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ORIGINAL ARTICLE

Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

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Summary. *Background:* Acquired hemophilia A (AHA) is a rare autoimmune disease caused by autoantibodies against coagulation factor VIII and characterized by spontaneous hemorrhage in patients with no previous family or personal history of bleeding. Although data on several AHA cohorts have been collected, limited information is available on the optimal management of AHA. *Objectives:* The European Acquired Hemophilia Registry (EACH2) was established to generate a prospective, large-scale, pan-European database on demographics, diagnosis, underlying disorders, bleeding characteristics, treatment and outcome of AHA patients. *Results:* Five hundred and one (266 male, 235 female) patients from 117 centers and 13 European countries were included in the registry between 2003 and 2008. In 467 cases, hemostasis investigations and AHA diagnosis were triggered by a bleeding event. At diagnosis, patients were a median of 73.9 years. AHA was idiopathic in 51.9%; malignancy or autoimmune diseases were associated with 11.8% and 11.6% of cases. Fifty-seven per cent of the non-pregnancy-related cases were male. Four hundred and seventy-four bleeding episodes were reported at presentation, and hemostatic therapy initiated in 70.5% of patients. Delayed diagnosis significantly impacted treatment initiation in 33.5%. Four hundred and seventy-seven patients underwent immunosuppression, and 72.6% achieved complete remission. *Conclusions:* Representing the largest collection of consecutive AHA cases to date, EACH2 facilitates the analysis of a variety of open questions in AHA.

Keywords: acquired hemophilia, demographics, diagnosis, outcome, registry, treatment.

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Introduction

Acquired hemophilia A (AHA) is an autoimmune disease caused by autoantibodies directed against functional epitopes of coagulation factor VIII (FVIII) [1–6]. The disease is characterized by spontaneous hemorrhage or by bleeding induced by surgery, trauma or other invasive procedures in patients with no previous family or personal history of bleeding [7]. Patients with congenital hemophilia A may also develop inhibitory antibodies against FVIII following exposure to exogenous FVIII during substitution therapy, but these alloantibodies have different laboratory and clinical properties [8]. In 1981, Green and Lechner published a retrospective survey on 215 patients with AHA referred to specialist centers and reported information on the characteristics of this disorder that remains central to our understanding of the disease [9]. Since then, two other important reports on AHA cohorts have been published that have had considerable impact on the management of this rare disease. In 2003, Delgado and coworkers performed a meta-analysis of all reports on AHA published between 1985 and 2002 [3], comprising 249 patients from 21 case series, and confirmed the demographic and clinical characteristics of AHA. Later, the UK Haemophilia Centre Doctors' Organisation performed a prospective surveillance

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study, collecting data on all (n = 172) patients with AHA who presented in the UK during a 2-year period (2001–2003) [10]. This created a consecutive cohort of patients, unaffected by referral and reporting bias, and allowed reliable calculations of incidence, characteristics and outcome of patients with AHA.

Despite this, limited information is available on the optimal management of AHA, especially with regard to hemostatic and immunosuppressive treatment. Due to the challenges associated with performing randomized trials among patients with rare diseases, the European Acquired Haemophilia Registry, version 2 (EACH2), was established to generate a prospective, large-scale, pan-European database, collecting extensive data on demographics, diagnosis, underlying disorders, bleeding characteristics, hemostatic and immunosuppressive therapies and outcome of patients with AHA.

Patients and methods

EACH2 was designed as a European prospective multicenter registry to collect data on patients with AHA according to predefined criteria. Cases were reported to the registry from 13 European countries and 117 different treatment centers. The approval of the local ethics committee was obtained before patients could be included. In five countries (Finland, Greece, Hungary, Italy and Portugal), comprising 43 centers, the local authorities restricted patient recruitment to surviving patients only, and did not allow data entry from individuals who had died. This may have affected the analysis of outcome and survival and, to a lesser extent, the demographic analysis. The registry used electronic, web-based case record forms and was hosted by Parexel International GmbH (Berlin, Germany) according to standard data protection requirements for registries. The project was performed according to the guidelines established in the Declaration of Helsinki [11].

Patients could be included if they had been diagnosed with AHA between 1 January 2003 and 31 December 2008. Mandatory requirements for inclusion were plasma FVIII activity < 50 U dL^{-1}, detection of an inhibitor to FVIII and signed informed consent. Patients of any age could be reported. Patients with congenital hemophilia A or coagulation inhibitors other than anti-FVIII antibodies, for example against von Willebrand factor or other coagulation factors, were excluded. The registry collected detailed data on demographics, underlying conditions, characteristics of bleeding episodes, hemostatic and immunosuppressive therapy, response to hemostatic and immunosuppressive therapy, adverse events and outcome at final follow-up.

Severe bleeding episodes were defined as a hemoglobin level below 8 g dL^{-1} or a drop by more than 2 g dL^{-1}, or life or limb threatening, central nervous system, deep muscle or retroperitoneal bleeding. The registry was supported by an unrestricted grant from Novo Nordisk Region Europe A/S, Zurich, Switzerland.

