Eradication of autoantibodies in acquired hemophilia A

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- Acquired hemophilia A (AHA) is a rare autoimmune disorder with an incidence of about 1.5 per million per year
- Autoantibodies formed against coagulation factor VIII (FVIII) may cause severe bleeding
- In most cases, older patients are affected (except 5-8% post partum inhibitors)
- Time to remission varies with current immunosuppressive regimens between a few days and several months, during which patients are at high risk of bleeding and adverse effects.


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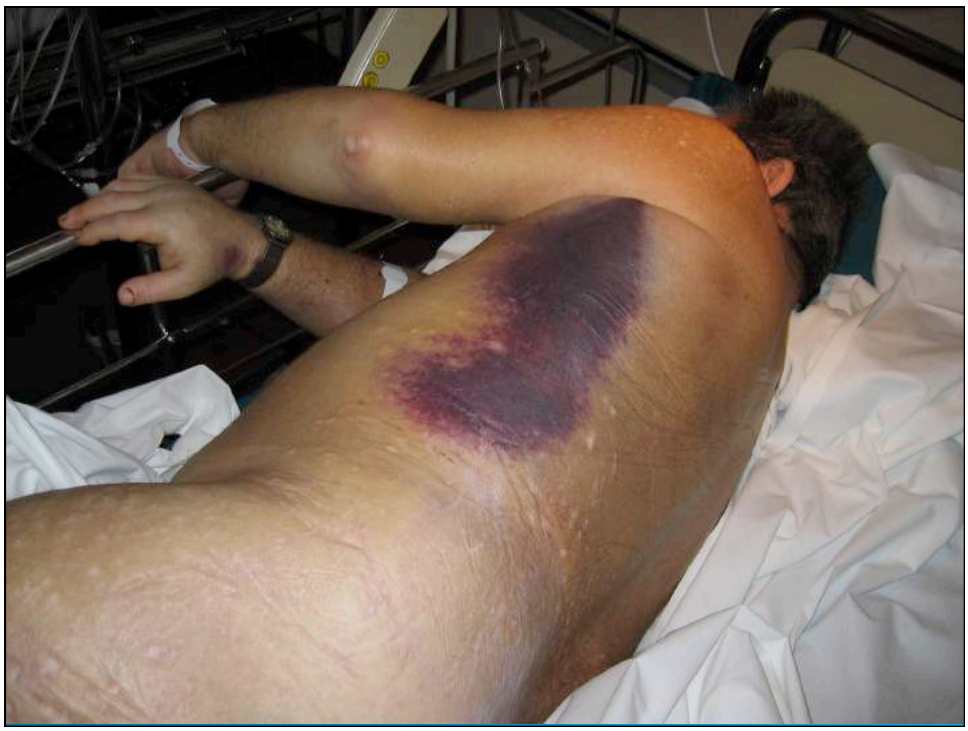

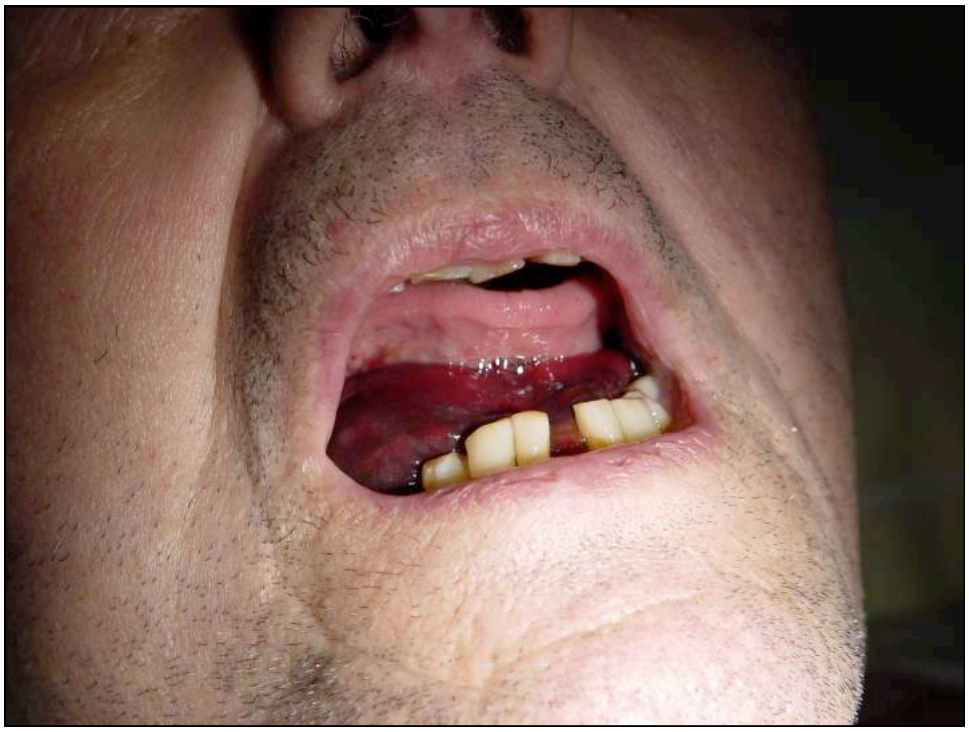

CT scan:

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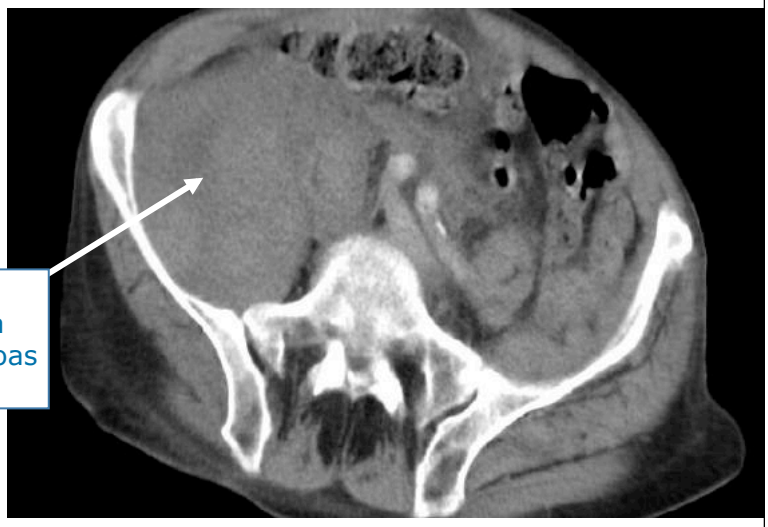

