

Review Article

Diffuse Alveolar Hemorrhage in Patients With Systemic Lupus Erythematosus. Clinical Manifestations, Treatment, and Prognosis[☆]

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ABSTRACT

Diffuse alveolar hemorrhage (DAH) in patients with systemic lupus erythematosus is a rare but potentially fatal condition. Although the pathogenesis of this condition is unknown, high disease activity is the main characteristic; moreover, histopathology in some studies showed alveolar immune complex deposits and capillaritis. Clinical features of DAH include dyspnea, a drop in hemoglobin, and diffuse radiographic alveolar images, with or without hemoptysis. Factors associated with mortality include mechanical ventilation, renal failure, and infections. Bacterial infections have been reported frequently in patients with DAH, and also invasive fungal infections including aspergillosis. DAH treatment is based on high dose methylprednisolone; other accepted therapies include cyclophosphamide (controversial), plasmapheresis, immunoglobulin and rituximab.

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Hemorragia alveolar difusa en pacientes con lupus eritematoso sistémico. Manifestaciones clínicas, tratamiento y pronóstico

RESUMEN

La hemorragia alveolar difusa (HAD) es una manifestación rara pero potencialmente fatal en pacientes con lupus eritematoso sistémico (LES). La patogenia de esta manifestación es desconocida, aunque los pacientes se presentan con datos clínicos de actividad del LES en el momento de la hemorragia; estudios de histopatología han implicado depósitos de complejos inmunes e infiltrado celular (capilaritis). El cuadro clínico clásico de la enfermedad consiste en disnea, descenso en la hemoglobina e imágenes radiográficas alveolares difusas habitualmente, con o sin la presencia de hemoptisis. Se han identificado diversos factores asociados a mortalidad, entre los que se encuentran la ventilación mecánica, falla renal e infecciones; estas últimas se han descrito como frecuentes en diversas series, aunque principalmente son bacterianas, también pueden observarse infecciones fúngicas invasivas como aspergilosis. El tratamiento de la HAD se ha basado en pulsos de metilprednisolona; pueden ser útiles también, ciclofosfamida (uso controversial), plasmaféresis, inmunoglobulina y rituximab.

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Palabras clave:

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Introduction

It's been over 100 years since Osler's description of a patient with erythema, and assumed pulmonary hemorrhage, who presented with systemic lupus erythematosus (SLE).¹ DAH, today, remains one of the most devastating complications in patients with SLE;

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having a high mortality² and representing a diagnostic and therapeutic challenge for the rheumatologist.

The frequency of the disease varies depending on the series consulted, from 0.63 to 5.4%⁴ cohorts of lupus and from 0.5⁵ to 9%² of hospital admissions to 5.7% of the internments to intensive care⁶ and 12.3% of autopsies.⁷ As in SLE, the frequency is higher in women and, although most of the case series reported that pulmonary hemorrhage occurs early, the mean or median progression of SLE at the time of DAH goes from 6 months⁸ to 14.1 years⁴ (Table 1).

The knowledge we have of this deadly association is based on reports and case series; Table 1 shows the main series; most are from Asia and Latin America, particularly Mexico.

Table 1
Selected Series' Demographic Characteristics.

