When and how to start prophylaxis in boys with severe hemophilia without inhibitors: communication from the SSC of the ISTH

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Introduction:
Regular replacement therapy (prophylaxis) with clotting factor concentrates (CFC) for hemophilia was first introduced in Sweden in the 1960s[1]. It has been very effective in improving long-term outcome and preventing hemophilic arthropathy, allowing people with hemophilia to lead a near normal life. From the first single center cohort studies spanning several decades, it became clear that starting prophylaxis early is a key driver of success. Primary prophylaxis is defined as: ‘Regular continuous replacement therapy 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 three years’[2]. This definition of primary prophylaxis deliberately did not include the exact time of initiation, dosing of CFC and frequency of administration due to lack of evidence regarding optimal strategies. When starting prophylaxis in young children, the benefits of preventing bleeds need to be balanced against the burden of frequent injections and the need for central venous access devices (CVADs).

The aim of this recommendation is to provide evidenced guidance on when and how to start prophylaxis in boys with severe hemophilia without inhibitors.

Methods:
The information contained in this recommendation was gathered from a MEDLINE search (haemophilia/hemophilia AND prophylaxis AND starting/start*/initiation/onset) including related articles searches and cross-referencing of references retrieved and references known to the authors.

When to start prophylaxis
When studying the effects of prophylaxis a follow-up of years, often decades, is needed to observe the clinically significant effects of any regimen. However, during extended follow-up, it is inevitable that other parameters of treatment will change; during the last decades, prophylaxis was started earlier and dose was increased[3][4]. This resulted in fewer bleeds and improved joint outcome on clinical and radiological examination. Based on their experience, Nilsson et al recommended that prophylaxis should be started before clinical and/or radiological evidence of joint
damage in order to prevent arthropathy[3]. These observations were first confirmed in a single-center study with 4 years of follow-up[5]. Table 1 shows five additional studies reporting on the effects of the age at starting prophylaxis on the index joints (ankles, knees and elbows) using the Orthopedic Outcome Score (Clinical Score)[6] and/or the Pettersson score based on plain radiographs[7]. These 4 cohort studies and one randomized controlled study (RCT) included both severe hemophilia A and B cases. Three studies reported a better outcome in boys who started prophylaxis before the age of 3 years[8][9][10], the other two reported better outcome in boys who started prophylaxis before the 2nd or 3rd joint bleed[11][12]. Only the two larger studies following cases until adulthood performed multivariate analysis and reported statistically significant improvement in outcome for prophylaxis started before age 3[9], or the 3rd joint bleed[11]. When interpreting these results, it is important to consider that the onset of joint bleeding varies widely (median age 1.7 years,( interquartile range: IQR 1.0-2.8)) and is a predictor of bleeding phenotype and long term outcome[14][15]. On the other hand, effects may have been overestimated, as early joint changes may not have been picked up by the Clinical Score and plain radiographs.

Over the last decades, this information has led to earlier initiation of prophylaxis; a recent report on 919 boys with severe hemophilia A from the International PedNet Registry showed that prophylaxis is currently initiated at a median age of 1.3 years (IQR 0.9-1.9) after a median of 1 joint bleed with 70% of patients fulfilling the criteria of primary prophylaxis[16].

Based on the information available, we recommend starting prophylaxis no later than immediately or shortly after the first joint bleed. This strategy will avoid undertreatment in those who bleed very early, as well as avoid overtreatment in the approximately 20% of patients who have their first joint bleed after 3 years[14][15]. However, this strategy depends on adequate detection of bleeding events, which requires frequent assessment and adequate instructions for parents/caregivers. Some physicians will prefer to initiate prophylaxis before reported joint bleeding. It is also recommended to start prophylaxis immediately after an intracranial or a clinically significant muscle bleed[2].
Choice of initial prophylaxis regimen

While using FVIII concentrates with an average half-life of 12 hours in adults, prophylaxis should be administered at least 3x/week for hemophilia A (and 2x/week for hemophilia B) in order to achieve optimum protection. Between 1-3 years of age, FVIII half-life is only 6-8 hours [17][18]. (The optimum frequency of infusions at initiation of prophylaxis is unknown. Even if joint bleeding rates tend to be lower before age 6[19][20], two recent studies have suggested that sub-clinical joint bleeding may occur, based on the finding of soft tissue changes on MRI in 31% of joints without reported bleeding in patients treated on demand or once weekly[20][21].

