Rheumatic diseases associated with alveolar hemorrhage: analysis of the national inpatient sample

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Abstract
Objective Diffuse alveolar hemorrhage (DAH) is a severe pulmonary complication of numerous diseases, including rheumatic conditions. We have conducted an observational study using inpatient data from the National Inpatient Sample to study the relationship of DAH with rheumatic conditions along with their descriptive characteristics.

Methods An observational study was conducted on hospitalizations in 2016–2018 with a principal diagnosis of DAH from the United States National Inpatient Sample database. A multivariate logistic regression analysis was performed to calculate adjusted odds ratios (ORadj) for risk factors of DAH.

Results A total of 5420 DAH hospitalizations were identified among 90 million hospitalizations. Mortality in this group was found to be 24.3%. Majority of patients admitted with DAH were white and male, with a mean age of 61.8 years and a mean LOS of 10.6 days. Multivariate analysis showed that multiple rheumatic diseases were associated with DAH, including antineutrophil cytoplasmic antibody–associated vasculitis (AAV) (ORadj 72.56) (95% C.I. 50.607–104.043), antiphospholipid antibody syndrome (APLS) (ORadj 6.51) (95% C.I. 3.734–11.366), eosinophilic granulomatosis with polyangiitis (EGPA) (ORadj 7.13) (95% C.I. 1.886–26.926), Goodpasture’s (ORadj 30.58) (95% C.I. 16.360–57.176), rheumatoid arthritis (RA) (ORadj 1.60) (95% C.I. 1.158–2.212), sarcoidosis (ORadj 3.99) (95% C.I. 2.300–6.926), and systemic lupus (SLE) (ORadj 5.82) (95% C.I. 3.993–8.481).

Conclusion Although DAH is a relatively rare entity, it carries a very high mortality. Multiple rheumatic diseases were associated with DAH hospitalizations including AAV, APLS, EGPA, Goodpasture’s, RA, sarcoidosis, and SLE.

Key points
• It is known that DAH carries a high morbidity and mortality based on prior literature. However, large datasets on the association of rheumatic diseases with DAH are lacking
• This study identifies the descriptive characteristics of patients admitted to the hospital with DAH
• This study also identifies the strength of association of rheumatic diseases with DAH

Keywords Alveolar hemorrhage · ANCA vasculitis · Lupus

Introduction
Diffuse alveolar hemorrhage (DAH) is a severe pulmonary complication of numerous diseases and carries a significant morbidity and mortality. DAH requires prompt diagnosis and aggressive treatment [1]. DAH has been shown to be a complication of multiple rheumatic conditions. A recent retrospective observational study by Bhushan et al. that was conducted at a tertiary-care academic center showed that 37.5% of DAH patients over a 12-year period had underlying immune causes, with granulomatosis with polyangiitis (GPA) (10.2%), microscopic polyangiitis (MPA) (9%), and
systemic lupus erythematosus (SLE) (9%) being the most common [2]. Other reports also show DAH to be associated with various immune and non-immune diseases including vasculitis [3–8], Goodpasture syndrome [9, 10], antiphospholipid antibody syndrome (APLS) [11–15], SLE [16, 17], infections [8], toxic exposures [8], cardiac conditions [18], idiopathic pulmonary hemosiderosis [19–22], and post-transplantation [10, 22–24]. However, large studies on DAH and its triggers are lacking. Here, the objective of our study is to obtain the descriptive characteristics of patients with DAH, and also to determine the strength of association of DAH with rheumatic conditions using a large population–based data set.

Methods

Data source

An observational study was conducted on hospitalizations in 2016–2018 with a diagnosis of DAH in acute-care hospitals across the USA. Hospitalizations were selected from the National Inpatient Sample (NIS) database (online at https://www.hcup-us.ahrq.gov). Diagnoses are divided into two categories in the NIS: principal and secondary diagnoses. A principal diagnosis was the main ICD-10 code for the hospitalization. Secondary diagnoses were any ICD-10 code other than the principal diagnosis. Institutional Review Board approval was not sought for our study as all the patient data are de-identified and publicly available.

