

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).

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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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INTRODUCTION

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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.