Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Hemophilia treatment in 2021: Choosing the"optimal" treatment using an integrative, patient-oriented approach to shared decision-making between patients and clinicians

Cedric Hermans [a,*], Declan Noone [b], Gary Benson [c], Gerry Dolan [d], Hermann Eichler [e], Víctor Jiménez-Yuste [f], Christoph Königs [g], Sébastien Lobet [a,h], Debra Pollard [i], Silva Zupančić-Šalek [j], Maria Elisa Mancuso [k]

[a] Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium
[b] Irish Haemophilia Society, Dublin, Ireland
[c] Haemophilia and Thrombosis Centre, Belfast City Hospital, Belfast, Ireland
[d] Centre for Haemostasis and Thrombosis, St Thomas' Hospital, London, UK
[e] University and University Hospital of Saarland, Institute of Clinical Haemostaseology and Transfusion Medicine, Homburg, Saar, Germany
[f] Hospital Universitario La Paz, Unidad de Coagulopatías, Servicio de Hematología, Autonoma University, Madrid, Spain
[g] Clinical and Molecular Haemostasis, Department of Paediatrics and Adolescent Medicine, Goethe University, Frankfurt, Germany
[h] Neuromusculoskeletal Lab (NMSK), Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium
[i] Katharine Dormandy Haemophilia & Thrombosis Centre, Royal Free London NHS Foundation Trust, London, UK
[j] Department of Medicine, University Hospital Center Zagreb, Zagreb, Croatia
[k] Center for Thrombosis and Hemorrhagic Diseases, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

ARTICLE INFO

Keywords:
Algorithm
Decision making
Shared
Hemophilia
Patient-centered care
Patient participation
Treatment outcome

ABSTRACT

The mainstay of hemophilia treatment is to prevent bleeding through regular long-term prophylaxis and to control acute breakthrough bleeds. Various treatment options are currently available for prophylaxis, and treatment decision-making is a challenging and multifaceted process of identifying the most appropriate option for each patient. A multidisciplinary expert panel convened to develop a practical, patient-oriented algorithm to facilitate shared treatment decision-making between clinicians and patients. Key variables were identified, and an algorithm proposed based on five variables: bleeding phenotype, musculoskeletal status, treatment adherence, venous access, and lifestyle. A complementary, patient-focused preference tool was also hypothesized, with the aim of exploring individual patients' priorities, preferences, and goals. It is hoped that the proposed algorithm and the hypothesized patient preference tool will assist in selecting a treatment for each patient that is as efficient as possible in preventing bleeds while also accounting for the patient's expectations and priorities.

1. Introduction

Hemophilia is a rare, congenital, X-linked bleeding disorder caused by deficiency of coagulation factor VIII (FVIII; hemophilia A) or factor IX (FIX; hemophilia B) [1]. Patients with moderate to severe hemophilia (<1–5% of normal FVIII/FIX levels) experience spontaneous bleeding, mainly into joints and muscles [1], and recurrent joint and intramuscular bleeds can lead to substantial musculoskeletal morbidity, including chronic synovitis, hemophilic arthropathy, compartment syndrome, and pseudotumors [1,2].

The mainstay of treatment is to enhance haemostasis sufficiently to prevent and control acute bleeding [1,3]. Historically, this could only partly be achieved through relatively standardized regimens of prophylactic replacement therapy involving frequent intravenous injections of FVIII or FIX concentrates. However, by 2020, therapeutic options had expanded to include a number of innovative and potentially transformative treatment modalities, including extended half-life (EHL) FVIII and FIX concentrates (which allow more flexible and personalized prophylaxis than standard FVIII and FIX products), non-replacement therapy with a FVIII-mimicking monoclonal antibody

* Corresponding author at: Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), 10 Avenue Hippocrate, 1200 Brussels, Belgium.
E-mail address: cedric.hermans@uclouvain.be (C. Hermans).

https://doi.org/10.1016/j.blre.2021.100890

or molecules rebalancing coagulation (still under investigation), and potentially curative gene therapy [1].

While the range of new therapeutic options helps to address previously unmet needs in hemophilia [1], it also adds complexity to treatment decisions. For instance, all treatment options have weaknesses as well as strengths, and not all options are accessible in all countries. Educating health care providers (HCPs), patients, and families about the mechanisms of action of novel agents can be challenging [4], and the use of novel therapies is further complicated by the current lack of long-term data regarding both efficacy and impact on the patient's overall health. Added to these complexities is the ambitious goal—now widely accepted in the developed world—of establishing personalized prophylaxis for all patients, with the combined aim of achieving high factor trough levels while also facilitating increased levels of physical activity and achieving zero bleeds [1,5,6].

In light of this complex treatment landscape, the mission of hemophilia treatment centers (HTCs) and multidisciplinary teams (MDT) is more challenging than ever. Treatment is no longer based on standardized protocols of factor concentrates administered intravenously; rather, selecting the best treatment is now a difficult and multifaceted process of identifying the most appropriate treatment option for each patient, from among the many options available. This process should involve the patient and their family/caregiver in an informed and interactive way.

Shared decision-making, whereby patients (and their families) and clinicians collaborate in health care decisions based on clinical evidence and patient priorities [1,4,7,8], is an established and aspirational concept. Patients with chronic diseases acquire expertise through their experience of illness [9], and often see things differently—and have different priorities and concerns—than their physicians [10,11]. Despite these differing perspectives, building an alliance with patients in terms of treatment decisions could be the key factor not only in establishing a successful therapeutic pathway that meets both medical goals and patient priorities, but also in improving adherence and clinical outcomes [12,13].