| Authors, year of publication | Country | No. episodes | Frequency | Females | Age | Evolution SLE | Decrease in hemoglobin |
|---|-------------|--------------|-------------------|-----------|-------------------------|--------------------------|-----------------------------|
| Araujo et al., 2012 ⁹ | Brazil | 28 | 1.6% ^a | JSLE: 77% | JSLE 15.3 ^d | JSLE 2.6 a ^d | JSLE: 2.9 g/dL ^d |
| Martínez-Martínez and Abud-Mendoza, 2011 ² | Mexico | 29 | 9% ^b | ASLE: 87% | ASLE: 28.7 ^d | ASLE: 5.6 a ^d | ASLE: 5.5 g/dL ^d |
| Kwok et al., 2011 ¹⁰ | South Korea | 21 | 1.4% ^b | 75.9% | 25.1 ^d | 1.5 a ^d | 3.4 g/dL ^d |
| Shen et al., 2010 ¹¹ | China | 29 | 1.4% ^b | 90.5% | 29.7 ^d | 5.4 a ^d | 2.1 g/dL ^d |
| Rojas-Serrano et al., 2008 ³ | Mexico | 14 | 0.6% ^a | 86.2% | 31 ^e | 42 m ^e | 32 g/L ^e |
| Cañas et al., 2007 ⁶ | Colombia | 7 | 5.7% ^c | 92.8% | 22.4 ^d | – | – |
| Badsha et al., 2004 ¹² | Singapore | 22 | 1.5% | 71.4% | 24.3 ^d | 15.7 m ^d | – |
| Chang et al., 2002 ⁵ | Taiwan | 8 | 0.5% ^b | 91% | 31.6 ^d | 0.96 ^e | 3.2 g/dL ^d |
| Lee et al., 2001 ¹³ | Korea | 9 | – | 100% | 32.5 ^e | 36 m ^e | 3.0 g/dL ^e |
| Santos-Ocampo et al., 2000 ¹⁴ | EE. UU. | 1 | 1% ^b | – | 26 ^e | 2m ^e | 1.9 g/dL ^e |
| Lee et al., 2000 ⁸ | Korea | 6 | – | 81.8% | 31.1 ^d | 4.5 a ^d | – |
| Liu et al., 1998 ¹⁵ | Taiwan | 13 | 4.3% ^b | 83.3% | 28 ^d | 6 m ^d | 2.1 g/dL ^d |
| Zamora et al., 1997 ¹⁶ | USA | 19 | 3.7% ^b | 92.3% | 26 ^d | 23 m ^d | 2.4 g/dL ^d |
| Koh et al., 1997 ¹⁷ | Singapore | 10 | – | 68.4% | 27 ^e | 31 m ^e | 7.1% Ht ^d |
| Barile et al., 1997 ⁴ | Mexico | 34 | 5.4% ^b | 80% | 25 ^e | 21.5 m ^d | – |
| Schwab et al., 1993 ¹⁸ | USA | 8 | – | 94.1% | 34.5 ^d | 14.1 a ^d | – |
| Abud-Mendoza et al., 1985 ¹⁹ | Mexico | 12 | 1.6% ^b | 75% | 37.9 ^d | 2.3 a ^d | – |
| Mintz et al. July 1978 | Mexico | 7 | – | 100% | 25 ^d | 24 m | – |

In the series of Lee et al.,⁸ the data was extracted from 6 patients with lupus and in 10 patients with DAH due to different causes.

y, years; Ht, hematocrit; SLE, systemic lupus erythematosus; ASLE, adult-onset SLE; JSLE, Juvenile-onset SLE; m, months; –, not reported.

^a Cohort.

^b Hospital admissions.

^c UCI internment.

^d Mean.

^e Medium.

Pathogenesis and Risk Factors

Active disease is part of the DAH associated with SLE; as shown in Fig. 1, the mean or median of disease activity is high (greater than or equal to 12), indicating that the activity of SLE can be a trigger, or at least associated with DAH (Fig. 1).

Additionally, the different series highlight the importance of disease activity of SLE by exposing the high frequency of nephritis, arthritis and neuropsychiatric disorders associated; for example, lupus nephritis is reported by the majority of studies in more than 70% of patients and in whom, very often, the histopathology was compatible with proliferative types (Table 2).

Immune complexes have been described in patients with DAH associated with SLE. Hughson et al.²⁰ made a compilation of the literature of 20 cases of DAH in SLE patients, 15 of which showed the so-called soft bleeding, the remaining 5 DAH had capillaritis;

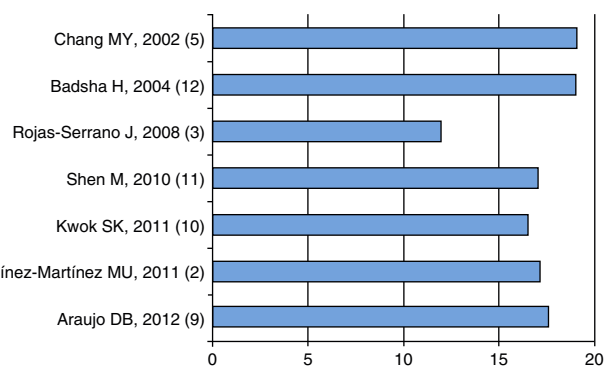


Fig. 1. Mean 2,10,11,3 or median 5,9,12 of disease activity as measured by the various scales (SLEDAI 2K2 {3 or SLEDAI}),^{3,5,9–12} The first author, year and reference, in parenthesis, are shown. Data extracted from each article.

