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ORIGINAL ARTICLE

Prognosis of autoimmune hemolytic anemia in critically ill patients

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Abstract

Patients with autoimmune hemolytic anemia (AIHA) may require intensive care unit (ICU) admission. In order to describe the characteristics of AIHA patients in ICU and identify prognosis factors, clinical and biological data from 44 patients admitted in one ICU between 2002 and 2015 were retrospectively analyzed. The main reasons for ICU admission were profound anemia without any organ failure in 19 patients (either for safer transfusion or continuous monitoring only). Twenty-five (57%) patients had a past history of hemopathy. Twenty patients presented with a direct anti-globulin test (DAT) positive for immunoglobulin G (DAT-IgG) only (46%), 8 with a DAT positive for both IgG and complement (DAT-IgG+C) (36%), and 16 with a DAT positive for complement only (DAT-IgG+C) (18%). Corticosteroids and rituximab were administered to respectively 44 (100%) and 12 (25%) patients. Red blood cell transfusion was required in 28 (64%) patients. Ten (23%) patients received vasopressors. Renal replacement therapy was necessary in 14 (31.8%) patients. Thirteen (30%) patients died in the ICU. There was no difference between survivors and non-survivors regarding associated comorbidities like hemopathy (18/31 [58%] vs. 7/13 [54%], $p = 0.80$). In decedents, age was higher (72 years [57.8–76.3] vs. 50 years [34.3–64], $p < 0.01$) and organ dysfunctions were more severe at day 1 (SOFA 8 [7–11] vs. 5.5 [3–7], $p < 0.01$). Patients with a DAT-IgG displayed poorer outcome in comparison with patients with DAT-IgG+C/C (hospital mortality 69% vs. 36%, $p = 0.04$). Mortality rate of AIHA patients requiring ICU admission is consequential and appears to be impacted by age, organ failures, and DAT-IgG.

Keywords Autoimmune hemolytic anemia · Intensive care unit · Hemopathy · Direct anti-globulin test · Prognosis

Introduction

Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disease, with an estimated annual incidence of 1 to 3 per 100,000 individuals [1]. The pathogenesis is characterized by an increased breakdown of red blood cells (RBC), which are targeted by autoantibodies, with or without complement activation.

The classification of AIHA is mainly based on the immunochemical properties of the anti-RBC autoantibodies [1], warm antibody mediated AIHA accounting for approximately 75–80% of all adult AIHA cases [2]. AIHA may also be subdivided into idiopathic and secondary AIHA, depending on the presence of an underlying disease, such as lymphoproliferative disorders [3], another well-defined autoimmune disease, solid malignancies, or infections. Secondary AIHA represents more than 50% of all AIHA cases [2]. The diagnostic features of AIHA combine clinical and laboratory arguments for RBC hemolysis together with the evidence of autoantibodies and/or complement deposition on RBC membrane, mostly detected by a positive direct anti-globulin test (DAT).

The prognosis of AIHA is intrinsically linked to the underlying disease [2]. Mediocre anemia tolerance and ineffective RBC transfusion can lead to intensive care unit (ICU) admission. Overall mortality rate of non-critically ill patients with AIHA has been estimated around 8% [4].

To this day, no study has focused on AIHA in critically ill patients. In this regard, we designed a study to provide new insights into the management and prognosis of AIHA in the ICU.

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Methods

Study design

We conducted a retrospective study in a University Hospital (Saint Louis Hospital, APHP, Paris, France) 12 beds adult medical ICU. The study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by our local institutional review board.

Patients

Patients with AIHA were identified in our computerized database using the International Classification of Diseases 10 code D62 "acquired hemolytic anemia." Medical charts were analyzed by the investigators and all consecutive patients with an age > 18 years and an effective diagnosis of AIHA, defined by a hemoglobin rate < 11 g/dL, with hemolysis features (low haptoglobin level and elevated lactate deshydrogenase (LDH) and/or elevated bilirubin level) and positive DAT were included in the study.