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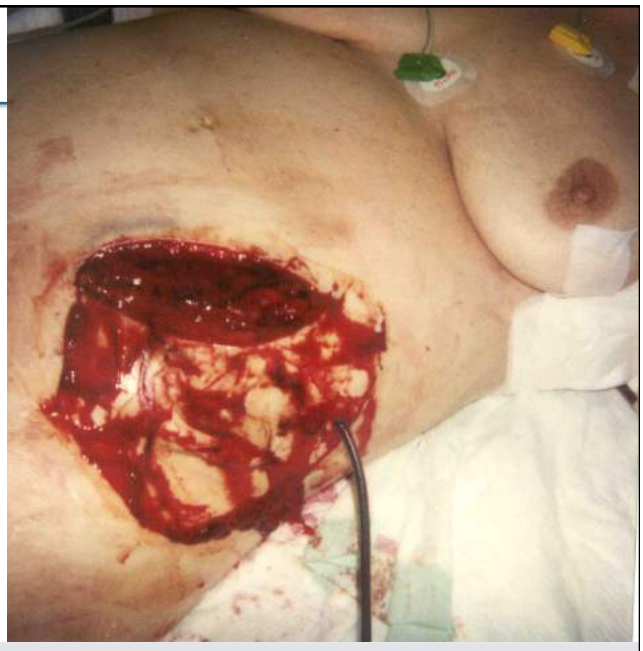
Intractable bleeding after (unnecessary) surgery in a patient with unrecognized AHA despite treatment with:

- 39 RBC concentrates
- 54 U plasma
- 3 U platelet concentrates
- 5000 U PCC
- 1250 U FXIII concentrate
- desmopressin, aprotinin, etc.



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- Immediate recognition of AHA in a bleeding patient is mandatory, lab analysis is easy.
- Adequate hemostatic therapy (recombinant human FVIIa, APCC, recombinant porcine FVIII, high-dose human FVIII concentrates) is highly effective to stop bleeding
- To avoid invasive procedures saves costs and reduces the complications of massive bleeding
- **The causal therapy is to eradicate the autoantibodies to obtain stable complete remissions**

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Methods for autoantibody eradication:

- **Immunosuppression**
  - to terminate the autoimmune process
- **Immunoadsorption**
  - to reduce the concentration of circulating autoantibodies
- **Immunotolerance**
  - to saturate the binding sites of circulating autoantibodies

Immunosuppression:

- **Steroids**
- **Cytotoxics**
  - Cyclophosphamide
  - Azathioprine
- **Immunomodulation**
  - Cyclosporine
  - Mycophenolat-mofetil
  - Tacrolimus
- **Others**
  - Bortezomib

EACH2 Registry
European Acquired Haemophilia Registry

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- An international, multicenter, prospective registry on acquired hemophilia
- Enrollment period: January 2003 – December 2008
- 501 patients with AHA from 117 treatment centers in 13 European countries (Austria, Finland, France, Germany, Greece, Hungary, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK)
- Web-based, secured case-record forms; informed consent obtained
- Hosted by Parexel, Germany
- Supported by an unrestricted grant from Novo Nordisk Region Europe A/S, Zurich, Switzerland

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Table 3. Response to first-line immunosuppression

			Days from start of immunosuppression, median (IQR)				
Regimen	n	CR, n (%)	Inhibitor negative	FVIII > 70 IU/dL	IS stopped	Relapse, n (%)	Stable CR, n (%)
Steroids alone	142	83 (58)	34 (17-76)	32 (15-51)	108 (55-208)	15 (18)	68 (48)
Steroids + cyclophosphamide	83	66 (80)	32 (12-77)	40 (18-81)	74 (52-151)	8 (12)	58 (70)
Steroids + rituximab	28	18 (64)	46 (28-109)	35 (26-189)	62 (31-113)	0 (0)	18 (64)
Cytotoxic + rituximab	3	2 (67)	ND	ND	ND	0 (0)	2 (67)
Steroids + cytotoxic + rituximab	8	6 (75)	50 (20-122)	67 (45-113)	67 (29-129)	1 (17)	5 (63)
Rituximab alone	12	5 (42)	53, 145, 209, 334*	145, 209, 252, 334*	21, 21, 21, 21, 22*	0 (0)	5 (42)
Rituximab + any other agent	39	26 (67)	49 (28-93)	42 (28-138)	67 (31-109)	1 (3)	25 (64)
All rituximab-based regimens	51	31 (61)	65 (29-144)	64 (28-206)	43 (22-96)	1 (3)	30 (59)

The outcome of first-line immunosuppressive therapy (IS) is shown. Complete remission (CR) was defined as inhibitor-negative, FVIII > 70 IU/dL, and immunosuppressive therapy stopped. Stable CR was defined as achieving CR with no relapse during follow-up. Because the groups are not matched, it is not appropriate to make statistical comparisons between the treatment arms.

*Actual days given resulting from limited data.

P.Collins, et al: Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood 2012; 120(1): 47-55.

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EACH2 Registry
European Acquired Haemophilia Registry

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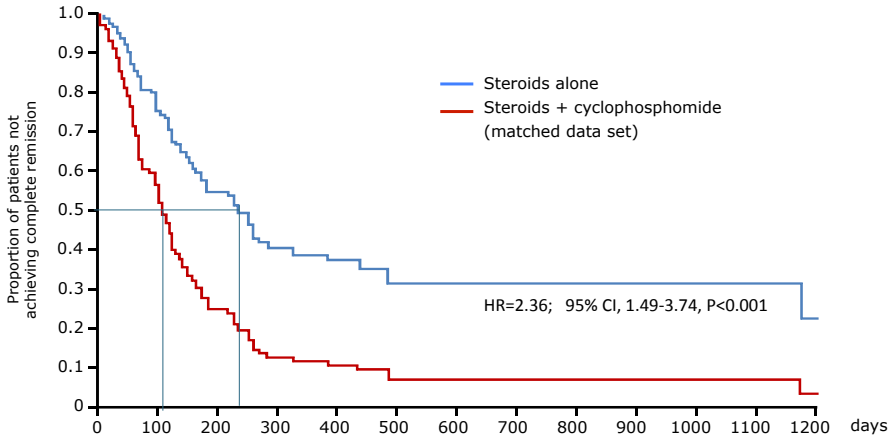

P.Collins, et al. Blood 2012; 120(1): 47-55.

