

Aquired Inhibitors

Meet the Hemostasis experts III
HELLENIC PASTEUR INSTITUTE ATHENS
11-12.Oct 2019

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Largest Studies Contributing to the Understanding of AHA

TABLE 1 The largest population studies contributing information about the understanding of AHA to date

Study (reference)	Design	Year	N	Incidence	Median age at diagnosis, y (range)	Male-to-female ratio
International Survey (Green and Lechner) ¹	Retrospective survey	Before 1981	215	NA	NA	52.7/47.3
Delgado et al ²	Meta-analysis	1984–2002	249 from 21 case series	NA	64 (8–93)	45/55
United Kingdom Haemophilia Centre Doctor's Organisation—UKHCDO (Collins et al) ³	Prospective surveillance of a predefined population	2001–2003	172	1.48 cases/million/y	78 (2–98)	43/57
South Australian Center (Tay et al) ⁴	Retrospective analysis	1997–2008	25	~1.2 cases/million/y	78 (27–99)	48/52
European Acquired Haemophilia Registry—EACH2 (Knoebl et al) ⁵	Prospective multicenter (117 centers in 13 European countries)	2003–2008	501	NA	73.9 (61.4–80.4)	53/47
Surveillance des Auto antiCorps au cours de l'Hémophilie Acquisée—SACHA (Borg et al) ⁶	Prospective surveillance in France	2001–2005	82	NA	76.7 (25–103)	61/39
Taiwan Centers (Huang et al) ⁷	Retrospective analysis in 2 Taiwanese centers	1987–2010	65	NA	64 (18–94)	64/36
German, Austrian and Swiss Society on Thrombosis and Haemostasis—GTH-AH 01/2010 (Tiede et al) ⁸	Prospective	2010–2013	102	NA	74 (26–97)	58/42

AHA: acquired hemophilia A; NA: not available.

Clinical evaluation of bleeds and response to haemostatic treatment in patients with acquired haemophilia: A global expert consensus statement

“...Due to its **rarity**, diagnostic and treatment guidelines rely on **registry data and expert advice**, with current guidance in the form of limited narrative literature reviews, expert panel recommendations based on literature searches, and ‘how I treat’ articles. While providing an excellent resource on diagnosis and treatment, existing guidance is limited in its methodology, being **based largely on clinical opinion of few experts** with a relatively narrow geographical spread and **derived from relatively unstructured methods**...”



It is better to have a bad plan than
no plan.

— *Garry Kasparov* —

AZ QUOTES

The Austrian Patient: 67yrs old, male

Previous diagnosis 2.7.14

- Chronic Liver cirrhosis Child C – ongoing alcohol abuse
- Hepatitis B
- COPD - (still: 20 Cigarettes/d)
- Atrial Fibrillation - CHADS2VASc Score -1

Lab-Tests - Coagulation

Part.Thrombopl.zeit(aPTT)	33 sec	(26 - 37)	(*)
Quicktest (PT)	91 %	(70 - 130)	(*)
INR (PT)	1.1		

The Austrian Patient: 67yrs old, male

- Admission to the local hospital due to melena and spontaneous hematoma 9/10/14
- Gastroscopy 10/10/14:

Adenom angefertigt. Im gesamten einsehbaren Duodenum zeigen sich frische Blutspuren. Eine eindeutige Blutungsquelle findet sich jedoch nicht. Es besteht eine diffuse Blutung im gesamten einsehbaren Duodenum bei hypertensiver Gastropathy und exzessiv verlängerter PTT. Der Pylorus rund und unauffällig. Im Magen sämtliche

- Colonoscopy: no signs of active bleeding
- Capsule endoscopy 15.10.14:

Multiple Angiodysplasien im oberen Jejunum, zT it frischen Blutspuren. In den unteren Dünndarmabschnitten dann nur mehr Melaena.

Transfer to the Medical University of Innsbruck on the 20/10/14 because of the prolonged PTT and active bleeding



The Austrian Patient: 67yrs old, male

»Harnstoff	148.0	mg/dl	(18.0 - 55.0)	() ->
»Creatinin (enzym.-IDMS)	1.80	mg/dl	(0.67 - 1.17)	() ->
»eGFR (MDRD-IDMS)	38 ml/min/1,73m ²			
»Natrium (indirekte Pot.)	136	mmol/l	(136 - 145)	(*)
<i>Hypo/Hyperproteinämien beeinflussen die Na-Bestimmung! Details: zim1.uki.at</i>				
»Kalium (indirekte Pot.)	4.9	mmol/l	(3.4 - 4.5)	() ->
»Chlorid (indirekte Pot.)	95	mmol/l	(98 - 107)	<-()
»Calcium	2.47	mmol/l	(2.20 - 2.55)	(*)
»Part.Thrombopl.zeit(aPTT)	80	sec	(26 - 37)	() ->
»Quicktest (PT)	71	%	(70 - 130)	(*)
»INR (PT)	1.2			
»Gamma-GT	27	U/l	(10 - 71)	(*)
»Lipase	121	U/l	(13 - 60)	() ->
»Lactat-Dehydrogenase(LDH)	206	U/l	(100 - 250)	(*)

Autoimmun/Infektion

»C-reaktives Prot. (CRP)	4.36	mg/dl	(0.00 - 0.50)+	() ->
Rheumafaktor	< 11	kU/l	(0 - 16)+	(*)
Leukozyten	7.6	G/l	(4.0 - 10.0)	(*)
Absolute Neutrophilenzahl	5.3	G/l	(2.0 - 7.0)	(*)
Erythrozyten	2.91	T/l	(4.40 - 5.90)	<-()
Hämoglobin	87	g/l	(130 - 177)	<-()
Hämatokrit	0.248	l/l	(0.400 - 0.520)	<-()
Thrombozyten	327	G/l	(150 - 380)	(*)
MCH	29.9	pg	(27.0 - 32.0)	(*)
MCHC	351	g/l	(310 - 360)	(*)
MCV	85.2	f l	(77.0 - 96.0)	(*)
Ery-Verteilungsbreite	16.2	%	(11.0 - 16.0)+	() ->

Workup: prolonged activated partial thromboplastin time (aPTT)

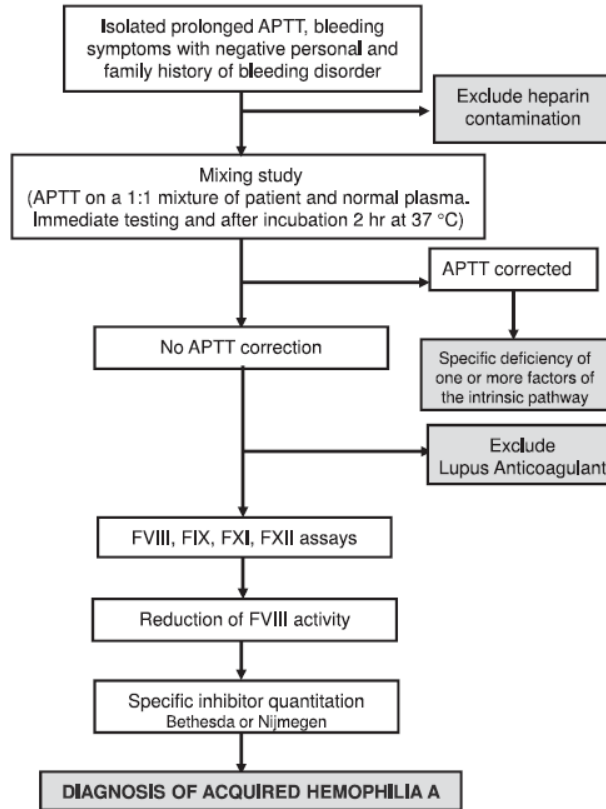
Causes of a prolonged prothrombin time (PT) and/or a prolonged activated partial thromboplastin time (aPTT)

Test result		Causes of test result pattern
PT	aPTT	
Normal	Prolonged	Inherited
		Deficiency of factors VIII, IX, or XI
		Deficiency of factor XII, prekallikrein, or HMW kininogen (not associated with a bleeding diathesis)
		von Willebrand disease (variable)
		Acquired
		Heparin administration
		Direct thrombin inhibitor administration (eg, argatroban, dabigatran)
		Inhibitor of factors VIII, IX, XI, or XII
		Acquired von Willebrand disease
		Lupus anticoagulant (may be associated with thrombosis rather than bleeding)

conditions for additional details.

PT: prothrombin time; aPTT: activated partial thromboplastin time; HMW: high molecular weight.

Algorithm: prolonged aPTT



The Austrian Patient: 67yrs old, male

»Fibrinogen funkt.n.Clauss	480	mg/dl	(210 - 400)	() ->
»Faktor II	75	%	(70 - 120)	(*)
»Faktor V	91	%	(70 - 120)	(*)
»Faktor VII	65	%	(70 - 120)	<-()
»Faktor VIII	1	%	(70 - 150)	<=()
<i>Achtung: bei Erwachsenen gilt für Blutgruppe 0 62% - 102% als Referenzbereich!</i>				
»FVIII Inhibitor Bethesda	4.10	BE	(0.00 - 0.40)+	() ->
»vWF: Antigen	223	%	(58 - 174)	() ->
<i>Achtung: bei Erwachsenen gilt für Blutgruppe 0 51% - 133% als Referenzbereich!</i>				
»vWF-Ratio (AC:AG)	0.9		(0.7 - 1.5)+	(*)
»vWF-Aktivität	193	%	(48 - 173)+	() ->
<i>Achtung: bei Erwachsenen gilt für Blutgruppe 0 46% - 146% als Referenzbereich!</i>				
»vWF:Kollagenbdg.Aktivität	135.0	%	(40.0 - 250.0)+	(*)
»Faktor IX	91	%	(70 - 120)	(*)
»Faktor X	74	%	(70 - 120)	(*)
»Faktor XII	40	%	(70 - 150)	<-()
»Plasminogen	92	%	(75 - 150)+	(*)

