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Curricula in hemophilia

Disclaimer: This curricula was realised with the EEA Financial Mechanism 2014-2021 financial support. Its content (text, photos, videos) does not reflect the official opinion of the Programme Operator, the National Contact Point and the Financial Mechanism Office. Responsibility for the information and views expressed therein lies entirely with the authors.

Acquired Hemophilia A

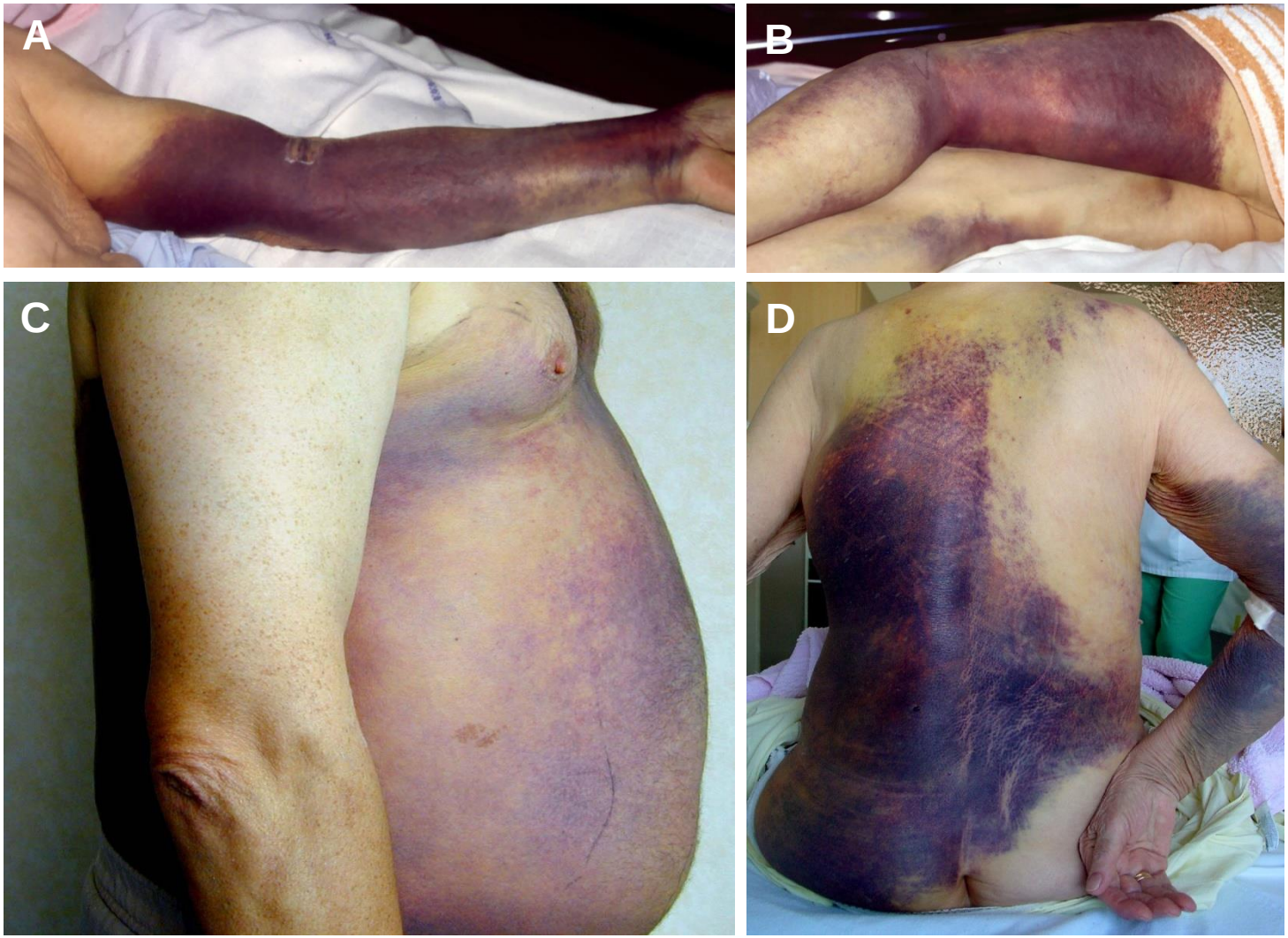
Acquired hemophilia A

- AHA is a bleeding disorder caused by an autoantibody to coagulation factor VIII
  - Estimated incidence of 1.5/million/year
  - Predominantly affects older cases
  - High mortality, estimated between 9-22%

