haematologica
Journal of the Ferrata Storti Foundation

Infectious complications in acquired haemophilia A: insights from the Spanish Registry (AHASR)

by Maria-Eva Mingot-Castellano, Jose Pardos-Gea, Ana Marco Rico, Patricia Alcalde-Mellado, Victoria Salvadores-Alvares, Alicia Jordano-Jimenes, Mariana Canaro Hirnyk, Angel Bernardo Gutierrez, Jose Maria Bastida, Jose Agustin Rodriguez Alen, Faustino Garcia Candel, Dolors Tassies Penella, Ana Moreto Quintana, Gala Aglaia Mendez Navarro, Elena Rosello Palmer, Marina Carrasco Exposito, Susana Asenjo Correa, Laura Torres Minana, Jose Antonio Rodriguez Garcia, Maria Teresa Alvarez-Roman, Rafael Lluch Garcia, Ramon Rodriguez Gonzalez, Jose Manuel Martin Antoran, Nieves Alonso Escobar, Reyes Aguinaco Culebras, Maria Paz Martinez Badas, Shally Marcellini Antonio, Marisol Uribe Barrientos, Nuria Fernandez Mosteirin, Monserrat Perez Sanchez, Sandra Valle Herrero, Carlos Cervero Santiago, Isabel Socorro Caparros Miranda, Miguel Angel Pozas Manas, Irene Vazquez Fernandez, Cristina Pascual Izquierdo, Sara Caracena Lopez and Pascual Marco Vera

Received: June 18, 2025.
Accepted: August 4, 2025.

Citation: Maria-Eva Mingot-Castellano, Jose Pardos-Gea, Ana Marco Rico, Patricia Alcalde-Mellado, Victoria Salvadores-Alvares, Alicia Jordano-Jimenes, Mariana Canaro Hirnyk, Angel Bernardo Gutierrez, Jose Maria Bastida, Jose Agustin Rodriguez Alen, Faustino Garcia Candel, Dolors Tassies Penella, Ana Moreto Quintana, Gala Aglaia Mendez Navarro, Elena Rosello Palmer, Marina Carrasco Exposito, Susana Asenjo Correa, Laura Torres Minana, Jose Antonio Rodriguez Garcia, Maria Teresa Alvarez-Roman, Rafael Lluch Garcia, Ramon Rodriguez Gonzalez, Jose Manuel Martin Antoran, Nieves Alonso Escobar, Reyes Aguinaco Culebras, Maria Paz Martinez Badas, Shally Marcellini Antonio, Marisol Uribe Barrientos, Nuria Fernandez Mosteirin, Monserrat Perez Sanchez, Sandra Valle Herrero, Carlos Cervero Santiago, Isabel Socorro Caparros Miranda, Miguel Angel Pozas Manas, Irene Vazquez Fernandez, Cristina Pascual Izquierdo, Sara Caracena Lopez and Pascual Marco Vera. Infectious complications in acquired haemophilia A: insights from the Spanish Registry (AHASR).
Haematologica. 2025 Aug 14. doi: 10.3324/haematol.2025.288480 [Epub ahead of print]

Infectious complications in acquired haemophilia A: insights from the Spanish Registry (AHASR)

Maria-Eva Mingot-Castellano[1]; Jose Pardos-Gea[2]; Ana Marco Rico[3], Patricia Alcalde-Mellado[4], Victoria Salvadores-Alvares[4], Alicia Jordano Jimenes[4], Mariana Canaro Hirnyk[5], Angel Bernardo Gutierrez[6], Jose Maria Bastida[7], Jose Agustin Rodriguez Alén[8], Faustino Garcia Candel[9], Dolors Tassies Penella[10], Ana Moreto Quintana[11], Gala Aglaia Mendez Navarro[12], Elena Roselló Palmer[13], Marina Carrasco Expósito[14], Susana Asenjo Correa[15], Laura Torres Miñana[16], Jose Antonio Rodriguez Garcia[17], Maria Teresa Alvarez-Roman[18], Rafael Lluch Garcia[19], Ramon Rodriguez Gonzalez[20], Jose Manuel Martín Antoran[21], Nieves Alonso Escobar[22], Reyes Aguinaco Culebras[23], Maria Paz Martínez Badás[24], Shally Marcellini Antonio[25], Marisol Uribe Barrientos[26], Nuria Fernández Mosteirin[27], Monserrat Perez Sanchez[28], Sandra Valle Herrero[28], Carlos Cervero Santiago[29], Isabel-Socorro Caparros Miranda[30], Miguel Angel Pozas Mañas[31], Irene Vázquez Fernandez[32], Cristina Pascual Izquierdo[33], Sara Caracena Lopez[34], Pascual Marco Vera[3] . On behalf of Acquired Haemophiila Spanish Registry (AHASR).

