# Factors Associated with Mortality and Infections in Patients with Systemic Lupus Erythematosus with Diffuse Alveolar Hemorrhage

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***ABSTRACT.*** ***Objective.*** To evaluate factors associated with mortality and infections in patients with systemic lupus erythematosus (SLE) and diffuse alveolar hemorrhage (DAH).

***Methods.*** A retrospective chart review was carried out for medical admissions of patients with a diagnosis of SLE and DAH in 9 hospitals. Clinical and laboratory data were recorded for each patient at DAH diagnosis.

***Results.*** We included 57 episodes of DAH of 50 patients (7 recurrences), 49 women (86%), 14 juvenile SLE (24.6%); 24 had died (42.1%). In the chart review we detected infection in 22 episodes (38.6%): 8 invasive fungal infections, 16 bacterial infections, and 2 patients had both types. In the bivariate analysis, factors associated with mortality were high Acute Physiology and Chronic Health Evaluation II scores, requirement of mechanical ventilation (OR 15.0, 95% CI 1.9 to 662.2), infections (fungal or bacterial; OR 3.2, CI 0.9 to 11.1), renal failure (OR 4.9, CI 1.4 to 18.0), and thrombocytopenia (OR 4.3, CI 1.2 to 15.6). We found similar mortality between children and adults. Infections were associated with treatment for SLE, requirement of mechanical ventilation, hypocomplementemia, and high levels of C-reactive protein.

***Conclusion.*** Infection is a frequent finding in patients with DAH and SLE; we found similar mortality between adult SLE and juvenile SLE. Factors that we describe associated with infections may influence the therapeutic selection for these patients. (J Rheumatol First Release July 1 2014; doi:10.3899/jrheum.130927)

*Key Indexing Terms:*
SYSTEMIC LUPUS ERYTHEMATOSUS
DIFFUSE ALVEOLAR HEMORRHAGE
MORTALITY
INFECTIONS

Systemic lupus erythematosus (SLE) is an autoimmune disease that may affect any human organ[1]. Pulmonary manifestations of SLE are pleuritis, pneumonitis, diffuse alveolar hemorrhage (DAH), and others[2].

DAH is considered a rare and severe manifestation of SLE[3,4,5]. Previous case series of DAH and SLE described factors associated with mortality: mechanical ventilation (MV)[3,6,7,8], renal failure[3,9], infections[6,7,8], and scores of mortality [Acute Physiology and Chronic Health Evaluation (APACHE) II[3,10] and organ system failure[10] scores]. But case series report dissimilar mortality, likely owing to differences in the frequency of these factors and the scarcity of patients.

Several authors reported that infections could be found

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accompanying DAH: Rojas-Serrano, *et al*, described 8/14 infected patients (57%) with DAH and SLE at admission[11]. Even though infection is a frequent finding in case series with DAH and SLE[3,10,11,12,13], its associated factors are unrecognized.

Our study was performed to evaluate factors associated with infections in patients with DAH and SLE in a large retrospective multicenter register. Our secondary objectives were to confirm factors associated with mortality, and differences between juvenile SLE (JSLE) and adult SLE.

## MATERIALS AND METHODS

A retrospective chart review was carried out for all medical admissions of patients with a diagnosis of SLE and DAH in 9 hospitals. For inclusion in our study, patients had to fulfill the revised criteria of the American College of Rheumatology for classification of SLE[14,15], and have DAH defined by the presence of new alveolar infiltrates on chest radiograph suggestive of alveolar hemorrhage, abrupt drop in hemoglobin level of at least 2 g/dl without evidence of bleeding elsewhere, with or without the presence of the following symptoms and signs: dyspnea, hemoptysis, and hemosiderophages in bronchoalveolar lavage.

Patients with bleeding of other organs or pulmonary infiltrates for other causes were excluded. Recurrent DAH was defined when a new episode occurred after complete resolution of previous DAH with an asymptomatic period and normal chest radiograph or computed tomography.

Each investigator recorded clinical and laboratory data for each patient at DAH diagnosis. We abstracted pertinent demographic, clinical, laboratory, histologic, therapeutic, disease activity [with SLEDAI (Systemic Lupus Erythematosus Disease Activity Index)][16], APACHE II[17], and outcome data.

We evaluated for presence of bacterial infection diagnosed at admission through bronchoalveolar lavage, blood culture, or sputum culture. Invasive fungal infection was considered a fungal infection at sites other than skin, urine, or mucous membranes[18].

