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Review

Future needs for continuing innovation in hemophilia: improving outcomes for individuals of all severities, including women and those in resource-constrained regions

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Jan Blatný, Jan Astermark, Cristina Catarino, Gerry Dolan, Karin Fijnvandraat, Cédric Hermans, Katharina Holstein, Víctor Jiménez-Yuste, Robert Klamroth, Michelle Lavin, Peter J. Lenting, Sébastien Lobet, Maria Elisa Mancuso, Jayashree Motwani, James S. O'Donnell and Christoph Königs

Correspondence to:
Jan Blatný
Hospital Bory, Nemocnica Bory, a.s., Ivana Kadlečíka 2, Bratislava 841 06, Slovakia

University Hospital Brno, Masaryk University, Brno, Czech Republic
jblatny@icloud.com

Jan Astermark
Department of Translational Medicine, Lund University, and Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Malmö, Sweden

Cristina Catarino
Immunochemotherapy Department, Congenital Coagulopathies Comprehensive Care Centre, Santa Maria University Hospital, Lisbon University, Lisbon, Portugal

Gerry Dolan
Centre for Haemostasis and Thrombosis, St Thomas' Comprehensive Care Centre, London, UK

Karin Fijnvandraat
Amsterdam UMC, University of Amsterdam, Emma Children's Hospital, Pediatric Hematology, Amsterdam, Netherlands

Cédric Hermans
Division of Haematology, Saint-Luc University Hospital, Catholic University of Louvain, Brussels, Belgium

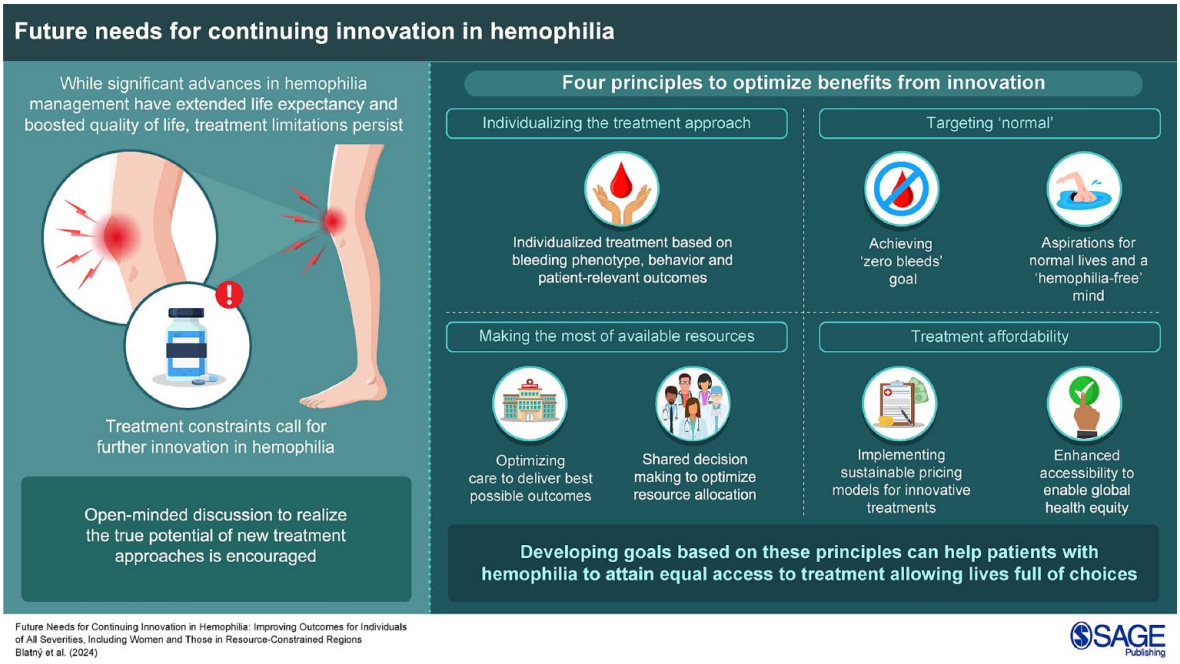
Katharina Holstein
Department of Haematology and Oncology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Víctor Jiménez-Yuste
Department of Haematology, La Paz University Hospital-IdiPaz, Autónoma University of Madrid, Madrid, Spain

