Prophylaxis treatment options for untreated children with severe hemophilia: starting time and dose regimen

This document prepares the clinician to discuss scientific evidence with the patient (or caretaker) so they can make an informed decision together.

**Decision 1: What are the options for when to start prophylaxis?**

- **Early:** before or at least after the first joint bleed or during the 1st or 2nd year of age, whichever comes first.
- **Late:** after 2 or more joint bleeds or at 3 years of age or older.

*Note: in the literature, early is usually called "primary" and late is usually called "secondary"; but we recommend against using these terms in clinical encounters.*

**Why do parent preferences matter when making this decision?**

There are pros and cons to *early start compared to late start*:

**PROS of early start:**
- Opportunity to prevent joint damage
- Decreased anxiety about bleeding
- Potential reduction of subclinical bleeding or rare life-threatening bleeds
- Other: ______________________________________

**CONS of early start:**
- Need for venous access and related problems (infections, blockage, thrombosis, inhibitors, increased anxiety)
- Increased treatment burden
- Other: ______________________________________

**Selection of the best available studies** (November 2012)

### Benefits of early start compared to late start

<table>
<thead>
<tr>
<th>Joint health</th>
<th>Outcomes after 4 years in 24 patients:1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (y) at start of prophylaxis</td>
</tr>
<tr>
<td>Early</td>
<td>1-2</td>
</tr>
<tr>
<td>Late</td>
<td>3-6</td>
</tr>
<tr>
<td>&gt;6</td>
<td>10</td>
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<1 joint bleed/year while on prophylaxis for all groups

<table>
<thead>
<tr>
<th>Outcomes after 10 years in 21 patients:2</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
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<table>
<thead>
<tr>
<th>Outcomes after 17 years in 76 patients:3</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
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**Parental reassurance**

Once their child was on prophylaxis, parents had:
- more confidence to let their child undertake more vigorous activities
- less concerns about their child.4

### Risks of early start compared to late start

**Venous access problems**

- Older children (4 years old) are more likely to infuse into peripheral veins compared to younger children (2 years old) who more often require an implantable central venous access device (CVAD).5
- Older children might also better accept the infusion and require less time.
- CVADs are associated with:
  - complications
    - high risk of infection: rate of 0.66 per 1,000 catheter-days6
    - of 53 children with CVADs, 30% experienced complications after 18 months7
    - of 15 children with CVADs, 53% had deep vein thrombosis after 5½ years8
  - need for rigorous training and frequent care9
  - limited physical activity (for tunneled CVADs only).9

**Risk of inhibitor development in 125 patients10**

<table>
<thead>
<tr>
<th>Age, months (n)</th>
<th>Developed inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 (35)</td>
<td>26%</td>
</tr>
<tr>
<td>1-6 (15)</td>
<td>25%</td>
</tr>
<tr>
<td>6-12 (37)</td>
<td>21%</td>
</tr>
<tr>
<td>12-18 (19)</td>
<td>20%</td>
</tr>
<tr>
<td>&gt;18 (9)</td>
<td>9%</td>
</tr>
</tbody>
</table>

Note: patients at high risk for inhibitor development might have developed inhibitors before starting prophylaxis. Also, the protective effect of prophylaxis compared to on demand treatment should not be confused with the comparison of early versus late start of prophylaxis.

**Risk of incomplete treatment**

For prophylaxis to be effective, infusions should not be missed.11

Of 34 families, 70% missed infusions primarily because of:
- time commitment - for 58%
- uncooperative child - for 8%.12

Very low dose started before the first bleed, e.g. Kurnik protocol
Tailored dose, e.g. escalating dose
Step 1: 50 IU/kg weekly; if bleeding, proceed to
Step 2: 30 IU/kg x 2 weekly; if bleeding, proceed to
Step 3: 25 IU/kg every other day
Intermediate dose 15-25 IU/kg x 2 or 3 weekly
High treatment dose, e.g. full-dose/Malmo protocol 24-40 IU/kg x 3 weekly or 30-40 IU/kg x 2 weekly

Risk of joint bleeds
The efficacy of very low dose prophylaxis in preventing joint bleeds has not yet been fully established. Note: Data is based on limited evidence from a single study, and was not confirmed by a recently stopped unpublished trial.

Benefits
Joint health after 17 years in 128 patients
Patients without joint bleeds | Patients with healthy joints
--- | ---
Full | 36% | 95%
Intermediate | 7% | 31%

Venous access problems in 53 patients
Need of central venous access
--- | ---
Full | 75%
Tailored | 29%

Joint impairment
Of 27 children on intermediate dose, 30% had significant breakthrough bleeding and required an increase in dose, and 7% required daily prophylaxis to reduce bleeding episodes.

Joint impairment
Risk of subjecting patients to some target joint development before escalation of therapy.

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Why do parent preferences matter when making this decision?
- High dose provides better joint protection.
- Low dose regimens require less frequent injections.
- Less frequent injections may prevent the need for venous access devices.

Selection of the best available studies (as of November 2012)

References:

How much confidence can we have in these results for these 2 decisions?
We have to acknowledge that even the best available evidence about the starting time and dose regimen might be subject to bias because the studies are observational and uncontrolled.