Inclusion criteria and study variables

The study group consisted of all hospitalizations recorded in the NIS from 2016 to 2018. Exclusion criteria was age ≤ 18 years. Study variables included age, gender, race, length of stay (LOS), total charges, and in-hospital mortality. DAH hospitalization was defined by the presence of a principal International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) of DAH (R048.9 or R049.9) or a principal ICD-10 code of respiratory failure (all J96 codes) combined with a secondary ICD-10 code of DAH (R048.9 or R049.9).

We used the following ICD-10 codes to identify diagnoses/comorbidities: antineutrophil cytoplasmic antibody (ANCA) vasculitis (AAV) codes M31.30, M31.31, M31.33, and M31.7; anticoagulants D68.32; anti-phospholipid antibody syndrome (APLS) D68.61; aortic valvular disorders all I35 codes; aspergillosis B44; HIV B20; bacterial pneumonia J13, J14, and J15; Behcet’s disease code M35.2; history of bone marrow transplant code Z94.81; chemotherapy codes Z51.11 and Z92.21; cocaine abuse all F14 codes; cryoglobulinemia code D89.1; cytomegaloviral (CMV) pneumonitis B.25.0; dermatomyositis (DM) and polymyositis (PM) all M33 codes; endocarditis all I33 codes; eosinophilic granulomatosis with polyangiitis (EGPA) codes M30.1; Goodpasture’s M31.0; graft versus host disease (GVHD) code D89.81; Hantavirus B33.4; Henoch Schoenlein Purpura (HSP) code D69.0, hemophilia code D66; heroin abuse code T40.1; herpes infection B00.7; human immunodeficiency virus (HIV) B20; immune-mediated thrombocytopenia (ITP) D69.3; inflammatory bowel disease K50 and K51; Legionnaires’ disease A48.1, leptospirosis A27; mitral stenosis I34.2; lymphangioleiomyomatosis J84.81; mixed connective tissue disease (MCTD) M35.9; myeloid leukemia all C92 codes; mycoplasma A49.3 and B96.0; myelodysplastic syndrome all D46 codes; pulmonary embolism (PE) I26; pulmonary hemosiderosis J84.03; rheumatoid arthritis (RA) all M05 and M06 codes; sarcoidosis all D86 codes; Sjogren’s disease all M35 codes; SLE M32, M32.1, M32.10, M32.11, M32.12, M32.13, M32.14, M32.19, M32.8, and M32.9; systemic sclerosis all M34 codes.

Outcomes

Three outcomes were studied: (1) the prevalence of DAH hospitalizations and the in-hospital mortality, (2) description of demographic characteristics of DAH patients, and (3) identification of rheumatic conditions statistically associated with DAH hospitalizations.

Statistical analysis

We have used STATA version 16 (StataCorp, TX, USA) to perform the analyses. A univariate logistic regression analysis was used to calculate unadjusted odds ratios (ORs) for a principal diagnosis of DAH. All variables with p-values < 0.2 were included in a multivariate logistic regression model. Adjusted OR (ORadj) were reported and considered significant when p-values were < 0.05. Risk factors for DAH were selected from extensive literature review.

Results

There were 90,879,561 adult hospital discharges in the combined 2016–2018 NIS database. Of those, 5420 met our case definition of DAH (Table 1). Compared to the control population, majority of the DAH patients were males (57.8% vs 44%, p < 0.001), were older (61.8 vs 57.9 years, p < 0.001), had longer LOS (10.6 days vs 4.7 days, p < 0.001), higher mean hospital charges ($160,898 vs $53,567, p < 0.001), and more likely to have in-hospital death (24.5% vs 2.2%, p < 0.001). Race/ethnicity were distributed among DAH patients as follows: White 71.7%, African American 13.4%, Hispanic 8.8%,
Asian or Pacific Islander 2.9%, Native American 0.9%, and other 2.3%.

Univariate analysis showed multiple variables and comorbidities were associated with DAH hospitalizations (Table 2). Several causes of DAH from the literature were not significant in our analysis. Additionally, there were zero secondary diagnoses of the following reported DAH triggers: Behcet’s, Hantavirus, herpes, HSP, Legionnaires’ disease, Lymphangioleiomyomatosis, mitral stenosis, or mycoplasma.