Abstract

Over recent decades, management of people with hemophilia (PwH) has been greatly improved by scientific advances that have resulted in a rich and varied therapeutic landscape. Nevertheless, treatment limitations continue to drive innovation, and emerging options have the potential to realize further improvement. We advocate four general principles to optimize benefits from innovation: individualizing the treatment approach, targeting 'normal,' making the most of available resources, and considering treatment affordability. Ultimately, all PwH—men and women, of all ages and severities, and worldwide—should have access to treatment that fully prevents bleeding, while allowing personal, social, family, and professional lives of choice. Clearly, we are not there yet, but developing goals/milestones based on the principles we describe may help to achieve this.

Graphical abstract



Robert Klamroth
Department of Internal Medicine, Vivantes Hospital Friedrichshain, Berlin, Germany, and Institute of Experimental Haematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany

Michelle Lavin
Irish Centre for Vascular Biology, School of Pharmacy and Biomedical Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland

National Coagulation Centre, St. James' Hospital, Dublin, Ireland

Peter J. Lenting
Université Paris-Saclay, INSERM, Hémostase Inflammation Thrombose HITh U1176, 94276, Le Kremlin-Bicêtre, France

Sébastien Lobet
Service d'ergothérapie et de kinésithérapie, Cliniques universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium

Neuromusculoskeletal Lab (NMSK), Secteur des Sciences de la Santé, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain (UCLouvain), Brussels, Belgium

Maria Elisa Mancuso
Center for Thrombosis and Hemorrhagic Diseases, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy and Humanitas University, Pieve Emanuele, Milan, Italy

Jayashree Motwani
Department of Paediatric Haematology, Birmingham Children's Hospital, Birmingham, UK

James S. O'Donnell
Irish Centre for Vascular Biology, School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland

Christoph Königs
Goethe University, University Hospital Frankfurt, Department of Paediatrics and Adolescent Medicine, Frankfurt, Germany

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Introduction

Tremendous progress in hemophilia management over recent decades has created a rich and varied therapeutic landscape. Scientific advances have increased life expectancy, while decreasing disease-related morbidity and treatment burden, with substantial improvements in quality of life and participation (in sport/work/school, etc.). The need to address limitations of previous and current therapies has driven innovation. Emerging treatment options have the potential to offer new possibilities to tailor therapeutic approaches to individuals' specific needs. Each person has his/her own unique characteristics, aspirations, and expectations, irrespective of age and sex. Goals and ambitions vary, for example, in individuals with inhibitors, those with comorbidities, persons engaged in high-level physical activity/sports, and patients living in resource-constrained countries.

We advocate four general principles to optimize benefit from innovation for all patients (Figure 1). These are generic and can be achieved in different ways. With these principles, our intention is to stimulate open-minded discussion to realize the real potential of new treatment approaches.

Principle 1: Individualizing the treatment approach

Historically, hemophilia has been classified based on residual plasma levels of factor VIII (FVIII) and factor IX (FIX) for hemophilia A and B, respectively.[1] Severe, moderate, and mild diseases are defined by laboratory levels of <1%, 1%–5%, and >5%–<40%, respectively.[1] This classification has been used to guide treatment, but has limitations,[2,3] As within these categories individuals can exhibit marked clinical heterogeneity with varied bleeding phenotypes. While acknowledging ongoing debate,[2–4] we advocate a gradual change of treatment paradigm, moving from consideration of factor levels to phenotype. This should encompass all people with hemophilia (PwH), including women for whom prophylaxis is appropriate, and not just individuals conventionally categorized as having severe hemophilia. In addition, differences between hemophilia A and B should also be recognized.[5] We support the view that a restrictive classification may not be fit for purpose, and a more inclusive and comprehensive way of assessing patients' clinical journeys and therapeutic needs is required.

