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Clinical profile of patients with systemic autoimmune diseases treated in the intensive care unit who developed diffuse alveolar haemorrhage – an observational retrospective cohort study

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Abstract

Background: Patients with autoimmune diseases constitute a relatively low percentage of the intensive care unit (ICU) population but their prognosis is particularly poor, partially due to involvement of multiple organs as well as complications related to immunosuppressive treatment. Diffuse alveolar haemorrhage (DAH) is one of the most life-threatening presentations of autoimmune diseases, associated with worse outcomes. The aim of this study is to report about clinical factors associated with DAH in the ICU setting and to assess the survival in 5-year follow-up.

Methods: This is an observational, retrospective, cohort study performed in the ICU of the University Hospital in Krakow, Poland. We enrolled 21 patients treated for the first time in the ICU due to autoimmune diseases, who developed DAH. Severity of patients' clinical condition was assessed on the first day using APACHE II, APACHE III, SAPS II and SOFA scores. Mortality was assessed during the ICU stay and in 5-year follow-up.

Results: The median age of the study population was 53 (18–78) years and 13 (61.9%) of patients were females. The most common diagnoses were granulomatosis with polyangiitis (38.1%), systemic lupus erythematosus (23.8%) and microscopic polyangiitis (14.3%). Most of the patients required mechanical ventilation (85.7%), renal replacement therapy (57.1%) and blood product transfusions (71.4%). Mortality in the ICU was 52.4%, while in both 1-year and 5-year follow-up it was 76.2%.

Conclusion: Patients who develop DAH in the course of autoimmune diseases and are treated in the ICU have a poor prognosis and often require advanced therapeutic measures.

Key words: autoimmune diseases, diffused alveolar haemorrhage, intensive care unit, mortality.

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Diffuse alveolar haemorrhage (DAH) is a potentially life-threatening condition defined as bleeding into alveolar space due to destruction of the pulmonary capillaries. It can be associated with numerous disorders, but it most commonly develops in the course of systemic autoimmune diseases, such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) e.g., granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), anti-glomerular basement membrane disease, and systemic lupus erythematosus (SLE) [1]. Diffuse alveolar haemorrhage is not a common condition, occurring in 10–47% of patients with MPA, 7–13% among patients with GPA and approximately 5% of patients with systemic lupus erythematosus [2-4].

It is hypothesized that the underlying mechanisms are capillaritis and granular immune complex deposition in alveolar septae [4]. Diffuse alveolar haemorrhage can have a mild course with unspecific symptoms such as fatigue, shortness of breath, through more alarming presentations, including haemoptysis and dyspnoea, up to severe respiratory failure requiring treatment in the intensive care unit (ICU). Moreover, the observed increase in incidence of autoimmune diseases [5, 6] might suggest that this syndrome will be more frequently seen in the ICU setting. According to our knowledge, studies concern-

ing patients with autoimmune diseases, treated in the ICU, who developed DAH, are very limited [7, 8].

Diagnosis of DAH is complex and poses a particular challenge in critically ill patients. The typical clinical symptom – hemoptysis – is present only in approximately one third of cases [1, 4]. The most crucial imaging method is chest computed tomography (CT), which most often reveals ground glass opacities and/or alveolar consolidation with air bronchogram. Another important diagnostic method is a fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) showing increasing haemorrhage in serial lavages and hemosiderin-laden macrophages found in the cytological examination. Basic laboratory tests usually show anaemia and, less specifically, increased lactate dehydrogenase (LDH) levels. One of the most typical features of DAH is increased diffusion lung capacity for carbon monoxide (DLCO) in lung function tests. The gold standard for the diagnosis of DAH is, however, surgical biopsy [4]. Obviously, in the ICU setting, some of the aforementioned methods pose too high a threat to patients. Therefore the diagnosis needs to be made on the basis of clinical examination, imaging and laboratory tests and bronchoscopy.

