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 1990: 626-30.*
- Efficacy was judged as good or excellent in:
  - *81%*
    - Including surgery **Negrier C. Thromb Haemost 1997: 1113-19.*
  - *96%*
    - Home treatment only **Negrier C. Haemophilia 1998: 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. Haemophilia 2008: 287-84.*

Not always successful: efficacy of rFVIIa in treatment of bleeding

Cessation of bleeding:

- 92%, but with recurrence in 5% **Key N. Thromb Haemost 1998: 912-18.*
- 91% **Laurian Y. Blood Coagul Fibrinolysis 1998 : 155-6.*
- 84-85% (< 100 μg/kg – 200 μg/kg)
- 97% (>200 μg/kg) **Parameswaran R. Haemophilia 2005: 100-106.*
- 93% (FENOC study) **Berntorp E. Blood 2006: 546-51.*

- Single mega-dose:
  - *83%, but 10% with recurrence* **Kenet G. Thromb Haemost 2003: 450-55.*
  - *90.5%* **Kavakli K. Thromb Haemost 2006: 600-5.*
  - *92%* **Young G. Haemophilia 2008: 287-294.*

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% rFVIII
    - 55% pdFVIII
  - 55% HR
    - 50% rFVIIa
    - 50% aPCC

**Auerswald G. Haemophilia 2004: 10:499-508.*

Expensive: Treatment on demand – retrospective expenditures

France 1998:

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

**Goudemand J. Haemophilia 1999: 387-401.*

Italy 2001:

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

**Gringeri A. Blood 2003: 2358-63.*

USA 1998:

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

**Bohn RL. Haemophilia 2004: 63-68.*

Evident reasons for inhibitor minimization

- Prevetion and prediction of inhibitor risk
- Immune tolerance induction

Inhibitor – prevalence

- Unselected haemophiliac population 5 - 7%
- Severe haemophilia A (GB, France) 12 – 13%

**Wight J. Haemophilia 2003: 418-435.*

- Mild and moderate haemophilia A 3 – 13%

**Peerlinck K. Haemophilia 2006 (Suppl. 6): 43-7.*

- Total haemophilia A population 3.6 – 21%

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

- Haemophilia B 1.5 – 3%
  - Severe type 3-4%

**Tandra A. In:Textbook of Hemophilia, Blackwell Publishing 2010: 97-1003*

Inhibitor – incidence

Severe haemophilia A: 20 - 30% (3.6 - 52%)

**Astermark J. Semin Hematol 2006 (Suppl.4): 3-7.*

	products	n FVIII <2%	inhibitor total (%)	inhibitor > 10 BU / ml	inhibitor > 5 BU / ml
Lusher 03	ReFacto	101	32	12	16
Gruppo 98	Recombinate	72	32	11	13
Lusher 04	Kogenate	64	38	16	23
Lusher 91	Monoclonate	25	24	16	20
Ehrenforth 92	mainly pd	27	52	41	44
Addiego 93	low.pur.+CP	89	28	21	24
de Biasi 94	various	48	22	17	19

**Lusher JM. In: Textbook of Hemophilia, Blackwell Publishing 2005: 34-38.*

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)

haemophilia B:
- 11 ED
- 19.5 months

- **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 Hemophilia, Blackwell Publishing 2005: 64-70.*

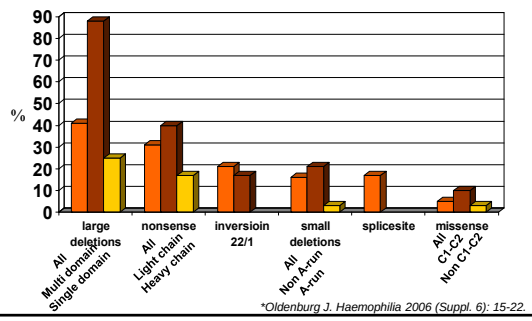
Factors influencing development of FVIII inhibitors

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

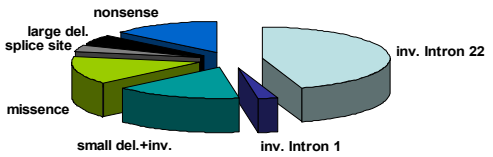
Hereditary risk factors: Gene defects causing haemophilia A

Inhibitor prevalence in severe haemophilia A



**Oldenburg J. Haemophilia 2006 (Suppl. 6): 15-22.*

Hereditary risk factors: Mutation profile in severe haemophiliacs A (Germany)