Multivariate analysis showed that many rheumatic diseases were associated with DAH including AAV (OR_adj 72.56, 95% CI 50.607–104), APLS (OR_adj 6.51, 95% CI 3.734–11.366), EGPA (OR_adj 7.13, 95% CI 1.886–26.926), Goodpasture’s (OR_adj 30.58, 95% CI 16.360–57.176), RA (OR_adj 1.60, 95% CI 1.158–2.212), sarcoidosis (OR_adj 3.99, 95% CI 2.300–6.926), and SLE (OR_adj 5.82, 95% CI 3.993–8.481) (Table 3).

Additionally many non-rheumatic diseases were associated with DAH in multivariate analysis including age (OR_adj 1.01; CI 1.002–1.008), anti-coagulants (OR_adj 20.31, 95% CI 14.822–27.834), Aspergillosis (OR_adj 9.45, 95% CI 5.172–17.283), bacterial pneumonia (OR_adj 8.26, 95% CI 6.742–10.126), chemotherapies (OR_adj 2.18, 95% CI 1.548–3.082), CMV (OR_adj 14.44, 95% CI 4.114–50.714), female gender (OR_adj 0.60, 95% CI 0.525–0.679), hemophilia (OR_adj 7.47, 95% CI 1.883–29.639), history of bone marrow transplant (OR_adj 4.73, 95% CI 1.857–12.065), ITP (OR_adj 2.47, 95% CI 1.169–5.230), Leptospirosis (OR_adj 54.44, 95% CI 3.696–801.724), MDS (OR_adj 2.63, 95% CI 1.419–4.892), pulmonary embolus (OR_adj 3.23, 95% CI 2.241–4.645), pulmonary hemosiderosis (OR_adj 177.97, 95% CI 49.625–638.274), African American (OR_adj 0.68, 95% CI 0.511–0.898), Hispanic (OR_adj 0.63, 95% CI 0.466–0.859), Other race (OR 0.59, 95% CI 0.375–0.941), White (OR_adj 0.75, 95% CI 0.596–0.955).

Discussion

DAH is often a catastrophic clinical syndrome. Ideally, the underlying cause should be identified to improve treatment choices and outcomes [10]. Our study identified a significant association of rheumatic conditions with inpatient DAH. AAV patients had a 72-fold increased odds of being hospitalized with DAH. One study found that 19% of patients admitted to the ICU for DAH were found to have vasculitis. Seventy-one percent of those vasculitis patients had AAV; the remaining were due to SLE or other causes [8]. Another study also showed that the most common cause of pulmonary vasculitis is AAV [25]. Studies have reported varying incidences in AAV, but DAH seems to be more frequent in MPA affecting 25–60% of the patients [26] compared to GPA (22–30%) and EGPA (4%) [27, 28]. A variety of mechanisms has been shown to cause disruption in the alveolar capillaries, eventually leading to DAH. These can be immune or non-immune mechanisms [10, 25]. A single-center cohort study of AAV-associated DAH patients found that the severity of hypoxia on initial presentation was shown to be the most significant predictor of impending

### Table 1

| Hospitalization characteristics | DAH (n = 5420) | Non-DAH (n = 90,874,141) | p-value |
|--------------------------------|---------------|------------------------|--------|
| Women, number (%)              | 2385 (44%)    | 52,467,357 (57.8%)     | <0.001 |
| Age, mean in years             | 61.8          | 57.9                   | <0.001 |
| Number (%) hospitalizations    |               |                        |        |
| Age 18–40 years                | 710 (13.1%)   | 21,949,436 (24.2%)     | <0.001 |
| Age 40–60 years                | 1375 (25.4%)  | 21,700,077 (23.9%)     | 0.256  |
| Age 60–80 years                | 2615 (48.2%)  | 32,357,086 (35.6%)     | <0.001 |
| Age > 80 years                 | 720 (13.3%)   | 14,867,542 (16.4%)     | 0.006  |
| Race (%)                       |               |                        |        |
| (a) White                      | 71.7%         | 67.3%                  | 0.040  |
| (b) African American           | 13.4%         | 15.2%                  | 0.079  |
| (c) Hispanic, number           | 8.8%          | 11.1%                  | 0.014  |
| (d) Asian or Pacific Islander  | 2.9%          | 2.7%                   | 0.812  |
| (e) Native American            | 0.9%          | 0.6%                   | 0.346  |
| (f) other                      | 2.3%          | 3.0%                   | 0.176  |
| Length of stay, mean days      | 10.6          | 4.7                    | <0.001 |
| Total charges, mean            | $160,898      | $53,567                | <0.001 |
| Inpatient mortality, number (%)| 1330 (24.5%)  | 2,019,004 (2.2%)       | <0.001 |