Frequency of infusions

Overall, prophylaxis can be started with a ‘full’ regimen of infusions ≥3x/week, or with infusions 1-2x/week using different step-up criteria to increase the frequency of infusions (Figure 1).

Starting prophylaxis with infusions ≥3x/week provides most protection, but requires the insertion of a CVAD in the majority of patients (88% in PedNet[13]). Prophylaxis started with once weekly infusions has been described to ‘train the vein’ and limit the use of CVADs, while at the same time allowing gradual acceptance of prophylaxis in children and their parents[22]. When starting with infusions 1-2x/week, the frequency of infusions can be increased as soon as possible or according to bleeding (Figure 1). ‘As soon as possible’ entails moving to 3x/week within 4-6 months, as is practiced in Sweden[9]. In PedNet centers, this strategy required CVADs in 34% and 3x/week prophylaxis was achieved at 1.8 years (IQR 1.2-3.1)[13]. When intensifying prophylaxis ‘according to bleeding’ the frequency is increased with one additional weekly infusion immediately after each joint/muscle bleed. This strategy is included in some guidelines[23][24], and was widely used in PedNet, requiring CVADs in 22% and achieving 3x/week prophylaxis at 3.9 years (IQR 2.3-6.0)[13][25]. A formal Canadian protocol used more lenient step-up criteria allowing up to 2 joint bleeds per joint in 3 months while on the same step[26]; this resulted in 40% of patients still receiving twice weekly prophylaxis after 10 years[27] and osteochondral changes on MRI in 50% of patients at age 8.8 years[21]. A more rapid escalation is now recommended (Fig 1).
Dose of prophylaxis

Due to the available vial sizes, the initial dose of prophylaxis is 250 or 500 IU per infusion. As children starting prophylaxis are usually age 1-3 years, their average weight is between 10 and 14 kg. A dose of 250 IU is equivalent to 18-25 IU/kg, and a dose of 500 IU to 36-50 IU/kg. Although many start with an initial dose of 500 IU[24][13], the use of 250 IU as initial dose has been increasing. This is due to the limited gain of only 6-8 hours’ (one half-life) added protection of a double dose, and the association of high initial doses of treatment with inhibitor development[28][29]. For hemophilia B, the usual starting dose is 500 IU, and the added protection of a double dose is slightly longer at ± 16 hours[30].

Monitoring during the first years of prophylaxis

The first and most important step in initiation of prophylaxis is instruction of parents/caregivers to recognize bleeding symptoms and keep a detailed diary of both symptoms and treatment. To establish this, frequent contact (at least quarterly) with the clinic is necessary. Documentation of bleeding should include location of the bleed, the presence/absence of preceding trauma, and the treatment required until full functional recovery[31]. This information is essential for short-term evaluation and the prophylactic regimen should be reconsidered after each bleeding episode. This clinically based approach of starting prophylaxis relies on clinically reported bleeding and not on factor levels. However, unexpected bleeding in a patient on ≥3x/week prophylaxis warrants testing of factor trough levels and screening for inhibitors.

Physical examination is most important for follow-up after a bleed. Routine physical examination, even when using a validated scoring system, is very unlikely to pick up musculoskeletal changes in boys < 6 years, as these usually develop later in life[9][20].

Recommendations

Prophylaxis should be started no later than immediately or shortly after the first joint bleed.
A detailed diary of bleeding events should be maintained and reviewed frequently (minimum every 3 months) to ensure that all bleeds are reported and prophylaxis is adjusted appropriately.

Prophylaxis can be started with either once weekly or more frequent infusions up to every other day. The initial dose can be 250 or 500 IU.

If prophylaxis is started once weekly, we recommend that the frequency of infusions should be increased after each joint, muscle or other critical/significant bleeding episode, or sooner if possible, until a minimum of 3x/week (hemophilia A, or 2x/week for hemophilia B) is reached.