Time to Diagnosis: Bleeding + prolonged aPTT

European Acquired Hemophilia (EACH2) Registry


13 Countries – 117 Centres

2003 – 2008

Table 4 Impact of diagnostic delay

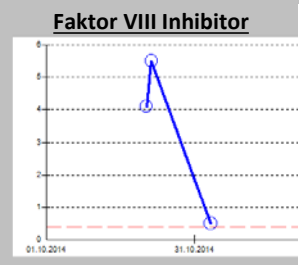
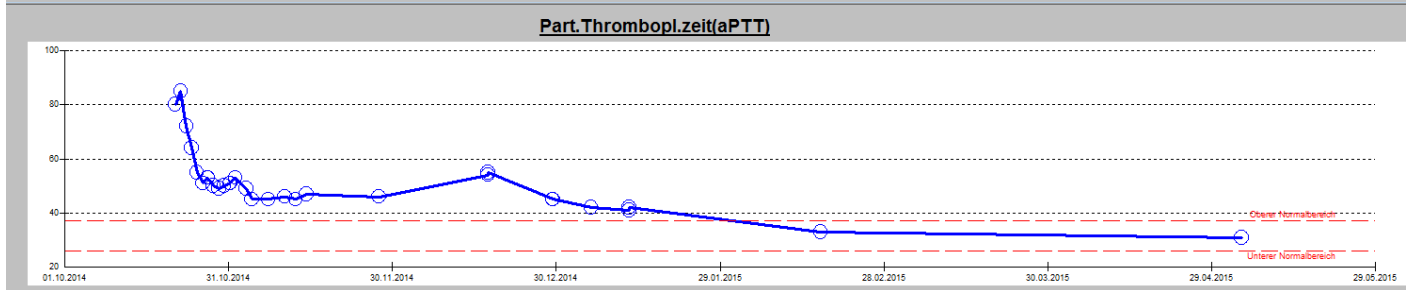
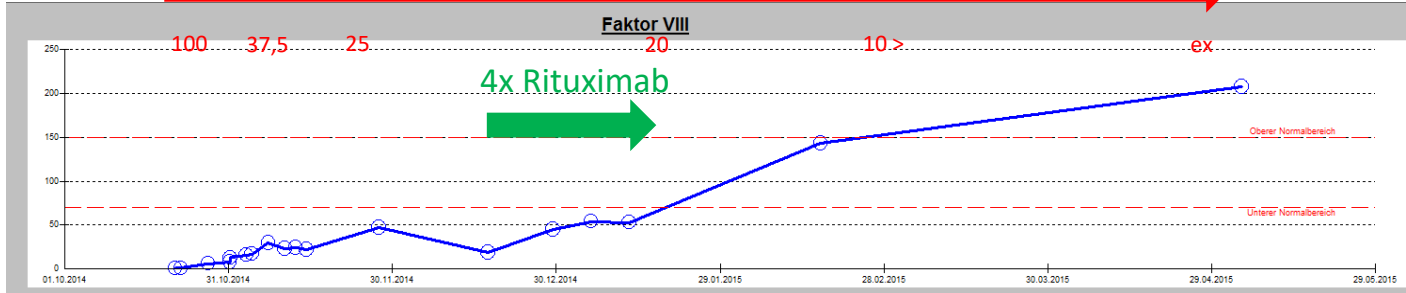
Time bleeding to definite diagnosis	No. of patients (%)	Median FVIII activity [U dL ⁻¹ (IQR)]	Median inhibitor titer [BU mL ⁻¹ (IQR)]	Hb [g dL ⁻¹ (IQR)]	Severe bleeding [n (%)]	Median time to start of hemostatic therapy [days (IQR)]	Median time to bleeding resolved [days (IQR)]
0–1 day	174 (38.2)	2 (1–4)	14 (6–58)	9.4 (7.6–9.4)	121 (70.0)	1 (0–3)	4 (2–11)
2–7 days	121 (26.5)	2 (1–5)	15 (5–41)	8.5 (7.1–10.7)	95 (78.5)	4 (2–5)	4 (2–9)
> 7 days	161 (35.3)	2 (0–6)	7 (2–30)	8.9 (7–11.3)	108 (67.1)	20 (12–43)	5 (2–13)
<i>P</i> *	NA	NS	NS	NS	NS	< 0.0001	NS

IQR, interquartile range; BU, Bethesda Units; Hb, hemoglobin; NA, not applicable; NS, not significant. Data are reported as *n* (%) and median (IQR) for categorical and continuous variables, respectively. *Kruskal–Wallis test.

 in more than 35% of all patients time to diagnosis longer than 7 days!

The Austrian Patient: 67yrs old, male

Prednisolon



Since 04/2015 No Prednisolon!
 Kontrolle 05/2015: ongoing complete remission
 No signs of bleeding

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- ▶ 1. Acquired haemophilia – a bleeding disorder
- 2. Associated conditions
- 3. Laboratory diagnosis
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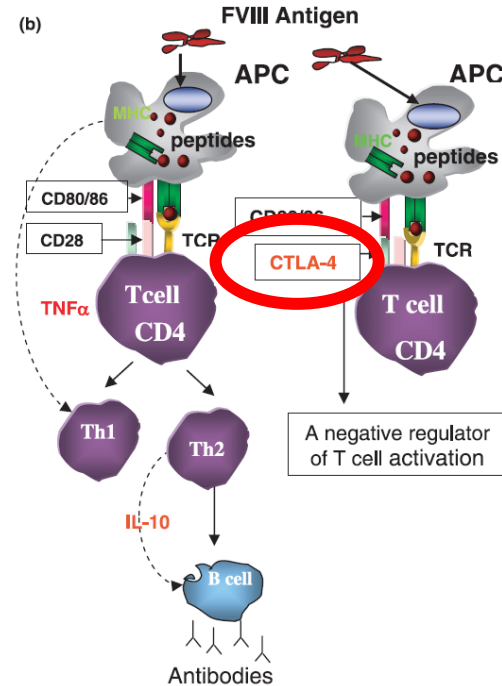
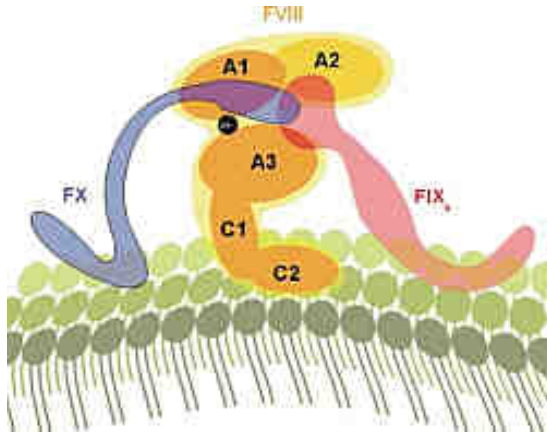
Acquired Haemophilia A (AHA)

Definition: + FVIII < 50%
+ FVIII Inhibitor >0.6BU
+ no congenital haemophilia



AHA- Pathophysiology

Polyclonal Autoantibodies (IgG1 und IgG4) against FVIII (A2/A3/C2 Domain)



A rare bleeding disorder

- Acquired inhibitors can develop against different coagulation factors²
 - Factors I, II, V, VII, VIII → Acquired haemophilia A
 - Factor IX → Acquired haemophilia B
 - Factors X, XI, XIII
 - Von Willebrand Factor
- Incidence AH: ~1.5 patients per 1 million population per year⁴
- Bleeding episodes are often spontaneous and may vary in severity³

A rare bleeding disorder

- Bleeding pattern is distinct from congenital haemophilia¹⁻³
 - More soft tissue bleeding
 - Fewer haemarthroses
- Mortality ranging between 3.3 and 41%
 - 22-31% in older reports with limited therapeutic options^{1,4}
 - 41% when patients were not treated³
 - 21% in a meta-analysis of 32 studies (1985-2008)⁵
 - 9% caused by bleeding in a more recent study²
 - 3.3% caused by bleeding in EACH2 registry⁶

1. Green D, Lechner K. Thromb Haemost 1981;45:200-3.

2. Collins PW, et al. Blood 2007; 109:1870-7.

3. Delgado J, et al. Br J Haematol 2003;121:21-35.

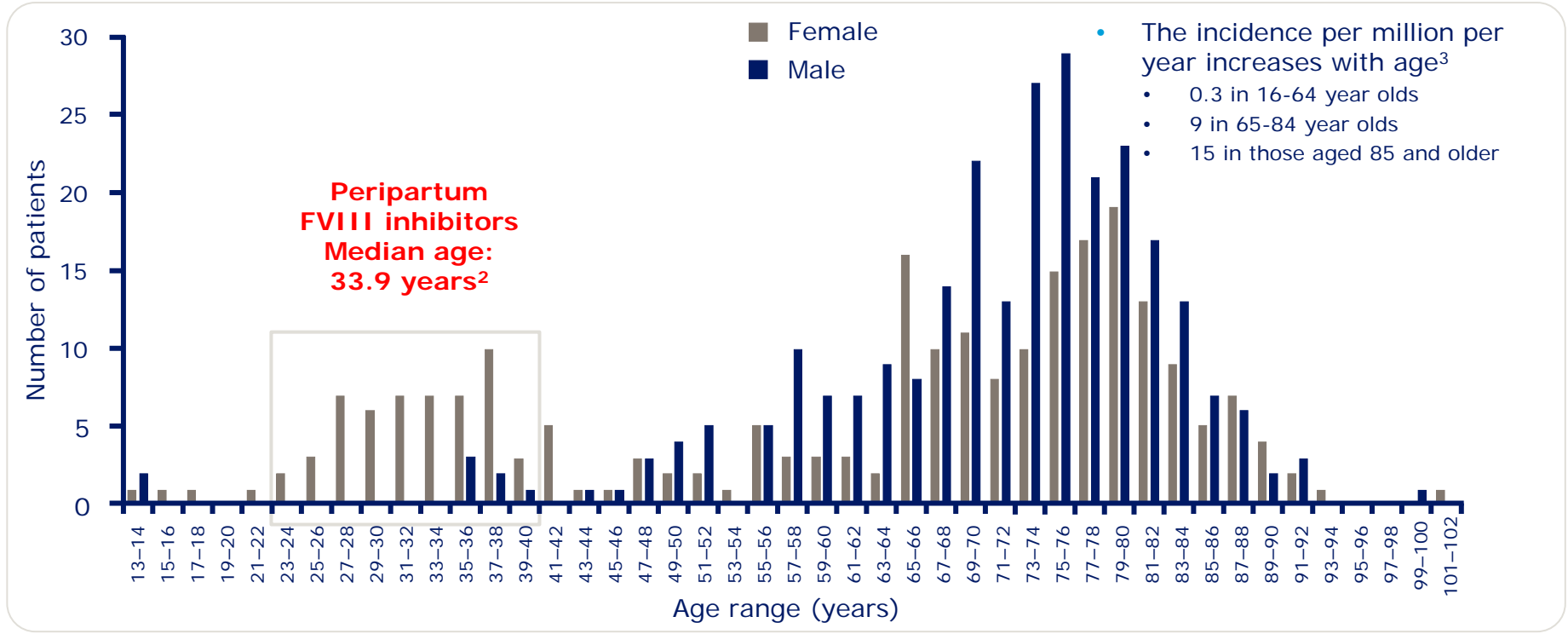
6. Lottenberg R, et al. Arch Intern Med 1987;147:1077-81.

7. Bitting RL, et al. Blood Coagul Fibrinolysis 2009; 20:517-23.

8. Baudo F, et al. Blood 2012;120:39-46.

9. Baudo F, de Cataldo F. In: Blood Disorders in the Elderly; 2007:389-407.

Gender and age distribution



1. Knoebel P, et al. J Thromb Haemost 2012;10:622-31.
 2. Tengborn L, et al. BJOG 2012;119:1529-37.
 3. Collins PW, et al. Blood 2007;109:1870-7.

Clinical symptoms

- Bruising (ecchymoses and haematomata), bleeding into soft tissues¹
- Bleeding into muscles and mucosae^{1,2}
 - Melena
 - Haematuria
 - Metrorrhagia
 - Epistaxis
 - Gingivorrhagia
- Gastrointestinal, intracranial, retropharyngeal, retroperitoneal bleeds^{1,2}
- Surgical bleeding^{1,3}
 - ~25% of cases



Clinical manifestations

- Bleeding may be severe and potentially life-threatening in >70% of cases¹
 - In the EACH2 registry 70.3% of the occurring bleeding episodes were rated as severe²
 - In another recent study, 97% of AH patients experienced life-threatening bleeding³
- 30% of cases present as mild bleeding and do not require haemostatic treatment^{4,5}
- Most deaths within the first week occur due to gastrointestinal and lung bleeding, later deaths happen from intracranial and retroperitoneal haemorrhages^{4,6}
- Fatal bleeding can occur up to 5 months after the first presentation if the autoantibodies are not eliminated^{4,6,7}

1. Toschi V, Baudo F. Intern Emerg Med 2010; 5:325-33.
2. Knoebl P, et al. J Thromb Haemost 2012; 10:622-31.
3. Zeitler H, et al. Haemophilia 2010; 16:95-101.
4. Collins PW, et al. Blood 2007; 109:1870-7.
5. Baudo F, et al. Blood 2012; 120:39-46.
6. Huth-Kuhne A, et al. Haematologica 2009; 94:566-75.
7. Lottenberg R, et al. Arch Intern Med 1987; 147:1077-81.

