Practical considerations in choosing a factor VIII prophylaxis regimen: Role of clinical phenotype and trough levels

Rolf Ljung; Kathelin Fischer; Manuel Carcao; Elena Santagostino; Marilyn J. Manco-Johnson; Prasad Mathew; on behalf of the INPH* group

Introduction

Prophylaxis in persons with haemophilia denotes the continuous routine infusion of replacement clotting factor to prevent any and all bleeding. Prophylaxis may be primary if it is initiated before the age of three years and before the second joint haemorrhage; secondary if it is initiated after the age of three years or after two or more joint haemorrhages but before the development of structural or functional arthropathy; and tertiary if initiated with established arthropathy (1). The goal of prophylaxis therapy in patients with severe haemophilia (particularly children), prophylaxis with continuous routine factor replacement has become standard of care in developed countries and is gradually becoming the standard of care in developing countries. The question arises then: what is an appropriate prophylaxis regimen to prevent bleeding events and arthropathy, while also maximizing patient quality of life and taking into consideration the costs of prophylaxis? Should all patients be treated with one standard, fixed prophylaxis regimen, or should prophylaxis be individualised for each patient? If so, what factors need to be considered in choosing the appropriate dose and frequency of factor administration? If prophylaxis is tailored to the individual patient, then patient-related factors (bleeding phenotype, activity profiles, age, joint status) and product-specific factors (half-life of the replacement factor in the individual patient) will determine the choice of regimen, whether it be a fixed-regimen prophylaxis or prophylaxis that is tailored to patient activity and bleeding risk. Regardless of the choice of prophylaxis regimen, for any regimen to be effective, adherence to therapy is key to optimising outcomes.

Keywords
FVIII, prophylaxis, phenotype, dose, frequency

Summary
Current therapy for haemophilia A is guided by severity of the disease, which in tum is best reflected in patients’ endogenous factor VIII activity levels. For patients with severe haemophilia (particularly children), prophylaxis with continuous routine factor replacement has become standard of care in developed countries and is gradually becoming the standard of care in developing countries. The question arises then: what is an appropriate prophylaxis regimen to prevent bleeding events and arthropathy, while also maximizing patient quality of life and taking into consideration the costs of prophylaxis? Should all patients be treated with one standard, fixed prophylaxis regimen, or should prophylaxis be individualised for each patient? If
As haemophilia A is a single protein deficiency disorder, it would be most desirable to replace all patients with FVIII:C deficiency to the normal range as soon as possible after birth and continuing lifelong. The current limitations to replacement therapy in clinical practice are the requirement for intravenous administration, short factor half-life of standard FVIII concentrates, and cost. Infants and young children, who are most vulnerable to the onset of arthropathy, often require indwelling venous access devices to support continuous prophylaxis, with concomitant risks of infection, thrombosis, and mechanical device failure. These limitations of current replacement therapy have spurred attempts to identify predictors of joint disease to enable the delay of physical and psychological trauma related to frequent venipuncture due to prophylaxis, while avoiding bleeding-related damage.

This consensus includes different perspectives regarding when patients should best commence prophylaxis; prophylaxis may be initiated before the onset of joint or any bleeding, or one might allow 1 or 2 joint bleeds before initiating prophylaxis. Whereas moderate haemophilia is defined by a FVIII:C level of 1% to 5%, many patients with FVIII:C between 1% and <3% exhibit a bleeding pattern similar to those with <1% FVIII:C (3). In contrast, most patients with mild haemophilia (FVIII:C between 6% and 40%) exhibit a bleeding phenotype at a later age, and bleeding events are generally related to trauma (3,7). In addition to timing of initiation of prophylaxis, choices must also be made regarding the frequency of prophylactic therapy. This article discusses three approaches to guide initiation, monitoring, and adjustment of prophylactic regimens.

Factors to consider in prescribing a prophylactic regimen

Identifying clinical bleeding phenotype

There is wide variability in clinical phenotype among patients with severe haemophilia. Bleeding phenotype is suggested by the age when joint bleeding is first manifest, which in one study varied between 0.2 and 5.8 years (8). In a single-centre study of 171 patients, children who experienced their first haemarthrosis earlier (<1.8 years) had higher annual clotting factor utilisation years later (p<0.01) and a trend toward more arthropathy (p=0.08) than those who experienced their first joint bleed later (>1.8 years; p<0.01) (8). This observation was confirmed in the Canadian Haemophilia Prophylaxis Study (CHPS) in which early age at first joint bleed was an important predictor of more severe bleeding later in life (9).

