

Current and Emerging Challenges: Risk factors for inhibitor development

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Haematology



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The Sydney Children's
Hospitals Network
(Randwick and Westmead)

Risk Factors

Genetic



Environmental/Treatment Related



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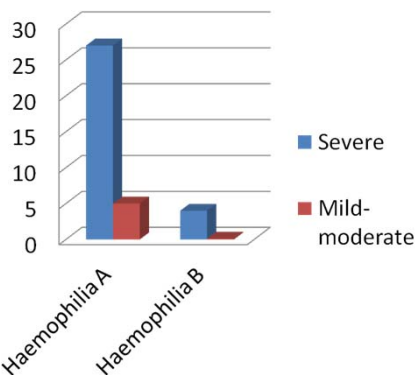


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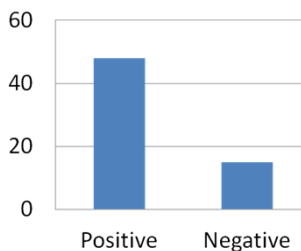
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Genetic Risk Factors

Severity of haemophilia



Family history



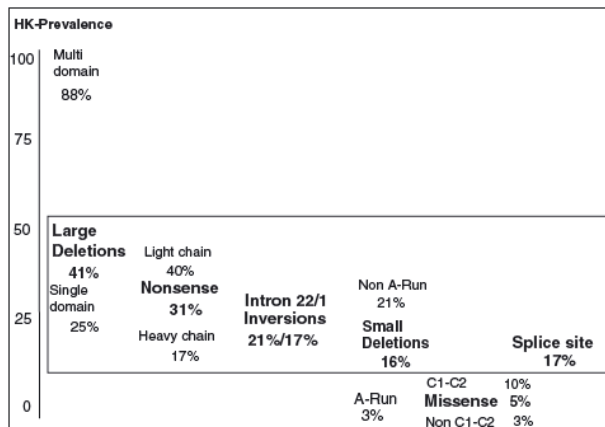
MIBS study (Astermark 2001)

RR 3.2 if have older brother with inhibitor



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Genetic Mutation as a risk factor



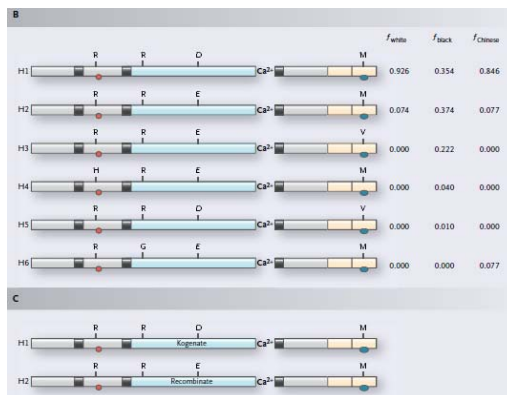
Oldenburg Haemophilia (2006) Suppl 6;15 - 22



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Race and Ethnicity

- Incidence in patients of African origin twice that of caucasians
- Differences in FVIII haplotypes
- Recombinant products have H1 and H2 haplotypes (as seen in caucasians)

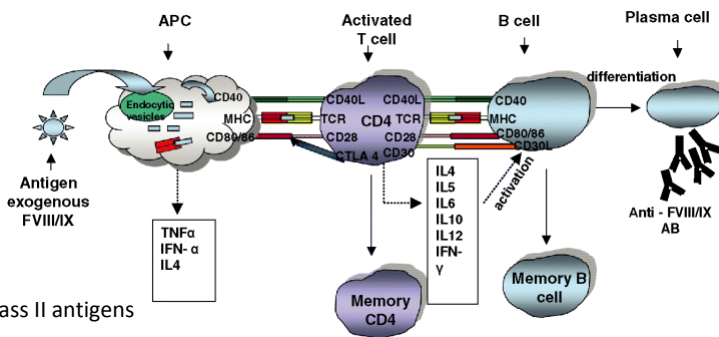


Viel *et al* NEJM 2009 360 (16): 1618 - 1627



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Immune Response Genes



MHC Class II antigens
II-10
CTLA-4
TNF α



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Non-Genetic Risk Factors

- Lack of robust data concerning the influence of these risk factors
- Clinical studies differ in key characteristics
 - Duration of follow-up
 - Definition of severe haemophilia, PTP
 - Methods of inhibitor assay
 - Use of central labs