Our group has recently reported on the high mortality rate of ICU patients with systemic autoimmune diseases reaching up to 70% in 5-year follow-up [9]. Considering that DAH is one of the most severe autoimmune disease manifestations, due to its sudden onset and potentially fatal outcome, prompt diagnosis and treatment are crucial [10]. Reported mortality of DAH in the available literature is high but variable, ranging from 20% to 80% [11]. Previous reports suggest that shock, impaired renal function, as well as plasmatic lactate dehydrogenase levels are factors associated with in-hospital mortality in this population [12].

The aim of this study is to describe patients with DAH in the course of systemic autoimmune disease treated in the ICU with survival analysis in a 5-year follow-up.

METHODS

This is an observational, retrospective cohort study, conducted in the ICU of the Allergy and Immunology Department at the University Hospital in Krakow, Poland. The study is a part of the ICU patient database project, which was approved by the Jagiellonian University Bioethics Committee. Due to the nature of the study there was no requirement for written informed consent.

The study personnel searched the hospital's electronic database from years 2001–2014 in order to identify patients with the diagnosis of systemic autoimmune diseases treated in the ICU. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes as well as the full names of the systemic autoimmune diseases were used in database screening. Each medical record was later thoroughly assessed to confirm patients' eligibility for the study. Among patients included in the study, those diagnosed with DAH were selected for the analysis. The study flowchart is provided in Figure 1.

If the patient was treated in the ICU more than once, only the first admission was analyzed. Patients admitted to the ICU only for a single procedure (e.g. dialysis catheter implantation or therapeutic plasma exchange) were excluded from the study. Diagnosis of DAH was made by experienced clinicians according to commonly used criteria including clinical examination, laboratory tests, CT as well as bronchoscopy.

The study personnel gathered demographic, clinical and laboratory data. The reason for the ICU admission, history of autoimmune diseases and immunosuppressive treatment, procedures performed in the ICU and all variables concerning ICU stay were also extracted.

Based on available data from the first 24 hours of ICU stay, the authors calculated the following indices: Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Simplified Acute Physiology Score (SAPS) II as well as the Sequential Organ Failure Assessment (SOFA) [13]. Patients' survival was assessed at the ICU discharge, 1 year and 5 years after the first ICU admission by phone call follow-up and other available resources (Outpatient Clinic Database, National Health Insurance Database).