Prophylactic treatment has traditionally relied on converting hemophilia from a severe to 'moderate' state,[6] improving hemostasis by increasing FVIII/FIX levels. Historically, aspirations of prophylaxis were modest—to generate measurable levels of FVIII/FIX and reduce bleeding. Initial regimens were not very flexible or individualized. This perhaps reflected short half-lives of earlier products, concerns over plasma safety, supply limitations, burden of frequent intravenous injections, and not taking inter-individual differences in pharmacokinetics into account. While the need for higher factor levels has been acknowledged, including a more individualized approach and extension of prophylaxis to some patients with nonsevere hemophilia (in whom joint damage can occur[7,8]), there is still a lack of consensus on optimal treatment for all PwH. This may impede true improvements in outcomes.

The development of extended half-life (EHL) recombinant factor products has increased flexibility of product administration, facilitating tailored prophylaxis via individualized treatment. Moreover, the first subcutaneously administered nonreplacement therapy, emicizumab, is also available.[9] The principle of individualized hemophilia treatment[10] should be generally accepted and extended to guide patient management, with empirical evidence based on product data.[11] To optimize patient outcomes and resource allocation, decision-making aimed at increasing protection should involve a range of considerations, allowing for patients' individual characteristics, with regard to both phenotype and behavior (Figure 2). Taking into account patient-reported outcomes helps to personalize care, and improvement of patient-relevant tools is required.[12]

In the near future, it may be possible to offer therapies targeting hemostasis in the non-hemophilia

Figure 1. General principles to guide goals for continuing innovation.

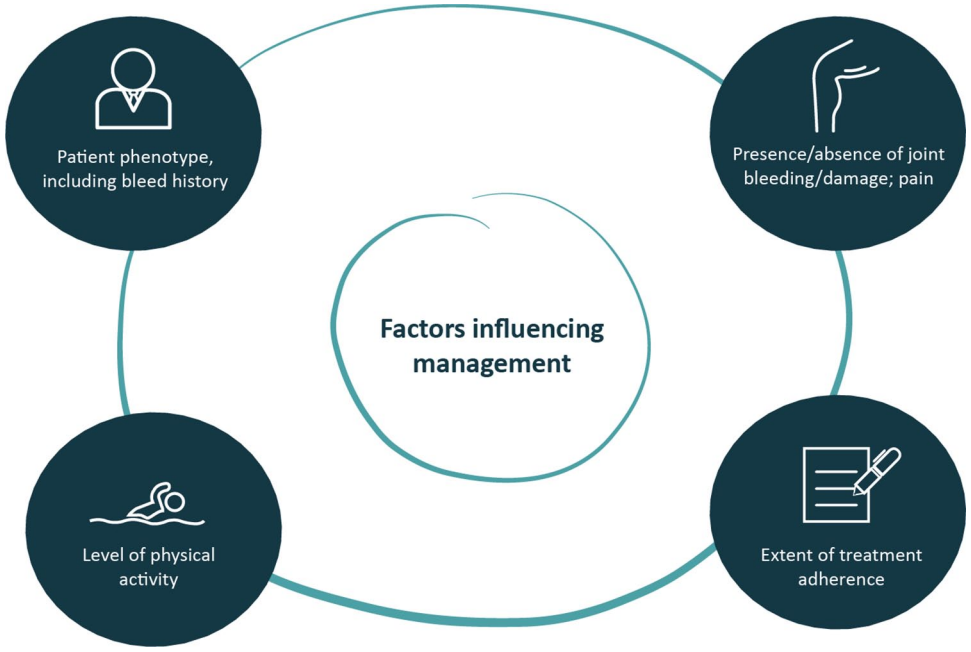

Figure 2. Considerations affecting treatment decision-making.

range, hence defining outcomes beyond peak and trough factor levels, supporting individuals' goals, preventing future morbidity, and removing restrictions in everyday life activities.

Principle 2: Targeting 'normal'

Therapeutic progress in hemophilia has broadened product choice to include EHL factors, as well as nonfactor treatment and gene therapy.