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European Acquired Haemophilia Registry

Side effects of IST

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Regimen	n	Adverse events n (%)				
		Any	Infection	Neutro-penia	Diabetes	Psychiatric disorder
Steroids alone	142	36 (25)	23 (16)	2 (1)	11 (8)	6 (4)
Steroids plus cyclophos-phamide	83	34 (41)	22 (27)	12 (14)	5 (6)	3 (4)
Rituximab-based regimens	51	19 (37)	6 (12)	9 (18)	11 (22)	1 (2)

P.Collins, et al. Blood 2012; 120(1): 47-55.

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EACH2 Registry
European Acquired Haemophilia Registry

Safety

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- Deaths due to bleeding 3.0 %
- Deaths due to IST complications 3.0 %
- Deaths due to underlying disease 9.0 %
- Myocardial infarction 1.4 %
- Stroke 0.2 %
- Venous thromboembolism 1.0 %

- *No significant association of death or severe adverse events with a specific hemostatic therapy*

P.Collins, et al. Blood 2012; 120(1): 47-55.

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EACH2 Registry
European Acquired Haemophilia Registry

Outcome

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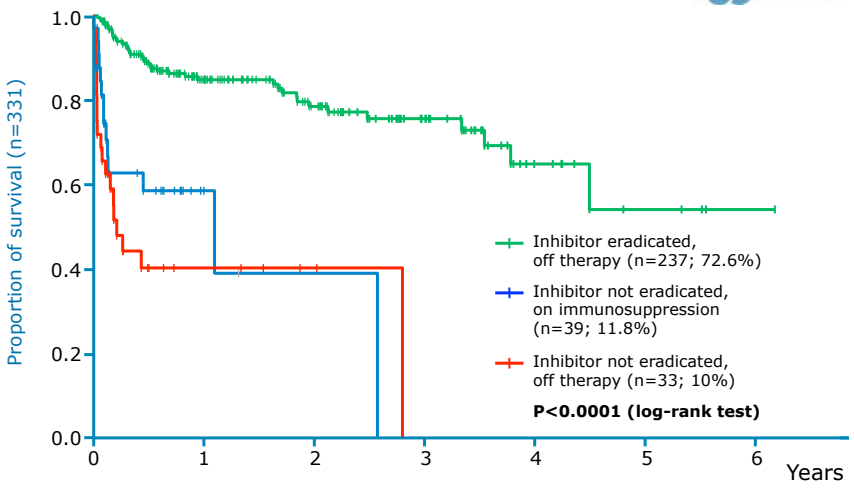

P.Knoebl, et al: Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J.Thromb.Haemost. 2012; 10: 622–631

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GTH-AH 01/2010

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CLINICAL TRIALS AND OBSERVATIONS

Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study

Andreas Tiede,[1] Robert Klamroth,[2] Rüdiger E. Scharf,[3] Ralf U. Trappe,[4,5] Katharina Holstein,[6] Angela Huth-Kühne,[7] Saskia Gottstein,[2] Ulrich Geisen,[8] Joachim Schenk,[9] Ute Scholz,[10] Kristina Schilling,[11] Peter Neumeister,[12] Wolfgang Miesbach,[13] Daniela Manner,[14] Richard Greil,[15] Charis von Auer,[16] Manuela Krause,[17] Klaus Leimkühler,[18] Ulrich Kalus,[19] Jan-Malte Blumtritt,[1] Sonja Werwitzke,[1] Eva Budde,[20] Armin Koch,[20] and Paul Knöbl[21]

(*Blood.* 2015;125(7):1091-1097)

- An international, multicenter, prospective registry on acquired hemophilia to identify prognostic factors in AHA
- Enrollment period: January 2003 – December 2008
- 154 screened patients (102 included) from 21 treatment centers in 3 European countries (Austria, Germany, Switzerland)
- Standardized escalating immunosuppression protocol

Patient Selection Criteria

- **Inclusion criteria:**
  - Age 18 years or older
  - Acquired hemophilia with FVIII activity <50 IU/dl and positive FVIII inhibitor in Bethesda assay
  - Immunsuppressive treatment not started >7 d ago
  - Informed consent
- **Exclusion criteria:**
  - Congenital hemophilia
  - Ongoing pregnancy or breastfeeding
  - Severe, uncontrolled infection
  - Concurrent participation in clinical trials with investigational drugs

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Study Endpoints

- Primary endpoint:
  - **Time to partial remission (PR)**, defined as
    - No active bleeding
    - FVIII:C increased to >50 IU/dl, and
    - Any hemostatic treatment stopped for >24 h
- Secondary endpoints:
  - **Time to complete remission (CR)**, defined as PR plus
    - Negative inhibitor
    - Steroid tapered to <15 mg/d prednisolone or equivalent, and
    - Any other IST stopped
  - **Overall survival (OS)**
  - **Adverse events (AEs)**
  - **Causes of death**

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Demography and Underlying Disorders

	GTH-AH 01/2010*	EACH2**
Median age [years (IQR)]	74 (64-82)	75 (64-81)
Male/female ratio	1.5	1.2
None (idiopathic)	67 %	52 %
Autoimmunity	20 %	13 %
Malignancy	13 %	12 %
Puerperium	5 %	8 %
Others (incl. Infections, skin disorders, drugs)	ND	20 %

** Tiede et al. Blood 2015; 125(7): 1091-1097*
*** Knöbl et al. J Thromb Haemost 2012; 10: 622-31.*
Patients from centers that could enter all patients (including those who died).

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Baseline Conditions

	GTH-AH 01/2010	EACH2
Concomitant disease		ND
Renal insufficiency	36 %	
Coronary artery disease	27 %	
Heart failure	29 %	
Diabetes mellitus	27 %	
Arterial hypertension	58 %	
WHO performance status		ND
0-1	40 %	
2-3	45 %	
4-5	15 %	
Factor VIII:C at baseline (local lab)		
Median (IQR), in IU/dl	1.4 (<1 to 3)	2 (1 to 5)
FVIII:C less than 1 IU/dl	48 %	18 %
Inhibitor at baseline (local lab)		
Median (IQR), in BU/ml	19 (7.7 to 78)	13 (4.3-42)

Tiede et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. Blood 2015; 125(7): 1091-1097