Distribution of AH bleeding symptoms

Type of bleeding	Collins et al. 2007 %
Subcutaneous / skin	81
Muscle	45
Muscle bleeding associated with compartment syndrome	
Subcutaneous only	24
Gastrointestinal / intra-abdominal	23
Genital urinary	9
Retroperitoneal / thoracic	9
Retropharyngeal	
Other	9
Post-operative	
Joint	7
None	4
Intracranial hemorrhage	3
Fatal	9
No haemostatic treatment required	34

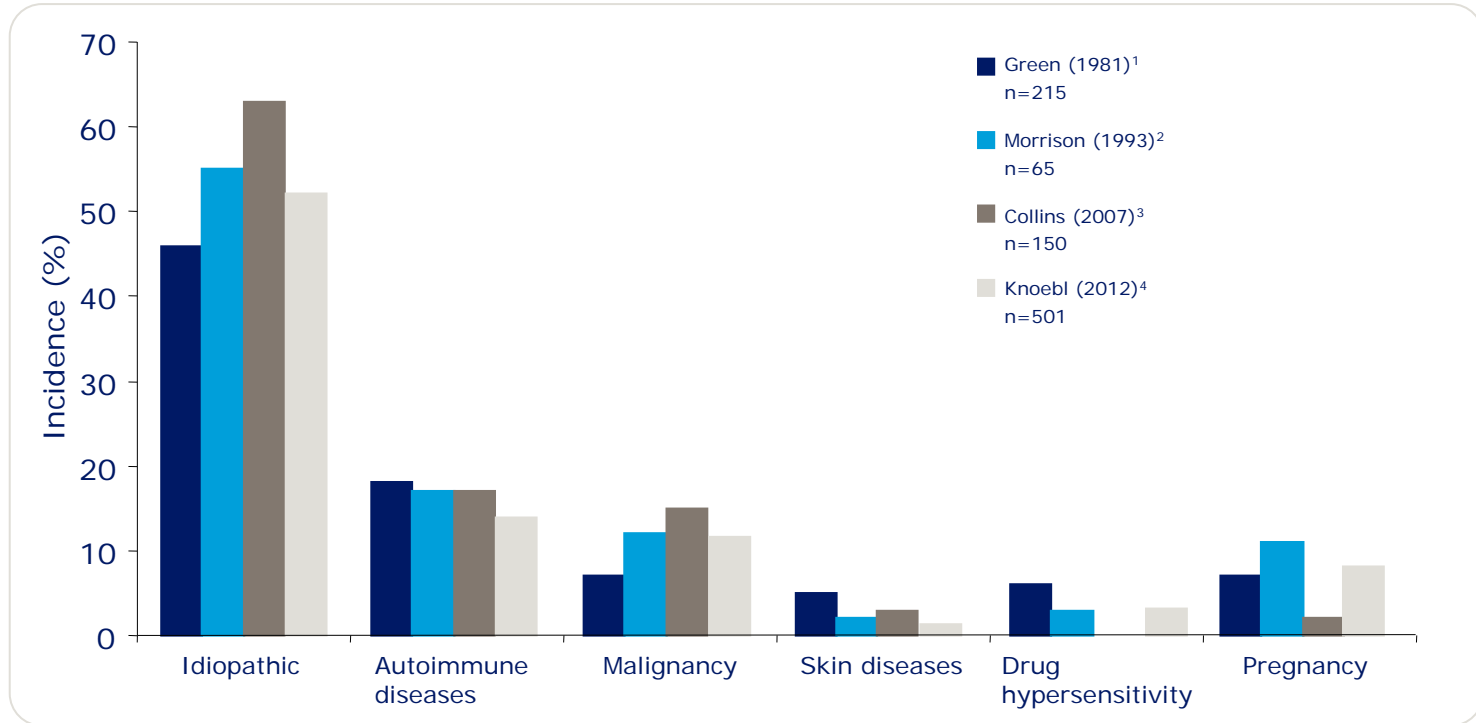
**Many patients presented with more than one type of bleeding.
In 8% of patients bleeding was the primary cause of death.¹**

1. Collins PW, et al. Blood 2007; 109: 1870-7.

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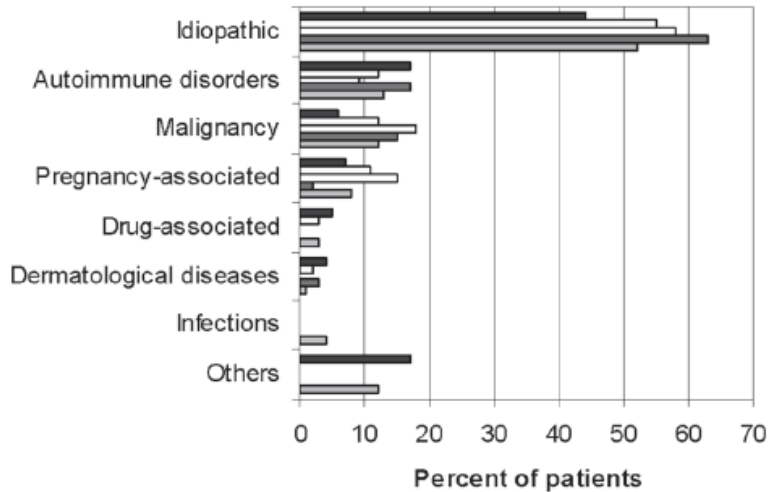
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Associated conditions: Incidence



1. Green D, Lechner K. Thromb Haemost 1981;45:200-3.
2. Morrison AE et al. Blood 1993;81:1513-20.
3. Collins PW et al. Blood 2007;109:1870-7.
4. Knoebl P, et al. J Thromb Haemost 2012;10:622-31.

Associated diseases



Autoimmune disorders

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Multiple sclerosis
- Temporal arteritis
- Sjögren syndrome
- Autoimmune hemolytic anemia
- Goodpasture syndrome
- Myasthenia gravis
- Graves disease
- Autoimmune hypothyroidism

Hematologic malignancies:

- Chronic lymphocytic leukemia
- Non-Hodgkin lymphoma
- Multiple myeloma
- Waldenstrom macroglobulinemia
- Myelodysplastic syndrome
- Myelofibrosis
- Erythroleukemia

Drug reactions:

- Penicillin and its derivatives
- Sulfamides
- Phenytoin
- Chloramphenicol
- Methyldopa
- Clopidogrel
- Interferon alfa
- Fludarabine
- Bacille Calmette-Guérin (BCG) vaccination

Malignancies-solid tumors

- Prostate
- Lung
- Colon
- Pancreas
- stomach, bile duct, head and neck, cervix, breast, melanoma, kidney

Associated conditions: Pregnancy

- Often appear after first pregnancy^{1,2}
 - EACH2: 74% primigravidas³
- Generally occur 2 to 5 months after delivery, but may occur up to 1 year post-partum^{4,5}
 - EACH2: Median time of 89 days from delivery to diagnosis of AH³
- Rarely become symptomatic during pregnancy⁴
- May disappear spontaneously after ~30 days in 76% of cases¹
- Inhibitors that do not persist rarely reappear with next pregnancy¹

1. Toschi V, Baudo F. Intern Emerg Med 2010; 5:325-33.

2. Hauser I, et al. Thromb Haemost 1995; 73:1-5.

3. Tengborn L, et al. BJOG 2012; 119: 1529-37.

4. Hay CR. Baillieres Clin Haematol 1998; 11:287-303.

5.

6.

.

Lottenberg R, et al. Arch Intern Med 1987; 147:1077-81.
Baudo F, de Cataldo F. BJOG 2003; 110:311-4.

Associated conditions: Malignancy

- Association of AH with malignancy in men is 3-fold greater than in women
 - No relation to tumour type
- AH is more common in solid tumours than in lymphoproliferative diseases
- Occasionally disappearance of the inhibitor is associated with a response to therapy

Mortality rate in AH grouped by associated conditions

Associated condition	Number of cases	Number of deaths	Mortality rate (%)
Idiopathic	198	37	19
Malignancy	59	26	44
Autoimmune	38	10	26
Peri-partum	26	1	4
Unknown	39	1	3
Overall*	359	75	21

*One patient with both autoimmune disease and malignancy.

AHA- Mortality and Complications

European Acquired Hemophilia (EACH2) Registry

No. of patients [<i>n</i> (%)]	331 (66.1%)
Observation time [median, IQR; (days)]	258 (74–685)
Survival	
Alive at final follow-up	191 (57.7%)
Death reported	87 (26.3%)
Unknown survival state	47 (14.2%)
Remission	
Complete remission [<i>n</i> /total (%)]	237 (71.6%)
Stable remission on IST [<i>n</i> /total (%)]	39 (11.8%)
No remission and off IST	33 (10.0%)
Unknown remission state	22 (6.7%)
Cause of death [<i>n</i> (%)]	
Fatal bleeding	15 (17.2% of deaths) (4.5% of group)
Hemostatic therapy	0 (0%)
IST complications	14 (16.1% of deaths) (4.2% of group) (4.8% of patients receiving IST)
Underlying disease	40 (46% of deaths) (12.1% of group) (25.2% of patients with underlying disease)
Unknown/other	33 (37.9% of deaths) (10.0% of group)

Adverse events [<i>n</i> (%)]	
Total	136 (41.1%)
Stroke	1 (0.3%)
Cardiac disorders (all)	10 (3.0%)
Myocardial infarction	7 (2.1%)
Venous thromboembolism	5 (1.5%)
Infection/sepsis	53 (16.0%)
Neutropenia	29 (8.8%)
Thrombocytopenia	4 (1.2%)
Decompensated diabetes	24 (7.3%)
Psychiatric disorders	10 (3.0%)

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Algorithm: prolonged aPTT

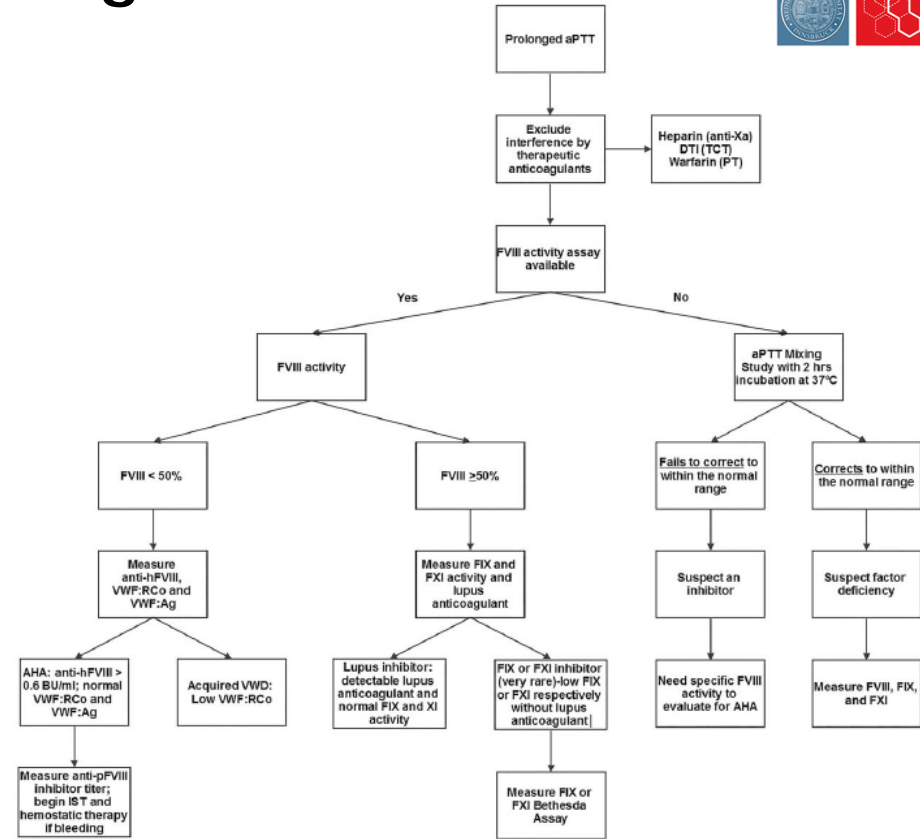
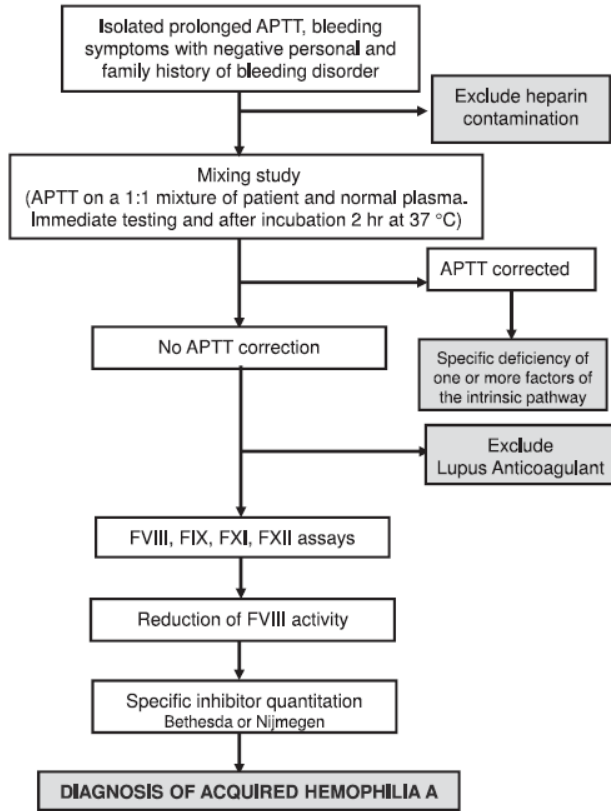
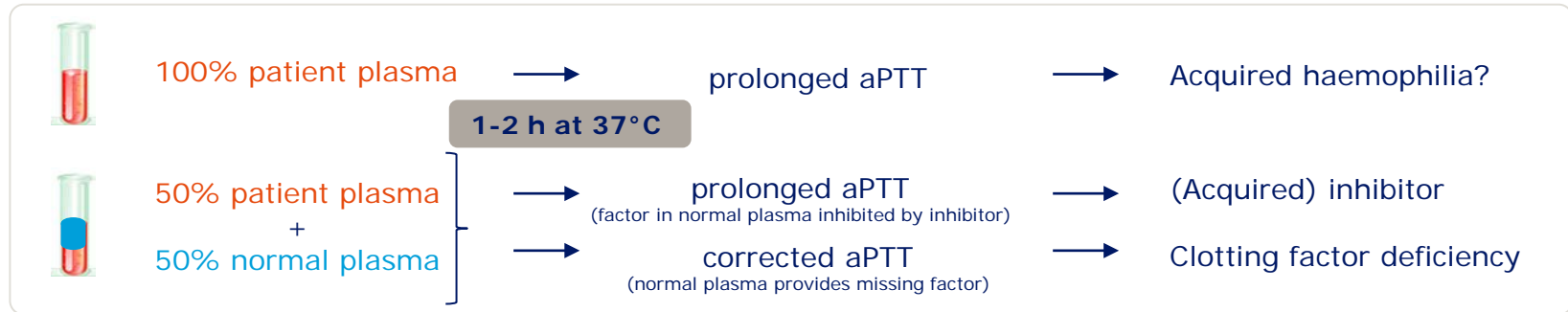


