A Special Supplement

DIALOGUES IN HEMOPHILIA

Perspectives and Insights on Hemophilia Treatment for Patients and their Families

Hemophilia Joint Health and Quality of Life: A Pediatric Perspective
Soumitra Tole, MD, FRCPC

Comparing Standard Half-life to Extended Half-life and Beyond: What You Need to Know
Heather Perkins, RN
Nancy Hodgson RN, BSN

Hemophilia Joint Health and Quality of Life: An Adult Perspective
Davide Matino, MD

Hemophilia Joint Health and Quality of Life: A Pediatric Perspective

Soumitra Tole, MD, FRCPC

Dr. Tole is a pediatric hematologist/oncologist in the Division of Hematology/Oncology at Children's Hospital – LHSC, and an Assistant Professor in the Department of Pediatrics at the Schulich School of Medicine, Western University. He is the Medical Director of the Pediatric Bleeding Disorders Program at Children's Hospital. He received his medical training at the University of Toronto before pursuing his residency in pediatrics and fellowship training in pediatric hematology/oncology at The Hospital for Sick Children, Toronto. He completed a clinical fellowship in Pediatric Hemostasis/Thrombosis. Dr. Tole is a member of the Association of Hemophilia Clinic Directors of Canada (AHCDC) and the treasurer of the Canadian Pediatric Hemostasis and Thrombosis Network (CPTHN). He is involved in clinical trials in hemophilia and thrombosis and has clinical and research interests in the fields of pediatric hemostasis, thrombosis, vascular anomalies, and hemoglobinopathies.

BACKGROUND

Hemophilia A and B are rare, inherited X-linked recessive disorders that result in low levels of clotting factor 8 (FVIII, Hemophilia A) or clotting factor 9 (FIX, Hemophilia B). The severity of hemophilia is classified according to the residual amount of FVIII, or FIX produced with <1 IU/dl of activity considered severe, 1-5 IU/dL considered moderate and >5 - <40 IU/dL considered mild hemophilia. Persons with hemophilia carry a lifelong risk of bleeding, and those with severe hemophilia are at risk for spontaneous joint and muscle bleeding starting in the first year of life. Increasingly, there is recognition that persons with moderate and mild hemophilia also carry a significant, albeit much smaller risk for spontaneous joint bleeding[1].

Joint bleeding typically occurs after the first year of life as children become increasingly mobile and mostly affects large joints, particularly the knees, ankles, and elbows. With each successive bleeding event, there is damage to the cartilage within the joint, leading to the thickening and development of new blood vessels (known as angiogenesis) which may predispose the child to further bleeding in the joint. With repeated bleeding in the joint, there can be decreased mobility, instability, muscle weakness, and pain as hemophilic arthropathy develops.

Prior to the availability of clotting factor concentrates, joint bleeding led to debilitating joint damage and arthropathy as well as a reduced lifespan. Over the last thirty years however, there have been tremendous advances in the care of individuals with hemophilia, with the development of recombinant factor concentrates, extended plasma factor half-life, and more recently non-factor therapies. As a result, there has been a shift in the goals of treatment from increasing life expectancy to preventing joint bleeding and protecting against joint damage and the development of hemophilic arthropathy.

HOW DO WE MANAGE BLEEDING EPISODES?

Prophylactic therapy to prevent bleeding is the standard of care for all persons with severe hemophilia and for those with moderate hemophilia with a severe bleeding phenotype[2]. Primary prophylaxis refers to the routine administration of clotting factor concentrates prior to three years of age or any major joint bleed. While primary prophylaxis can be challenging in young children because of poor intravenous access, there is clear evidence that prophylaxis is most effective when initiated early in life[3,4]. In a study of Dutch patients followed over two decades, patients had an 8% worse joint score for every year that prophylaxis was delayed. More recently, the Joint Outcome Continuation Study (JOCS) found that 35% of patients on early prophylaxis had evidence of joint damage as compared to 77% of those who started prophylaxis after 6 years of age[5].

Thankfully, in Canada, we are fortunate to have clotting factor concentrates readily available (**Table 1**). Thus, the vast majority of children with severe hemophilia are started on primary prophylaxis early in life. However, primary prophylaxis can be difficult to initiate in young children due to the difficulties associated with finding venous access (i.e. good veins). Access challenges may then lead to delays in starting prophylaxis, suboptimal regimens, or the insertion of central venous access devices (CVAD). It is during this time, that children with severe hemophilia are at the highest risk of developing an inhibitor, which is the most significant treatment related complication and results in decreased response to therapy and a markedly increased risk of bleeding.

In a Canadian study, the health-related quality of life for youth with hemophilia was comparable to the published data for Canadian males of the same age. However, youth with severe hemophilia had lower scores in physical functioning

	Hemophilia A	Hemophilia B
SHL	Zonovate Xyntha Kovaltry	Benefix
EHL	Eloctate (rFVIII-Fc) Adynovate (rFVIII-PEG) Jivi (rFVIII-PEG) Esperoct (rFVIII-PEG)	Alprolix (rFIX-Fc) Rebinyn (rFIX-PEG)
Non-factor therapy	Emicizumab	

Table 1: *Currently available therapies through Canadian Blood Services; adapted from CBS website*

and higher scores in bodily pain. The lower physical functioning score were directly related to their joint health and having a history of joint bleeding. In the JOCS study that was previously mentioned, participants commented on the inconvenience and pain of regular infusions and the limitations related to entering certain professions (e.g., the military)[5]

However, despite early prophylaxis, patients may still have breakthrough bleeding and may experience subclinical or unrecognized bleeding that can be associated with a risk for joint damage. In a report by the PedNet Study Group, 27% of adolescents with severe hemophilia A without inhibitors and 36% of those with inhibitors had evidence of joint damage when assessed by ultrasound[6]. However, when assessed by the more sensitive MRI scan in the JOCS, over 80% of patients had evidence of joint damage in adolescence, despite early initiation of full prophylaxis[5]. Together, these studies suggest, that more intense prophylaxis may be necessary to improve long-term joint health outcomes and quality of life.