Intensification of any prophylactic regimen should be considered if a spontaneous significant bleed occurs.

The recommendations presented relate to use of standard FVIII/IX concentrates. The use of extended half-life FVIII/IX concentrates does not affect the start of prophylaxis, but may require regimen modifications of especially the frequency of infusions.

**Addendum:**
KF wrote the first draft of the manuscript, which was subsequently discussed during a face to face meeting of the Project Group (including KF, VB, GY, MO, AS) and adapted according to the comments of the co-authors in several rounds. All authors provided input in all versions of the manuscript. And all reviewed and approved the final version of the recommendations for starting prophylaxis in boys with severe hemophilia without inhibitors.

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K.F. reports having received speaker's fees from Bayer, Baxter, CSL Behring, Octapharma, Pfizer, NovoNordisk, consultancy fees from Bayer, Baxter, Biogen, NovoNordisk and Pfizer; and research support from Bayer, Wyeth/Pfizer, Baxter, and Novo Nordisk.
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<table>
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<th>Study</th>
<th>Design (follow up)</th>
<th>Numbers of patients</th>
<th>Outcome parameter</th>
<th>Age (yrs) at evaluation</th>
<th>Results</th>
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<tr>
<td>Kreuz 1998[8]</td>
<td>Single center cohort (FU 4 yrs)</td>
<td>19 severe &amp; 2 moderate</td>
<td>Clinical &amp; X-ray *</td>
<td>12.2</td>
<td>-All 8 patients (100%) who started prophylaxis &lt; age 3 years had normal joints at evaluation, vs &lt;25% of those who started prophylaxis later (p-value unknown)</td>
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<td>Astermark 1999[9]</td>
<td>Nationwide cohort (FU 18 yrs)</td>
<td>121 severe</td>
<td>Clinical</td>
<td>Up to 18</td>
<td>-Joint changes occurred from age 6 onwards -85% of 75 patients who started prophylaxis &lt; age 3 yrs had normal joints vs 50% of patients who started later (p&lt;0.001) -outcome was dependent on age at start prophylaxis only, not on dose and interval of prophylaxis at initiation (multivariate analysis),-</td>
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<td>Fischer 2002[11]</td>
<td>Single center cohort (FU 16 yrs)</td>
<td>76 severe</td>
<td>X-ray</td>
<td>19</td>
<td>-at age 19, Pettersson score increased with 8% for each years’ delay in starting prophylaxis following the first joint bleed, independent of prophylactic dose, age at first joint bleed and age at evaluation. -in a subgroup analysis in 43 patients, 13 patients who started prophylaxis &lt; 3rd joint bleed had better outcome (70% normal joints vs 24% in those who started later, p&gt;0.05)</td>
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<td>Study</td>
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<td>Yee 2002[12]</td>
<td>Single center cohort (FU 4 yrs)</td>
<td>38 severe</td>
<td>Clinical</td>
<td>5 and 9.5 respectively</td>
<td>9 patients who started &lt; 2\textsuperscript{nd} joint bleed had better outcome (90% with normal joint scores at age 5 years) vs 70% in patients who started later (evaluated at age 9.5 years, p&gt;0.05)</td>
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<tr>
<td>Gringeri 2011[10]</td>
<td>Multicenter RCT (FU 10 yrs)</td>
<td>21 severe</td>
<td>X-ray</td>
<td>12.3</td>
<td>Better outcome in 8 patients who started prophylaxis&lt; age 3 years (100% normal joints vs 84.6%, p&gt;0.05)</td>
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* The Orthopedic Outcome Score[6] was used for clinical evaluation and X-rays were scored according to Pettersson[7]
Figure 1: prophylactic treatment strategies for hemophilia A

- Start prophylaxis
- 1-2x/week: step up as soon as possible
- ≥3x/week: full prophylaxis from start
  - Consider increase to alternate day in case of bleeding
  - Increase to ≥3x/week within 3-6 months
  - Increase by one additional infusion/week following each significant bleed*

subscript with Figure

* joint bleed, muscle bleed or other critical/significant bleeding episode
REFERENCES