Laboratory diagnosis

FVIII activity was measured in the local laboratories. FVIII inhibitor titer was determined using either the Bethesda method [12] or the Nijmegen modification of the assay [13] according to local usage. There was no central testing of FVIII levels or inhibitor titers, therefore, the inhibitor titers presented in this manuscript give an approximate titer but inter-laboratory variability will be present.

A first round of data cleaning was performed by Parexel according to criteria defined by the authors and data queries were generated for centers to respond to via the electronic data system. At a meeting in September 2009, attended by a subgroup of the steering committee, all data were reviewed and possible inconsistencies identified. Centers were contacted directly to clarify these data inconsistencies. An audit trail of all changes to registry data was maintained.

Statistical analysis

Data were reported as frequency (percentage) or median and interquartile range (IQR) for categorical and continuous variables, respectively. Comparisons were performed using Pearson's chi-squared test or the Mann–Whitney U-test. Correlation between continuous variables was assessed with Spearman rank correlation. A comparison was made between the 331 patients from countries that could enter all patients and the 170 patients from countries that could not enter individuals who had died. Survival and outcome analyses were performed using the Kaplan–Meier method and log-rank test, considering deaths as an event and censoring patients with unknown survival state at the time of their last follow-up. Assuming an incidence of acquired hemophilia of 1.5 patients per million population per year [10], a rough estimation of the median enrollment rate from each country was calculated. P-values < 0.05 were considered significant. All of the analyses were performed using SAS Statistical Package release 9.1 (SAS Institute, Cary, NC, USA).

Results

Demographics

In total, 501 patients with AHA were included in the registry between January 2003 and December 2008 by 117 centers in 13 European countries. A list of participating centers can be found in Appendix S1. The estimated median (IQR) recruitment rate for each country was 12.1% (8.4–22.8%) of potential patients. A detailed description of recruitment data is also provided in Appendix S1, Table S1.

The cohort comprised 266 male (53.1%) and 235 female (46.9%) patients, resulting in a male:female ratio of 1:0.88 (Table 1). The median age at diagnosis was 73.9 years (IQR, 61.4–80.4). The age distribution at diagnosis according to gender is presented in Fig. 1 and not only demonstrates the preponderance of older patients, but also reveals a small population (n = 42; 8.4%) of younger women with a median age of 33.9 years who presented with peripartum FVIII inhibitors. The male:female ratio was also calculated without

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Table 1 EACH2 cohort characteristics[1]

	Entire collective	All patients entered*	Patients who had died not entered†	*P*
Demographics				
Patients [*n* (%)]	501 (100)	331 (66.1)	170 (33.9)	NA
Median age at diagnosis [years (IQR)]	73.9 (61.4–80.4)	75.4 (63.6–81.2)	70.4 (59.3–77.0)	< 0.0001
Male:female [*n* (%) ratio]	266:235 (53–1:46.9) 1:0.88	179:152 (54.1:45.9) 1:0.85	87:83 (51.2:48.8) 1:0.95	NS
FVIII activity at diagnosis				
Median [U dL^{-1} (IQR)]	2 (1–5)	2 (1–6)	2 (1–5)	NS
Less than 1 U dL^{-1} [*n* (%)]	89 (17.8)	61 (18.4)	28 (16.5)	NS
1–5 U dL^{-1} [*n* (%)]	290 (57.9)	185 (55.9)	105 (61.8)	NS
More than 5 U dL^{-1} [*n* (%)]	122 (24.3)	85 (25.7)	37 (21.8)	NS
Inhibitor titer				
Median [BU mL^{-1} (IQR)]	12.8 (4.3–42.4)	15.0 (5.0–54.0)	9.4 (3.5–26.3)	0.005
0–10 BU mL^{-1} [n (%)]	225 (44.9)	133 (40.2)	92 (54.1)	0.01
11–100 BU mL^{-1} [*n* (%)]	214 (42.7)	152 (45.9)	62 (36.5)	0.01
101–1000 BU mL^{-1} [*n* (%)]	62 (12.4)	46 (13.9)	16 (9.4)	0.01
Hb [g dL^{-1} (IQR)]	9.0 (7.5–11.3)	8.8 (7.1–11.0)	9.7 (7.5–11.6)	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. *P*-values refer to Pearson's chi-squared test or the Mann–Whitney *U*-test. *Centers could enter all patients. †Centers could not enter patients who had died.

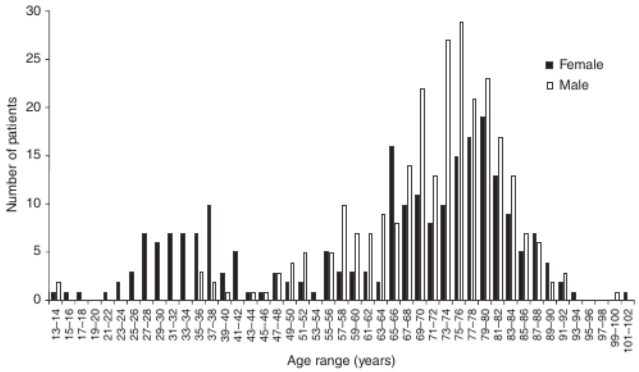

Fig. 1. Histogram of age at diagnosis according to gender.

the pregnancy-related subgroup and found to be 1:0.73 in a population with a median age of 74.9 (66.7–80.8) years. Because women generally have a longer life expectancy than men, the expected male to female ratio in the European population over the age of 65 years is 1:1.4 [14]. Therefore, it appears that there is a marked excess of men presenting with non-pregnancy-related AHA in this cohort.