WHAT ARE SOME OF THE WAYS THIS CAN BE ACHIEVED?

The goal of prophylactic therapy has long been to keep a trough factor level between 1-3%. Recently, researchers compared targeting trough FVIII levels of 8-12% to the traditional 1-3% in adolescents and adults[7]. A much larger proportion of those in the higher trough group (67%) had zero bleeds as compared to the lower trough level group (40%). But, while there was less bleeding by targeting higher trough levels, this approach required much more intensive factor replacement which was burdensome and led to many more patients discontinuing the study. Recognizing that patients with a trough level of 1-3% remain at risk for bleeding, the World Federation of Hemophilia guidelines suggest clinicians consider targeting higher trough levels while considering patient preferences and lifestyle[2]. Although this data comes from patients with Hemophilia A, the importance of achieving trough levels above 1-3% in Hemophilia B patients is yet to be established.

Patients and their families should know that the dose and frequency of factor replacement therapy needed to prevent bleeding varies both amongst individuals and within the same individual over time. The half-life, or how long it takes for the infused factor activity to reduce by 50%, is much shorter in young children as compared to adolescents and adults. This means, a fixed regimen may not provide sufficient protection for all individuals. As such, measuring factor activity after an infusion to determine an individual's response to therapy can allow for tailoring the prophylaxis regimen to the individual. In this way, the "right amount of prophylaxis can be given to the right patient"[2].

The development of extended half-life (EHL) factor concentrates has improved the quality of life in patients with severe hemophilia by decreasing the number of infusions and allowing patients to maintain higher factor trough levels. These EHL products utilize technologies such as PEGylation or Fc-fusion to improve the half-life of FVIII concentrates by 1.5 times and FIX concentrates by 3.5-times as compared to standard half-life products. In particular, EHL FIX products allow for infusions every 7-14 days thereby greatly improving the quality of life for children[8]. **Figure 1** compares the PK profile of SHL and EHL products.

Non-factor replacement therapies are transforming prophylaxis for children with hemophilia. Emicizumab is a bi-specific antibody that mimics the function of FVIII by bridging FIX and FX. In doing so, it achieves equivalence of approximately 10-15% of FVIII activity. Notably, unlike traditional factor prophylaxis which has peaks and troughs, Emicizumab provides a steady level of protection without variation (**Figure 1**). Emicizumab has shown significant improvements in bleeding compared to prophylaxis with clotting factors in patients without inhibitors, and similar improvements as compared to bypassing agents in patients with inhibitors[9]. Emicizumab is administered subcutaneously and may be given as infrequently as every 2-4 weeks, eliminating the need for a CVAD. Children treated with emicizumab, and their caregivers, have reported improvements in their quality of life, with "sports and school" and "physical health" being the most improved domains of health[10]. However, it remains unclear how the lack of exposure to FVIII during childhood will impact long-term bone and joint health outcomes. Additionally, although emicizumab is used to help prevent bleeding, it will not stop an active bleed once it has started. Therefore, a factor product is needed in conjunction with emicizumab to help control active bleeds. Several novel non-factor therapies for prophylaxis use in patients with hemophilia A and B, both with and without inhibitors, are currently in clinical trials.

Finally, participation in physical activities should be encouraged from a young age for the associated social, physical, and mental health benefits. A major benefit of physical activity is the prevention of weight gain which places increased stress on joints and is believed to result in worse long-term joint health. Children and caregivers should be counselled to wear

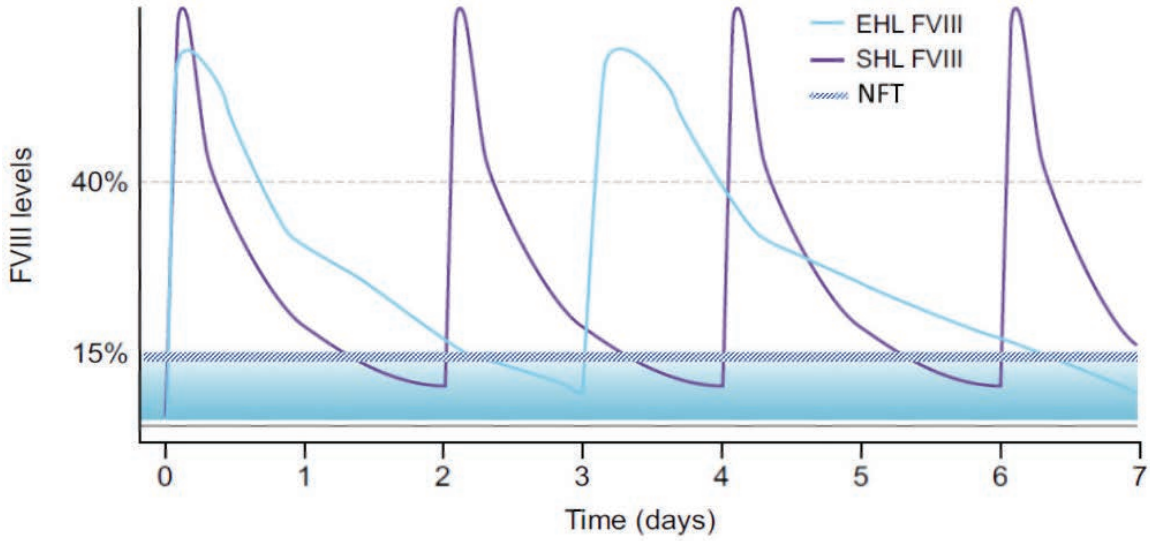

Figure 1: *Comparison of the pharmacokinetic profile of standard half-life (SHL) and extended half-life (EHL) factor concentrates. Non-factor therapies (NFT), such as emicizumab, do not provide FVIII but result in clotting ability equivalent to roughly 10-15% of FVIII activity;* adapted from Berntorp et al., *Blood Reviews,* 2021[11]

appropriate protective equipment such as helmets and knee pads, and the need for physical activity should be balanced. In the JOCS, sport participation was common and did not lead to an increase in hemophilic arthropathy in children on prophylaxis. This suggests that sport participation is related to a transient elevation in bleeding risk and may be mitigated by the factor level at the time of participation. While non-factor therapies provide a steady-state level to prevent bleeding most of the time, they may not be sufficient to protect children who wish to participate in vigorous, high-impact activities or sports.