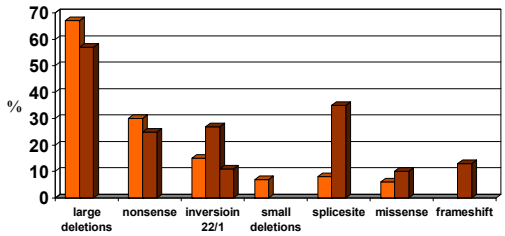


- 17-41% risk ofinhibitor in more than 80% of severe haemohiliacs A
- 88% risk with multidomain deletion
- 3-10% risk with missense mutation and A-run small deletions

**Oldenburg J. Haemophilia 2006 (Suppl. 6): 15-22.*

Hereditary risk factors: Gene defects causing haemophilia A

Inhibitor prevalence in severe haemophilia A



**Gouw S.Haemophilia 2011; 17:275-281*
**Miller CH.Haemophilia 2012;18:375-382*

Hereditary risk factors: Non-severe haemophilia A

- **Arg593cys:**
  - 10-fold increased risk of inhibitor

    **Eckhardt CL. J Thromb Haemost 2009;7: 930-7*
  - 20% (5/25)

    **Mauser-Bunschoten EP. Haemophilia 2012;18:263-267.*
- **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%

    **Schwaab R. Thromb Haemost 2013;109: 464-470.*

Hereditary risk factors: Gene defects causing haemophilia B

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

**Warrier I. In: Textbook of Hemophilia, Blackwell Publishing 2005: 97-100.*

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

**Oldenburg J. Haemophilia 2006 (Suppl. 6): 15-22.*

Prevalence of FIX inhibitors is lower than in HA:

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

Hereditary risk factors: Immunologic response characteristics

HLA alleles:	**Relative risk**
• A3, B7, C7, DQA0102, DQB0602, DR15	2-4
• C2, DQA0103, DQB0603, DR13	0.1-0.2

**Astermark J. Semin Hematol 2006 (Suppl.4): 3-7.*

IL-10:

• Microsatellite polymorphism in promotor (allele 134)	4.4

TNF-α:

• Polymorphism in promotor –G 308 A	4.0
– For severe haemophilia A with genotype AA	19.2

**Oldenburg J. Haemophilia 2006 (Suppl. 6): 15-22.*

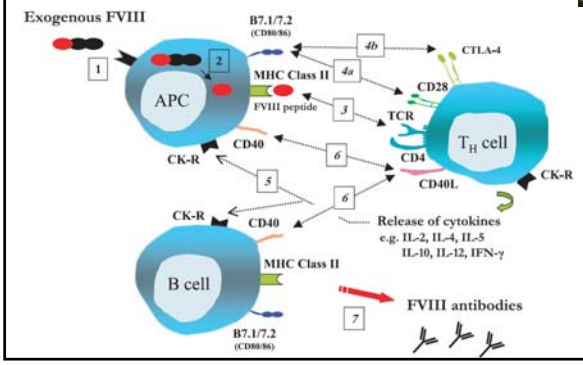
CTLA-4:

- Polymorphism –C 318 T
  - Protective down regulatory effect

**Astermark jJ Haemophilia 2012;18(Suppl..4): 38-42*

Hereditary risk factors: Immunologic response characteristics

**Astenmark J. Haemophilia 2006; 12 (Suppl. 3): 52-60.*



Hereditary risk factors: Immunologic response characteristics

Fig. 2. Schematic model showing the principles of inhibitor formation in patients with haemophilia A. Exogenous infused factor VIII (FVIII) binds to the antigen-presenting cells (APC) (*Step 1*). After endocytosis, oligopeptides will be formed by proteolytic cleavage (*Step 2*). These peptides bind to the major histocompatibility complex (MHC) class II molecules having the correct recognition sequence. The MHC–FVIII peptide complexes are then transferred to the cell membrane and presented to the T-cell receptors (TCR) on the CD4+ T_H-lymphocytes (*Step 3*). Co-stimulatory signals have to be provided by the binding of B7.1 (CD80) and B7.2 (CD86) to CD28 (*Step 4a*) to fully activate the T_H-lymphocytes and to stimulate the release of cytokines (*Step 5*). The subsequent binding of these cytokines to the corresponding receptors (CK-R) up-regulates immune response genes and co-stimulatory molecules on the cell surfaces of both B- and T-cells (*Step 6*). The enhanced action of cytokines and co-stimulatory molecules, including the interaction between CD40 and CD40L, induces B-cell proliferation, differentiation and FVIII antibody production (*Step 7*). The activation of the T_H-cells is down-regulated by the competitive binding of cytotoxic T-lymphocyte antigen 4 (CTLA4) to the B7 molecules on the APC (*Step 4b*).