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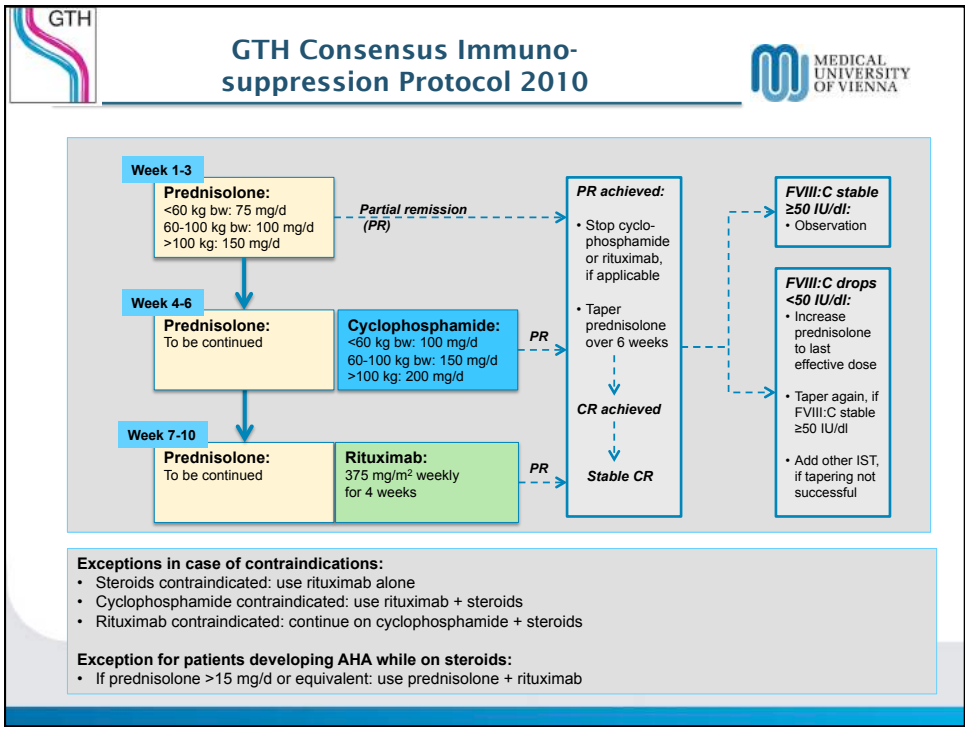
GTH
GTH Consensus Immuno-suppression Protocol 2010
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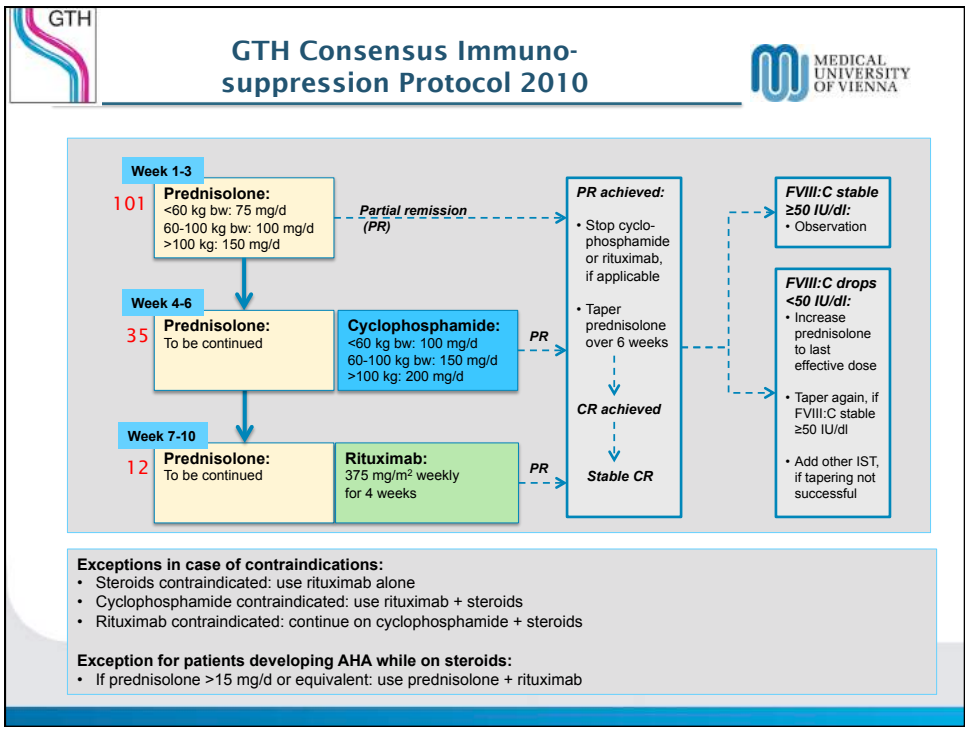
Week 1-3
Prednisolone:
<60 kg bw: 75 mg/d
60-100 kg bw: 100 mg/d
>100 kg: 150 mg/d
Partial remission (PR)
Week 4-6
Prednisolone:
To be continued
Cyclophosphamide:
<60 kg bw: 100 mg/d
60-100 kg bw: 150 mg/d
>100 kg: 200 mg/d
PR
Week 7-10
Prednisolone:
To be continued
Rituximab:
375 mg/m² weekly
for 4 weeks
PR
PR achieved:
• Stop cyclo-phosphamide or rituximab, if applicable
• Taper prednisolone over 6 weeks
CR achieved
Stable CR
FVIII:C stable ≥50 IU/dl:
• Observation
FVIII:C drops <50 IU/dl:
• Increase prednisolone to last effective dose
• Taper again, if FVIII:C stable ≥50 IU/dl
• Add other IST, if tapering not successful
Exceptions in case of contraindications:
• Steroids contraindicated: use rituximab alone
• Cyclophosphamide contraindicated: use rituximab + steroids
• Rituximab contraindicated: continue on cyclophosphamide + steroids
Exception for patients developing AHA while on steroids:
• If prednisolone >15 mg/d or equivalent: use prednisolone + rituximab


GTH
GTH Consensus Immuno-suppression Protocol 2010
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Week 1-3
101
Prednisolone:
<60 kg bw: 75 mg/d
60-100 kg bw: 100 mg/d
>100 kg: 150 mg/d
Partial remission (PR)
Week 4-6
35
Prednisolone:
To be continued
Cyclophosphamide:
<60 kg bw: 100 mg/d
60-100 kg bw: 150 mg/d
>100 kg: 200 mg/d
PR
Week 7-10
12
Prednisolone:
To be continued
Rituximab:
375 mg/m² weekly
for 4 weeks
PR
PR achieved:
• Stop cyclo-phosphamide or rituximab, if applicable
• Taper prednisolone over 6 weeks
CR achieved
Stable CR
FVIII:C stable ≥50 IU/dl:
• Observation
FVIII:C drops <50 IU/dl:
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Exception for patients developing AHA while on steroids:
• If prednisolone >15 mg/d or equivalent: use prednisolone + rituximab

Endpoints

Table 2. Primary and secondary end points for the entire study population

End point	End point achieved n (%)	Time to end point in days		
		Median	IQR	Range
Primary end point				
PR	85 (83)	31	19-51	7-362
Secondary end points				
CR	62 (61)	79	48-102	26-856
Mortality	34 (33)	66	23-235	1-599