- Presentation:
  - Soft tissue bleeding in cases with no personal or family history of bleeding
  - Bleeding ranges from life- and limb-threatening to mild

Delgado J et al. *Br J Haematol* 2003;121:21-35. Hay CR. *Baillieres Clin Haematol* 1998;11:287-303. Kessler CM, Asatiani E. *Textbook of Hemophilia*; 2007:86-90. Morrison AE, Ludlam CA. *Br J Haematol* 1995;89:231-6. Collins PW et al. *Blood* 2007;109:1870-7. Collins P et al. *Br J Haematol* 2004;124:86-90. Borg JY et al. *J Thromb Haemost* 2007;5. Green D, Lechner K. *Thromb Haemost* 1981;45:200-3.

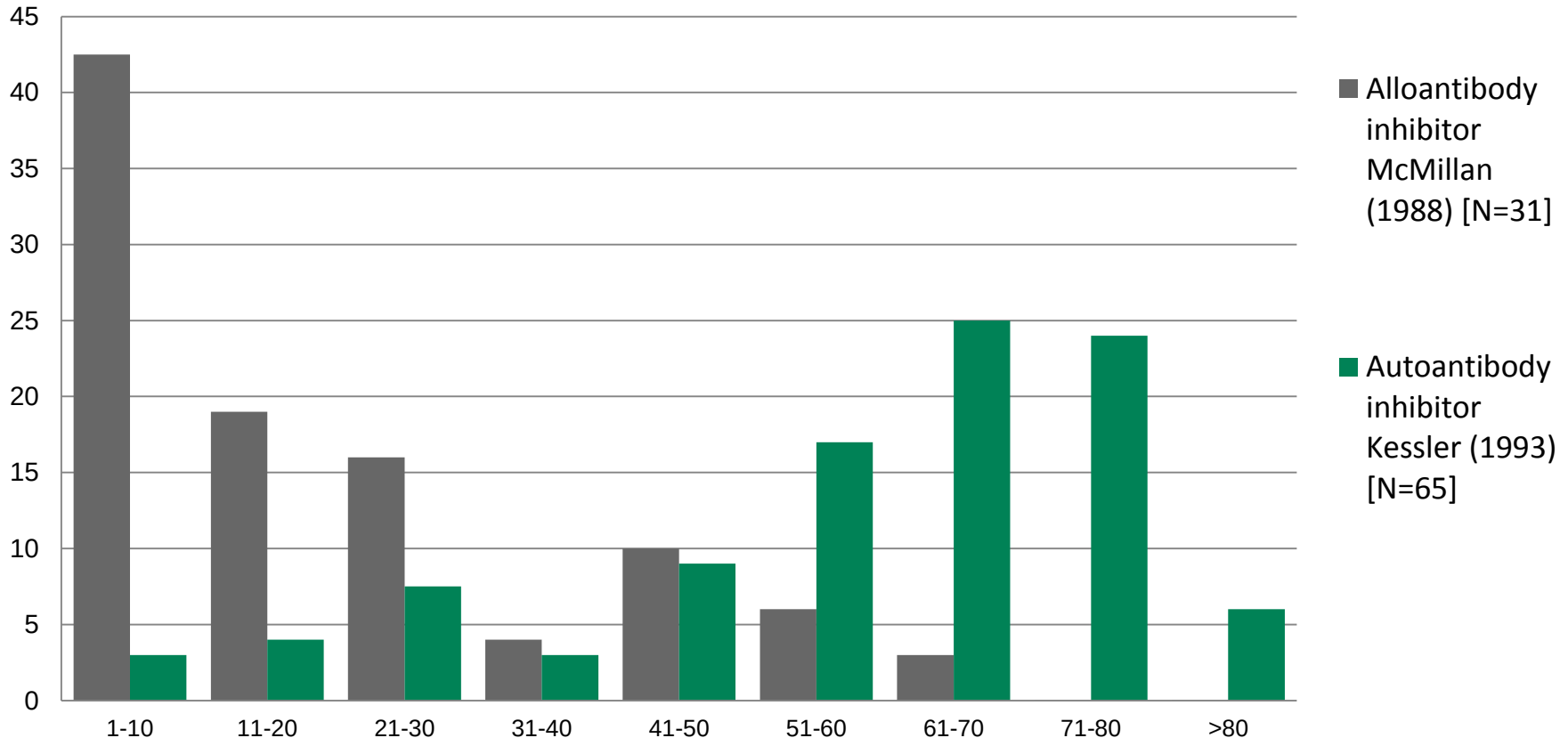
Extensive subcutaneous ecchymoses of the limbs, thorax and abdomen