Patients younger than 18 years were defined as JSLE; otherwise patients were defined as adult SLE (ASLE). We distributed patients with high C-reactive protein (CRP; higher than 5 mg/dl) from patients with lower levels of CRP (≤ 5 mg/dl of CRP). Glomerular filtration rate (GFR) was obtained through the Modification of Diet in Renal Disease Study equation[19] or Schwartz's equations[20]. Renal failure was defined as GFR < 60 ml/min, thrombocytopenia as platelets lower than 150,000/mm$^3$.

Because this was a retrospective study, patient inclusion did not interfere with a patient's medical treatment. Ethics committees of the 9 hospitals approved our study.

*Statistical analysis*. Continuous data are expressed as median and percentiles 25–75; categorical variables are expressed as percentages. Medians were compared using Mann-Whitney U test; categorical data were compared using chi-squared test or Fisher's exact test. P values < 0.05 were considered significant. We verified that the population OR was constant across the strata with the test of homogeneity. Quantification of confounding was done through the Mantel-Haenszel method (comparing crude OR with the adjusted OR). Statistical analysis was performed using Software Stata/IC 13.0 (Stata Corp.).

## RESULTS

We describe the findings of 57 episodes in 50 patients (7 recurrences): 49 women (86%), 14 JSLE (24.6%), median age 23 years, median disease duration 1 year, and median SLEDAI 14; 43 episodes required MV and 24 patients died (42.1%); 15.8% of the episodes were in autumn, 42.1% in winter, 19.3% in spring, and 22.8% in summer. DAH was the first SLE manifestation in 20 patients (35.1%). Clinical manifestations at diagnosis of DAH included dyspnea (87.7%), proteinuria (78.9%), low complement (68.4%), hemoptysis (57.9%), fever (54.4%), arthritis (50.9%), neuropsychiatric SLE (NPSLE; 26.3%), and mucositis (17.5%). Twenty-eight episodes (49.1%) resulted in administration of cyclophosphamide for treatment of DAH and 3 in rituximab (5.3%), and 4 patients (7.0%) received intravenous immunoglobulin.

*ASLE or JSLE*. NPSLE was more frequent in JSLE and mucositis in ASLE (Figure 1). Patients with ASLE presented lower lymphocytes and higher CRP than did patients with JSLE, and similar mortality (Table 1).

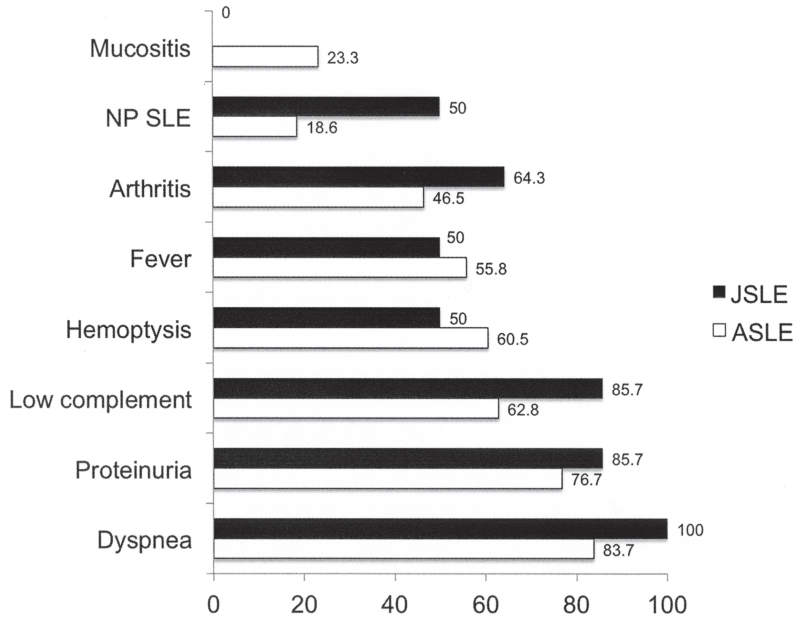


*Figure 1*. Clinical manifestations in adult systemic lupus erythematosus (ASLE) or juvenile SLE (JSLE). NPSLE: neuropsychiatric lupus.