*Astenmark J. Haemophilia 2006; 12 (Suppl. 3): 52-60.

Hereditary risk factors: Ethnicity

African origin versus Caucasians 51,9% vs 25,8%

- 2 x ↑ risk

*Scharrer I. Haemophilia 1999: 145-54.

- 2.4 x ↑ risk (Afro-Americans and Hispanics)

*Gouw SC.J Thromb Haemost 2007: 1383-90

- 3.6 x ↑ risk in patients with FVIII H3, H4 haplotype

*Viel KR. N Engl J Med 2009;360:1618-2

- 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

*Kruse-Jarres 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

*Gouw SC. Blood 2007: 4648-54.

- 50% risk for brother versus 9% in extended relatives

*Gill JC. 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, IF-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

**Goudemand J. Blood 2006: 46-51.*

  - Blocks uptake of FVIII by:
    - Antigen-presenting cells

**Lacroix-Desmazes S. XXIst ISTH Congress 2007, * Kruse-Jarres R. Haemophilia 2013; 19 (Suppl.1):2-7*

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

r-FVIII product	Observation median ED	Inhibitor No	Inhibitor %	HR %
Recombinate	**11** **NK**	**17/71** **NK**	**23.9** **30.1**	**11.3** **NK**
Kogenate	**126**	**19/65**	**29.2**	**15.7** **Any severity**
Kogenate Bayer	**114**	**9/60**	**15**	**10**
Refacto	**197**	**32/101**	**31.7**	**15.9**

**Peerlinck K. Haemophila 2006: 579-90.*

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

r-FVIII product	FVIII	ED median	Inhibitor No	Inhibitor %	HR %
Recombinate	< 1%	**64**	**14/50**	**28**	**12**
Kogenate	any severity	**NK**	**15/43**	**34.9**	**14**
Refacto	any severity	**NK**	**3/16**	**18.8**	**12.5**

**Peerlinck K. Haemophila 2006: 579-90.*

Treatment-related factors: Pivotal studies with r-FVIII in PTPs

r-FVIII product	FVIII	ED median	Inhibitor No	Inhibitor %	HR %
Recombinate	< 5%	**184**	**2/69**	**2.9**	**1.4**
Kogenate	any severity 93% < 2%	**NK** **226**	**2/86** **2/58**	**2.3** **1.7**	**2.3** **NK**
Kogenate Bayer	< 1%	**NK**	**1/71**	**1.4**	**0**
Refacto	< 2%	**≥ 30**	**1/113**	**0.9**	**0.9**
Advate	< 2%	**117**	**1/117**	**0.9**	**0**

**Peerlinck K. Haemophila 2006: 579-90.*

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

r-FVIII product	FVIII	ED median	Inhibitor N	Inhibitor %	HR %
Recombinate	any severity	**NK**	**0.06% / year**		**NK**
Kogenate	any severity	**NK**	**10/304**	**3.3**	**NK**
Refacto	any severity any severity	**NK** **NK**	**3/172** **1/91**	**1.7** **1.1**	**1.1** **1.1**

**Peerlinck K. Haemophila 2006: 579-90.*

Treatment-related factors: Studies comparing inhibitor incidence in severe haemophilia PUPs

