Outcomes from different ITI registries

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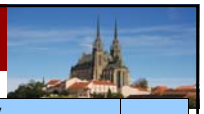
Patients with inhibitor of FVIII without ITI

**Caram C, Thromn Haemost 2011: 59-65*



iFVIII 60/486, 46 observed ≥ 2 years

Peak of iFVIII	Inhibitor stability						
	Stable negative		Stable positive		Unstable		Total
	N	%	N	%	N	%	N
< 5 BU / ml	5	55.6	0		4	44.4	9
5 - 9.9 BU / ml	4	50	0		4	50	8
≥ 10 BU / ml	1	3.4	13	44.8	15	51.7	29
Total	10	21.7	13	28.3	23	50	46
Treatment:							
CRYO/FVIII	10				2		12
CRYO/PCC/FVIII	0		10		18		28
PCC			1		1		2
No					1		1
Not known			2		1		3
Haemophilia A severe	3	33.3	2	22.2	4	44.4	9
Haemophilia A moderate	7	18.9	11	29.7	19	51.4	37

Immune tolerance induction
high / low dose protocol

Bonn:

- 100-150 IU / kg 2x daily
- iFVIII<1 BU/ml 150 IU/kg 1xD until normal recovery and t1/2
  - Feiba 50-100 j / kg 2x denně
  - high responders
- LR 50-100 IU / kg / day or every other day

- Success definition:
  - iFVIII < 0,6 BU/ml
  - t1/2 > 12 h
    - children t2 > 8 h
  - normal recovery

**Paisley S, Haemophilia 2003: 405-417*

Success definition:
- iFVIII < 0,6 BU/ml
- t1/2 ≥ 6 h
- recovery ≥ 66%

**Astrmark J, Haemophilia 2006:363-371*

Van Creveld Clinic:

- 25-50 IU / kg every other day or 3x a week
- if onset due to bleed or surgery:
  - inhibitor neutralization
  - 25 IU/kg 2x daily 1-2 weeks
- iFVIII in all patients:
  - before ITI < 10 BU/ml
  - historical peak < 200 BU/ml

Success definition:
- iFVIII < 2 BU/ml
- no anamnestic response
- t1/2 > 6 h
- recovery > 50%

**Mauser-Bunschoten EP, Blood 1995: 983-8*

Malmö protocol

	Dosage	days
Plasmaapheresis with immune-adsorption	Target iFVIII < 10 BU / ml	Before onset Daily according to iFVIII
Cyclophosphamide	12-15 mg / kg i.v.	Day 1-2
	2-3 mg / kg p.o.	Day 3-10
Immunoglobulins	2.5 - 5 g i.v.	Day 1
	0.4 g / kg i.v.	Day 4-8
FVIII	i.v., target level 30-80%	From day 1
	i.v. 60 – 90 IU / kg / week	After iFVIII erradication

**Berntorp E, Haematologica 2000 (Suppl . N10): 48-51*
**Wight J, Haemophilia 2003: 436-463*

Results of ITI protocols

ITI protocol	Dose of FVIII (IU / kg / D)	Success (%)	Median to eradication (months)	Notes
Bonn	100-150 á 12 h iFVIII<1 BU/ml 150 1xD	92-100	14	Application b.i.d. The most expensive
Malmö	PF+IA iFVIII<10 BU/ml IgG, CFS FVIII 30-80%	59-82	1	Immunesuppression cheaper
Van Creweld (Dutch)	25 á 12 h 1-2 weeks 25 alternate day or thrice weekly	61-88	1-22	Only in good prognostic factors The cheapest

**Coppola A.BJH 2010; 150: 515-528*

Main features of published ITI registries and predictors of ITI outcome **Coppola A. BJH2010;150:515-28*