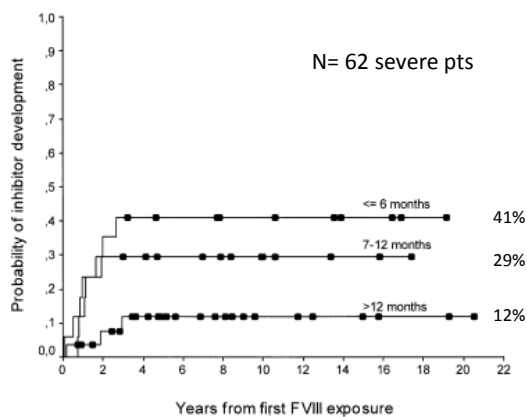
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Importance of Age at First Treatment



Lorenzo *et al* British Journal of Haematology (2001) 113; 600 - 6023



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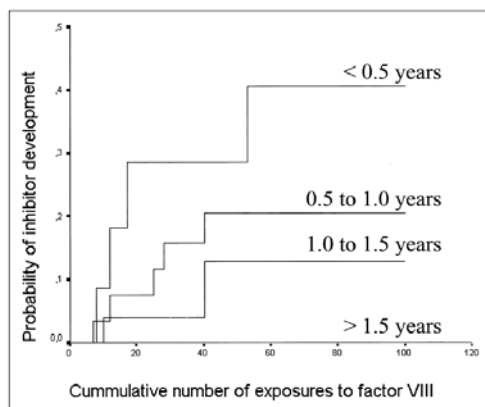


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Age at First Treatment

N = 81pts
Retrospective



Johanna G. van der Bom, Eveline P. Mauser-Bunschoten, Kathelijn Fischer, H. Marijke van den Berg *Thrombosis and Haemostasis* 2003; 89:475-479



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Can activated recombinant factor VII be used to postpone the exposure of infants to factor VIII until after 2 years of age?

Rivard *et al* *Haemophilia* (2005) 11 335 - 339



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Can activated recombinant factor VII be used to postpone the exposure of infants to factor VIII until after 2 years of age?

- 4/14 mouth bleeds not controlled with rFVIIa
- 2/6 haemathroses not controlled with rFVIIa
- Only 3/11 pts postponed until >2 yrs
- Postponement of exposure to FVIII Mean 5.5 months (range 0 – 12 mos)
- 5/11 patients developed inhibitors

Rivard *et al* Haemophilia (2005) 11 335 - 339



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UKHCDO Paediatric Working Party

Table 2. Intron 22 subgroup: age at first exposure to FVIII and inhibitor development.

Age, months (days)	Number treated	All inhibitors, <i>n</i> (%)
<1 (<30)	14	4 (29)
1–6 (30–180)	18	5 (28)
6–12 (180–360)	50	16 (32)
12–18 (360–540)	25	7 (28)
>18 (>540)	15	3 (20)
Total	122	35 (29)

N= 348 total, intron 22 group 122 pts

Chalmers *et al* Haemophilia (2007) , 13, 149 - 155



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Table 5. Odds ratios for inhibitor development.

Variables	Univariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Onset of treatment <1 month	1.22	0.53-2.81	1.15	0.47-2.85
Non-caucasian origin	1.61	0.86-3.02	1.14	0.46-2.8
Positive family history	1.78	0.77-4.09	1.5	0.52-4.31
Onset of treatment <18 months	2.82	1.16-6.83	1.43	0.5-4.09
Recombinant FVIII product	2.24	1.24-4.04	1.83	0.9-3.72
Major genetic defect	2.67	1.31-5.41	3.34	1.45-7.71

Chalmers *et al* Haemophilia (2007) , 13, 149 - 155



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CANAL Cohort Study

366 PUPs with severe haemophilia born 1990 – 2000

Table 4. Risk of inhibitor development according to treatment characteristic

	All inhibitors				High-titer inhibitors*				
	Proportion of Inh (%)	Crude RR (CI)	P for trend	Adjusted RR (CI)	P for trend	Proportion of Inh (%)	Crude RR (CI)	Adjusted RR (CI)	P for trend
At first factor VIII exposure									
Age at first exposure									
More than 18 mo	10/57 (18)	1.0	.005	1.0§	.21	9/57 (16)	1.0	1.0§	.63
12 to 18 mo	16/82 (20)	1.1 (0.5-2.5)		1.2 (0.5-2.9)		13/82 (16)	1.0 (0.4-2.4)	1.0 (0.4-2.6)	
6 to 12 mo	30/130 (23)	1.3 (0.7-2.7)		1.5 (0.6-3.4)		23/130 (18)	1.1 (0.5-2.5)	1.1 (0.4-2.6)	
1 to 6 mo	13/43 (30)	1.9 (0.8-4.3)		1.8 (0.7-4.7)		10/43 (23)	1.6 (0.6-3.9)	1.3 (0.5-3.8)	
Less than 1 mo	16/39 (41)	2.7 (1.2-5.9)		1.6 (0.6-4.1)		13/39 (33)	2.4 (1.0-5.6)	1.1 (0.4-3.2)	