FIGURE 1 Laboratory diagnosis of AHA. AHA = acquired hemophilia A; anti-h-FVIII = anti-human factor VIII inhibitor; anti-pFVIII = anti-porcine factor VIII; aPTT = activated partial thromboplastin time; DTI = direct thrombin inhibitor; FIX = factor IX; FVIII = factor VIII; FXI = factor XI; IST = immunosuppressive therapy; PT = prothrombin time; TCT = thrombin clotting time; VWD = Von Willebrand disease; VWF:Ag = von Willebrand factor-antigen; VWF:RCo = von Willebrand factor-Ristocetin co-factor

Laboratory diagnosis (1)

- **Activated partial thromboplastin time (aPTT)¹⁻⁵**
 - Irrespective of the presence or absence of bleeding, an isolated prolonged aPTT outside the normal range should be investigated further
- **Mixing tests³⁻⁶**
 - To differentiate between an inhibitor and a factor deficiency



1. Hay CR. Baillieres Clin Haematol 1998;11:287-303.
 2. Lossing TS, et al. Blood 1977;49:793-7.
 3. Huth-Kuhne A, et al. Haematologica 2009;94:566-75.

4. Collins P, et al. BMC Res Notes 2010;3:161.
 5. Wagenman BL, et al. Clin Lab Med 2009;29:229-52.
 6. Kasper CK. Blood Coagul Fibrinolysis 1991;2:7-10.

Laboratory diagnosis (2)

- **Bethesda assay**^{1,2}
 - To quantify autoantibody titre
 - Acquired FVIII inhibitors display complex and non-linear type 2 kinetics, therefore the Bethesda assay may not be able to estimate the true potency of the autoantibody³

	Autoantibodies	Alloantibodies
Bleeding manifestations	Soft tissue haematomas, bruising, muscle bleeds, GI and urinogenital bleeding	Haemarthroses or muscle bleeds
Sites	May have multiple sites	Usually single site – “target” joint
Inhibitor kinetics	Type 2	Type 1
Residual FVIII activity	May have some residual FVIII activity	Generally <u>no</u> detectable residual FVIII activity

1. Kasper CK, et al. Thromb Diath Haemorrh 1975;34:612.
 2. Verbruggen B, et al. Semin Thromb Hemost 2009;35:752-9.
 3. Huth-Kühne A, et al. Haematologica 2009;94:566-75.
 4. Galli M, et al. Blood 2003;101:1827-32.

Laboratory diagnosis (2)

- **Clotting factor measurement: FVIII:C**
- **Lupus anticoagulant**
 - May be associated with a prolonged aPTT, low intrinsic factor levels and a positive Bethesda assay²
 - Specific tests should be undertaken to distinguish between lupus anticoagulant and acquired FVIII inhibitors
 - The clinical picture in patients with a lupus anticoagulant usually is different
 - Thrombosis⁴ rather than haemorrhages

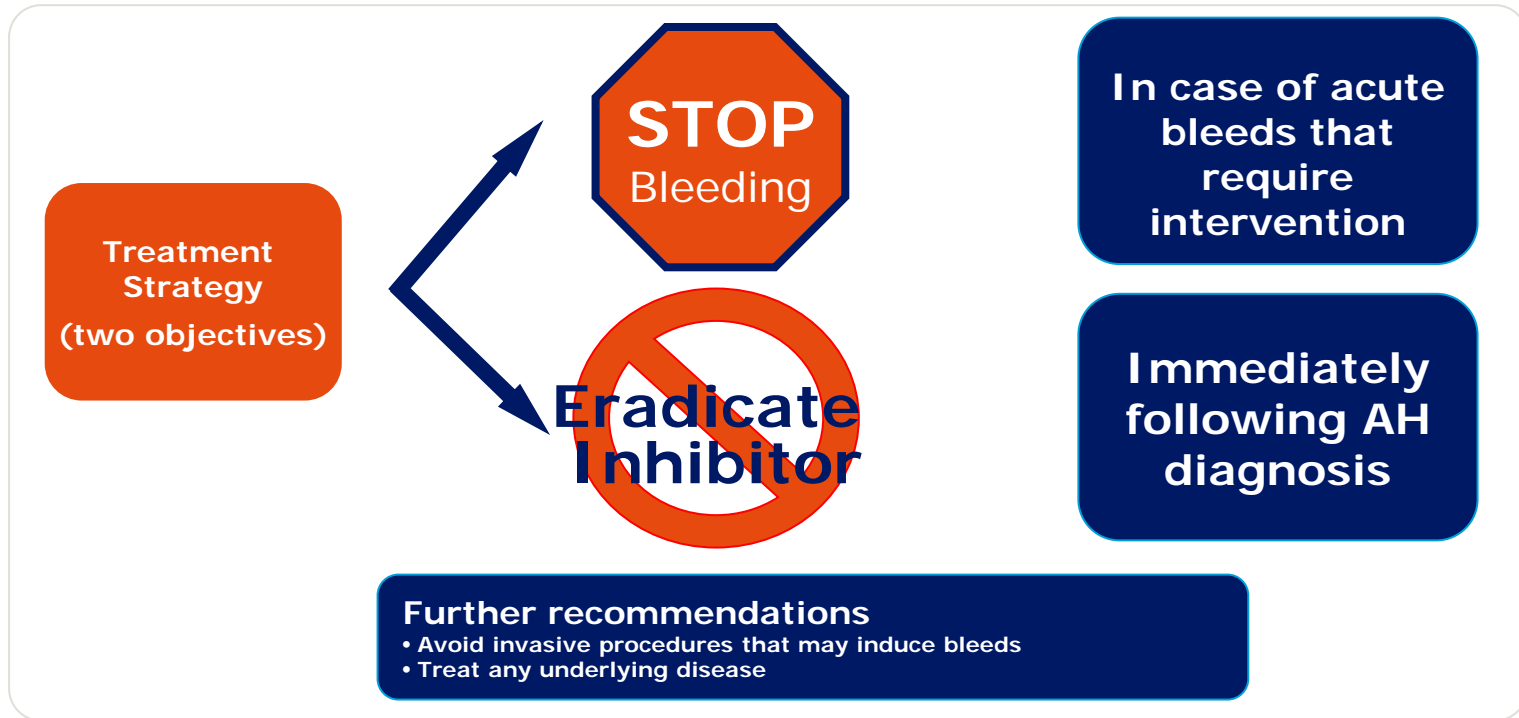
Limitations of laboratory diagnosis

- Autoantibody titre and residual FVIII levels correlate poorly with clinical severity¹⁻⁴
- Non-linear relationship between inhibitor concentration and residual FVIII:C activity¹⁻³
- Autoantibody titre and FVIII levels do not predict bleeding risk^{2,3,5}
- Treatment decisions should not be based upon autoantibody titre or FVIII levels^{2,3}

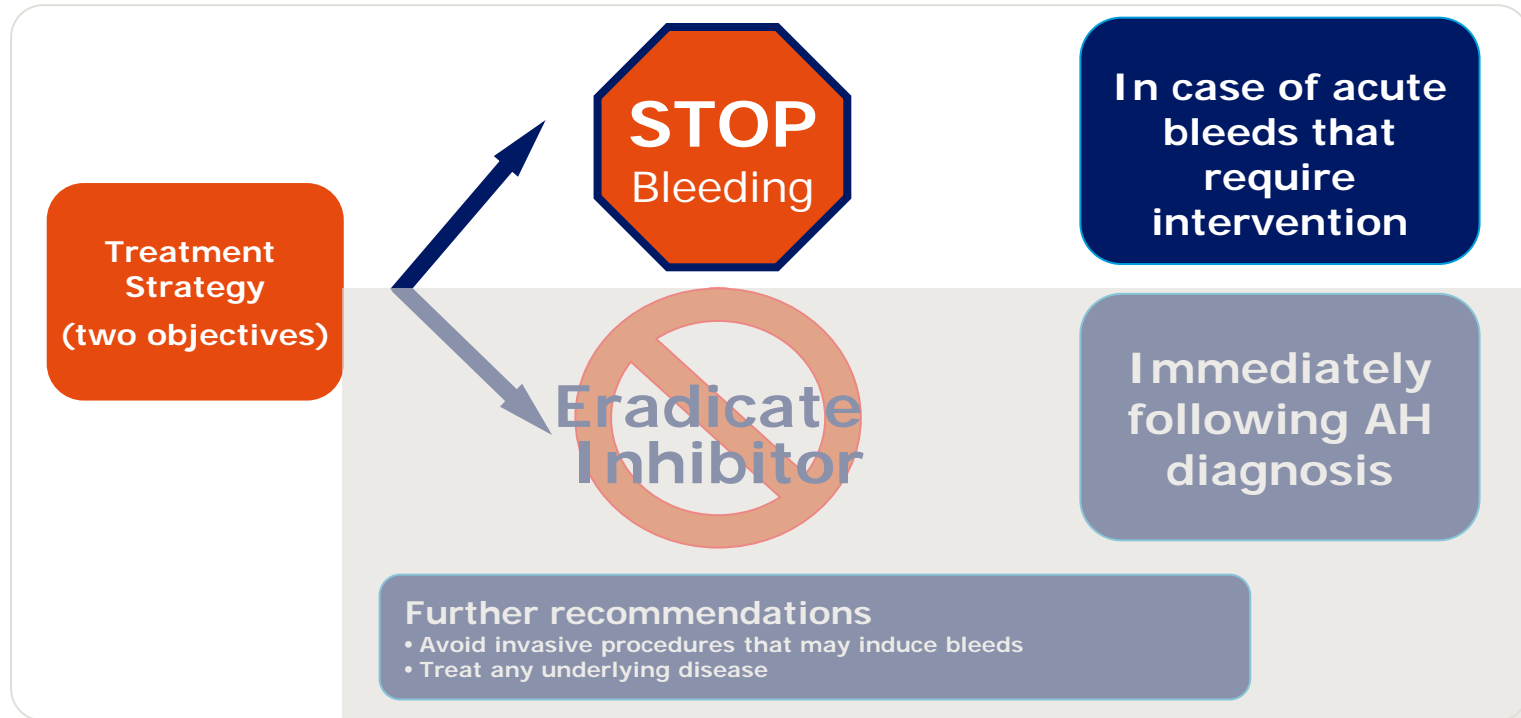
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Clinical management of AH



Clinical management of AH



1. Goal: Stop Bleeding

agent		dosing	note
bypassing agents	recombinant human factor VIIa (eptacog alfa [activated], NovoSeven™)	90 µg/kg every 2–3 h	prolong dosing interval to 4, 6, 8, or 12 h after achieving haemostasis
	activated prothrombin complex concentrate (human plasma protein with FVIII:C inhibitor bypassing activity, FEIBA™)	50–100 U/kg every 6 to 12 h	maximum single dose 100 U/kg, maximum daily dose 200 U/kg
factor VIII concentrates	various brands	required dose difficult to predict, start with 50 IU/kg every 6 to 8 h	limited efficacy, not recommended for severe bleeds. Close monitoring of peak and trough levels required
	porcine recombinant FVIII:C	in development (29, 30)	licensed by FDA, but not yet by EMA
other agents	desmopressin	0.3 µg/kg every 12–24 h	very limited efficacy, usually only for mild bleeds and low inhibitor titres
	tranexamic acid	0.5–1.0 g every 6–12 h	adjunct treatment. Use caution when combining with bypassing agents.

