

Latin American consensus on hemophilia

Consenso latinoamericano de hemofilia

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Abstract

Hemophilia is an inherited bleeding disorder linked to the X chromosome, which is classified into type A and type B. This Latin American consensus addresses the gaps in the treatment and follow-up of patients with this disease in the region, aligning local needs with international recommendations. Nominal group and the modified Delphi Panel methodologies were used to reach consensus on 16 key recommendations, including the use of ultrasound for joint monitoring, access to specialized laboratories, patient registries, and the implementation of prophylactic and replacement therapies. Additionally, the importance of multidisciplinary teams, continuous training, and robust public policies is highlighted to improve the comprehensive care of patients with hemophilia in Latin America.

Keywords: Hemophilia. Consensus. Latin America. Ultrasound. Prophylaxis. Multidisciplinary team. Public policies. Patient registry.

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Resumen

La hemofilia es un trastorno hemorrágico hereditario ligado al cromosoma X, que se clasifica en tipo A y tipo B. Este consenso latinoamericano aborda las brechas en el tratamiento y el seguimiento de pacientes con esta enfermedad en la región, alineando las necesidades locales con las recomendaciones internacionales. Se utilizaron las metodologías de grupos nominales y Panel Delphi modificado para alcanzar consenso en 16 recomendaciones clave, que incluyen el uso del ultrasonido para el monitoreo articular, el acceso a laboratorios especializados, el registro de pacientes y la implementación de terapias profilácticas y de reemplazo. Además, se destaca la importancia de los equipos multidisciplinarios, la formación continua y las políticas públicas robustas para mejorar la atención integral de los pacientes con hemofilia en Latinoamérica.

Palabras clave: Hemofilia. Consenso. Latinoamérica. Ultrasonido. Profilaxis. Equipos multidisciplinarios. Políticas públicas. Registro de pacientes.

Introduction

Hemophilia is a severe bleeding disorder of genetic origin, characterized by a recessive inheritance pattern linked to the X chromosome. Among congenital coagulopathies, it is the second most frequent; it is estimated that up to 70% of hemophilia cases are genetic, while the remaining 30% are due to de novo mutations¹. Hemophilia is categorized into hemophilia A and B based on the deficient clotting factor, factor VIII or factor IX, respectively¹. Individuals with hemophilia experience spontaneous bleeding or prolonged traumatic bleeding episodes in any part of the body, with muscular and joint bleeding being the hallmark of the disease².

Throughout the years, the prevalence of hemophilia A has been estimated at 1 in 5,000 to 10,000 men, while hemophilia B affects 1 in 30,000 to 60,000 men³. The prevalence of hemophilia depends on life expectancy and access to treatment for affected individuals. Although, ideally, all hemophilia patients should be systematically registered and followed up in national health centers, this is not the case in more than 50% of countries^{4,5}. A key study in this regard was conducted by Soucie et al.⁶ in 1998, which identified a prevalence of 13.4 per 100,000 men for both types of hemophilia, with 10.5 for hemophilia A and 2.9 for hemophilia B.

In 2019, Iorio et al.⁷ demonstrated that the current and birth prevalence of hemophilia exceeds these figures, with an estimated prevalence of 17.1 per 100,000 men for hemophilia A and 3.8 per 100,000 men for hemophilia B. Considering the global population in 2019 was 7.5 billion (3.8 billion men), there would be approximately 1,125,000 men with hemophilia, of whom 418,000 would have the severe form of the disease. These estimates were based on data from hemophilia patients in 6 developed countries and the male populations of those nations.

The treatment of hemophilia primarily focuses on prophylaxis, aiming to prevent joint bleeding and thereby avoid or delay joint damage⁸.

In Latin America, significant gaps hinder timely and adequate access to treatment and follow-up regimens recommended by the World Federation of Hemophilia (WFH). These include the lack of multidisciplinary specialist teams, government-supported hemophilia treatment centers, and organized systems for continuing medical education. Additionally, timely and accurate diagnosis is often lacking, deficient, or delayed. Another major barrier is the high cost of recommended treatments, compounded by the lack of awareness among national health leaders, resulting in insufficient budgets and suboptimal care for hemophilia patients.

The goal of this consensus is to align the needs and realities of Latin America with international recommendations.

Method

This Latin American consensus of expert recommendations was developed in 2 different stages. Stage #1 involved in-person meetings using the nominal group technique to identify priority topics related to hemophilia in each country. These topics were organized into 3 broad groups, and participants joined the group of their interest. This process identified a total of 16 topics requiring consensus. Stage #2 was conducted virtually, where each group discussed and gathered scientific evidence to support the recommendations from the first stage. The work of all groups was integrated, resulting in 16 recommendations, which were shared with all participants for review.

Subsequently, a modified Delphi panel methodology was used to vote on the recommendations. A scale of 1 to 6 was used, where 1 indicated complete agreement, 2 agreement with minor reservations, 3 agreement with

major reservations, 4 disagreement with minor reservations, 5 disagreement with major reservations, and 6 complete disagreement. Consensus was defined as at least 75% agreement (combining scores of 1, 2, and 3).

In the first voting round, 22 participants responded, and all recommendations reached the agreed consensus. Of the 16 recommendations, 14 achieved 100% agreement, and the remaining 2 achieved 95%.

Laboratory and imaging, data, follow-up, access to clinical trials, and technology

Recommendation 1. Ultrasound is a useful tool and should be performed for all hemophilia patients to:

- Monitor joint health and detect subclinical bleeding.
- Manage bleeding events to ensure proper treatment.
- Perform procedures such as joint aspiration.