In severe haemophilia A, the FVIII gene mutation correlates moderately with endogenous FVIII:C. The effect of mutation on haemophilic phenotype was shown recently in a large cohort of newborns with severe haemophilia A, in which babies with non-null mutations experienced their first haemarthrosis on average 2.3 months later than those with null mutations (10). In addition, coexisting inherited prothrombotic traits such as FV Leiden or the prothrombin mutation (G20210A) have also been reported to delay the presentation of clinical bleeding by six months (11). To date, plasma levels of other proteins involved in clot formation and clot lysis have not explained bleeding phenotype in severe haemophilia A (12). Currently there is no clinical rationale for extended coagulation testing in persons with severe haemophilia A. Blood group, particularly later on in life when a patient is on prophylaxis, is likely to have an effect on predicting who needs more or less frequent prophylaxis injections; individuals with O blood type are likely to need more frequent infusions due to their more rapid clearance of von Willebrand factor and FVIII than individuals with non-O blood type (13, 14).

In addition to the genetic modifiers of clinical bleeding phenotype, there are likely to be behavioural determinants (e.g. patient’s level of caution, activity, and agility) and environmental determinants (e.g. protectiveness of caregivers, etc.) of bleeding phenotype. Other biologic host factors impact individual patient susceptibility to joint damage from bleeding. Osteochondral changes have been detected on magnetic resonance imaging (MRI) in joints of some patients using on-demand therapy who have not experienced clinical haemarthroses; this has rarely been seen in patients using prophylaxis (15, 16). In contrast, some joints have experienced more than 10 episodes of haemorrhage without structural damage on MRI (16). These paradoxical findings suggest the phenomenon of subclinical “microbleeding” in patients with severe haemophilia not on prophylaxis, as well as variability in individual susceptibility to bone and cartilage damage in response to blood in the joint (16).

Variability in phenotype is also found in moderate haemophilia. A report from a single-centre cohort of 75 patients with moderate haemophilia with a median age of 37 years and with 15 years of follow-up showed that 45% of patients had not experienced any joint bleeding in five years, while 29% of such “moderate” patients required prophylaxis to suppress frequent bleeding (17). Use of prophylaxis correlated more with age at first joint bleed (p=0.01) than with baseline FVIII:C (p=0.12); these data confirm the importance of age at first joint bleeding event over baseline FVIII:C as a predictor of phenotype (17).

The initiation of prophylaxis after the onset of joint bleeding carries some limitations. A joint bleed in an infant or young child has a propensity to rapidly recur. A target joint is, according to a recent paper on definitions from the FVIII/IX subcommittee of the Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), defined as a single joint with three or more spontaneous bleeds within a consecutive six-month period (18). On imaging and histology, target joints show synovial hypertrophy (synovitis) with haemosiderin deposition. Clinical experience has shown that patients with target joints need a higher dose and more frequent factor replacement to suppress bleeding at initiation of prophylaxis, which may be tapered later after several months without bleeding (19). For long-term prophylaxis, patients with preexisting synovitis require higher troughs to prevent bleeds. However, some adult patients do well with lower trough levels, whether because of absence of synovitis, a lifestyle with fewer traumatic sports and activities, a better developed muscular system, or compromised mobility with
end-stage joint fibrosis (20). Nevertheless, for both children and adults using primary, secondary, or tertiary prophylaxis, adherence to prophylaxis is critical to outcome.

### Age of initiation of prophylaxis

Age of initiation of prophylaxis has been determined to be a strong predictor of clinical outcome. Astermark et al. showed that arthropathy was best prevented if prophylaxis was initiated before the age of three years (21). These results were supported by similar Swedish, Dutch, and German data (22–24).