When comparing the demographic data from patients included by centers allowed to enter data from all patients with those of centers not allowed to enter data from patients who had died (Table 1), there was no difference in the male:female ratio, but a significant difference in the age of the patients (75.4 [63.6–81.2] vs. 70.4 [59.3–77.0] years; $P < 0.0001$). There was no seasonal variation in the occurrence of AHA. The frequency of the first manifestation of the disease (measured by the month of the first bleeding episode) was similar throughout the year (median 40 cases per month; IQR, 34.8–43.5).

A comparison of the EACH2 data with other large cohorts of patients with AHA [3,9,10] (Table 2) indicates very consistent baseline characteristics and demographic data without obvious changes in different populations during the 30-year observation period. This also indicates that the EACH2 cohort is representative of the recognized phenotype of the disease.

Diagnosis

In most cases (89.0%) the diagnosis of AHA was precipitated by a bleeding event that led to further hemostatic investigation and confirmation of the disorder (Table 3). Forty-eight patients were diagnosed with AHA on the basis of a prolonged aPTT. In 33 of these cases no bleeding event was reported, and in 15 patients a bleeding event occurred after diagnosis. In most patients the

1. **Table 1 EACH2 cohort characteristics**
Anchor Name: gender and age *[Agency W2O - Claudia Alves]*

Table 2 Comparison of large collections of patients with AHA

Publication/author(s)	Green and Lechner [9]	Delgado *et al.*, [3]	Collins *et al.*, [10]	EACH2, 2011
Patients (*n*)	215	234	172	501
Collection period	Before 1981	1985–2002	2001–2003	2003–2009
Median age [years (IQR)]	ND	64 (8–93)	78 (2–98)	74 (62–80)
Male sex (%)	53	45	43	53
Median FVIII activity [U dL^{-1} (IQR)]	ND	2 (0–30)	3 (1.7–7)	2 (1–5)
Median inhibitor titer [BU mL^{-1} (IQR)]	ND	10 (0.9–32,000)	13 (4–38)	12.8 (4.3–42.5)
Underlying disorder [*n* (%)]				
None (idiopathic)	82 (43.6)	135 (57.7)*	95 (63.3)	260 (51.9)
Malignancy (any type)	12 (6.4)	43 (18.4)	22 (14.7)	59 (11.8)
Autoimmune disorder	32 (17.0)	22 (9.4)	25 (16.7)	67 (13.4)
Postpartum	13 (7.0)	34 (14.5)	3 (2.0)	42 (8.4)
Infections	ND	ND	ND	19 (3.8)
Dermatological conditions	8 (4.3)	ND	5 (3.3)	7 (1.4)
Drug induced	10 (5.3)	ND	ND	17 (3.4)
Others	21 (16.5)	ND	ND	58 (11.6)

ND, data not reported. Data are reported as *n* (%) and median (IQR) for categorical and continuous variables, respectively. *Includes 'others' and 'unidentified' disorders; some patients may have more than one associated disease.

diagnosis was made promptly after the onset of bleeding at a median (IQR) of 3 (0–12) days. The time from the finding of a prolonged aPTT to diagnosis was 1 (0–8) days. For patients from centers that could enter all patients it was 1 (0–7) day, whereas it was 2 (0–9) days for patients from centers that could not enter patients who had died (*P* not significant). Diagnostic delay had a significant impact on the interval between onset of bleeding and the start of hemostatic therapy (Kruskal–Wallis test, $P < 0.0001$) (Table 4). The delay in diagnosis and initiation of hemostatic therapy, however, had no influence on FVIII levels or inhibitor titers, severity of bleeding, doses or duration of hemostatic therapy, time to bleeding resolved or overall survival.

In the whole cohort the median FVIII activity at diagnosis was 2 (1–5) U dL^{-1} (Table 1). Most patients (75.6%) had FVIII activity < 5 U dL^{-1}, but one-quarter had FVIII levels > 5 U dL^{-1}. The median inhibitor titer at diagnosis was 12.8 (4.3–42.4) BU mL^{-1}, although the different methods for determining the inhibitor titer must be taken into consideration and there was a wide range of inhibitor titers (between 0.1 and 2800 BU mL^{-1}). There was an inverse correlation between the inhibitor titer and residual FVIII activity (Spearman, $r = -0.47$, $P < 0.0001$). Patients in whom a bleeding event triggered the diagnosis of AHA had significantly lower FVIII activity at presentation (2 [1–5] vs. 5 [1–9] U dL^{-1}; $P = 0.007$), higher inhibitor titers (14 [5–45] vs. 3.9 [2–6.9] BU mL^{-1}; $P < 0.0001$) and lower hemoglobin levels (8.9 [7.3–11.1] vs. 10.5 [8.3–12.4] g dL^{-1}; $P = 0.02$) than patients who were diagnosed on the basis of coagulation laboratory abnormalities alone.