Several models for shared decision-making in clinical practice have been proposed, including the "three-talk model" [14], the "deliberation dialogue model" [15], and the SHARE approach (https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html). Some hemophilia-specific approaches have also been published [10,12,16–19], but all pre-date the current range of emerging and newly available novel therapies. Goal attainment scaling (GAS) is an established, patient-centric initiative that evaluates the extent to which personalized goals, selected through patient-physician collaboration, are attained over time [20,21]. This strategy has been used successfully in patients with various chronic conditions [22–24], and an instrument for GAS in hemophilia (GOAL-Hēm) [25], which may allow incorporation of newer therapeutic options, is being evaluated.

To facilitate patient involvement in important treatment decisions, HCPs need a deeper understanding of patient experiences and values than is provided by currently available models [13]. Specifically, any model for determining optimal treatments needs to account for every relevant variable that influences hemophilia treatment and the individual patient's preferences. Therefore, in this article, we present a strategy for developing a patient-oriented algorithm to facilitate and guide treatment choice, considering the multiplicity of variables involved and the need to identify clinically indicated treatment options that also meet patient priorities on an individual level.

2. Developing a patient-oriented strategy to facilitate and guide treatment choice

The expert panel of the Zürich Hemophilia Forum convened for the 22nd time in three virtual, online meetings in September and October 2020. The Forum's expert panel comprised one pediatric and seven adult hemophilia physicians, one hemophilia nurse, one physiotherapist, and one representative of a hemophilia patients' organization (European Hemophilia Consortium); therefore, representing a broad range of perspectives on hemophilia care from seven European countries.

2.1. Aim

The objective of the panel's meeting was to develop practical algorithms for facilitating shared treatment decisions between clinicians and patients in a way that allows selection of the optimal treatment for modern management of hemophilia. "Optimal treatment" is defined as that which is not only the most clinically appropriate but which also reflects each patient's priorities and preferences. The goal is to define a patient-oriented process that guides patients and HCPs through all the variables so that together, they can determine the best treatment options and enable the best clinical outcomes for all patients, including those who do not wish to switch to one of the newer treatment options.

This process of algorithm development focused on previously treated patients (PTPs). Previously untreated patients (PUPs) are discussed briefly in Section 2.7, but an adapted decision-making process is likely to be required when considering the selection of initial treatment in PUPs; therefore, the algorithm development described in the following sections is currently applicable mainly to PTPs.

2.2. Methodology

The expert panel gathered for three "live" online discussions regarding the practicalities of developing treatment algorithms for different patient age groups. Algorithm development involved a threefold process:

i. agree upon a set of general principles to guide algorithm development;
ii. identify, refine, and summarize the variables that influence treatment choices in hemophilia; and
iii. develop an algorithm to facilitate and guide treatment choice, founded upon the general principles, the multiplicity of variables (objective and subjective), and the need to identify clinically indicated treatment options that meet each patient's expectations, aspirations, and priorities on an individual level.

A key focus therefore was how to characterize patients according to both patient age and key variables that affect treatment choice. Another vital focus was how variables could be ranked and prioritized to make the algorithms applicable to individual patients. To address these key questions, the first two meetings involved a period of offline activity in which the physicians of the panel were divided into four pairs to consider how different variables affect treatment choices in the specific patient age group represented by each pair. Therefore, there was one pair of physicians each for i) children; ii) young adults; iii) adults; and iv) elderly patients. Paired physicians were guided by a series of questions to answer in relation to their assigned patient age group: How credible are these variables for each age group? How clinically relevant? What is the clinical evidence? Which factors are important for this age group? What drives treatment choices?

Each pair of experts presented their feedback (specific to their patient group) for further discussion at the next virtual meeting. All panel members contributed input when the panel gathered at each meeting, so that the variables and proposed algorithm were further developed and refined at each successive meeting based on expert contributions from a range of perspectives.

Ultimately, this process led to development of an algorithm for treatment selection based on objective clinical variables. In addition, a complementary patient-focused preference tool was also hypothesized, based on subjective variables, with the aim of exploring each patient's individual priorities, preferences, and goals. As the proposed algorithm is completed using data from patient records, and as the hypothesized

patient tool involves dialogue between the patient/family and the MDT, the two approaches are complementary and not mutually exclusive. The remainder of this article will present i) the general principles and variables underpinning these approaches; and ii) the preliminary algorithm and hypothesized patient preference tool.

2.3. General principles of algorithm development

The panel agreed that any proposed algorithm should be sustainable and multi-directional to account for different perspectives (e.g., health care providers, payers, patients), and that it should be available and applicable across different countries. With these central tenets in place, the panel then devised a set of key principles for algorithm development that can be loosely categorized into four groups: patient involvement; education; tools; and variables (Fig. 1).

2.4. Objective and subjective variables

The starting point for algorithm development was a proposed list of key patient variables considered to be i) applicable to all hemophilia patients; and ii) the most important influencers of treatment choice (Table 1). These lists were amended with expert clinical commentary on how each variable affects treatment choices in young adult, adult, and elderly patients (Table 2), variables which are also applicable to children. The panel next identified commonality across age groups by selecting variables that are broad, critical, and overlapping. These five "objective" variables, applicable to all patients regardless of age, were bleeding phenotype, musculoskeletal status, treatment adherence, venous access, and lifestyle. Assessment methods deemed appropriate for evaluating these objective variables are summarized in Fig. 2. The remaining variables were considered individual and subjective.

The panel agreed that variables may differ between patient age groups, but older age need not be a limiting factor when considering treatment options; additionally, all variables should be discussed with the patient, so that treatment decisions involve close collaboration between the patient and the MDT.

