Characteristics and outcome of adults with severe autoimmune hemolytic anemia admitted to the intensive care unit: Results from a large French observational study

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To the Editor:

Adult'autoimmune hemolytic anemia (AIHA), which is often seen as a rare and "benign" autoimmune hematological disease, can be life-threatening with an overall mortality rate from 8% to 20% depending on the series[1–3] and a short-term mortality rate that can be up to 30% in intensive care units (ICUs).[4] Factors associated with the need for ICU management of patients with severe AIHA remain partially unknown because only few data are available in the literature.[3–5] The aims of this retrospective observational multicenter study set up by the French reference center for adult immune cytopenias were to: (1) better describe the baseline characteristics and outcome of adults with severe AIHA admitted to an ICU, (2) investigate the factors associated with mortality in the ICU, and (3) identify factors at AIHA diagnosis associated with admission to an ICU. To be included in the study, patients had to (1) be ≥16 years old at the time of AIHA onset; (2) have a diagnosis of AIHA defined as hemoglobin level <12 g/dL, with ≥2 features of hemolysis among low haptoglobin level and/or elevated lactate dehydrogenase (LDH) level and/or elevated free bilirubin level, and a positive direct antiglobulin test (DAT) with no other cause of acquired or hereditary hemolytic anemia; and (3) at least one admission to an ICU specifically for AIHA management between January 2013 and December 2020. We excluded patients with non-autoimmune hemolytic anemia, DAT-negative AIHA and drug-induced immune hemolytic anemia and those admitted to the ICU for another reason than severity of AIHA. Baseline data in the ICU included the Charlson Comorbidity Index, the Knaus score, the Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score (SAPS) II. The Bone Marrow Reticulocytes Index (BMRI) was calculated from these data using the formula (absolute reticulocyte count $\times 10^9$/L $\times$ patient's hemoglobin level [g/dL]/normal hemoglobin level [g/dL]). Inadequate reticulocytosis was defined as BMRI <121.[3] Response to treatment for warm AIHA (wAIHA) was defined according to standard definition.[3,6]

In the ICU group, characteristics of patients who died in the ICU or at 1 year after ICU discharge were compared to survivors by the Fisher exact test for categorical variables and Student *t* test or Mann–Whitney test for quantitative variables as appropriate. We also compared the characteristics of patients from the ICU group and adults with AIHA diagnosed over the same period (2000–2021) who had never been admitted to an ICU (the non-ICU group). The characteristics of the ICU and non-ICU groups were compared by univariate logistic regression. Clinically relevant variables and variables associated on univariate analyses with at $p < .20$ were selected for multivariable analysis. In case of correlation (assessed by using the Cramer V for qualitative variables or Spearman coefficient >0.3 for quantitative non-normally distributed variables), the most clinically relevant variable was introduced into the model. The multivariable logistic regression model was created using a backward stepwise selection procedure, and interactions were tested. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. $p < .05$ was considered statistically significant. Statistical analysis was performed with STATA 16.

We included 62 patients (42% females, median age 55 years [interquartile range 39–65]) with mostly warm (79%), newly diagnosed (69.3%), and secondary AIHA (64.5%). The median hemoglobin level at ICU admission was 4.3 g/dL [3.7–5.1]; 92% of patients had a low (< 121) BMRI. Baseline characteristics of the 62 patients admitted in the ICU are summarized in Table S1, half of the patients had at least one organ failure at time of admission. Despite systematic thromboprophylaxis with enoxaparin, venous thrombotic event occurred in 6 (9.7%) patients and 10 (16%) patients experienced severe infectious complications. Overall, eight (12.9%) patients died in the ICU after a median of 3.5 [1–9] days after admission. Causes of death were hypoxic cardiac arrest due to refractory AIHA for 5 (62.5%) patients and massive pulmonary embolism for three (37.5%) patients. Factors significantly associated with the probability of death in the ICU were increased C-reactive protein level ($p = .011$) and leukocytes level ($p = .01$); need for red blood cell transfusion ($p = .008$); high SOFA and SAPS II scores at admission ($p = .006$); increased number of organ failures ($p < .001$), thrombotic events ($p = .024$) and sepsis ($p = .019$) (Table S2). Median ICU stay was 3 days [2–6]. Half of the patients (31/62) presented at least one organ dysfunction during the ICU stay. For 90.3% of patients, transfusions were required in the ICU, with a median number of packed RBC units of 4 [2–7] or 1.5 units per day [1.0–2.5]. Among other supportive measures, recombinant erythropoietin was given to 14 (22.6%) patients. For managing AIHA, 10 (16.1%) patients received intravenous immunoglobulin (IV Ig) and 5 (8.1%) plasma exchange. More "specific" therapies included corticosteroids, which were administered to 59/62 (95.2%) patients, and 29 (46%) received at least one other treatment line. Among the 54 survivors, median stay in hospital was 20 days [11–38], and 32 (59.3%) patients

TABLE 1 Comparison of the main characteristics between the "ICU group" and the "non-ICU group" by multivariable logistic regression analysis