A young age at first exposure was associated with an increase risk

- However this association largely disappeared after adjustment for intensity of treatment

Gouw *et al* Blood (2007) 109: 4648 - 4654



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(Randwick and Westmead)

CANAL Cohort Study

Table 4. Risk of inhibitor development according to treatment characteristic

	All inhibitors				High-titer inhibitors*					
	Proportion of Inh (%)	Crude RR (CI)	P for trend	Adjusted RR (CI)	P for trend	Proportion of Inh (%)	Crude RR (CI)	P for trend	Adjusted RR (CI)	P for trend
All first factor VIII exposure										
Reason for first factor VIII treatment										
Blood	65/286 (23)	1.0		1.0		50/286 (17)	1.0		1.0	
Prophylaxis	8/37 (22)	1.0 (0.5-2.0)	.92	1.0 (0.5-2.2)	.95	7/37 (19)	1.1 (0.5-2.4)	.82	1.2 (0.5-2.8)	.63
Surgical procedure	11/17 (65)	3.7 (2.0-7.1)	< .001	2.6 (1.3-5.1)	.007	10/17 (59)	4.4 (2.2-8.7)	< .001	3.2 (1.6-6.7)	.002
Peak treatment moment at first treatment episode†										
None	44/229 (19)	1.0		1.0		31/229 (14)	1.0		1.0	
3 to 4 days	7/36 (19)	1.0 (0.5-2.3)	.98	1.1 (0.5-2.4)	.87	6/36 (17)	1.2 (0.5-2.9)	.66	1.3 (0.5-3.1)	.63
At least 5 days	32/57 (56)	3.3 (2.1-5.3)	< .001	3.1 (1.9-5.0)	< .001	30/57 (53)	4.3 (2.6-7.1)	< .001	4.1 (2.4-7.0)	< .001

➤ Intensive treatment (early surgical procedures, early major peak treatment moments and high dosing factor VIII) – related to higher risk

Gouw *et al* Blood (2007) 109: 4648 - 4654



CANAL study On demand v's Prophylaxis

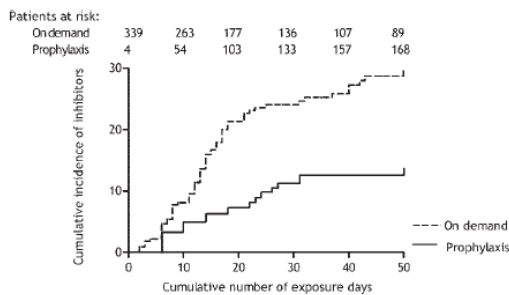


Figure 2. Cumulative incidence of inhibitor development according to treatment regimen: prophylaxis versus on demand.

Gouw *et al* Blood (2007) 109, 4648-4654



Early prophylaxis/FVIII tolerization regimen that avoids immunological danger signals is still effective in minimizing FVIII inhibitor developments in previously untreated patients – long-term follow-up and continuing experience

G. AUERSWALD,* C. BIDLINGMAIER† and K. KURNIK†
 *Prof. Hess Childrens Hospital, Klinikum Bremen-Mitte, Bremen, Germany; and †Klinikum der Universitaet Muenchen, Dr von Haunersches Childrens Hospital, Munich, Germany

Table 1. Inhibitor incidence of the study group compared to the control group.

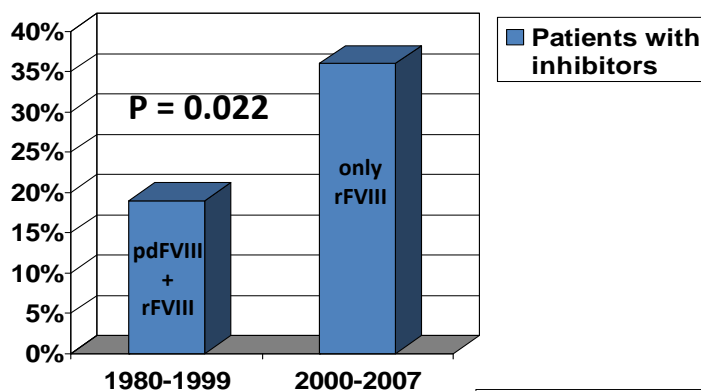
	Historical control group (standard prophylaxis regimen) n = 30	Study group (new early tolerization regimen) n = 40
Inhibitors (%)	14 (47)	1 (2.5)
High responders (%)	8 (27)	0
Low responders (%)	6 (20)	1 (2.5)

Auerswald *et al* Haemophilia (2011) epub Sept 27



Frequency of inhibitors increasing among Swedish children with severe hemophilia A?