1. Hospital Universitario Virgen del Rocio, Instituto de biomedicina de Sevilla (IBIS/CSIC). Universidad de Sevilla, Spain.
2. Hospital Universitario Vall d´Hebró, Barcelona, Spain
3. Hospital General Universitario Dr. Balmis, Alicante. Universidad Miguel Hernández, Alicante, Spain
4. Hospital Universitario Virgen del Rocio, Instituto de biomedicina de Sevilla (IBIS/CSIC), Sevilla, Spain.
5. Hospital Universitario Son Espases, Palma de Mallorca, Spain
6. Hospital Universitario Central de Asturias, Oviedo, Spain
7. Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL). Salamanca, Spain.
8. Hospital Universitario de Toledo, Toledo, Spain
9. Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain
10. Hospital Clinic, Barcelona, Spain

11. Hospital Universitario de Cruces, Bilbao, Spain.
12. Hospital Universitario Marqués de Valdecilla, Santander, Spain.
13. Hospital Bellvitge, Barcelona, Spain
14. Hospital Sant Pau, Barcelona, Spain.
15. Hospital Clinico San Carlos, Madrid, Spain
16. Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas, Spain.
17. Asistencial Universitario de Leon, Leon, Spain.
18. Hospital Universitario de la Paz, Madrid, Spain.
19. Hospital Universitario la Rivera, Alcira, Spain
20. Hospital Universitario Severo Ochoa, Madrid, Spain.
21. Hospital Rio Carrion, Palencia, Spain
22. Hospital Universitario de Badajoz, Badajoz, Spain.
23. Hospital Joan XXIII. ICO. Tarragona, Spain.
24. Hospital Nuestra Señora de Sonsoles, Avila, Spain
25. Complejo Asistencial de Segovia, Segovia, Spain.
26. Hospital General Universitario de Valencia, Valencia, Spain
27. Hospital Universitario Miguel Servet, Zaragoza, Spain
28. Hospital Virgen de la Concha, Zamora, Spain
29. Hospital Virgen de la Luz, Cuenca, Spain
30. Hospital Universitario Virgen de la Victoria, Málaga, Spain
31. Hospital Universitario Rio Hortega, Valladolid, Spain
32. Hospital Universitario Son Llàtzer, Palma de Mallorca, Spain
33. Hospital Universitario Gregorio Marañon, Madrid, Spain
34. Hospital General Universitario Morales Meseguer, Murcia, Spain

On behalf of Acquired Haemophila Spanish Registry (AHASR).

Corresponding autor

Maria-Eva Mingot-Castellano

mariae.mingot.sspa@juntadeandalucia.es

Hospital Universitario Virgen del Rocío, Instituto de biomedicina de Sevilla (IBIS/CSIC).

Universidad de Sevilla, Spain. Corresponding author

Key words: Acquired haemophilia, coagulopathy, infections, adverse events, immunosuppression, mortality, morbidity

Words: 1594

Tables: 2

Bibliography: 15

Data sharing: They are available contacting the corresponding author.

Author contributions

Study conception and design: MEMC, PMV, JMB; data acquisition and interpretation: all authors; drafting of the manuscript: MEMC, VSA, PAM, AJJ; critical revision of the manuscript for important intellectual content: all authors; final approval of the manuscript: all authors.

Acknowledgments

Spanish Society of Thrombosis and Haemostasis (SETH), for the data base support.

Conflict of Interest Statement

No conflict of interest for this paper for any author.

Acquired haemophilia (AH) is a rare autoimmune bleeding disorder caused by spontaneous development of autoantibodies against any protein coagulation factor, but the most frequent ones are antibodies against factor VIII (AHA)[1,2]. AHA can affect both men and women, with a higher prevalence in elderly patients and women at the postpartum period[1,2]. It is often associated with underlying conditions such as autoimmune diseases, postpartum or cancer[3-8]. The main symptom of AHA are spontaneous bleedings, with life-threatening bleedings in close to 70% of this patients[3-8].

Treatment focuses on controlling bleeding episodes and eliminating the autoantibodies[1,2]. Haemostatic agents, such as activated recombinant factor VII (rFVIIa) or activated prothrombin complex concentrates (aPCC) are used to stop bleedings[2,9]. Recently, emicizumab, a bispecific antibody that mimics the function of FVIIIa intrinsic tenase complex, is being used as haemostatic prophylaxis in this group of patients[10,11]. To eliminate inhibitors, immunosuppressive therapy is used, including steroids, cyclophosphamide and rituximab[1,2].