SUMMARY

In summary, most children and youth with hemophilia in Canada have an overall quality of life comparable to their peers, despite the considerable burden of prophylactic therapy. Even with early initiation of prophylaxis, many adolescents will have MRI evidence of joint damage, suggesting that more intensive prophylaxis may be needed for optimizing joint health into adulthood. EHL and non-factor therapies allow maintenance of higher trough levels while reducing the burden of prophylactic infusions. Tailoring prophylactic regimens to the individual patient based on patient preferences and lifestyle is important to maximize long-term joint health and quality of life.

REFERENCES

1. Di Minno MN, Ambrosino P, Franchini M, Coppola A, Di Minno G. Arthropathy in patients with moderate hemophilia a: a systematic review of the literature. Semin Thromb Hemost. 2013;39(7):723-731.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158.
3. Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. Blood. 2002;99(7):2337-2341.
4. Astermark J, Petrini P, Tengborn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. Br J Haematol. 1999;105(4):1109-1113.
5. Warren JT, Link DC. Clonal hematopoiesis and risk for hematologic malignancy. Blood. 2020;136(14):1599-1605.
6. Schmidt DE, Michalopoulou A, Fischer K, et al. Long-term joint outcomes in adolescents with moderate or severe haemophilia A. Haemophilia. 2022.
7. Klamroth R, Windyga J, Radulescu V, et al. Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study. Blood. 2021;137(13):1818-1827.
8. Astermark J, Hermans C, Ezzalfani M, et al. rFIXFc prophylaxis improves pain and levels of physical activity in haemophilia B: Post hoc analysis of B-LONG using haemophilia-specific quality of life questionnaires. Haemophilia. 2022;28(1):18-26.
9. Callaghan MU, Negrier CG, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with/without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 2020.
10. Mancuso ME, Mahlangu J, Sidonio R, Jr., et al. Health-related quality of life and caregiver burden of emicizumab in children with haemophilia A and factor VIII inhibitors-Results from the HAVEN 2 study. Haemophilia. 2020;26(6):1009-1018.
11. Berntorp E, Hermans C, Solms A, Poulsen L, Mancuso ME. Optimising prophylaxis in haemophilia A: The ups and downs of treatment. Blood Rev. 2021;50:100852.

Comparing Standard Half-life to Extended Half-life and Beyond: What You Need to Know

Heather Perkins, RN

Heather Perkins completed a diploma of Nursing at St Lawrence College in 1989. She started her nursing career the same year at the Children's Hospital of Eastern Ontario (CHEO) and remains there presently. In 2006 she obtained her Post RN, BScN from St Francis Xavier University distance nursing program. In the early years at CHEO she worked on infant surgery, transitional living and Pediatric Intensive Care Units. After working in the Oncology program for 13 years, she took the opportunity to transition to the Bleeding Disorder Program in 2015 as a clinical nurse coordinator. She is affiliated with the CHEO Research Institute as the research nurse on several Hemophilia clinical trials.

Heather's affiliation with Canadian Nursing Association (CNA) and American Pediatric Hematology Oncology Nursing Association (APHON) included pediatric expertise for CNA Oncology Certification exam development and as a certified APHON chemotherapy/biotherapy instructor. At this time, she is the President of the Canadian Association of Nursing in Hemophilia Care (CANHC). She has co-authored journal articles and presented at symposiums within the bleeding disorder community.

Nancy Hodgson RN, BSN

Nancy Hodgson completed her nursing in 1993. She started her nursing career by working in the pediatric intensive care unit, looking after the most critically ill children in Saskatchewan. In 1998 she joined the newly developed Saskatchewan Pediatric Transport Team which moves sick and injured children between medical centers in Saskatchewan. In 2008 Nancy took the opportunity to join the Saskatchewan bleeding disorders program (SBDP) as a clinical nurse coordinator and has been part of this team ever since. The SBDP treatment center looks after both adult and pediatric patients and consists of approximately 450 registered patients combined.

Nancy is also a clinical research nurse coordinator with the Saskatchewan Bleeding Disorders Program and with the Office of the Vice Dean Research – Clinical Trial Support Unit through the University of Saskatchewan. Research clinical trials she has been involved in includes congenital bleeding disorder related, gastrointestinal clinical trials for crohn's and ulcerative colitis, cardiology, post myocardial infarction (MI) trials, and COVID19 convalescent plasma clinical trials.

Nancy is affiliated with several associations, including the Registered Nurses Association of Saskatchewan (SRNA), Canadian Nursing Association (CNA) and the Canadian Association of Nursing in Hemophilia Care (CANHC). She recently finished her term on the CANHC executive as President Elect, President, and Past President. She has presented at regional and national symposiums and has been involved as a co-author in published articles in journals such as *Blood* and *Hemophilia*.

INTRODUCTION

For patients with Hemophilia A or B, treatments have evolved significantly over the years. Standard half-life (SHL) products have been a great option however the need for frequent treatments can be burdensome for most.

The development of extended half-life (EHL) products has the potential to provide better coverage and less frequent infusions which can also lead to improved quality of life without compromising treatment effectiveness and safety.