Human FVIII

- Treatment option used for acute bleeding only when:
 - Inhibitor titre is very low (<5 BU/mL)¹⁻⁵
 - Bleeding manifestations or potential therefore are minor^{1,4}
 - Bypassing agent is not available^{1,3-5}
- High doses must be administered to overcome the inhibitor before FVIII levels can be increased¹⁻⁴
- Variable and unpredictable FVIII activity levels in AH^{1,2,5}
 - Close monitoring of FVIII levels necessary^{2,3}

1. Huth-Kuhne A, et al. Haematologica 2009;94:566-75.
2. Collins PW. Am Soc Hematol Educ Program 2012;2012:369-74.
3. Coppola A, et al. Semin Thromb Hemost 2012;38:433-46.

4. Sborov DW, Rodgers GM. Br J Haematol 2013;161:157-65.
5. Webert KE. Semin Thromb Hemost 2012;38:735-41.
6. Baudo F, et al. Blood 2012;120:39-46.

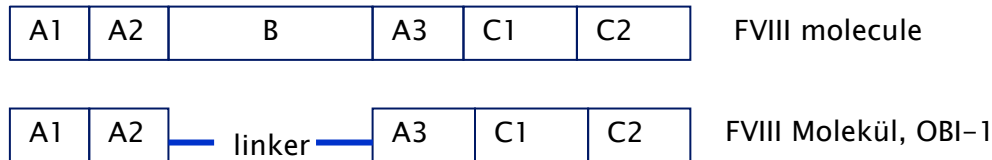
Desmopressin (DDAVP; 1-deamino-8-D-arginine vasopressin)

- DDAVP was reported to be for:¹⁻⁴
 - Minor bleeding episodes
 - Very low titre inhibitors
- Inability to predict
 - Efficacy¹
 - Whether tachyphylaxis will occur following subsequent dosing¹
- Water retention, with consecutive hyponatraemia and convulsions may occur following injections of DDAVP¹

1. Huth-Kuhne A, et al. Haematologica 2009;94:566-75.
2. Collins PW. Am Soc Hematol Educ Program 2012;2012:369-74.
3. Sborov DW, Rodgers GM. Br J Haematol 2013;161:157-65.
4. Webert KE. Semin Thromb Hemost 2012;38:735-41.

Porcine FVIII

- Human FVIII autoantibodies often have a low cross-reactivity with porcine FVIII¹
 - Inhibitor titre to porcine FVIII in AH is usually 5-10% of that of the human titre²
- Plasma-derived porcine FVIII concentrate was **formerly** available and effective in the treatment of AH¹⁻⁴
- A recombinant porcine B-domain-deleted FVIII molecule was developed⁵

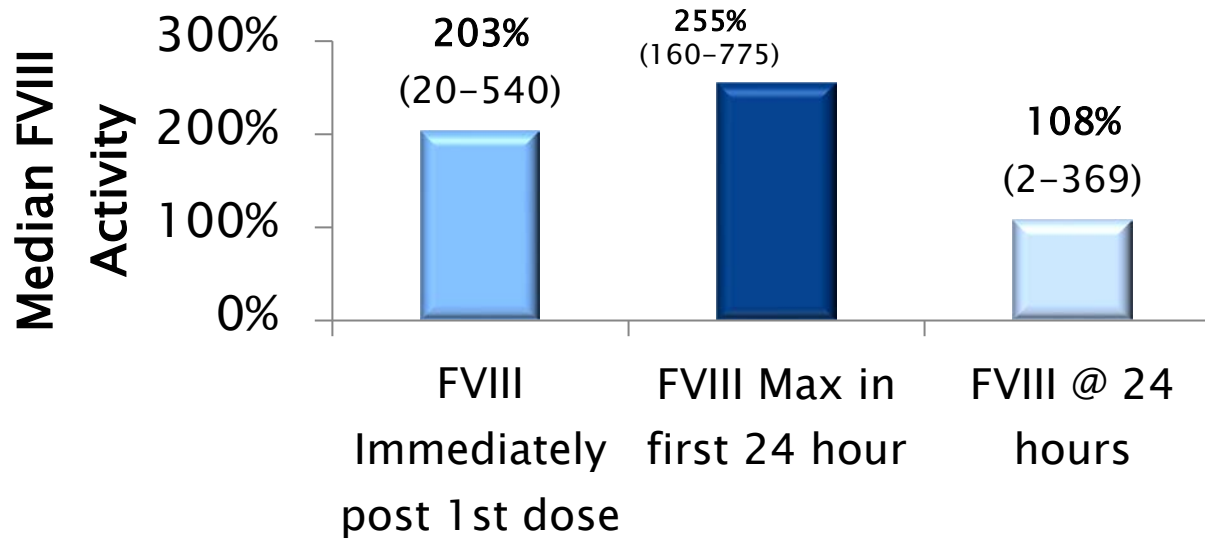


EFFICACY AND SAFETY OF OBI-1, AN ANTIHAEMOPHILIC FACTOR VIII (RECOMBINANT), PORCINE SEQUENCE, IN SUBJECTS WITH ACQUIRED HAEMOPHILIA A

Rebecca Kruse-Jarres, Jean St-Louis, Anne Greist, Amy Shapiro, Hedy Smith, Pratima Chowdary, Anja Drebes, Edward Gomperts, Christelle Bourgeois, Min Mo, Aaron Novack, Heinrich Farin, and Bruce Ewenstein

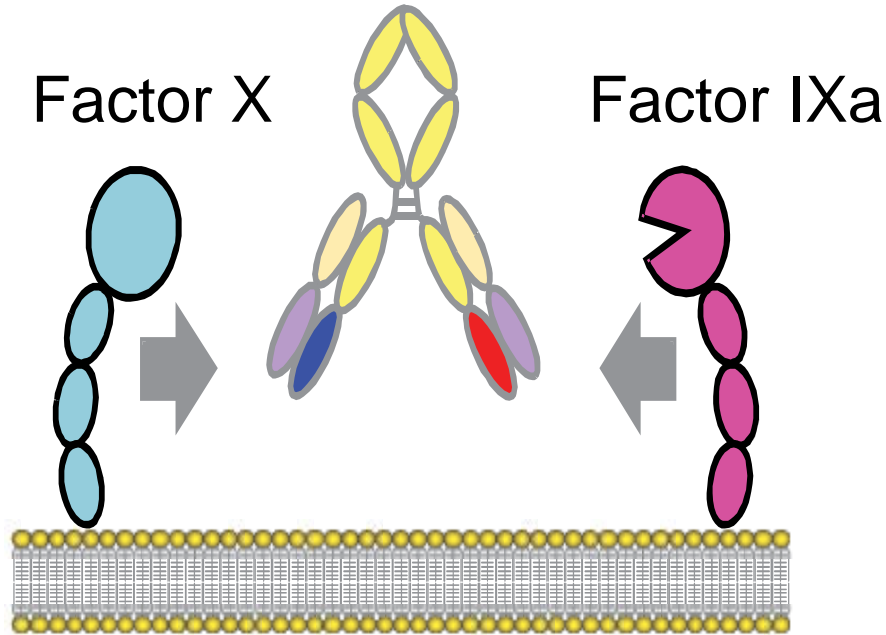
Haemophilia (2015), 21, 162-170

FVIII levels during the first 24h of treatment



- High FVIII Activity → no thromboembolic events

Humanized Bispecific Antibody Mimicking FVIIIa



Approved in the US and Europe for the treatment of patients of **congenital** Hemophilia A with or without inhibitor

Kitazawa T, et al. *Nat Med* 2012;18:1570–4.

Sampei Z, et al. *PLoS One* 2013;8:e57479.

Uchida N, et al. *Blood* 2016;127:1633–41.

Shima S, et al. *N Engl J Med* 2016;374:2044–53.

Bypassing Therapy

Activated prothrombin complex concentrate (aPCC)	50–100 U/kg every 8–12 h Do not exceed 200 U/kg/d	ADVANTAGE Proven efficacy for clinical bleeding DISADVANTAGE No laboratory to monitor underdosing or overdosing Potential arterial or venous thrombotic risk CONSIDER First LINE Where drug readily available If underlying high titer rpFVIII inhibitor (>10 BU) FVIII activity measurement not readily available Non-life-threatening/limb-threatening bleeding
Recombinant FVII activated (rFVIIa)	70–90 mcg/kg every 2–3 h until hemostasis achieved, then prolong dosing interval	ADVANTAGE Proven efficacy for clinical bleeding DISADVANTAGE No laboratory to monitor underdosing or overdosing Short half-life (2 h) Potential arterial or venous thrombotic risk CONSIDER First LINE Where drug readily available If underlying high titer rpFVIII inhibitor (>10 BU) FVIII activity measurement not readily available Non-life-threatening/limb-threatening bleeding

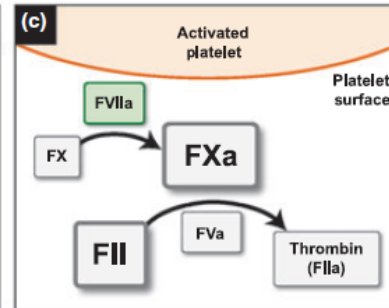
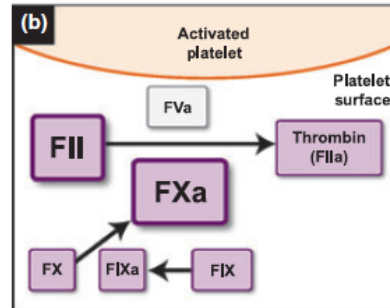
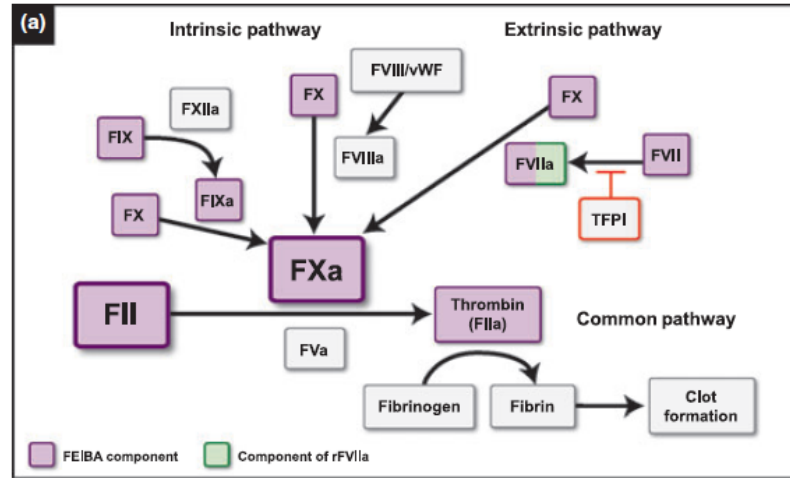
Comments

Patients should also be started on IST and FVIII level monitors regularly.
 Head to head comparison of these hemostatic agents have not been done and the first line agent should be chosen based on availability, prior efficacy in the patient and economic considerations.
 Hemostatic efficacy is largely based on clinical assessment and changing to an alternate hemostatic agent should be considered after 12–24 h.
 Once hemostasis is achieved, the dosing frequency of any hemostatic agent should be decreased as tolerated to prevent the risk for thrombosis.
 Hemostatic agents should not be given in a patient with rising factor levels and no active or increased risk for bleeding.
 In hospitalized patients consider thromboembolism prophylaxis when FVIII levels exceed 50 IU/dL.