Despite the risk of bleeding, in european registries, infections represent the leading cause of death among patients with AHA, particularly within the first 100 days following diagnosis[3,5,6]. Patients with AHA have an increased risk of infections due to prolonged hospitalizations, frequent use of immunosuppressive therapies, and underlying conditions that compromise the immune system. Infections in these patients, particularly sepsis and pneumonia, can significantly worsen outcomes[2,4,6,7,12]. Therefore, early recognition, infection control measures, and appropriate antimicrobial therapy are crucial in managing these cases. Prophylaxis against pathogens has been suggested for patients undergoing steroid treatment[1,13,14]. Prolonged or high-dose corticosteroid use in non-malignant haematological diseases increases the risk of serious infections. Prophylaxis against tuberculosis, hepatitis B, Strongyloides stercoralis, and Pneumocystis jirovecii pneumonia is recommended in patients receiving prednisone-equivalent doses greater than 30 mg per day for over four weeks, or doses between 15 and 30 mg for eight weeks or longer. The combination of cyclophosphamide with corticosteroids also warrants prophylaxis until the dose is tapered to 5 mg or less per day[13].

This report describes not only frequency but other information not communicated in registries as infection location, microorganism, severity and mortality related from the AHASR. Data on infections were analysed in the global series and before and after the publication in 2020 of the international guidelines to evaluate their influence on outcomes[2].

The AHA Spanish Registry (AHASR), retrospectively collected data regarding patients diagnosed with AHA in 36 Spanish hospitals from May 2014 to December 2024. The AHASR is located in the Spanish Society of Thrombosis and Haemostasis website. Institutional review boards of all participating hospitals explicitly approved participation. A total of 257 patients were enrolled, 80 of whom were diagnosed from 2021 onwards. Of the whole serie, 57.5% are male, with a median age of 73.5 years old (IQR, 63.3–82). The mean inhibitor titer was 24.5 BU (IQR, 11.3–63.5). Fifty-four percentage of patients had an underlying disease (31.5% autoimmune, 15% neoplasms, 6% postpartum). At diagnosis, 89% of patients presented clinically relevant bleeds and 69% of patients needed haemostatic treatment during AHA (35% rFVIIa, 14.2% aCCP, 20% both). Emicizumab was used in 8 patients under several regimens. Regarding inhibitor eradication, 91.2% of patients received immunosuppressive treatment (42.7% steroids plus oral cyclophosphamide, 15.8% based on rituximab schemes, 26.5% steroid monotherapy) with a median time to complete response of 6 weeks (IQR, 3–12 weeks). Reference guideline define patients as having a good prognosis when inhibitor titer is <20BU and factor VIII levels are >1%[1,2]. The implementation of this definition has resulted in an increased use of steroid monotherapy as first-line treatment before and after 2021 (20% vs 42%, p = 0.009).

We recorded 46 episodes of infection in 40 patients (Table 1). Regarding the infections described in the serie, whether or not they caused mortality, the incidence of infections requiring treatment and/or hospitalization was 15.5%, with 67.4% being fatal. There were no significant differences with regard to infections between the immunosuppressive schemes of treatment used (p=0.476). In 23/46 episodes, patients had been treated with immunosuppression before acquired haemophilia or they had additional risk factors for infections such as diabetes or surgery. Only the 26% of patients who developed infection received antimicrobial prophylaxis. Patients on prophylaxis, received trimethoprim sulfamethoxazole in 100% of these patients and fluconazole only in 23% of cases.

Infection location and microorganisms are described in table 2. Microorganisms were isolated in 31 out of 46 episodes, all with a single microorganism, except for one episode with two different pathogens, both gram-negative. Most isolates were bacterial (27/31), mainly gram-negative bacilli; followed by SARS-CoV-2 (3/31), and lastly aspergillus (1/31). With regard to location, pneumonia was the most common type of infection in 24 episodes (53%), followed by sepsis in 15 episodes (32.6%) and infection of the urinary system in 3 episodes (6.5%). The treatment followed the standard approach used for the rest of the population. In patient who need hospitalization, initial treatments were empirical consisted of beta-lactam antibiotics, starting with third-generation cephalosporins or

piperacillin-tazobactam. In cases with respiratory or urinary focus, levofloxacin was added in 30% of cases. Cases of sepsis were initially treated with carbapenems. In patients with SARS-CoV-2, oseltamivir was added in 100% of cases without complications. Ambulatory patients were managed with amoxicillin or levofloxacin in all cases.