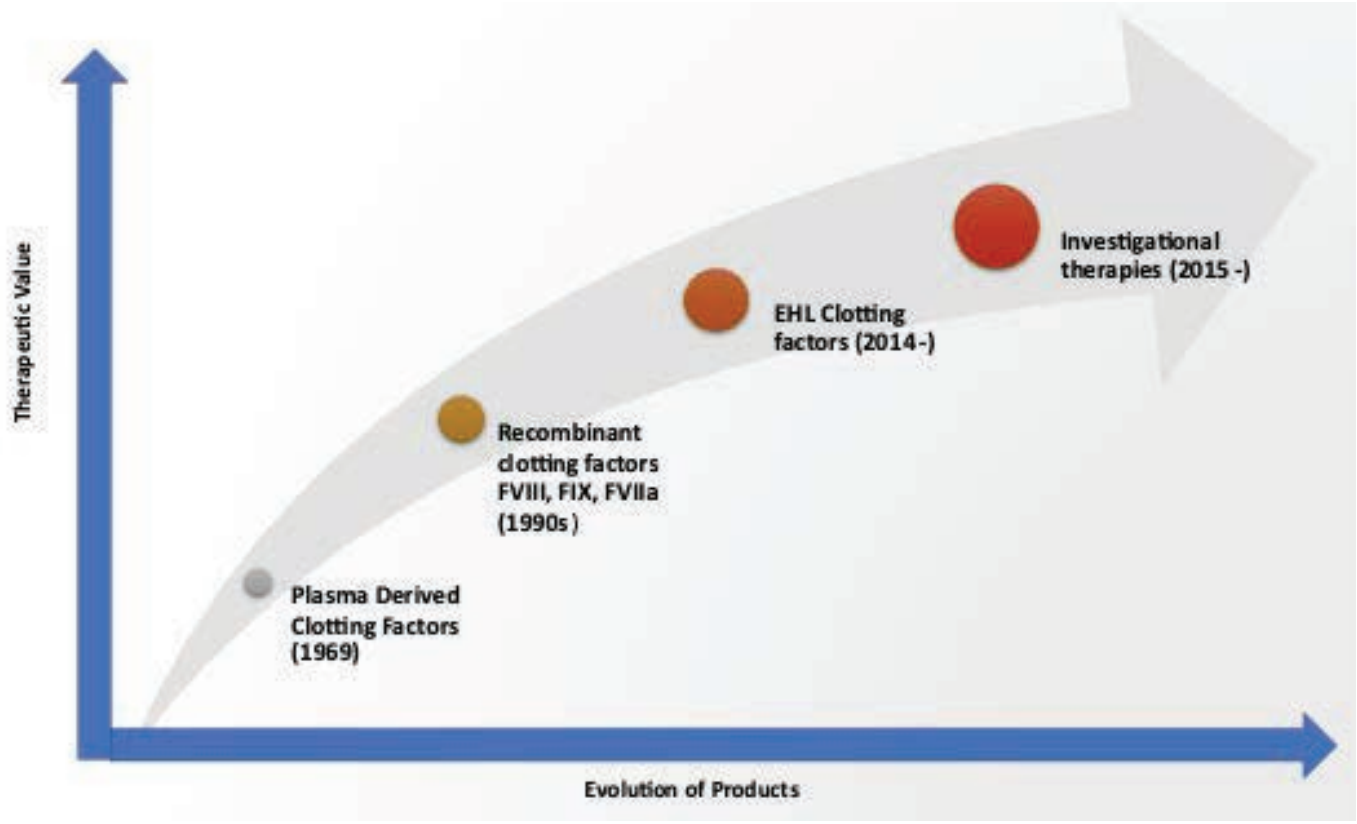

Figure 1. *Evolution of Hemophilia Treatment;* adapted from Dabney, 2022[1]

WHO CAN USE SHL AND EHL PRODUCTS?

Both SHL and EHL products are available to pediatric and adult patients who have hemophilia A or B. With some EHL products there may be restrictions on their use, such as pediatric vs adult use, or prophylaxis vs surgical use. Be sure to discuss these restrictions with your treatment team if you are considering using an EHL product.

When discussing either SHL or EHL products for your child with hemophilia, consider inquiring if the product has been studied in a pediatric clinical trial. Clinical trials can provide information about important elements such as product safety, usefulness and the occurrence of possible inhibitor development when used in children. Published clinical trial results can be made available to you by your treatment center.

HOW DO EHL PRODUCTS WORK COMPARED TO SHL PRODUCTS?

With EHL products, a variety of innovative technologies have been used to prolong the half-life of recombinant factor VIII (8) (rFVIII) and recombinant factor IX (9) (rFIX) protein. These technologies include fusion of the fragment-crystallizable (Fc) part of immunoglobulin G (IgG) or albumin to recombinant protein and attachment of a polyethylene glycol (PEG), which groups to the protein and results in pegylation[2]. Products using Fc fusion allow factor to use a naturally occurring biological pathway for the extension of half-life. Pegylated products contain a synthetic molecule that increases the half-life by allowing the factor to be eliminated from the body at a slower rate. SHL products are considered much simpler in their structure as they are either plasma-derived or they use standard recombinant technology, however their half-life is typically shorter as compared with EHL products.

WHAT ARE SOME OF THE BENEFITS OF USING EHL PRODUCTS COMPARED TO SHL PRODUCTS?

Each individual may respond differently to treatment. Some benefits of EHL therapies include fewer injections and higher trough levels compared with SHL products which may result in better protection against spontaneous bleeding events.