Clinical presentation

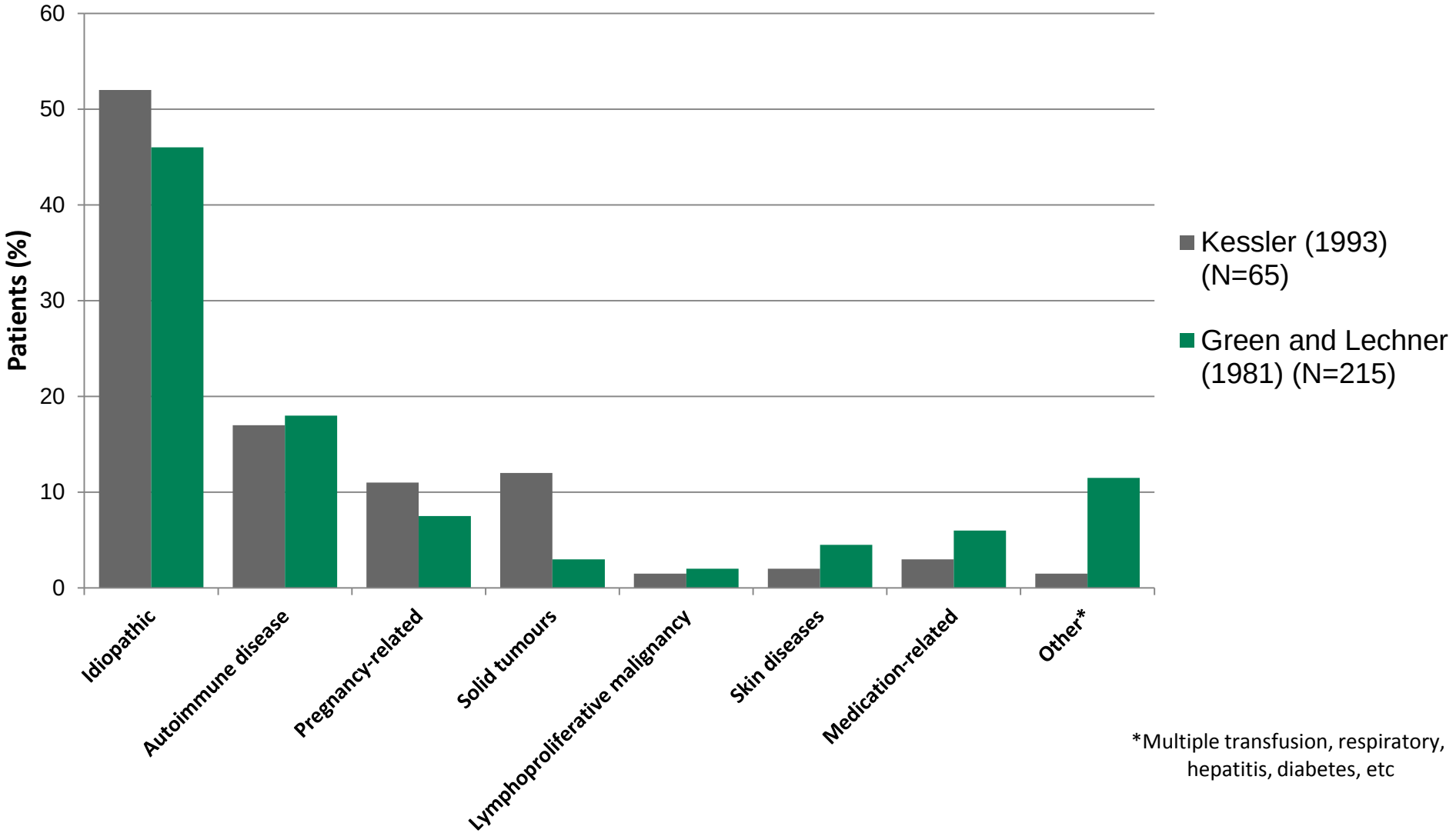
- Acute onset of severe and life-threatening bleeding or widespread subcutaneous bleeds
- Bleeding sites atypical of congenital hemophilia
- High mortality with both early and late deaths
- Presence of underlying diseases and conditions
- Advanced age

