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Diffuse alveolar hemorrhage in immunocompetent patients: Etiologies and prognosis revisited

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Summary
Background: Diffuse alveolar hemorrhage (DAH) represents a diagnostic challenge of acute respiratory failure. Prompt identification of the underlying cause of DAH and initiation of appropriate treatment are required in order to prevent acute respiratory failure and irreversible loss of renal function. More than 100 causes of DAH have been reported. However, the relative frequency and the differential presentation of those causes have been poorly documented, as well as their respective prognosis.
Methods: We retrospectively reviewed the charts of 112 consecutive patients hospitalized for DAH in a tertiary referral center over a 30-year period.
Results: Twenty-four causes of DAH were classified into four etiologic groups: immune ($n = 39$), congestive heart failure (CHF; $n = 33$), miscellaneous ($n = 26$), and idiopathic DAH ($n = 14$). Based on this classification, clinical and laboratory features of DAH differed on hospital admission. Patients with immune DAH had more frequent pulmonary-renal syndrome ($p < 0.001$), extra-pulmonary symptoms ($p < 0.01$), and lower blood hemoglobin level than others ($p < 0.001$). Patients with CHF-related DAH were older and received more

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anticoagulant treatments than others ($p < 0.05$). Those with miscellaneous causes of DAH exhibited a shorter prodromal phase ($p < 0.001$) and had more frequent hemoptysis >200 mL ($p < 0.05$). Patients with idiopathic DAH had more bronchoalveolar lavage siderophages ($p < 0.01$). In-hospital mortality was 24.1%, ranging from 7.1% in patients with idiopathic DAH to 36.4% in those with CHF.

Conclusions: Arbitrary classification of DAH in four etiologic groups gives the opportunity to underline distinct presentations and outcomes of various causes of DAH.

Introduction

Diffuse alveolar hemorrhage (DAH), commonly defined as the association of hemoptysis, new pulmonary infiltrates on chest x-ray and anemia, is a rare syndrome resulting from diffuse bleeding into the acinar portion of the lung.[1,2] However, DAH can present in about 40% of the cases without hemoptysis.[3] DAH is a diagnostic and therapeutic challenge because it may be revealed by nonspecific pulmonary manifestations and caused by multiple immune and non-immune disorders. Moreover, reported prognosis is poor, with in-hospital mortality ranging from 20 to over 50%.[4–6] Prompt identification of the underlying cause of DAH and initiation of appropriate treatment is required in order to prevent acute respiratory failure. When DAH is a manifestation of systemic illness, early targeted treatment can also prevent the development of acute renal failure and the potential subsequent renal death.[7,8] The standard regimen for remission induction of immune causes is based mainly on high-dose steroids.[9] However, such treatment will be ineffective and potentially deleterious if the DAH is due to non-immune causes, such as congestive heart failure or infection. Consequently, identification of the cause is crucial for adequate management of a patient with DAH.

Over 100 causes of DAH have been reported in immunocompetent patients (Table 1 of the online supplement).[1,3,10,11] Most of the published series focus primarily on immune causes,[2,5,8,12–14] but numerous non-immune causes of DAH have been reported as case reports.[15–24] The relative frequency of the underlying causes of DAH, as well as their respective prognosis, is not well documented. We recently showed that the global picture of DAH has changed over the last decades; non-immune causes being largely underestimated.[10] We also reported similar outcome for immune and non-immune causes. This finding challenged the belief that immune DAH exhibits a worse prognosis than non-immune DAH.

Based on a retrospective cohort of 112 consecutive immunocompetent patients, we aimed to report the causes of DAH and their relative frequency and presentation to a referral tertiary center in order to classify them into distinct etiologic groups, and the mortality for each etiologic group.

Methods

Study design

A retrospective cohort study was performed in the Chest Department including an Intensive Care Unit (ICU) of an 800-bed tertiary hospital in France (Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, France). This observational, non-interventional analysis of medical

Table 1 Etiology of DAH syndromes ($N = 112$).

Immune	$N = 39$
Small-vessel vasculitides	*28*
Microscopic polyangiitis	16
Wegener's granulomatosis	11
Churg and Strauss syndrome	1
ABMAD	*5*
Connective tissue disease	*6*
Systemic lupus erythematosus	4
Rheumatoid arthritis	1
Mixed connective tissue disease	1
Congestive heart failure	$N = 33$
Systolic dysfunction of the left ventricle[a]	*20*
Diastolic dysfunction of the left ventricle	*8*
Valvular heart disease[b]	*5*
Miscellaneous	$N = 26$
Infection	*8*
Staphylococcus aureus[c]	5
Leptospirosis	1
Anaerobic bacteria	1
Dirofilaria immitis	1
Barotrauma	*6*
Clotting disorder	*6*
Thrombocytopenia	3
Anticoagulant and/or antiaggregant treatment	3
Cancer[d]	*2*
Uterine leiomyosarcoma	1
Small cell lung cancer	1
Toxic-induced DAH	*2*
Cannabis	1
Glue solvent inhalation	1
Drug-induced DAH	*1*
Clomifene	1
Fat embolism[e]	*1*
Idiopathic	$N = 14$

DAH, diffuse alveolar hemorrhage; ABMAD, anti-glomerular basement membrane antibody disease.