Agreement level: 85.71% completely agree, 4.76% agree with minor reservations, 4.76% agree with major reservations, 4.76% disagree with minor reservations.

Recommendation 2. We recommend training at least one member of the multidisciplinary team in ultrasound at each treatment center.

Agreement level: 95.45% completely agree, 4.55% agree with minor reservations.

Recommendation 3. All patients should have access to a treatment center with a laboratory capable of performing basic coagulation tests and diagnosing hemophilia A and B, including inhibitor and pharmacokinetic studies. Specific monitoring methods are recommended for extended half-life and non-replacement therapies.

Agreement level: 86.36% completely agree, 9.09% agree with minor reservations, 4.55% agree with major reservations.

Recommendation 4. Every country should have access to genetic testing to provide counseling to patients and their families.

Agreement level: 81.82% completely agree, 18.18% agree with minor reservations.

Recommendation 5. Every country should maintain an updated annual registry of carriers and individuals with hemophilia, including data such as hemophilia type, date of birth, sex, severity, inhibitors, treatment type, and deceased status. When possible, the number of bleeding episodes should also be included.

Agreement level: 90.91% completely agree, 9.09% agree with minor reservations.

Recommendation 6. Government authorities should facilitate the development of clinical studies on hemophilia, preferably through collaborative efforts.

Agreement level: 90.91% completely agree, 9.09% agree with minor reservations.

Recommendation 7. We recommend using technological tools to facilitate education, reporting, management, and follow-up of hemophilia patients. Treatment centers should promote their implementation.

Agreement level: 86.36% completely agree, 13.64% agree with minor reservations.

Discussion

The systematic use of ultrasound in hemophilia patients has been highly valuable. Its utility lies in two main objectives:

- Diagnosing acute bleeding events, whether joint or muscular (without delaying hemostatic therapy), and monitoring treatment effectiveness and duration⁹⁻¹¹.
- Early detection of joint damage through systematic use during consultations (point of care)¹²⁻¹⁵.

Compared to magnetic resonance imaging (MRI)¹⁶, the gold standard, ultrasound offers similar diagnostic capabilities with advantages such as lower cost, no need for sedation in children, rapid assessment, ability to evaluate multiple joints during a single consultation, portability, and the ability to be performed by non-radiologists, depending on national regulations^{12,14,15,17}. These benefits enable clinicians to intervene early in patient management, such as optimizing primary prophylaxis¹⁸.

The expert group believes that every hemophilia center should have, at least, 1 professional trained in point-of-care ultrasound.

Training, at least, 1 multidisciplinary team member in ultrasound is essential for diagnosing bleeding and joint health, ensuring appropriate clinical management in hemophilia¹⁹. This professional should undergo certified training programs, either in-person or virtual, to acquire imaging diagnostic skills, including for pediatric patients^{15,19-21}.

All individuals with hemophilia should have access to laboratory studies for diagnosis and monitoring, including inhibitor testing²².

Traditional 1-stage assays for measuring factor VIII and IX levels remain fundamental, though they have diagnostic limitations in certain cases and challenges in monitoring new therapies. Therefore, combining one-stage assays with chromogenic (or two-stage) assays is recommended for more accurate evaluation²³⁻²⁵.

A multidisciplinary approach, including pharmacokinetic studies, is important for monitoring therapeutic response and personalizing treatment²⁶.

For hemophilia A patients on non-replacement therapy, a chromogenic factor VIII assay containing bovine factor X is recommended^{24,15}.

Genetic evaluation of hemophilia is useful for predicting inhibitor risk, identifying female carriers, and offering prenatal diagnosis, including informed reproductive decision-making, in full compliance with national legislation^{22,27}.

Genetic diagnostic laboratories should follow strict protocols, including proper classification systems, accreditation, and quality control²². Genetic counseling, initiated with informed consent, is an essential component of comprehensive hemophilia care for affected individuals and their families^{22,27,28}.

Each country should maintain a registry of hemophilia patients and other congenital coagulopathies, including female carriers with factor VIII or IX levels < 50 IU/dL, who exhibit symptoms similar to mild hemophilia in men²². This registry serves as a lobbying tool for health authorities and insurers to improve therapies, treatment centers, and healthcare teams, ultimately enhancing patient access to comprehensive care²⁹.

Registries can be managed by a hematologist, nurse coordinator, or registry manager as part of the patient care team^{22,30}.

Registries can be web-based, in Microsoft Access, or Excel, with treatment centers having access to update information. Biannual updates are suggested³¹.

Research in hemophilia documents the natural history of the disease, tests new therapies, compares treatments, documents outcomes, and informs cost-related decisions²².

Given hemophilia's rarity, national and international collaboration in research should be encouraged²². This is supported by international guidelines promoting research as a core function of comprehensive care centers^{4,22,28,32,33}.

Accurate documentation of bleeding events and home treatment administration is crucial for evaluating treatment efficacy, as treating physicians can verify this information electronically during routine clinical follow-ups³⁴. Over the years, electronic documentation tools, such as portable devices, have been developed to address these issues, enabling closer patient monitoring, better care outcomes, faster resolution of therapy administration problems, and improved adherence^{35,36}.

Recent studies show that health applications collecting data via mobile or wearable devices for real-time interventions have greater potential to optimize hemophilia patient care³⁷.

Access to treatment, prophylaxis, and new therapies

Recommendation 8. All patients in each country diagnosed with hemophilia, with or without inhibitors, should have lifelong access to treatment, including:

- Replacement therapy: plasma-derived, standard half-life, and extended half-life recombinant concentrates.
- Mimetic agents.
- Hemostasis rebalancing agents.
- Bridging agents for patients with inhibitors.

Agreement level: 90.91% completely agree, 9.09% agree with minor reservations.