Inhibitor age distribution



Age distribution of alloantibodies: McMillan CW et al. Blood 1988;71:344-8.
Age distribution of autoantibodies: Kessler CM and Ludlam CA. Semin Hematol 1993;30(S1):22-7.

Underlying disease states



*Multiple transfusion, respiratory, hepatitis, diabetes, etc

Kessler CM and Ludlam CA. *Semin Hematol* 1993;30(S1):22-7. Green D and Lechner K. *Thromb Haemost* 1981;45:200-3.

Laboratory diagnosis

- Prolonged aPTT
- Decreased FVIII level
- Mixing studies
  - Equal volumes of the persons plasma in various dilutions and normal plasma do not correct a prolonged aPTT

Pharmacokinetics

- Alloantibodies
  - Linear and complete inactivation of FVIII in the presence of excess inhibitor[1]
    - Type I kinetics
- Autoantibodies
  - Non-linear, incomplete inactivation of FVIII in the presence of inhibitor[2]
    - Type II kinetics

[1]Shapiro SS. J Clin Invest 1967;46:147-56. Green D and Lechner K. Thromb Haemost 1981;45:200-3. [2]Collins PW et al. Blood 2007;109:1870-7.

Bleeding risk and inhibitor level

- People remain at risk of fatal bleeding until the inhibitor has been eradicated, even if they initially present with mild or no bleeding
- Unlike congenital hemophilia, the factor VIII level does not correlate with the severity of bleeding

Collins PW et al. Blood 2007;109:1870-7. Kessler CM, Asatiani E. In: *Textbook of Hemophilia*; 2007:86-90.

Principles of AHA treatment

- Control bleeding
- Avoid procedures that may induce bleeds
- Initiate immunosuppression to eradicate the inhibitor
- Treat any underlying condition

Kessler CM, Asatiani E. In: *Textbook of Hemophilia*; 2007:86-90. Morrison AE, Ludlam CA. *Br J Haematol* 1995;89:231-6. Collins PW. *J Thromb Haemost* 2007;5:893-900. Hay CR et al. *Br J Haematol* 2006;133:591-605. Franchini M, Lippi G. *Blood* 2008;112:250-5.

General anti-hemorrhagic treatment strategy

- Control of acute bleeding in AHA is the immediate priority
  - Not all people with AHA bleed
  - Not all types of bleeding require intervention
- In view of the potential side effects of hemostatic therapies, particularly in the elderly with co-morbidities, the risks, benefits and costs of treatment must be weighed carefully and on an individual basis
- Ecchymosis and subcutaneous hematomas, even if extensive, may require only close observation but no specific treatment
- In addition to clinical assessment, frequent monitoring of the hemoglobin (Hb) or hematocrit (Hct) is often a more reliable indicator of significant bleeding than radiologic imaging

Mortality due to bleeding

- The incidence of fatal bleeding in people with acquired hemophilia is high
  - 22% and 31% in older reports with limited therapeutic options
  - 9% in a more recent study
- Death within the first week
  - Gastrointestinal and lung bleeding
- Later deaths
  - intracranial and retroperitoneal haemorrhages
- Fatal bleeding can occur up to 5 months after the first presentation, if the autoantibody is not eliminated
  - Morbidity related to bleeding remains high

[1]Green D, Lechner K. Thromb Haemost 1981;45:200-3. [2]Lottenberg R et al. Arch Intern Med 1987;147:1077-81.
[3]Collins PW et al. Blood 2007;109:1870-7.