**DAH**, diffuse alveolar hemorrhage
Table 2 Univariate analysis: DAH associations

| Non-rheumatologic variables | Odds ratio | p-value | 95% C.I. |
|------------------------------|-----------|---------|----------|
| Age                          | 1.01      | <0.001  | 1.007–1.013|
| Anticoagulants               | 2.89      | <0.001  | 22.207–40.065|
| Aortic valvular disease      | 1.66      | 0.004   | 1.173–2.351|
| Aspergillosis                | 33.25     | <0.001  | 20.255–54.573|
| Pneumonia                    | 11.85     | <0.001  | 9.880–14.219|
| Chemotherapy                 | 2.47      | <0.001  | 1.768–3.441|
| CMV                          | 120.42    | <0.001  | 45.085–321.624|
| Cocaine                      | 0.81      | 0.479   | 0.462–1.437|
| Endocarditis                 | 2.37      | 0.082   | 0.895–6.291|
| Female                       | 0.57      | <0.001  | 0.509–0.649|
| GVHD                         | 3.61      | 0.069   | 0.903–14.408|
| Hemophilia                   | 8.89      | 0.002   | 2.222–35.575|
| Heroin                       | 3.64      | 0.197   | 0.512–25.855|
| HIV                          | 0.87      | 0.806   | 0.279–2.695|
| History of BMT               | 8.24      | <0.001  | 3.431–19.809|
| IBD                          | 1.07      | 0.843   | 0.555–2.057|
| ITP                          | 4.81      | <0.001  | 2.401–9.624|
| Leptospirosis                | 136.45    | <0.001  | 19.053–977.159|
| MDS                          | 4.30      | <0.001  | 2.385–7.751|
| Multiple myeloma             | 1.74      | 0.175   | 0.781–3.887|
| Myeloid leukemia             | 3.68      | <0.001  | 1.909–7.101|
| Pulmonary embolus            | 4.99      | <0.001  | 3.538–7.048|
| Pulmonary hemosiderosis      | 395.96    | <0.001  | 147.093–1065.900|
| African-American             | 0.85      | 0.079   | 0.711–1.019|
| Asian/Pacific Islander       | 1.05      | 0.812   | 0.726–1.504|
| Hispanic                     | 0.76      | 0.014   | 0.611–0.945|
| Native American              | 1.37      | 0.346   | 0.712–2.633|
| Other Race                   | 0.76      | 0.176   | 0.507–1.132|
| White                        | 1.15      | 0.040   | 1.006–1.308|