Recommendation 9. Prophylaxis with hemostatic agents (replacement and non-replacement) should be initiated early and remain the standard treatment throughout the lives of patients with severe hemophilia, with or without inhibitors, and those with moderate or mild hemophilia with a bleeding phenotype (patients with more bleeding than expected for their factor level).

Agreement level: 95.45% completely agree, 4.55% agree with minor reservations.

Recommendation 10. Since hemophilia is a chronic disease requiring high-cost treatment, it is important to include it in health budgets to ensure continuous and appropriate treatment for all diagnosed patients.

Agreement level: 100% completely agree.

Recommendation 11. The inclusion of new therapies in official drug lists should be timely, based on the best available scientific evidence and pharmacoeconomic justification.

Agreement level: 95.45% completely agree, 4.55% agree with minor reservations.

Recommendation 12. The use of clinical and imaging assessment tools is recommended to document, monitor disease progression, and evaluate physical health (joint health), functional capacity, activity levels, participation, and health-related quality of life in hemophilia patients.

Agreement level: 100% completely agree.

Discussion

The foundation of hemophilia treatment is to prevent bleeding through long-term prophylaxis (prophylactic

treatment) and to manage acute bleeding episodes (episodic treatment) by replacing or supplementing clotting factors^{8,22,28,38}. The available treatment options for hemophilia include^{22,28}:

- Clotting factor concentrates for replacement therapy, which can be plasma-derived or recombinant, with standard or extended half-life. These are highly safe and effective for treating and preventing bleeding; however, their efficacy decreases with the development of inhibitory antibodies, which is the main complication, increasing bleeding episodes and reducing the patient's quality of life.
- Bridging therapies (activated prothrombin complex concentrates and recombinant activated factor VII), used for preventing and treating bleeding in hemophilia A or B patients with inhibitors.
- Bispecific antibody mimetics (e.g., emicizumab), a subcutaneous prophylaxis option for hemophilia A patients with or without inhibitors, offering extended half-life and high efficacy in preventing bleeding episodes.

Treatment decision-making is a challenging and multifactorial process to identify the most suitable option for each patient. Important factors to consider include the product's efficacy, safety, quality, purity, and viral inactivation. Additionally, the patient's bleeding phenotype, joint status, and preferences must be evaluated to improve hemostasis, effectively prevent joint bleeding, avoid or delay hemophilic arthropathy, and reduce emergency visits, hospitalizations, surgeries, and school or work absenteeism²².

Scientific evidence demonstrates that prophylactic treatment in hemophilia patients should begin early to limit bleeding and reduce complications. It should be maintained throughout life to achieve the goals of prophylaxis, which are to maintain hemostasis and provide a healthy, active life that allows participation in physical and social activities²², which contributes to improving the results of joint health³⁹⁻⁴⁵. Moreover, home-based prophylactic treatment also improves therapeutic adherence and enhances patients' quality of life²².

As hemophilia is a rare, chronic, and high-cost disease, its treatment, particularly prophylaxis, helps prevent disease-related comorbidities and reduces long-term treatment costs.

Despite recent advances, unmet needs persist, and hemophilia patients continue to experience bleeding, functional and joint deterioration, and acute and chronic pain, even though evidence supports the cost-effectiveness of prophylactic treatments⁴⁶⁻⁵⁰.

The expert group emphasizes the need for pharmacoeconomic studies in all countries, considering not only the product price but also the overall process costs.

Suggested tools for evaluating hemophilia patients include^{22,51,52}:

- Physical examination tools:
 - WFH Physical Examination Score (Gilbert Score)^{53,54}.
- Pain assessment tools:
 - Wong-Baker FACES Pain Rating Scale^{55,56}.
 - Multidimensional Pain Questionnaire for Hemophilia⁵⁷.
- Disease and therapy efficacy assessment:
 - Laboratory tests (inhibitor measurement and factor titration).
 - Annual bleeding rate.
- Tools for measuring body structure and function in hemophilia patients:
 - Hemophilia Joint Health Score (HJHS)^{54,58,59}.
 - Imaging modalities^{60,61} using MRI⁶², ultrasound^{12,63-65}, and X-rays⁶⁶.
- Instruments for measuring activities and participation⁶⁷:
 - Haemophilia Activities List (HAL)⁶⁸⁻⁷⁰.
 - Pediatric Haemophilia Activities List (PedHAL)⁷¹⁻⁷³.
 - Functional Independence Score in Hemophilia (FISH)^{74,75}.
- Health-related quality of life instruments:
 - EuroQol-5D⁷⁶⁻⁷⁸.
 - SF-36^{79,80}.

Multidisciplinary team, training, patient association empowerment, clinical guideline implementation, and public policy strengthening

Recommendation 13. The core care team for hemophilia patients should include a pediatric hematologist, a physical therapist nurse, and a psychosocial counselor trained in hemophilia, with immediate access to a specialized coagulation laboratory. A hemophilia center must have a multidisciplinary team of specialists trained in hemophilia to ensure comprehensive care for these patients.

Agreement level: 72.73% completely agree, 22.73% agree with minor reservations, 4.55% agree with major reservations.

Recommendation 14. Patient associations should organize activities to manage resources for the

comprehensive care of patients. Disease-specific training should be provided by the health care team.

Agreement level: 81.82% completely agree, 9.09% agree with minor reservations, 9.09% agree with major reservations.

Recommendation 15. Every country should have a treatment guideline, updated at least every 5 years, that includes carriers and women with hemophilia.

Agreement level: 90.91% completely agree, 4.55% agree with minor reservations, 4.55% disagree with major reservations.