Anti-hemorrhagic treatment strategies in AHA

First-line treatment	• rFVIIa (90 mcg/kg initially every 2-3 h) • APCC (50-100 IU/kg every 8-12 h to a maximum of 200 IU/kg/day)
Alternative treatment	• Human FVIII • DDAVP
	• Porcine FVIII
	• Immunoadsorption and/or • Plasmapheresis

Recombinant Porcine FVIII

Haemophilia (2016), 1–8 DOI: 10.1111/hae.13040

ORIGINAL ARTICLE

Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients

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Expericence of Recombinant Porcine FVIII

- Retrospective review of 7 patients with AHA (age 56 to 90 years) and unsatifactory effect of by-passing agents
- Loading dose 100-200 IU/kg > FVIII activity levels of 109-650%
- Subsequent doses of 30-100 IU/kg for 3 to 26 days
- Mean total dose 1,230 IU/kg
- Median dose 1,450 IU/kg
- No adverse events associated with the drug
- Outcome – 3 died - 2 in hospital
  4 survived with inhibitor eradication (3) / persistent inhibitor (1)

Tarantino et al Haemophilia 2016;1-8

Expericence of Recombinant Porcine FVIII

Table 3. Detailed summary of rpFVIII exposure.

Patient	Dose to stop bleeding U kg^{-1} (U)	Dose to prevent re-bleed U kg^{-1} (U	Total dose U kg^{-1} (U)	Median dose U kg^{-1} (range)	Median infusions/day (range)	Total infusions	Total exposure days
1	290 (20 880)	1790 (128 880)	2080 (149 760)	50 (40–100)	2 (0.5–3)	43	26
2	100 (4500)	2000 (90 000)	2100 (94 500)	100 (100–200)	2 (1–3)	15	8
3*			1500 (162 000)	30 (30–100)	2 (1–4)	42	17
4*			427 (35 526)	71 (47–96)	3 (1–3)	6	3
5	250 (31 500)	1200 (151 200)	1450 (182 700)	50 (50–100)	1 (1–2)	28	24
6	200 (17 628)	200 (17 628)	400 (35 256)	50 (50–200)	1 (1–2)	5	4
7	100 (9702)	550 (53 362)	650 (63 064)	100 (50–100)	1 (1)	7	14
Mean			1230 (103 258)			21	14
Median			1450 (94 500)			15	14

