Risk factors of inhibitor development

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Content

• Why is inhibitor the worst complication of haemophilia treatment?
• Epidemiology
• Risk factors
  - Genetic
  - Treatment related
• EHTSB consensus report - recommendations

Management of bleeds in high titre inhibitors: only with bypassing agents

• Less effective for treatment of bleeding compared with FVIII in non-inhibitor patients
• Expensive
• Increased mortality rates:
  - is 2.9-fold higher than general population
  - for severe haemophiliacs is 1.3-fold higher

*Knight C. Haemophilia 2003: 521-540
Bypassing agents: treatment monitoring

The treatment with bypassing agents:
- It is not only substitution
- We have no standardized tests for monitoring yet:
  - Thrombin generation assay:
    - High interlaboratory variation
    - Depends on amount of added TF and phospholipids
    - Assay is preferred in PRP
  - Thromboelastography:
    - High variability between subjects, within the same subject

Bypassing agents: Dosing regimes

Wide range of doses:
- Defined in accord to manufacturer’s and literature recommendations and clinical efficacy
- According to the clinical status
  - aPCC:
    - 50-100 IU/kg á 6-12 h
    - Limitation: maximum 200 IU/kg per day
  - rFVIIa:
    - 90-270 µg/kg á 2-3 (6) h

Not always successful: efficacy of aPCC in treatment of bleeding

- Bleeding episodes controled in:
  - 88-93% *Hilgartner M. Blood 1983: 36-40; Transfusion 1983: 626-30
  - Efficacy was judged as good or excellent in:
    - 96% *Home treatment only *Negrier C. Hemophilia 2008: 238 (abst. 330).
  - Cessation of bleeding with single dose reported in:
    - 95% (85 IU / kg) (FENOC study) *Berntorp E. Blood 2006: 546-51
    - 64% (75 IU / kg) *Young G. Hemophilia 2008: 267-68
Not always successful: efficacy of rFVIIa in treatment of bleeding

Cessation of bleeding:
- 92%, but with recurrence in 5% *Key N. Thromb Haemost 1998: 901-16
- 84-85% (<100 µg/kg - 200 µg/kg) *Reussenaar R. Haemophilia 2005: 109-16
- 93% (FENDC study) *Sorrentino F. Blood 2006: 146-51.
- Single mega-dose:

Expensive: Cost calculated for treatment on demand

- rFVIIa: 0.70 € / µg
- aPCC: 1.12 € / IU
- 353 794 € / year
  - 75 kg
  - 12.5 bleeds / year
  - 45% LR
  - 45% rFVIIa
  - 55% pdFVIII
  - 55% HR
  - 50% rFVIIa
  - 50% aPCC

Expensive: Treatment on demand - retrospective expenditures

France 1998:
- 56 000 € / year (LR)
- 278 000 € / year (HR)
- Included surgery, without ITT
- >23 years

Italy 2001:
- 216 000 € / year (HR)
- Included surgery, without ITT
- Mean age 36 years, >14 years

USA 1998:
- 141 000 $ / year (4 LR, 3 HR, 5 about 5 BU/ml)
- 8 >14 years, 4 >14 years

*Auerswald G. Haemophilia 2004: 10:499-508
*Goudemand J. Haemophilia 1999: 387-401
*Gringeri A. Blood 2003: 2358-63
*Bohn RL. Haemophilia 2004: 63-68.
**Evident reasons for inhibitor minimization**

- Prevention and prediction of inhibitor risk
- Immune tolerance induction

**Inhibitor – prevalence**

- Unselected haemophilic population 5 - 7%
- Severe haemophilia A (GB, France) 12 - 13%
- Mild and moderate haemophilia A 3 - 13%
- Total haemophilia A population 3.6 - 21%
- Haemophilia B 1.5 - 3%
  - Severe type 3-4%