Recommendation 16. Treatment decisions should include economic considerations and scientific advice from the health care team or treating physician.

Agreement level: 81.82% completely agree, 9.09% agree with minor reservations, 9.09% agree with major reservations.

Discussion

Globally, the importance of comprehensive care for hemophilia patients is recognized, addressing all medical and psychological aspects affecting patients and their families. The primary goal is to enable patients to lead daily lives like those without the disease, requiring a positive and collaborative approach among health care disciplines⁸¹.

The WFH proposes a core team consisting of a medical director (typically a pediatric hematologist), a nurse coordinator, a physical therapist, a laboratory specialist, and a psychosocial counselor, all specifically trained in hemophilia care. Patients with severe disease or complications often require care from an extended team of specialists²².

Advancing the specialization of hemophilia care teams, the multidisciplinary team could include specialists in hematology and pediatrics, orthopedics and physical therapy, dentistry and oral surgery, gynecology, genetic counseling, nursing, psychology and social work, emergency care, clinical technology, and clinical pharmacy⁸¹.

In many Latin American countries, disparities in health care access are a significant challenge, often exacerbated by socioeconomic inequalities. Education and awareness initiatives are crucial to empower patients and their families through workshops, seminars, and informational campaigns.

Education and awareness initiatives are crucial for empowering patients and their families through the organization of workshops, seminars, and informational campaigns to educate the public about specific health

conditions, treatment options, and preventive measures.

Conflicts between patient groups and physicians can arise from various sources, including differing expectations, communication failures, and disagreements over treatment decisions. A study by Hullur et al.⁸² indicated that dissatisfaction with treatment and disagreements with doctors are common causes of conflict, often exacerbated by long wait times and rushed consultations. Understanding these conflicts is essential to fostering a collaborative healthcare environment that prioritizes patient-centered care. Proposed treatment plans should be reconciled with patients and their families, while taking into account the characteristics of each patient, family, social environment, and drug availability.

Patient groups play a crucial role in improving health care delivery, advocating for patient rights, and optimizing health outcomes across various medical conditions⁸³. They are in an ideal position to provide peer-centered education tailored to patients' lived experiences. This type of education often focuses on self-care strategies, emotional support, and practical advice that empower patients to take an active role in their health care.

Health care professionals, on the other hand, are responsible for providing evidence-based medical education that includes clinical knowledge, treatment options, and the management of specific health conditions. This education often includes detailed explanations of medical procedures, medication management, and the implications of various treatment choices.

By recognizing the distinct roles of each group, healthcare systems can foster a more collaborative and effective educational environment that ultimately enhances patient care and outcomes.

Clinical practice guidelines are essential for optimizing patient care, based on systematic reviews of evidence and assessments of treatment risks and benefits⁸⁴. Implementing guidelines for hemophilia improves care quality, ensures evidence-based approaches, and standardizes clinical practices. Benefits include^{84,85}:

- Uniformity and consistency: guidelines provide a common framework for managing hemophilia, helping to standardize clinical practices and reduce variations in patient care.
- Improved decision-making: evidence-based guidelines offer up-to-date information on diagnosis, treatment, and follow-up. This enables physicians to make informed and personalized decisions, potentially improving patient outcomes.

- Resource optimization: adhering to guidelines helps prevent the inappropriate use of medical resources and maximizes efficiency in patient care.
- Patient and caregiver education and empowerment: guidelines can also serve as an educational tool for patients and their families, helping them understand hemophilia management and the importance of treatment adherence.

Studies evaluating the frequency of clinical practice guideline updates indicate that they are revised every 1 to 5 years after the last publication, depending on each institution's policies^{86,87}.

In many cases, regional treatment guidelines and protocols are adaptations of international guidelines individualized to the local context. Experts recommend updating them at least every 5 years, depending on new evidence that could introduce innovative therapies into health care systems and improve patient care by optimizing available resources. The latest WFH guidelines consider these aspects, recommending the preparation of medical treatment protocols to ensure continuity of care in case of changes in clinic personnel²².

Another crucial aspect in enhancing hemophilia care is incorporating health economics tools into disease management. Cost analyses have shown that the severity of hemophilia is associated with a higher economic burden².

To overcome the limitations of conventional cost-effectiveness analyses—where decision-making is often influenced more by short-term budgetary impact than by long-term cost-effectiveness ratios⁸⁸—it is essential to consider innovative health care access models. These models include the role of pharmacoeconomics in drug acquisition processes, allowing for the evaluation of new health technologies with the goal of maximizing effective resource utilization while minimizing budgetary impact.

Health technology assessment (HTA) is a systematic and multidisciplinary process aimed at identifying, evaluating, and synthesizing all available scientific evidence to support decision-making. This process applies to drugs, medical devices, vaccines, procedures, and services, guiding health policy decisions⁸⁹⁻⁹¹. The following aspects are considered in HTA: characterization of the specific health problem and current treatment alternatives, description of the technology under review, evidence on safety and clinical effectiveness (comparative effectiveness), cost-effectiveness analysis, budget impact analysis, ethical considerations, and organizational, social, and legal aspects⁹².

Currently, some countries are implementing innovative access models for certain health care products. These models involve agreements between healthcare technology manufacturers or producers and healthcare funders or providers, facilitating access (coverage or reimbursement) to health technologies under specific conditions⁹³. One example is risk-sharing agreements, which link reimbursement or coverage to the real-world performance of a medical technology.

Conclusions

Implementing hemophilia care guidelines and recommendations contributes to more effective, safe, and patient-centered care. Hemophilia experts in Latin America are encouraged to collaborate, publish real-world evidence, and make informed decisions to provide personalized care for individuals with this condition.