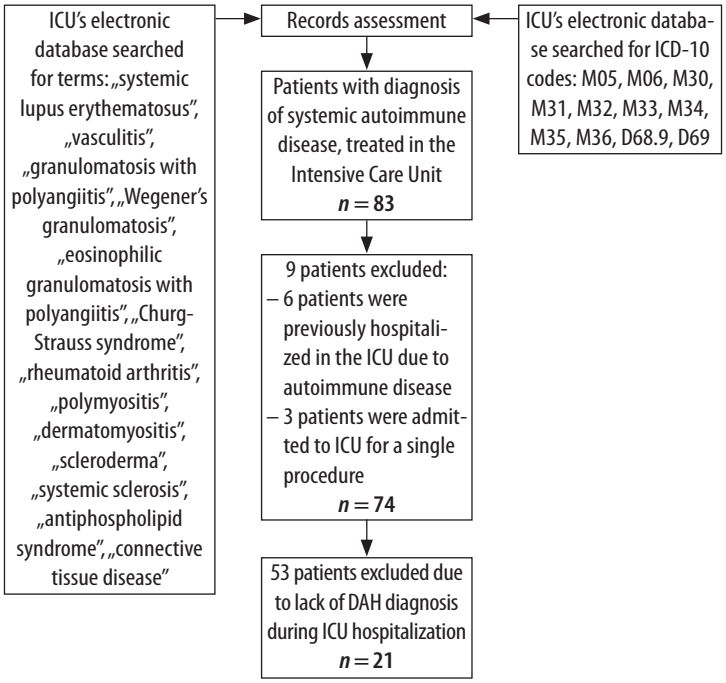

FIGURE 1. The study flowchart

TABLE 1. Basic demographic and clinical characteristics of the study group

Factor	
Demographics	
Females	13 (61.9%)
Age (years)	53 (18–78)
Primary diagnosis	
Granulomatosis with polyangiitis	8 (38.1%)
Systemic lupus erythematosus	5 (23.8%)
Microscopic polyangiitis	3 (14.3%)
Polymyositis and dermatomyositis	2 (9.5%)
Rheumatoid arthritis	1 (4.8%)
Goodpasteur's syndrome	1 (4.8%)
Scleroderma	1 (4.8%)
Comorbidities	
Chronic kidney disease	12 (57.1%)
Hypertension	7 (33.3%)
Diabetes mellitus	5 (23.8%)
Pre-ICU treatment	
Long-term steroids (> 3 months)	9 (42.9%)
Cyclophosphamide	12 (57.1%)
Steroids + cyclophosphamide	7 (33.3%)

Categorical variables are presented as number (%). Continuous variables are presented as median (range).

TABLE 2. Management in the intensive care unit (ICU)

ICU management	
Diagnosis of autoimmune disease in the ICU	4 (19.0%)
ICU stay duration (days)	11 (2–21)
Steroid pulses	6 (28.6%)
Steroids	14 (66.7%)
Cyclophosphamide	6 (28.6%)
Plasmapheresis	4 (19.0%)
Mechanical ventilation	18 (85.7%)
Number of days on mechanical ventilation	6 (1–15)
Renal replacement therapy	12 (57.1%)
Blood products transfusion	15 (71.4%)

Categorical variables are presented as number (%). Continuous variables are presented as median (interquartile range).

Variables are described as mean with standard deviation (SD) or median with interquartile ranges depending on the data distribution. Comparisons between groups were performed using the χ^2 test for categorical variables, whereas continuous variables were compared using Student's t test and the Mann Whitney *U*-test, depending on data distribution. Survival was defined as the time from the ICU admission to death from any cause and event-time distribution was graphically presented using Kaplan-Meier curves. Differences in mortality between the two study groups were assessed using the log-rank test. Statistical analysis was performed with StatSoft Statistica 13 software (StatSoft, Tulsa, OK, USA) and RStudio version 1.1.383 (RStudio, Boston, MA, USA); packages: survival, survminer. Graphs were prepared with GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) and RStudio version 1.1.383 (RStudio, Boston, MA, USA); packages: survival, survminer.

RESULTS

Baseline demographic clinical characteristics

Of 74 patients with systemic autoimmune diseases treated in the ICU between 2002 and 2014, we selected 21 who developed DAH. The median age of patients was 53 (range: 18–78) years and 13 (61.9%) of them were female. The majority of the patients were diagnosed with granulomatosis with polyangiitis (8/21; 38.1%), systemic lupus erythematosus (5/21; 23.8%) and microscopic polyangiitis (3/21; 14.3%). The autoimmune disease was diagnosed during the ICU hospitalization in 4 cases (19.0%). Diffuse alveolar haemorrhage was the reason for admission in 6 patients (28.6%) and developed during ICU hospitalization in 15 cases (71.4%). The most common comorbidity in this cohort was chronic kidney disease, which was diagnosed in 12 patients (57.1%), 7 (33.3%) of whom had end-stage chronic kidney disease. Detailed information concerning basic characteristics of the study group and autoimmune disease diagnosis can be found in Table 1.

Pre-ICU immunosuppressive therapy

The majority of the patients (17/21; 81.0%) were administered at least one immunosuppressive medication prior to admission to the ICU. Nine patients (42.9%) received long-term steroid therapy, twelve patients (57.1%) cyclophosphamide and in seven patients (33.3%) a combination of these medications was used.

ICU hospitalization

The most commonly used causal treatment was steroids in maintenance doses only (14/21, 66.7%), steroid pulses (6/21, 28.6%), cyclophosphamide infusions (6/21, 28.6%) and plasmapheresis (4/21, 19.0%). The majority of the patients required mechanical ventilation (18/21, 85.7%), renal replacement therapy (12/21, 57.1%) and blood product transfusions (15/21, 71.4%). A detailed description of the ICU management is summarized in Table 2.

