Clinical significance of low and high titer inhibitors

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FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

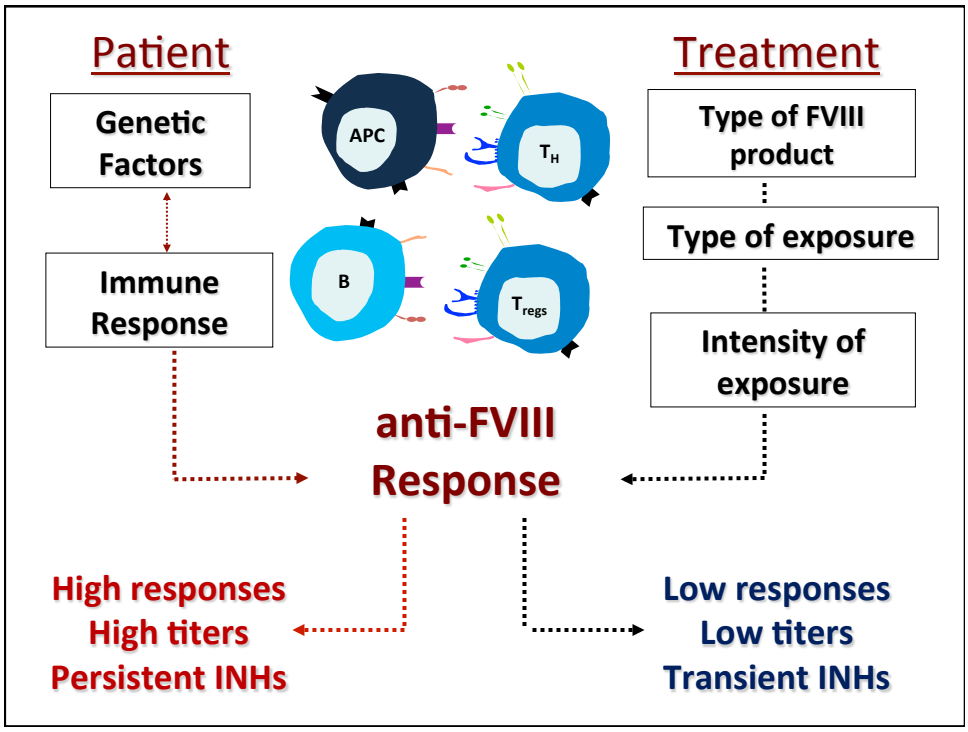
RECOMMENDATIONS AND GUIDELINES

Definitions in hemophilia: communication from the SSC of the ISTH

V. S. BLANCHETTE,* N. S. KEY,† L. R. LJUNG,‡ M. J. MANCO-JOHNSON,§ H. M. VAN DEN BERG¶ and A. SRIVASTAVA,** FOR THE SUBCOMMITTEE ON FACTOR VIII, FACTOR IX AND RARE COAGULATION DISORDERS

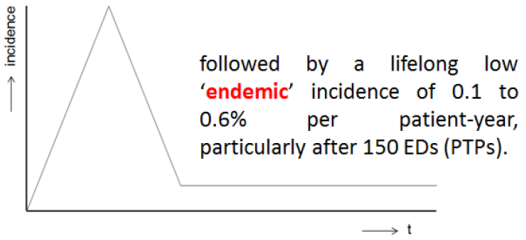
J Thromb Haemost 2014; 12:1935–9.

- **Inhibitors: ≥ 0.6 BU/mL** (Nijmegen mod. – Bethesda) **on 2 consecutive** occasions within a 1-4 week period
  (washout from conventional FVIII replacement of at least 48 h)
- **Clinically relevant: < 66% recovery and/or $T^{1/2}$ < 7 h**.
  (conventional FVIII products).
- **Low-response inhibitors: ≤ 5 BU/mL**
- **High-response inhibitors: > 5 BU/mL**
- **Transient inhibitors: < 0.6 BU/mL within 6 months** of first detection despite continuing FVIII challenge



Inhibitor incidence: a biphasic curve

An early exposure (20-50 EDs) high peak '**epidemic**' rate (up 30'%) in previously untreated patients (PUPs)



followed by a lifelong low '**endemic**' incidence of 0.1 to 0.6% per patient-year, particularly after 150 EDs (PTPs).