AHA: acquired hemophilia A; FVIII: factor VIII; IST: immunosuppressive therapy; rpFVIII: recombinant porcine factor VIII.
²rpFVIII dosing recommendations differ from package inset and are based on the postmarketing clinical experience with this medication.

Mechanism of Action

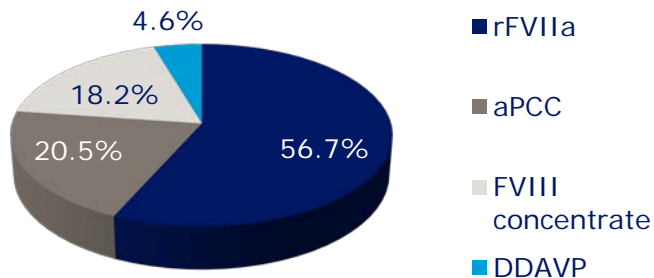
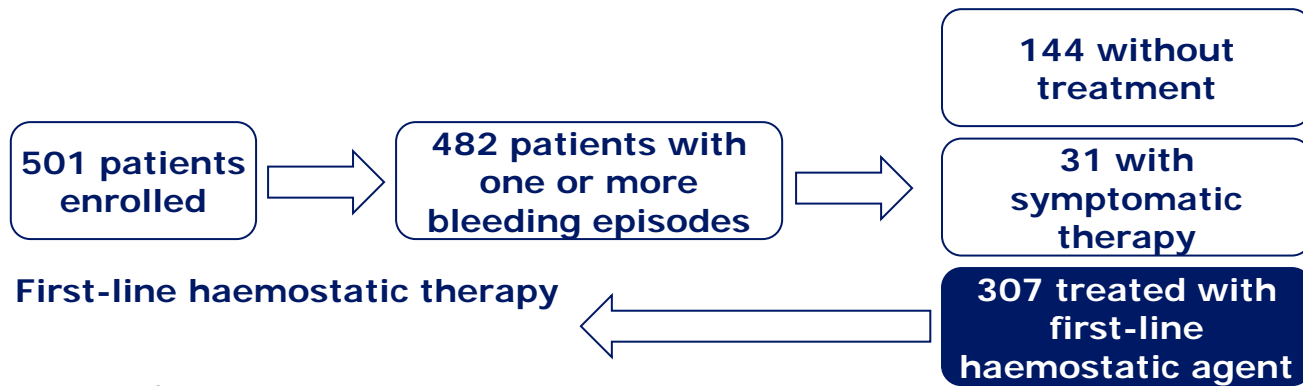
aFVIIa (Novoseven) vs. aPCC (FEIBA)



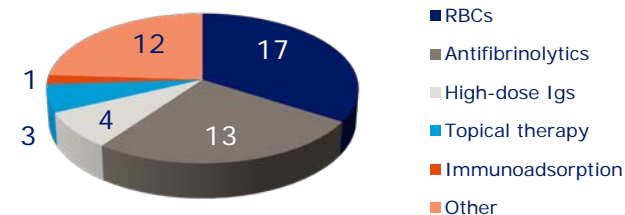
EACH2 – European Acquired Haemophilia Registry

- Prospective, multi-centre, large-scale, pan-European registry
- **501 AH patients** from 117 centres and 13 European countries
- Enrolment period: **January 2003 – December 2008**
- **No treatment protocol** – patients managed according to local clinical practice
- Reporting of data using a web-based electronic case report form

EACH2 – Europ. Acquired Haemophilia Registry



Ancillary therapy



rFVIIa, recombinant activated factor VII; aPCC, activated prothrombin complex concentrate; DDAVP, 1-desamino-8-D-arginine-vasopressin; RBCs, red blood cells; Igs, immunoglobulins

EACH2 – Europ. Acquired Haemophilia Registry

Haemostatic agent	First-line bleeding control	
	n	%
<i>Unmatched samples</i>		
Bypassing agent	219	91.8
rFVIIa	159	91.2
aPCC	60	93.3
Replacement therapy	69	69.6
FVIII	55	70.1
DDAVP	14	64.3
<i>PS-matched samples</i>		
Bypassing agent	60	93.3
Replacement therapy	60	68.3
rFVIIa	57	93.0
aPCC	57	93.0

PS, propensity score; rFVIIa, recombinant activated factor VII; aPCC, activated prothrombin complex concentrate; FVIII, coagulation factor VIII; DDAVP, 1-desamino-8-D-arginine-vasopressin.

Acute bleeding management^{1,2}

- First-line treatment
 - rFVIIa
 - aPCC
- Alternative treatment, if first-line treatment fails
 - Switch to alternative agent
 - Immunoabsorption and/or plasmapheresis
- Alternative treatment, if bypassing agents are not available
 - Human FVIII
 - Desmopressin (DDAVP)

Recombinant activated factor VII (rFVIIa)

- 81-100% efficacy as first-line treatment¹⁻⁶
- 79-92% efficacy as salvage therapy¹⁻⁴
- Efficacy independent of inhibitor titre^{5,7,8}
- Response to treatment effective or partially effective in
 - 90% of non-surgical bleeding¹
 - 86% of surgical cases¹
- Treatment regimen^{7,8}
 - Bolus injection of 90 mcg/kg every 2-3 h until haemostasis is achieved

1. Sumner MJ, et al. Haemophilia 2007; 13:451-61.
2. Hay CR, et al. Thromb Haemost 1997; 78:1463-7.
3. Baudo F, et al. Haematologica 2004; 89:759-61.
4. Franchini M, et al. Clin Chim Acta 2008; 395:14-8.

5. Baudo F, et al. Blood 2012; 120:39-46.
6. Borg JY, et al. Haemophilia 2013; 19:564-70.
7. Huth-Kuhne A, et al. Haematologica 2009; 94:566-75.
8. Collins P, et al. BMC Res Notes 2010; 3:161.

aPCC

- Treatment regimen¹
 - Bolus injection of 50-100 IU/kg every 8-12 h to a maximum of 200 IU/kg/day
- Anti-fibrinolytic agents should be avoided for 12 h after administration of pd-aPCC^{1,2}
- Anamnestic response with increase in FVIII inhibitor titre reported in both congenital and acquired haemophilia^{1,4,5}
 - EACH2: An anamnestic response was reported for 6 of 63 patients (9.5%) treated with aPCC⁶

Thromboembolic risk and Bypassing agents

TABLE 3 Thromboembolic risk in patients receiving bypassing agents

Study	Treatment	N	Thromboembolic events
Sumner et al ⁴⁰	Recombinant factor VIIa	139	6 events in 4 patients (2.9%)
Ingerslev et al ⁴¹	Combined or alternating bypassing agents	9	55%
Baudo et al ¹⁶	Recombinant factor VIIa	174	2.9%
	aPCC	63	4.8%
	Factor VIII/desmopressin	70	0%
Seita et al ⁴²	Recombinant factor VIIa	132	2.3%
Borg et al ⁶	Recombinant factor VIIa	28	0%
	aPCC	6	0%
Tiede et al ⁸	Recombinant factor VIIa	63	5%
	Recombinant factor VIIa + tranexamic acid	21	10%

aPCC: activated prothrombin complex concentrate; factor VIIa: activated factor VII.

Dosing considerations

- Treatment decisions should not be based upon autoantibody titre or FVIII levels^{1,2}
- Further considerations
 - Many AH patients will have a severe concomitant disorder, e.g. malignancy which needs to be taken into account when managing AH
 - The AH population is generally older and the following risks are frequently present¹:
 - Smoking
 - Hypertension
 - Previous cardiovascular events
 - Type 2 diabetes
 - High body mass index
 - Caution is suggested in elderly patients with underlying cardiovascular disease or risk factors for thromboembolic complications^{1,4}

1. Huth-Kuhne A, et al. Haematologica 2009;94:566-75.
2. Collins P, et al. BMC Res Notes 2010;3:161.
3. Sumner MJ, et al. Haemophilia 2007;13:451-61.
4. Zeitler H, et al. Haemophilia 2010;16:95-101.

Assessment of response to haemostatic therapy

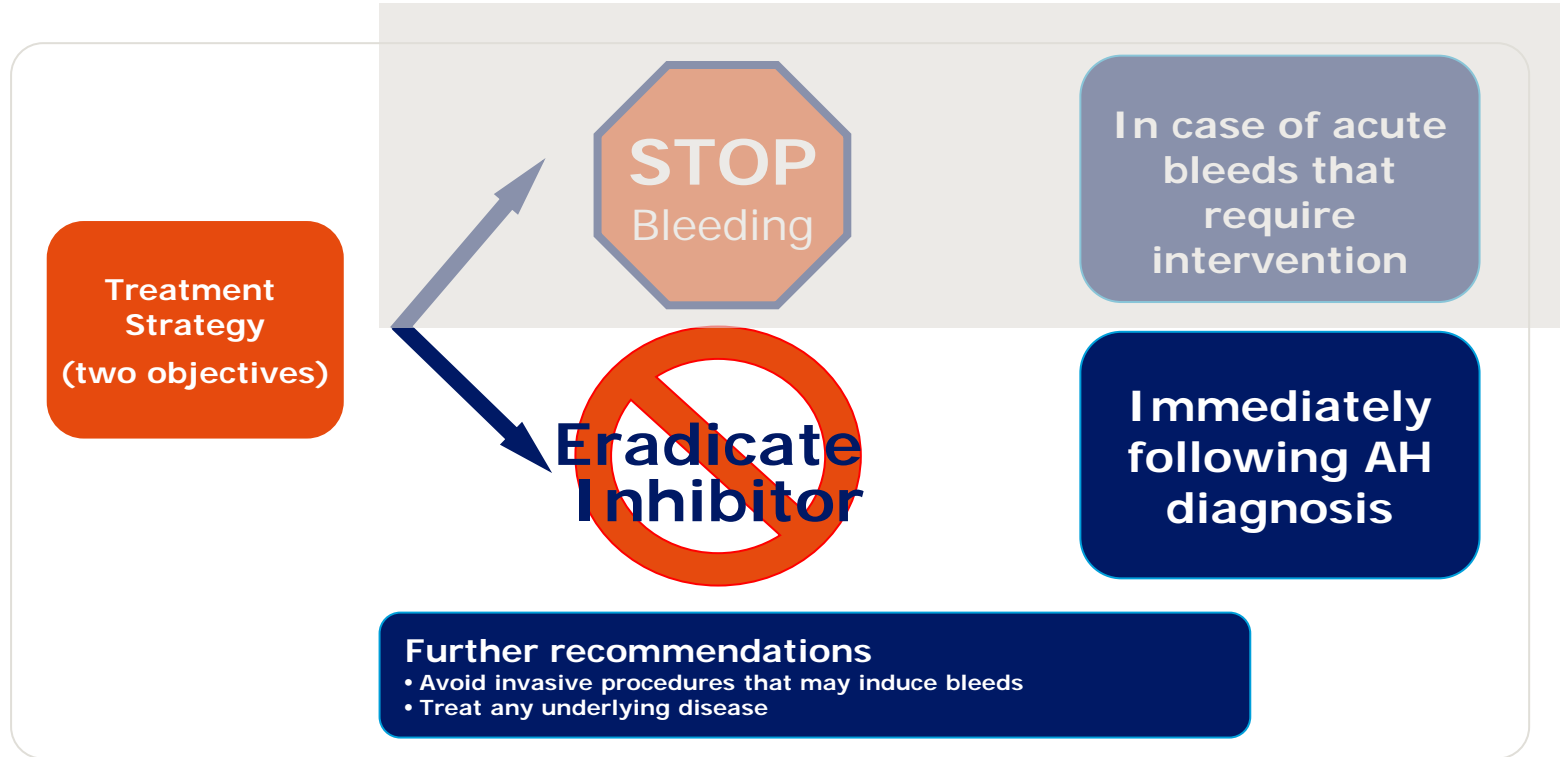
- Efficacy of treatment must be assessed clinically in terms of¹
 - Bleeding tendency
 - Size of haematoma
 - Stability of Hb/Hct
 - Pain caused by haematoma
- There are no laboratory tests that have been demonstrated to be useful for monitoring the efficacy of bypassing agents in AH²
- Treatment failure can be defined by the following criteria¹:
 - Evidence of continued bleeding after 48 hours of appropriate treatment (24 h if site critical)
 - Bleeding at a new site while on anti-haemorrhagic treatment
 - Increasing pain associated with haematoma despite treatment