Registry reference	Patients (severe)	HR %	FVIII dose regimens (IU/kg/d)	Type of FVIII products	Success rate %	Time to success, months	Predictors of success (P value)†
IITR (Mariani, Kroner, 2001)	314 (263)	94	32%≥200; 20%100–199 23% 50–100 25% <50 steroids 7%	IP or HP plasma-derived 88%; recombinant 12%	51	10·5 median	age at ITI start (0·008) pre-ITI inhibitor titre (0·04) historical peak titre (0·04) FVIII dose (higher, 0·03)
NAITR (DiMichele & Kroner, 2002; DiMichele, 2009)	164 (150)	78	14%≥200 33% 100–199 28% 50–100 25% <50 immune modulation 40%	IP or HP plasma-derived 25%; monoclonal or recombinant 75%	63	16·3 mean	pre-ITI inhibitor titre (0·005) historical peak titre (0·04) peak titre on ITI (0·0001) FVIII dose (lower, 0·01)

Main features of published ITI registries and predictors of ITI outcome *Coppola A. BJH2010;150:515-28

Registry reference	Patients (severe)	HR %	FVIII dose regimens (IU/kg/d)	Type of FVIII products	Success rate %	Time to success, months	Predictors of success (P value)
GITR (Lenk, 2000)	126 (109)	83	most patients 200–300	IP or HP plasma-derived	76	7·6–15·5 mean	Historical peak titre (0·0012)
Spanish Registry (Haya et al, 2001)	37 (35)	100	42%≥200 24% 100 29% <100 5% others immune modulation 37%	IP or HP plasma-derived 88%; recombinant 12%	63	9·85 median	Pre-ITI inhibitor titre (0·03) historical peak titre (0·02) FVIII dose (lower, 0·01)
Italian PROFIT study (Coppola, 2009)	103 (100)	96	median 100 (range: 21–220)	IP or HP plasma-derived 24% monocl. 2% recomb. 74%	53	8 median	pre-ITI inhibitor titre (<0·001) peak titre on ITI (<0·001) F8 mutation (non-null, 0·04)

Registries – results and success prediction

Registry	N	Dose of FVIII IU/kg/D	success (%)	Time to remision (months)	Prediction of success (P < 0,05)					
					Age at ITI start	Inhibitor titre: pre ITI	Inhibitor titre: hist. peak	Inhibitor titre: on ITI	dose	FVIII mutation
IITR	314	<50 - ≥200	51	10.5 Median	+	+	+		+	
NAITR	164 128 HR	50 – 200	63 HR	16.3 Mean		+	+	+	+	
GITR	126 104 HR	≥ 200	76 HR	7.6-15.5 Mean			+			
Spain	38	100 - 200	63 HR	9.85 Median		+	+		+	
PROFIT	103 86 HR	median 100	53 HR	8 Median		+		+		+ (47% / 81%)

*Franchini M, JTH 2011: 10.1007/s11239-011-6243-3

ITI –success rate (%) by titre and dose-combined data: n = 278 (IITR + NAITR)

*Kroner BL. Vox Sang 1999; 77 (Suppl 1): 33-37

maximum	pre ITI	FVIII dosage (IU)	success	percentage
< 50 BU / ml	< 10 BU / ml	< 50 50 - 99 100 - 199 ≥ 200	30 / 36 33 / 38 18 / 19 23 / 24	83 87 95 96
	10 – 20 BU / ml	< 50 50 - 199 ≥ 200	2 / 3 11 / 14 3 / 4	67 79 75
	> 20 BU /ml	50 - 199 ≥ 200	3 / 9 1 / 3	33 33

ITI –success rate (%) by titre and dose- combined data: n = 278 (IITR + NAITR)