Factor concentrate	Manufacturer	Indicated for all ages for routine prophylaxis, on-demand treatment, surgery	Storage temp. (°C)/max RT(°C) x (months of RT storage)‡	Rate of admin	Average t1/2 (h)	Molecule & Cell line	Assay (for selected products)	Home care services ¥
Factor VIII recombinant (rFVIII), human –standard half-life								
KOVALTRY® **CBS**	BAYER	Yes	2 - 8/25 (12 mths at RT)	over several min (comfort level)	13.8	Full length rFVIII (BHK)	Standard aPTT based clotting assay	Bayshore Speciality RX
XYNTHA **CBS**	Pfizer	Yes	2 - 8/25 (3 mths at RT)	over several mins (comfort level)	14.8	B-domain deleted FVIII (CHO)	Standard aPTT based clotting assay	Shoppers Drug Mart Specialty Health Network Inc.
ZONOVATE® **CBS**	novo nordisk	Yes	2 - 8/30 (12 mths at RT)	at 1-2 ml/min	0.69 (age ≥12y) 8.92 (age 6 - 11y) 7.65 (age <6y)	B-domain deleted (CHO)	Standard aPTT based clotting assay	Innomar Strategies
Factor VIII recombinant – extended half-life								
ADYNOVATE **CBS**	Takeda	Yes	2 - 8/30 (3 mths of RT)	over ≤ 5 mins (Max. 10 ml/min)	14.69 (age ≥ 18y) 13.43 (age 12 - 17y)	Recombinant FVIII conjugate with 20 kDa polyethylene glycol (PEGylated rFVIII) (CHO)	Chromogenic or one-stage (no reagent preference)	Innomar Strategies
JIVI® **CBS**	BAYER	"No." **Indicated for Patients ≥12 yrs for** routine prophylaxis, on-demand treatment, surgery	2 - 8/25 (6 mths of RT) 30 (3 mths at RT)	Max 2.5 ml/min	~17.6h (age ≥12 y)	B-domain deleted rFVIII conjugated with 60 kDa polyethlene glycol. (PEGylated rFVIII) (BHK)	Chromogenic or one-stage (preference reagents: SynthASil® [Instrumentation Lab]; Pathrombin® [Siemens])	Bayshore Speciality RX
ELOCTATE® **CBS (available in QC via special access)**	sanofi	Yes	2 - 8/30 (6 mths at RT)	over several mins (comfort level)	19	Recombinant fusion protein (B-domain deleted FVIII and dimeric Fc component of human IgG1) (HEK)	Standard aPTT based clotting assay	Bayshore Speciality RX
ESPEROCT® **CBS HQ**	novo nordisk	Yes	2 - 8/24 (6 mths at RT) 2 - 8/30 (3 mths at RT)	over 2 min	19.9 (age ≥18y) 15.8 (age 12 - <18y) 14.2 (age 6 - <12y) 13.6 (age <6y)	B-domain truncated (21 aa remaining) rFVIII conjugated with 40 kDa polyethylene glycol (PEGylated rFVIII) (CHO)	Chromogenic, or one-stage (avoid silica-based aPTT reagents - some silica-based aPTT reagents can underestimate FVIII level by up to 50%)	Innomar Strategies

Factor concentrate	Manufacturer	Indicated for all ages for routine prophylaxis, on-demand treatment, surgery	Storage temp. (°C)/max RT(°C) x (months of RT storage)‡	Rate of admin	Average t1/2 (h)	Molecule & Cell line	Assay (for selected products)	Home care services ¥
Factor IX recombinant (rFIX) – standard half-life								
BENEFIX® **CBS**	Pfizer	Yes	2 - 8/25 (6 mths at RT)	over several mins (comfort level)	18.8	(CHO)	Standard aPTT based clotting assay	Shoppers Drug Mart Specialty Health Network Inc.
RUXUBIS **HQ**	Takeda	Yes	2 - 8/30 (36 mths at RT)	Max 10 ml/min	26.7	(CHO)	Standard aPTT based clotting assay	Innomar Strategies
Factor IX recombinant – extended half-life								
ALPROLIX® **CBS (available in QC via special access)**	sanofi	Yes	2 - 8/30 (6 mths at RT)	over several mins (comfort level)	82.1	Recombinant fusion protein of FIX and dimeric Fc component of human IgG1 (rFIXFc) (HEK)	Standard aPTT based clotting assay	Bayshore Speciality RX
REBINYN® **CBS**	novo nordisk	Yes	2 - 8/30 (6 mths at RT)	Max 4ml/min	115 (age ≥ 18y) 103 (age 13 - 17y)	Recombinant FIX conjugate with 40 kDa polyethylene glycol (PEGylated rFIX) (CHO)	Chromogenic or one-stage (preferred reagents: SynthAFax®, [Instrumentation Lab]; STA®-Cephascreen [Diagnostica Stago]	Innomar Strategies
IDELVION® **CBS (available in QC via special access)**	CSL Behring	Yes	2 - 25 (no RT indication)	over several mins (comfort level)	104.2 (age ≥ 18y) 87.3 (age 12 - <18y) 91.0 (age 1 - <12y)	Recombinant fusion protein of FIX and albumin (CHO)	One-stage clotting (NOTE: use of kaolin-based aPTT reagent or Actin FS aPTT reagent will likely result in an underestimation of FIX activity)	None

Note: Some products may be licensed by Health Canada but not carried on the Canadian Blood Services and/or Héma-Québec formulary. **CBS** = carried by Canadian Blood Services, **HQ** = carried by Héma-Québec, NA = not available; licensed in Canada but not distributed by Canadian Blood Services or Héma-Québec. NOTE: ‡ Maximum room temperature (RT) (usually ≤25°C or ≤30°C) storage period in months is stated only if the concentrate is to be stored refrigerated (2–8°C). Manufacturers recommend that once the concentrate has been removed from the required refrigeration and stored at RT, the date removed from refrigeration should be marked on the box and the product should not be returned to refrigeration. Cell lines: Baby hamster kidney (BHK) Chinese hamster ovary (CHO) Human embryo kidney (HEK) ¥ Home care services offered at the time of publication.

Poon M, Goodyear D, Rydz N, Lee A. Chapter 5, Concentrates for hemostatic disorders and hereditary angioedema. In: Clarke G, Abe T, editors. Clinical Guide to Transfusion [Internet]. Ottawa: Canadian Blood Services, 2022. Accessed on March 4, 2023. https://professionaleducation.blood.ca/en/transfusion/clinical-guide/concentrates-hemostatic-disorders-and-hereditary-angioedema

Table 1 contains examples of currently available EHL and SHL FVIII and FIX products.Personal goals & individualization of prophylaxis.

When discussing the differences between SHL and EHL products, your personal goals play an important role in ensuring that an individualized approach is considered during conversation with your hemophilia care team[3]. For example, you may be a very active individual in sports, or you may have a very physically demanding job. Your factor choice, dose and regimen will look very different as compared to someone with a desk job, who may be more sedentary. If you bleed very easily or have target joints that have had numerous past bleeds resulting in joint damage and subsequent hemarthrosis. Again, your choice of product, dosing and treatment regimen will vary compared to someone that hasn't experienced these same issues. These scenarios can hold true for both adult and pediatric patients with hemophilia. Additionally, there may be important life changes such as starting a family, a new job or going away to school that can influence your factor choice and the regimen that fits in with these new life changes.