1. Huth-Kuhne A, et al. Haematologica 2009;94:566-75.
2. Collins P, et al. BMC Res Notes 2010;3:161.

Management during invasive procedures^{1,2}

- Invasive procedures and surgery should be delayed until inhibitor eradication unless essential²
- Prophylactic use of bypassing agents prior to minor or major invasive procedures is recommended^{1,2}
- Acute reduction or removal of the inhibitor to facilitate haemostasis using plasmapheresis or immunoadsorption may be applied under special circumstances²

Clinical management of AH



Inhibitor eradication strategy

TABLE 4 Options for first-line immunosuppression in AHA

Recommended first-line immunosuppression	Recommended dose	Comment
Corticosteroids alone	Prednisone 1 mg/kg PO daily (alternative dexamethasone 40 mg PO daily \times 4–7 d) ²	Unlikely to be effective in ≤ 3 wk in patients with FVIII < 1 IU/dL or inhibitor > 20 BU/mL at presentation Monitor for adverse events (elevated glucose, infection, psychiatric disorders)
Corticosteroid and cyclophosphamide	Corticosteroid same as above; cyclophosphamide 1–2 mg/kg PO daily (alternative ~ 5 mg/kg IV q 3–4 wk) ²	May have faster response rate than steroids alone, but higher adverse event profile Associated with the highest CR rate Monitor for marrow suppression (WBC, platelets) and infection
Corticosteroids and rituximab	Corticosteroid same as above; rituximab 375 mg/m ² IV weekly \times 4 (alternative 100 mg weekly \times 4) ²	Rituximab is not recommended as initial monotherapy unless other IST is contraindicated
Comments		

Median time to response (FVIII activity level restored to >50 IU/dL) is 5 wk. Patients with FVIII activity level < 1 IU/dL at baseline require significantly longer times to remission compared to patients with FVIII activity level ≥ 1 IU/dL and may require combination IST rather than corticosteroids alone.

FVIII activity and inhibitor levels should be monitored at least weekly.

Apply individualized therapy according to the patient's general condition, underlying and concomitant diseases, and prognostic factors (ie, FVIII < 1 IU/dL, inhibitor titer > 20 BU/mL, presence of anti-FVIII-IgA antibodies, etc), when available.

AHA: acquired hemophilia A; CR: complete remission; IST: immunosuppressive therapy; IV: intravenous; PO: orally; WBC: white blood cell.

²Few data available in AHA, but reports available in other autoimmune disorders.

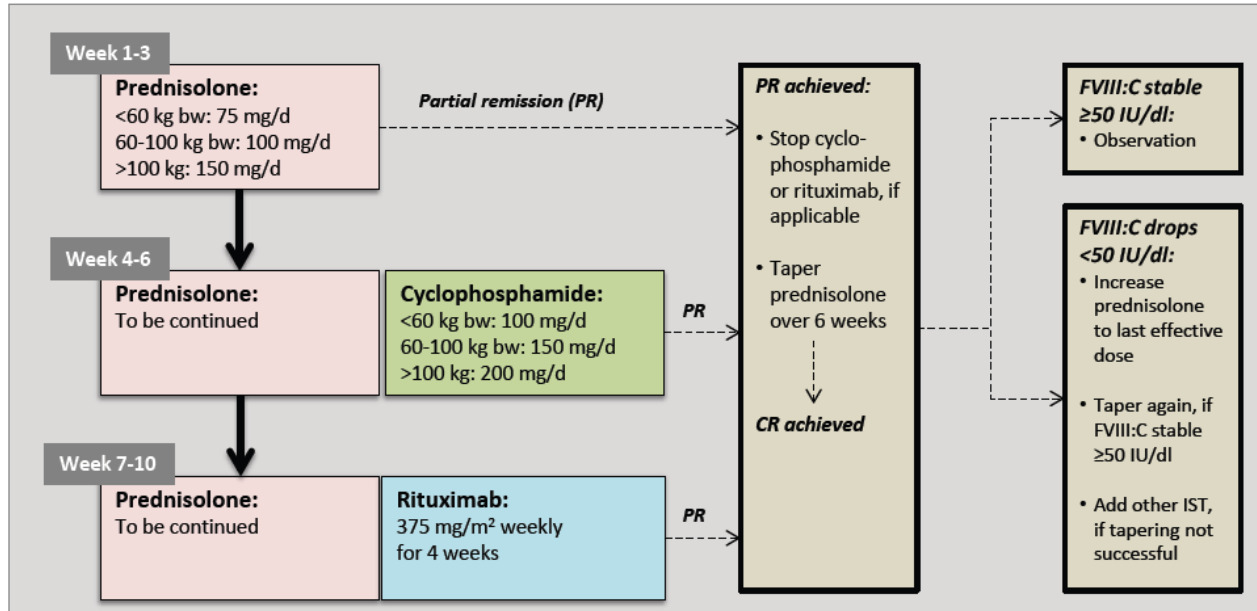
Inhibitor eradication strategy

- A survey of current practice in Germany, Austria and Switzerland showed a high diversity of first- and second-line immunosuppressive treatments for AH¹
- A high diversity of immunosuppressive treatments was also reported in the EACH2 registry²

	First-line N (%) ¹	Second-line N (%) ¹	EACH2 first-line N (%) ²
Response rate	71 (97)	64 (88)	(48-70)
No preferred protocol (individual treatment)	16 (23)	29 (45)	
Steroids alone	8 (11)	0 (0)	142 (43)
Steroids, cyclophosphamide (p.o., daily)	21 (30)	4 (6)	
Steroids, cyclophosphamide (i.v. pulse therapy)	10 (14)	1 (2)	83 (25)
Rituximab alone	1 (1)	9 (14)	12 (4)
Rituximab, steroids	1 (1)	2 (3)	28 (8)
Rituximab, cyclophosphamide			3 (1)
Rituximab, steroids, cyclophosphamide	1 (1)	8 (13)	8 (2)
Immunoabsorption	7 (10)	6 (9)	
FVIII-based regimen			7 (2)
Other protocols			11 (3)
I.v. immunoglobulin as part of first-line treatment	6 (8)	5 (8)	34 (10)

1. Tiede A, et al. Ann Hematol 2009;88:365-70.
 2. Collins Pet al. Blood 2012;120:47-55.

GTH-AH Consensus-Protocol 01/2010



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

Definition of Response

Tab. 1 Definitions according to GTH-AH 01/2010

item	criteria
acquired haemophilia A	<ul style="list-style-type: none"> ● FVIII:C activity reduced to <50% (<50 IU/dl), ● FVIII:C inhibitor detectable by Bethesda assay (≥ 0.6 BU*/ml), and ● congenital haemophilia A excluded
partial remission	<ul style="list-style-type: none"> ● no active bleeding, and ● FVIII:C activity restored to >50% after stopping any haemostatic treatment for >24 h
complete remission	<ul style="list-style-type: none"> ● PR, plus ● FVIII inhibitor undetectable (<0.6 BU*/ml) ● prednisolone reduced to <15 mg/d (or equivalent glucocorticoid dose), and ● any other immunosuppressive drug discontinued
relapse	<ul style="list-style-type: none"> ● FVIII:C activity declined to <50% after achieving PR or CR, and ● FVIII:C inhibitor detectable

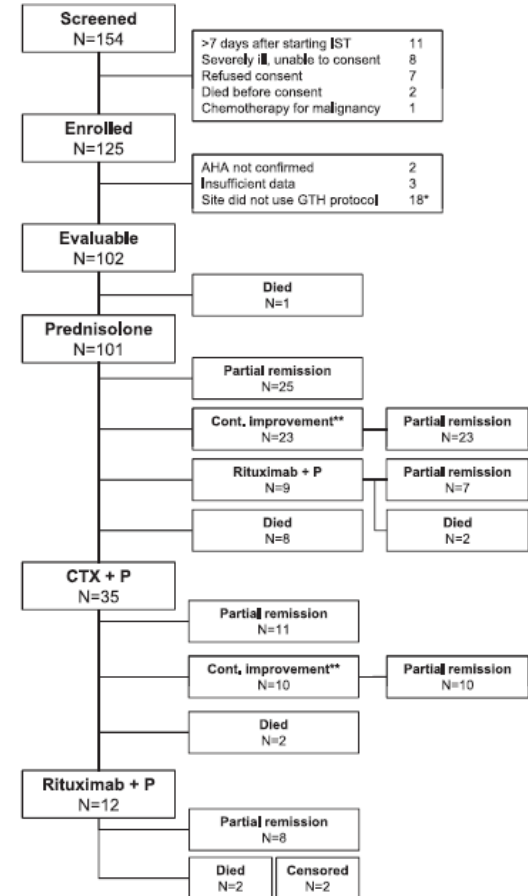
*BU: Bethesda units

Hämophilie GTH-AH 01/2010 Multicentre Study

Prospective multicentre Study 04/2010-04/2013 – 29 study centres

Patient - Characteristics

- 102 Patients (43 women/59 men) – Median Age 74a
- **Co-Morbidities:**
 - Autoimmune (20%)
 - Malignancy (13%)
 - Pregnancy (5%)
 - Idiopathic (67%)
- Mediane VIII at enrollement: 1.4 IU/dl (< 1-31)
- Medianer Inhibitor-Titer: 19 BU/dl (1 - 1449)



Hämophilie GTH-AH 01/2010 Multicentre Study

Response rates

Partial remission: 83%

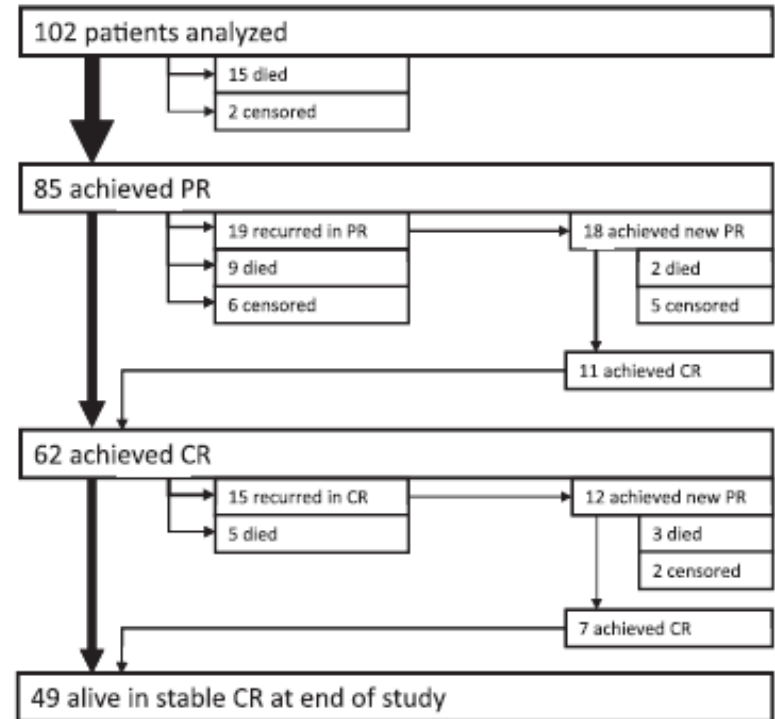
Complete remission: 62%

Median to:

