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COMMENTARY

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Prophylaxis re-visited: The potential impact of novel factor and non-factor therapies on prophylaxis

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Prophylaxis, defined, as the regular replacement of the missing clotting factor given, in anticipation of, and with the intent to, prevent bleeding in persons with haemophilia (PWH; without inhibitors) was pioneered by a few European haemophilia treatment centres beginning in the late 1950s.[1-3] The initial objective of prophylaxis was to convert a person with severe haemophilia (baseline factor [F] VIII/IX level <0.01 IU/mL [1%]) to a bleeding phenotype in keeping with moderate haemophilia by maintaining factor levels >1% at all times.

Traditional full dose prophylaxis, begun early in life, has been associated with a >90% reduction in the rate of joint bleeding, an annualized joint bleed rate of <1, and a significant reduction in joint deterioration.[4] Longer term benefits include a reduction in musculoskeletal pain, less patient disability and less need for orthopaedic surgery, reduced hospitalization rates and length of hospital stays, improved school and work attendance, and greater participation in professional and leisure activities resulting in improved quality of life (QOL).[5] Prophylaxis also protects from other forms of haemorrhage (including intracranial haemorrhage).[6] Recognizing its benefits, prophylaxis has become widely adopted, beginning first in more affluent and more recently in less affluent countries, as the ideal way of managing PWH.[7,8]

Consensus definitions of prophylaxis have been developed according to when it is commenced (Table 1a) and according to its intensity (Table 1b). In addition, full time (or continuous prophylaxis) has been defined as being on prophylaxis for a minimum of 45 wk/y.[9] In general, these definitions of prophylaxis were focused on preventing joint bleeds and maintaining musculoskeletal health.

Having prophylaxis regimens that vary in intensity fits with the understanding that patients differ greatly with respect to their propensity to bleed as well as their pharmacokinetic handling of FVIII/IX. Thus tailoring of prophylaxis to individual patients' needs might allow for more efficient allocation of therapy such that it will not be "wasted" on patients that may not require as much replacement haemostatic products and yet not be denied to patients who require more.[11] Tailoring of prophylaxis has consequently become widely practiced over the last 10-20 years. Tailoring of prophylaxis to the ability of a society to pay for it has also led to the development of low dose prophylaxis regimens.[12] These regimens have also been shown to achieve considerable, albeit, smaller reductions in rates of joint bleeding. [13]

Interventional studies on prophylaxis showing dramatic reductions in bleeding rates probably led to an overinflated view of what could be achieved with the clotting factor concentrates (CFCs) that we have had and led to some in the haemophilia community advocating for a goal of "zero bleeds". However standard prophylaxis has relied on the frequent intravenous replacement of costly but short-acting (standard half-life; SHL) CFCs and has been burdensome for many patients and families, somewhat tempering

TABLE 1 Current definitions of prophylaxis. (a) Prophylaxis defined according to when commenced (applies equally to haemophilia A and B). (b) Prophylaxis defined according to its intensity (doses are with standard half-life clotting factor concentrates (SHL-CFC))

(a)		
Primary	Prophylaxis started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and age 3 years	
Secondary	Prophylaxis started after two or more joint bleeds but before the onset of joint disease documented by physical examination and/or imaging studies	
Tertiary	Prophylaxis started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints. Typically tertiary prophylaxis applies to prophylaxis commenced in adulthood	
(b)	**Haemophilia A**	**Haemophilia B**
High (or full) dose	25-40 U FVIII/kg/q2d (>4000 U/kg/y)	40-60 U FIX/kg/2×/wk (>4000 U/kg/y)
Intermediate dose	15-25 U FVIII/kg/3×/wk (2000-4000 U/kg/y)	20-40 U FIX/kg/2×/wk (2000-4000 U/kg/y)
Low dose	10 U FVIII/kg/1-2×/wk (<2000 U/kg/y)	10-20 U FIX/kg/once/wk (<2000 U/kg/y)

1a) Taken from .... Taken from a recommendation from the F8, F9, and Rare Coagulation Subcommittee of the SSC of the ISTH.[10]
CFC, clotting factor concentrates; SHL, standard half-life; U, units.

