FXIII	factor XIII
GenQA	Genomics Quality Assessment
GI	gastrointestinal
GMP	Good Manufacturing Practices
GPTF	Guidelines Process Task Force
HAL	Haemophilia Activities List
HAV	hepatitis A virus
HAEMO-QoL-A	Hemophilia-specific quality of life questionnaire for adults
HBsAg	surface antigen of the hepatitis B virus
HBV	hepatitis B virus
HCCC	Hemophilia comprehensive care centre
HCV	hepatitis C virus
HDL	high density lipoprotein
HEAD-US	Haemophilia Early Arthropathy Detection with Ultrasound
HGVS	Human Genome Variation Society
HIV	human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
HMWK	high-molecular-weight kininogen
HRQoL	health-related quality of life
HTC	hemophilia treatment centre
ICF	International Classification of Functioning, Disability and Health (WHO)
ICH	intracranial hemorrhage; intracerebral hemorrhage
ICU	intensive care unit
IDB	inferior alveolar dental block, inferior alveolar nerve block
IEQAS	International External Quality Assessment Scheme

IgG	immunoglobulin G (IgG1, IgG2, IgG3, IgG4)
Inv1	intron 1 inversion
IPAQ	International Physical Activity Questionnaire
IPSG	International Prophylaxis Study Group
IQC	internal quality control
ISTH	International Society on Thrombosis and Haemostasis
ITI	immune tolerance induction
IU	international unit
IUD	intrauterine device
IV	intravenous
LA	lupus anticoagulant
LDL	low density lipoprotein
MACTAR	McMaster Toronto Patient Disability Questionnaire
MLPA	multiplex ligation-dependent probe amplification
MMR	measles, mumps, rubella
MPS	massively parallel sequencing
MRI	magnetic resonance imaging
MSK	musculoskeletal
MSKUS	musculoskeletal ultrasound
NAT	nucleic acid testing
NGC	National Guideline Clearinghouse
NGS	next generation sequencing
NMO	national member organization
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PedHAL	Paediatric Haemophilia Activities List
PEG	polyethylene glycol
PGD	pre-implantation genetic assessment
PICO	Population/Intervention/Comparators/Outcomes
PK	pharmacokinetics
PND	prenatal diagnosis
PNP	pooled normal plasma
POLICE	protection, optimum loading, ice, compression, elevation
PPP	platelet-poor plasma
PRICE	protection, rest, ice, compression, elevation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	patient-reported outcome
PROBE	Patient-Reported Outcomes, Burdens and Experiences
PT	prothrombin time
PUPs	previously untreated patients
QA	quality assurance
QoL	quality of life
rFIX	recombinant factor IX
rFIXFc	recombinant FIX-Fc
rFVIIa	recombinant activated factor VII
rFVIII	recombinant factor VIII
rIX-RFP	recombinant FIX fusion protein
rFVIIIFc	recombinant FVIII–Fc
rVIII-SingleChain	single-chain recombinant FVIII
RICE	rest, compression, ice, elevation
RNA	ribonucleic acid
SF-36	36-Item Short Form Survey Instrument
SHL	standard half-life
siRNA-AT	small interfering RNA agent targeting antithrombin
SNV	single nucleotide variant
SSC	Scientific and Standardization Committee of the ISTH
STEMI	ST segment elevation myocardial infarction
STR	short tandem repeat
SV	structural variant
t½	half-life
TCBS	Trustworthy Consensus-Based Statement
TFPI	tissue factor pathway inhibitor
UK NEQAS	U.K. National External Quality Assessment Service
US	ultrasonography, ultrasound
VAS	visual analogue scale
vCJD	variant Creutzfeldt-Jakob disease
VKA	vitamin K antagonist
VTE	venous thromboembolism
VWD	von Willebrand disease
VWF	von Willebrand factor
WBDR	World Bleeding Disorders Registry
WFH	World Federation of Hemophilia
WGS	whole genome sequencing
WHO	World Health Organization
XCI	X chromosome inactivation

Symbols and Measurements

µg	microgram (mcg)
°C	Celsius degrees
>	greater than
<	less than
=	equal to
≥	greater than or equal to
≤	less than or equal to
±	plus or minus
×	multiplied by (times)
BU	Bethesda Unit

cm	centimetre
dL	decilitre
g	gram
IU	international unit
kDa	kilodalton
kg	kilogram
m	metres
mcg	microgram, also known as µg
mg	milligram
mL	millilitre

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