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Infectious Complications in Autoimmune Hemolytic Anemia: A Multi-Center Italian Experience

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Introduction: Infections may play an important role in the development or relapse of autoimmune hemolytic anemia (AIHA) as well as possible complications of long-term immunosuppression secondary to its management. The prevalence and severity of infection in AIHA are still under-investigated.
Methods: Hereby we studied retrospectively 324 patients older than 18 years old, diagnosed with AIHA and followed at 10 Italian centers between 1981 and 2022, focusing on infectious complications and their predictors.
Results: At diagnosis, median age was 60 years (range 18-94), with 27% of patients older than 70 years and with a slight male predominance (65%) and classified as warm AIHA in 53% (Table 1). Median Hb was 7.3 g/dL (2-14), median WBC of 7,5x10 ^{9}/L (1,4-94) and median platelets of 260x10 ^{9}/L (4-695). Sixty-two (60%) out of 103 patients presented lymphopenia. Among 111 evaluable patients, reduced serum IgG/IgA/IgM levels were detected in 37%, 27%, and 23%, respectively. Twenty-nine (9%) patients had Evans Syndrome.
During a median follow-up of 35 months (1-553 months), patients received a median of 1 line of therapy (1-7), including steroids, rituximab, chemotherapy, and immunosuppressive (IS) drugs in 90%, 45%, 10% and 12% of cases, respectively. Twenty (6%) patients underwent splenectomy and 43 (13%) received intravenous Ig supplementation.
Sixty-five (20%) patients presented at least one infection episodes, with 17 experiencing recurrences. Pneumonia was the most frequent (44 cases), followed by 11 sepsis and 4 urinary tract infections, requiring hospitalization in 37 (71%) of cases. Pathogens were isolated in 23 patients (62% viral and 38% bacterial agents). Overall, 17 (16%) suffered from SARS-CoV-2 infection, of whom 8 requiring specific therapy. Eleven (18%) patients were receiving prophylaxis at the time of infection, including acyclovir (18%), cotrimoxazole (18%), both (55%) or anti-HBV prophylaxis (18%). Forty-seven (77%) patients were on active treatment for AIHA at the time of infection (32 steroids, 8 rituximab, 1 IS and 11 not specified), and 16 (25%) also experienced a thrombotic event.
Patients receiving more than one therapy lines had 2-fold higher probability of developing infections (RR 2.03, 1.27-3.25, p=0,0017), particularly for those treated with IS (RR 1.77, 1.04-3.01, p=0,041) and with rituximab (RR 1.96, 1.20-3.20, p=0,0048).

Among patients with infections, median time from the last dose of rituximab was 15 months (range 1-147 months). Moreover, patients with thrombotic events were more likely to experience infection episodes (RR 2.41, 1.52-3.83, p=0,001).
During observation, 55 patients (23%) died, among them 10 for AIHA complications, including 6 infections.
Conclusions: In conclusion, infections complicate about 20% of AIHA. Most episodes occurred during active AIHA-therapy and were more common in patients with prior exposure to rituximab or IS, suggesting an iatrogenic effect. The association with thrombotic events may indicate a relationship with more severe AIHA. Strategies to reduce the burden of IS in AIHA should be pursued.

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	with infections (63)	without infections (261)	Risk ratios
Median Age, years	61 (19-85)	61 (19-95)	ns
Over 70 ys	16 (25)	72 (28)	ns
Males/Females	17/21	86/135	ns
Type of AIHA			
warm AIHA IgG	25 (42)	104 (40)	ns
warm AIHA IgG+C	12 (20)	26 (10)	RR 1,77 (1,04-3,00) p=0,041
cold AIHA	16 (27)	93 (36)	ns
mixed AIHA	6 (10)	16 (6)	ns
atypical AIHA	1 (1)	21 (8)	ns
Evans Syndrome	8 (13)	21 (8)	ns
Median Hb, g/dL	7 (2-13)	7,3 (2-14)	ns
Median Plt, x10^9/L	256 (5-592)	263 (4-695)	ns
Median WBC, x10^9/L	7,5 (1,4-94)	7,7 (1,6-88)	ns
Median Neutrophiles, x10^9/L	5,6 (1,5-52)	4,6 (0,3-31,8)	ns
Median Lymphocytes, x109/L	1,4 (0,1-90)	1,8 (0,2 – 79,2)	ns
Median LDH, IU/L	601 (197-4000)	610 (174-8681)	ns
Hypogammaglobulinemia IgA	12 (32)	18 (24)	ns
Hypogammaglobulinemia IgG	17 (46)	24 (32)	ns
Hypogammaglobulinemia IgM	11 (30)	14 (19)	ns
Median N. of therapy lines	2 (1-6)	1 (1-7)	RR 2,03 (1,27-3,25) p=0,0017
1	21 (34)	140 (55)	
2	21 (33)	69 (27)	
>=3	21 (33)	52 (18)	
Type of therapy			
Steroids	56 (90)	227 (89)	ns
Rituximab	40 (65)	101 (40)	RR 1,96 (1,20-3,20) p=0,0048
Splenectomia	6 (10)	14 (5)	ns
CHT	9 (14)	25 (10)	ns
IS	12 (19)	26 (10)	RR 1,77 (1,04-3.01) p=0,0412
IVIG	11 (17)	32 (12)	ns
Thrombosis	16 (25)	24 (9)	RR 2.41 (1.52-3.83) p=0,001
Arterial	4 (6)	5 (2)	
Venous	8 (13)	13 (5)	
Prophylaxis	11/37 (30)	24/101 (24)	ns
Cotrimoxazole	8 (13)	19 (7)	
Acyclovir	8 (13)	18 (7)	
Others	2 (3)	0	
Status at last follow-up			
Alive	46 (87)	142 (75)	
Dead	7 (13)	48 (25)	

Table 1. Characteristics of patients with autoimmune hemolytic anemia (AIHA) with and without infections
**Hb: hemoglobin; Plt: platelets; WBC: white blood cells; LDH: lactate dehydrogenase; Ig: immunoglobulin; CHT: chemotherapy; IS: immunosuppressive; IVIG: intravenous immunoglobulin; ns: not significant*
**Values are given as number (%) unless otherwise specified*

Figure 1

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