(Dimichele DM, et al. Design of clinical trials for new products in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13:876-9)

Licensure trials with rFVIII in PUPs

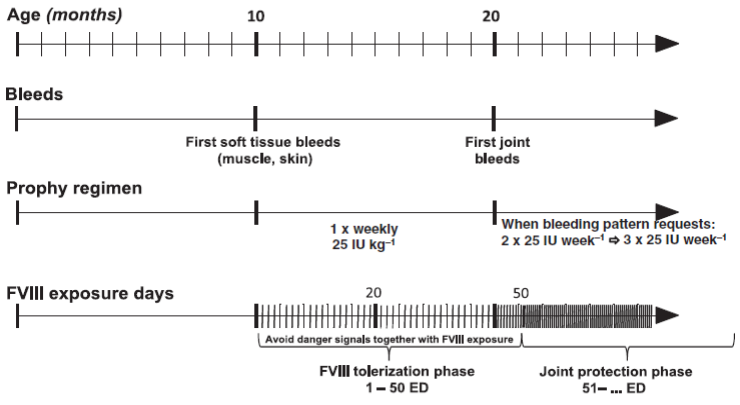
STUDY	N*	All inhibitors (%)	HR (%)	LR (%)	Type of FVIII product
Bray et al (1994) Gruppo et al (1998) Goodeve et al (2000)	72	22 (30.5)	9 (12.5)	13 (18.1)	Recombinate
Lusher et al (1993) (2004)	65	19 (29.2)	15 (23.1)	4 (6.1)	Kogenate
Kreuz et al (2005) Oldenburg et al (2006)	37^	5 (13.5)	4 (10.8)	1 (2.7)	Kogenate-FS
Courter & Bedrosian (2001) Lusher et al (2003) (2005)	101	32 (31.7)	16 (15.8)	16 (15.8)	ReFacto
Auerswald et al (2012)	18	5 (27.8)	NA	NA	Advate

* Patients with FVIII < 2% included

^ MTPs excluded

New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development

K. KURNIK,* C. BIDLINGMAIER,* W. ENGL,† H. CHEHADEH,† B. REIPERT† and G. AUERSWALD‡



Haemophilia (2010), 16, 256–262

The EPIC study: a lesson to learn

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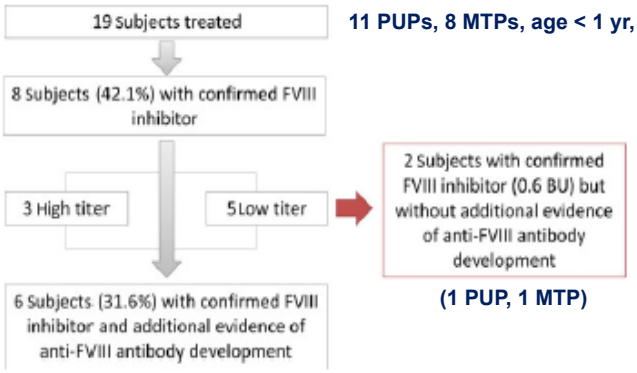


Haemophilia (2015), 1–7 DOI: 10.1111/hae.12666

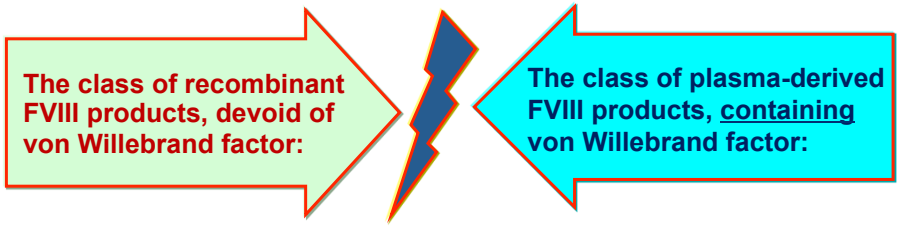
Inhibitor patients in the Epic study

Subject	EDs at 1° pos. INH	1° & Max INH titer (BU/mL)	Binding Antibodies
HR1	11	7.7	IgG, IgG1
HR2	19	28.0	IgG, IgG1, 2, 3, 4
HR3	5	>38	Negative on screening, NA on follow-up
LR1	23	0.9	IgG, IgG1
LR2	5	1.5	IgG, IgG1, 3
LR3	16	1.1	IgG, IgG1, 3, 4
LR4	16	0.6	Negative on all visits
LR5	28	0.6	Negative on all visits