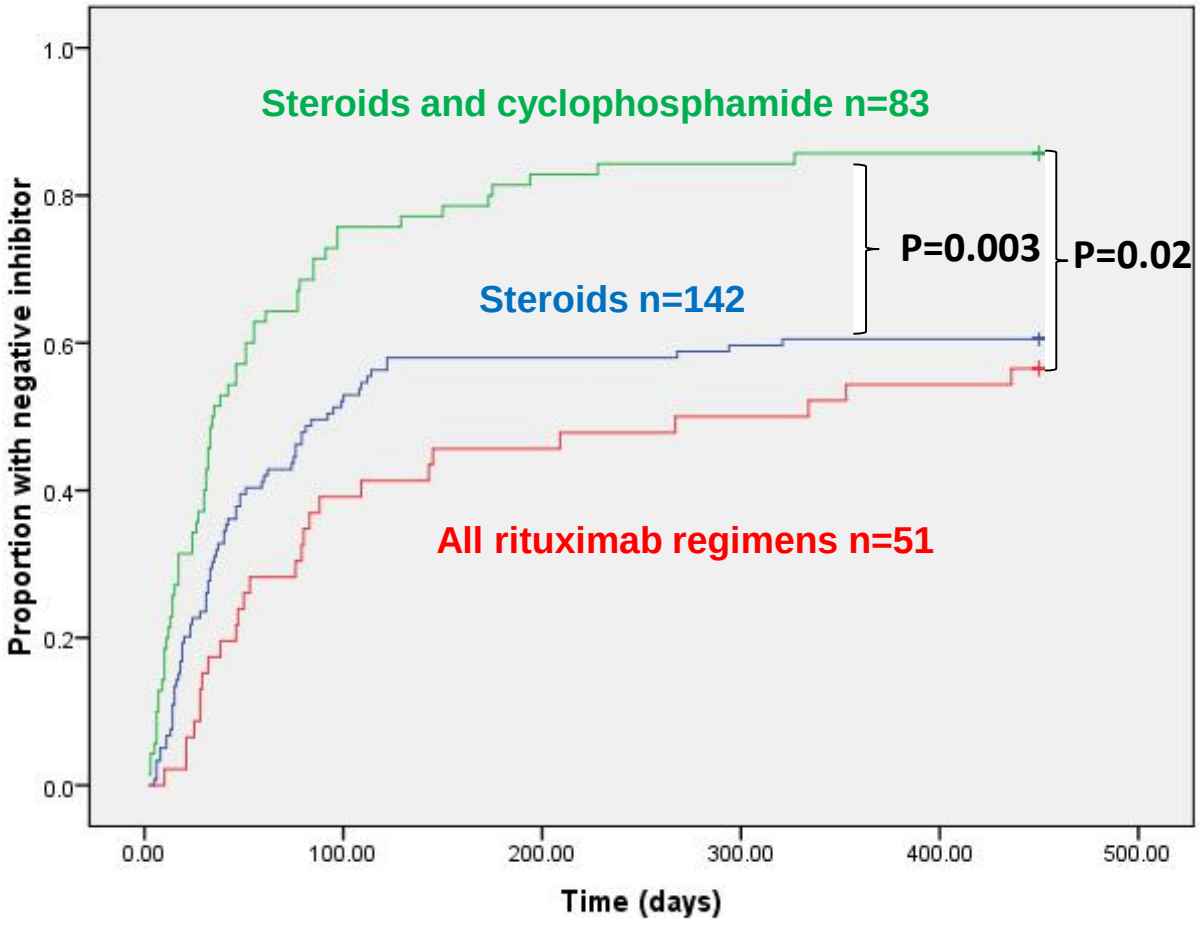
*Bleeding did not completely stop.