*Kroner BL. Vox Sang 1999; 77 (Suppl 1): 33-37

maximum	pre ITI	FVIII dosage (IU)	success	percentage
50 – 200 BU / ml	< 10 BU / ml	< 50	8 / 12	67
		50 - 99	14 / 17	82
		≥ 200	3 / 4	75
	10 – 20 BU / ml	50 - 199	2 / 6	33
		≥ 200	3 / 4	75
	> 20 BU /ml	50 - 199	8 / 12	67
		≥ 200	5 / 7	71
> 200 BU / ml	< 10 BU / ml	50 - 199	5 / 11	45
		≥ 200	7 / 7	100
	10 – 20 BU / ml	50 - 199	1 / 3	33
		≥ 200	3 / 4	75
	> 20 BU /ml	50 - 199	1 / 23	4
		≥ 200	12 / 18	67

Prognostic factor of ITI: titre of iFVIII

- **iFVIII before ITI < 10 BU / ml:**
  - IITR + NAITR:
    - success in 85% in month 11 of ITI
    - > 10 BU / ml success in 43% in month 15 of ITI

*Textbook of Hemophilia, Blackwell Publishing 2005

- **Historical peak < 50 - 200 BU / ml:**
  - IITR + NAITR:
    - iFVIII before ITI < 10 BU / ml + historical peak:
      - < 50 BU / ml: success 83 – 96%
      - 50-200 BU / ml: success 67-75%
    - historical peak > 200 BU / ml:
      - any inhibitor titre before ITI: success rate 44%

*Textbook of Hemophilia, Blackwell Publishing 2005

- **Peak during ITI < 100 BU / ml:**
  - PROFIT study success OR = 11.4

NAITR : dependence of success on FVIII dose and pre-ITI inhibitor titre

Dose of FVIII IU/kg	≥ 200	100-199	50-99	< 50	
N	14%	33%	28%	25%	
Haemophilia A					**Total**
Success	41%	74%	72%	83%	70%
Time to success	11 months	8.5 months	8 months	13 months	
High responders, FVIII inhibitor pre-ITI < 10 BU/ml					**Total**
Success	-	84%	78%	100%	83%
Time to success	-	6.4 months	6.5 months	18.8 months	14.4 mo.
High responders, FVIII inhibitor pre-ITI ≥ 10 BU/ml					**Total**
Success					40%
Time to success					21.7 mo.

*Coppola A, BJH 2010: 515-528
*Dimichele D, Haemophilia 2009: 320-28

IITR + NAITR dependence of success on historical and pre-ITI peak of FVIII inhibitor

historical peak of FVIII inhibitor (BU/ml)					
	< 50	50-200	201-500	> 500	total
IITR – success (%)	64 (82%)	24 (65%)	9 (56%)	17 (50%)	114/165 69%)
NAITR – success (%)	71 (82%)	18 (69%)	4 (40%)	1 (7%)	94/137 (69%)

FVIII inhibitor pre-ITI					
	<2	< 10	10-20	21-50	>50	total
IITR – success (%)		65 (79%)	16 (76%)	5 (36%)	15 (53%)	101/145 (70%)
NAITR - success (%)	22 (100%)	73 (87%)	9 (50%)	3 (38%)	6 (33%)	93/133 (70%)

*Dimichele D, Haemophilia 2007 (Suppl 1): 1-22

ITI results from the Spanish registry

*Haya S. Haemophilia 2001;7:154-159

Patient	Inhibitor titre (BU/ml) max	Inhibitor titre (BU/ml) pre-ITI	Time from inhibitor dg. to ITI (months)	Age at start of ITI (years)	FVIII (1xFIX) IU/kg/ day	Time to inhibitor elimination (months)	Inhibitor after ITI (BU/ml)
Median adults 1-7	41	12	84	32	75	4	CR 6/7 (86%)
median All: 1-38	67	11	25	7	140	10	CR 26/38 (68%)

Multivariante logistic regression analysis – higher probability of success:
- inhibitor titre pre-ITI < 10 BU/ml (p = 0.0286)
- lower historical maximum of inhibitor (p = 0.0214)
- paradoxical higher success:
  - FVIII dose ≤ 100 IU/kg/D (p = 0,0106)
  - older patients: trend for better results