Haemophilia (2015), 1–7 DOI: 10.1111/hae.12666

RCT - THE SIPPET STUDY

PUPs and MTPs randomised to receive one product of 2 classes up to 50 exposure days (EDs):



N	All inhibitors (%)	HR (%)	LR (%)	Type of FVIII product
251	76 (30.3)	50 (19.9)	26(10.3)	rFVIII and pdFVIII

Peyvandi F, et al. Blood 126; 23, ASH Meeting, 3 Dec 2015

Factor VIII Products and Inhibitor Development in Severe Hemophilia A

Samantha C. Gouw, M.D., Ph.D., for the PedNet and RODIN Study Group*

The NEW ENGLAND JOURNAL of MEDICINE JANUARY 17, 2013

- Inclusion of PUPs with FVIII <0.01 IU/ml
- Detailed data on baseline and date of diagnosis
- Prospective data collection
- All dates and reason for treatments, dose and product brands, surgery, intensive treatment until 75 EDs
- Definition of clinically relevant INH, HT and LT
- Local inhibitor testing

FranceCoag Network study

- Inclusion of PUPs with FVIII <0.01 IU/ml
- Detailed data on baseline and date of diagnosis
- All dates and reason for treatments, dose and product brands, surgery, intensive treatment until 75 EDs
- Prospective data collection
- Definitions used similar that in RODIN study
- Local inhibitor testing

Calvez T, et al. Blood 2014;124:3398-408.

UKHCHDO Study

- Inclusion of PUPs with FVIII <0.01 IU/ml treated with recombinant products
- Follow-up time until 75 EDS was calculated from 50 non-inhibitors that participated in RODIN study
- Local inhibitor testing

Collins PW, et al. Blood 2014;124:3389-97.

Inhibitors in PUPs – the dimension of the risk

STUDY	N	All inhibitors (%)	HR (%)	LR (%)	Type of FVIII product
RODIN	574	177 (30.8)	116(20.2)	61(10.6)	rFVIII and pdFVIII
France Coag	303	114 (37.6)	63 (20.8)	51 (16.8)	rFVIII
UKHCDO*	407	118 (29.0)	60 (14.7)	58 (14.3)	rFVIII

* with RODIN overlap (88 patients)

FranceCoag Network study

Réseau FranceCoag

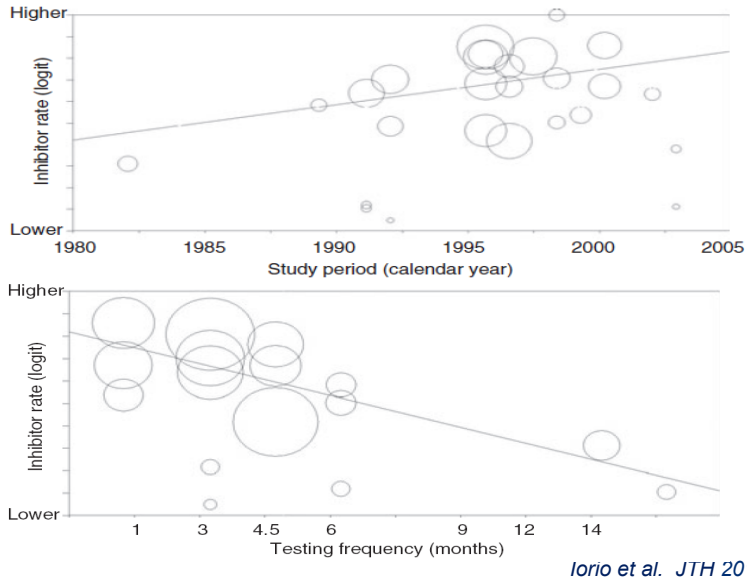
Inhibitors in PUPs – treatment during follow-up

All patients	N 303	%
All Inhibitors	**114**	**37.6**
HR Inhibitors	63	20.8
Treated with bypassing agents	77	25.4
Treated with ITI	79	26.1
Treated with bypassing agents and/or ITI	95	31.4
LR not treated with bypassing agents and/or ITI	19	6.3

Calvez T, et al. Blood 2014;124:3398-408.