Outcomes

Clinical and biological data including past medical history, etiologic diagnosis, type of DAT, organ failures, treatments, and follow-up were abstracted from the patients' charts. Knaus chronic health status score [5], Sequential Organ Failure Assessment (SOFA) score [6], and SAPS2 score [7] were calculated from this data. Other outcomes recorded were ICU and hospital mortality, and ICU and hospital lengths of stay.

Statistical analysis

Data are presented as numbers (%) or medians (inter-quartile range). Survivors and decedents were compared using chi-squared test for binary variables and Mann-Whitney test for continuous variables. To assess the independent predictors of death, a multivariable logistic regression model including the parameters associated with mortality in univariate analysis was performed, using a logistic regression model. Survival curves were constructed using the Kaplan-Meier method. Crude event rates were determined from Kaplan-Meier rates and compared with the use of the log-rank test. Data on patients with no information were censored at the time of last follow-up available. Two-sided p values below 0.05 were considered significant.

Results

Patients' characteristics

From 2002 to 2015, a total of 270 ICU patients (3%) with hemolytic anemia were identified. Among them, we excluded 226 patients (84%) with non-autoimmune hemolytic anemia (mostly thrombotic microangiopathy patients). Forty-four patients (16%) were finally included in the statistical analysis. The flow chart is presented in Fig. 1.

Table 1 reports the characteristics of the 44 patients. Overall 24 patients (55%) were male, and the median age was 57 years old (31–76). Functional status prior to ICU admission was good (Knaus score A or B) for 24 patients (55%). Most patients presented with comorbidities with a median Charlson comorbidity index of 2 (0–8). Twenty-five patients (56.8%) had a past history of hemopathy, 5 (11%) had solid cancer, and 5 (11%) had HIV infection. Median SAPS2 and SOFA scores at admission were respectively 23 (7–58) and 6 (2–11). Hemoglobin level at admission was 6.8g/dL (4.6–9.1), platelet count was 110000/mm^3 (50,000–213,000), and haptoglobin rate was 0.1g/L (0.1–0.1). Troponin level was elevated in 2 patients (5%).

The main reasons for ICU admission were profound anemia without any organ failure in 19 patients (either for safer transfusion or for continuous monitoring only), acute respiratory failure in 8 patients, acute kidney injury in 5 patients, sepsis in 5 patients, shock in 4 patients, and coma in 3 patients. Twenty-one patients were admitted to the ICU due to direct consequences of AIHA: 19 for profound anemia without organ dysfunction, 2 patients for post-RBC transfusion acute respiratory failure, and 1 patient for myocardial infarction.

The time from first hospitalization to ICU admission was 3 days (0–24). The time from diagnosis of AIHA to hospitalization was inferior to 1 day (0–0).

AIHA characteristics

Twenty patients presented with a DAT positive for immunoglobulin G (IgG) only (46%), 16 with a DAT positive for both IgG and complement (36%), and 8 with a DAT positive for complement only (18%).

Thirty-nine cases of AIHA (89%) were considered to be secondary: 25 (57%) were associated with another hemopathy (8 with chronic lymphocytic leukemia, 8 with low grade lymphoma, 4 with high grade lymphoma, 5 with Castleman disease); 9 (21%) with an autoimmune disease (4 with mixed connective tissue disease, 2 with Evan's syndrome, 2 with anti-phospholipid syndrome), 3 with drugs (1 with cotrimoxazole, 1 with tazocilline, 1 with the association tenofovir + rilpivirine and emtricitabine), and 2 with infectious diseases (mycoplasma pneumonia and parvovirus B19). Characteristics of AIHA are presented in Table 1.