Table 3 Bleeding before and after diagnosis

	Entire collective
Bleeding as trigger for diagnosis [*n* (%)]	467 (89.0)*
Time from bleeding event to definite diagnosis	
Median [days (IQR)]	3 (0–12)
More than 6 months [*n* (%)]	6 (1.3)
1–6 months [*n* (%)]	46 (9.8)
1 week–1 month [*n* (%)]	105 (22.4)
1 week [*n* (%)]	122 (26.1)
0 (−1 to 1 day) [*n* (%)]	174 (37.2)
Bleeding after diagnosis [*n* (%)]	
1 week–1 month	6 (1.3)
1 month–1year	4 (0.9)
> 1 year	5 (1.1)
No bleeding [*n* (%)]	33 (6.6)

Data are reported as *n* (%) and median (IQR) for categorical and continuous variables, respectively. *Bleeding as a trigger for diagnosis in patients from centers that could enter all patients, 310; in patients from centers that could not enter patients who had died, 157; *P* not significant

Underlying disorders

In 260 patients (51.9%) no underlying disorders that might have been associated with the development of an autoimmune phenomenon ('idiopathic' AHA) were identified (Table 5). An association with other autoimmune diseases was reported in 11.6% of the cases, about one-third of which were associated with rheumatoid arthritis. There is a well-known association between malignant diseases and AHA. Malignancy was reported in 11.8% of our patients, with two-thirds of associated malignancies being solid tumors. A detailed description of the malignancy-associated cases will be published elsewhere. An association with pregnancy was reported in 42 cases confined to the subgroup of younger women, with an interval between delivery and diagnosis of 89 (IQR 21–120) days (Fig. 1). A detailed description of these cases will be published elsewhere [L. Tengborn, F. Baudo, A. Huth-Kühne, P. Knoebl, H. Lévesque, P. Marco, F. Pellegrini, L. Nemes, P. Collins, unpublished data]. There was a relatively low proportion of other potentially causative risk factors for FVIII inhibitors, such as exposure to drugs, blood transfusions or infections. As these modalities are common in an elderly population, it remains unclear whether these were causative or coincidental. The number of these cases is too small to allow any reliable statistical analysis.

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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)
*P**	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.

Table 5 Underlying disorders

Disorder	No. of patients (%)	
	Of total	Of subgroup
Idiopathic (no underlying disorder reported)	260 (51.9)	
Malignancy	59 (11.8)	
Solid tumors		40 (67.8)
Hematologic neoplasia		19 (32.2)
Treatment of malignancy		
Not treated		27 (45.8)
Treated		32 (54.2)
Chemotherapy		17 (28.8)
Radiotherapy		15 (25.4)
Immunotherapy		4 (6.8)
Surgery		3 (5.1)
Response to cancer treatment		
Remission		15 (46.9)
Partial remission		8 (25.0)
Progression		2 (6.3)
Autoimmune diseases	58 (11.6)	
Rheumatoid arthritis		20 (34.5)
Other connective tissue diseases		8 (13.8)
Systemic lupus erythematosus		5 (8.6)
Autoimmune thyroiditis		4 (6.9)
Sjögren syndrome		3 (5.2)
Antiphospholipid syndrome		2 (3.4)
Other autoimmune disorders		19 (32.8)
Pregnancy	42 (8.4)	
Infections	19 (3.8)	
Drug induced	17 (3.4)	
Beta-lactam antibiotics		4 (23.5)
Clopidogrel		3 (17.6)
Non-beta-lactam antibiotics		2 (11.8)
Interferon		2 (11.8)
NSAID		2 (11.8)
Amiodarone		1 (5.9)
Rivastigmin		1 (5.9)
Sunitinib		1 (5.9)
Heparin		1 (5.9)
MGUS	13 (2.6)	
Polymyalgia rheumatica	11 (2.2)	
Dermatology	7 (1.4)	
Psoriasis		3 (42.9)
Pemphigus		3 (42.9)
Other		1 (14.3)
Blood product transfusion	4 (0.8)	
Others disorders	41 (8.2)	

NSAID, non-steroidal anti-inflammatory drug; MGUS, monoclonal gammopathy of undetermined significance.

Initial bleeding events

Among the 501 enrolled patients, 474 had bleeding episodes reported at presentation (94.6%). The bleeding event that precipitated diagnosis was reported as spontaneous in 367 patients (77.4%), caused by trauma in 40 (8.4%), by surgery in 39 (8.2%), and associated with the peripartum period in 17 (3.6%) of the cases. In 13 cases (2.7%) no information on the cause of bleeding was recorded. Details are provided in Table 6. Bleeding was severe in 333 (70.3%) and mild in 137 (28.9%) cases. No grading of severity was provided in four cases (0.8%). Bleeding sites were predominantly subcutaneous (53.2%) and deep muscle or retroperitoneal bleedings (50.2%). Mucosal bleeding (respiratory, gastrointestinal or urogenital bleeding) was reported in 31.6% and intracerebral bleeding events were rare (1.1%). In contrast to congenital hemophilia A, joint bleeding episodes were also rare (4.9%). Patients with more severe bleeding had significantly higher inhibitor titers, lower hemoglobin levels and more deep tissue bleeding events (Table 6).