[a] Due to Churg and Strauss syndrome in one patient, median left ventricle ejection fraction was 40% (30–45).

[b] Mitral stenosis ($n = 4$), aortic stenosis ($n = 1$).

[c] Including two meticillin-resistant and three Panton-Valentine leukocidin producing strains.

[d] DAH related to endovascular metastasis in both cases.

[e] Following a tibial fracture.

records was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine - Société de Pneumologie de Langue Française.

Inclusion criteria

The medical records of consecutive patients admitted between January 1980 and December 2009 for suspected DAH were reviewed. For patients with multiple admissions, the first admission was used for the study. All adult patients with symptomatic DAH were eligible. The definition of symptomatic DAH was based on the following criteria. First, the clinical and radiological presentation was compatible with the diagnosis of DAH, including hemoptysis and/or new pulmonary infiltrates on chest x-ray (Fig. 1A) and/or anemia (*i.e.*, DAH triad).[2] Second, the bronchoalveolar lavage (BAL) fluid was macroscopically bloody (Fig. 1B). Alternatively, hemorrhagic and siderophagic alveolitis were evidenced on BAL cytology (Fig. 1C),[19,25,26] trans-bronchial lung biopsy or surgical lung biopsy.

Patients with immunocompromised status (human immunodeficiency virus infection, hematological malignancies, bone marrow or solid organ transplantation, immunosuppressive drugs therapy, cytotoxic chemotherapy or radiotherapy, steroids at a daily dose higher than 20 mg of prednisone-equivalent for more than two months) were excluded. Patients with hemorrhage of bronchial origin and patients receiving hemodialysis for chronic renal failure were also excluded.

Data collection

Data were abstracted from medical charts using a standardized procedure (see the methods section of the online supplement for more details). Variables available during the first 24 h of hospitalization included demographics, clinical and laboratory features. Pulmonary-renal syndrome was defined clinically by the presence of DAH and the following criteria: hematuria, proteinuria $>$ 1g/L, and glomerular filtration rate (GFR) $<$ 60 mL/min. The prodromal phase was the time elapsed between the first symptom related to the cause of DAH and hospital admission. The severity of DAH was assessed from generic scores of organ dysfunction including the Logistic Organ Dysfunction (LOD) score[27] and the Simplified Acute Physiology Score (SAPS) II.[28]

Variables available during hospitalization included hospital length of stay, vital status at hospital discharge, need for invasive mechanical ventilation, hemodialysis, blood transfusion, peak plasma lactic dehydrogenase (LDH) level, anti-neutrophil cytoplasm antibody (ANCA)-test immunofluorescence pattern (*i.e.*, a granular cytoplasmic neutrophil fluorescence with central interlobular accentuation (c-ANCA), and a perinuclear fluorescence (p-ANCA)) and specificity (*i.e.*, directed against proteinase-3 (PR3) or myeloperoxydase (MPO), as detected by ELISA),[29] lung and kidney tissue histology and immunofluorescence analysis, administration of steroids or cyclophosphamide, and institution of plasma exchange.

Variables available after hospital discharge included death during the follow-up period, end stage renal disease (*i.e.*, need for chronic hemodialysis) and need for long-term oxygen therapy.

Definitions and classification of the underlying causes of DAH

The etiologic diagnoses of DAH were specifically defined and classified into four groups.

Immune causes

The American College of Rheumatology criteria were used for defining a necrotizing vasculitis. A histological proof of