No influence:
- time between inhibitor development and start of ITI
- type of FVIII concentrate

ITI results in patients with VWF/FVIII: ≥ 1 poor prog factors (age >6 years, >1 year from inhibitor development, >200 BU hist. peak, > 10 BU pre-ITI, previously failed ITI)

*Gringeri A. Haemophilia 2007;13:373-79

Patient	Inhibitor titre (BU/ml) max	Inhibitor titre (BU/ml) pre-ITI	Time from inhibitor dg. to ITI (years)	Age at ITI start (years)	FVIII IU/kg/ day	ITI duration (months)	Inhibitor after ITI (BU/ml)
Median adults N = 9	54	5	14	33	21.5	12	CR 6/9 (67%) PR 2/9 (22%)
Median children N = 8	54	6.5	6	13	100	26.5	CR 3/8 (37.5%) PR 5/8 (62.5%)
Median all N = 17	54	5	8	23	25	23	CR 9/17 (53%) PR 7/17 (41%)

- **pdVWF/FVIII concentrates used only**
- high success rate16/17 (94%):
  - 9 CR
  - 7 PR
  - 1 failure
- **partial response:**
  - inhibitor ≤ 3 BU/ml
  - recovery and half life ≤ 66%

ITI results from Turkey

*Unuvar A. Haemophilia 2008;14:315-322

Complete response:
- iFVIII < 0,6 BU
- t1/2 ≥ 6 h
- recovery ≥ 66%

Partial response:
- inhibitor < 5 BU
- sometimes anamnesis > 5 BU

Patient	Inhibitor titre (BU/ml)		Time from inhibitor dg. to ITI (months)	Age at start of ITI (years)	FVIII IU/kg/ week	Time to inhibitor elimination (months)	Inhibitor after ITI (BU/ml)
	max	pre-ITI					
Median N = 19	80 60-517	19.2 3.6-515	2.5 0.3-60	9 1.2-20	20-50 2-3x weekly	7.5	CR 5/19 (26%) PR 7/19 (37%)

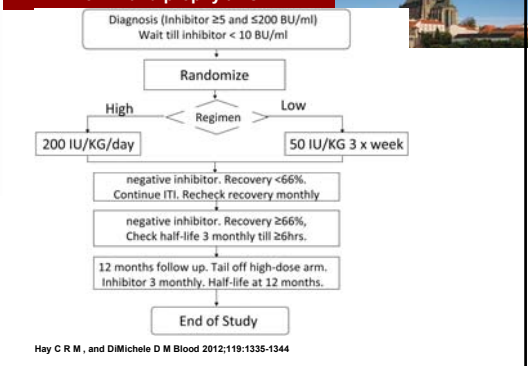
	CR + PR group	Failed group	OR	P value
Inhibitor titre pre-ITI ≤ 10 BU/ml	6	0	2.1	0.04
Historical preak inhibitor titre < 50 BU/ml	8	1	2.2	0.05
Time between inhibitor detection to ITI start < 12 months	8	1	2.2	0.05

Prognostic factor in PROFIT study

*Coppola A, JTH 2009: 1809-15

- **PROFIT study:**
  - Low risk mutation success rate 13/16 (81%):
    - OR = 1,7, but in multivariant analysis **OR = 6,2**
    - Small insertions and deletions
    - Missense mutations
  - High risk mutations success rate 33/70 (47%):
    - Large deletions
    - Inversions
    - Nonsense mutations
    - Splice site mutations
  - Inhibitor at ITI start < BU/ml **OR = 11.8**
  - Inhibitor peak during ITI < 100 BU/ml **OR = 11.4**

Flow-chart summarizing the protocol for the study, randomization, and monitoring of ITI and prophylaxis

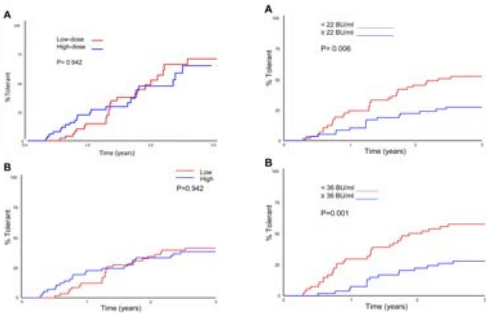


Hay C R M , and DiMichele D M Blood 2012;119:1335-1344

Flow chart showing the disposition of all 115 patients randomized and started on ITI.