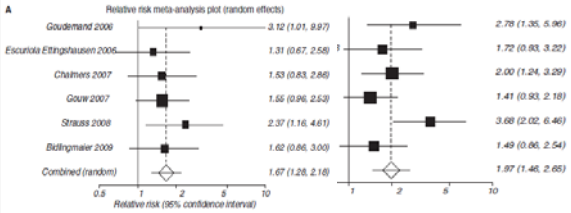
	pd-FVIII			r-FVIII			difference
	n	FVIII inhibitor		No	FVIII inhibitor		
		all	HR		all	HR	
**Goudemand J. Blood 2006: 46-51*	**62**	**11%**	**5%**	**86**	**31%**	**15%**	**RR=2.4 (HR 2.6)**
**Escuriola-Ettinghausen C. Haemophilia 2006 (S6): 102-6*	**57**	**21%**	**NK**	**47**	**36%**	**NK**	**P=0.08**
**Chalmers EA. Haemophilia 2007: 149-55*	**132**	**14%**	**10%**	**172**	**27%**	**15%**	**P=0.009 (HR=NS)**
**Gouw SC. Blood 2007: 4693-97.*	**135**	**21.5%**	**17%**	**181**	**29%**	**24%**	**RR=0.8 (HR 0.9)**
**Knobe KE. Acta Paediatr 2003: 17-20*	**52**	**17%**	**NK**	**48**	**21%**	**NK**	**NS Prophyl.**
**Iorio A. J Thromb Haemost 2010; 8: 1256-65*	**1167** any severity	**14.3%**	**9.3%**	**927**	**27.4%**	**17.4%**	**RR = 2 (HR = 1,7)**

ORIGINAL ARTICLE

Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review

A. IORIO,* S. HALIMEH,† S. HOLZHAUER,‡ N. GOLDENBERG,§ E. MARCHESINI,* M. MARCUCCI,* G. YOUNG,¶ C. BIDLINGMAIER,‡‡ L. R. BRANDAO,§§ C. E. ETTINGSHAUSEN,¶¶ A. GRINGERI,** G. KENET,*** R. KNÖFLER,††† W. KREUZ,¶¶ K. KURNIK,‡‡ D. MANNER,††† E. SANTAGOSTINO,** F. M. MANNUCCI** and U. NOWAK-GÖTTL†††

- **High responding inhibitors**
- **All inhibitors**



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	pd-FVIII	r-FVIII	P value
All studies	14.3%	27.4%	< 0.001
Prospective studies			
All patients	9.1%	23.7%	< 0.001
Severe HA, HR only	6.0%	19.4%	0.195
HR, all patients	9.3%	17.4%	0.004
HR, severe HA	9.0%	18.2%	0.009
Non-transient, all patients	11.8%	19.8%	0.076
Non-transient, severe HA	16.3%	25.8%	0.317

Multi-way ANOVA study design:

- study period
  - **recent higher detection**
- testing frequency
  - **more frequent**
    - **higher detection**
- follow-up
  - **duration – no trend**
- intensity treatment
  - **insufficient data**

Concentrate lost statist. significance

Treatment-related factors: switching between products

	Cumulative risk of all inhibitors		Cumulative risk of high responders	
	Means in studies	Mean of studies	Means in studies	Mean of studies
low / intermed. purity pdFVIII > 1 products	20,3 – 33%	25,9%	19,2–26,4%	21,9%
low / intermed. purity pdFVIII only 1 products	0 – 12,4%	6,8%	0 – 2,5%	1,4%
recombinant FVIII only 1 product	32 – 38%	33%	13 – 23%	16,9%

**Wight J. Haemophilia 2003: 418-435*

Treatment-related factors:Inhibitor incidence according to VWF content at first treatment

	r-FVIII products	pd-FVIII products		Total
		Low VWF	High VWF	
No. of patients	181	33	102	316
No. of all inhibitors	53 (29%)	5 (15%)	24 (24%)	82 (26%)
No. of high titre inhibitors	43 (24%)	4 (12%)	19 (19%)	66 (21%)
No. of switched product type	5 (3%)	14 (42%)	35 (34%)	54 (17%)
prophylaxis within the first 50 ED	105 (58%)	23 (70%)	44 (43%)	172 (54%)

- 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)

*Gouw SC. Blood 2007: 4693-97.

Treatment-related factors:Inhibitor incidence according to VWF content at first treatment

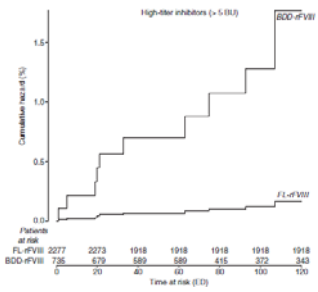
- Products with high VWF content : the same risk for inhibitor as r-FVIII

Trends in evaluated groups – possible explanation? (speculation)

	r-FVIII	pd-FVIII ↓VWF	pd-FVIII ↑VWF
switched product type	**3%**	**42%**	**34%**
start prophylaxis within 50 EDs	**58%**	**70%**	**43%**
treatment on at least 3 consecutive days	**71%**	**70%**	**91%**

*Gouw SC. Blood 2007: 4693-97.