**Inhibitor – incidence**

<table>
<thead>
<tr>
<th>products</th>
<th>n FVIII-2%</th>
<th>inhibitor total (%)</th>
<th>inhibitor &gt; 10 BU / ml</th>
<th>inhibitor &gt; 5 BU / ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lusher '93</td>
<td>101</td>
<td>32</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Gruppo 98</td>
<td>72</td>
<td>32</td>
<td>11</td>
<td>13</td>
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<tr>
<td>Lusher '04</td>
<td>64</td>
<td>38</td>
<td>16</td>
<td>23</td>
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<tr>
<td>Lusher '91</td>
<td>25</td>
<td>24</td>
<td>16</td>
<td>20</td>
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<tr>
<td>Ehrenfroh '92</td>
<td>mainly pd</td>
<td>27</td>
<td>52</td>
<td>41</td>
</tr>
<tr>
<td>Addiego 93</td>
<td>low.pur.+CP</td>
<td>89</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>de Biasi 94</td>
<td>various</td>
<td>48</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>

When does inhibitor rise?

- **PUP and severe haemophilia A:**
  - median 12 ED (9 - 36), till 40-50 ED
  - median age 2 years (1,7 - 3,3)

- **PTP studies and severe haemophilia A:**
  - pdFVIII (n=1306):
    - risk after 150 - 250 ED: 0.6%
  - rFVIII (n=307):
    - risk: 1.6% (high responder 0.3%)

*DiMichele D. In: Textbook of Haemophilia, Blackwell Publishing 2005: 64-70

Factors influencing development of FVIII inhibitors

### Hereditary risk factors:
- Gene defects causing haemophilia
- Immunologic response characteristics
- Family history of inhibitors
- Ethnicity

### Treatment-related factors:
- FVIII product type:
  - pd versus recombinant
  - Switching between FVIII products
  - Content of vWF
- Age at first FVIII exposure
- Intensity of treatment
- Mode of administration (bolus, CI)
- Immunologic costimulation
  - Breastfeeding
  - Antenatal FVIII exposure
  - Infection and vaccination
  - Bleeding and surgery

Inhibitor prevalence in severe haemophilia A

*Oldenburg J. Haemophilia 2006 (Suppl. 6): 15-22.*
Hereditary risk factors: Mutation profile in severe haemophiliacs A (Germany)

- 17-41% risk of inhibitor in more than 80% of severe haemophiliacs A
- 88% risk with multidomain deletion
- 3-10% risk with missense mutation and A-run small deletions


Hereditary risk factors: Gene defects causing haemophilia A

- Arg593cys: 10-fold increased risk of inhibitor
  - 20% (5/25)

- C1/C2 domain missence mutation:
  - 8.7% vs. 3.6% non-C1/C2

- Substitution of amino acid of different physical-chemical class
  - 5.8% vs. 1.8%
Hereditary risk factors:

Gene defects causing haemophilia B

- **Large deletions:**
  - ½ of patients with inhibitor
  - only 1-3% of haemophilia B population
  

- **Nonsense mutations:**
  - Inhibitor prevalence is only 6% (in HA is 30%)
  

Prevalence of FIX inhibitors is lower than in HA:

- More patients have low risk mutations
- Similarity with other vitamin K dependent factors

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Hereditary risk factors:

Immunologic response characteristics

<table>
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<th>HLA alleles:</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3, B7, C7, DQA0102, DQB0602, DR15</td>
<td>2.4</td>
</tr>
<tr>
<td>C2, DQA0103, DQB0603, DR13</td>
<td>0.1-0.2</td>
</tr>
</tbody>
</table>


**IL-10:**
- Microsatellite polymorphism in promotor
  - Allele 134
  

**TNF-α:**
- Polymorphism in promoter -G 308 A
  - For severe haemophilia A with genotype AA
  

**CTLA-4:**
- Polymorphism -C 318 T
  - Protective down regulatory effect
  
  * Astermark J. Haemophilia 2012;18(Suppl..4): 38-42

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Hereditary risk factors:

Immunologic response characteristics

* Astermark J. Haemophilia 2000; 12 (Suppl. 3): S2-60

(Exogenous FVIII)
Hereditary risk factors:
Immunologic response characteristics

Hereditary risk factors:
Ethnicity

African origin versus Caucasians
51.9% vs 25.8%

- 2 x ↑ risk
  *Scharrer I. Haemophilia 2000: 145-54
- 2.4 x ↑ risk (Afro-Americans and Hispanics)
  *Ninan SC. Thromb Haemost 2007: 1066-90
- 3.6 x ↑ risk in patients with FVIII H3, H4 haplotype
- FVIII H3 haplotype is not independent predictor of inhibitor risk
  *Schwarz J. Haemophilia 2013;19:113-119

At least six wild-type FVIII haplotypes:
- H1 and H2 have been occurred in all racial groups
- H3,4,5 found only in black people
- H5 found only in Chinese
  *Krasar Zarfert R. Haemophilia 2013; 19 (Suppl.1):2-7

Hereditary risk factors:
Family history of inhibitors

Family history of FVIII inhibitors:
- 3.2 x ↑ risk for brother
  *Astermark J. Haematologica 2005: 924-31
- 3 x ↑ risk with positive family history
  *Krasar Zarfert R. Blood 2007: 4048-54
- 50% risk for brother versus 9% in extended relatives
  *Ahldholt M. Thromb Haemost 1999: 500-4
Treatment-related factors: product type
FVIII plasma-derived versus recombinant

- Immunomodulatory activities:
  - Antigenic competition:
    - Antibodies against other proteins than FVIII
  - Various cytokines expression:
    - pdFVIII higher levels of IL-4, IL-5, TGF-β: Th2 response
    - rFVIII higher levels of IL-2, IL-10, IFN-γ: Th1 response* Kruse-Jarres R. Haemophilia 2013; 19 (Suppl.1):2-7
  - Presence of von Willebrand factor:
    - VWF binds to C2 domain of FVIII, which contains:
      - Frequently binding site for inhibitor
      - Binding site for phospholipids
    - r-FVIII ♦ phospholipids affinity:
      - Correlates with ♦ risk of FVIII inhibitor
  - Blocks uptake of FVIII by:
    - Antigen-presenting cells

Treatment-related factors:
Pivotal studies with r-FVIII in PUPs, FVIII < 2%

<table>
<thead>
<tr>
<th>r-FVIII product</th>
<th>Observation median ED</th>
<th>Inhibitor</th>
<th>No</th>
<th>%</th>
<th>HR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinate</td>
<td>11 NK</td>
<td>17/71</td>
<td>30.1</td>
<td>NK</td>
<td></td>
</tr>
<tr>
<td>Kogenate</td>
<td>126 19/65</td>
<td>29.2</td>
<td>15.7</td>
<td>NK</td>
<td></td>
</tr>
<tr>
<td>Kogenate Bayer</td>
<td>114 9/60</td>
<td>15</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refacto</td>
<td>197 32/101</td>
<td>31.7</td>
<td>15.9</td>
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<td></td>
</tr>
</tbody>
</table>


Treatment-related factors:
Post-marketing studies with r-FVIII in PUPs

<table>
<thead>
<tr>
<th>r-FVIII product</th>
<th>FVIII</th>
<th>ED median</th>
<th>Inhibitor</th>
<th>No</th>
<th>%</th>
<th>HR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinate</td>
<td>&lt; 1%</td>
<td>64</td>
<td>28</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Kogenate</td>
<td>any severity</td>
<td>15/43</td>
<td>34.9</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refacto</td>
<td>any severity</td>
<td>3/16</td>
<td>18.8</td>
<td>12.5</td>
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### Treatment-related factors: Pivotal studies with r-FVIII in PTPs