*Table 1*. Characteristics and test significance for ASLE and JSLE. Results are written as median (percentiles 25%–75%) unless otherwise indicated.

| Characteristic | ASLE, n = 43 | JSLE, n = 14 | p |
|---|---|---|---|
| Women, n (%) | 39 (90.7) | 10 (71.4) | 0.091† |
| Age, yrs | 25.0 (22–32) | 13 (10–15) | < 0.0001 |
| SLE duration of disease, yrs | 1.0 (0.08–3.5) | 0.1 (0.04–3) | 0.2115 |
| WBC, $10^3$/ml | 8.2 (5.6–12.6) | 9.9 ± (5.5–19.5) | 0.3258 |
| Lymphocytes, $10^3$/ml | 0.6 (0.42–0.82) | 1.6 (0.75–2.25) | 0.0036 |
| Creatinine, mg/dl | 1.2 (0.6–2.9) | 0.8 (0.6–0.9) | 0.0624 |
| Platelets, $10^3$/ml | 145 (94–256) | 185 (121–274) | 0.4041 |
| APACHE II | 20 (14–23) | 16 (13–20) | 0.2198 |
| CRP, mg/dl | 13.5 (4.2–24.3) | 1.1 (0.4–4.1) | 0.0031 |
| MV, n (%) | 34 (79.1) | 9 (64.3) | 0.297† |
| Infection, n (%) | 19 (44.2) | 3 (21.4) | 0.129 |

† Fisher's exact test, otherwise chi-square. ASLE: adult SLE; JSLE: juvenile SLE; WBC: white blood cells; CRP: C-reactive protein; MV: mechanical ventilation; APACHE: Acute Physiology and Chronic Health Evaluation score.

*Mortality*. Factors associated with mortality included higher APACHE II score, MV, infections (fungal or bacterial), renal failure, and thrombocytopenia (Table 2). Because the main factor associated with mortality was MV, we assessed its effects for the other statistically significant factors. Table 3 shows the crude and MV-adjusted OR: after adjusting for MV, crude OR for renal failure and thrombocytopenia were modified, suggesting that the link between these factors was the confounding effect of MV. Because the test of homogeneity for infections suggested effect modification (interaction), we did not calculate adjusted OR.

*Infections*. In the chart review we detected 22 culture-confirmed episodes with infections (38.6%); 16 bacterial and 8 fungal (2 patients with both bacterial and fungal). Bacterial infections were 8 *Staphylococcus aureus*, 3 *Pseudomonas aeruginosa*, 2 gram-negative bacilli, and 1 each with *Citrobacter freundii, Rothia dentocariosa,* and *Enterococcus* species. Fungal infections were 3 *Aspergillus* species, 2 *Candida* species, and 1 each with *Criptococcus* species, *Coccidioides* species, and both *Mucor* species and *Aspergillus* species. In 2 patients who also had bacterial infections, cytomegalovirus infections were diagnosed (in both patients the diagnosis was established through histologic studies). For the statistical analysis we included 22 patients with any infection (bacterial, viral, and/or fungal). Treatment-naive patients had lower frequency of infections (OR 0.26, CI 0.05 to 1.06), MV (OR 12.4, CI 1.5 to 551.8), and hypocomplementemia (OR 8.4, CI 1.6 to 82.4); high

*Table 2*. Characteristics and statistical significance in patients according to survival or death. Results are written as median (percentiles 25%–75%) unless otherwise indicated.

| Characteristics | Survivors, n = 33 | Dead, n = 24 | p |
|---|---|---|---|
| Women, n (%) | 29 (87.9) | 20 (83.3) | 0.709† |
| Age, yrs | 23.0 (17–29) | 23.5 (18.5–32.5) | 0.910 |
| Disease duration of SLE | 1.23 (0.08–3.6) | 0.3 ± (0.07–2.5) | 0.526 |
| WBC, $10^3$/ml | 7.7 (5.6–13) | 8.8 (5.7–13.0) | 0.859 |
| Lymphocytes, $10^3$/ml | 0.77 (0.5–1.02) | 0.57 (0.45–0.90) | 0.2478 |
| Creatinine, mg/dl | 0.75 (0.5–1.5) | 2.0 (0.9–2.9) | 0.012 |
| Platelets | 205 (133–296) | 123.5 (73–170.5) | 0.016 |
| APACHE II | 16.0 (12–21) | 23.0 (16–24) | 0.003 |
| Hemoglobin drop | 3.0 (2.4–3.9) | 3.0 (2.2–4.0) | 0.7895 |
| CRP, mg/dl | 9.3 (0.9–16.4) | 14.6 (1.6–20.4) | 0.5486 |
| MV, n (%) | 20 (60.6) | 23 (95.8) | 0.002 |
| Hemoptysis, n (%) | 19 (19.1) | 14 (58.3) | 0.954 |
| CYC, n (%) | 17 (51.5) | 11 (45.8) | 0.672 |
| Infection, n (%) | 9 (27.3) | 13 (54.2) | 0.039 |
| IVIG, n (%) | 3 (9.1) | 1 (4.2) | 0.300† |
| RTX, n (%) | 0 (0.0) | 3 (12.5) | 0.069† |