Can B-domain deletion alter the immunogenicity of recombinant factor VIII? A meta-analysis of prospective clinical studies



- 3 012 PTPs evaluated
- for a median 79 EDs

ED	Cumulative hazard (CI), %		
	BDD-rFVIII	*FL-rFVIII*	*Total*
20	0.45 (0.00–0.90)	0.04 (0.00–0.10)	0.07 (0.00–0.16)
40	0.70 (0.10–1.29)	0.06 (0.00–0.15)	0.12 (0.00–0.24)
60	0.70 (0.10–1.29)	0.06 (0.00–0.15)	0.12 (0.00–0.24)
80	1.06 (0.25–1.88)	0.10 (0.00–0.22)	0.18 (0.00–0.36)
100	1.28 (0.34–2.22)	0.12 (0.00–0.27)	0.21 (0.00–0.42)
120	1.76 (0.57–2.95)	0.16 (0.00–0.36)	0.29 (0.01–0.57)

Hazard ratio of BDD-rFVIII compared with FL-rFVIII in PTPs:
7.26 - all inhibitors
10.8 - high-titre inhibitors > 5 BU

Factor VIII Products and Inhibitor Development in Severe Hemophilia A

- 2000-2010 **Gouw SC. N Engl J Med 2013; 368:231-9*
- 574 PUPs for up 75 EDs
- Inhibitor 177/574 (32.4%)

product	Any inhibitor				High-titre inhibitor			
	Unadjusted Hazard rat.	P value	Adjusted Hazard r.	P value	Unadjusted Hazard rat.	P value	Adjusted Hazard r.	P value
rFVIII	1	NA	1	NA	1	NA	1	NA
pdFVIII	1.14	0.54	0.96	0.87	1.24	0.4	0.85	0.85
Specific products								
r-3rd-gen-FL	1	NA	1	NA	1	NA	1	NA
r-2nd-gen-FL	1.37	0.11	**1.6**	**0.02**	1.47	0.12	**1.79**	**0.02**
r-1st-gen-FL	1.12	0.72	0.99	0.96	1.44	0.31	1.26	0.53
r-2nd-gen-BDD	1.0	0.99	1.01	0.97	0.93	0.82	0.97	0.92
pd	1.31	0.27	1.16	0.56	1.51	0.17	1.23	0.51

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

pdFVIII and / or rFVIII:

• No. of patients	62	209	81	348	366
• observation	3 years	100 ED	3-26 ys	> 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%		
• 12-18 months				20%	20%
• > 18 months				9%	18%

Lorenzo JI. BJH 2001; 600-3.* **Fontes E. Haemophilia 2004 (S3); 55 (12 OC 14)* **van der Bom JG. Thromb Haemost 2003; 475-9.* **Chalmers EA. Haemophilia 2007; 149-55.* **(depended on mutation and treatment with rFVIII) **Gouw SC. Blood 2007; 4648-54.*

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

**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%

** Santagostino E. BJH 2005: 422-27.*

- 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

Age at first FVIII exposure	All inhibitors			High-titre inhibitors		
	proportion	Crude RR	Adjusted RR	proportion	Crude RR	Adjusted RR
< 2 months	41%	2.7	1.6	33%	2.4	1.1
2-6 months	30%	1.9	1.8	23%	1.6	1.3
7–12 months	23%	1.3	1.5	18%	1.1	1.1
12-18 months	20%	1.1	1.2	16%	1.0	1.0
>18 months	18%	1.0	1.0	16%	1.0	1.0
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

**Gouw SC. Blood 2007: 4648-54.*

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

**Gouw SC. Blood 2007: 4648-54.*

Dose of 5 consecutive ED	All inhibitors		High-titre inhibitors	
	Crude RR	Adjusted RR	Crude RR	Adjusted RR
< 35 IU/kg	1.0	1.0	1.0	1.0
35 - 50 IU/kg	1.4	1.2	1.7	1.5
> 50 IU/kg	3.3	2.3	4.2	3.0
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
< 10 days	1.9	1.5	1.9	1.3
Regular prophylaxis	0.4	0.5	0.5	0.5

Despite late onset of prophylaxis: started at median age of 20 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

	40 - 50 IU / kg 3x a week N = 30 Historical group	**25 - 35 IU / kg 1x a week** N = 40 > 40 EDs
Inhibitor	14 (47%)	1 (3,8%)
High-responder	8 (27%)	0