Nonfactor treatment targeting anticoagulant pathways[13] may become more widely available. Advances have ameliorated the burden of prophylaxis and delivered more sustained protection against bleeds, making the prospect of 'zero bleeds' a reality for many more PwH. 'Zero bleeds' should include asymptomatic joint bleeds ('silent bleeds' or microbleeds[14]). Increasing evidence supports the relevance of asymptomatic bleeds as a cause of joint damage in patients with no clinically evident joint bleeds, and to avoid this progression, synovitis, and bone/cartilage damage should be detected via ultrasonography.[14] This approach underlies the importance of preventing all joint bleeds to achieve optimal outcomes.[15,16] Of note, further research is needed to define the optimal treatment for otherwise asymptomatic joint disease detected only by imaging.

Currently, prophylaxis targeting FVIII trough levels in the mild range (e.g., 8%–12%[17]), or mean FVIII activity >40% for around 4 days after weekly administration,[18] has achieved further benefits, including for joint health and quality of life. With data demonstrating that FVIII/FIX levels >30% are needed to abolish the residual risk of joint bleeds in PwH,[19] novel approaches may benefit joint health. Data from gene therapy trials show that factor levels >40% can be achieved in some trial participants, and they can remain bleed-free during clinical trial periods.[20–23] However, long-term results have yet to be obtained, and it is not possible to predict results for individual patients, resulting in complex decision-making.[24]

The goal of hemophilia treatment should be compared with other diseases involving deficient or missing proteins (e.g., diabetes or hypothyroidism), where the aim is to achieve similar levels of protein activity to unaffected people. The concept of targeting the physiologically normal range has only more recently been promoted for hemophilia with the advent of novel therapeutic modalities. Indeed, recent advances have raised expectations of 'health equity' and 'functional cure.'[25] PwH can now live relatively normal lives,[26] beyond concerns of bleed risk. 'Normal' participation, including sporting activity as appropriate, with freedom from joint damage/deterioration and pain, reduced treatment burden and mental well-being are the new targets.

With continuing innovation, particularly reducing prophylactic burden while still delivering functionally 'normal' factor levels, concepts of normal hemostasis, and a 'hemophilia-free mind' (free from constraints, fears and restrictions[27]) are becoming reality.

Principle 3: Making the most of available resources

Within the constraints of any healthcare budget, resource use should be optimized. Ideally, this should be a joint venture between payers, healthcare professionals, patients, and caregivers, maximizing outcomes in an environment of mutual respect and responsibility.

If resources are limited, primary low/intermediate dose prophylaxis can provide cost-effective hemophilia care.[28,29] In an era of evolving treatment, this approach provides better outcomes/joint protection than on-demand therapy but will not prevent joint disease in the long term.

Optimal hemophilia management includes other important aspects of treatment, as well as lifestyle choices; for example, regular physical activity/sport can improve muscle strength, protecting joints.[30] Physiotherapy is also key to improve coordination, posture, joint load, and balance. In the past, risk of bleeding because of inadequate hemostatic cover restricted the potential of physiotherapy. With optimal prophylaxis, regular physiotherapy may have a real impact,[31] improving health and reducing bleeds, while containing costs.

Regardless of the treatment patients receive, strategies encouraging adherence will always improve outcomes,[28] and good-quality education and support is effective in addressing this. Whatever resources are available, a multidisciplinary team is key to ensuring coordinated support and care[28] aiming to align clinical and patient-relevant outcomes, with shared decision-making, to achieve health equity.

