Infectious complications in acquired hemophilia A: insights from the Spanish registry (AHASR)

Acquired hemophilia (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] Hemostatic 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 hemostatic 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 hematological 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 4 weeks, or doses between 15 and 30 mg for 8 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 analyzed 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 on 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 (interquartile range [IQR], 63.3-82). The mean inhibitor titer was 24.5 BU (IQR, 11.3-63.5). Fifty-four percent 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 hemostatic treatment during AHA (35% rFVIIa, 14.2% aCCP, 20% both). Emicizumab was used in eight 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 guidelines define patients as having a good prognosis when the inhibitor titer is <20 BU 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 series, 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 of 46 episodes, patients had been treated with immunosuppression before AH or they had additional risk factors for infections such as diabetes or surgery. Only 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 the microorganisms involved are described in Table 2. Microorganisms were isolated in 31 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 three episodes (6.5%). The treatment followed the standard approach used for the rest of the population. In patients who needed hospitalization, initial treatments were empirical and consisted of β-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

Table 1. Main clinical characteristics of patients with aquired hemophilia and infections.

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

IQR: interquartile range, IS: Immunosuppressive.

Table 2. Infection site and microorganism isolated.

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

IQR: interquartile range.

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 seven of the 15 reported after 2021 (58%). There was no difference in mortality with regard to prophylaxis, but as it is short series of patients efficacy was difficult to evaluate. Some bias may exist as the follow-up of patients in the 2021-onward cohort 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 hemorrhage 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, shows variability in different registries regarding the incidence of infections and their mortality, but lacks the description of microorganism responsible for the infections. The Dutch registry reports infection-related mortality of 19.2%, with 81 infection episodes in 49 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 of 102 patients (33.3%) died because of infections, without any further information given.[5] The United Kingdom registry describes sepsis in 37 of 112 patients (33%), with a mortality of 12 of 112 (10.7%).[7] 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 hemorrhage-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 favorable clinical response. It is important to take in account that close to 40% of patients with AHA were 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, two because of bleeding, one due to infection and one due to cardiac arrest.[11] Despite of these valuable results, we need longer follow-up data to clearly establish a reduction in mortality-related infections, as the median time from AHA diagnose to severe and or mortal infections is close to 3 months with a range up to to 12 months according to our data, and the German series follow-up period of 6 months. Based on this data and the bleeding mortality in patients treated with steroid monotherapy in our series, early consideration of hemostatic prophylaxis in these patients appears to be a reasonable option.

There are several limitations in this study. Patients' data were obtained from multiple centers, 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, which was used in a small, non-uniform subset of patients, making it difficult to evaluate its true clinical impact in this setting.

In conclusion, AH remains 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.

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