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<th>r-FVIII product</th>
<th>FVIII</th>
<th>ED median</th>
<th>Inhibitor</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinate</td>
<td>&lt; 5%</td>
<td>184</td>
<td>2/69</td>
<td>2.9</td>
</tr>
<tr>
<td>Kogenate</td>
<td>any severity</td>
<td>93% &lt; 2%</td>
<td>2/86</td>
<td>2.3</td>
</tr>
<tr>
<td>Kogenate Bayer</td>
<td>&lt; 1%</td>
<td>NK</td>
<td>226</td>
<td>1.7</td>
</tr>
<tr>
<td>Refacto</td>
<td>&lt; 2%</td>
<td>≥ 30</td>
<td>NK</td>
<td>1/113</td>
</tr>
<tr>
<td>Advate</td>
<td>&lt; 2%</td>
<td>117</td>
<td>1/171</td>
<td>0.9</td>
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<td>Recombinate</td>
<td>any severity</td>
<td>NK</td>
<td>0.06% / year</td>
<td>NK</td>
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<tr>
<td>Kogenate</td>
<td>any severity</td>
<td>NK</td>
<td>10/304</td>
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<td>Refacto</td>
<td>any severity</td>
<td>NK</td>
<td>3/172</td>
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### Treatment-related factors: Studies comparing inhibitor incidence in severe haemophilia PUPs

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<th>pd-FVIII</th>
<th>FVIII inhibitor</th>
<th>n</th>
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<tr>
<td>all</td>
<td>11%</td>
<td>62</td>
<td>5%</td>
<td>15%</td>
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15.4.2013

- High responding inhibitors

- All inhibitors

<table>
<thead>
<tr>
<th></th>
<th>pd-FVIII</th>
<th>r-FVIII</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>All studies</td>
<td>14.3%</td>
<td>27.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prospective studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>9.1%</td>
<td>23.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Severe HA, HR only</td>
<td>6.0%</td>
<td>19.4%</td>
<td>0.195</td>
</tr>
<tr>
<td>HR, all patients</td>
<td>9.3%</td>
<td>17.4%</td>
<td>0.004</td>
</tr>
<tr>
<td>HR, severe HA</td>
<td>9.0%</td>
<td>18.2%</td>
<td>0.009</td>
</tr>
<tr>
<td>Non-transient, all patients</td>
<td>11.8%</td>
<td>19.8%</td>
<td>0.076</td>
</tr>
<tr>
<td>Non-transient, severe HA</td>
<td>16.3%</td>
<td>25.8%</td>
<td>0.317</td>
</tr>
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Treatment-related factors: switching between products

<table>
<thead>
<tr>
<th></th>
<th>Cumulative risk of all inhibitors</th>
<th>Cumulative risk of high responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means in studies</td>
<td>Mean of studies</td>
</tr>
<tr>
<td>low / intermed. purity pdFVIII only 1 products</td>
<td>20.3 – 33%</td>
<td>25.9%</td>
</tr>
<tr>
<td>low / intermed. purity pdFVIII &gt; 1 products</td>
<td>0 – 12.4%</td>
<td>6.8%</td>
</tr>
<tr>
<td>recombinant FVIII only 1 product</td>
<td>32 – 38%</td>
<td>33%</td>
</tr>
</tbody>
</table>

*Wight J. Haemophilia 2003: 418-435
Treatment-related factors: Inhibitor incidence according to VWF content at first treatment

<table>
<thead>
<tr>
<th>r-FVIII products</th>
<th>pd-FVIII products</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low VWF</td>
<td>High VWF</td>
</tr>
<tr>
<td>No. of patients</td>
<td>181</td>
<td>53 (29%)</td>
</tr>
<tr>
<td>No. of all inhibitors</td>
<td>53 (29%)</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>No. of high titre inhibitors</td>
<td>43 (24%)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>No. of switched product type</td>
<td>8 (3%)</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>prophylaxis within the first 50 EDs</td>
<td>105 (58%)</td>
<td>23 (70%)</td>
</tr>
</tbody>
</table>