Characteristics	Adjusted OR [95% CI]	*p* value
Age at AIHA onset (years)		.178
≤43.5	Reference	
>43.5 and ≤61	1.03 [0.31–3.41]	
>61 and ≤73	1.20 [0.31–4.70]	
>73	0.25 [0.06–1.12]	
Cold AIHA	2.87 [0.39–21.44]	.303
Evans syndrome	3.14 [0.90–11.02]	**.074**
Causes		
Primary	Reference	
Secondary	1.91 [0.69–5.28]	.213
Hemoglobin (g/dL)	0.55 [0.40–0.75]	**<.001**
BMRI < 121	1.86 [0.59–5.84]	.285
LDH (UI/L)	1.00 [1.00–1.00]	.179
Indirect bilirubin level (μmol/L)	1.03 [1.02–1.05]	**<.001**
Direct antiglobulin test pattern: IgG + C3	1.58 [0.56–4.48]	.392

Note: Analysis performed on the 155 patients for whom no data were missing on all variables studied. Bold values represent significant or close to significancy *p* values

Abbreviations: 95% CI, 95% confidence interval; AIHA, autoimmune hemolytic anemia; BMRI, bone marrow reticulocytes index; LDH, lactate dehydrogenase; OR, odds ratio.

received additional AIHA therapy. When combining treatments received during the ICU stay and hospitalization after ICU discharge, the median number of treatment lines was 2 [2, 3], with rituximab ($n = 37$), the second most frequently prescribed drug after corticosteroids. Management of wAIHA during hospitalization including the stay in the ICU and patterns of response to treatment are summarized in Figure S1. Median follow up after ICU stay was 24 months [11–47]. Five (9.3%) patients were readmitted to the ICU for severe AIHA relapse/flare at a median of 26 days [3–93] after the first stay in the ICU. Overall, the rate of AIHA relapse was 29.6% (16/54), with a median number of relapses of 1 [1, 2]. At last visit, AIHA was still active in 9/54 (16.7%) cases. 9 of 49 (18%) patients (five lost to follow-up) died within a year after ICU discharge, which led to an overall mortality rate at 1 year of 30% (17/57). Eight of the nine patients had secondary AIHA and at the time of death, AIHA was active in 6/9 (66.7%) patients. Causes of deaths after the first stay in the ICU were: underlying disease progression ($n = 3$, including 2 T-cell lymphoma and 1 diffuse large B-cell lymphoma); infection ($n = 3$); pulmonary embolism ($n = 1$); hemorrhagic shock due to iatrogenic wound ($n = 1$); and multiorgan failure due to massive hemolysis associated CAD ($n = 1$).

On univariate analyses, a comparison between survivors and patients who died within 1 year after discharge from ICU did not reveal any factors significantly associated with risk of death, apart from increased SAPS II score at the time of admission to the ICU ($p = .035$).

The characteristics of the 62 ICU patients were compared to those of 138 adults diagnosed with AIHA who were never admitted to an ICU (non-ICU group) seen over a same period in one of the seven main recruiting centers. On univariate analyses, factors associated with admission to an ICU were young age, Evans syndrome, low hemoglobin level (<6 g/dL), low reticulocytes count ($<100 \times 10^9$/L), BMRI <121, high leukocytes count, and high median indirect bilirubin level (Table S3). On multivariable analysis, two factors were significantly associated at diagnosis with an admission in ICU: a low hemoglobin level and a high indirect bilirubin level (Table 1).

As compared with the few data available in the literature, our study has several strengths, including its multicenter design limiting recruitment bias; the fact that the eligibility criteria were not based on hemoglobin level but rather on admission to the ICU, which is more likely to reflect the disease severity; the relatively substantial number of patients included ($n = 62$); the extended follow-up up to 2 years; and last but not least, the comparison of the baseline characteristics of the ICU group and 138 unmatched adults with AIHA seen over the same period but never admitted to the ICU.

This study also has some limitations, which are mostly due to its retrospective design and also a lack of statistical power. Additionnaly, the association of admission to ICU with severe anemia and increased indirect bilirubin may reflect a selection bias and assessing treatment efficacy was difficult, especially the relevance of IVIg treatment and plasma exchange, which were administered as rescue therapy in association with other treatments and to a small number of patients.

In conclusion, AIHA in adulthood can be life-threatening regardless of age, with a short-term mortality rate in the ICU of 13% in our study whatever the treatment administered. Of note, 64.5% of AIHA patients admitted to the ICU had secondary AIHA and 25.8% Evans syndrome,[7] and among survivors, mortality rate at 1 year after ICU discharge remained particularly high and mainly related to the progression of the underlying disease. Patients with low (≤6 g/dL) and/or rapidly decreasing hemoglobin level (partly due to inadequate reticulocytosis, which can be easily assessed by the BMRI) and high median indirect bilirubin level should promptly receive treatment including recombinant EPO, which has been shown to be effective and safe in the literature[8]; and be monitored in the ICU. The place of IVIg treatment and plasma exchange as rescue therapy during the critical phase of the disease remains to be assessed prospectively as well as the best strategy for optimizing thromboprophylaxis. Patients who are discharged from the ICU and from the hospital must be carefully monitored and followed on a long-term.

CONFLICT OF INTEREST

Bertrand Godeau has received honoraria (advisory boards, speaker fees) from Griffols, Amgen, and Novartis. Marc Michel has received honoraria (advisory boards, speaker fees) from Novartis, Sanofi, Rigel; Alexion and UCB.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.