Further bleeding events

Of the 474 patients with bleeding events at presentation, 315 patients (66.5%) had only one bleeding episode without relapse following successful initial therapy. In 159 patients (33.5%) more than one bleeding episode occurred (108 patients had two bleeding events, 35 had three bleedings, and 16 patients had four or more bleedings, with a maximum of seven). Median time between the first and the second bleeding episode was 28 days (IQR 14–69).

Hemostatic therapy

Hemostatic therapy was initiated in 70.5% of patients with bleeding episodes at presentation, 85.3% of patients with severe bleeding events and 14.4% of patients with mild bleeding. First-line therapy consisted of bypassing agents (recombinant FVIIa in 50.9%, activated prothrombin complex concentrates in 19.2%) or means to elevate FVIII levels (FVIII concentrates in 18%, desmopressin in 6%). The median initial doses used were near the doses recommended by the manufacturers of the respective agents. Concomitant therapy consisted of red blood cell transfusions (in 54.2% of the bleeding episodes, with median 4 [IQR 2–6] units per episode), antifibrinolytic drugs

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Table 6 Bleeding episodes

	All	Severe	Non-severe	*P**
Total no. of bleeding episodes [*n* (%)]	474	333 (70.3)	137 (28.9)	NA
Cause [*n* (%)]				
Spontaneous	367 (77.4)	250 (76.0)	113 (83.7)	NS
Trauma	40 (8.4)	33 (10.0)	7 (5.2)	NS
Surgery	39 (8.2)	30 (9.1)	9 (6.7)	NS
Peripartum	17 (3.6)	14 (4.3)	2 (1.5)	NS
Other	13 (2.7)	8 (2.4)	4 (3.0)	NS
Site/type [*n* (%)]				
Skin	252 (53.2)	152 (46.2)	97 (71.9)	< 0.0001
Deep (musculoskeletal, retroperitoneal)	238 (50.2)	214 (65.0)	21 (15.6)	< 0.0001
Mucosa	150 (31.6)	113 (34.4)	35 (25.9)	NS
Hemarthrosis	23 (4.9)	17 (5.2)	6 (4.4)	NS
Central nervous system	5 (1.1)	5 (1.5)	0 (0)	NS
Bleeding episodes by clinical and laboratory assessments [median (IQR)]				
Median age [years]	74.0 (61.1–80.3)	74.4 (64.1–80)	71.7 (51.8–80.9)	NS
Gender male:female [*n* (ratio)]	242:222 (1.1)	175:154 (1.14)	67:68 (1.0)	NS
Median FVIII activity [U dL^{-1}]	2 (1–5)	2 (1–5)	2 (0–5)	NS
Median inhibitor titer [BU mL^{-1}]	19 (5.5–64.0)	13 (4.9–40.8)	10 (1.9–32.5)	0.02
Hb [g dL^{-1}]	8.9 (7.3–11.1)	8.5 (7.0–10.0)	11.1 (9.2–12.8)	< 0.0001
Body weight [kg]	69 (60–78)	70 (60–78)	67.5 (60–77)	NS
Time to diagnosis [days]	3 (0–12)	3 (0–11)	2 (0–25)	NS
Bleeding episodes by underlying condition [*n* (%)]				
None identified	238 (51.3)	170 (51.7)	68 (50.4)	NS
Autoimmune	61 (13.1)	40 (12.2)	21 (15.6)	NS
Malignancy	57 (12.3)	44 (13.4)	13 (9.6)	NS
Postpartum	41 (8.8)	25 (7.6)	16 (11.9)	NS
Drug exposure	17 (3.7)	11 (3.3)	6 (4.4)	NS
Infections	19 (4.1)	11 (3.3)	8 (5.9)	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. **P*-values refer to chi-squared test or Mann–Whitney *U*-test, respectively, comparing patients with severe vs. non-severe bleeding episodes.

(18%), high-dose immunoglobulin infusions (11.1%), extracorporeal immunoadsorption (5.4%), plasmapheresis (0.6%) or topical hemostyptic therapy (3%). Details of the hemostatic therapy will be published elsewhere [F. Baudo, P. Collins, A. Huth-Kühne, H. Lévesque, P. Marco, L. Nemes, F. Pellegrini, L. Tengborn, P. Knoebl, unpublished data].