Tiede et al. Blood 2015; 125(7): 1091-1097

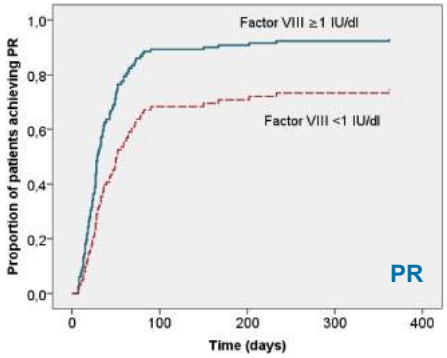
Table 4. Predictors of remission and survival: multivariate analysis

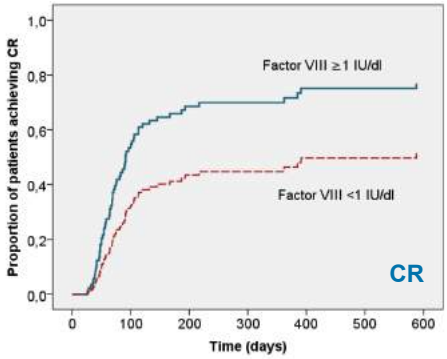
Baseline variable	PR	CR	OS
FVIII activity <1 IU/dL	0.52 (0.33-0.81)**	0.49 (0.29-0.85)*	2.40 (1.10-5.22)*
Inhibitor concentration >20 BU/mL	0.77 (0.49-1.21)	0.75 (0.43-1.29)	1.20 (0.54-2.67)
Female gender	1.22 (0.77-1.91)	1.30 (0.76-2.24)	0.58 (0.26-1.31)
Age >74 y	0.94 (0.58-1.50)	0.76 (0.43-1.32)	1.76 (0.82-3.78)
Underlying disorder			
Autoimmunity	1.32 (0.77-2.28)	0.88 (0.45-1.72)	1.02 (0.36-2.84)
Malignancy	0.58 (0.28-1.21)	0.62 (0.27-1.44)	2.91 (1.12-7.52)*
Pregnancy	0.61 (0.23-1.65)	0.74 (0.27-2.04)	—
WHO-PS >2	0.76 (0.48-1.21)	0.39 (0.21-0.72)**	3.38 (1.55-7.37)**

Data are presented as adjusted HR (CI).
*$P < .05$.
**$P < .01$.

Tiede et al. Blood 2015; 125(7): 1091-1097

Complete and Partial Remission





Variable	PR achieved N (%)	Time to PR in days Median (IQR)	Crude HR (95% CI)	Adjusted HR (95% CI)	P value
FVIII:C <1 IU/dl	36 (77)	43 (28-64)	0.54 (0.35-0.83)	0.52 (0.33-0.81)	<0.01
FVIII:C ≥1 IU/dl	49 (89)	24 (15-44)			

Tiede et al. Blood 2015; 125(7): 1091-1097

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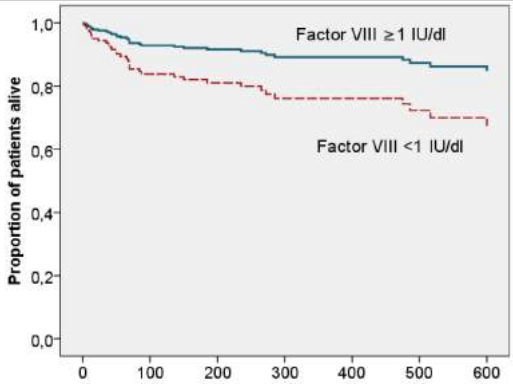
Overall survival



Variable	Adjusted HR (95% CI)	P value
FVIII:C <1 IU/dl	2.40 (1.10-5.22)	<0.05
Malignancy	2.91 (1.12-7.52)	<0.05
WHO performance status >2	3.38 (1.55-7.37)	<0.01

Tiede et al. Blood 2015; 125(7): 1091-1097

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Survival and Causes of Death

	UK Surveillance[1]	EACH2[2]	SACHA[3]	GTH[4]
N	134	331	82	102
Median age	78	74	77	74
Estimated 1 year survival	55% (Steroid) 72% (Steroid +CTX)	72%	62%	68%
Fatal bleeds	9.1%	4.5%	3.5%	2.9%
Fatal IST complications	11%	4.2%	12%	16%
Fatal CV complications	n.r.	n.r.	7.3%	6%

Abbreviations: IST, immunsuppressive treatment; CV, cardiovascular; CTX, cyclophosphamide; n.r., not reported

1. Collins et al. Blood 2007;109:1870-7
2. Knöbl et al. J Thromb Haemost 2012; 10: 622–31
3. Borg et al. Haemophilia 2013;19:564-70
4. Tiede et al. Blood 2015; 125(7):1091-7

Unmet needs?

- Reduce duration of immunosuppression
- Reduce side effects of immunosuppression
- Identify prognostic parameters to predict response to therapy and survival
- Establish individualized therapeutic strategies

Immunoadsorption

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- Extracorporeal adsorption of patient's plasma to protein A- or anti-immunoglobuline sepharose columns (re-usable)
- Removal of circulating antibodies (all subclasses) and antigen-antibody complexes
- Processing of large plasma volumes (7.000 ml in 4 h)
- Fast reduction of inhibitor titers enables use of FVIII concentrates insteas of bypassing agents or rpFVIII
- Safe procedure, low rate of adverse events

- Complex procedure, need for experienced team and equipment
- Need for good venous access (if possible, use peripheral veins)
- Complex anticoagulation of the extracorporeal circuit
- Immunoglobuline depletion – risk of infections?