With a median follow-up of 135 weeks (IQR, 7.3–145.5), the mortality rate was 25.7%, related to infections (51.6%), bleeding (12.9%), or underlying conditions (21%). We found no differences in infection-related mortality rate across the different immunosuppressive regimens used (steroids plus cyclophosphamide 40%, rituximab-based regimens 20.7%, and steroid monotherapy 13.3%, p = 0.739). Despite the increased number of patients treated with steroid monotherapy, infection remains the leading cause of death, accounting for 24 of the 51 deaths prior to 2021 (49%) and 7 of the 15 reported after 2021 (58%). There was no difference in mortality with regard to prophylaxis, but it is a short serie of patients to evaluate its efficacy. Some bias may exist because the follow-up of patients in the 2021 cohort onward is shorter, and no deaths due to the underlying disease have been reported. In patients treated with steroid monotherapy, the rate of death due to haemorrhage was higher than in the rest (8.1% vs. 1.2%, p=0.01).

The leading cause of death in the Spanish series was infectious diseases, highlighting the need for initiatives to optimize immunosuppressive treatment or infectious prophylaxis[3]. Reviewing the literature, there is variability in different registries regarding the incidence of infections and their mortality, but there is no description about microorganism responsible of the infections. The Dutch registry reports infection-related mortality at 19.2%, with 81 infection episodes in 49 out of 136 patients, predominantly respiratory infections (43.6%), and sepsis in 28.6% of cases. Of these infections, 71.4% were non-complicated[6]. In the german registry, 34/102 patients (33.3%) died because of infections, without more information[5]. The United Kingdom registry describes sepsis in 37 out of 112 patients (33%), with a mortality of 12 out of 112 (10.7%)[7]. Vuokko Nummi et al. described in the finnish registry an infection-related mortality of 9% compared to 13% from bleeding. In this registry, 94% of patients with severe infections were on two or more immunosuppressive agents[8].

Although no differences in the incidence of infections have been described between the different treatment regimens[3,12], current AHA treatment guidelines recommend the use of steroid monotherapy as first-line therapy in frail patients and in those with FVIII levels above 1 IU/dL and/or inhibitor titers below 20 BU, to prevent toxicities. In our series, the incidence of infections with this regimen is not lower; however, the rate of haemorrhage-related deaths is higher compared to other regimens. Furthermore, a recent study by the French group[15] reports that infection rates in patients with AHA are directly related to the duration of steroid therapy. For this reason, treatment must be

individualized to minimize steroid exposure, introducing combined therapy as early as possible in low-risk patients if there is no favourable clinical response. It is important to take in account that close to 40% of patients with AHA has been treated with steroids before AHA because of underlying autoimmune conditions, potentially increasing the risk of infection for this reason.

Tiede et al. used an initial treatment with emicizumab, delaying the start of immunosuppressive schemes until week 12, reporting lower rates of both bleeding and infection. Four deaths were reported in 46 patients, 2 because of bleeding, 1 because of an infection y 1 from a cardiac arrest[11]. Despite of this valuable results, we need longer follow up to clearly stablish a reduce in mortality related with infections, because median time from AHA diagnose to severe and or mortal infections is close to 3 months with a range to 12 months according to our data, and the german serie follow up is 6 months. Based on this data and the bleeding mortality in patients treated with steroid monotherapy in our series, early consideration of haemostatic prophylaxis in these patients appears to be a reasonable option.

There are several limitations in this study. Patients' data were obtained from multiple centres, which may introduce variability in diagnostic criteria, therapeutic decisions, data completeness and follow-up periods. Prophylactic strategies were not standardized, limiting the assessment of their efficacy. Finally, although emicizumab is a promising agent, it was used in a small, non-uniform subset of patients, making it difficult to evaluate its true clinical impact in this setting.

In conclusion, acquired haemophilia remains a life-threatening, where bleeding predominates early mortality and infections drive late mortality due to IST. New therapeutic strategies, including early use of emicizumab and delayed IST, may help reduce complications. Prophylactic antimicrobial use and refined risk stratification are essential to improving outcomes in this vulnerable population.