Partial remission : 31d (7-362)

Complete remission : 79d (26-856)

Median Follow up: 262d



Hämophilie GTH-AH 01/2010 Multicentre Study

Initial Factor VIII levels as prognostic markers

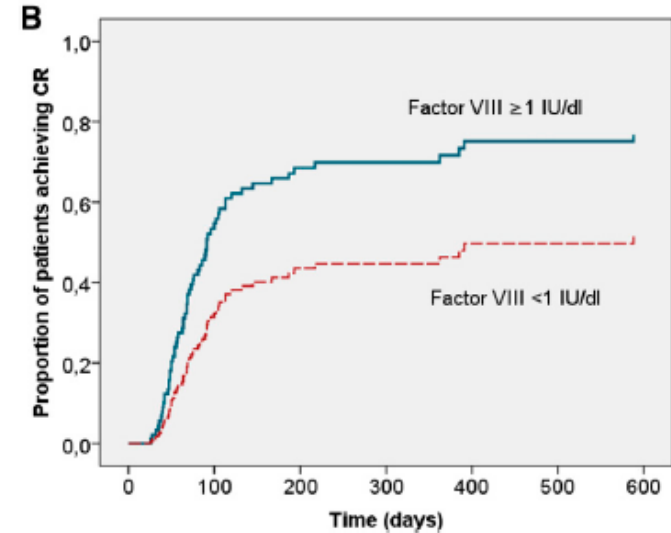
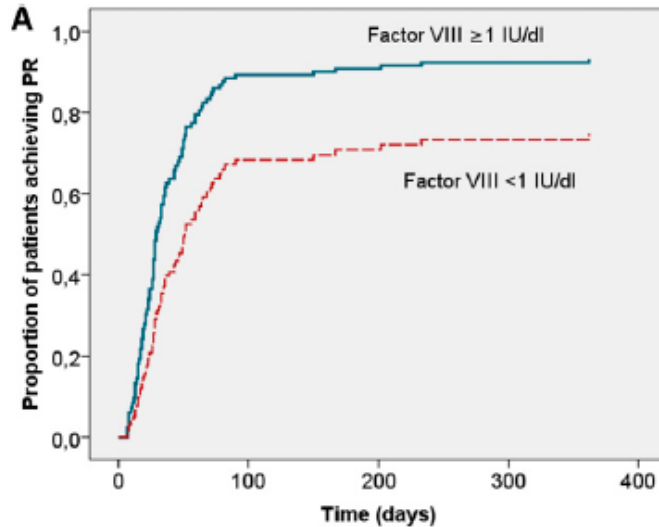
FVIII <1 IU/dL

-> PR 77%, 43 d

FVIII >1 IU/dL

-> PR 89%, 24 d

No correlation with Inhibitor-Titre



Hämophilie GTH-AH 01/2010 Multicentre Study

Mortality

34 (33%) Patients

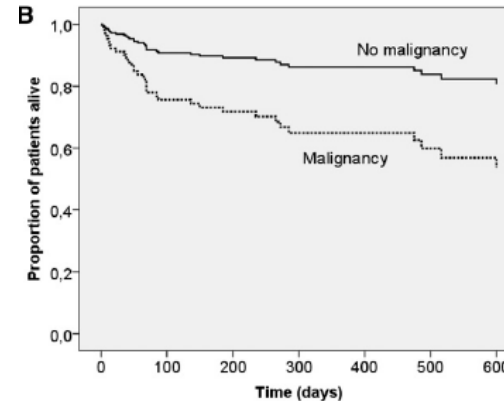
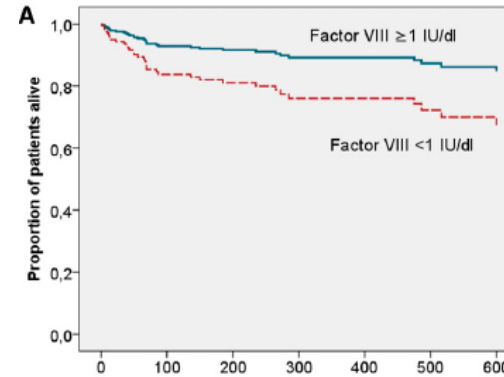
- Infections n=16
- Cardiovasc. n=6
- Bleeding n=3
- Underlying disease n=3

Significant risk factors

- FVIII <1U/dl
- WHO-PS >2
- Malignancy

No Significant correlation:

Inhibitor > 20BU; Age >74a; male gender, acute kidney failure



Inhibitor eradication

- Immunosuppressive therapy should be initiated as soon as the diagnosis of acquired haemophilia is established^{1,2}
- Immunosuppressive therapy reduces mortality, but is associated with complications and co-morbidity³⁻⁵
- Spontaneous remission is unpredictable^{2,6}

1. Collins P, et al. BMC Res Notes 2010;3:161.
2. Huth-Kuhne A, et al. Haematologica 2009;94:566-75.
3. Delgado J, et al. Br J Haematol 2003;121:21-35.
4. Hay CR, et al. Br J Haematol 2006;133:591-605.
5. Toschi V, Baudo F. Intern Emerg Med 2010;5:325-33.
6. Lottenberg R, et al. Arch Intern Med 1987;147:1077-81.

7. Bitting RL, et al. Blood Coagul Fibrinolysis 2009;20:517-23.
8. Collins P et al. Blood 2012;120:47-55.
9. Green D. Am J Med 1991;91:14S-9S
10. Green D, et al. Thromb Haemost 1993;70:753-7.
11. Aggarwal A, et al. Haemophilia 2005;11:13-9.
12. Sperr WR, et al. Haematologica 2007;92:66-71.

Immunoadsorption in AH

- Immunoadsorption
 - Should only be performed by centres with the necessary experience and expertise¹
 - Modified Bonn-Malmö protocol²⁻⁴
 - Modified Heidelberg-Malmö protocol⁵

1. Huth-Kühne A, et al. Haematologica 2009;94:566-75.
2. Zeitler H, et al. Blood 2005;105:2287-93.
3. Zeitler H, et al. Dtsch Med Wochenschr 2006;131:141-7.
4. Zeitler H, et al. Haemophilia 2010;16:95-101.
5. Huth-Kühne A, et al. Haematologica 2003;88:86-92.

Immunadsorption

35 Patienten – Inhibitor >5 BU

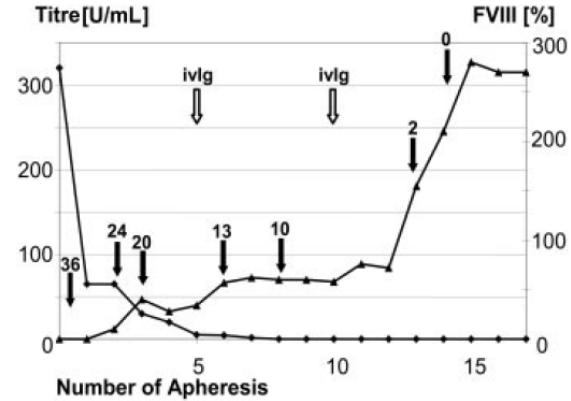
Modified Bonn-Malmö-Protokoll:

- Immunadsorption d1-5 + iv Immunglobuline 0.3g/kg d6+7
- FVIII substitution (Aim FVIII 80-100%)
- Cyclophosphamid 1-2m/kg/d+Predisolon 1mg/kg/d

Bleeding control 1-2d

Inhibitor not detectable: median 3d

Overall response: 88%



Follow-up after inhibitor eradication

- Follow-up after a complete sustained response using aPTT and monitoring of FVIII:C is recommended¹
 - Monthly during the first 6 months
 - Every 2-3 months up to 12 months
 - Every 6 months during the second year and beyond
- The median time to relapse is 7-9 months after cessation of immunosuppressive therapy^{2,3}

1. Huth-Kuhne A, et al. Haematologica 2009;94:566-75.

2. Collins PW, et al. Blood 2007; 109: 1870-7.

3. Delgado J, et al. Br J Haematol 2003;121:21-35.

Content

1. Acquired haemophilia – a bleeding disorder
2. Associated conditions
3. Laboratory diagnosis
4. Clinical management
- ▶ 5. Summary

Acquired Haemophilia: Summary

- Rare, but often life-threatening disorder
- Usually sudden, unexpected onset in patients with no family or personal history of a bleeding disorder
- Serious bleeding complications in >70% of pts
- High mortality ranging between 3.3 and 41%
 - 3.3% mortality rate reported in EACH2 registry
 - 41% mortality rate when patients are not treated
- Predominantly affects older patients
 - Median age of 74 years in EACH2 registry
- Patients often have associated conditions such as pregnancy, autoimmune disorders, cancer
- ~50% of cases are idiopathic


Acquired Haemophilia: Summary

- No relationship between risk or severity of bleeding and FVIII:C level or FVIII inhibitor titre
- Lack of disease awareness may contribute to suboptimal and/or delayed treatment
- Dual-objective treatment strategy
 - Treatment of acute bleeding episodes
 - Immediate initiation of immunosuppressive therapy / inhibitor eradication

Acquired Haemophilia: Summary

- Treatment of bleeding episodes
 - First-line treatment options for bleeding episodes:
 - rFVIIa
 - aPCCs
 - Not all bleeding episodes require treatment
- Immunosuppressive therapy
 - First-line immunosuppressive therapy:
 - Corticosteroids ± cyclophosphamide ± Rituximab
 - Immunosuppressive therapy should be initiated in all patients, independent of inhibitor titre or FVIII:C level

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Ewers RM. Nature. 2018.

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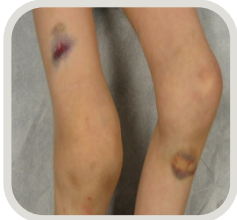

Multidisciplinary Management of Acquired Haemophilia

Pathology, Incidence, Modern Therapy, Recommendations

Haemophilia Expert Meeting,
Bucharest 22 June 2019

Clemens Feistritzer
Medical University of Innsbruck
Internal Medicine V - Hematology and Oncology
Anichstrasse 35
A- 6020 Innsbruck

Congenital vs acquired inhibitors: Alloantibodies vs autoantibodies

	Congenital Haemophilia (alloantibodies)	Acquired Haemophilia (autoantibodies)
Inhibitor incidence	<p>20% to 30% (severe haemophilia)¹</p> <p>3% to 13% (mild/moderate haemophilia)²⁻⁴</p> 	<p>1.5/10⁶/yr⁷</p> 
Risk factors for inhibitor development	<p>Type of mutation</p> <p>Immune system factors</p> <p>→ genetic</p> <p>→ environmental</p> <p>Ethnicity</p>	<p>Autoimmune disease</p> <p>Pregnancy</p> <p>Tumours</p> <p>Idiopathic ~50%</p>
Age at inhibitor diagnosis/development	<p>49% <5 yrs⁵</p> <p>Peak: <30 infusion days⁶</p>	<p>Mean: 78 yrs⁷</p> <p>Range: 2-92 yrs^{7,8}</p>

1. Berntorp E, et al. Haemophilia 2006;12 Suppl 6:1-7.
 2. Lusher JM, et al. N Engl J Med 1993;328:453-9.
 3. Rizza CR, Spooner RJ. Br Med J (Clin Res Ed) 1983;286:929-33.
 4. Sultan Y. Thromb Haemost 1992;67:600-2.

5. Hay CR, et al. Blood 2011;117:6367-70.
 6. Gouw SC, et al. Blood 2007;109:4693-7.
 7. Collins PW, et al. Blood 2007;109:1870-7.
 8. Yee TT, et al. Clin Lab Haematol 2000;22:275-8.

Inhibitor eradication strategy II

- Alternative therapies
 - Azathioprine
 - Vincristine
 - Mycophenolate
 - Cyclosporine