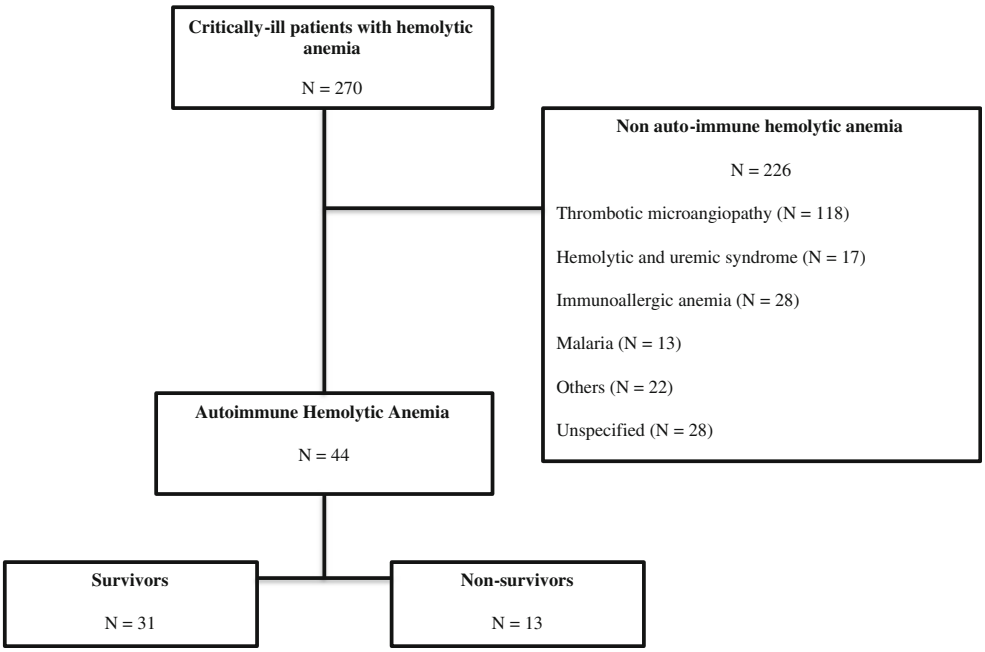

Fig. 1 Flow chart

Outcomes

Thirteen patients (30%) died in the ICU and none of the survivors died during post-ICU hospitalization. Cause of death was organ ischemia in 5 (39%) patients (4 myocardial infarction, 1 mesenteric ischemia), sepsis in 5 (39%) patients (4 with septic choc, 1 pneumonia with refractory hypoxemia), and hemorrhage in 3 (23%) patients (2 intracranial, 1 massive hemoptysis).

ICU and AIHA therapies

Ten patients (23%) received vasopressors and renal replacement therapy was necessary in 14 patients (32%). Fourteen patients (32%) underwent mechanical ventilation during a median duration of 9 (1.3–14.8) days.

Corticosteroids were administered to 44 patients (100%) and other immunosuppressive therapy to 20 patients (45%). Eleven patients (25%) received anti-CD20 monoclonal antibody rituximab. Four patients (9%) underwent plasma exchange therapy because of an initial suspicion of thrombotic microangiopathy. Overall, 28 patients (64%) required red blood cell transfusion during the ICU stay. AIHA and ICU treatments are summarized in Table 2.

ICU stay was 2.5 days (2–6) and hospital stay was 15 days (9–42). Follow-up was 6.8 months (0.4–44.8).

Risk factors for short-term mortality

In non-survivors, age was higher (72 years old [57.8–76.3] vs. 50 years old [34.3–64], $p < 0.01$). Organ dysfunctions at admission were most severe in decedents (SOFA 8 [7–11] vs. 5.5 [3–7], $p < 0.01$). This difference was also remarkable regarding single organ specific parameters at day 1, such as oliguria (8 [62%] in decedents vs. 5.5 [17%] in survivors, $p < 0.01$), Glasgow score (14 [13–15] in decedents vs. 15 [15–15] in survivors, $p < 0.01$), transcutaneous oxygen saturation rate (97% [93–98.5] in decedents vs. 99% [97–100] in survivors, $p = 0.03$), cardiologic SOFA score defined by hypotension and/or need for vasopressors (4 [0–4] in decedents vs. 0 [0–1] in survivors, $p < 0.01$).