Hay C R M , and DiMichele D M Blood 2012;119:1335-1344

Time to success by treatment arm. AQ Time to tolerance by median peak inhibitor titres



Hay C R M , and DiMichele D M Blood 2012;119:1335-1344

Bleeding hazard ratio according to each phase of international ITI study

Hay C R M , and DiMichele D M Blood 2012;119:1335-1344

Time to achieve ITI milestones by treatment arm as median (mo):

	n	LD	n	HD	P
Phase 1: start of ITI to negative titer	29	9.2 (4.9-17.0)	31	4.6 (2.8-13.8)	.017
Phase 2: negative titer to first normal recovery	27	13.6 (8.7-19.0)	23	6.9 (3.5-12.0)	.001
Phase 3: normal recovery to tolerance	24	15.5 (10.8-22.0)	22	10.6 (6.3-20.5)	.096

Bleeding by treatment arm and phase of ITI:

	Regimen	Bleeds, n	HR	95% CI	P
All ITI (n = 58 vs 57)	LD	684	2.2	1.34-3.62	.0019
	HD	282			
Phase 1 (n = 58 vs 57)	LD	573	2.27	1.29-4.01	.0046
	HD	241			
Phase 2 (n = 27 vs 23)	LD	47	3.4	0.84-13.8	.088
	HD	4			
Phase 3 (n = 24 vs 22)	LD	9	5.18	0.71-38.0	.110
	HD	3			
Phase 4 (n = 24 vs 22)	LD	54	1.70	0.80-3.63	.170
	HD	32			

International immune tolerance induction study

- Endpoint: 66/115
- **Tolerance was achieved: 46/66 (70%)**
  - **LD: 24/58 (41%)**
  - **HD: 22/57 (39%)**
- Time to negative inhibitor and normal recovery
  - LD: about 50% longer
- **Bleeding per month:**
  - **LD: OR = 2,4** 0,62 without bleeding: 8/58
  - HD 0,28 21/57
- Prediction of tolerance:
  - FVIII inhibitor historical peak and peak during ITI (univariant analysis)
  - FVIII inhibitor peak during ITI (multivariant analysis)
- CVK without influence to tolerance achievement and time to tolerance:
  - LD: 45/58
  - HD 52/57

**Hay C R M , and DiMichele D M Blood 2012;119:1335-1344*

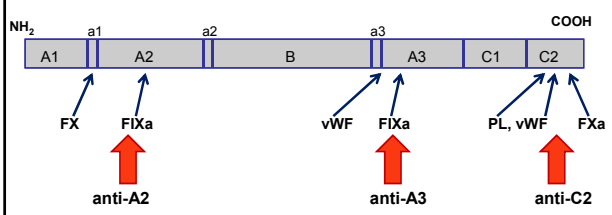
Inhibitor relapse after successful ITI

**Di Minno G. Haemophilia 2013, 19 (Suppl. 1): 18-23*

Study, year [ref.]	Follow-up, years	Relapses, n (%)
Cohort studies		
Mauser-Bunschoten [10]	8.25 (median)	1/21 (4.7)
Kucharski [28]	8.5 (median)	0/5 (0)
Batlle [26]	Nd	1/9 (11.1)
Unuvar [11]	Nd	1/8 (12.5)
Rocino [12]	5.3 (median)	1/26 (3.8)
Registries		
Di Michele(NAITR) [15]	1–9	9/103 (8.7)
Mariani (IITR) [13]	1–15	6/128 (4.7)
Coppola (PROFIT) [16]	4.3 (median)	2/58 (3.4)