Immunosuppressive therapy

Immunosuppressive therapy was reported in 477 (95%) patients and, of these, outcome data were available for 449. First-line immunosuppression consisted of steroids alone in 268 patients, a combination of steroids and cytotoxic agents in 130 patients and cytotoxics alone in seven. Rituximab alone was used in 13 patients and other combination regimens based on rituximab (some including immunotolerance) in 51 patients. A combination of steroids and cyclosporine was used in six patients. Different types of immunotolerance strategy (immunosuppression plus high-dose FVIII infusion; Bonn [$n = 9$], Malmö [$n = 2$] or Budapest protocol [$n = 20$]) were applied in 31 patients. The response and outcome to first-line immunosuppression was dependent on the recruitment criteria. There were 331 cases entered from countries from which all patients could be entered and 170 cases from countries that excluded patients who had died. There was a significantly better outcome in the group that excluded patients who had died; therefore a detailed analysis was performed only in the subgroup of 331 patients from countries that included all patients, which will be published elsewhere [P. Colllins, F. Baudo, P. Knoebl, H. Lévesque, L. Nemes, F. Pellegrini, P. Marco, L. Tengborn, A. Huth-Kühne, unpublished data].

Outcome

Hemostatic therapy was reported to be associated with seven myocardial infarctions, one cerebrovascular accident and five venous thrombotic events; no allergic reactions were reported (Table 7). First-line immunosuppressive therapy was reported to be associated with 64 episodes of sepsis, 33 cases of neutropenia, 35 cases of steroid-induced diabetes and 12 cases of steroid-induced psychiatric disorders.

Survival and outcome analysis was performed on the 331 patients from countries allowed to enter all patients. Of these, follow-up data were available in 312 cases (94.3%). At final follow-up, 191 patients (61.2%) were alive, 87 (27.9%) had died a median time of 75 (IRQ 25–240) days after diagnosis of AHA, and in 34 patients (10.9%) the survival state was unknown. A Kaplan–Meier plot of the overall survival of all patients, according to the recruitment criteria, is presented in Fig. 2(A), censoring the patients with unknown survival state.

Further Kaplan–Meier analysis of patients from centers allowed to include all patients, excluding pregnancy-associated

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Table 7 Outcome and adverse events

	All patients entered*	Entire collective
No. of patients [*n* (%)]	331 (66.1%)	501 (100%)
Observation time [median, IQR; (days)]	258 (74–685)	318 (111–759)
Survival		
Alive at final follow-up	191 (57.7%)	340 (67.9%)
Death reported	87 (26.3%)	100 (20%)
Unknown survival state	47 (14.2%)	34 (6.8%)
Remission		
Complete remission [*n*/total (%)]	237 (71.6%)	365 (72.6%)
Stable remission on IST [*n*/total (%)]	39 (11.8%)	63 (12.6%)
No remission and off IST	33 (10.0%)	47 (9.4%)
Unknown remission state	22 (6.7%)	26 (5.2%)
Cause of death [*n* (%)]		
Fatal bleeding	15	16
	(17.2% of deaths)	(16% of deaths)
	(4.5% of group)	(3.2% of group)
Hemostatic therapy	0 (0%)	0 (0%)
IST complications	14	16
	(16.1% of deaths)	(16% of deaths)
	(4.2% of group)	(3.2% of group)
	(4.8% of patients receiving IST)	(3.3% of patients receiving IST)
Underlying disease	40	45
	(46% of deaths)	(45% of deaths)
	(12.1% of group)	(9.0% of group)
	(25.2% of patients with underlying disease)	(18.8% of patients with underlying disease)
Unknown/other	33	39
	(37.9% of deaths)	(39% of deaths)
	(10.0% of group)	(7.8% of group)
Adverse events [*n* (%)]		
Total	136 (41.1%)	171 (34.1%)
Stroke	1 (0.3%)	1 (0.2%)
Cardiac disorders (all)	10 (3.0%)	15 (3.0%)
Myocardial infarction	7 (2.1%)	9 (1.8%)
Venous thromboembolism	5 (1.5%)	5 (1.0%)
Infection/sepsis	53 (16.0%)	64 (12.8%)
Neutropenia	29 (8.8%)	33 (6.6%)
Thrombocytopenia	4 (1.2%)	6 (1.2%)
Decompensated diabetes	24 (7.3%)	35 (7.0%)
Psychiatric disorders	10 (3.0%)	12 (2.4%)

IST, immunosuppressive therapy. *Centers could enter all patients.

AHA, as all of these women survived, demonstrated a significantly better survival among patients younger than the median age (76.3 years): younger patients, 4-year survival 62%, mortality 24/148 (16%) vs. older patients, 4-year survival 40%, mortality 64/149 (43%), $P < 0.0001$, log-rank and chi-squared. Multiple stepwise regression analysis revealed that higher age ($P < 0.0001$) and lower hemoglobin levels ($P = 0.003$) at diagnosis, the presence of a malignant disease ($P = 0.008$) and failure to clear the autoantibody ($P < 0.0001$) were significant independent predictors of death, but gender and initial FVIII activity or inhibitor titer had no influence. Significantly more older patients died from bleeding (11/150 [9.3%] vs. 3/149 [3%]; $P = 0.03$) or from sepsis (13/150 [8.7%] vs. 1/149 [0.7%]; $P = 0.001$), whereas death from the underlying disease was not significantly more frequent, nor were the rates of complications such as myocardial infarction, stroke or venous thromboembolism.