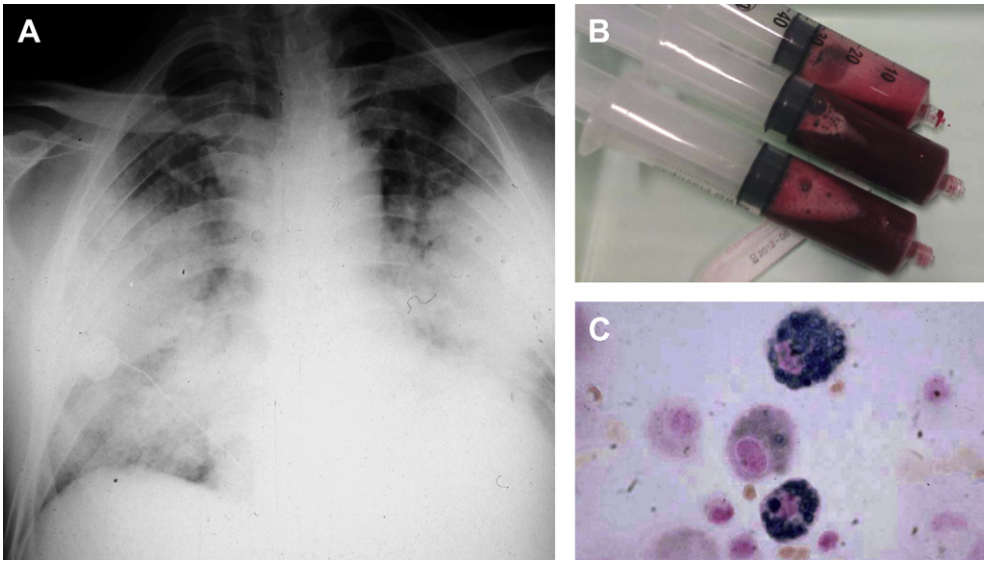

Figure 1 A) Chest x-ray of a patient with diffuse alveolar hemorrhage, showing diffuse pulmonary infiltrates; B) Macroscopically bloody bronchoalveolar lavage fluid. An increasing red blood cell count in sequential bronchoalveolar lavage aliquots from the same location is considered diagnostic of diffuse alveolar hemorrhage; C) Bronchoalveolar lavage fluid stained by Perl's Prussian blue method, showing deep blue throughout the cytoplasm of two alveolar hemosiderin-laden macrophages. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

necrotizing vasculitis was required.[30–33] The American Rheumatism Association criteria were used for defining a connective tissue disease.[34,35] The anti-glomerular basement membrane antibody disease (ABMAD; *i.e.*, Goodpasture's syndrome) was diagnosed when the serologic test for anti-glomerular basement membrane antibodies was positive. Alternative diagnosis was made on the presence of a linear immunofluorescent glomerular immunoglobulin deposit.[8]

Congestive heart failure

Clinical and radiological features suggestive of DAH related to a congestive heart failure (CHF)[36] were an increased left atrial pressure, as diagnosed by echocardiography-doppler or right heart catheterization.

Miscellaneous causes

The diagnosis of a barotraumatic-stress capillary failure due to high transpulmonary pressures (tracheal extubation or scuba diving) was made in a suggestive context.[17,37] For cancer, the presence of histological evidence was required in the diagnosis. For infection, positive microbiological or serological tests allowed for diagnosis. Clotting disorders were diagnosed by a platelet count less than 150,000 cells/ml, a patient-to-control subject ratio of activated partial thromboplastin time greater than 1.5, or a thromboplastin time less than 60%. The diagnosis of toxin- or drug-induced disease was established when there was a compatible chronology after exposure to a known pneumotoxic substance and required the exclusion of all the other causes of DAH.[38]

Idiopathic DAH

Idiopathic DAH was defined when a thorough search for the above-mentioned causes remained negative.

Data presentation and statistical analysis

Continuous variables were reported as median [25th–75th interquartile range] (IQR 25–75) or mean ± SD and compared with the *t* test when normally distributed or otherwise with the Mann–Whitney test. Analysis of variance was used to compare the etiologic groups. Bonferroni corrected post hoc tests were performed when overall *p* value was less than 0.05. The Shapiro–Wilk normality test was performed. Categorical variables were reported as percentages and compared with the χ^2 test or the Fischer Exact test as required. The comparison of the outcome of each etiologic group of DAH was performed by the Kaplan–Meier method with the log-rank test. Two-tailed *p* values less than 0.05 were considered statistically significant. Analyses were carried out using Statview statistical software (SAS Institute Inc., Calasabas, USA).

Results

Etiology of DAH and patient characteristics on hospital admission

One hundred and sixty-six patients were hospitalized for suspected DAH over the study period. We included 112 patients in the cohort [54 patients were excluded because of missing data ($n = 10$), hemorrhage of bronchial origin ($n = 43$), and discovery of an immunocompromised status during hospitalization (HIV infection, $n = 1$)], including 98 patients who were also included in a previous study.[10]

The whole DAH triad was observed in only 34% ($n = 38/112$) of the patients. Anemia, as defined by blood hemoglobin <12 g/dL,[39] was only present in 59% ($n = 66/112$), and hemoptysis in 66% ($n = 74/112$) of cases. In contrast, pulmonary infiltrates were almost always present (93%, $n = 104/112$).

There were 24 causes of DAH, which were classified into four etiologic groups (Table 1): immune, CHF, miscellaneous and idiopathic. The distribution of the etiologic groups over time was relatively stable ($p = 0.33$, Fig. 2). Differences in clinical (Table 2) and laboratory (Table 3) features, based on the etiology of DAH, were observed upon hospital admission.