Jansen et al. Treatment of coagulation inhibitors with extracorporeal immunoadsorption (Ig-Therasorb) British Journal of Haematology 2001; 112:91-97

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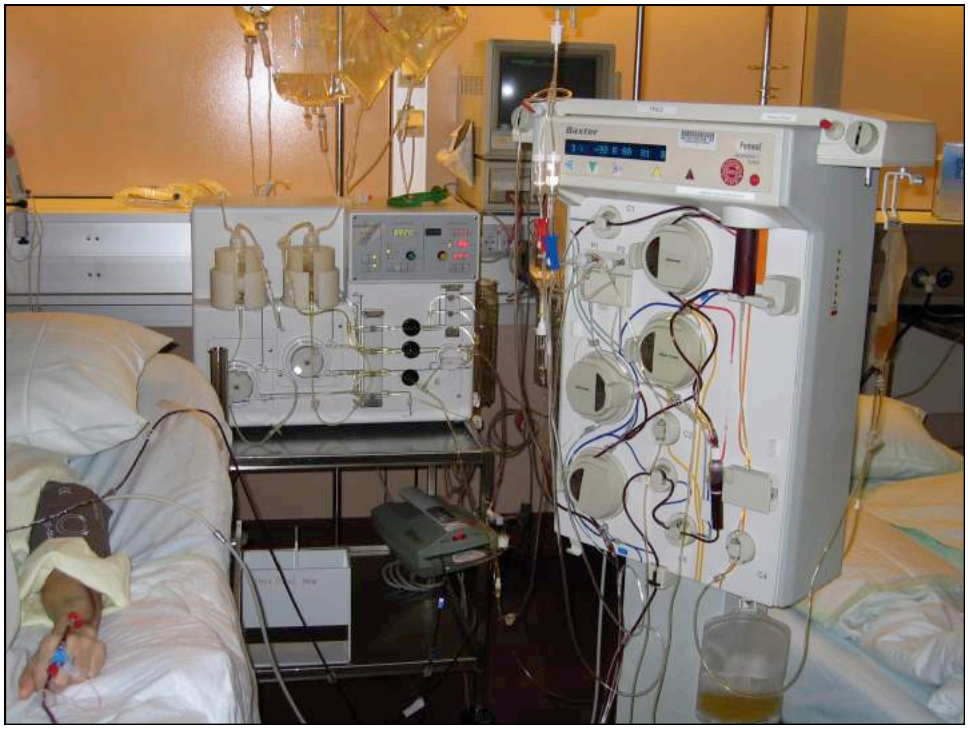

Immunotolerance Protocols

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- Modified Bonn Malmö Protocol
- Budapest Protocol
- Vienna Protocol

Combinations of:

- Immunosuppression
- Immunoadsorption
- High-dose human FVIII concentrates (saturation of circulating antibodies by antigen excess)

Modified Bonn-Malmö Protocol

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Large-volume immunoadsorption:
2.5 to 3 times the total plasma volume on days 1 to 5

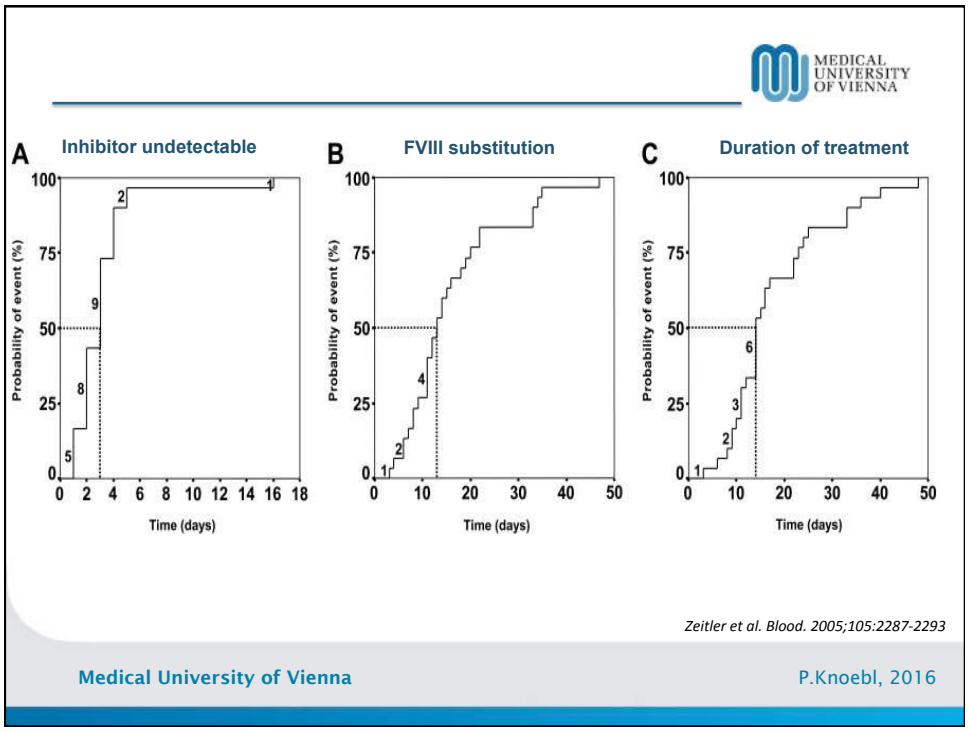
iv immunoglobuline substitution:
(0.3 g/kg body weight [BW]/d, on days 5-7)

Immunosuppression:
Cyclophosphamide (1-2 mg/kg BW/d)
Prednisolone (1 mg/kg BW/d) from day 1 until remission

Human FVIII concentrates
100 U/kg BW every 6 hours. Dose reductions on the level of recovery achieved (50%-80% FVIII residual activity after 4-6 hours)

Treatment cycles (days 1-7) were repeated several times, depending on the clinical response and the coagulation factor activity.

Zeitler et al. Treatment of acquired hemophilia by the Bonn-Malmö Protocol: documentation of an in vivo immunomodulating concept. Blood. 2005;105:2287-2293



Modified Bonn-Malmö Protocol Outcome:

Overall CR rate: 88% (31 of 35 patients)

When patients with underlying cancer were excluded, the CR rate was 97% (31 of 32 patients).

No deaths during therapy

Zeitler et al. Blood. 2005;105:2287-2293

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Modified Bonn-Malmö Protocol
Resource utilization

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Amount of FVIII concentrates (all 35 patients):

median 140.000 IU (range 24.000 - 1.870.000 IU)

Amount of rFVIIa (5 patients):

Median 250 mg (range 44 – 600 mg)

Amount of APCC (2 patients):

700.000 IU and 4.200.000 IU

Zeitler et al. Blood. 2005;105:2287-2293

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Modified Bonn-Malmö Protocol
Resource utilization

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Amount of FVIII concentrates (all 35 patients):

median 140.000 IU (range 24.000 - 1.870.000 IU)

110.000 € 20.000 € 1.500.000 €

Amount of rFVIIa (5 patients):

Median 250 mg (range 44 – 600 mg)

250.000 € 44.000 € 600.000 €

Amount of APCC (2 patients):

700.000 IU and 4.200.000 IU

840.000 5.000.000 €

Zeitler et al. Blood. 2005;105:2287-2293

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Novel Prognostic Markers?