The use of SHL products continues to be a sought-out treatment approach for many adult patients with hemophilia. Some adult patients prefer to treat themselves daily with a low dose approach. The benefit of this approach is that patients will have good knowledge of where their factor levels are throughout a 24-hour period and patients will have incorporated infusions as part of their daily routine, making them less likely to miss treatments. The downside to using SHL therapies on a daily basis is that patients would have to be comfortable with giving themselves daily needles and would need to have excellent venous access. Patients will also need to have a large inventory of factor therapy at home which can take up a lot of space.

Another approach that may be considered with SHL therapy is a regimen of every other day or two-to-three times a week.[4] These prophylaxis regimens have been used by hemophilia treatment centers for years in both the adult and pediatric population. The benefit with this type of regimen is that it results in a lower frequency of infusions, resulting in less needle-sticks and a lower amount of factor needed to keep at home. For many, this approach is easy enough to keep incorporate into a weekly routine, for others it may not fit, which can make it easy to forget. The downside to the SHL approach of every other day or two-to-three times per week is that it is still requires many injections and in spite of the intensity of the treatment regimen, patients may still encounter periods between infusions where they are left with low factor levels. This could leave patients unprotected until such time that the next infusion is required. Data from real world utilization shows that patients who switch from SHL to EHL products have improvement in their bleeding outcomes.

The introduction and utilization of EHL products has provided benefit for those who struggle with maintaining a frequent and regular prophylaxis routine, while also providing a great option for those who may have difficult venous access. EHL products offer the possibility of less frequent infusions such as weekly or even biweekly for adults with hemophilia B, while still providing excellent factor levels for effective bleeding coverage compared to the SHL products[5]. Less frequent infusions result in fewer needle-sticks, and the need for a lower amount of factor needed to be kept in the home or when traveling. Patients with hemophilia A likely won't be able to extend their time between infusions as much someone with hemophilia B, however EHL products will still provide those patients with hemophilia A with more options for individualizing their treatment approach and optimizing their coverage during and between treatments.

Exercise and Sports

Regular exercise throughout a person's life with hemophilia is important. Traditionally with SHL products, prior to any type of sports or physical activity, patients with hemophilia would have to treat prophylactically just prior to the activity in order to ensure high enough factor levels to protect against trauma. This would be necessary because of the short half-life of the SHL product, keeping in mind that factor levels would have already gone down to a baseline level since the last prophylactic treatment. Research has also shown us that every patient's genetics are unique with respect to the factor level needed to help prevent bleeding episodes[6]. Using a patient's previous bleeding history and pharmacokinetic (PK) profile with the product that they are currently taking, may provide valuable information that can further guide appropriate treatment.

A PK assessment is not necessary when starting on an EHL product, however, knowing what the patient's PK profile looks like will allow the hemophilia treatment center to plan out a treatment regimen that works best for the patient's activity schedule.[7]

Traveling

Traveling with SHL products requires significant preparation including planning for storage space. Having to pack many bulky boxes of factor concentrates and supplies (needles and syringes) for these items can fill up a patient's carry-on luggage. On the other hand, traveling with EHL products can be more convenient, as generally patients do not need to pack as many treatments and supplies. Most SHL and EHL products have been approved for storage at room temperature, up to 25°C or 28°C for periods of 3 to 12 months, depending on the product. Always check the product's package insert for specific storage recommendations or ask your hemophilia treatment center.

WHAT ABOUT NONFACTOR MEDICATIONS?

Hemlibra®(emicizumab) is a nonfactor medication approved for use in Hemophilia A patients with some restrictions. Please ask your hemophilia care team about these restrictions and how they might impact you. Hemlibra is a monoclonal antibody that functions in place of the missing factor VIII in people with Hemophilia A. It is used to help prevent bleeding but will not stop an active bleed once it has started. Therefore, a SHL or EHL factor product is used in conjunction to help control bleeding. Hemlibra is administered under the skin (subcutaneously) every 1 to 4 weeks depending on your personalized treatment plan. There are also nonfactor medications in clinical trials for adults and children affected with Hemophilia B.

CONCLUSION

A good understanding of the differences between SHL and EHL products offers those with hemophilia the ability to better individualize their treatment options and to choose the therapy that works best for their lifestyle. For certain patients, treating with low dose factor on a more frequent schedule may be the best option and for others it may be higher doses and fewer injections. The nonfactor medications can provide patients with coverage alongside reduced burden of care, however patients should take note that these therapies will not stop an active bleed once it has started. Therefore, a factor product is needed in conjunction with these nonfactor medications to help control active bleeds. Understanding products that are currently available allows patients and their families to revise treatment plans in alignment with their ever-changing lifestyle and needs. The right treatment option can be achieved through open communication with your hemophilia treatment center. Having an individualized treatment plan has the potential to improve quality of life.

REFERENCES

1. Jillian Dabney. The Evolution of Hemophilia Treatment—And What It Means for BioMarin. Market Realist. July 7, 2016. Retrieved on July 26, 2022 from https://marketrealist.com/2016/06/evolution-hemophilia-treatment-means-biomarin/

2. Ar MC, Balkan C, Kavaklı K. Extended Half-Life Coagulation Factors: A New Era in the Management of Hemophilia Patients. Turk J Haematol. 2019;36(3):141-154. doi:10.4274/tjh.galenos.2019.2018.0393

3. Poon MC, Lee A. Individualized prophylaxis for optimizing hemophilia care: can we apply this to both developed and developing nations?. Thromb J. 2016;14(Suppl 1):32. Published 2016 Oct 4. doi:10.1186/s12959-016-0096-y

4. Johannes Oldenburg; Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. Blood 2015; 125 (13): 2038–2044. doi: https://doi.org/10.1182/blood-2015-01-528414