R. Ljung, P. Petrini and F. Holmberg



Haemophilia 2010, 16 (Suppl. 4)



Factor Products

Table 5. Exposure Days to Factor VIII Preparations of Type A Inhibitor Patients in Dutch and US Cohorts

	Cumulative Exposure to FVIII Preparations	
	<250 d (no. of patients)	>250 d (no. of patients)
US cohort* (n = 24)	24	0
Cohort 1984-1989 (n = 2)	2	0
National study		
Period I (March 1988-May 1990) (n = 4)	4	0
Period II (June 1990-November 1991) (n = 11)	2	9

FVIII CPS-P licensed in 1990 in Netherlands
1991 – began seeing inhibitors in PTPs
Belgium had similar problem

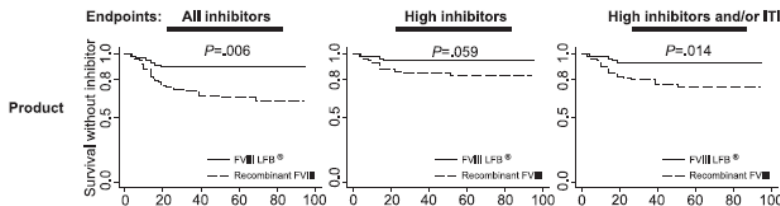
* Data from McMillan et al.¹⁹

Rosendaal FR et al Blood 1993 81 2180 - 2186



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Plasma Derived v's Recombinant FVIII



N= 148 PUPs in France

Goudemand et al Blood (2006) 107, 46 - 51



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Pd FVIII v's rFVIII CANAL study

Table 2. Risk of inhibitor development according to type of factor VIII product

	NED	All clinically relevant inhibitor development				High-titer inhibitor development*				
		Crude		Adjusted		Crude		Adjusted		
		RR (CI)	P	RR (CI)	P	RR (CI)	P	RR (CI)	P	
Recombinant	8493	1.0		1.0		1.0		1.0		
Plasma-derived	4425	0.8 (0.5-1.3)	.34	0.7 (0.4-1.1)	.14	0.9 (0.5-1.5)	.72	0.8 (0.4-1.3)	.33	
Recombinant	8493	1.0		1.0		1.0		1.0		
Plasma-derived										
Low VWF content†	1272	0.3 (0.1-1.1)	.07	0.4 (0.1-1.1)	.08	0.3 (0.1-1.2)	.09	0.3 (0.1-1.3)	.11	
High VWF content†	3153	1.0 (0.6-1.6)	.91	0.8 (0.5-1.4)	.45	1.1 (0.7-2.0)	.61	0.9 (0.5-1.6)	.79	
Kogenate	4267	1.0		1.0		1.0		1.0		
Kogenate Bayer	378	1.1 (0.2-4.5)	.94	1.2 (0.3-5.4)	.79	1.5 (0.3-6.5)	.60	1.6 (0.3-7.3)	.55	
Recombinate	1639	1.1 (0.5-2.3)	.75	1.0 (0.5-2.1)	.99	1.4 (0.6-3.1)	.39	1.2 (0.5-2.7)	.70	
Refacto	2209	1.4 (0.8-2.6)	.24	1.6 (0.9-3.2)	.14	1.5 (0.7-3.0)	.30	1.4 (0.6-3.1)	.38	

N= 316 patients, 23 different pd FVIII, 4 different rFVIII

Some switched product during time reviewed – no affect on inhibitor risk

Gouw *et al* Blood (2007) 109, 4693-4697



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Systematic review of inhibitors on PUPS treated with pdFVIII or rFVIII

Table 1 Inhibitor development rates (per cent) in relation to factor VIII source

	Main analysis		
	Plasma-derived FVIII	Recombinant FVIII	P value (pdFVIII vs. rFVIII)
	Event rate (95% CI)	Event rate (95% CI)	(Cohran Q)
All studies	14.3 (10.4–19.4)	27.4 (23.6–31.5)	< 0.001