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Conflicts of interest

M. Berro: speaker for Roche, Werfen, and Scienza Uruguay. M.G. Arbesú-Ponce: speaker for Novo Nordisk, Roche, Octapharma, Pfizer, CSL Behring, Bayer, and Takeda; has participated in Advisory Boards for Novo Nordisk, Roche, Pfizer, Bayer, and Takeda. A.J. Bustinza-Álvarez: speaker for Roche, Novo Nordisk, and Takeda; has participated in Advisory Boards for Novo Nordisk. M.V. Canonico-Zavalla: speaker for Novo Nordisk; has participated in Advisory Boards for Novo Nordisk and Takeda. C.P. Casas-Patarroyo: speaker for Takeda, Roche, Octapharma, Novo Nordisk, and Pfizer; has participated in Advisory Boards for Roche, Novo Nordisk, Takeda, and Biopass. D. Castillo-González: Speaker for Roche. A.R.

Estrada-Romero: speaker for Roche, CSL Behring, Novo Nordisk, and Viphor. N.E. Loayza-Urcia: speaker for Roche and Octapharma; has participated as a Clinical Investigator for Roche. K. Moreno-Peñarrieta: speaker for Roche and Takeda (Shire); has participated in Advisory Boards for Roche. C. Ochoa: speaker for Roche Ecuador; has participated in Advisory Boards for Medicamenta Ecuatoriana and Roche Ecuador. S. Oliva-Lara: speaker for Pfizer and Novo Nordisk; has participated in Advisory Boards for Bayer, Pfizer, Novo Nordisk, Roche, and Octapharma. G. Ramos-Ramos: speaker for Octapharma, Bayer, Novo Nordisk, Roche, and Takeda; has participated in Advisory Boards for Siemens and Novo Nordisk. I. Rodríguez-Grecco: has participated in Advisory Boards for Novo Nordisk, Octapharma, and CSL Behring. G.F. Rojas Alba: speaker for Roche and Octapharma. P. Sepúlveda: has participated in Advisory Boards for Roche and Novo Nordisk. The remaining participants declared no conflicts of interest whatsoever.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines have been followed according to the nature of the study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

- García-Chávez J, Majluf-Cruz A. Hemofilia. *Gac Med Mex*. 2013;149:308-21.
- Peral C, De Lössada Juste A, Lwoff N, Espinoza-Cámac N, Casado MA, Burke T, et al. Economic and humanistic burden of moderate and severe hemophilia A and B in Spain: real-world evidence insights from the CHES II study. *J Heal Econ Outcomes Res*. 2024;11:112-33.
- Máseide RJ, Berntorp E, Astermark J, Hansen J, Olsson A, Bruzelius M, et al. Haemophilia early arthropathy detection with ultrasound and haemophilia joint health score in the moderate haemophilia (MoHem) study. *Haemophilia*. 2021;27:e253-9.
- Boadas A, Ozelo MC, Solano M, Berges A, Ruiz-Saez A, Linares A, et al. Haemophilia care in Latin America: assessment and perspectives. *Haemophilia*. 2018;24:e395-e401.
- Castillo González D, Lardoezt Ferrer R, Almagro Vázquez D, Lam-Díaz RM, Lavaut-Sánchez K, Gutiérrez-Díaz A, et al. Prevalence of hemophilia in six Cuban provinces. *Rev Cubana Hematol Inmunol Hemoter*. 2014;30:155-61.
- Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. *Am J Hematol*. 1998;59:288-94.
- Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, et al. Establishing the prevalence and prevalence at birth of hemophilia in males a meta-analytic approach using national registries. *Ann Intern Med*. 2019;171:542-6.
- Coppola A, Franchini M, Pappagallo G, Borchellini A, De Cristofaro R, Molinari AC, et al. Current choices and management of treatment in persons with severe hemophilia A without inhibitors: a mini-Delphi consensus. *J Clin Med*. 2022;11:1-10.
- Ceponis A, Wong-Sefidan I, Glass CS, von Drygalski A. Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patientse. *Haemophilia*. 2013;19:790-8.
- Berro M, Elichiry M, Wasen K, Insagaray J, Rodríguez I. Use of ultrasound for evaluation of painful joint episodes perceived as haemarthrosis in adult patients with severe haemophilia. *Haemophilia*. 2018;24:e124-5.
- Sierra Aisa C, Lucía Cuesta JF, Rubio Martínez A, Fernández Mosteirín N, Iborra Muñoz A, Abío Calvete M, et al. Comparison of ultrasound and magnetic resonance imaging for diagnosis and follow-up of joint lesions in patients with haemophilia. *Haemophilia*. 2014;20:e51-7.
- Martinoli C, Della Casa Alberighi O, Di Minno G, Graziano E, Molinari AC, Pasta G, et al. Development and definition of a simplified scanning procedure and scoring method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). *Thromb Haemost*. 2013;109:1170-9.
- Querol F, Rodríguez-Merchán EC. The role of ultrasonography in the diagnosis of the musculo-skeletal problems of haemophilia. *Haemophilia*. 2012;18:e215-26.
- Di Minno A, Spadarella G, Nardone A, Mormile M, Ventre I, Morfini M, et al. Attempting to remedy sub-optimal medication adherence in haemophilia: the rationale for repeated ultrasound visualisations of the patient's joint status. *Blood Rev*. 2019;33:106-16.
- De la Corte-Rodríguez H, Rodríguez-Merchán EC, Jiménez-Yuste V. Point-of-care ultrasonography in orthopedic management of hemophilia: multiple uses of an effective tool. *HSS J*. 2018;14:307-13.
- Dobón M, Lucía JF, Aguilar C, Mayayo E, Roca M, Solano V, et al. Value of magnetic resonance imaging for the diagnosis and follow-up of haemophilic arthropathy. *Haemophilia*. 2003;9:76-85.
- Querol F, Rodríguez-Merchán EC. The role of ultrasonography in the diagnosis of the musculo-skeletal problems of haemophilia. *Haemophilia*. 2012;18:e215-26.
- Li J, Liu W, Guo XJ, Ding XL, Lyu BM, Xiao J, et al. [HEAD-US-C quantitative ultrasound assessment scale in evaluation of joint damage in patients with moderate or severe hemophilia A received on-demand versus prophylaxis replacement therapy]. *Zhonghua Xue Ye Xue Za Zhi*. 2018;39:817-21.
- Strike KL, Iorio A, Jackson S, Lawson W, Scott L, Squire S, et al. Point of care ultrasonography in haemophilia care: recommendations for training and competency evaluation. *Haemophilia*. 2015;21:828-31.
- Strike K, Uy M, Lawson W, Squire S, Iorio A, Stein N, et al. Point-of-care ultrasonography in haemophilia care: training and competency for muscular haematomas. *Haemophilia*. 2018;24:335-7.
- Bailey C, Bakeer N, Wood A, von Drygalski A, Steiner B, Quon D, et al. National Hemophilia Foundation for all bleeding disorders. Practice guidelines for implementation and use of musculoskeletal ultrasound in the management of individuals with hemophilia and other bleeding disorders. Endorsed by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation. August 8, 2020. (Consultado el 27-05-2024.) Disponible en: <https://www.bleeding.org/sites/default/files/document/files/MASAC%20%20MSKUS%20%20Guideline%20w%20ALL%20authors%20%20Aug.%202021.pdf>.
- Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26:1-158.
- Bowyer AE, Gosselin RC. Factor VIII and factor IX activity measurements for hemophilia diagnosis and related treatments. *Semin Thromb Hemost*. 2023;49:609-20.
- Kitchen S, Tiefenbacher S, Gosselin R. Factor activity assays for monitoring extended half-life FVIII and factor IX replacement therapies. *Semin Thromb Hemost*. 2017;43:331-7.
- Gray E, Kitchen S, Bowyer A, Chowdary P, Jenkins PV, Murphy P, et al. Laboratory measurement of factor replacement therapies in the treatment of congenital haemophilia: a United Kingdom Haemophilia Centre Doctors' Organisation guideline. *Haemophilia*. 2020;26:6-16.
- Kraemmer D, Königsbrügge O, Moik F, Wildner B, Ay C, Pabinger I. Pharmacokinetic-guided versus standard prophylaxis in hemophilia: a systematic review and meta-analysis. *J Thromb Haemost*. 2023;21:3432-49.
- Pezeshkpoor B, Oldenburg J, Pavlova A. Insights into the molecular genetic of hemophilia A and hemophilia B: the relevance of genetic testing in routine clinical practice. *Hamostaseologie*. 2022;42:390-9.
- Álvarez Román MT, coordinadora. Guías españolas para el manejo del paciente con hemofilia. Real Fundación Victoria Eugenia. Madrid: Arán; 2022. Disponible en: https://rfve.es/wp-content/uploads/GUIAS-espanolas-hemofilia-RFVE-26_06.pdf.