Tarantino et al Haemophilia 2016;1-8

EACH2 (European Acquired Haemophilia) registry

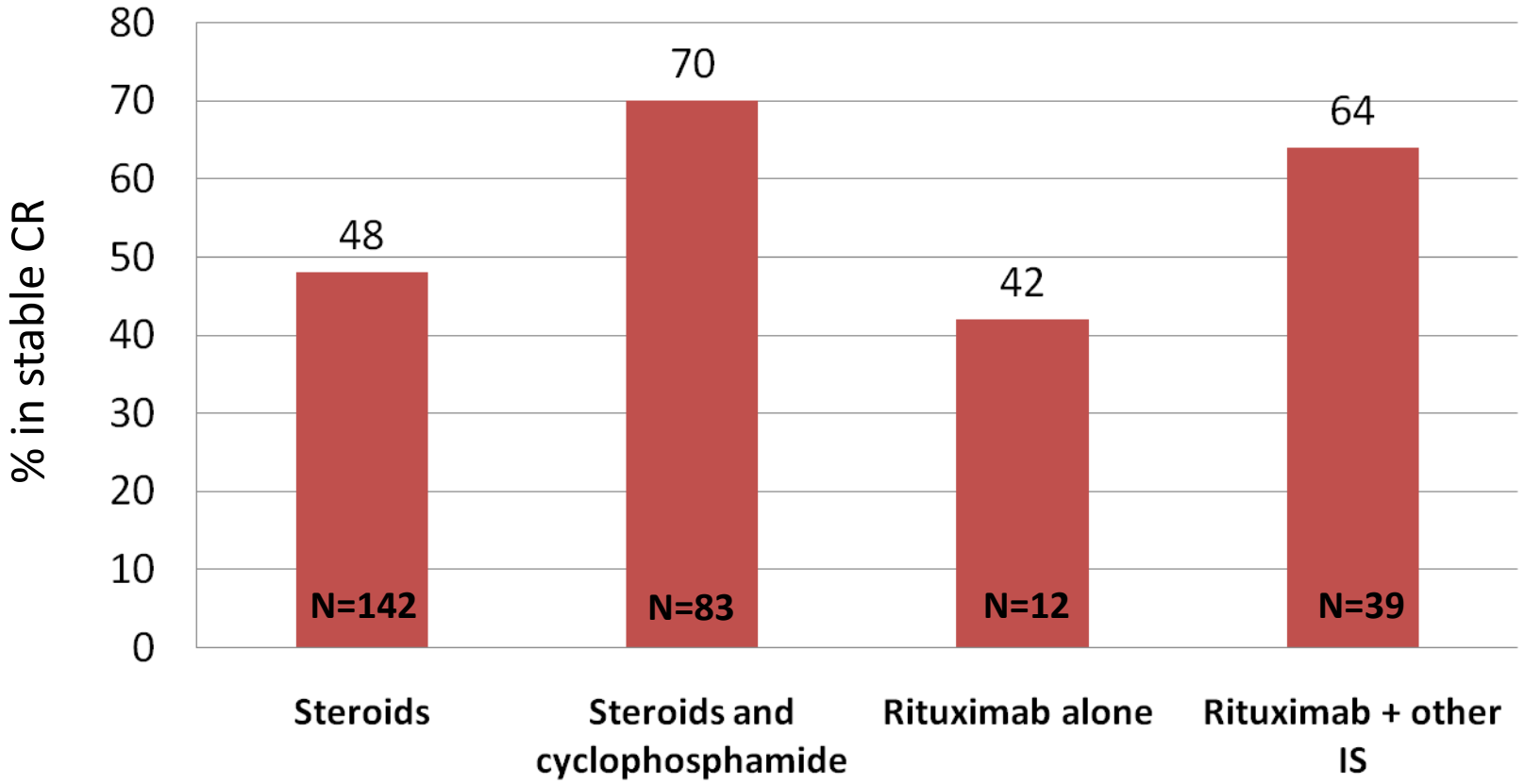
- International, multicenter, prospective registry on AH
- Enrollment period: January 2003 – January 2009
- 90 centers from 12 European countries
  - (Austria, France, Germany, Hungary, Italy, Netherland, Portugal, Spain, Sweden, Switzerland, UK)
- Treatment at the discretion of the investigator
- Largest dataset collected on acquired hemophilia to date

Time to negative inhibitor after first line immunosuppression



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

Patients in stable CR after first line IS



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

Inhibitor eradication treatment strategies in AHA

First-line	• Corticosteroids **(1 mg/kg/day po for 4-6 weeks)** • Corticosteroids + cyclophosphamide **(1.5-2 mg/kg/day for up to 6 weeks)**
Second-line	• Rituximab
Alternative	• Azathioprine • Vincristine • Mycophenolate • Cyclosporine
Not recommended	• Intravenous immunoglobulins

Outcome: first line immunosuppression

Regimen	CR n (%)	Days from start of IS			Relapse n (%)	Stable CR %
		Inhibitor negative	FVIII >70IU/dL	IS stopped (CR)		
Steroids alone n=142	83 (58)	34 (17-76)	32 (15-51)	108 (55-208)	15 (18)	48
Steroids and cyclophos-phamide n=83	66 (80)	32 (12-77) 0-386	40 (18-81) 2-386	74 (52-151) 11-386	8 (12)	70
Rituximab regimens n=51	31 (61)	65 (29-144)	64 (28-206)	43 (22-96)	1 (3)	59
Rituximab alone n=12	5 (42)	53 145 209 334*	145 209 252 334*	21 21 21 21 22*	0 (0)	42

Data are median and inter-quartile range, * actual days given because too few data