5. Michael McCall, Pamela Koerner, Rick Miller & Melanie Radi (2019) Comparison of extended to standard half-life recombinant factor VIII therapy in patients with hemophilia A on prophylactic therapy, Journal of Drug Assessment, 8:sup1, 46-47, DOI: 10.1080/21556660.2019.1658327

6. Christine L. Kempton. Prophylaxis in hemophilia: how much is enough?. Blood 2021; 137 (13): 1709–1711. doi: https://doi.org/10.1182/blood.2020009603

7. Croteau, S.E. and Neufeld, E.J. (2015), Transition considerations for extended half-life factor products. Haemophilia, 21: 285-288. https://doi.org/10.1111/hae.12683

Hemophilia Joint Health and Quality of Life: An Adult Perspective

Davide Matino, MD

Dr. Davide Matino is an Assistant Professor of Medicine at McMaster University in Hamilton, Ontario, Canada. Dr. Matino obtained his medical degree at the University of Perugia and completed his residency training at the University of Rome “Tor Vergata”. He completed his Clinical Fellowship in Bleeding disorders at McMaster University where he also received his MSc in Health Research Methodology. Prior to joining faculty at McMaster University in 2020 he was working at the University of Perugia as Assistant Professor in the Department of Experimental Medicine, leading a research project focused on the study of the immune response to FVIII in hemophilia, funded by the Italian Ministry of Health. He is actively engaged in the care of patients with bleeding disorders and his research is focused on inhibitor development in hemophilia A, personalized-prophylaxis regimens in hemophilia, and the treatment of hemophilia patients with inhibitors. Dr. Matino contributes to education in the field of bleeding disorders locally, nationally and internationally. He is an active clinical trial investigator involved in numerous trials in the field of thrombosis and haemostasis. Dr Matino also directs a basic research lab investigating coagulation factor VIII and factor IX and the molecular mechanisms of hemophilia A and B. His work has received several awards and has been presented both nationally and internationally at the International Society for Thrombosis and Haemostasis, American Society of Hematology, and other scientific meetings. He is an active member of the Association of Hemophilia Clinic Directors of Canada (AHCDC) and a member of the Local Organising Committee for the Montreal 2023 International Society on Thrombosis and Haemostasis (ISTH) scientific meeting.

BACKGROUND

Patients with severe hemophilia (coagulation factor < 1% of normal) can experience spontaneous bleeding (i.e., bleeding for no apparent reason/in the absence of notable trauma), and these bleeds can occur in the joints, muscles, and soft tissues. Patients may also experience excessive bleeding following trauma or surgery.

Treatment of patients with hemophilia involves the administration of clotting factor concentrate (CFC) either in response to a bleeding episode or to prevent these episodes (prophylaxis). These must be given intravenously. An alternative approach for the prevention of hemorrhages that does not involve factor replacement in severe hemophilia A specifically consists of the subcutaneous administration of a monoclonal antibody (emicizumab) that mimics the activity of FVIII. The goal of this therapy is to avoid all bleeds, with the aim of ensuring that patients are protected from the detrimental consequences of bleeding episodes. In situations where a bleed does occur, clotting factors are needed to manage those acute situations. These consequences can develop acutely (e.g. a life-threatening, major gastrointestinal bleeding episode) or may also have chronic, long term consequences, including bleeding into the joints (hemarthrosis) as shown in **Figure 1**.

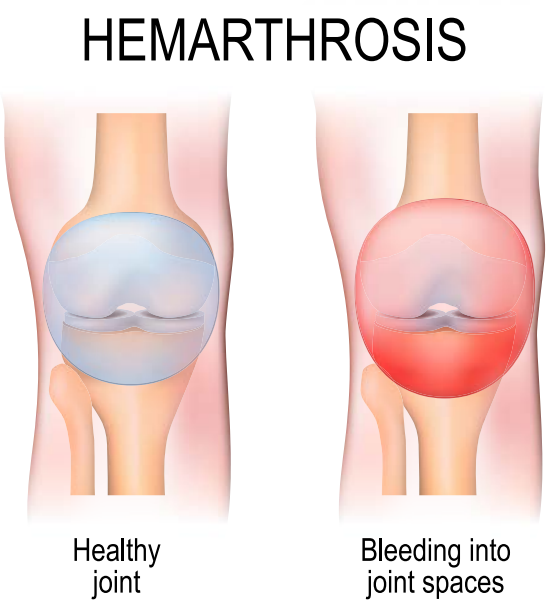

Figure 1. *Difference between a healthy joint and one with hemarthrosis*

In fact, in the absence of prophylaxis, patients with severe hemophilia can experience recurrent joint bleeds, most frequently in the knee, ankle and elbow joints. These repeated bleeding episodes are the cause of joint damage which results in chronic pain, functional limitations, joint deformities, and difficulty with activities of daily living; ultimately, this can impact the health-related quality of life (HRQoL) of people with hemophilia.

Prophylactic replacement therapy is very effective in preventing bleeds and reduces or even prevents subsequent haemophilic arthropathy[2] Numerous studies have tried to assess the burden of haemophilia on HRQoL[3,4]. The EQ-5D is one of the most frequently used disease non-specific generic tools for assessing HRQOL[5] together with the 36 -item Short Form Survey (SF36)[6]. However, a specific tool for hemophilia has also been validated and used in several studies (Haem-A-QoL)[3]

The relationship between joint health and health-related quality of life has been explored recently and is an important consideration for patients. The main results of these studies are discussed in this article.

RESULTS FROM A MULTI-CENTER STUDY IN THE UNITED STATES: JOINT HEALTH AND QUALITY OF LIFE IN SEVERE HEMOPHILIA A.

In the USA, data collected from May 1998 through September 2011 at hemophilia treatment centers were used to explore the association between joint disease and quality of life[7]. The study looked at 1859 males (>14 years of age) with severe haemophilia A who had completed at least one quality of life survey. Interestingly, researchers found that there was a strong association between joint disease and quality of life in this study. Patients with indicators of joint disease were found to have a substantially decreased health-related quality of life within each age group. The results suggested that this risk factor alone (joint disease) is primarily responsible for the decreased quality of life observed in persons with severe haemophilia. Interestingly, after considering the presence of joint disease, bleeding episodes did not appear to have a significant direct impact on quality of life.