29. Stoffman J, Andersson NG, Branchford B, Batt K, D'Oiron R, Escuriola Ettingshausen C, et al. Common themes and challenges in hemophilia care: a multinational perspective. *Hematology*. 2019;24:39-48.
30. Teixeira L, Saavedra V, Sousa Santos B, Ferreira C. Portuguese haemophilia registry. Set of variables for a computerized solution. *Haemostaseologie*. 2017;37:131-7.
31. Tran H, Yang R, Fischer K, Makris M, Konkle BA. The importance and evolution of bleeding disorder registries. *Haemophilia*. 2024;30(Suppl 3):21-8.
32. Colvin BT, Astermark J, Fischer K, Gringeri A, Lassila R, Schramm W, et al. European principles of haemophilia care. *Haemophilia*. 2008;14:361-74.
33. Dunkley S, Lam JCM, John MJ, Wong RSM, Tran H, Yang R, et al. Principles of haemophilia care: the Asia-Pacific perspective. *Haemophilia*. 2018;24:366-75.
34. Walker I, Sigouin C, Sek J, Almonte T, Carruthers J, Chan A, et al. Comparing hand-held computers and paper diaries for haemophilia home therapy: a randomized trial. *Haemophilia*. 2004;10:698-704.
35. Dirzu N, Hotea I, Jitaru C, Brinza M, Urian L, Peters MC, et al. Mobile health technology for the personalized therapy of hemophilia. *Front Med*. 2021;8:1-11.
36. Mondorf W, Siegmund B, Mahnel R, Richter H, Westfeld M, Galler A, Pollmann H. Haemoassist — a hand-held electronic patient diary for haemophilia home care. *Haemophilia*. 2009;15:464-72.
37. Zapotocka E, Batorova A, Bilic E, Boban A, Escuriola Ettingshausen C, Faganel Kotnik B, et al. First experience of a hemophilia monitoring platform: florio HAEMO. *Res Pract Thromb Haemost*. 2022;6:1-9.
38. Góis ACL de, Rabelo DA, Marques TF, Sá NM de. Equidad en situaciones límite: acceso al tratamiento para personas con hemofilia. *Rev Bioética*. 2022;30:181-94.
39. Valentino LA, Mammon V, Hellmann A, Quon DV, Chybicka A, Schroth P, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost*. 2012;10:359-67.
40. Gringeri A, Lundin B, Von Mackensen S, Mantovani L, Mannucci PM; ESPRIT Study Group. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT study). *J Thromb Haemost*. 2011;9:700-10.
41. Meijón Cortigueira MM, Álvarez-Román MT, De La Corte Rodríguez H, Butta Oli N, Jiménez-Yuste V. Long-term impact of primary prophylaxis on joint status in patients with severe hemophilia A. *Res Pract Thromb Haemost*. 2023;7:100005.
42. Manco-Johnson MJ, Lundin B, Funk S, Peterfy C, Raunig D, Werk M, et al. Effect of late prophylaxis in hemophilia on joint status: a randomized trial. *J Thromb Haemost*. 2017;15:2115-24.
43. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379:811-22.
44. Callaghan MU, Negrier C, Paz-Priel I, Chang T, Chebon S, Lehle M, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. *Blood*. 2021;137:2231-42.
45. Antunes SV, Tangada S, Stasyshyn O, Mammon V, Phillips J, Guzman-Becerra N, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia*. 2014;20:65-72.
46. Seth T, Garg K, Mandal PK, Datta A, Verma S, Hanagavadi S, et al. Cost-effectiveness analysis of low-dose prophylaxis versus on-demand treatment for moderate-to-severe hemophilia A in India. *Hematology*. 2023;28:2277497.
47. Colombo GL, di Matteo S, Elisa Mancuso M, Santagostino E. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. *Clin Outcomes Res*. 2011;3:55-61.
48. Shen MC, Chou SC, Chiou SS, Lin PC, Chen YC, Lin HY, et al. Efficacy, safety and cost of emicizumab prophylaxis in haemophilia A patients with inhibitors: a nationwide observational study in Taiwan. *Haemophilia*. 2023;29:1499-508.
49. Castillo-González D, Álvarez Sardiñas I, Macías Abraham C, Muñoz Bedoya AG. Emicizumab in hemophilia A with inhibitors: clinical and economic impact of its use in a Cuban patient. *AboutOpen*. 2022;9:83-6.
50. Polack B, Trossaert M, Cousin M, Baffert S, Pruvot A, Godard C. Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France. *Haemophilia*. 2021;27:e1-11.
51. Beeton K, Feldman B, Mulder K, Poonnoose P, Van der Net J, Young N. Compendio de herramientas de valoración — eLearning Platform. Federación Mundial de la Hemofilia. 2017. (Consultado el 24-06-2024.) Disponible en: <https://elearning.wfh.org/es/resource/compendio-de-herramientas-de-valoracion/>.
52. Fischer K, Poonnoose P, Dunn AL, Babyn P, Manco-Johnson MJ, David JA, et al. Choosing outcome assessment tools in haemophilia care and research: a multidisciplinary perspective. *Haemophilia*. 2017;23:11-24.
53. Federación Mundial de Hemofilia. Puntaje de la FMH para examen físico (puntaje Gilbert) — eLearning Platform. Federación Mundial de Hemofilia. 2011. (Consultado el 03-07-2024.) Disponible en: <https://elearning.wfh.org/es/resource/puntaje-de-la-fmh-para-examen-fisico-puntaje-gilbert/>.
54. Gouw SC, Timmer MA, Srivastava A, de Kleijn P, Hilliard P, Peters M, et al. Measurement of joint health in persons with haemophilia: a systematic review of the measurement properties of haemophilia-specific instruments. *Haemophilia*. 2019;25:e1-10.