Inhibitor of FVIII: epitopes

- Polyclonal immunoglobuline: IgG , mostly IgG4
- Non-binding complement



Influence of VWF on FVIII inhibitor

- **Impurities in pdFVIII concentrates:**
  - soluble HLA-I, soluble Fas-ligand, TGFβ1:
    - inhibit lymphocyte proliferation
    - IL-2 secretion
- **vWF:**
  - in C2 domain inhibitors:
    - VWF binds to C2 domain
    - ↑ recovery FVIII concentrate containing VWF
      - no difference in A2 domain inhibitors
  - ↓ ability of APCs to process FVIII:
    - ↓ first step of immunologic responce
    - theoretically ↓ tolerance mediated by regulatory T cells

**Franchini M, JTH 2011:339-447*

Recent ITI studies according to type of FVIII product and patients´ features

Di Minno G. Haemophilia 2013, 19 (Suppl. 1): 18-23

Study, year [ref.]	n	Dose regimen	Type of FVIII	First ITI	Previous ITI failure	age >8 years, n	Other clinical features	Success rate (%)
Orsini et al. [31]	8	Variable	pdFVIII	8	0	1	Pre-ITI inhibitor titre <10 BU mL−1 in 7/8	88
Barnes et al. [27]	29	Variable	Mostly rFVIII	29	0	4	Pre-ITI inhibitor titre <10 BU mL−1 in 25/29. Two mild haemophiliacs	79
Rocino et al. [12]	26	Variable	rFVIII	26	0	6	Pre-ITI inhibitor titres <10 BU mL−1 in 22/26	73
Gringeri et al. [32]	17	Variable	pdFVIII	13	4	17	All patients at first ITI with one or more predictors of poor prognosis	53
Greninger et al. [33]	11	100-200 IU kg−1 day−1	pdFVIII	7	4	11	6/7 patients at first ITI with one or more predictors of poor prognosis	45
Valentino et al. [34]	10	Variable	rFVIII	10	0	0	Pre-ITI inhibitor titres <10 BU mL−1in 7/10	75
Kurth et al. [35]	33	100-200 IU kg−1 day−1	pdFVIII	8	25	7	One or more predictors of poor prognosis in 6/8 patients at first ITI	33
Bidlingmaier et al. [36]	14	Mostly high dose	pdFVIII	7	7	3	5/7 patients at first ITI with one or more predictors of poor prognosis	64

ITI ongoing study in HA

RESIST

- FVIII 200 IU/kg/D, 1-2 boluses
- HR: peak > 5 BU/ml
- **Naive** (≥1 criteria):
  - historical peak of iFVIII > 200 BU/ml
  - pre-ITI iFVIII > 10 BU/ml
  - age > 7 years
  - > 2 years from iFVIII diagnosis
- **FVIII/VWF or FVIII**
- **Experienced (FVIII/VWF):**
  - previous ITI failure:
    - lasting at least 9 months
  - iFVIII relapse after previous ITI

OBSITI

- Bonn protocol
- tailored pdFVIII concentrate :
  - Malmö inhibitor U:
    - how many IU of FVIII inactivates 1 ml of pateint´s PPP
  - TGA:
    - Titre of iFVIII which ↓ TGA of 50%
- IgG subclasses
- epitopes of iFVIII
- immunologic markers

ITI – the role of anti-CD20

*Franchini M, Haemophilia 2008: 903-912

- **49 cases**
- **CR:**
  - 33/49 = 67% mild/moderate 12/16 = 75% severe 12/28 = 43%
  - in 1-15 month
  - **FVIII concentrates in all cases**
- **Relapses rate:**
  - 7/33 = 21%
- **Sustained CR:**
  - 53%
- **No influence of inhibitor titre:**
  - CR: median 23, mean118 BU/ml
  - relapses: median 40, mean 107 BU/ml