Improvements in healthcare, as a whole, can heighten the competition for resources. This may exacerbate global health inequities as situations differ between countries, a 'one-size-fits-all' approach is not possible. In less-developed economies, with competing healthcare priorities, including infectious diseases and malnutrition,

spending on acute disorders may be prioritized over certain chronic conditions.[28] Appropriate government commitment will help allocate resources to rare diseases such as hemophilia,[28] as will manufacturers' flexibility negotiating products' price. Affordable payment structures are essential. Efficient supply chain management helps capitalize on available medicines while reducing waste.[29] Resource allocation is also strictly related to epidemiology, and despite the incidence of hemophilia being relatively constant across different populations, diagnosis rates are lower in resource-limited settings.[28]

Principle 4: Treatment affordability

Innovative treatments do not have to incur high upfront costs; it may be feasible to implement innovations with sustainable pricing. It is important to look at available pricing options, considering, for example, annual treatment costs and predictability of costs. Moreover, sustainability evaluation should include the spared costs to treat breakthrough bleeds according to demonstrated efficacy of given products (i.e., innovative therapies might offer better protection with less breakthrough bleeds and related cost of care upon prophylaxis).

Certain medicines may have efficacy across a range of approved dose levels; for more expensive medicines, concentration or dosing frequency may be adjusted to reduce costs while maintaining benefit. Ensuring that patients receive optimum levels of therapy may require more advanced understanding of mechanisms of action of innovative treatments.

Long-term benefits (costs over time) should be considered; direct treatment costs may be partially offset by health benefits, as evaluated in Health Technology Assessment; for example, EHL products may enable overall cost savings through improved joint health and lower annualized bleeding rates, while also benefiting health-related quality of life.[32] Costs of uncontrolled disease can include hospitalization and low productivity and participation; ameliorating health problems saves such costs, while providing opportunities for increased productivity and participation.

Resource-constrained countries have seen profound benefits in hemophilia management after receiving innovative treatments free of charge via global humanitarian initiatives.[33] Through national health programs and participation in international clinical trials, gene therapy could also become available in lower socioeconomic countries, providing opportunities to close the gap in hemophilia care globally.[34] To help address health inequity, regulators, payers, and pharmaceutical companies should accept their responsibilities and seek ways to finance innovation and negotiate pricing to allow access for all without disparities, attempting to overcome differences impacting treatment. This should take into account individualized needs and patient-based recommendations.

Efforts to identify and close the gap between those with and without hemophilia provide motivation for improvement. The 'Treatment for All' vision promoted by the World Federation of Hemophilia aims to provide care for all those with the condition, with the 'Theory of Change' initiative developed to facilitate global stakeholder collaboration.[35]

Final thoughts

While factor administration still remains the unique option to manage bleeds, ultimately, all PwH—men and women, of all ages and severities, and worldwide—should have access to treatment that fully prevents bleeding, while allowing personal, social, family, and professional lives of choice. Clearly, we are not there yet, but developing goals/milestones based on the principles described above may help to achieve this, as may consideration of these ideas when developing future guidelines. Identifying appropriate targets can create a pathway to guide the journey, globally, across systems with differing rates of progress, and maybe eventually to those with other congenital bleeding disorders.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Jan Blatny: Conceptualization; Writing – original draft; Writing – review & editing.

Jan Astermark: Writing – review & editing.

Cristina Catarino: Writing – review & editing.

Gerry Dolan: Writing – review & editing.

Karin Fijnvandraat: Writing – review & editing.

Cedric Hermans: Writing – review & editing.

Katharina Holstein: Writing – review & editing.

Víctor Jiménez-Yuste: Conceptualization; Writing – review & editing.

Robert Klamroth: Writing – review & editing.

Michelle Lavin: Writing – review & editing.

Peter J. Lenting: Writing – review & editing.

Sébastien Lobet: Writing – review & editing.

Maria Elisa Mancuso: Writing – review & editing.

Jayashree Motwani: Conceptualization; Writing – review & editing.

James O'Donnell: Writing – review & editing.

Christoph Königs: Conceptualization; Writing – original draft; Writing – review & editing.

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ORCID iDs

Jan Blatný https://orcid.org/0000-0001-6261-9157

Cédric Hermans https://orcid.org/0000-0001-5429-8437

Katharina Holstein https://orcid.org/0000-0003-3753-0972

Víctor Jiménez-Yuste https://orcid.org/0000-0003-3937-3499

Sébastien Lobet https://orcid.org/0000-0002-3829-6850

Maria Elisa Mancuso https://orcid.org/0000-0002-7113-4028

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