- Products with high VWF content had the same risk for inhibitor as r-FVIII
- Switching between FVIII products did not increase the risk for inhibitors (RR=1.1)


Trends in evaluated groups - possible explanation? (speculation)

<table>
<thead>
<tr>
<th></th>
<th>r-FVIII</th>
<th>pd-FVIII</th>
<th>pd-FVIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>switched product type</td>
<td>3%</td>
<td>42%</td>
<td>34%</td>
</tr>
<tr>
<td>start prophylaxis within 50 EDs</td>
<td>58%</td>
<td>70%</td>
<td>43%</td>
</tr>
<tr>
<td>treatment on at least 3 consecutive days</td>
<td>71%</td>
<td>70%</td>
<td>91%</td>
</tr>
</tbody>
</table>

### Factor VIII Products and Inhibitor Development in Severe Hemophilia A

- **2000-2020**
- 574 PUPs for up 75 EDs
- Inhibitor 177/574 (32.4%)  

<table>
<thead>
<tr>
<th>Product</th>
<th>Unadjusted Hazard Rat.</th>
<th>Adjusted Hazard Rat.</th>
<th>P value</th>
<th>Unadjusted Hazard Rat.</th>
<th>Adjusted Hazard Rat.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIII</td>
<td>1</td>
<td>1</td>
<td>NA</td>
<td>1</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>pdFVIII</td>
<td>1.14</td>
<td>1.24</td>
<td>0.54</td>
<td>0.87</td>
<td>0.85</td>
<td>0.85</td>
</tr>
</tbody>
</table>

### Specific products

<table>
<thead>
<tr>
<th>Product</th>
<th>Unadjusted Hazard Rat.</th>
<th>Adjusted Hazard Rat.</th>
<th>P value</th>
<th>Unadjusted Hazard Rat.</th>
<th>Adjusted Hazard Rat.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-3rd-gen-FL</td>
<td>1</td>
<td>1.37</td>
<td>0.11</td>
<td>1.6</td>
<td>1.79</td>
<td>0.02</td>
</tr>
<tr>
<td>r-2nd-gen-FL</td>
<td>1.2</td>
<td>1.37</td>
<td>0.09</td>
<td>0.96</td>
<td>1.26</td>
<td>0.03</td>
</tr>
<tr>
<td>r-1st-gen-FL</td>
<td>1.0</td>
<td>1.47</td>
<td>0.99</td>
<td>0.97</td>
<td>0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>r-2nd-gen-BDD</td>
<td>1.1</td>
<td>1.51</td>
<td>0.16</td>
<td>1.56</td>
<td>1.23</td>
<td>0.51</td>
</tr>
</tbody>
</table>

### Treatment-related factors: Age at first FVIII exposure and inhibitor incidence

- No. of patients: 62, 209, 81, 348, 366
- Observation: 3 years, 50 ED, 3-26 yrs, > 50 ED, 50 ED
- < 2 months: 26%, 41%
- 2-6 months: 25%, 30%
- > 7 months: 41%, 24%, 34%
- 7-12 months: 29%, 18%, 20%, 21, 23%
- > 12 months: 12%, 20%, 13%
- > 18 months: 20%, 20%

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*Kenet G. Haemophilia 2006 (S2): 63 (14 PO 395)*
- sHA, 62 PUP, observation median 7 year, pd-FVIII or r-FVIII
- Age at first FVIII exposure:
  - 1-6 months: 10/50 = 20%
  - > 6 months: 2/12 = 16.7%

- only r-FVIII products
- Age at first FVIII exposure:
  - crude OR adjusted OR
  - 11 months: 2.8 3.3
  - 11-16 months: 1.7 2.5
  - > 16 months: 1 1
  - Prophylaxis: 0.2 0.2