Survival analysis

Almost half of the patients survived the ICU hospitalization (10/21; 47.6%). The survival rate was 23.8% (5/21) in both 1-year and 5-year follow-up. Five of the total eleven deaths during ICU stay were related to infection (45.5%). A detailed description

of the survival and the calculated SAPS II, APACHE II, APACHE III and 1st day SOFA scores can be found in Table 3. The Kaplan-Meier curve for 1-year survival is presented in Figure 2.

Comparison of study groups

Patients who developed DAH were less often administered steroids before admission to the ICU (42.9% vs. 69.8%, $P = 0.03$), were more often diagnosed with autoimmune disease in the ICU (19.0% vs. 3.8%, $P = 0.03$) and achieved a higher SAPS II score (55.0 vs. 41.0, $P = 0.014$). In terms of treatment during ICU hospitalization, patients with DAH more often received steroid pulses (28.6% vs. 9.4%, $P = 0.04$), cyclophosphamide (28.6% vs. 5.7%, $P = 0.007$) and renal replacement therapy (57.1% vs. 28.3%, $P = 0.02$) compared to those who did not develop DAH. We did not observe any significant differences in survival between the groups. Exact data are presented in Tables 4 and 5. The Kaplan-Meier curve comparing survival in the two groups is shown in Figure 3.

DISCUSSION

In this retrospective cohort study, we analysed 21 patients with systemic autoimmune diseases complicated by diffuse alveolar haemorrhage, treated in the intensive care unit. It showed that this condition is associated with high short-term and long-term mortality as well as significant requirement for advanced life-support procedures. This is, to our best knowledge, the first study describing characteristics and outcomes of Polish patients with systemic autoimmune diseases, treated in the intensive care unit, who developed DAH. It also provides a unique insight into long-term outcomes of this very specific group of patients.

Our study confirms that among patients with systemic autoimmune diseases, DAH occurs most commonly among patients with ANCA-associated vasculitis. Interestingly, in almost 20% of patients in the study, autoimmune diseases were diagnosed during ICU hospitalization. Similar findings were obtained in the study by Monti *et al*., where 30% of ICU-diagnosed vasculitis patients had DAH [14]. It highlights the fact that this life-threatening complication is a hallmark presentation of autoimmune disease in a significant number of patients. In our opinion, these results suggest that there is still room for improvement in early detection of autoimmune diseases before the most severe presentations, such as DAH, occur and higher vigilance of clinicians is warranted.

Typically, causal treatment of DAH consists of pulse corticosteroids and other intravenous immunosuppressants such as cyclophosphamide [11]. Other reports suggest the use of a monoclonal chimeric antibody targeting CD20 (rituximab) [4], plasmapheresis [8, 15] as well as recombinant activated factor VII (rFVIIa) [16]. There are also case report series of extracorporeal membrane oxygenation (ECMO) use in severe, hypoxic respiratory failure due to

TABLE 3. Prognostic scale scores and survival in the ICU as well as 1-year and 5-year follow-up

Prognostic scales	
SAPS II	55 (22–99)
APACHE II	25 (10–48)
APACHE III	82 (43–167)
SOFA on 1st day	8 (2–19)
Survival	
ICU	10 (47.6%)
1 year	5 (23.8%)
5 years	5 (23.8%)*

Categorical variables are presented as number (%). Continuous variables are presented as median (interquartile range). *None of the patients died between 1-year and 5-year follow-up