INHIBITOR DEVELOPMENT IN PUPs - SYSTEMATIC REVIEW

24 studies - 2,094 patients: **significant differences (*multi-way ANOVA*) in study design, study period, testing frequency**



Iorio et al. JTH 2010;8:1256-65

Increased inhibitor incidence in severe haemophilia A since 1990 attributable to more low titre inhibitors

Thrombosis and Haemostasis 115.3/2016

H. Marijke van den Berg[1*]; S. Mojtaba Hashemi[1*]; Kathelijn Fischer[1,2]; Pia Petrini[3]; Rolf Ljung[4]; Anne Rafowicz[5]; Manuel Carcao[6]; Günter Auerswald[7]; Karin Kurnik[8]; Gili Kenet[9]; Elena Santagostino[10]; for the PedNet Study group#

- **Aim: to report the cumulative incidence of LR and HR inhibitors** adjusted for genetic and non-genetic risk factors over a 20-year period in the cohort of PUPs with severe hemophilia A from the CANAL Study (1990-2000) and PedNet Registry (2000-2009)

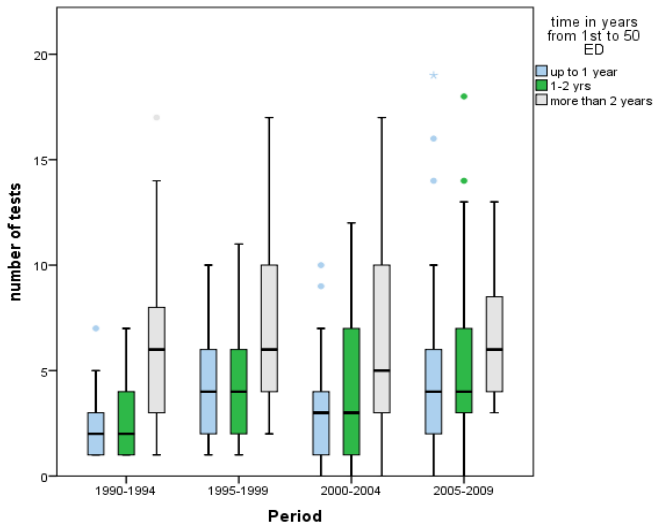
- **Inhibitor testing: locally performed** using the Nijmegen modification of the Bethesda assay after 2000 (cut-off values: 0.3-0.6 BU).

Inhibitor development in birth cohorts

	Birth cohort 1990-1994 N = 144	Birth cohort 1995-1999 N = 178	Birth cohort 2000-2004 N = 299	Birth cohort 2005-2009 N = 305	Entire cohort 1990-2009 N = 926
Clinically relevant INHs					
Cumulative incidence	**19.5**	**27.6**	**30.9***	**29.0***	**27.9**
95% CI	13.0- 26.0	20.9 – 34.3	25.6 – 36.2	23.9 – 34.1	25.0 – 30.8
ED at INH development					
Median (IQR)	15 (10 – 25)	12 (8 – 20)	14 (9 – 22)	14 (9 – 17)	14 (9 – 19)
High titer INHs					
Cumulative incidence	**16.9**	**22.7**	**23.5**	**20.5**	**21.4**
95% CI	10.6 – 23.2	16.4 – 29.0	18.6 – 28.4	15.8 – 25.2	18.7 – 24.1
Low titer INHs					
Cumulative incidence	**3.1**	**6.3**	**9.6***	**10.5***	**8.2**
95% CI	0.2 – 6.0	2.6 – 10.0	6.1 – 13.1	6.8 – 14.2	6.2 – 10.2
Inhibitor testing rate					
Tests/year, median (IQR)	**1.9** (1.3 – 3.2)	**2.9** (1.7 – 4.6)*	**2.7** (1.7 – 5.6)*	**4.3** (2.5 – 8.9)*	**3.1** (1.9 – 5.9)
Tests/50ED, median (IQR)	**3** (2 – 6)	**5** (3 – 7)*	**4** (2 – 7)*	**5** (3 – 8)*	**5** (3 – 7)