Of the 331 patients, 237 (72.6%) reached complete remission (cleared the autoantibody and had stable FVIII activities > 70 U dL^{-1} without replacement therapy), 39 patients (11.8%) had FVIII activities > 70 U dL^{-1} but were still on immunosuppressive therapy, and 33 (10%) were off immunosuppression and had persistent AHA (FVIII levels < 70 U dL^{-1}). In 22 patients (6.6%) the response state was unknown. Figure 2(B) presents the overall survival according to the response state. Survival of patients in complete remission was similar to that of the general population in this age group. Patients who did not achieve remission had a significantly worse survival.

There were 16 deaths caused by bleeding, representing 3% of the cohort and 16% of all deaths (Table 7). There were no deaths reported to be associated with hemostatic therapy, but 16 deaths were considered to be secondary to immunosuppressive therapy, or 3% of the whole cohort and 16% of all

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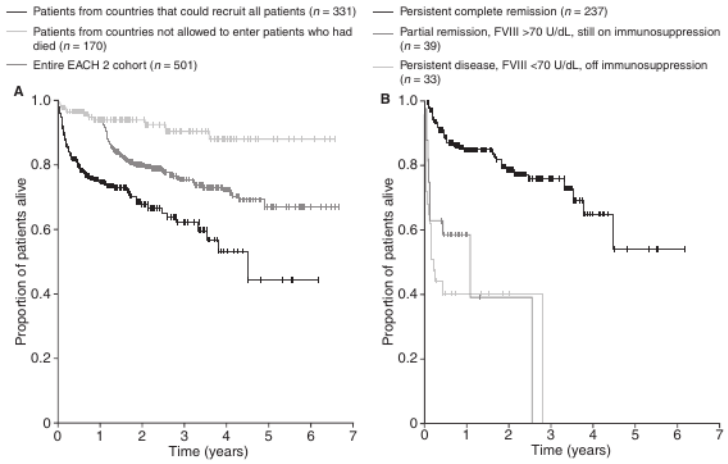

Fig. 2. (A) Overall survival according to recruitment criteria. (B) Overall survival according to inhibitor status from countries that could enter all patients.

deaths. In 45 cases (9% of the cohort and 45% of all deaths) death was reported to be due to the underlying condition.

Discussion

The EACH2 registry currently represents the largest collection of patients with acquired hemophilia A and was intended to supplement local patient collections [10,15] in a prospective matter and on a larger scale. EACH2 enrolled approximately 12% of the estimated number of patients with AHA in participating countries, but recruited consecutive patients in participating centers. The accepted estimate of the incidence of AHA is based on data from the UK surveillance study, [10] but may not necessarily be representative of the prevalence in the rest of Europe. Moreover, this disorder frequently remains unrecognized, leading to an underestimation of its incidence. Nevertheless, the prospective design, the enrollment of consecutive patients, the size of the collective and the long-term observation period (up to 6 years) generated the largest dataset currently available to characterize most aspects of this rare hematological disorder. A comparison of EACH2 data with those from previous collections [3,9,10,16] shows consistent disease and population characteristics over more than 30 years. In addition, the very similar demographics observed in the EACH2 registry compared with previous reports supports the view that EACH2 is a representative cohort of patients with AHA and strengthens the validity of any conclusions derived from the data.

A novel finding reported here is the preponderance of men presenting with AHA, which is especially marked if pregnancy-related AHA is excluded and despite the fact that more women are expected in older populations. This is a novel finding of the EACH2 registry and contrasts with previous reported cohorts where a preponderance of women was seen [3,10].

The collected data permitted a detailed analysis of the baseline data and their impact on outcome. The disease was diagnosed with considerable delay after the occurrence of (in many cases severe) bleeding in a significant proportion of patients, despite abnormal coagulation tests (aPTT). This suggests that a proportion of patients with AHA remain undiagnosed for a worrying length of time, despite the fact that an isolated, prolonged aPTT is key to the diagnosis of AHA [17]. Although the analysis of patients with a delay in diagnosis failed to demonstrate differences in response to therapy, intensity of therapy or outcome, it is recognized that patients remain at risk of fatal bleeding until the inhibitor has been eradicated [10].

The distribution of underlying conditions possibly associated with the development of anti-FVIII antibodies is consistent with previous reports, [3,9,10,16] with about half of the cases apparently idiopathic (Table 5). Malignancy and autoimmune diseases account for about 12% of patients each. It is possible that the evolution of AHA in patients already receiving immunosuppressive agents may be distinct from other groups. Cancer was confirmed in 11.8% of patients and was in progression in 6% of treated cases. Our registry corroborates the results of the study by Green and Lechner [9] and the UK registry, [10] in which a cancer association was found in 6.7% and in 14.6% of the population, respectively. A distinct and well-recognized subgroup of younger female patients acquires anti-FVIII antibodies in association with pregnancy, and this was confirmed. The proportion of pregnancy-associated disease was higher than reported in the UK prospective surveillance study and may reflect referral of this patient subgroup to specialist centers.