Table 3 Multivariate analysis, DAH associations

| Non-rheumatologic variables | Odds ratio | p-value | 95% C.I. |
|------------------------------|-----------|---------|----------|
| Age                          | 1.01      | 0.001   | 1.002–1.008|
| Anticoagulants               | 20.31     | <0.001  | 14.822–27.834|
| Aortic valvular disease      | 1.32      | 0.127   | 0.924–1.882|
| Aspergillosis                | 9.45      | <0.001  | 5.172–17.283|
| Bacterial pneumonia          | 8.26      | <0.001  | 6.742–10.126|
| Chemotherapy                 | 2.18      | <0.001  | 1.548–3.082|
| CMV                          | 14.44     | <0.001  | 4.114–50.714|
| Endocarditis                 | 1.01      | 0.984   | 0.367–2.781|
| Female                       | 0.60      | <0.001  | 0.525–0.679|
| GVHD                         | 0.65      | 0.572   | 0.150–2.854|
| Hemophilia                   | 7.47      | 0.004   | 1.883–29.639|
| Heroin                       | 3.87      | 0.177   | 0.543–27.594|
| History of BMT               | 4.73      | <0.001  | 1.857–12.065|
| ITP                          | 2.47      | 0.018   | 1.169–5.230|
| Leptospirosis                | 54.44     | <0.001  | 3.696–801.724|
| MDS                          | 2.63      | 0.002   | 1.419–4.892|
| Multiple myeloma             | 1.11      | 0.797   | 0.493–2.516|
| Myeloid leukemia             | 1.91      | 0.078   | 0.930–3.936|
| Pulmonary embolus            | 3.23      | <0.001  | 2.241–4.645|
| Pulmonary hemosiderosis      | 177.97    | <0.001  | 49.625–638.274|
| African American             | 0.68      | 0.007   | 0.511–0.898|
| Hispanic                     | 0.63      | 0.003   | 0.466–0.859|
| Other Race                   | 0.59      | 0.027   | 0.375–0.941|
| White                        | 0.75      | 0.019   | 0.596–0.955|
| Rheumatologic variables     |           |         |          |
| ANCA vasculitis              | 72.56     | <0.001  | 50.607–104.043|
| APLS                         | 6.51      | <0.001  | 3.734–11.366|
| Cryoglobulinemia             | 6.37      | 0.139   | 0.548–73.949|
| DM and PM                    | 2.57      | 0.194   | 0.619–10.706|
| EGPA                         | 7.13      | 0.004   | 1.886–26.926|
| Goodpasture                  | 30.58     | <0.001  | 16.360–57.176|
| MCTD                         | 3.23      | 0.138   | 0.686–15.166|
| Rheumatoid arthritis         | 1.60      | 0.004   | 1.158–2.212|
| Sarcoidosis                  | 3.99      | <0.001  | 2.300–6.926|
| Sjogren’s                    | 1.66      | 0.073   | 0.953–2.899|
| SLE                          | 5.82      | <0.001  | 3.993–8.481|
| Systemic sclerosis           | 1.99      | 0.190   | 0.710–5.602|

ANCA, antineutrophil cytoplasmic antibody; APLS, Antiphospholipid antibody syndrome; BMT, bone marrow transplant; C.I., confidence interval; CMV, cytomegalovirus; DAH, diffuse alveolar hemorrhage; DM, dermatomyositis; EGPA, eosinophilic granulomatosis with polyangiitis; GVHD, graft versus host disease; ITP, immune-mediated thrombocytopenia; MDS, myelodysplastic syndrome; MCTD, mixed connective tissue disease; PM, polymyositis; SLE, systemic lupus

respiratory failure. Other indicators included serum CRP and high number of neutrophils in the bronchoalveolar lavage. The AAV phenotype (GPA vs MPA) or the ANCA type did not influence the outcomes [3]. Unfortunately, relapses in AAV-associated DAH are high, ranging from 22 to 58% [7, 29–32].
In our study, SLE patients were nearly six times more likely to be hospitalized with DAH. The reported incidence of DAH in SLE is 3.7% [17] and it carries a high mortality. Older studies reported a mortality of 91% [33] but this seems to have improved over the years. A systematic review study performed by Christina Ednalino et al. [34] showed that survival rates improved from 25% in the 1980s to 67% over the last decade. Increased use of cyclophosphamide appears to be associated with better survival (71% vs 49%). Although the use of plasmapheresis increased from 0 to 68% in the last two decades, it did not seem to account for the better survival rates.

In our study, patients with APLS were nearly seven times more likely to be hospitalized with DAH. Prior studies have shown that incidence of DAH in APLS ranged from 0.7 to 2% [15, 35], whereas the incidence is higher in catastrophic APLS at nearly 12% [36]. APLS can affect the lung in a variety of ways. The inherent hypercoagulability of this disease can cause thrombotic complications like PE, microthrombosis, and resultant infarction [12], but it can also result in adult respiratory distress syndrome (ARDS) [11], likely from pulmonary capillaritis. There have been case reports of perivascular immune-complex deposition leading to pulmonary capillaritis and resultant DAH [37]. Cartin-Ceba et al. conducted a retrospective review of primary APLS-associated DAH at the Mayo clinic over a 15-year period. In total, 3 of the 5 people who underwent lung biopsy showed capillaritis and DAH with no evidence of thrombosis which in part supports a non-thrombotic mechanism for DAH [13]. Case series show that almost all APLS patients presenting with DAH require immunosuppression with corticosteroids in addition to other agents such as cyclophosphamide or rituximab [11, 13].