the benefits that have been obtained with prophylaxis. The short half-life of SHL-CFC results in: (i) the need for frequent venepunctures - this in young children often leads to the need for central venous access devices (CVADs) and in older children/adults to reduced patient adherence[14]; and (ii) to prophylaxis being a sinusoidal curve of factor peaks (factor levels of 50%-80%) and troughs (factor levels of 1%-3%) corresponding to times when patients can safely be more active and times when they cannot. There has been an increasing recognition that trough levels of 1%-3% are insufficient to prevent all bleeds in all PWH.[15]

The development and introduction of new haemostatic therapies in haemophilia are forcing us to revisit the concepts and definitions of prophylaxis. These new therapies (some already in clinical use and others still in development) include extended half-life (EHL) intravenously administered CFCs, subcutaneously administered CFCs,[16] FVIII mimetics (Emicizumab) and non-factor drugs that inhibit natural endogenous anticoagulants (antithrombin [AT], tissue factor pathway inhibitor [TFPI] and activated protein C [APC]).[17]

Many of these agents (particularly non-factor therapies) do not fit with the current concept of prophylaxis as they do not replace the missing coagulation factor, are administered subcutaneously, and in some cases given as infrequently as once or twice monthly. Additionally, many of these agents will eliminate the peak and trough curves of protection that we now see with SHL-CFC prophylactic regimens.

Aspirations and expectations of what will be possible with prophylaxis with these new agents are changing. EHL-CFCs allow for less frequent infusions of FVIII/IX, attaining higher trough FVIII/IX levels, or both. This is particularly the case with EHL-FIXs - their half-life extension of 3-5 fold over SHL FIXs permits patients to receive factor once every 7-14 days and still, in the case of some of these EHL-FIXs, maintain FIX trough levels of >10% to 20%.[18,19] More modest reductions in frequency of administration or modest increases in factor trough levels (likely not both) may be accomplished with EHL-FVIIIs. FVIII mimetics and non-factor therapies can similarly be given subcutaneously and very infrequently and yet achieve good/excellent bleed protection.

Extended half-life-CFCs, particularly FIX-EHLs, as well as FVIII mimetics may make it easier to start patients at an earlier age on prophylaxis without the need for CVADs. This may cause a reevaluation of what constitutes primary prophylaxis (see Table 1a) as perhaps we will start prophylaxis without waiting for any joint bleeds to occur, and before the age of 1 year of age. EHL-CFCs, as well as FVIII mimetics and non-factor therapies, may allow for more convenient dosing days/times (which might improve adherence) and might lead to increased uptake of prophylaxis among patients not currently on prophylaxis (eg those with moderate haemophilia). Better prophylactic coverage should permit greater level of sports participation (potentially including some sports involving vigorous physical activity that have traditionally been discouraged).[20] All of these developments are transforming the concepts of prophylactic intensity. No longer can one refer to full dose prophylaxis as prophylaxis that results in factor trough levels of 1%-3%.

With the steady advance of modified clotting factors as well as effective subcutaneous non-factor drugs and promising gene therapies currently in clinical trials,[21] it seems that improved clinical outcomes are within reach for our patients: extremely low bleed rates, full or near full prevention of haemophilic arthropathy, fewer restrictions in activities and improved QOL. Whether this will be on the basis of achieving much higher factor trough levels through EHL-CFCs, or through subcutaneously administered CFCs or by means of non-factor therapies or using a combination of both is still to be determined.

With these changes, new definitions for prophylaxis are required. Modern prophylaxis definitions will need to be inclusive of a wide variety of haemostatic agents with diverse mechanisms of action, and modes of administration.

We propose the following as a new definition of prophylaxis: the regular administration of a haemostatic agent/agents that safely, effectively and conveniently prevent bleeding while allowing PWH to lead active lives.