2.5. Algorithm

An algorithm to help guide treatment decisions was developed using the five objective variables previously identified: bleeding phenotype, musculoskeletal status, treatment adherence, venous access, and lifestyle

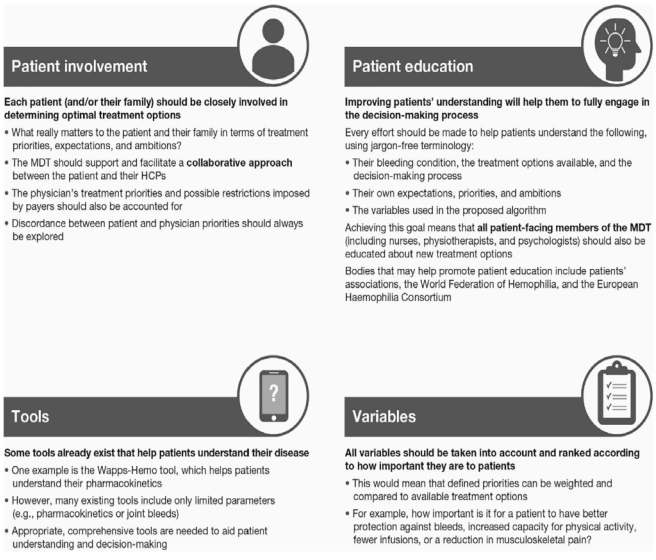

Fig. 1. Overview of key principles for algorithm development.
HCPs, health care providers; MDT, multidisciplinary team.

Table 1
Key patient variables influencing treatment choice in hemophilia patients.

Variables	
• Bleeding phenotype	• (history of) inhibitor development
• Joint status	• Comorbidities
• Current treatment	• Age
• Individual pharmacokinetics	• Presence of neutralizing antibodies
• Venous access	• Morphometrical characteristics
• Perception of new treatments	• Concomitant treatments
• Lifestyle	• Acceptability of subcutaneous injections
• Adherence	• Treatment history (including product type and exposure days)
• Psychological ecosystem	• Local environment
• Appropriate environment for switching	• Other hemophilia-related variables

(Fig. 3). Data from patient records are strongly recommended to complete the algorithm.

Four treatment strategies were identified for the algorithm, applicable to all patient age groups: i) maintain current treatment, ii) intensification with current standard half-life (SHL) or switch to EHL with similar frequency, iii) consider a non-factor replacement product, or iv) consider switching to EHL. Ultimately, this approach creates a decision-making tree covering key objective variables that can be adapted to include any additional variables that are considered important. The aim of the algorithm is to enable selection of a treatment option to improve patient care.

This proposed algorithm allows the best available treatment option to be selected for each patient, as the data used to create it are compiled by the clinician based on important clinical factors drawn from patient records. For example, the algorithm could indicate whether a patient who is adherent to their current treatment might still benefit from switching to an EHL or non-factor replacement product. Further, the algorithm may be particularly useful for countries with limited treatment access. One potential limitation of this algorithm is that certain patients may have a range of values for particular items that do not fit into the algorithm.

2.6. Patient preference tool

To supplement the clinician's algorithm, a complementary patient preference tool was hypothesized to help explore patients' treatment expectations and thus facilitate shared decision-making. The ultimate aim of this tool (which has not yet been developed or validated) would be to suggest the treatment that best meets the patient's priorities and ambitions. These priorities and ambitions relate not only to treatment expectations, but also to what the patient wishes to achieve in terms of lifestyle and goals. For example, does the patient wish to participate in high intensity sports? Do they aspire instead to be a musician or artist? Do their goals mainly revolve around family life, or a very physical career? All these goals and ambitions may impact product choice or regimen. It is also important for the MDT to know whether the patient manages their hemophilia independently or whether they need help. Additionally, it is often important to understand the experiences and opinions of those closest to the patient (such as their partner or parents).

2.6.1. Prioritizing variables

The importance of each variable, and the expected benefits of each potential treatment option, will change from one patient/family to the next. Therefore, the patient preference tool would allow patients to rank each variable according to how important it is to them. The clinician would also rank each variable independently from the patient, so that the perspectives from both stakeholders can be compared and discussed.

A potential method for ranking variables was proposed. For determining which variables are the most important (for example, lifestyle or joint protection), each variable would be assigned a weighting based on relative benefit for each treatment option. Clinicians would account for

Table 2
Patient variables influencing treatment selection in hemophilia according to age group.