Patients with a positive DAT-IgG displayed a poorer short-term outcome in comparison with patients with a Coombs test positive for IgG+complement or complement only (DAT-IgG+C/C) (hospital mortality 45% vs. 17%, $p = 0.035$). In comparison to patients with DAT-IgG+C or DAT-C, DAT-IgG patients were older (65 years old [52–73.5] vs. 49 years old [34.5–59.5], $p = 0.01$), presented with worse previous health status (13/20 [68%] vs. 5/24 [21%] patients with Knaus score C or D), higher hemoglobin level at admission (8.3 [6.7–9.8] vs. 5.5 [3.7–7.5] g/dL, $p < 0.01$) and were less likely to receive rituximab in the ICU (2/20 [10%] vs. 9/24 [38%], $p = 0.03$).

There was no difference between survivors and non-survivors regarding associated comorbidities like hemopathy (18/31 [58%] vs. 7/13 [54%], $p = 0.80$), solid cancer (3/31 [10%] vs. 2/13 [15%], $p = 0.59$) or HIV infection (4/31 [13%] vs. 1/13 [8%], $p = 0.62$). There was a trend toward better outcome in patients admitted to the ICU for profound anemia without any organ failure (either for safer transfusion or for continuous monitoring only): 15/19 (79%) vs. 16/25 (64%) survivors, $p = 0.063$).

In univariate analysis, main risk factors associated with hospital mortality were age, organ dysfunctions at admission

Table 1 Characteristics of 44 patients with severe AIHA requiring ICU admission

Characteristics	Patients ($N = 44$)	Survivors ($N = 31$)	Non-survivors ($N = 13$)	p
Median age, years (IQR)	57 (31–76)	50 (28–74)	72 (49–81)	0.003
Gender, *n* (%)				0.546
Female	20 (46)	15 (48)	5 (39)	
Male	24 (55)	16 (52)	8 (62)	
Knaus score, *n* (%)				0.939
A	9 (21)	7 (24)	2 (15)	
B	15 (36)	10 (35)	5 (39)	
C	15 (36)	10 (35)	5 (39)	
D	3 (7)	2 (7)	1 (8)	
Comorbidities, *n* (%)				
Other hemopathy	25 (57)	18 (58)	7 (54)	0.797
Solid cancer	5 (11)	3 (10)	2 (15)	0.586
HIV infection	5 (11)	4 (13)	1 (8)	0.619
Autoimmune disease	12 (27)	6 (19)	6 (46)	0.069
Time from hospitalization to ICU admission, days (IQR)	3 (0–24)	3 (0–18)	1 (0–60)	0.537
Reasons for ICU admission, *n* (%)				0.063
Hematological disorders	19 (32)	15 (48)	3 (23)	
Respiratory failure	8 (18)	5 (16)	3 (23)	
AKI	5 (11)	3 (10)	2 (15)	
Sepsis	5 (11)	3 (10)	2(15)	
Shock	4 (9)	2 (7)	2 (15)	
Coma	3 (7)	2(7)	1(8)	
SAPS2, median (IQR)	23 (7.2–58)	23 (4.8–32.4)	57.5 (21–94)	0.345
Charlson, median (IQR)	2 (0–8)	2 (0–6.8)	1 (0–12.4)	0.877
SOFA, median (IQR)	6 (3.8–8)	5.5 (3–7)	8 (7–11)	0.003
AIHA characteristics, *n* (%)				
DAT positive	44 (100)	31 (100)	13 (100)	
IgG	20 (46)	11 (36)	9 (69)	0.035
IgG+C	16 (36)	15 (48)	1 (8)	
C	8 (18)	5 (16)	3 (23)	
Idiopathic AIHA	5 (11)	3 (10)	2 (15)	
Secondary AIHA (%)	39 (89)	28 (90)	11 (85)	0.647
Hemopathy	25 (57)	18 (58)	7 (53)	
Autoimmune disease	9 (21)	6 (19)	3 (23)	
Drugs	3 (7)	2 (7)	1 (8)	
Infectious disease	2 (5)	2 (7)	0 (0)	