Prophylaxis in the future will create new challenges:

- How to assess the pharmacodynamic effects of, and pharmacokinetics of new therapies - it will be more complex than simply measuring FVIII or FIX levels!
- How to assess the intensity of prophylaxis with non-factor replacement therapies especially given current challenges in monitoring such therapies?[22]
- How to treat breakthrough bleeds in patients on prophylaxis with new therapies, particularly non-factor therapies?
- How best to monitor short and long-term clinical outcomes and adverse events?
- How do we approach inhibitor development (traditionally the greatest threat to managing haemophilia patients) and inhibitor eradication in the face of new therapies?
- How best to select a haemostatic therapy, or a combination of therapies tailored to an individual patient?

The development of new therapies for haemophilia will likely have considerable economic ramifications. Traditionally when new therapies are introduced they tend to be more expensive then available "older therapies". This may limit the willingness of countries/societies to pay for these newer therapies. However, the price of "older therapies" often tends to drop in such scenarios. This may lead to the increased uptake of traditional prophylaxis with SHL factor concentrates where their reduced price may make traditional prophylaxis much more affordable.

Prophylaxis has come a long way from the initial observations of Inga Marie Nilsson and her colleagues beginning in the 1950s. Prophylaxis up until now has been limited by the therapies available (ie CFCs intravenously administered, with short half-lives that create peaks and troughs in factor levels and protection). Excitingly prophylaxis appears to be poised for a dramatic change that will more effectively reduce bleeding risks. As the haemophilia community moves into these new treatment paradigms much work will be needed to optimize this transformation of care.

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REFERENCES

1. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med*. 1992;232:25-32.
2. Van Creveld S. Prophylaxis of joint hemorrhages in hemophilia. *Acta Haematol*. 1971;45:120-127.
3. Berntorp E, Astermark J, Bjorkman S, et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia*. 2003;9(Suppl 1):1-4.
4. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357:535-544.
5. Soucie JM, Grosse SD, 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. *Haemophilia*. 2017;23:e287-e293.
6. Andersson NG, Auerswald G, Barnes C, et al. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B - the impact of prophylactic treatment. *Br J Haematol*. 2017;179:298-307.

7. Carcao MD, Avila L, Leissinger C, et al. An International Prophylaxis Study Group (IPSG) survey of prophylaxis in inhibitor positive children/adults with severe haemophilia. *Haemophilia*. 2017;23:e444-e447.
8. Carcao MD, Avila L, Leissinger C, et al. An International Prophylaxis Study Group (IPSG) survey of prophylaxis in adults with severe haemophilia. *Haemophilia*. 2017;23:e447-e450.
9. Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med*. 1994;236:391-399.
10. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:1935-1939.
11. Feldman BM, Pai M, Rivard GE, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost*. 2006;4:1228-1236.
12. Wu R, Luke KH. The benefit of low dose prophylaxis in the treatment of hemophilia: a focus on China. *Expert Rev Hematol*. 2017;10:995-1004.
13. Wu R, Luke KH, Poon MC, et al. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China. *Haemophilia*. 2011;17:70-74.
14. Duncan N, Shapiro A, Ye X, Epstein J, Luo MP. Treatment patterns, health-related quality of life and adherence to prophylaxis among haemophilia A patients in the United States. *Haemophilia*. 2012;18:760-765.
15. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125:2038-2044.
16. Vollack N, Werwitzke S, Solecka-Witulska BA, Kannicht C, Tiede A. Novel Von Willebrand Factor (vWF) fragment supports subcutaneous administration of factor VIII: pharmacokinetic Data from Hemophilia A Mouse Model. *Blood*. 2017;130(Suppl 1):4877.
17. Arruda VR, Doshi BS, Samelson-Jones BJ. Novel approaches to hemophilia therapy: successes and challenges. *Blood*. 2017;130:2251-2256.
18. Collins PW, Young G, Knobe K, et al. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial. *Blood*. 2014;124:3880-3886.
19. Santagostino E, Martinowitz U, Lissitchkov T, et al. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. *Blood*. 2016;127:1761-1769.
20. Broderick CR, Herbert RD, Latimer J, et al. ASsociation between physical activity and risk of bleeding in children with hemophilia. *JAMA*. 2012;308:1452-1459.
21. Nathwani AC, Davidoff AM, Tuddenham EGD. Gene therapy for hemophilia. *Hematol Oncol Clin North Am*. 2017;31:853-868.
22. Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? *Blood*. 2017;130:2463-2468.