Bibliography:

1. Mingot-Castellano ME, Rodríguez-Martorell FJ, Nuñez-Vázquez RJ, et al. Acquired Haemophilia A: A Review of What We Know. J Blood Med. 2022;13:691-710.
2. Tiede A, Collins P, Knoebl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105(7):1791-1801.
3. Mingot-Castellano ME, Pardos-Gea J, Haya S, et al. Management of acquired hemophilia A: results from the Spanish registry. Blood Adv. 2021;5(19):3821-3829.
4. Sun B, Xue F, Feng Y, et al. Outcome of CARE: a 6-year national registry of acquired haemophilia A in China. Br J Haematol. 2019;187(5):653-665.
5. Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHAA): results from the GTH-AHA 01/2010 study. Blood. 2015;125(7):1091-1097.
6. Schep SJ, van Dijk WEM, Beckers EAM, et al. Treatment of acquired hemophilia A, a balancing act: results from a 27-year Dutch cohort study. Am J Hematol. 2021;96(1):51-59.
7. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood. 2007;109(5):1870-1877.
8. Nummi V, Hiltunen L, Szanto T, et al. Acquired haemophilia A in Finland: A nationwide study of incidence, treatment and outcomes. Haemophilia. 2024;30(5):1130-1137.
9. Mingot-Castellano ME, Álvarez-Román MT, López-Fernández MF, et al. Spanish consensus guidelines on prophylaxis with bypassing agents for surgery in patients with haemophilia and inhibitors. Eur J Haematol. 2016;96(5):461-474.
10. Ellsworth P, Chen SL, Jones LA, et al. Acquired hemophilia A: a narrative review and management approach in the emicizumab era. J Thromb Haemost. 2025;23(3):824-835.
11. Tiede A, Hart C, Knöbl P, et al. Emicizumab prophylaxis in patients with acquired haemophilia A (GTH-AHAA-EMI): an open-label, single-arm, multicentre, phase 2 study. Lancet Haematol. 2023;10(11):e913-e921.

12. Wang P, Zhou R, Xue F, et al. Single-dose rituximab plus glucocorticoid versus cyclophosphamide plus glucocorticoid in patients with newly diagnosed acquired hemophilia A: A multicenter, open-label, randomized noninferiority trial. Am J Hematol. 2024;99(1):28-37.
13. Malpica L, Moll S. Practical approach to monitoring and prevention of infectious complications associated with systemic corticosteroids, antimetabolites, cyclosporine, and cyclophosphamide in nonmalignant hematologic diseases. Hematology Am Soc Hematol Educ Program. 2020;2020(1):319-327.
14. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020;41:100648.
15. Lévesque H, Viallard JF, Houivet E, et al. Cyclophosphamide vs rituximab for eradicating inhibitors in acquired hemophilia A: A randomized trial in 108 patients. Thromb Res. 2024;237:79-87.

Table 1. Main clinical characteristics of patients with AHA and infections

IQR: interquartile range, IS: Immunosuppressive.

Category	Variable	Value
Demographics	Sex - Male	32/46 (69.5%)
Demographics	Age (median, IQR)	78 (73–88) years
Underlying Disease	Any underlying disease	23/46 (53%)
	Diabetes	3/46 (6.5%)
	Heart disease	3/46 (6.5%)
	Surgery	1/46 (2.2%)
	Chemotherapy	2/46 (4.4%)
	Previous IS treatment	15/46 (32.6%)
	Dialysis	1/46 (2.2%)
Immunosuppressive Scheme	Steroids and cyclophosphamide	20/46 (43.48%)
	Rituximab regimens	13/46 (26.26%)
	Steroids monotherapy	10/46 (21.74%)
	Other schemes	3/46 (6.5%)
Antimicrobial Prophylaxis	Trimethoprim-sulfamethoxazole	9/40 (22.5%)
	Fluconazole	2/40 (5%)
Infection Episodes	One episode	36/40 (90%)
	Two episodes	2/40 (5%)
	Three episodes	2/40 (5%)

Table 2. Infection site and microorganism isolated.

IQR: interquartile range, IS: Immunosuppressive.

Category	Variable	Value
	Time from diagnosis to infection (median, IQR)	87.5 days (50–165)
Infection Site	Pneumonia	24/46 (52.1%)
	Sepsis	15/46 (32.6%)
	Urinary infection	3/46 (6.5%)
	Abdominal	3/46 (6.5%)
	Endocarditis	1/46 (2.3%)
Microorganisms Isolated	Klebsiella pneumoniae	6/31 (19.4%)
	Pseudomonas	5/31 (16.1%)
	E. coli	3/31 (9.7%)
	Pneumococcus	3/31 (9.7%)
	SARS-CoV-2	3/31 (9.7%)
	Acinetobacter baumannii	2/31 (6.5%)
	Staphylococcus aureus	2/31 (6.5%)
	Staphylococcus epidermidis	1/31 (3.2%)
	Clostridium difficile	1/31 (3.2%)
	Enterococcus faecalis	1/31 (3.2%)
	Enterobacter cloacae	1/31 (3.2%)
	Corynebacterium	1/31 (3.2%)
	Providencia rettgeri	1/31 (3.2%)
	Aspergillus	1/31 (3.2%)