HRQOL IN SEVERE HEMOPHILIA A AND B: RESULTS FROM A WESTERN EUROPEAN STUDY.

An analysis from Europe conducted in 2018[8] provided insights into how joint damage can influence quality of life . This study included patients with severe haemophilia A and B from five European countries (France, Germany, Italy, Spain, and the UK) who averaged 37 years of age.

Almost two-thirds (61.0%) of these patients were on factor prophylaxis therapy at the time of the study. Overall, the findings of this analysis suggested an association between musculoskeletal complications of haemophilia and quality of life: patients with no recorded target joints affected by their hemophilia had the highest mean quality of life scores; also, the number of target joints affected by hemophilia was inversely correlated with both scores.

HAEMOPHILIA JOINT HEALTH SCORE AND HRQOL: RESULTS FROM NORTHERN EUROPE

In another study with hemophilia A patients from Denmark, Norway and Sweden it was shown that an increase in a patient's hemophilia joint health score was significantly associated with a reduced quality of life score. This study confirmed the significance of the impact of joint manifestations on quality of life among people with hemophilia. Other studies from Greece, Korea, France, The Netherlands and Belgium have also supported the data that has been presented and confirms that there is a strong association between quality of life and joint health.

CONCLUSIONS

Joint health has been shown to have a significant impact on the quality of life of patients with hemophilia A and B in numerous studies. The prevention of the detrimental, long-term consequences of the joint bleeding remains an important goal of prophylactic therapy. A continued effort to reduce the risk of joint damage among patients with hemophilia with adequate prophylaxis, particularly beginning at a young age, is important in order to reduce the potential future burden on their quality of life.

REFERENCES

1. Iorio A, Stonebraker JS, Chambost H, 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(8):542-546. doi:10.7326/M19-1208
2. Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database of Systematic Reviews. 2011;(9). doi:10.1002/14651858.CD003429.PUB4/INFORMATION/EN
3. Wyrwich KW, Kri Shn An S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Wiley Online Library. 2015;21(5):578-584. doi:10.1111/hae.12642
4. Fischer K, van der Bom JG, van den Berg HM. Health-related quality of life as outcome parameter in haemophilia treatment. Haemophilia. 2003;9(SUPPL. 1):75-82. doi:10.1046/J.1365-2516.9.S1.13.X
5. Brazier J, Ratcliffe J, Saloman J, Tsuchiya A. Measuring and Valuing Health Benefits for Economic Evaluation.; 2017. Accessed September 18, 2022. https://books.google.it/s?hl=en&lr=&id=r3R4DQAAQBAJ&oi=fnd&pg=PP1&dq=Brazier+J,+Ratcliffe+J,+Tsuchiya+A,+Salomon+J.+Measuring+and+valuing+health+benefits+for+economic+evaluation.&ots=y0cTzSPF1m&sig=IWJN0P2SVpsq364_5SCV1t-Q9ys
6. Jr JW, care CSM, 1992 undefined. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. JSTOR. Accessed September 18, 2022. https://www.jstor.org/stable/3765916
7. Soucie JM, Grosse I S D, Siddiqi AEA, et al. The effects of joint disease, inhibitors and other complications on health-related quality of life among males with severe haemophilia A in the United States. Wiley Online Library. 2017;23(4):287-293. doi:10.1111/hae.13275
8. O'Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. Health Qual Life Outcomes. 2018;16(1). doi:10.1186/S12955-018-0908-9
9. So MO, Li O, Steen Carlsson † K, et al. The association between health utility and joint status among people with severe haemophilia A: findings from the KAPPA register. Wiley Online Library. 2017;23(3):e180-e187. doi:10.1111/hae.13231
10. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. Wiley Online Library. 2006;12(5):518-525. doi:10.1111/j.1365-2516.2006.01312.x
11. Varaklioti A, Kontodimopoulos N, Niakas D, Kouramba A, Katsarou O. Health-related quality of life and association with arthropathy in Greek patients with hemophilia. journals.sagepub.com. 2018;24(5):815-821. doi:10.1177/1076029617733041
12. Haemophilia CY, 2013 undefined. The impact of haemarthropathy on the QoL of Korean severe haemophilia A patients: the critical level of haemarthropathy for the QoL. Wiley Online Library. 2013;19(4):637-641. doi:10.1111/hae.12131
13. Fischer K, van der Bom JG, Molho P, et al. Prophylactic versus on-demand treatment strategies for severe haemophilia: A comparison of costs and long-term outcome. Haemophilia. 2002;8(6):745-752. doi:10.1046/J.1365-2516.2002.00695.X
14. Molho P, Rolland N, Lebrun T, et al. Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. Haemophilia. 2000;6(1):23-32. doi:10.1046/J.1365-2516.2000.00358.X
15. Fisc Her K, de Kleijn P, Negrier C, et al. The association of haemophilic arthropathy with Health-Related Quality of Life: a post hoc analysis. Wiley Online Library. 2016;22(6):833-840. doi:10.1111/hae.13120
16. Pettersson H, Ahlberg Å, and INC orthopaedics, 1980 undefined. A radiologic classification of hemophilic arthropathy. europepmc.org. Accessed September 18, 2022. https://europepmc.org/article/med/7408294
17. Carvalhosa AM, Henrard S, Lambert C, Hermans C. Physical and mental quality of life in adult patients with haemophilia in Belgium: The impact of financial issues. Haemophilia. 2014;20(4):479-485. doi:10.1111/HAE.12341

A Special Supplement

DIALOGUES IN HEMOPHILIA

Perspectives and Insights on Hemophilia Treatment for Patients and their Families

Hemophilia Joint Health and Quality of Life: A Pediatric Perspective
Soumitra Tole, MD, FRCPC

Comparing Standard Half-life to Extended Half-life and Beyond: What You Need to Know
Heather Perkins, RN
Nancy Hodgson, RN

Hemophilia Joint Health and Quality of Life: An Adult Perspective
Davide Matino, MD

MAT-CA-2300562