In our study, we found that patients with Goodpasture’s disease were 30 times more likely to be hospitalized with DAH. Goodpasture’s disease is an autoimmune disease with both renal and pulmonary manifestations. This is due to expression of the auto-antigen on the basement membrane of glomerular and alveolar capillaries [38]. DAH can occur in Goodpasture’s without renal involvement in about 10% patients [39]. The prognosis for Goodpasture’s disease has improved over the last several years due to the aggressive management with plasmapheresis, glucocorticoids, and immunosuppressants. One study showed improved survival rates, exceeding 80% at 5 years with less than 30% of them requiring chronic dialysis [40].

Despite frequent pulmonary involvement in sarcoidosis, literature review revealed only rare reports of DAH in this disease [41]. Unexplainably, our study showed sarcoidosis patients were nearly four times more likely to be hospitalized with DAH.

Several non-rheumatic conditions reported in the literature to produce DAH [8, 10] [18–22] were confirmed in our study including idiopathic pulmonary hemosiderosis, infections, use of anti-coagulants, hemophilias, BMT, and PE.

This study was aimed to obtain the descriptive characteristics of patients hospitalized with DAH and quantify the association of rheumatic diseases with DAH. One of the main strengths of our study is that it leveraged a nationwide dataset to provide a large sample size. This is the first such study to report a comprehensive estimate of in-hospital incidence and mortality of DAH. The findings in our study support prior case series and case reports showing a strong association of rheumatic diseases with DAH. An additional strength is that we utilized a comprehensive list of DAH risk factors from the literature to build our multivariate model.

**Limitations**

The study also has some limitations. First, the study relies solely on coding without clinical details pertaining to the hospitalization. Second, most ICD-10 billing codes do not grade disease severity or duration. Thus, it is difficult to discern if underlying disease severity or duration resulted in DAH. Third, NIS does not contain data on individual patients but rather shows data on total hospitalizations. Multiple hospitalizations of the same individual for DAH could not be separated. Fourth, smoking was not included in our multivariable regression model. Smoking can cause hemoptysis and could possibly be misdiagnosed as diffuse alveolar hemorrhage. Also, the smoking ICD-10 code is underutilized in US hospital admissions. And finally, NIS lacks data from outpatient setting, medications utilized, and radiological data.

**Conclusion**

Our study represents the largest sample to date to assess the incidence, mortality, and disease associations of DAH. The mean age of patients admitted with DAH was 61.8 years; a majority of patients were white (71.7%), majority of them were males (57.8%), and the average LOS was 10.6 days. Nearly 1 out of 4 suffered in-hospital mortality. Numerous rheumatic diseases were associated with inpatient DAH including AAV, APLS, EGPA, Goodpasture’s, RA, sarcoidosis, and SLE. A non-rheumatic condition, pulmonary hemosiderosis, showed the strongest association with inpatient DAH. With this knowledge, physicians might better recognize DAH in the early stages and hopefully improve outcomes. Further research is required to identify the factors that are resulting in such high mortality of DAH.

**Author contribution** Author contributions in accordance with the ICMJE four authorship criteria are as follows:

- [Author 1]
- [Author 2]
- [Author 3]
- [Author 4]

**ICMJE** ICMJE four authorship criteria are as follows:

1. **Conception and design**
2. **Acquisition of data**
3. **Analysis and interpretation of data**
4. **Drafting the article**
5. **Critical revision of the article for important intellectual content**

**Role of the funding source**

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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Compliance with ethical standards

Disclosures None.

References

1. Collard HR, Schwarz MI (2004) Diffuse alveolar hemorrhage. Clin Chest Med 25(583–92):vii. https://doi.org/10.1016/j.ccm.2004.04.007

2. Bhushan A, Choi D, Maresh G, Deodhar A (2022) Risk factors and outcomes of immune and non-immune causes of diffuse alveolar hemorrhage: a tertiary-care academic single-center experience. Rheumatol Int 42:485–492. https://doi.org/10.1007/s00296-021-04842-2