### Prophylaxis dose and dose frequency

By definition, dose, frequency of dosing, and half-life determine FVIII:C levels during prophylaxis. Pharmacokinetically, more frequent FVIII dosing results in the most conservative use of factor product (25). Because of rapid early decrease in FVIII:C following infusion due to a rapid distribution phase, increases in dose are less efficient to increase the trough level compared with increases in dose frequency. Despite the superiority of frequent infusions over infrequent infusions, frequent dosing is problematic when initiating prophylaxis in young children due to limitations in venous access. Consequently, most very young children are started with once-weekly infusions and then the infusion frequency is escalated to twice per week and finally to every-other-day dosing. However, there are two different philosophies to escalation of prophylaxis therapy: the Swedish protocol aims to escalate patients within a matter of months regardless of whether they show demonstrable bleeding, whereas the Dutch and French protocols escalate after each bleed, and the Canadian protocol only escalates patients if they demonstrate repeated bleeding. The Swedish protocol has demonstrated the best reported joint outcomes (26). The Canadian prophylaxis study, which maintained infrequent infusions while tolerating a larger number of joint haemorrhages (27), resulted in osteochondral damage in 12/24 boys at a mean age of 8.8 years (28). Astermark et al. reported that the mean ± SEM annual number of joint haemorrhages decreased from 2.6 ± 0.4 on once-weekly infusions to 1.6 ± 0.3 (range 0–15.4) with 2–3 infusions per week (p<0.005) (21).

### Relevance of trough levels

Trough factor activity level is that measured just before a routine replacement infusion. The original severity classification of haemophilia was based on the observation that persons with ≥1% FVIII:C had far less arthropathy than those with <1% (3, 7). Extrapolating from this, the goal of prophylaxis initially was to infuse regular replacement doses of FVIII to convert a person with undetectable FVIII:C to one who continually had some measurable factor and as such was phenotypically more like a person with moderate or mild haemophilia. For individual patients, however, there is much debate on what the optimal trough level should be (20, 29, 30). Time below a targeted trough level is primarily driven by the patient-specific terminal half-life of the replacement factor, the frequency of infusions, and treatment adherence, while dose and volume of distribution contribute less to trough levels (4). In the study by Collins et al. (2009), it was demonstrated that increasing time with a FVIII below 1 IU/dl was associated with increased total bleeds and haemarthroses and that lack of adherence to the intended frequency of injections was the most important determinant for low FVIII and increased bleedings. In children aged 1–6 years, the rate of bleeding was also influenced by FVIII half-life and clearance (4). However, FVIII:C does not completely predict bleeding, and the propensity of patients with severe haemophilia A to bleed when FVIII:C falls below a target threshold following a prophylactic dose is variable (20, 29).

Studies on the association of FVIII:C trough levels and bleeding in patients with severe haemophilia have shown conflicting results. A Swedish analysis of 232 treatment-years in 43 patients on “full-dose prophylaxis” found no association between trough levels and bleeding frequency, although bleeding rates were low in all patients in this study (20). In a post-hoc analysis of data from studies on the pharmacokinetics (PK), safety, and efficacy of a recombinant FVIII (rFVIII) product in 143 patients with severe haemophilia, trough levels ≥1% prevented joint bleeding in 90% of children aged 1–6 years but in only 50% of patients aged 10–65 years (29). The authors postulated that preexisting synovitis/arthropathy in the older cohort predisposed them to more frequent joint bleeding on prophylaxis compared with young children with normal joint architecture (29). Patients with severe haemophilia using a Dutch prophylaxis regimen, which used lower and less-frequent dosing that was not adjusted based on trough levels, were determined to have joint outcomes that were slightly inferior to that of moderate haemophilia patients, but physical activity and quality of life in these patients were similar to patients with moderate haemophilia as well as the general population (30).