Variable	Feature	Age-specific comments		
		Young adults	Adults	Elderly
Bleeding phenotype	• Number/severity of bleeds • Location • Timing with respect to infusions (ABR/AJBR/AJSBR)	• Analysis of bleeds • Is goal of zero joint bleeding realistic • Linking trough level to bleeds	• Patients with >2 joint bleeds/month	• Severe bleeder: EHL
Joint status	• Current status: preserved or damaged (severity, location) • Ambitions in terms of joint protection (respective to age)	• Joint bleeds/year • Target joints or chronic synovitis • Spontaneous vs. total bleeds • Individualized prophylaxis to preserve joint status • Measure factor kinetics • Switch to EHL products	• Presence of target joints or chronic synovitis • Resolution of target joints/synovitis	Joint status, deformity, presence of target joints, mobility
Current treatment	• Modalities: Dose/injection, timing, weekly frequency • Acceptance: for how long • Trust, satisfaction	• Does treatment modality suit the patient's life • Treatment adherence • Changing family status • Peer group • What does patient know about treatment alternatives • HRQoL • Treatment satisfaction	• Currently on intensive regimen: 3 times/week or every other day • Current treatment regimen • Skips infusions at least once weekly	
Individual PK	• $T_{½}$, AUC, • Time to reach 10%, 5%, 1% • Trough levels before switch • VWF level	• PK should be performed once • Need to educate patient on PK parameters; they should know their current treatment trough level and link it to their (planned) activities	• No need for full PK prior to switch • If replacement therapy: start with a product licensed for administration every 5 days • Check trough levels after 1–2 months of regular use and adjust the treatment schedule accordingly	
Venous access	• Quality of venous access • Ability to self-treat • Acceptance of IV • Compatibility of IV infusions with lifestyle • Logistic issues	• Ability for independent IV treatment • Full responsibility in all aspects of home treatment	• Poor venous access • Reluctance to self-inject • Unable to adhere to a tight infusion schedule due to work/family commitments or frequent travel	• Self-treatment or not • Logistics
Perception of new treatments	• Awareness • Understanding • Perceived safety: efficacy, experience	• Patient educated on new treatment options (i.e., advantages/disadvantages of non-replacement therapy/GT) • Is patient in active exchange with other hemophilia patients	• Patient aware of the differences between replacement and non-replacement therapies	• Availability of EHL concentrates and non-factor replacement products • Acceptance of new treatment possibilities
Lifestyle	• Sedentary versus active (time, frequency, intensity) • Needs for peaks • Required trough	• How physically active is the patient • Which sporting goals do they want to achieve • What is their (planned) profession	• Sedentary patients and/or those with established advanced stage joint damage may benefit from EHL products with longer intervals between doses or non-replacement therapies • Physically active patients and/or those with synovitis or joint bleeds might benefit from some peaks and higher troughs	• Sedentary versus highly active
Adherence	• Current adherence and potential to improve	• What does the patient really want to achieve • What are their treatment dreams	• Adherent patient; however, not adherent for many reasons	• Low adherence in elderly patients, especially those with dementia • Dependence
Psychological 'ecosystem'	• Motivation • Understanding • Degree of conservatism • Flexibility to change product/adapt to new treatment regimen • Ambitions • Acceptance of disease	• Need to open brain borders: new treatment options might result in (almost) phenotypical cure • What are the next steps to reach this goal • The patient can always rely on expert HTC team	• Open to exploring new therapies • Needs reassurance on safety • Understands that it is possible to go back	• Depression, anxiety, dementia, immobile pts., etc.: non-factor replacement product
Appropriate environment for switching	• Patients ready to accept logistic requirements when switching	• Switching needs patient's adherence by accepting closer controls over a defined period	• Accepts closer controls in the first 3–6 months after switching	
Past history of inhibitor development	• Could affect treatment choice and eligibility for inclusion in trial	• Why should I leave an effective replacement therapy • What about immune tolerance following switch to non-replacement therapy	• Patient could be reluctant to change if they are afraid of tolerance disruption	
Comorbidities	• Liver disease • CV disease/risk factors • Other	• Some clinical data of replacement therapy available; very limited data on non-replacement products	• Limited data from clinical trials on impact of comorbidities on new treatments	• Malignancy, surgery, investigations, chemotherapy: EHL concentrates

(*continued on next page*)

Table 2 (*continued*)

Variable	Feature	Age-specific comments		
		Young adults	Adults	Elderly
				• CV diseases, atrial fibrillation, anticoagulation: non-factor replacement product vs EHL • HCV, HIV, COVID-19 infection • Visual disturbances: non-factor replacement product; timing of bleeds
Age	• Could impact treatment choice	• Young adults are quite open to new/better treatment options • Less treatment conservativism	• Elderly patients with poor venous access may benefit from regimens with fewer (but regular) infusions to schedule homecare	• Patients should be categorized according to age: 65–75, >75–85, and > 85 years
Presence of neutralizing antibodies	• Eligibility for GT	• Hope of later eligibility (i.e., high-dose GT); meanwhile, EHL concentrates or non-replacement options	• Eligible for non-replacement therapy	
Morphometrical characteristics	• Body weight • Obesity	• Need for intensive education/ patient empowerment • Strategies to enhance self-responsibility • Active weight loss programs		• Obesity/malnutrition • PK • Dose
Concomitant treatment	• Anti-thrombotic • Anti-depressive • Other	• Mostly not applicable in young adults		Concomitant therapy is an important consideration
Acceptability of SC injections		• This should already be established, or additional training programs may be needed		Already established or helped by nurse
Past-treatments	• IV FVIII or FIX • Naïve or non-naïve		Not applicable	Not applicable
Local environment	• Family support • Treatment modalities of other hemophilia patients in the family members/HTC patients • Insights into new treatments	• The individual social situation of young adult hemophiliacs has to be evaluated • Does the patient need any external social support		• No social networking • No information about new treatment possibilities
	• Availability of treatments • Reimbursement • Marketing • Approval	• Is the patient treated by an HTC expert team • Do they have the chance to get recruited in clinical trials		
EQ-5D-VAS		• Significant reporting of moderate/ extreme pain vs older patients; need access to social workers/ physical therapists/career counsellors • Anxiety/depression <50% as moderate/extreme requiring psychological treatment being sought quoting hemophilia as the cause		• Depression, anxiety, dementia, immobility (non-factor replacement product)
Caught in transition		• A lot of change between centers/ cities and education to university		
Pain				• Acute pain (bleeding, arthropathy, trauma): SHL concentrates • Chronic pain: non-factor replacement product

ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; AJSBR, annualized joint spontaneous bleeding rate; AUC, area under the concentration curve; CV, cardiovascular; EHL, extended half-life; EQ-5D-VAS, European quality of life 5 Dimension Visual Analog Scale; FIX, factor IX, FVIII, factor VIII; GT, gene therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTC, hemophilia treatment center; HRQoL, health-related quality of life; IV, intravenous; PK, pharmacokinetics; SC, subcutaneous; SHL, standard half-life; $T_{½}$, terminal half-life; VWF, von Willebrand factor.

patient-specific variables, and the patient/family would add additional weighting on key patient-relevant variables to determine overall rank of each treatment option. For example:

$$W_1[f(x_1)] + W_2[f(x_2]) + W_3[f(x_3)] + W_4[f(x_4)] + \ldots + W_n[f(x_n)] = \textit{Treatment Score}$$

Where:$f(x_n)$ = an objective function of how each treatment option responds to a particular variable, e.g., venous access is one of 25 variables identified. A Delphi process has defined the overall points available for that variable is 5 points out of a total 100 points available for all variables. In relation to venous access, switching to EHL from SHL with the same frequency would maintain current issues and score 2 out of 5, increasing frequency with SHL/EHL would decrease the variable in the comparison (1/5) and subcutaneous (4/5) and gene therapy (5/5) would increase the benefit. W_n = Patient preference weighting, which is more subjective in nature, e.g., one individual is extremely concerned about venous access, which causes even more anxiety than the MDT thought and rates the venous access on a scale of 3 out of 3. As a result, the patient ranks this higher in the decision process, hence increasing the overall weighting of that specific variable in the overall ranking (3 ×