additional Immune complexes were identified in the alveolar wall in 11/15 cases of patients with soft hemorrhage and 3/5 cases of capillaritis. In the same study, the authors describe the similarity between the vascular pathology observed in the soft hemorrhage with renal microangiopathy in lupus nephritis.²⁰

Although the above may indicate the involvement of immune complexes as an expression of disease activity in its pathogenesis, Haupt et al.,²¹ study of 120 autopsies of patients with SLE, in the pursuit of alternative explanations, reported 29 patients with DAH and in only 2/29 (6.9%) there was no other factor to explain the DAH; in 5/29 (17.2%) there was evidence of aspiration as an associated factor and in 7/29 (24.1%), congestive heart failure, 9/29 (31%) presented infection and 6/29 (20.7%) renal insufficiency. We consider that, in addition to the activity of the disease, there may be other factors or conditions that favor DAH, as aforementioned.

Infections are common in SLE associated with DAH and they deserve a special section within this review.

It is reported that DAH is more common in winter²; although the cause of this fact is unknown, however, there are symptoms exacerbated by cold conditions, including epistaxis and hemoptysis,^{22,23} to mention an association of cold and respiratory tract bleeding.

Little is known about the type of immune response that triggers DAH in patients with SLE. In a model of DAH pristane-induced SLE in susceptible mice, the involvement of the innate immune response has been shown; severity or recovery from the insult (DAH) is dependent on adaptive immunity with significant participation of B²⁴ cells. In this mouse model of SLE and pulmonary hemorrhage, hemorrhage is preceded by infiltration of macrophages and neutrophils²⁴; although, on the other hand, immune deposits have not been demonstrated in this model.²⁵

Risk factors for the development of DAH in SLE patients have been poorly described by the different series. Liu et al. report that 4 of 13 patients developed DAH the third day after treatment initiation¹⁵ plus 3 patients received cyclophosphamide in the

Table 2
Kidney, Joint and Neuropsychiatric Manifestations in Patients With DAH Described by Different Series.

| Authors, year | Nephritis | Arthritis | Lupus NP |
|---|------------------------|------------------------|------------------------|
| Araujo et al., 2012 ⁹ | JSLE: 77% ASLE: 80% | JSLE: 69% ASLE: 73% | JSLE: 15% ASLE: 20% |
| Martínez-Martínez and Abud-Mendoza, 2011 ² | 100% | 75.9% | 24.1% |
| Kwok et al., 2011 ¹⁰ | 76.1% | 33.3% | 47.6% |
| Shen et al., 2010 ¹¹ | 90% | – | – |
| Cañas et al., 2007 ⁶ | 71.4% | 57.1% | 28.6% |
| Badsha et al., 2004 ¹² | 77.3% | 68.2% | 31.8% |
| Chang et al., 2002 ⁵ | 100% | 25% | 37.5% |
| Lee et al., 2001 ¹³ | 100% | 33.3% | 22.2% |
| Santos-Ocampo et al., 2000 ¹⁴ | 70% | 10% | 10% |
| Lee et al., 2000 ⁸ | 83.3% | – | 16.7% |
| Liu et al., 1998 ¹⁵ | 100% | 15.4% | 61.5% |
| Zamora et al., 1997 ¹⁶ | 93% | 15.8% | 42.1% |
| Barile et al., 1997 ⁴ | 32.4% | 44.1% | 14.7% |
| Abud-Mendoza et al., 1985 ¹⁹ | 66.6% | 16.6% | 58.3% |

ASLE, adult-onset SLE; JSLE, Juvenile-onset SLE; NP, neuropsychiatric; –, not reported.

previous month. In an analysis of 21 patients with lupus and DAH, and 83 controls without lupus and DAH, Kwok et al.,¹⁰ in a univariate analysis, reported that patients with DAH more frequently developed neuropsychiatric lupus, serositis, SLEDAI >10 nephritis and pulmonary hypertension; in the multivariate analysis, the coexistence of neuropsychiatric lupus and SLEDAI >10 is considered an independent factor associated with the development of DAH. In this same study, an association with the development of DAH autoantibodies was found. DAH can be the first manifestation of SLE, which probably suggests that it represents a manifestation of SLE activity. Badsha et al. report a significant increase in the activity of the disease in the month prior to the development of DAH.¹²

Clinical Features

Inclusion criteria of patients for the different series presented here include dyspnea, decrease in hemoglobin, pulmonary radiographic images and hemoptysis; all these features are almost always present in patients with DAH and SLE; however, hemoptysis may not be present in more than 50% of patients, as shown in Fig. 2.