55. Wong-Baker FACES Foundation. Wong-Baker FACES® Pain Rating Scale. 2016. (Consultado el 03-07-2024.) Disponible en: <https://wong-bakerfaces.org/>.
56. Manco-Johnson MJ, Nuss R, Funk S, Murphy J. Joint evaluation instruments for children and adults with haemophilia. *Haemophilia*. 2000;6:649-57.
57. Paredes AC, Costa P, Almeida A, Pinto PR. A new measure to assess pain in people with haemophilia: the multidimensional haemophilia pain questionnaire (MHPQ). *PLoS One*. 2018;13:e0207939.
58. St-Louis J, Abad A, Funk S, Tilak M, Classey S, Zourikian N, et al. The Hemophilia Joint Health Score version 2.1 Validation in Adult Patients Study: a multicenter international study. *Res Pract Thromb Haemost*. 2022;6:1-11.
59. World Federation of Hemophilia. Hemophilia Joint Health Score (HJHS) — eLearning Platform. World Federation of Hemophilia. 2011. (Consultado el 03-07-2024.) Disponible en: <https://elearning.wfh.org/resource/hemophilia-joint-health-score-hjhs/>.
60. Doria AS. State-of-the-art imaging techniques for the evaluation of haemophilic arthropathy: present and future. *Haemophilia*. 2010;16(Suppl 5):107-14.
61. Keshava SN, Gibikote S, Doria AS. Imaging evaluation of hemophilia: musculoskeletal approach. *Semin Thromb Hemost*. 2015;41:880-93.
62. Chan MW, Leckie A, Xavier F, Ulerik E, Tadros S, Blanchette V, et al. A systematic review of MR imaging as a tool for evaluating haemophilic arthropathy in children. *Haemophilia*. 2013;19:e324-34.
63. Keshava SN, Gibikote SV, Mohanta A, Poonnoose P, Rayner T, Hilliard P, et al. Ultrasound and magnetic resonance imaging of healthy paediatric ankles and knees: a baseline for comparison with haemophilic joints. *Haemophilia*. 2015;21:e210-22.
64. De la Corte-Rodríguez H, Rodríguez-Merchán EC, Álvarez-Román MT, Martín-Salces M, Martinoli C, Jiménez-Yuste V. The value of HEAD-US system in detecting subclinical abnormalities in joints of patients with hemophilia. *Expert Rev Hematol*. 2018;11:253-61.
65. Kandagaddala M, Sundaramoorthy M, Keshava SN, Gibikote S, Mahata KM, Kavitha ML, et al. A new and simplified comprehensive ultrasound protocol of haemophilic joints: the Universal Simplified Ultrasound (US-US) protocol. *Clin Radiol*. 2019;74:897.e9-16.
66. Pettersson H, Ahlberg A, Nilsson I. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res*. 1980;149:153-9.
67. Timmer MA, Gouw SC, Feldman BM, Zwagemaker A, de Kleijn P, Pisters MF, et al. Measuring activities and participation in persons with haemophilia: a systematic review of commonly used instruments. *Haemophilia*. 2018;24:e33-e49.
68. Van Genderen FR, Westers P, Heijnen L, de Kleijn P, van den Berg HM, Helden PJ, et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. *Haemophilia*. 2006;12:36-46.
69. van Genderen FR, van Meeteren NLU, van der Bom JG, Heijnen L, de Kleijn P, van den Berg HM, et al. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. *Haemophilia*. 2004;10:565-71.
70. Kempton CL, Schutgens REG, Buckner TW, Fischer K. Shortening the Haemophilia Activities List (HAL) from 42 items to 18 items. *Haemophilia*. 2021;27:1062-70.
71. Schutgens REG. The Paediatric Haemophilia Activities List (pedHAL) in routine assessment: changes over time, child-parent agreement and informative domains. *Haemophilia*. 2019;25:953-9.
72. Kuijlaars IAR, van der Net J, Bouskill V, Hilliard P, Juodyte A, Khair K, et al. Shortening the paediatric Haemophilia Activities List (pedHAL) based on pooled data from international studies. *Haemophilia*. 2021;27:305-13.
73. Groen WG, van der Net J, Helden PJ, Fischer K. Development and preliminary testing of a paediatric version of the Haemophilia Activities List (pedHAL). *Haemophilia*. 2010;16:281-9.
74. Poonnoose PM, Thomas R, Keshava SN, Cherian RS, Padankatti S, Pazani D, et al. Psychometric analysis of the Functional Independence Score in Haemophilia (FISH). *Haemophilia*. 2007;13:620-6.
75. Poonnoose PM, Manigandan C, Thomas R, Shyamkumar NK, Kavitha ML, Bhattacharji S, et al. Functional independence score in haemophilia: a new performance-based instrument to measure disability. *Haemophilia*. 2005;11:598-602.
76. Devlin N, Parkin D, Janssen B. An introduction to EQ-5D instruments and their applications. En: *Methods for analysing and reporting EQ-5D data*. Cham (CH): Springer; 2020. p. 1-22.
77. Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res*. 2010;19:875-86.
78. EuroQol. EQ-5D-5L. 2024. (Consultado el 03-07-2024.) Disponible en: <https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/>.
79. RAND Health Care. 36-item Short Form Survey Instrument (SF-36). RAND Health Care. 2016. (Consultado el 03-07-2024.) Disponible en: https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html.
80. Ware JE, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol*. 1998;51:903-12.