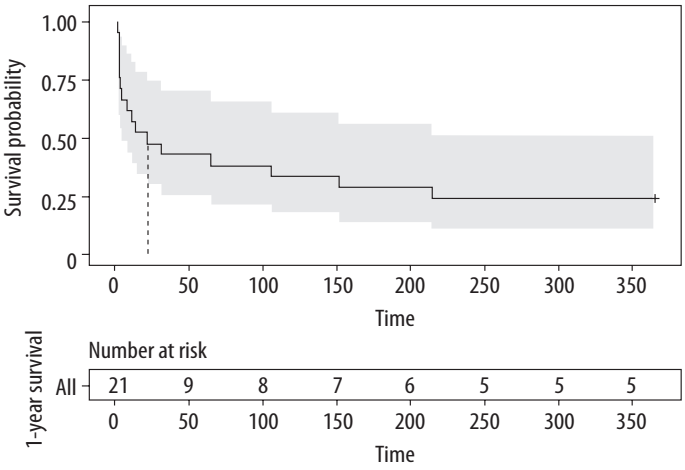

FIGURE 2. The Kaplan-Meier curve for 1-year survival among patients who developed diffuse alveolar haemorrhage. Gray area presents 95% confidence interval of survival probability while vertical line shows median survival time

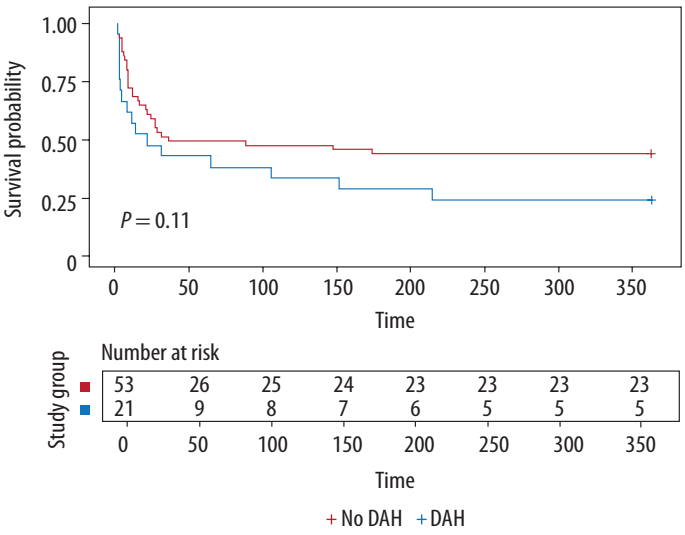

FIGURE 3. The Kaplan-Meier curves comparing 1-year survival between patients with diffuse alveolar haemorrhage (DAH) (blue line) and those who did not develop DAH (red line)

TABLE 4. Comparison of study groups in terms of demographics, comorbidities and immunosuppressive treatment before intensive care unit (ICU) admission

Feature	DAH ($n = 21$)	No DAH ($n = 53$)	*P*-value
Demographics			
Females	13 (61.9%)	40 (75.5%)	0.24
Age (years); median (range)	53 (18–78)	54 (20–81)	0.9
Comorbidities			
Chronic kidney disease	12 (57.1%)	22 (41.5%)	0.22
Hypertension	7 (33.3%)	19 (35.8%)	0.84
Diabetes mellitus	5 (23.8%)	9 (17.0%)	0.5
Pre-ICU treatment			
Long-term steroids (> 3 months)	9 (42.9%)	37 (69.8%)	0.03
Other immunosuppressants	12 (57.1%)	36 (67.9%)	0.77
Steroids + other immunosuppressants	7 (33.3%)	28 (52.8%)	0.13

Categorical variables are presented as number (%). Continuous variables are presented as median (interquartile range).
DAH – diffuse alveolar haemorrhage

TABLE 5. Comparison of study groups in terms of intensive care unit (ICU) management, prognostic scales scores and survival