AIHA autoimmune hemolytic anemia, *IQR* inter quartile range, *ICU* intensive care unit, *AKI* acute kidney injury, *DAT* direct anti-globulin test, *Knaus score* fonctional status prior to admission, *SAPS2* simplified acute physiology score, *Charlson* Charlson comorbidity index, *SOFA* sepsis-related organ failure assessment

and DAT positive for IgG only (DAT-IgG) (Table 1). However, only age and organ dysfunctions at admission were significantly associated with hospital mortality in multivariate analysis (Table 3).

Long-term outcome

Thirty-one patients were discharged from hospital and were followed for 38 months (4–50). At this time, 15 patients were lost to follow-up. Twelve patients were alive and in remission of AIHA, 4 patients died after hospital discharge. Median time from hospitalization to death was 5 months (4–7). Two patients had presented with a DAT-IgG, 2 with a DAT-IgG+C. AIHA was considered to be secondary in all 4 cases (associated with a chronic lymphocytic leukemia in 1 patient, with low-grade lymphoma in 1 patient, with mixed connective tissue disease in 1 patient, and with Evans syndrome in 1 patient). The long-term survival curves of patients according to DAT are presented in Fig. 2.

Discussion

This first retrospective study focusing on AIHA in critically ill patients reveals a hospital mortality rate of 30%, much higher than the 8% observed in the general population of AIHA patients [4]. This high mortality rate is even

Table 2 ICU and AIHA therapies in 44 severe AIHA patients

Treatments	Patients ($N = 44$)	Survivors ($N = 31$)	Non-survivors ($N = 13$)	p
ICU therapies, *n* (%)				
Vasopressors	10 (23)	3 (10)	7 (54)	0.002
Renal replacement therapy	14 (32)	8 (26)	6 (46)	0.333
Mechanical ventilation	14 (32)	3 (10)	11 (85)	< 0.001
MV duration, median (days)	9 (1.3–14.8)	14 (11–17)	3 (1–13.5)	< 0.001
AIHA therapies, *n* (%)				
Corticosteroids	44 (100)	31 (100)	13 (100)	0.113
Other immunosuppressive therapy	20 (45)	12 (39)	8 (62)	0.328
Rituximab	11 (25)	7 (23)	4 (31)	
Cyclophosphamide	4 (9)	4 (13)	0 (0)	
Etoposide	3 (7)	2 (6)	1 (8)	
Eculizumab	2 (4)	0 (0)	2 (2)	
CHOP	1 (2)	0 (0)	1 (8)	
Mycophenolate mofetil	1 (2)	1 (3)	0 (0)	

ICU intensive care unit, *AIHA* autoimmune hemolytic anemia, *MV* mechanical ventilation, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone

more unexpected in light of the favorable characteristics at admission (good functional status and comorbidity index, median age of 57 years old) and the therapeutic expertise of our center. It should also be pointed out that in 32% of cases, patients were admitted in ICU for hematological disorder without any organ dysfunction at admission (either for safer transfusion or for continuous monitoring only).

These findings along with the positive trend for a lower mortality rate observed in patients admitted for profound anemia without any organ dysfunction may encourage an "early" ICU admission for patients with AIHA. Providing the optimal support to this high-risk population, before any organ dysfunction, as previously demonstrated for others hemopathies such as acute myeloid leukemia [8], might improve outcomes. Considering the high mortality rate and the fact that cases with a severe onset are frequently refractory to different therapies [9], a specific therapeutic strategy could also be discussed for critically ill patients with AIHA. For example, given its efficacy and safety along with its delayed action [10], it may be of interest to evaluate the indication of early rituximab as a first line therapy for AIHA patients requiring ICU admission.