Median of age at onset of prophylaxis was 35 months
### Treatment-related factors: Age at first FVIII exposure and inhibitor incidence

<table>
<thead>
<tr>
<th>Age at first FVIII exposure</th>
<th>All inhibitors</th>
<th>High-titre inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>proportion</td>
<td>Crude RR</td>
</tr>
<tr>
<td>&lt; 2 months</td>
<td>41%</td>
<td>2.7</td>
</tr>
<tr>
<td>2-6 months</td>
<td>30%</td>
<td>1.9</td>
</tr>
<tr>
<td>7-12 months</td>
<td>23%</td>
<td>1.3</td>
</tr>
<tr>
<td>12-18 months</td>
<td>20%</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;18 months</td>
<td>18%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Treatment**
- for bleed: 23% 1.0 1.0 17% 1.0 1.0
- prophylaxis: 22% 1.0 1.0 19% 1.1 1.2
- surgery: 65% 3.7 2.6 59% 4.4 4.1
- > 5 days: 56% 3.3 3.1 53% 4.3 4.1


### Treatment-related factors: Age at first 50 ED and inhibitor incidence

<table>
<thead>
<tr>
<th>Dose of 5 consecutive ED</th>
<th>All inhibitors</th>
<th>High-titre inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>proportion</td>
<td>Crude RR</td>
</tr>
<tr>
<td>&lt; 35 IU/kg</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>35-50 IU/kg</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt; 50 IU/kg</td>
<td>3.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Major surgery:**
- 1.4 1.3 1.3 1.2

**Treatment > 5 days:**
- 2.0 1.6 2.3 1.9

**Duration between ED**
- > 50 days: 1.0 1.0 1.0 1.0
- 10 – 50 days: 0.8 0.8 0.6 0.6
- 0 – 10 days: 1.0 1.0 1.0 1.0

**Regular prophylaxis:**
- 0.4 0.5 0.5 0.5

Despite late onset of prophylaxis, started at median age of 25 months and after 16 ED.


### Early prophylaxis/FVIII tolerization regimen

**Start:**
- at median age of 10.7 months
- after minimum ED: median 1 ED
- based on subcutaneous haematomas not required FVIII substitution
- 250 IU (25 - 35 IU/kg) once weekly

<table>
<thead>
<tr>
<th>40-50 IU / kg 3x a week</th>
<th>25-35 IU / kg 1x a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 30</td>
<td>N = 40</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>High-responder</td>
</tr>
<tr>
<td>14 (47%)</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>1 (3.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Auerswald G. Haemophilia2012;18, e1-e41.*
Treatment-related factors: Mode of administration - continuous infusion

- Higher risk in mild and moderate haemophilia A
  - 10 patients developed inhibitors in Germany following CI
    - 7/10 had mild or moderate form of HA
  - 29 mild HA patients in Toronto exposed to r-FVIII
    - 7 CI - 4 developed inhibitors
    - 22 had bolus treatment - non FVIII inhibitor
  - Not confirmed in severe HA, less clear in mild and moderate HA:
    - Inhibitor of FVIII in non-severe HA 7.2% (6/83)
    - Development of inhibitor depends on high risk genotype:
      - < 50 ED except one patient
      - 5/6 high risk mutation: Arg593Cys
    - Inhibitor of FVIII in severe HA 0.45% (3/659)
  *

Treatment-related factors: Immunologic costimulation

- Breastfeeding
  - Protective effect was not proved
  *

- Antenatal FVIII exposure
  - Amniocentesis, villocentesis, prematurity delivery
    - No difference was found
  *

- Infections, vaccinations
  - No association with inhibitor risk
  - No data in the literature despite the theoretical presentation of danger signals
  *
  *Arnemark J. Haemophilia 2012;18(Suppl 4):38-42