81. Nomura S. Current status and challenges in delivering comprehensive care for patients with hemophilia. *J Blood Med*. 2023;14:629-37.
82. Hullur HM, Dandekar AA, Raje SS. Doctor-patient interactions with respect to type of practice. *Int J Community Med Public Health*. 2020;7:537.
83. Henao C, Lis-Gutiérrez JP, Lis-Gutiérrez M. Inequality in access to healthcare: a Latin American perspective. *Salud, Ciencia y Tecnología*. 2023;(3):355.
84. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical practice guidelines we can trust*. National Academies Press (US); 2011. Disponible en: <https://nap.nationalacademies.org/catalog/13058/clinical-practice-guidelines-we-can-trust>.
85. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *BMJ*. 1999;318:527-30.
86. Vernooij RW, Sanabria AJ, Solà I, Alonso-Coello P, Martínez García L. Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks. *Implement Sci*. 2014;9:1-9.
87. Alonso-Voello P, Martínez García L, Carrasco JM, Solà I, Qureshi S, Burgers JS. The updating of clinical practice guidelines: insights from an international survey. *Implement Sci*. 2011;6:1-8.
88. Puig-Junoy J, Meneu R. Aplicación de los contratos de riesgo compartido a la financiación de nuevos medicamentos. *Gestión Clínica y Sanitaria*. 2044;7:88-94.
89. Rejón-Parrilla JC, Espin J, Epstein D. How innovation can be defined, evaluated and rewarded in health technology assessment. *Health Econ Rev*. 2022;12:1-11.
90. World Health Organization. 2015 Global Survey on Health Technology Assessment by National Authorities: main findings. *World Heal*. World Health Organization; 2015. Disponible en: <https://www.who.int/publications/i/item/9789241509749>.
91. World Health Organization. Evaluating properties, effects and impacts of health technology. World Health Organization/Sweden National Authority for Containment. 2021. (Consultado el 14-09-2024.) Disponible en: <https://www.who.int/europe/activities/evaluating-properties-effects-and-impacts-of-health-technology>.
92. Mincaroni P, Leo CG, Sabina S, Sarriá-Santamera A, Taruscio D, Serrano-Aguilar PG, et al. Reimbursed price of orphan drugs: current strategies and potential improvements. *Public Health Genomics*. 2017;20:1-8.
93. Klemp M, Frønsdal KB, Facey K. What principles should govern the use of managed entry agreements? *Int J Technol Assess Health Care*. 2011;27:77-83.