Table 3 Short-term mortality risk factors of AIHA in intensive care unit

Risk factors	Odds ratio	95% CI	p
Age (per year)	1.078	1.078–1.001	0.047
SOFA score at day 1 (per point)	1.638	1.111–2.415	0.013
DAT-IgG	4.573	0.599–34.924	0.143

AIHA autoimmune hemolytic anemia, *SOFA* sepsis-related organ failure assessment, *DAT-IgG* direct anti-globulin test positive for IgG only

In this context of peripheral anemia, 64% of the patients required red blood cells transfusion in ICU. There was no specific protocol and transfusion's indication was based on clinical tolerance. Unfortunately, our database did not include transfusional tolerance and efficacy parameters.

Three risk factors for short-term mortality could be identified in univariate analysis. If age and organ dysfunctions are expected risk factors, DAT positive for IgG only should in contrast get our attention. In the CEREVANCE cohort [11], involving pediatric cases of autoimmune cytopenias, DAT positive for IgG only was already a risk factor for mortality. To our knowledge, this is the first time that DAT-IgG was associated to an increased mortality rate in adult patients with AIHA.

In the same cohort, DAT positive for IgG and IgG+C were associated with a lower rate of survival with continuous complete remission (adjusted HR 0.43; 95% confidence interval, 0.21–0.86). In this pediatric population, this result was shown to be related with underlying disease (mostly Evan's syndrome). However, this finding does not seem extendable to our cohort as there was no difference between survivors and decedents regarding associated comorbidities such as hemopathy, solid cancer, or HIV infection.

With 89% of secondary AIHA (mostly hemopathy associated), specific patient recruitment of Saint Louis Hospital generates a center bias which makes interpretation difficult. Further, multicentric studies are necessary to explain these trends and evaluate the potential benefit of specific therapeutic strategies.

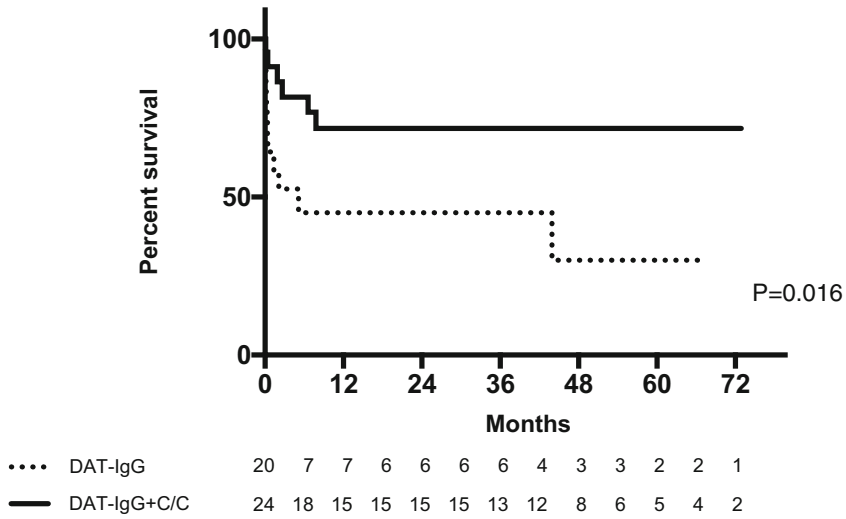

Fig. 2 Long-term survival curves of patients with AIHA according to DAT

Conclusion

Short-term mortality rate of AIHA critically ill patients is consequential and higher than previously described for AIHA in general population. Prognosis appears to be impacted by age, organ failures, and DAT-IgG. This finding may encourage an early admission in ICU for patients with AIHA. Further studies are necessary to explain these trends.

Compliance with ethical standards

The study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by our local institutional review board.

Conflict of interest The authors declare that they have no conflict of interest.

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