van den Berg et al. Thromb Haemost 2016; in press

Number of INH tests in patients who reached 50 EDs in 1 yr, 1-2 yrs or > 2 yrs



van den Berg et al. Thromb Haemost 2016; in press

Distribution of confounding factors in birth cohorts

	Birth cohort 1990-1994	Birth cohort 1995-1999	Birth cohort 2000-2004	Birth cohort 2005-2009	p
Caucasian ethnicity, %	89.6	89.9	86.6	84.3	0.24
Family history of inhibitors %	6.3	7.3	9.0	9.8	0.41
Large F8 gene mutations, %	59.0	59.0	64.9	56.4	0.34
Peak treatment at first exposure (≥5 EDs), %	11.8	19.1	18.4	12.5	0.06
Dose during first 5 EDs, IU/kg					
All patients, median (IQR)	43 (31–50)	47 (37–66)	48 (38–67)	44 (33–58)	0.06
Peak of ≥5 EDs, median (IQR)	**56** (37–91)	**88** (54–106)	**72** (50–110)	**78** (46–120)	**<0.05**
Prophylaxis started before 50th ED, %	**48.6**	**50.6**	**66.9**	**74.8**	**<0.05**
EDs at start prophylaxis Median (IQR)	**17** (9 – 29)	**17** (8 – 28)	**13** (6 – 22)	**11** (4 – 19)	**<0.05**

van den Berg et al. Thromb Haemost 2016; in press

Risk of inhibitor development in birth cohorts

Birth cohorts	All inhibitors		High titer INHs		Low titer INHs
	Unadjusted Hazard ratio	Adjusted Hazard ratio	Unadjusted Hazard ratio	Adjusted Hazard ratio	Unadjusted Hazard ratio
1990-1994	Reference	Reference	Reference	Reference	Reference
1995-1999	1.52 (0.95–2.41)	1.53 (0.94–2.50)	1.41 (0.85–2.34)	1.43 (0.83–2.44)	2.17 (0.68–6.91)
2000-2004	1.70 (1.11–2.60)	1.96 (1.06–2.83)	1.45 (0.91–2.31)	1.35 (0.74–2.13)	3.24 (1.13–9.30)
2005-2009	1.61 (1.05–2.47)	2.34 (1.42–4.92)	1.27 (0.79–2.04)	1.71 (1.00–3.13)	3.68 (1.29–10.49)

van den Berg et al. Thromb Haemost 2016; in press

Relevance of low titer inhibitors – How do we judge/define them?

- **INH pattern over time** (regular testing & treatment records)
  - persistent / transient / recurrent
  - anamnestic response
  - influence on FVIII recovery and $T^{1/2}$
- **Bleeding pattern**
  - type, severity, frequency, response to treatment
- **Inhibitor outcome** (correlation with treatment regimens)
  - in the absence of FVIII challenge
  - on demand with FVIII
  - on FVIII prophylaxis
  - on ITI (low, intermediate, high dose)

Treatment of low titer inhibitors

- **FVIII replacement**
  - on demand
  - prophylaxis
- **ITI**
  - who are the candidates
  - what is the regimen
- **Bypassing agents**
  - selected indications?

Open issues on low titer inhibitors

- CLINICAL RELEVANCE
- OPTIMAL FOLLOW-UP (CLINICAL & LABORATORY)
- OPTIMAL TREATMENT STRATEGIES
- PREDICTORS OF LOW-TITER INHIBITOR FORMATION
- IMMUNE PATHWAY LEADING TO LOW TITER AND TRANSIENT INHIBITORS