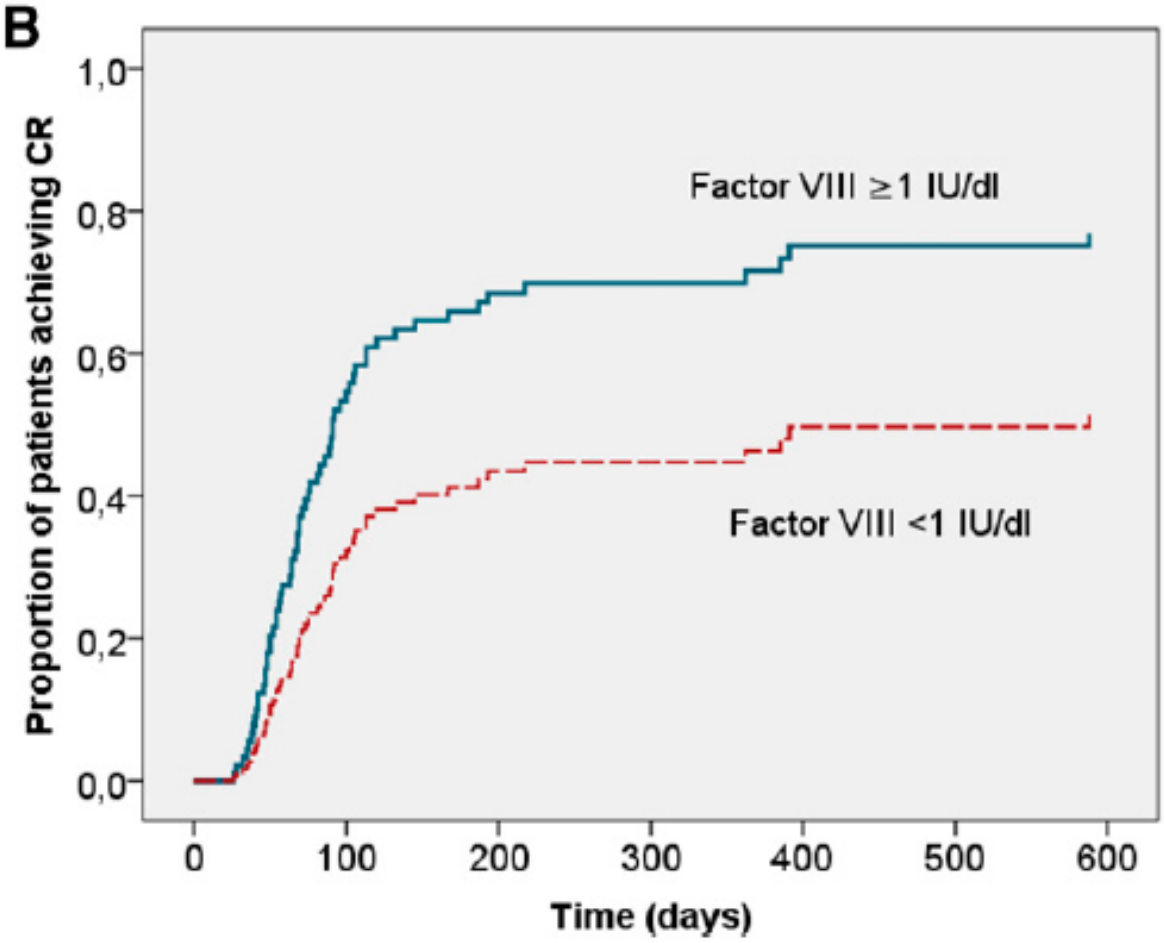
CLINICAL TRIALS AND OBSERVATIONS

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;125:1091-97

Prognostic factors for remission in AHA



Tiede A et al Blood 2015;125:1091-97

Follow-up of tolerized AHA patients

- aPTT (FVIII:C) monthly during the first 6 months,

  then

- Less frequently - every 2-3 months up to 12 months and every 6 months during the second year and beyond, if possible

Conclusions and outlook

- AHA is a rare disorder
  - Heterogeneous bleeding phenotypes
  - Often undiagnosed or diagnosis delayed
  - High-level evidence based on randomized clinical trials not practicable
  - Management often empirical or based on anecdotal or retrospective study data

- Physicians who treat patients with AHA should contribute cases to patient registries
  - Data on clinical characteristics, management and outcomes
  - May serve as the basis for more evidence-based treatment