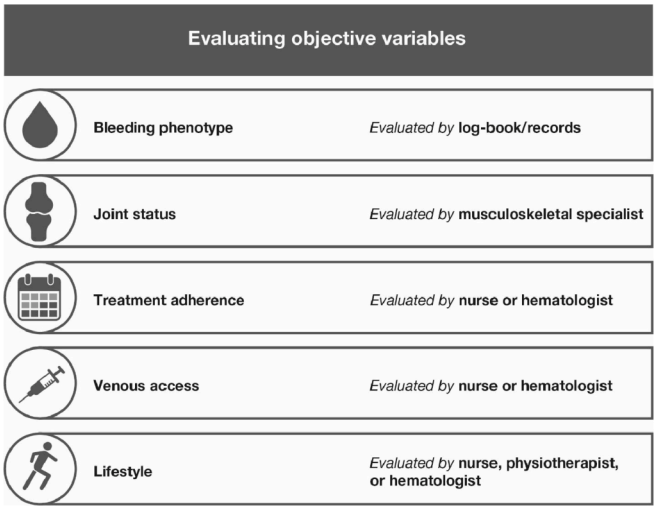

Fig. 2. Assessment methods for evaluating objective variables.

$2 = 6$) for switching to EHL with same frequency (3 for increasing frequency, $3 \times 4 = 12$ for subcutaneous, etc.). If the patient is not anxious about venous access, a lower weighting is applied resulting in different overall total score, changing the ranking. The Supplementary material outlines an illustrative example.

The tool can also include aspects that can be dropped based on specified inputs, e.g., if the patient has a history of inhibitors, then it would be included but if there was no history, then it would be zero, removing it from the calculation and hence re-adjusting the overall weighting for the other variables. Patient weightings are not relevant if there is no subjective component to a given variable (e.g., patient half-life) and in this case W_n would be 1.

2.6.2. *Patient preference tool*

This hypothesized tool, the purpose of which would be to facilitate selection of a treatment that best meets the patient's expectations, would be based on the ranked and weighted variables (described above in Section 2.6.1).

A method for developing and using this tool was proposed. First, four treatment strategies, similar to those used in the clinician's algorithm (Fig. 3), were selected: intensification with SHL products; switch to EHL product; switch to EHL and intensify; switch to a non-factor replacement product. Gene therapy could be included as an option in the future.

The tool, which would be used by the patient/family in conjunction with their MDT, would consist of three major sections. The first would be a "patient/clinical characteristics" section, listing clinical variables that differentiate each patient (e.g., trough levels, bleed frequency, lifestyle, comorbidities, concomitant treatments). The second section would allow clinicians to select which treatment options are currently available. Finally, a "patient preferences" section would be a survey completed by the patient/family according to their preferences, goals, and priorities. This survey would include questions such as, how important to you is having improved protection for your joints and muscles in the future? How difficult is it for you to adhere to your current regimen? How much benefit do you see in having subcutaneous injections over intravenous injections? How much does your mobility concern you? How important are periods of potentially higher protection to you? How comfortable are