† Fisher's exact test, otherwise chi-square. WBC: white blood cells; CRP: C-reactive protein; MV: mechanical ventilation; CYC: cyclophosphamide; IVIG: intravenous immunoglobulin; RTX: rituximab; SLE: systemic lupus erythematosus; APACHE: Acute Physiology and Chronic Health Evaluation score.

*Table 3*. Stratified evaluation of factors associated with mortality.

| | Not MV, n = 14 | | MV, n = 43 | | | | |
|---|---|---|---|---|---|---|---|
| | Survivors, n = 13 | Deceased, n = 1 | Survivors, n = 20 | Deceased, n = 23 | Crude OR (CI) | Test of Homogeneity, p | Adjusted OR (CI)* |
| Infections, n (%) | 0 (0.0) | 1 (100) | 9 (45.0) | 12 (52.1) | 3.2 (0.91–11.1) | 0.0027 | |
| Renal failure, n (%) | 1 (7.7) | 1 (100) | 10 (50.0) | 16 (69.6) | 4.9 (1.4–18.0) | 0.0952 | 2.8 (0.9–9.2) |
| Thrombocytopenia, n (%) | 3 (23.1) | 1 (100) | 9 (45.0) | 16 (69.6) | 4.3 (1.2–15.6) | 0.3208 | 3.3 (0.98–11.0) |

* Adjusted for mechanical ventilation. MV: mechanical ventilation.

levels of CRP (OR 4.8, CI 1.2 to 22.7) were associated with infections (Table 4, Figure 2).

## DISCUSSION

Our series describes factors associated with infections and differences between JSLE and ASLE, and confirms factors associated with mortality.

Infections are involved in the pathogenesis of many autoimmune diseases[21], including rheumatic fever[22], post-infectious glomerulonephritis[23], thrombocytopenic purpura[24], granulomatosis with polyangiitis (GPA; previously Wegener granulomatosis)[25] and Guillain Barré syndrome[26]. Moreover, prophylactic treatment with cotrimoxazole is effective in reducing the relapse rate of

*Table 4*. Factors associated with infection and statistical significance in patients with systemic lupus erythematosus (SLE) who have diffuse alveolar hemorrhage.

| Characteristic | Infected, n = 22 | Uninfected, n = 35 | p |
|---|---|---|---|
| Women, n (%) | 21 (95.5) | 28 (80.0) | 0.134† |
| JSLE, n (%) | 3 (13.6) | 11 (31.4) | 0.129 |
| Treatment-naive, n (%) | 4 (18.1) | 16 (45.7) | 0.034 |
| Mechanical ventilation, n (%) | 21 (95.5) | 22 (62.9) | 0.005 |
| Fever, n (%) | 14 (63.6) | 17 (48.6) | 0.266 |
| Hypocomplementemia, n (%) | 20 (90.9) | 19 (54.3) | 0.004 |
| SLEDAI * | 15.5 (8–20) | 14 (9–18) | 0.0249 |
| WBC/mm$^3$* | 8.3 (4.9–12.6) | 8.1 (5.8–14.0) | 0.1586 |
| CRP* | 16.4 (5.6–24.3) | 4.15 (0.9–16.4) | 0.0532 |

* Results written as median (percentiles 25%–75%). † Fisher's exact test, otherwise chi-square. WBC: white blood cells; CRP: C-reactive protein; JSLE: juvenile SLE; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