With current availability of safe recombinant replacement factors, there is a demand for prophylaxis adequate to support sports and activities practised in the community at large, and this has brought into question the adequacy of a 1% trough level. Based on data from 195 patients with moderate and mild haemophilia, it was shown that as endogenous FVIII:C increased above 1%, the age at diagnosis, age at first treatment, and age at first joint bleeding increased linearly (31). The number of joint bleeds decreased to minimal rates at FVIII:C >10% and approximated 0 in patients with an endogenous FVIII:C of 15% (31). Regression analysis showed an 18% reduction (rate ratio, 0.82; 95% confidence interval [CI], 0.77–0.86) of bleeding frequency with every IU/dl increase (above 1%) in endogenous FVIII:C (31). A single-centre cohort study of 411 Dutch patients suggested that a minimum level of 15% is needed to achieve an annual joint bleed rate of 0 (32). Of note, the incremental improvement in bleeding rate is far greater comparing troughs of 1% and 5% than that achieved comparing troughs of 10% and 15%, and the increased cost of factor and increased number of infusions required to achieve a trough of 15% using conventional products is substantial. Most importantly, good adherence to treatment regimen is key to success, and any discussion of minimal required trough becomes irrelevant if doses are regularly missed (33).
Pharmacokinetics of FVIII and relevance of PK in dosing

Pharmacokinetics can be used to increase precision in FVIII:C dosing. The effect of half-life on FVIII:C levels in patients aged 10 to 65 years was studied by mathematical modelling (29). In this model, the time taken to reach 1% after infusing 30 IU/kg was 59 hours (h) longer in patients with a long half-life (95th percentile) compared with patients with a short half-life (5th percentile) (Figure 1). Thus, in an adult who has received an infusion of 30 IU/kg, the FVIII:C level at 48 h may vary between 2% and 12%, and the time to reach a 1% FVIII:C trough can vary between 51 and 110 h. In adults on alternate-day replacement with 20–40 IU/kg, the median FVIII:C trough at 48 h was shown to be >6% (34).

Half-life of an infused FVIII product is dependent on many factors, some of which are known, such as age, blood group, and von Willebrand factor levels, and some of which are not (25, 29, 35, 36). Half-life increases with age, with the median (P25-P75) elimination half-life for FVIII being 9.3 (8–10.9) h in 1- to 6-year-old children, 10.9 (9.5–12.5) h in 10- to 17-year-olds, and 11.5 (10.3–13.3) h in adults (18- to 65-year-olds); this is related to increased clearance in young children with age-related physiologic maturation in metabolic processes (37–39). Furthermore, not only is half-life shorter in younger patients, but, additionally, younger and smaller children have larger volumes of FVIII distribution and thus lower incremental recovery. The combination of lower recoveries and shorter half-lives in younger and smaller children leads to lower trough levels in younger children. To somewhat mitigate this, younger children are often given higher doses (on a per-weight basis and available vial sizes).

When tailoring prophylaxis to PK, the patient’s activity schedule needs to be taken into account, and both peaks and troughs are important for active participation. An Australian study determined that the highest risk of bleeding in active children with severe haemophilia was in the hour following sports participation (40); these data suggest that bleeding risk associated with activity can be predicted and may be prevented by achieving a threshold peak FVIII activity before participation. Evidence supports that the trough factor level required to prevent haemarthroses varies among patients and that 1% is not universally adequate. PK is an important tool in optimising haemophilia treatment but is not a substitute for clinical assessment.

Tailoring prophylaxis to FVIII:C PK involves determination of the half-life of the infused product in the individual patient; this requires repeated blood sampling, which may prove challenging in very young children. The Bayesian approach to half-life evaluation, which is based on population PK and requires a small number of samplings in any individual patient, may circumvent some of the challenges of frequent blood sampling and permit easier determination of a patient’s half-life (41).

Anticipated impact of new longer-acting FVIII:C recombinant products

Recently, a number of novel molecules have been developed to prolong the plasma half-life of FVIII:C (42–47). Two strategies that have reached advanced stages of clinical development are fusion molecules and pegylation (42–47). Clinical trials with these molecules have shown that, for most of these extended half-life FVIII:C products, there is an approximately 50% prolongation in half-life over standard rFVIII. The impact of the extended half-life FVIII:C products on prophylaxis adoption, adherence, and patient satisfaction is currently unknown but is expected to be substantial.