Pulmonary radiological images have been described as diffuse bilateral alveolar infiltrates in most series^{6,26}; some have reported alveolar-interstitial infiltrates,^{12,14} which, in up to 20%, may be unilateral or patchy¹⁴ from 33¹³ to 42%.¹⁶ The resolution of radiographic infiltrates is reported by Schwab et al. in 72 h.¹⁸ High-resolution CT is more sensitive than conventional radiography in detecting DAH.²⁷

In terms of lung biopsy, some of the first studies by Myers and Katzenstein, who describe small vessel vasculitis or microangiitis in 4 patients with lupus highlight the characteristic expression of DAH in SLE and immune complex deposits²⁸. Currently, it is known that not all patients with DAH capillaritis have immune complexes associated with SLE²⁰; e.g. Zamora et al.,¹⁶ reported capillaritis in 8 of 10 cases with biopsy (80%); one patient with DAH had diffuse alveolar damage and another infectious pneumonia. We reiterate that many patients with DAH in SLE described in the literature are reported with “soft bleeding” or without capillaritis.¹²

The diffusion of carbon monoxide is diagnostically useful in DAH when it is increased, a fact which occurs in 91% of patients reported by Badsha et al.¹²; meanwhile, Koh et al. reported this¹⁷ in 4 of 5 patients. Note that this study implies the difficulty or impossibility of its performance when patients are unstable or on mechanical ventilation, as frequently occurring in DAH.

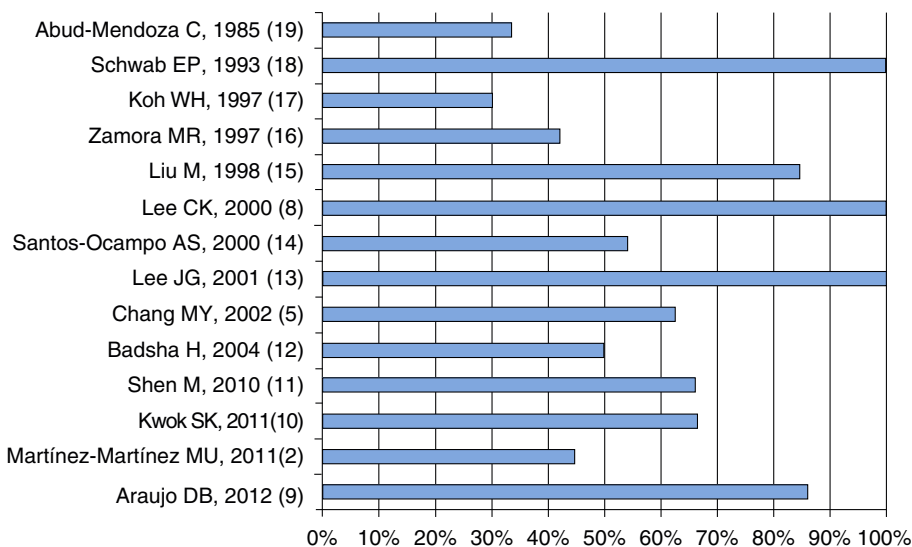


Fig. 2. Presence of hemoptysis in different series. We noted the first author, year of publication and the reference, in parentheses.