N= 2113 pts from 24 studies

1170 treated with pdFVIII

943 treated with rFVIII

lorio *et al* Journal of thrombosis and haemostasis (2010) 8 1256- 65



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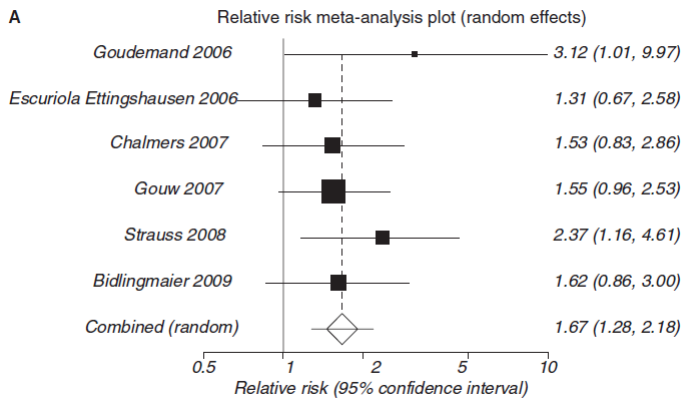


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Risk ratios for High Titre Inhibitors

6 studies with parallel cohorts

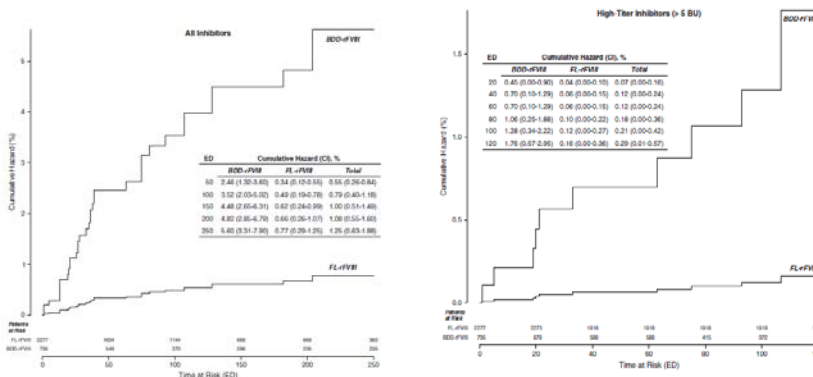


lorio *et al* Journal of thrombosis and haemostasis (2010) 8: 1256- 65



BDD v's FL-rFVIII Meta-analysis

3012 PTPs in 29 studies



Aledort *et al* J Thrombosis and haemostasis 2011 August epub



BDD v's FL-rFVIII Meta-analysis

Table 2 Univariate Cox regression*

Variable	All inhibitors		High-titer inhibitors	
	HR (CI)	p	HR (CI)	p
BDD-rFVIII exposure [†]	7.26 (2.12-24.9)	0.0016	10.8 (2.17-53.7)	0.0037
Group size [‡]	2.60 (0.43-15.9)	0.30	4.11 (0.41-41.4)	0.23
Time period reported [§]	1.59 (0.39-6.48)	0.51	3.71 (0.58-23.6)	0.17
Prior ED cutoff for PTPs	1.65 (0.45-6.10)	0.45	1.96 (0.40-9.75)	0.41
Surgery**	2.98 (0.19-46.3)	0.43	— ^{¶¶}	— ^{¶¶}
Prophylaxis ^{‡‡}	1.17 (0.26-5.26)	0.84	0.34 (0.03-3.63)	0.38
Hemophilia severity ^{§§}	1.45 (0.38-5.54)	0.58	1.21 (0.25-5.91)	0.81
Time on study ^{¶¶}	1.80 (0.44-7.38)	0.42	3.05 (0.64-14.5)	0.16
Study completion rate***	2.30 (0.56-9.43)	0.27	2.74 (0.57-13.0)	0.28

*All included data used in analysis of each variable with no exclusions. Cox models include study as a random effect.

[†]BDD-rFVIII compared with FL-rFVIII as the reference category

Aledort et al J Thrombosis and haemostasis 2011



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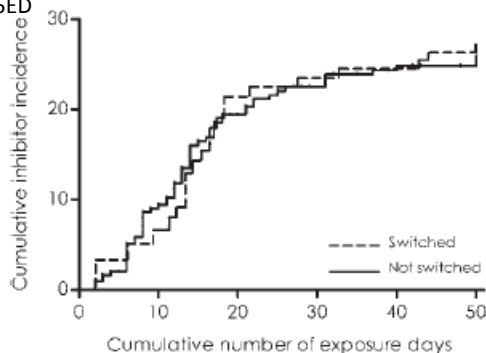
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Risk when switching products

CANAL study

N= 104 PUPs

switch after median 5ED



Gouw et al Blood (2007) 109, 4693-4697



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Conclusions

- Genetic Risk Factors – particularly gene mutation is important
- Environmental/treatment related factors play a role – but evidence questionable
- Need for more data preferably from large randomised studies with sufficient power to answer the questions