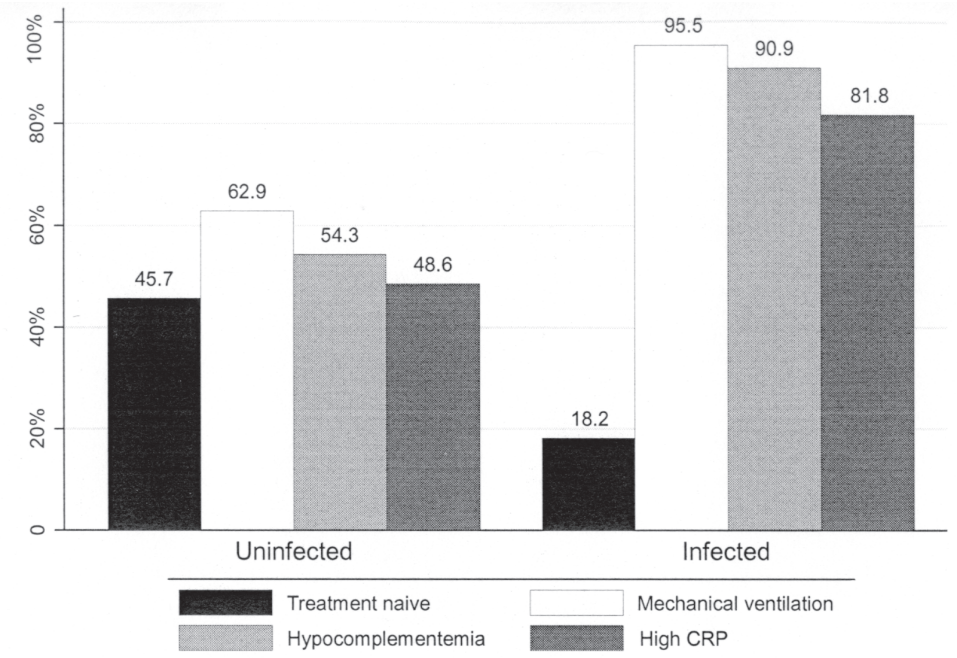


*Figure 2*. Factors associated with infections. CRP: C-reactive protein.

patients with GPA[27], and erythromycin for *Helicobacter pylori* eradication is a successful treatment in thrombocytopenic purpura[28]. Seasonal variation in our study may support the association with infections[29], but other factors influence seasonal presentation of DAH[30]. Apart from infection, several investigators have documented an increase in respiratory and cardiovascular morbidity and mortality during cold weather[31,32,33,34]. Moreover, hospitalizations for epistaxis are more frequent during dry and cold winter months[35].

Our study emphasizes the challenge in therapy selection presented by the presence of infections and disease activity in patients with DAH and SLE[36]. Rheumatologists must be aware of the factors described in the actual series when treating patients with SLE and DAH to evaluate the risk-benefit of immunosuppressive drugs. Additionally, not only is disease activity associated with DAH in patients with SLE[37,38,39,40]; infection may represent an important factor in the pathogenesis of this mortal manifestation in patients with SLE[41].

Unlike the Araujo, *et al* series[5], we found similar mortality between ASLE and JSLE. These dissimilar results could be explained because Araujo, *et al* reported that a higher percentage of their patients with JSLE required MV, which in ours and other series is a factor associated with mortality[3,8].

Our results confirm that hemoptysis was not present as a clinical manifestation in DAH[42,43].

Our series confirms the presence of factors associated with mortality for JSLE and ASLE for bivariate analysis[3,8,10]: renal failure, thrombocytopenia, MV, high APACHE II score, and the presence of infection. However, MV-adjusted OR highlight that MV is the main factor associated with death, and we must consider the effect of confounding with the other statistically significant factors in the bivariate analysis.

We acknowledge, as limitations of our study, primarily the retrospective design and the heterogeneity of DAH therapies. We must consider that infection was not evaluated in the same way in all centers; for example, not all patients had bronchoalveolar lavage the first day of DAH diagnosis. Another important factor is that it is very difficult to differentiate between infection at admission or nosocomial infection in SLE and DAH, as in the case of invasive fungal infection or viral infections diagnosed through necropsy. Despite the large number of patients in our series, multivariate analysis is not possible. In our series, few patients received biological therapies or intravenous immunoglobulin, so we could not define the potential value of those therapies.

Our results suggest that patients with DAH suffer a complex association of disease activity and other factors including infection. Rheumatologists must include evaluation and treatment for infections in patients with DAH and SLE. Treatments for this potentially fatal condition must be assessed with special attention to risk-benefit consideration for potentially infected patients.

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