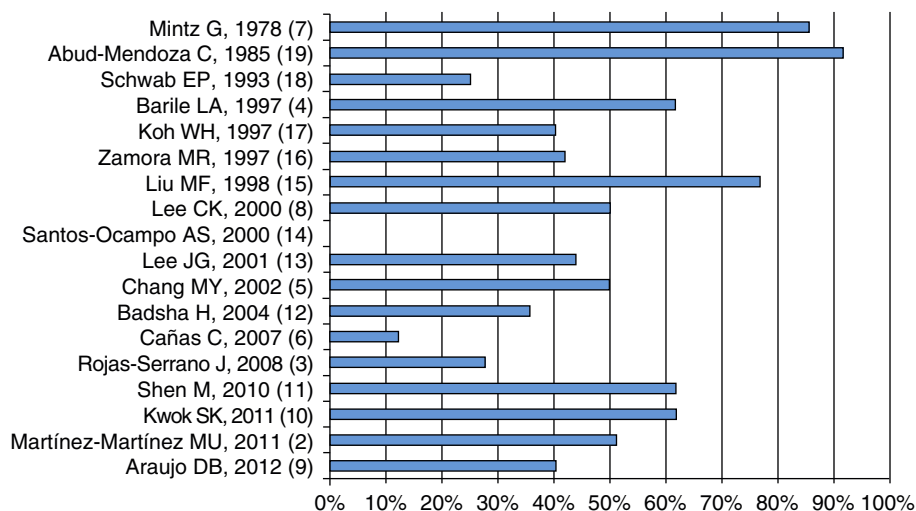


Fig. 3. Mortality in patients with DAH and SLE. The first author, the year and the reference, in parenthesis, are shown.

Bronchoalveolar lavage is useful in determining the occurrence of infection³ plus it serves to identify hemosiderin-laden macrophages.²⁹

The profile of autoantibodies including anti-DNA, lupus anticoagulant, anticardiolipin, anti-beta2-GP1, anti-Sm, anti-Ro, anti-La and anti-RNP seems no different in patients with DAH compared with SLE patients without DAH.¹⁰

Described recurrences of the disease occur in varying degrees, so a prior episode of DAH, even after receiving adequate treatment, does not preclude a new episode.^{2,6,9,13–16,30}

Patients who survive may have alterations in respiratory function tests.³¹

Factors Associated With Mortality

Several case series have tried to highlight the factors associated with mortality; the main condition associated with mortality^{2,10,13,16} has been mechanical ventilation and other factors are associated with the severity of the APACHE II index,²⁵ such as azotemia^{2,12} and infectious processes associated with DAH.^{10,13,16}

As shown in Fig. 3, mortality seems to have decreased over time; on average, it is about 50%, although there are series like Santos-Ocampo et al.,¹⁴ who reported a mortality rate of 0%. In this series, only 36% required mechanical ventilation, which is a factor associated with mortality, and other series with higher mortality report higher frequency of mechanical ventilation.^{2,10}

With mortality we also have to evaluate the treatment received, mentioned later in this review.

Infections

Infections have been reported by different series as an important factor associated with DAH and, in these patients with SLE and DAH, it reaches almost 60%.^{2,3,10,11} Bacterial infections have been reported, including *Pseudomonas* sp.^{2,5,11,3,8,16,18,32} and *Staphylococcus aureus*, cytomegalovirus²³ infection and fungal infections, especially *Aspergillus*.^{2,11,13,16} It is difficult to separate whether the infections occurred at the time of diagnosis of pulmonary hemorrhage or after this complication. Rojas-Serrano et al.,³ reported 14 events of DAH in SLE, which were evaluated during the first 48 h with bronchoscopy and bronchoalveolar lavage, finding infection in 57%; the infectious agents were *Pseudomonas aeruginosa*

Table 3

Treatments Used in the Different Series.

| Authors, year | mPDN | Cyclophosphamide | Plasmapheresis |
|---|------------|------------------|----------------|
| Araujo et al., 2012 ⁹ | JSLE: 100% | JSLE: 69% | JSLE: 15% |
| Martínez-Martínez and Abud-Mendoza, 2011 ² | ASLE: 100% | ASLE: 47% | ASLE: 20% |
| Kwok et al., 2011 ¹⁰ | 100% | 58.6% | OR |
| Shen et al., 2010 ¹¹ | 95.2% | 38.1% | 66.6% |
| Shen et al., 2010 ¹¹ | 79.3% | 70.0% | 10.3% |
| Rojas-Serrano et al., 2008 ³ | 57.1% | 7.1% | – |
| Cañas et al., 2007 ⁶ | 100% | 100% | 57.1% |
| Badsha et al., 2004 ¹² | 86.4% | 86.4% | 50% |
| Chang et al., 2002 ⁵ | 100% | 12.5% | 37.5% |
| Lee et al., 2001 ¹³ | 66.7% | 33.3% | OR |
| Santos-Ocampo et al., 2000 ¹⁴ | 81.8% | 70% | 45.5% |
| Lee et al., 2000 ⁸ | 100% | 33.3% | 83.3% |
| Liu et al., 1998 ¹⁵ | 76.9% | 15.4% | – |
| Zamora et al., 1997 ¹⁶ | 94.7% | 52.6% | 63.2% |
| Koh et al., 1997 ¹⁷ | 80% | 70% | 40% |
| Barile et al., 1997 ⁴ | 73.5% | 5.9% | 5.9% |
| Schwab et al., 1993 ¹⁸ | 87.5% | 62.5% | – |
| Abud-Mendoza et al., 1985 ¹⁹ | 25% | 8.3% | – |