Feature	DAH ($n = 21$)	No DAH ($n = 53$)	*P*-value
ICU management			
Diagnosis of autoimmune disease in the ICU	4 (19.0%)	2 (3.8%)	0.03
ICU stay duration (days)	11 (2–21)	8 (5–17)	0.88
Steroid pulses	6 (28.6%)	5 (9.4%)	0.04
Steroids	14 (66.7%)	39 (73.6%)	0.55
Cyclophosphamide	6 (28.6%)	3 (5.7%)	0.007
Plasmapheresis	4 (19.0%)	3 (5.7%)	0.08
Mechanical ventilation	18 (85.7%)	35 (66.0%)	0.09
Number of days on mechanical ventilation	6 (1–15)	6 (0–10)	0.45
Renal replacement therapy	12 (57.1%)	15 (28.3%)	0.02
Blood products transfusion	15 (71.4%)	28 (52.8%)	0.14
Prognostic scales			
SAPS II	55 (22–99)	41 (27.5–58)	0.014
APACHE II	25 (10–48)	22.5 (16–29)	0.33
APACHE III	82 (43–167)	76.5 (55–106.5)	0.24
SOFA on 1st day	8 (2–19)	7.5 (4–11)	0.23
Survival			
ICU	10 (47.6%)	32 (60.4%)	0.32
1 year	5 (23.8%)	23 (43.4%)	0.11
5 years	5 (23.8%)*	14 (26.4%)	0.29

Categorical variables are presented as number (%). Continuous variables are presented as median (interquartile range).
*None of the patients died between 1-year and 5-year follow-up.
DAH – diffuse alveolar haemorrhage

DAH [17, 18]. In our cohort the majority of patients were treated with steroids, more than 1 in 4 patients required steroid pulses or cyclophosphamide infusions, in less than 20% of cases plasmaphereses were performed, while none of the patients received rituximab. Due to the lack of well-designed studies and low prevalence of the described syndrome, there is lack of evidence-based guidelines concerning treatment of DAH in autoimmune diseases. Hopefully, upcoming publication of PEXIVAS study results [19] will shed more light on the usefulness of plasmapheresis in treatment of DAH, especially considering that this topic is controversial, as there is not enough evidence of the treatment benefits, and the plasmapheresis procedure may also be associated with some complications [15]. It is important to remember that the key to DAH management is the successful treatment of underlying disease [10].

Another interesting observation is high use of advanced therapeutic procedures – the majority of our patients required mechanical ventilation, blood product transfusions and renal replacement therapy. Available literature mentions mainly invasive mechanical ventilation use, which is very variable and ranges from 17% to 70%. However, most of the studies concern patients treated outside the ICU [7, 12, 20]. Such frequent use of renal replacement therapy is probably associated with common renal involvement in autoimmune diseases, while blood product transfusions are related to blood loss resulting from haemorrhage.

Patients enrolled in our study were in a severe clinical condition from the moment of admission, which is reflected in high scores in all prognostic scales. As an example, the median score in SAPS II corresponds with predicted mortality of 57%. Our study showed that more than 50% of patients with systemic autoimmune diseases who developed DAH do not survive ICU hospitalization. In longer follow-up, there is a significant drop in survival to less than 25% at 1 year. Interestingly, none of the patients died within the following 4 years of observation. This finding has emphasized how important for patients' prognosis is the ICU treatment and then check-ups during the following year. Compared to previous studies, the mortality in our cohort is markedly higher. This is probably associated with the fact that our group consists exclusively of patients treated in the ICU. When compared to the study by Rabe *et al*., where DAH was assessed in the ICU setting (but not only in autoimmune diseases), the mortality rate is similar [7].

Additional analysis involving comparison of study groups, suggests that, even among patients with systemic autoimmune diseases, those who develop DAH are admitted to the ICU in worse clinical condition, receive more intensive immunosuppressive therapy and more often require renal replace-

ment therapy. Interestingly, there is no statistically significant difference in terms of survival between the groups. However, this is probably related to the limited sample size as 1-year survival in the DAH group is almost two times lower compared to the remaining patients.

Our study has several limitations. First, the study group is small, which limits our ability to perform multivariable analysis to assess e.g. mortality risk factors. Moreover, the retrospective character of the study hinders precise assessment of several crucial features, e.g. cause of death. Also, follow-up analysis concerned only mortality, and we had no information concerning DAH relapses and rehospitalizations.

CONCLUSIONS

Patients who develop DAH in the course of systemic autoimmune disease and require hospitalization in the ICU are at particularly high risk for mortality, and most of them require mechanical ventilation, renal replacement therapy and blood product transfusions.

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