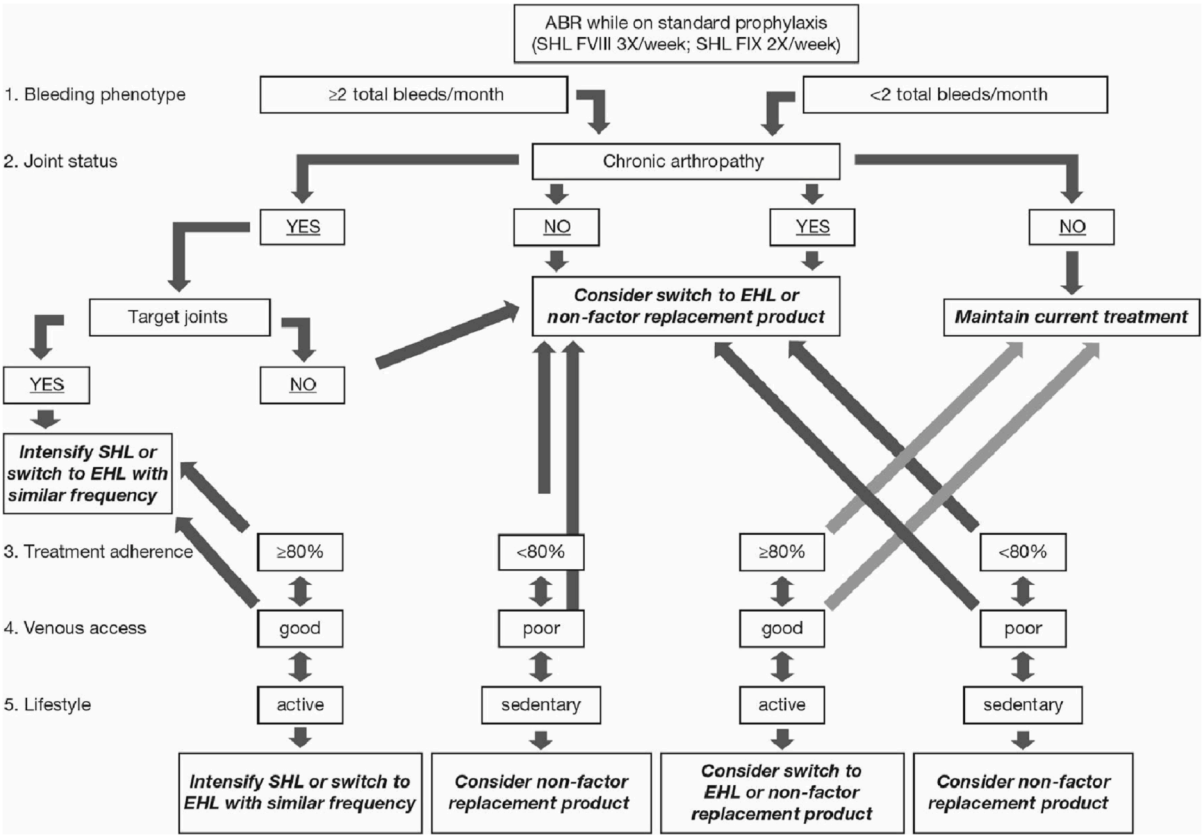

Fig. 3. Algorithm based on objective clinical variables for guiding treatment decisions in hemophilia.
The algorithm should be followed from top to bottom and vice versa. Four main treatment options were identified: maintain current treatment, intensification with current SHL or switch to EHL with similar frequency, consider a non-factor replacement product, or consider switching to EHL, which could be applied to all age-specific categories.
ABR, annualized bleeding rate; EHL, extended half-life; FIX, factor IX; FVIII, factor VIII; SHL, standard half-life.

you when you think about switching treatments? Each question in this survey would have a range of appropriate answers for the patient to select from.

When the clinician and patient have each completed their sections, the tool would calculate a ranking for each of the treatment outcomes, based on the responses given and the weighting of variables. The top three treatment outcomes would be highlighted for each perspective (clinician and patient); it is hoped that these would align, but any discrepancies would be an opportunity for discussion.

This tool could be useful for framing discussions with patients and families to determine what would be right for them over the short-, medium-, and long-term, creating a series of priorities, which could be maximized to guide patients into making the right decision for them. Further, flexibility can be created by adding/removing and reassessing variables as necessary. A potential limitation of assigning relative weight to variables concerns subclinical features, such as synovitis: a patient may be unaware of this condition, but the MDT knows it is important, as the current therapy may no longer be effective. Therefore, when applying a weighting score to variables, some degree of sensitivity may be diminished, and this would need to be considered when determining the relative weight of each variable.

2.7. PUPs

While the expert panel considered the approach described above to be useful for children and older patients, they agreed that a different decision-making process would be required for PUPs, as parents/caregivers of PUPs may be new to hemophilia or unaware of current treatments and recent developments in the field; further, licensed treatment options for this patient group could be different from those available for PTPs and may be supported by less robust data. Therefore, prioritizing variables and treatment options for PUPs may require a different tool incorporating different aims and perspectives.

However, the panel proposed a few considerations regarding shared decision-making for PUPs. Switching is not an issue in these young patients, but decisions about treatment choice should be shared with parents/caregivers. For example, for hemophilia A patients, one such decision is whether treatment should be initiated with replacement therapy or a non-factor replacement product. Comprehensive, long-term data on FVIII prophylaxis are available, but data on PUPs treated with non-factor replacement products are currently limited. Another question regarding replacement therapy concerns the type of product to use (recombinant vs plasma-derived). The inhibitor risk associated with recombinant and plasma-derived FVIII concentrates should be discussed with parents/caregivers, as currently available data are not consistent. Further, while immune tolerance may be desirable, the role of immune tolerance is not always clear and may be changing. Furthermore, it is not yet known how to establish or maintain tolerance with non-replacement therapy without regular FVIII exposure.

Hemophilia B treatment options to date include plasma-derived and recombinant FIX (standard and EHL) products. Non-replacement therapies are not yet available and inhibitor risk is much lower than in hemophilia A. Thus, discussions with parents/caregivers include fewer options and clinical aspects compared to hemophilia A, but follow the same principles discussed above.

3. Discussion

This is the first attempt to develop tools to help the process of selecting optimal treatments for individual patients in the new hemophilia environment. The algorithm for clinicians and the patient preference tool are complementary, and it is hoped that they can be used together in shared decision-making between patients (and the ir families) and HCPs to achieve globally accepted objectives for treatment options that are acceptable to both the patient and the clinician.

Development of these tools is an ambitious but necessary goal in the current era of multiple, heterogeneous treatments. The approach is a holistic, integrative one that actively involves the patient. Allowing the patient's priorities, expectations, and preferences to play such a fundamental role in treatment decisions—and helping patients understand this new, shared decision-making process—may improve their adherence to treatment and thus improve subsequent clinical outcomes. For the hypothesized patient preference tool to be the most beneficial, the language used when asking patients to prioritize variables should be simplified and easy to understand, but the "background" mathematics would be complex to ensure accurate ranking of variables.

As the algorithm and hypothesized patient preference tool have been developed by different health professionals, they offer a multidirectional perspective which overcomes potential bias that may exist among clinicians or patients. This may help all key stakeholders (HCPs, payers, patients) to make more informed treatment decisions. Importantly, the algorithm and patient tool are also applicable across different age groups (children, young adults, adults, elderly patients) as they are based on age-specific consideration of all relevant variables.

The tools and overall approach are currently still in the preliminary stages of development, and the next stage is to fully develop and validate them. It is hoped that, once they have been validated, the tools will offer a way of taking all available therapies and translating them into optimal treatment options for patients, with treatment choices fully supported and understood by patients and their families. When patients decide not to switch to an alternative treatment option, the tools will facilitate discussions between the patient, their family, and MDT, which will enable better understanding of why the patient is making a choice to remain on the current treatment. This may help to establish long-term trust and dialogue that increases the patient's understanding of the technical and clinical aspects of the new treatment options while also allowing a better appreciation of the emotional, social, and psychological context of the patient and the family by MDT members, thus potentially leading to mutual understanding or a change in opinion.