Paradigms for prophylactic regimens

The goal of all prophylaxis regimens for people of all ages and all degrees of joint damage is similar: to reduce or completely prevent all bleeding while allowing the person to lead an active life and

![Figure 1: Predicted probability of having no bleeds per year dependent on time per week spent with factor VIII < 1 IU/dL. The calculated probability of having no bleeds per year is shown compared with increasing time per week spent with factor VIII less than 1 IU/dL. Open circles (*) and asterisks (†) represent haemarthroses in patients aged 1 to 6 and 10 to 65 years, respectively. (Reproduced with permission from Collins et al. J Thromb Haemost 2009; 7: 413–420.)](https://www.thrombosis-online.com)
achieve good quality of life. There are three basic approaches to the initiation and adjustment of prophylaxis, as follows:

1. Early standard full-dose prophylaxis that is not tailored to either bleeding or PK

This philosophy espouses initiation of prophylaxis for babies with severe haemophilia A beginning before any bleeding events, as young as ≤12 months of age, and maintained on a continuous schedule. Initial dosing is 25 to 40 IU/kg three times weekly to every other day. In principle, this regimen is designed to keep the FVIII:C trough level >1% but is generally adjusted by clinical bleeding frequency rather than PK numbers. Prophylaxis may be initiated weekly but is rapidly escalated based on any clinical bleeding that occurs. This approach to prophylaxis will achieve the best joint outcomes and allows for close to normal activities of daily living, but it is associated with the highest factor utilisation and necessitates more central venous access devices (CVADs, Port-A-Cath) and hospitalisations for port placements and removals; factor utilisation is of lesser concern in small infants. A disadvantage to this approach is that it may over-treat some patients who have a milder phenotype. Novel products may increase the feasibility of this approach. A fixed regimen of 25 to 40 IU/kg every other day to 3 times weekly results in factor utilisation of 4562 to 7300 IU/kg/year.

2. Prophylaxis adjusted on the basis of clinical bleeding/phenotype

This approach is used for severe haemophilia A patients of all ages. The rationale behind tailoring prophylaxis to patient bleeding patterns is the considerable inter-patient heterogeneity in bleeding phenotype arising from a variety of factors as discussed previously. Tailoring prophylaxis might allow the right amount of prophylaxis to be given to the right patient. Such tailored prophylaxis might lead to some patients using less prophylaxis than they otherwise would if placed on a “one size fits all” regimen, while still protecting their joints. A starting regimen, which can be of any frequency, is selected, and patients are carefully monitored for bleeding, especially into joints. However, this strategy depends heavily on the bleeding criteria used to adjust treatment. Some use bruising as a surrogate for bleeding, while others adjust at the occurrence of unprovoked joint/muscle bleeding only. Dose and particularly dose frequency are adjusted as needed to suppress clinical bleeding; factor utilisation can vary widely. In the Joint Outcomes Study (JOS), by age 6, factor utilisation for children on 25 IU/kg every other day (calculated 4562 IU/kg/year) reached 6000 IU/kg/year, accounting for extra dosing for bleeding events, traumas, and procedures (16). The Dutch and Canadian regimens tolerate some degree of joint bleeding and utilise between 2000 and 3500 IU/kg/year. The disadvantage of tailoring according to bleeding phenotype is that it demands that some patients experience bleedings in order to reveal their more severe phenotype. In some patients, but not all, these bleeds may result in long-term joint damage. Furthermore, a regimen with one or two injections per week will not offer a measurable FVIII:C at all times and may consequently put the patient at risk of a serious bleed (e.g. an intracranial bleed).

3. Prophylaxis adjusted on the basis of PK

Pharmacokinetic-based prophylaxis dosing requires knowledge of the terminal half-life of a specific product in a specific patient. PK-based dosing is focused on the concept of maintaining a patient’s FVIII:C trough above a certain predetermined level. This target trough level goal generally ranges from 1% to 5% based on bleeding history and activity level of the individual. Trough levels are monitored periodically, and dose frequency adjustments are made based on laboratory results. PK-guided dosing is predicted by some to result in the most cost-effective use of product (4, 25). Modified assessments including peak, trough, and two additional levels beyond 24 h give data that can estimate PK reasonably well and are feasible even in young children (41). A regimen of 30 IU/kg given to maintain FVIII >1% requires dosing every two days or every four days (representing the 5th and 95th percentile of FVIII half-life in adults) and utilizes 2300 or 4500 IU/kg/year (41). This regimen has the advantage that patients are treated with the same intensity with cost savings. However, the major limitation with this approach is that it focuses solely on one attribute that contributes to bleeding (trough FVIII:C) and ignores all the other differences among patients, including their physical activity levels as well as FVIII:C at the time of maximal physical activity and related trauma. When tailoring prophylaxis to PK, it is important that the patient’s activity schedule be taken into account, as both peaks and troughs are important for active participation (40).