3. Cartin-Ceba R, Diaz-Caballero L, Al-Qadi MO et al (2016) Diffuse alveolar hemorrhage secondary to antineutrophil cytoplasmic antibody-associated vasculitis: Predictors of respiratory failure and clinical outcomes. Arthritis rheumatol 68:1467–1476. https://doi.org/10.1002/art.39562

4. Lin Y, Zheng W, Tian X et al (2009) Antineutrophil cytoplasmic antibody-associated vasculitis complicated with diffuse alveolar hemorrhage. J Clin Rheumatol 15:341–344. https://doi.org/10.1097/RHU.0b013e3181b59581

5. Cordier J-F, Cotton V (2011) Alveolar hemorrhage in vasculitis: primary and secondary. Semin Respir Crit Care Med 32:310–321. https://doi.org/10.1055/s-0031-1279827

6. Guillemin L, Durand-Gasselin B, Cevallos R et al (1999) Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 42:421–430. https://doi.org/10.1002/1529-0131(199904)42:3%3c421::AID-ANR5%3e3.0.CO;2-6

7. Kostianovsky A, Hauser T, Pagnoux C et al (2012) Alveolar haemorrhage in ANCA-associated vasculitides: 80 patients’ features and prognostic factors. Clin Exp Rheumatol 30:877-82

8. Rabe C, Appenrodt B, Höff C et al (2010) Severe respiratory failure due to diffuse alveolar hemorrhage: clinical characteristics and outcome of intensive care. J Crit Care 25:230–235. https://doi.org/10.1016/j.jccr.2009.04.009

9. Tobler A, Schürch E, Altermatt HJ, Im Hof V (1991) Antibasement membrane antibody disease with severe pulmonary haemorrhage and normal renal function. Thorax 46:68–70. https://doi.org/10.1136/thx.46.1.68

10. Lara AR, Schwarz MI (2010) Diffuse alveolar hemorrhage. Chest 137:1164–1171. https://doi.org/10.1378/chest.08-2084

11. Asherson RA, Cervera R, Piette JC et al (1998) Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore) 77:195–207. https://doi.org/10.1097/00005792-199805000-00005

12. Espinosa G, Cervera R, Font J, Asherson RA (2002) The lung in the antiphospholipid syndrome. Ann Rheum Dis 61:195–198. https://doi.org/10.1136/ard.61.3.195

13. Cartin-Ceba R, Peikert T, Ashrani A et al (2014) Primary antiphospholipid syndrome-associated diffuse alveolar hemorrhage. Arthritis Care Res (Hoboken) 66:301–310. https://doi.org/10.1002/acr.22109

14. Kanakis MA, Kapsimali V, Vaiopoulos AG et al (2013) The lung in the spectrum of antiphospholipid syndrome. Clin Exp Rheumatol 31:452–457

15. Yachoui R, Sehgal R, Almani B, Goldberg JW (2015) Antiphospholipid antibodies-associated diffuse alveolar hemorrhage. Semin Arthritis Rheum 44:652–657. https://doi.org/10.1016/j.semarthrit.2014.10.013

16. Jiang M, Chen R, Zhao L, Zhang X (2021) Risk factors for mortality of diffuse alveolar hemorrhage in systemic lupus erythematosus: a systematic review and meta-analysis. Arthritis Res Ther 23:57. https://doi.org/10.1186/s13075-021-02435-9

17. Zomara MR, Warner ML, Tuder R, Schwarz MI (1997) Diffuse alveolar hemorrhage and systemic lupus erythematosus: clinical presentation, history, survival, and outcome. Medicine 76(3):192–202

18. Saha BK, Chong WH (2021) Diffuse alveolar hemorrhage in cardiac diseases. Lung 199:103–112. https://doi.org/10.1007/s00408-021-04433-x

19. Ioachimescu OC, Sieber S, Koch A (2004) Idiopathic pulmonary haemosiderosis revisited. Eur Respir J 24:162–170. https://doi.org/10.1183/09031936.04.00116302

20. Kjellman B, Elinder G, Garwicz S, Svahn H (1984) Idiopathic pulmonary haemosiderosis in Swedish children. Acta Paediatr 73:584–588. https://doi.org/10.1111/j.1651-2227.1984.tb00778.x

21. Chen X-Y, Sun J-M, Huang X-J (2017) Idiopathic pulmonary hemosiderosis in adults: review of cases reported in the latest 15 years. Clin Respir J 11:677–681. https://doi.org/10.1111/crj.12440