Measurement of FVIII-binding IgG autoantibodies in AHA to overcome the shortcomings of the Bethesda Assay

- Influenced by intrinsic patient FVIII
- Influenced by lupus anticoagulants
- Influenced by anticoagulants
- Non-linear assay kinetics
- Complex technical procedure
- High intra- and inter-assay variability
- High inter-laboratory variability

Werwitzke et al.:
Diagnostic and Prognostic Value of Factor VIII Binding Antibodies in Acquired Hemophilia A: Data from the GTH-AH 01/2010 Study. J.Thromb.Haemost. 2016, in press

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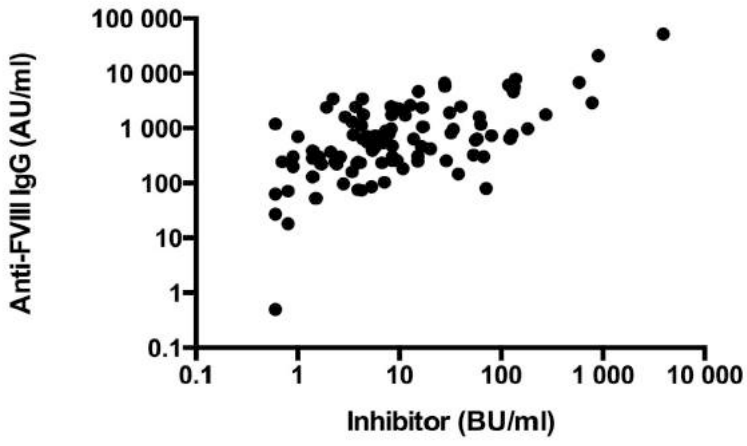
ELISA vs. Bethesda



Werwitzke et al. Diagnostic and Prognostic Value of Factor VIII Binding Antibodies in Acquired Hemophilia A: Data from the GTH-AH 01/2010 Study. J.Thromb.Haemost. 2016, in press

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Table 3 Partial remission according to baseline Bethesda inhibitor or Anti-FVIII IgG concentration

Baseline variable	PR achieved n (%)	Time to PR in days median (IQR)	Crude HR (CI)	Adjusted HR (CI)#
NBA inhibitor concentration				
– <10 BU/ml (n=53)	47 (89)	27 (15-39)	1	1
– 10 to <100 BU/ml (n=26)	20 (77)	32 (28-57)	0.60 (0.36-1.02)*	0.53 (0.30-0.93)*
– ≥100 BU/ml (n=13)	10 (77)	54 (33-80)	0.50 (0.25-1.00)*	0.46 (0.22-1.00)*
ELISA anti-FVIII IgG concentration				
– <100 AU/ml (n=10)	10 (100)	14 (11-19)	1	1
– 100 to <1,000 AU/ml (n=51)	44 (86)	28 (21-45)	0.37 (0.18-0.74)**	0.40 (0.17-0.95)*
– ≥1,000 AU/ml (n=31)	23 (74)	51 (33-71)	0.22 (0.10-0.46)***	0.21 (0.08-0.54)**

Adjusted for age, gender, underlying disorder, World Health Organization performance status, and baseline FVIII:C. Statistical significance from Cox regression analysis: * not significant; * p<0.05; ** p<0.01; *** p<0.001.

Abbreviations: IQR, interquartile range; HR, hazard ratio; CI, 95% confidence interval.

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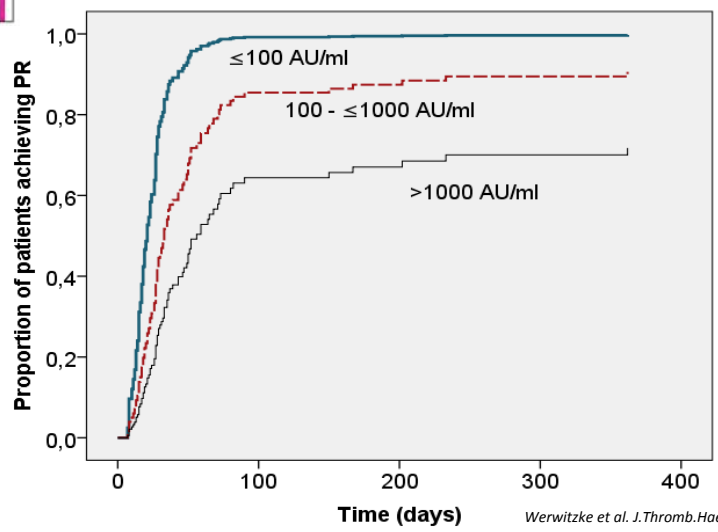

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Novel Prognostic Markers?

Immunoglobuline subclass typing of anti-FVIII autoantibodies

- The autoimmune response in AHA is oligo-/ polyclonal and can evolve during the course of disease
- The autoantibodies can be of various subclasses and can have different affinity to the FVIII domains
- One patient can have antibodies of more than one subclass

Tiede et al. Anti-Factor VIII IgA as a Potential Marker of Poor Prognosis in Acquired Hemophilia A: Results from the GTH-AH 01/2010 Study. Blood 2016, in press

Medical University of Vienna P.Knoebl, 2016

Ig subclasses in AHA

Isotype or subclass	Positive screening	Titer in positive patients	Apparent affinity (main cluster)	Apparent affinity (second cluster, if detected)
	n (%)	median (IQR)	n, K_A [M^{-1}] – median (IQR)	n, K_A [M^{-1}] – median (IQR)
IgG1	71 (88)	1:640 (1:320-1:2560)	70, 1.4×10^{10} (0.8×10^{10}-4.2×10^{10})	15, 7.5×10^{7} (4.5×10^{7}-9.4×10^{7})
IgG2	62 (77)	1:80 (1:40-1:320)	40, 1.9×10^{9} (1.0×10^{9}-3.2×10^{9})	2, 5.7×10^{7} (4.8×10^{7}-6.6×10^{7})
IgG3	33 (41)	1:80 (1:40-1:320)	19, 1.3×10^{10} (0.5×10^{10}-1.8×10^{10})	5, 9.7×10^{7} (6.8×10^{7}-9.9×10^{7})
IgG4	79 (98)	1:5120 (1:1280-1:20480)	77, 5.8×10^{10} (2.4×10^{10}-1.3×10^{11})	6, 3.8×10^{9} (2.9×10^{9}-5.2×10^{9})
IgA	37 (46)	1:80 (1:40-1:160)	18, 1.7×10^{9} (0.9×10^{9}-4.6×10^{9})	8, 5.4×10^{7} (4.6×10^{7}-5.5×10^{7})
IgM	7 (9)	1:80 (1:40-1:80)	n/d	n/d

Abbreviations: IQR, interquartile range; K_A, affinity constant; n/d, not determined.