Considerations for sports and activities

Using a prophylactic regimen, there is evidence that children can safely participate in many sports, including collision sports (40, 48, 49). Broderick et al. demonstrated that the risk of bleeding is within 1 h of sports participation and can be effectively mitigated by FVIII:C levels of 30% to 40% (40). Sports participation may be better supported by attention to FVIII:C level at the time of participation rather than by trough level alone. Any type of factor product may be used for athletic children and adults, including native and modified recombinant proteins, as long as dosing is altered to achieve target peak level prior to sports participation.

Considerations for synovitis and courses of rehabilitation

As stated above, individuals with inflammatory synovitis require a higher trough level to suppress clinical bleeding and allow recovery of the synovitis. In these individuals, prophylaxis can be tailored clinically to suppress bleeding at initiation of prophylaxis and physical therapy. Once joint inflammation is reduced, prophylaxis dose and frequency can usually be reduced.

Commonly used prophylactic regimens are highlighted in Table 1. Below are a few case summaries to illustrate the approaches discussed above.
Case 1: The Malmö regimen of prophylaxis

A one-year-old white male with severe haemophilia A caused by an intron 22 inversion mutation was diagnosed at birth because of known haemophilia in the family. He developed frequent haematomas in the skin after beginning to walk but did not require treatment with FVIII. Recombinant FVIII was initiated at the age of one year at a dose of approximately 25 U/kg (1 vial of 250 U) once per week to get the child and parents accustomed to venipuncture. The frequency was increased over a few months to reach the goal of every second day. The parents were educated by the nurse as soon as possible to perform the venipuncture themselves. Although the intent is to avoid ports, when venous access is problematic, a port will be inserted. Surgical procedures are avoided before the first 20 exposure days because of the potential for increasing the risk of inhibitor development. With this approach, a central line is needed in approximately 30% of the children.

Case 2: Initiation and dose adjustment of prophylaxis tailored to clinical bleeding pattern

Patient S, born 1997 to an unknown carrier of severe haemophilia, had a suspected first joint bleed at eight months, but diagnosis of severe haemophilia was only made after a second joint bleed at 11 months of age. He was then started on prophylaxis with 25 IU/kg twice weekly. He needed a Port A Cath from age 23 months to six years. At the time of joint bleeding at age 2.5 years, his prophylaxis was increased to 20 IU/kg three times weekly. He had rare trauma-induced joint haemorrhages, and dosing was increased for weight. At age 15, he suffered a spontaneous elbow bleed on day 3 following an infusion, and prophylaxis was increased to 20 IU/kg every other day. There have been no joint bleeds or other bleeds since then. At age 17, he had a trough level of 3% with no limitations in physical activity and has a 5° limitation of extension in the left elbow; x-ray of this elbow at age 13 years and six months showed no abnormalities.

Case 3: PK-tailored prophylaxis

A 10-year-old boy wants to use (and adjust) prophylaxis to participate in soccer. He undergoes a full PK study with his current treatment product. The PK results are used to predict that a certain dose will achieve a peak level (in this case 40%) immediately before soccer participation and will be adequate for activities of daily living the following morning. Based on a recovery of 2.2%/IU FVIII/kg infused and a half-life of 12 h, he infuses 17 IU/kg (based on vial size used) after school on weekday afternoons just before soccer practice, achieves a 37% FVIII:C for soccer participation, and reaches a trough level of 2% before his next dose. During the sports season, he engages in no organised activity on weekends and does not infuse these days. He completes a 10-week sport season with no bleeding events and returns to his usual schedule of 25 IU/kg three times weekly. FVIII utilisation during soccer season was 85 IU/kg/week, which is minimally greater than his usual 75-IU/kg/week consumption.