ASLE, adult-onset SLE; JSLE, Juvenile-onset SLE; mPDN, methylprednisolone pulses; –, not reported.

and *Aspergillus fumigatus*, which allowed to confirm the presence of infection in the diagnosis of pulmonary hemorrhage, leading to the observation that it could be a precipitating or contributing factor.

Treatment

Table 3 shows the main treatments used in the different series, of which 3 are the most frequently used: methylprednisolone, cyclophosphamide and plasmapheresis. Antibiotics were included empirically in several series.²³

The use of high-dose intravenous “pulses” of methylprednisolone is one of the most widely used treatments in SLE associated with DAH. In a retrospective study, Barile et al.,⁴ divided 34 patients with DAH associated with SLE into 3 groups: patients who received prednisone 1 mg/kg, another “conventional” form of pulse methylprednisolone (3g in 3 days) and those who received pulse methylprednisolone until the resolution (more than 3g); survival was higher for patients receiving prolonged pulses and reduced in those which only received prednisone 1 mg/kg.

The use of cyclophosphamide is controversial; while Zamora et al. reported a higher mortality in patients who received the drug,¹⁶ the series probably benefited due to the association of SLE disease activity with DAH.¹² Zamora et al.,¹⁶ reported that all patients who received cyclophosphamide required mechanical ventilation, plus 6/7 patients died. DAH also presented infection, factors associated with mortality in the same study, making it unlikely that cyclophosphamide confers, by itself, an increase in mortality, as patients who received it had more factors associated with mortality.¹⁶

As shown in Table 3, plasmapheresis has been used in several series; it is difficult to assess its utility alone, since although some studies show a lower mortality of 20%, patients were treated with or without cyclophosphamide⁶; the same could be said for intravenous immunoglobulin, which has been used in some series, such as Shen et al.,¹¹ and case reports.

Biological therapies for DAH in SLE may also be associated with benefits that have been reported in case reports, as in the likely benefit of rituximab^{33–35}; although in the series by Martínez-Martínez and Abud-Mendoza this was not beneficial in 2 patients.² Note that the mechanism of action of rituximab on autoantibodies could not occur quickly, as required in SLE associated DAH; however, other mechanisms of action of B cell depleting therapy may be involved in fast beneficial effects, such as antigen presentation and activation of T regulatory cells.^{24,36,37} Rituximab may be more useful to prevent recurrences.^{2,30}

Other therapies include transplantation of umbilical cord mesenchymal cells,³⁸ reporting a benefit in 4 patients as published by Shi et al.³⁹ There are also reports of treatment with extracorporeal membrane oxygenation,⁴⁰ factor vii⁴¹ and⁴² mycophenolate mofetil.

Conclusions and Future Prospects

Despite the passage of time and new therapies, DAH associated with SLE remains a diagnostic and therapeutic challenge, with high mortality; identifying factors associated with mortality and the measures and strategies to diminish or avoid it could improve the survival rate. Controlled studies or continuation of the series and a combination of cases is required to analyze and evaluate the potential benefit of current therapies, which include biological drugs.

DAH can result from joint factors such as the activity of the disease, which leads to a potentially fatal process which

can be accompanied by infections, heart and renal failure, in addition to immunoregulation alterations, and they are all characteristics of SLE. We suggest that all patients with DAH be assessed and monitored from admission to rule out infectious processes and receive appropriate comprehensive therapy, with the inclusion of antibiotics and immunosuppressants, with ongoing assessments to identify factors associated with morbidity and mortality.

Ethical Responsibilities

Protection of people and animals. The authors declare that this research has not performed experiments on humans or animals.

Data privacy. The authors state that patient data does not appear in this article.

Right to privacy and informed consent. The authors state that patient data does not appear in this article.

Conflicts of Interest

The authors have no conflicts of interest.

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