ITI recommendations in haemophlia A

Practice	Europ.HTSB	Internat.W.ITI	UKHCDO	ItalianAHC
start <10 BU/ml	preferably	wait 1-2 years except LT bleed	yes, wait 1 year	
HR	yes		yes	yes
LR	children: >6 months adults: if impossible therapy with FVIII		If interference with FVIII therapy	if impossible FVIII therapy lasting>6 mm.
bleed th. before ITI		no FVIII	rFVIIa	
Immunosupression	not as 1st line resist ITI, ↑level, persist. titre iFVIII	not as 1st line	↓iFVIII <20% á 6 months or ↓mild/moderate HA and bleeding type similar acq.HA	resistant to ITI, high risk to fail
FVIII dosage	>100 IU/kg/D	peak >200 BU preITI >10 BU >5 years lasting ~ ≥200 IU/kg/D	h.peak>5BU ~ 50IU/kg alt.d. h.peak<200BU, pre-ITI<10BU ~ 100IU/kg/D h.peak>200BU, pre-ITI>10BU ~ > 200 IU/kg/D	>100 IU/kg/D seems to be supported
pdFVIII	after ITI failure	after ITI failure	↓<20% á 6mo	after ITI failure
ITI cessation	If not 50% iFVIII↓ within 6-12 months, no iFVIII↓ á 6 months	iFVIII↓ <20% á 6 months from month 4 to 33	↓ iFVIII <20% á 6 months after the peak inhibitor titre has been reached	↓ iFVIII <20% á 6 months
prophylaxis after ITI	at least 6-12 months			

ITI in haemophilia B

*DiMichele DM. BJH 2012; 159: 123-134

- **Tolerance:**
  - registry ISTH: 5 / 34 (**15%**)
    - nephrotic syndrome 13/34 (38%)
  - NAITR 5/39 (**13%**)
    - 5/16 (31%) completed course of ITI
  - Malmö protocol 5/7 (71%)
  - case reports: CSA or anti-CD20
    - Malmö protocol (mycophenolate instead of CFA))
- **Anaphylaxis – cause?**
  - FIX is small molecule
  - exogennous proteines
  - IgE reaction
  - complement activation
  - higher in large deletions
    - » 26% risk
- **Nephrotic syndrome – cause?**

  (membraneous glomerulonefphitis)
  - Mostly in 8-9th month of HD ITI
  - FIX as small molecule
  - exogennous proteines
  - genetic predispositions

ITI - guidelines

- Collins PW, Chalmers E, Hart DP et al. Diagnosis and management of factor VIII and IX inhibitors in congenital haemophilia: (4th edition) **United Kingdom Haemophilia Centre Doctors´ Organisation**. Br J Haematol 2013; 160: 153-170.
- DiMichele DM, Hoots WK, Pipe SW et al. **International workshop on immune tolerance induction:** consensus recommendations. Haemophilia 2007; 13 (Suppl. 1): 1-22.
- Astermark J, Morado M, Rocino A et al. Current European practise in immune tolerance induction therapy in patiens with haemophilia and inhibitors. **European Haemophilia Therapy Standardisation Board (EHTSB).** Haemophilia 2006; 12: 363-371.
- Gringeri A, Mannucci PM. **Italian guidelines** for the diagnosis and treatment of patiens with haemophilia and inhibitors. Haemophilia 2005; 11: 611-619.
- Inhibitor Subcommittee of the **Assotiation of Hemophilia Clinic Directors of Canada.** Suggestion for the management of factor VIII inhibitors. Haemophilia 2000; 6 (Suppl. 1): 52-29.
- Brakmann HH, Lenk H, Scharrer I et al. **German** recommendation for immune tolerance therapy in type A haemophiliacs and antibodies. Haemophilia 1999; 5: 203-6