Summary

Choosing a prophylaxis regimen for patients with severe haemophilia A (and for the many patients with moderate haemophilia who manifest a bleeding phenotype) necessitates that a clinician consider many factors. There is likely no one regimen that is best for all patients and for all economies. General principles that should guide all prophylactic decisions include the following:

- Prophylaxis should be started early in life.
- Frequent infusions of factor are likely to be more protective of bleeding than infrequent infusions of factor.
- Peak as well as trough levels are important to optimise prevention of spontaneous and traumatic bleeds.
- Prophylaxis is generally more efficient when factor is given in mornings rather than in evenings.
- Prophylaxis needs of patients may change over time and throughout life, particularly with changes in patient activity levels.
- Prophylaxis can be tailored in different ways: both PK and clinical bleeding-based dosing can be employed.
- Ultimately, as clinicians, we should “treat a patient rather than a laboratory result/factor level.”

The laboratory, clinical, and lifestyle issues discussed must be considered when deciding about dosing and may be useful in developing individualised treatment protocols. Availability of extended half-life FVIII concentrates will also change the regimens used for prophylaxis, with the possibility of maintaining higher FVIII trough levels between infusions as well as the possibility of higher peaks.

---

### Table 1: Commonly used prophylaxis dosing regimens

<table>
<thead>
<tr>
<th>Prophylactic dosing regimen</th>
<th>Dose</th>
<th>Dosing frequency</th>
<th>Dosing adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish (Malmö) high-dose protocol (24, 50, 51)</td>
<td>25–40 IU/kg</td>
<td>3 times weekly or every other day</td>
<td>Dosing adjusted to maintain FVIII levels &gt; 1%</td>
</tr>
<tr>
<td>Utrecht (intermediate-dose) protocol (2, 52)</td>
<td>15–30 IU/kg</td>
<td>2 or 3 times weekly</td>
<td>Dosing adjusted based on patient’s bleeding pattern</td>
</tr>
<tr>
<td>Canadian dose-escalation protocol (27)</td>
<td>50 IU/kg</td>
<td>Once weekly</td>
<td>Escalate to 30 IU/kg twice weekly or 25 IU/kg on alternate days based on patient’s bleeding frequency</td>
</tr>
</tbody>
</table>

Thrombosis and Haemostasis 115.5/2016 © Schattauer 2016
Acknowledgements
The activities of the International Network of Pediatric Haematologists (INPH) group are supported by an unrestricted grant from Bayer HealthCare, Whippany, NJ. Formatting for submission per the journal guidelines was performed by Complete Healthcare Communications, Inc., Chadds Ford, PA.

Author contributions
R.L., K.F., and P.M. contributed to the concept and design of the study. R.L., M.C., K.F., and M.M.J. contributed the cases. R.L., K.F., M.C., E.S., M.M.J., and P.M. contributed to the review and edits of the manuscript. P.M., K.F., M.C., M.M.J., and E.S. contributed to the writing of the manuscript.

Conflicts of interest
Rolf Ljung has received speaker fees or consultancy fees from Bayer, Baxter, Novo Nordisk, and Octapharma during the last five years. Kathelijn Fischer has received speaker’s fees from Bayer, Baxter, CSL Behring, Pfizer, and Novo Nordisk; performed consultancy for Bayer, Baxter, Biogen, CSL Behring, Novo Nordisk, and Pfizer; and has received research support from Bayer, Wyeth/Pfizer, Pfizer, and Novo Nordisk. Manuel Carcao has received research funding from Bayer HealthCare, Baxter, Biogen, Novo Nordisk, and Pfizer; additionally, he has received honoraria for advisory board participation and for speaking from Bayer HealthCare, Baxter, Biogen, Biostet, CSL Behring, Novo Nordisk, Octapharma, and Pfizer. Elena Santagostino has received research support from Pfizer; additionally, she has received honoraria for advisory board participation and for speaking from Bayer, Baxter/Baxalta, Biogen/Sobi, Grifols, Kedrion, Roche, Biotest, CSL Behring, Novo Nordisk, Octapharma, and Pfizer. Marilyn Manco-Johnson received research funding from Bayer HealthCare and EASAI and receives honoraria for advisory boards from Bayer HealthCare, Baxter BioScience, Biogen Idec, CSL Behring, and Novo Nordisk. Prasad Mathew is an employee of Bayer HealthCare.

References