** 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

**von Auer Ch. Ann N Y Acad Sci 2005: 498-505.*

  - 29 mild HA patinents in Toronto exposed to r-FVIII
    - 7x CI - 4 developed inhibitors
    - 22 had bolus treatment - non FVIII inhibitor

**Sharathkumar A. J Thromb Haemost 2003: 1228-36.*

- 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)

**Batorova A. Haemophilia 2012; 18: 753-9*

Treatment-related factors: Immunologic costimulation

- **Breastfeeding**
  - Protective effect was not proved

** Santagostino E. BJH 2005: 422-27.*

**Knobe KE. Haemophilia 2002: 657-9.*

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

** Santagostino E. BJH 2005: 422-27.*

- **Infections, vacciations**
  - No assotiation with inhibitor risk
  - No data in the literatue despite the theoretical presentation of danger signals

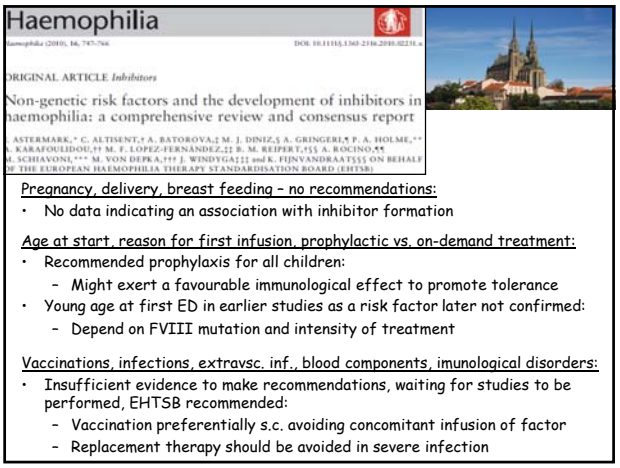
** Santagostino E. BJH 2005: 422-27.*
**Astermark J. Haemophilia 2012;18Suppl.4):38-42*

Risk stratification for inhibitor development at first treatment for severe hemophilia A: a tool for clinical practice

	Total number of patients	Predicted inhibitors	Observed inhibitors	Positive predictive value	Negative predictive value
Risk categories					
CANAL cohort					
Low (0 points)	95	8	6	0.06	0.68
Medium (2 points)	170	38	39	0.23	0.73
High (3 points or higher)	67	36	38	0.57	0.83
Validation cohort					
Low (0 points)	20	2	1	0.05	0.64
Medium (2 points)	28	6	8	0.29	0.75
High (3 points or higher)	16	8	8	0.50	0.81

Results are shown by low, medium 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, resulting in the fact that a patient in the low risk category has a 94% (100–6%) probability of not developing an inhibitor. A negative predictive value of 68% is the probability that a patient (outside the low category) in the medium or high risk category will not develop an inhibitor.

Family history of inhibitor:
- OR = 3.1 = 2 points
Risk gene mutations:
- OR = 3.0 = 2 points
Initial intensive treatment:
- OR = 5.9 = 3 points



Pregnancy, delivery, breast feeding – no recommendations:

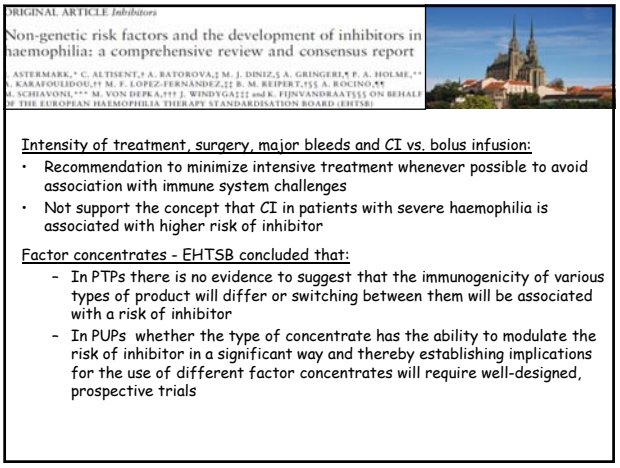
- No data indicating an association with inhibitor formation

Age at 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, extravsc. inf., blood components, imunological disorders:

- Insufficient evidence to make recommendations, waiting for studies to be performed, EHTSB recommended:
  - Vaccination preferentially 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: **prefered > 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, iFVIII in family)**
  - **Low dose 25-35 IU/kg a week**

Thank you for your kind attention!