Bleeding events precipitated a diagnosis in the majority of the patients (Table 3). The bleeding pattern is distinct from congenital hemophilia, [3,6,10,18,19] and not necessarily dependent on the residual activity of FVIII, [3,7,10,17] as evidenced by severe bleeding in some cases even in the presence of relatively high levels of FVIII. Most bleeding events occurred spontaneously, with < 10% induced by surgical or accidental trauma. Hemostatic therapy is necessary to treat bleeding in

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AHA, but at least 4.5% of the patients still died from bleeding. Further analysis will be performed on the relationship between treatment intensity and survival rate in order to define the optimal balance of efficacy, cost and possible side-effects of hemostatic therapy; these results will be published elsewhere [F. Baudo, P. Collins, A. Huth-Kühne, H. Lévesque, P. Marco, L. Nemes, F. Pellegrini, L. Tengborn, P. Knoebl, unpublished data]. The expected efficacy and the economic implications of AHA therapy with bypassing agents, factor concentrates or extracorporeal devices warrant the consultation of specialists as soon as a patient has been diagnosed with AHA, and treatment should be directed by a team experienced in the management of this disorder. Complications of hemostatic therapy were rare; arterial and venous thromboembolic events associated with bypassing agents occurred in about 4% of cases. This is lower than previously reported [20] but higher than seen in congenital hemophilia and must be interpreted in the context of the advanced age of the population. No fatal thrombotic events were recorded, but the incidence of thrombotic events seen with both bypassing agents means that the risks and benefits of hemostatic treatment need to be carefully weighed and strengthens the recommendation that patients with AHA should be managed in specialist centers.

An important but unavoidable source of potential bias resulted from the variable responses of ethics committees in different countries. Of the 501 patients, 331 were recruited from countries that could include all patients (i.e. also patients who had died before signing informed consent), while 170 were from countries that were not permitted to recruit such patients. Not unexpectedly, this group was significantly younger (Table 1), as age has an impact on survival and excluding decedents selects for a younger population. Thus, analysis of outcome parameters was performed only on the group of 331 patients from countries who could enter data from all patients to avoid selection bias. In this group, 57.7% were reported to be alive and 26.3% to have died at final follow-up. Kaplan–Meier analysis revealed a 54% survival at 5 years after diagnosis in patients who cleared the antibodies, whereas patients with persisting antibodies had an unfavorable prognosis. This suggests that it is important to eliminate the antibodies, although side-effects of immunosuppression are frequent, severe and fatal in 4.8% [7,17]. Different strategies with different immunosuppressive agents [3,10,21–24] or other means, such as immunotolerance induction and extracorporeal immunoadsorption [25–29] or high-dose immunoglobulin infusions [30–32], have been applied. The diversity of therapeutic approaches and lack of evidence to support one approach over another highlights one of the important contributions a data collection such as the EACH2 registry can provide. In addition to the potential benefits of therapy, the considerable side-effects, such as neutropenia and sepsis [3,10,33,34], associated with many immunosuppressive regimens must be taken into consideration. To optimize the therapeutic strategies is of special importance in the population of older patients, as they more frequently die from bleeding or sepsis, but interestingly do not experience more thromboembolic complications. A detailed analysis on the outcomes of the immunosuppressive regimens reported to the EACH2 registry will be published separately [P. Collins, F. Baudo, P. Knoebl, H. Lévesque, L. Nemes, F. Pellegrini, P. Marco, L. Tengborn, A. Huth-Kühne, unpublished data]. Rigorous scientific evidence to guide the type, dosing, duration and intensity of immunosuppressive therapy is lacking, and adequately powered randomized controlled trials in AHA are neither available nor logistically feasible due to the rarity of the disorder. Registry data such as those collected in the EACH2 database or in the ongoing registry by the German, Austrian and Swiss Society on Thrombosis and Haemostasis Research (GTH) investigating a standardized, escalating immunosuppression protocol may therefore represent the best available means of generating a basis for therapeutic decisions.

As for all registry data, quality depends on the contributions of the participating centers. Inconsistent data can result from reporting bias, typing errors or missing information. To overcome such potential shortcomings, EACH2 collected data from centers with experience in treating AHA that prospectively recruited consecutive patients during the predefined study period. Extensive data review for plausibility and consistency was performed. Moreover, appropriate statistical tools such as propensity score matched pair analysis can be used to retrieve reliable information from the EACH2 database. Further analysis may identify patient groups who respond better to specific therapeutic options, which may lead to the development of improved treatment strategies.

The EACH2 dataset will allow further analysis to answer open questions in AHA management, including risk factors for recurrence of bleeding or poor outcome, response to hemostatic or immunosuppressive therapy and an in-depth analysis of distinct subgroups of patients. The EACH2 steering committee will continue the analysis of this valuable data collection.

Addendum

All of the authors (P. Knoebl, P. Marco, F. Baudo, P. Collins, A. Huth-Kühne, L. Nemes, F. Pellegrini, L. Tengborn and H. Lévesque) participated in definition of data fields to be collected in the registry and the development of the electronic case report form. All authors coordinated recruitment of patients in their respective countries. P. Knoebl and F. Pellegrini were primarily responsible for the statistical analyses presented here. The manuscript was drafted by P. Knoebl. All of the authors participated in the review, revision and approval of the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Contributing centers.
Table S1. Recruitment according to participating countries.

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