22. Ioachimescu OC, Stoller JK (2008) Diffuse alveolar hemorrhage: diagnosing it and finding the cause. Cleve Clin J Med 75:258. https://doi.org/10.1097/CCJ.0b013e31817b7c20

23. Alexs A, Tefferi A, Liztov MR et al (2002) Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med 166:641–645. https://doi.org/10.1164/rccm.200112-141cc

24. Xu X, Guaig Y, Chen B (2012) Diffuse alveolar hemorrhage after haploidentical hematopoietic stem cell transplantation: two cases report and literature review. Zhonghua Xue Ye Xue Za Zhi 33:674–676

25. Krause ML, Cartin-Ceba R, Specks U, Peikert T (2012) Update on diffuse alveolar hemorrhage and pulmonary vasculitis. Immunol Allergy Clin North Am 32:587–600. https://doi.org/10.1016/j.iacr.2012.08.001

26. Karras A (2018) Microscopic polyangiitis: new insights into pathogenesis, clinical features and therapy. Semin Respir Crit Care Med 39:459–464. https://doi.org/10.1055/s-0038-1673387

27. Unizony S, Villarreal M, Miloslavsky EM (2016) Clinical outcomes of treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. Ann Rheum Dis 75:1166–1169. https://doi.org/10.1136/annrheumdis-2015-208073

28. Nguyen Y, Guillemin L (2018) Eosinophilic granulomatosis with polyangiitis (Churg–Strauss). Semin Respir Crit Care Med 39:471–481. https://doi.org/10.1055/s-0038-1669454

29. Tang S, Li X, Zhao K-Y et al (2021) Clinical characteristics and prognostic analysis of microscopic polyangiitis with diffuse alveolar hemorrhage. J Rheumatol 48:410–416. https://doi.org/10.3899/jrheum.191042
Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. Medicine (Baltimore) 96:e6083. https://doi.org/10.1097/MD.0000000000006083

31. Klemmer PJ, Chalermskulrat W, Reif MS et al (2003) Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis 42:1149–1153. https://doi.org/10.1053/ajkd.2003.08.015

32. Hruskova Z, Casian AL, Konopasek P et al (2013) Long-term outcome of severe alveolar haemorrhage in ANCA-associated vasculitis: a retrospective cohort study. Scand J Rheumatol 42:211–214. https://doi.org/10.3109/03009742.2012.754939

33. Abdul-Mendoza C, Diaz-Jouanen E, Alarcón-Segovia D (1985) Fatal pulmonary hemorrhage in systemic lupus erythematosus. Occurrence without hemoptysis J Rheumatol 12:558–561

34. Ednalino C, Yip J, Carsons SE (2015) Systematic review of diffuse alveolar hemorrhage in systemic lupus erythematosus. J Clin Rheumatol 21:305–310. https://doi.org/10.1097/rhu.000000000000291

35. Cervera R, Piette J-C, Font J et al (2002) Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 46:1019–1027. https://doi.org/10.1002/art.10187

36. Rodríguez-Pintó I, Moitinho M, Santacreu I et al (2016) Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev 15:1120–1124. https://doi.org/10.1016/j.autrev.2016.09.010

37. Crausman RS, Achenbach GA, Pluss WT et al (1995) Pulmonary capillaritis and alveolar hemorrhage associated with the antiphospholipid antibody syndrome. J Rheumatol 22:554–556

38. McAadoo SP, Pusey CD (2017) Anti-glomerular basement membrane disease. Clin J Am Soc Nephrol 12:1162–1172. https://doi.org/10.2215/CJN.01380217

39. Shiferaw B, Miro V, Smith C et al (2016) Goodpasture’s disease: an uncommon disease with an atypical clinical course. J Clin Med Res 8:52–55. https://doi.org/10.14740/jocmr2379w

40. Shah MK, Huggins SY (2002) Characteristics and outcomes of patients with Goodpasture’s syndrome. South Med J 95:1411–1418

41. Russakoff AH (1954) Massive pulmonary hemorrhage due to sarcoidosis. Dis Chest 26:217–223. https://doi.org/10.1378/chest.26.2.217

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