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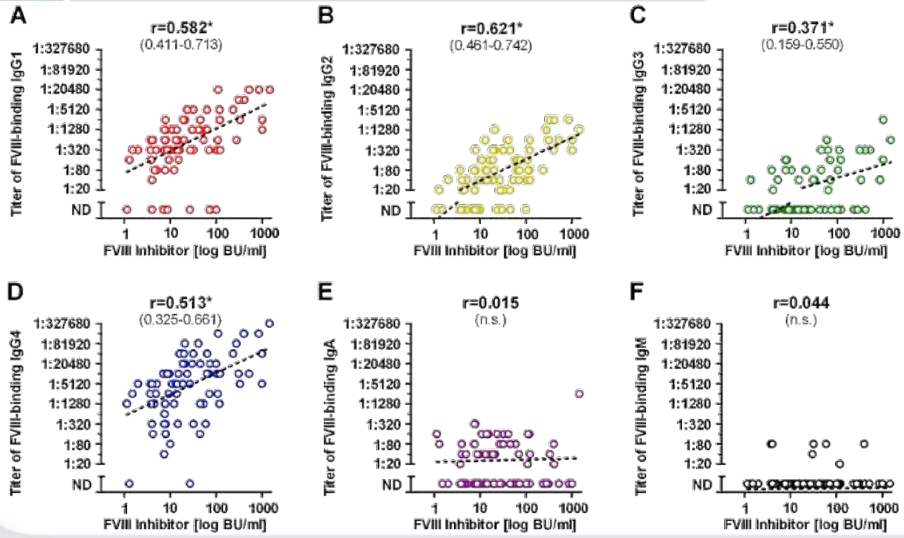
Anti-FVIII Isotypes vs. Inhibitors



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Influence of anti-FVIII IgA on outcome

Isotype/Subclass	PR		CR	
	HR (CI)	aHR (CI)	HR (CI)	aHR (CI)
IgG4				
• negative (n=2)	1	--	1	--
• ≤median (≤1:5120, n=44)	0.69 (0.16-2.87)	--	0.30 (0.07-1.29)	--
• >median (>1:5120, n=35)	0.43 (0.10-1.84)	--	0.30 (0.07-1.28)	--
IgA				
• negative (n=44)	1	--	1	1
• ≤median (≤1:80, n=24)	0.66 (0.38-1.15)	--	0.47 (0.24-0.89)*	0.46 (0.23-0.93)*
• >median (>1:80, n=13)	0.57 (0.29-1.15)	--	0.15 (0.05-0.50)**	0.15 (0.04-0.55)**

Multivariate Cox regression model with adjustment for baseline FVIII:C, inhibitor, gender, age, underlying disorder and WHO performance status

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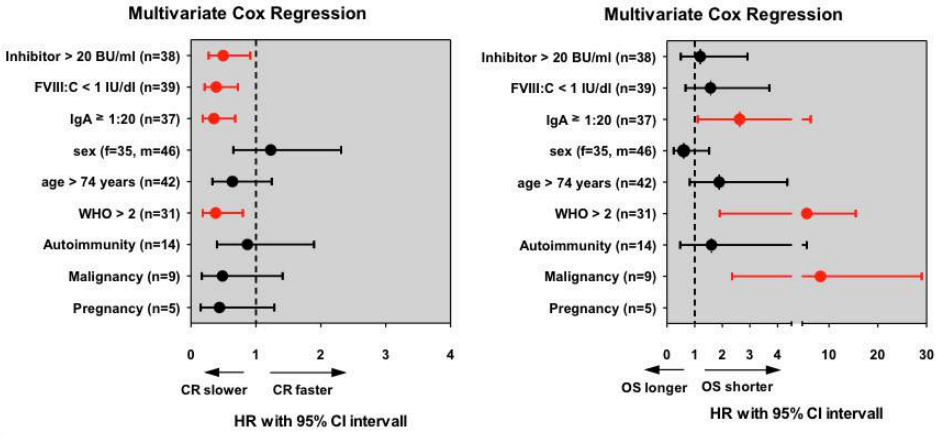
Multivariate analysis



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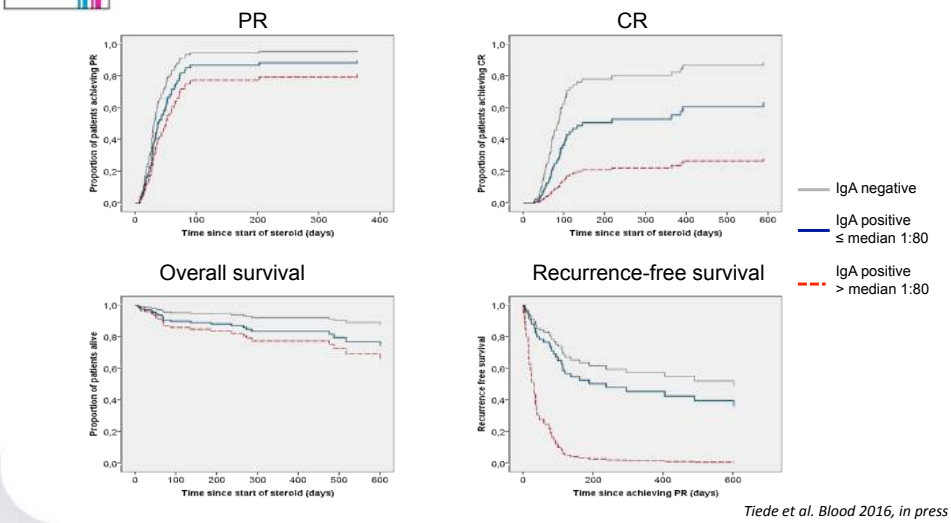
Anti-FVIII IgA as a Marker for Recurrence



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Conclusion

- Prognostic markers were established for remission, recurrence, and overall survival
- Infection-related mortality is still high
- Immunosuppressive regime needs improvement

How to reduce IST toxicity

- Reduce steroid exposure
  - Dexamethason pulse therapy on days 1 and 8
- Reduce duration of immunosuppressive therapy
- Replace cytotoxics with other, less toxic immunomodulators
  - MMF, bortezomib
- Go for trials with front-line rituximab
- Treat good-risk patients less intensely
  - Steroids only +/- FVIII concentrates when FVIII >1% or titer <20 BU/ml
- Treat poor-risk patients more intensely
  - Rituximab +/- cyclophosphamide from day 1 if FVIII:C <1%
- Develop variant immunotolerance protocols
- New treatment goals for IgA patients