Ultimately, the new approach described in this article potentially offers a way of leading current hemophilia practices in comprehensive care centers into a new way of finding ideal treatments for each patient. However, three important caveats should be noted. First, it is critical that the tools are used within the context of an HTC and not as a substitute for comprehensive, multidisciplinary care; patients, families, and MDT members must all be engaged and involved. Second, while choosing the optimal treatment option is crucial, optimal hemophilia care requires more than hemostatic management alone. Other aspects of patient care will remain important, such as physiotherapy, orthoses, counseling regarding physical activity, and ability to follow a healthy lifestyle. Third, the global therapeutic landscape is very diverse and available resources can vary greatly even within countries. Therefore, some countries may not be able to aspire to this kind of optimal management approach. However, these tools could still be useful and valid, even if a given HTC only has one or two treatment options available. Furthermore, the approach could be used by payers or regulators to drive treatment standards and set the bar high for individual HTCs.

4. Conclusions and future considerations

This article outlines an approach for improving shared decision making between patients and clinicians in the current era of multiple, heterogenous therapeutic options. The overall aim is to aid patients and their MDTs in selecting a treatment that is as efficient as possible for bleed prevention while also considering the patient's clinical needs and expectations. Specifically, it is hoped that the proposed approach will offer substantial benefit to hemophilia teams in three key ways: i) by assisting the decision-making process in terms of treatment selection; ii) by helping the team to set treatment goals that could improve adherence and satisfaction; and iii) by aiding the evaluation and monitoring of treatment efficacy and satisfaction over time. Additionally, the hypothesized patient

preference tool will help patients and their families to better identify th eir own priorities and allow them to play a central role in treatment decisions.

Ideally, the algorithm and patient preference tool should be validated in a real-life setting, such as a study protocol for a multi-site clinical trial. The calculations underpinning the ranking of variables would also be detailed in a study protocol. Another future goal would be to translate the algorithm and patient preference tool into multiple languages so that it can be used more widely and throughout Europe, with other local adaptations related to different treatment-option settings and cultural contexts.

Practice points

- Tools for shared decisions in the new hemophilia treatment landscape are needed
- A treatment algorithm based on objective clinical variables is proposed
- A complementary tool for prioritizing the patient's preference is also hypothesized
- The tools could help select treatments that meet clinician and patient priorities

Research agenda

- Further development of the preliminary treatment algorithm and patient preference tool, along with validation in a real-life setting such as a clinical trial protocol
- Translation of the tools into multiple languages and adaptation for different cultural and treatment contexts

Funding

Funded by a grant from Novo Nordisk.

Author contributions

The manuscript was developed by the experts of the Hemophilia Zürich Forum independent of Novo Nordisk; it does not refer to any commercial products and has no promotional ambition.

C. Hermans initiated and designed the entire project (concept, strategies, and the involvement of co-authors), and developed the first draft. All authors contributed to analysis and/or interpretation of data (tables, figures and algorithm), critical writing, and revising the intellectual content and final approval of the manuscript.

Declaration of Competing Interest

Cedric Hermans: has received grants/research support from: Bayer, CAF-DCF, CSL-Behring, Novo Nordisk, Pfizer, and Sobi; honoraria or consultation fees from: Bayer, Biomarin, CAF-DCF, CSL-Behring, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Sobi, and Uniqure; and speaker bureau fees from Bayer, Biomarin, CAF-DCF, CSL-Behring, LFB, Novo Nordisk, Pfizer, and Sobi.

Declan Noone: declares no conflicts of interest.

Gary Benson: Speaker/advisory board fees from: Bayer, Novo Nordisk, SOBI, Takeda.

Gerry Dolan: Grants from: Pfizer. Honoraria for advice/speaker bureau from: Bayer, Biomarin, CSL Behring, Freeline, Novo Nordisk, Roche, Spark Therapeutics, Takeda.

Hermann Eichler: Honoraria or consultation fees, advisory boards or speaker fees and research grants from: Bayer, Biotest, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire, and SOBI.

Victor Jiménez-Yuste: has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or consulting and/or funds for research from Takeda, Bayer HealthCare, CSL Behring, Grifols, Novo Nordisk, Octapharma, Biomarin, Sanofi, and Pfizer.

Christoph Königs: Speaker or advisory boards for Bayer, Biotest, CSL Behring, Novo Nordisk, Roche/Chugai, Sanofi/Sobi, and Takeda. Institutional research support from Bayer, Biotest, CSL Behring, Intersero, Novo Nordisk, Pfizer, Sanofi/Sobi and Takeda.

Sébastien Lobet: Speaker and advisory board fees from Bayer, Novo Nordisk, Sobi, Takeda, Biomarin, Roche, and Pfizer. Grants from Pfizer and Bayer.

Debra Pollard: Speaker fees/honoraria from: Bayer, BioMarin, CSL Behring, Novo Nordisk, Roche-Chugai, Takeda, Uniqure.

Silva Zupančić Šalek: Reimbursement for attending symposia/congresses and honoraria for speaking and consulting from: Baxter, Novo Nordisk, Pfizer, Roche.

Maria Elisa Mancuso: Speaker, advisory board, and consultancy fees from Bayer, CSL Behring, Catalyst, Biomarin, LFB, Novo Nordisk, Octapharma, Sobi, Takeda, Roche, Pfizer, Grifols, Kedrion, and Spark Therapeutics.

Acknowledgements

Medical writing and editorial assistance (final version) were provided by Jo Fetterman and Julie Smith, Parexel, and funded by a grant from Novo Nordisk. Novo Nordisk neither influenced the content of this publication nor was it involved in the interpretation of its findings. Logistical support for the virtual meetings (Hemophilia Zürich Forum) to produce the manuscript was offered by Novo Nordisk.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2021.100890.