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Total number of patients</th>
<th>Predicted positive inhibitors</th>
<th>Observed positive inhibitors</th>
<th>Negative predictive value</th>
<th>OR</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CANAL cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (9 points)</td>
<td>95</td>
<td>8</td>
<td>6</td>
<td>0.05</td>
<td>0.61</td>
<td>2</td>
</tr>
<tr>
<td>Median (2 points)</td>
<td>170</td>
<td>38</td>
<td>39</td>
<td>0.23</td>
<td>0.73</td>
<td>1</td>
</tr>
<tr>
<td>High (3 points)</td>
<td>07</td>
<td>56</td>
<td>56</td>
<td>0.37</td>
<td>0.83</td>
<td>1</td>
</tr>
<tr>
<td><strong>Validation cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (9 points)</td>
<td>20</td>
<td>8</td>
<td>2</td>
<td>0.05</td>
<td>0.64</td>
<td>2</td>
</tr>
<tr>
<td>Median (2 points)</td>
<td>26</td>
<td>6</td>
<td>8</td>
<td>0.20</td>
<td>0.75</td>
<td>1</td>
</tr>
<tr>
<td>High (3 points)</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>0.50</td>
<td>0.81</td>
<td>1</td>
</tr>
</tbody>
</table>

Results are shown by low, median and high risk categories. For example, a patient of the CANAL cohort, in the low risk category has a probability of 6% to develop an inhibitor, meaning that the fact that a patient in the low risk category has a 0.5% (1/200) probability of not developing an inhibitor. A negative predictive value of 65% is the probability that a patient outside the low risk category of high risk categories will not develop an inhibitor.
Pregnancy, delivery, breast feeding – no recommendations:
• No data indicating an association with inhibitor formation

Age of start, reason for first infusion, prophylactic vs. on-demand treatment:
• Recommended prophylaxis for all children:
  - Might exert a favourable immunological effect to promote tolerance
  - Young age at first ED in earlier studies as a risk factor later not confirmed
  - Depend on FVIII mutation and intensity of treatment

Vaccinations, infections, extravasation, blood components, immunological disorders:
• Insufficient evidence to make recommendations, waiting for studies to be performed, EHTSB recommended:
  - Vaccination preferably s.c. avoiding concomitant infusion of factor
  - Replacement therapy should be avoided in severe infection

Intensity of treatment, surgery, major bleeds and CI vs. bolus infusion:
• Recommendation to minimize intensive treatment whenever possible to avoid association with immune system challenges
• Not support the concept that CI in patients with severe haemophilia is associated with higher risk of inhibitor

Factor concentrates: EHTSB concluded that:
- In PTPs there is no evidence to suggest that the immunogenicity of various types of product will differ or switching between them will be associated with a risk of inhibitor
- In PUPs whether the type of concentrate has the ability to modulate the risk of inhibitor in a significant way and thereby establishing implications for the use of different factor concentrates will require well-designed, prospective trials

What to do to decrease incidence of (FVIII) inhibitor?
Risk of FVIII inhibitor could be increased by:
• Treatment intensity (high dose, > 5 days, surgery):
  - At first exposure, probably during 20–40 Eds: postpone surgery
  - Continuous infusion: do only in severe form
  - It seems true only in mild/moderate haemophilia A: use DDAVP in mild HA
• Dangerous signal: avoid factor administration
  - FVIII infusion during infection, vaccination, first treatment for bleeding
• Not clear if it could be negatively influenced:
  - By type of FVIII concentrate: no clear recommendation
  - Recombinant have been monitored in more details
  - In an independent way by early FVIII exposure: preferred > 6–12 months
  - By switching of FVIII products: not to switch FVIII concentrates

Risk of FVIII inhibitor is probably decreased by:
• Prophylactic treatment:
  - Start before the first bleeding
  - In high risk (mutation, FVIII in family)
  - Low dose 25–35 IU/kg a week
Thank you for your kind attention!