References

[1] Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia 2020;26(Suppl. 6):1–158. https://doi.org/10.1111/hae.14046.
[2] Valentino LA. Blood-induced joint disease: the pathophysiology of hemophilic arthropathy. J Thromb Haemost 2010;8:1895–902. https://doi.org/10.1111/j.1538-7836.2010.03962.x.
[3] Muhlbacher AC, Sadler A, Lamprecht B, Juhnke C. Patient preferences in the treatment of hemophilia A: a best-worst scaling case 3 analysis. Value Health 2020;23:862–9. https://doi.org/10.1016/j.jval.2020.02.013.
[4] Woollard L, Gorman R, Rosenfelt DJ. Addressing patient education priorities in the era of gene therapy for haemophilia: towards evidence-informed shared decision-making. Haemophilia. 2021;27:e302–4. https://doi.org/10.1111/hae.14214.
[5] Soucie JM, Monahan PE, Kulkarni R, Konkle BA, Mazepa MA, Network USHTC. The frequency of joint hemorrhages and procedures in nonsevere hemophilia A vs B. Blood Adv 2018;2:2136–44. https://doi.org/10.1182/bloodadvances.2018020552.
[6] den Uijl IE, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. Haemophilia 2011;17:41–4. https://doi.org/10.1111/j.1365-2516.2010.02383.x.
[7] Nossair F, Thornburg CD. The role of patient and healthcare professionals in the era of new hemophilia treatments in developed and developing countries. Ther Adv Hematol 2018;9:239–49. https://doi.org/10.1177/2040620718784830.
[8] Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. J Gen Intern Med 2012;27:1361–7. https://doi.org/10.1007/s11606-012-2077-6.
[9] Karazivan P, Dumez V, Flora L, et al. The patient-as-partner approach in health care: a conceptual framework for a necessary transition. Acad Med 2015;90:437–41. https://doi.org/10.1097/ACM.0000000000000603.
[10] Scalone L, Mantovani LG, Borghetti F, Von Mackensen S, Gringeri A. Patients', physicians', and pharmacists' preferences towards coagulation factor concentrates to treat haemophilia with inhibitors: results from the COHIBA study. Haemophilia. 2009;15:473–86. https://doi.org/10.1111/j.1365-2516.2008.01926.x.
[11] von Mackensen S, Campos IG, Acquadro C, Strandberg-Larsen M. Cross-cultural adaptation and linguistic validation of age-group-specific haemophilia patient-reported outcome (PRO) instruments for patients and parents. Haemophilia. 2013;19:e73–83. https://doi.org/10.1111/hae.12054.
[12] Gue D, Squire S, McIntosh K, et al. Joining the patient on the path to customized prophylaxis: one hemophilia team explores the tools of engagement. J Multidiscip Healthc 2015;8:527–34. https://doi.org/10.2147/JMDH.S93579.
[13] Wiley RE, Khoury CP, Snihur AWK, et al. From the voices of people with haemophilia A and their caregivers: challenges with current treatment, their

impact on quality of life and desired improvements in future therapies. Haemophilia. 2019;25:433–40. https://doi.org/10.1111/hae.13754.
[14] Elwyn G, Durand MA, Song J, et al. A three-talk model for shared decision making: multistage consultation process. BMJ. 2017;359:j4891. https://doi.org/10.1136/bmj.j4891.
[15] Lamiani G, Bigi S, Mancuso ME, Coppola A, Vegni E. Applying a deliberation model to the analysis of consultations in haemophilia: implications for doctor-patient communication. Patient Educ Couns 2017;100:690–5. https://doi.org/10.1016/j.pec.2016.11.021.
[16] Nilson J, Schachter C, Mulder K, et al. A qualitative study identifying the knowledge, attitudes and behaviours of young men with mild haemophilia. Haemophilia. 2012;18:e120–5. https://doi.org/10.1111/j.1365-2516.2011.02714.x.
[17] Lane SJ, Walker I, Chan AK, et al. Treatment decision-making among Canadian youth with severe haemophilia: a qualitative approach. Haemophilia. 2015;21:180–9. https://doi.org/10.1111/hae.12543.
[18] Gringeri A, Doralt J, Valentino LA, Crea R, Reininger AJ. An innovative outcome-based care and procurement model of hemophilia management. Expert Rev Pharmacoecon Outcomes Res 2016;16:337–45. https://doi.org/10.1080/14737167.2016.1178066.
[19] Sun HL, McIntosh KA, Squire SJ, et al. Patient powered prophylaxis: a 12-month study of individualized prophylaxis in adults with severe haemophilia A. Haemophilia 2017;23:877–83. https://doi.org/10.1111/hae.13319.
[20] Recht M, Konkle BA, Jackson S, Neufeld EJ, Rockwood K, Pipe S. Recognizing the need for personalization of haemophilia patient-reported outcomes in the prophylaxis era. Haemophilia. 2016;22:825–32. https://doi.org/10.1111/hae.13066.
[21] McGarrigle L, Roberts JC, Denne M, Rockwood K. Exploring the responsiveness of goal attainment scaling in relation to number of goals set in a sample of hemophilia A patients. J Patient Rep Outcomes 2019;3:20. https://doi.org/10.1186/s41687-019-0110-9.
[22] Anderson DR, Christison-Lagay J, Procter-Gray E. Self-management goal setting in a community health center: the impact of goal attainment on diabetes outcomes. Diabetes Spectr 2010;23:97–105. https://doi.org/10.2337/diaspect.23.2.97.
[23] Ertzgaard P, Ward AB, Wissel J, Borg J. Practical considerations for goal attainment scaling during rehabilitation following acquired brain injury. J Rehabil Med 2011;43:8–14. https://doi.org/10.2340/16501977-0664.
[24] Rockwood K, Fay S, Song X, MacKnight C, Gorman M. Video-imaging Synthesis of Treating Alzheimer's Disease (VISTA) Investigators. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. CMAJ 2006;174:1099–105. https://doi.org/10.1503/cmaj.051432.
[25] Roberts JC, Lattimore S, Recht M, et al. Goal attainment scaling for haemophilia (GAS-Hem): testing the feasibility of a new patient-centric outcome measure in people with haemophilia. Haemophilia 2018;24:e199–206. https://doi.org/10.1111/hae.13454.