Pulmonary-renal syndrome was more frequently present in immune DAH patients than in others ($p < 0.001$) and exhibited the following diagnostic performances [95% CI] for the diagnosis of immune DAH: sensitivity = 0.41 [0.25–0.58], specificity = 0.96 [0.88–0.99], positive predictive value (PPV) = 0.84 [0.60–0.97], and negative predictive value (NPV) = 0.75 [0.65–0.84].

Immunological tests and histological features

ANCA tests were positive for indirect immunofluorescence in 86% ($n = 24/28$) of patients with vasculitides (Table 4). Kidney biopsy was performed in 67% ($n = 26/39$) of patients with immune DAH. Histological examination revealed a necrotizing crescentic glomerulonephritis in 24 cases, including nine patients with Wegener's granulomatosis (WG), nine patients with microscopic polyangiitis (MP), and five patients with ABMAD, and was normal in one patient

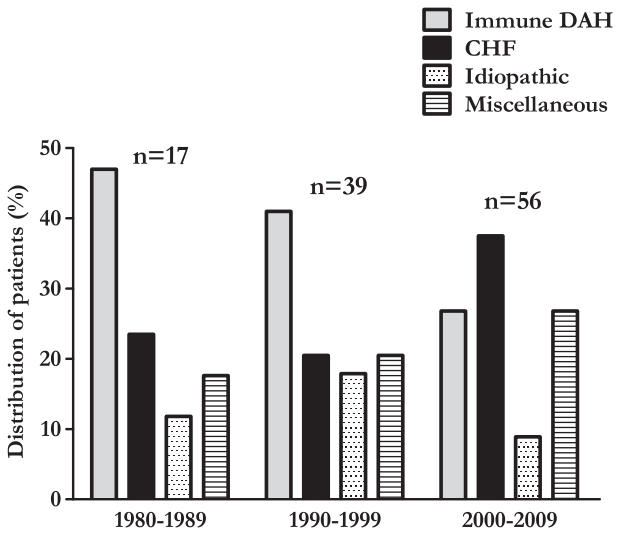

Figure 2 Distribution of the etiology of diffuse alveolar hemorrhage over three 10-year time periods. There was no significant change in the proportion of each etiologic group over time ($p = 0.33$). DAH, diffuse alveolar hemorrhage; CHF, chronic heart failure.

Table 2 Demographic and clinical presentation of 112 patients with DAH upon hospital admission.

Variables	All patients ($N = 112$)	Immune ($N = 39$)	CHF ($N = 33$)	Miscellaneous ($N = 26$)	Idiopathic ($N = 14$)	P
Age, year	53 (32–68)	48 (24–64)	64 (46–71)[e]	45 (28–59)	52 (33–63)	0.019
Male gender	73 (65.2)	19 (48.7)	23 (69.7)	22 (84.6)	9 (64.3)	0.58
Weight loss > 5%	42 (37.5)	24 (61.5)	9 (27.3)	6 (23.1)	3 (21.4)	0.09
Tobacco > 20 pack-years	33 (29.5)	8 (20.5)	10 (30.3)	9 (34.6)	6 (42.8)	0.65
Alcohol use	23 (20.5)	6 (15.4)	6 (18.2)	7 (26.9)	4 (28.6)	0.74
Previous cardiovascular disease[a]	51 (45.5)	13 (33.3)	24 (72.7)	8 (30.8)	6 (42.8)	0.17
Previous respiratory disease[b]	27 (24.1)	10 (25.6)	9 (27.3)	5 (19.2)	3 (21.4)	0.94
Anticoagulant treatment	16 (14.3)	1 (2.6)	10 (30.3)	4 (15.4)	1 (7.1)	0.034
Antiaggregant treatment	20 (17.8)	5 (12.8)	5 (15.1)	7 (26.9)	3 (21.4)	0.65
ICU admission	86 (76.8)	26 (66.7)	29 (87.9)	24 (92.3)	7 (50.0)	0.59
Prodromal phase, days	21 (4–181)	53 (21–365)	10 (5–195)	3 (0–9)[g]	165 (6–440)	<0.001
First symptom-admission, days[c]	8 (3–21)	18 (10–30)	6 (3–15)	3 (1–4)[f]	15 (3–75)	<0.001
Temperature, °C	37.3 (37.0–38.2)	38 (37.0–38.5)	37.3 (37.0–38.0)	37.2 (37.0–37.8)	37.5 (37.2–39.0)	0.15
DAH triad[d]	38 (33.9)	18 (46.1)	10 (30.3)	7 (26.9)	3 (21.4)	0.55
Hemoptysis	74 (66.1)	23 (59.0)	22 (66.7)	18 (69.2)	11 (78.6)	0.94
Hemoptysis > 200 mL/24 h	9 (8.0)	1 (2.6)	1 (3.0)	6 (23.1)	1 (7.1)	0.039
Use of accessory muscles	31 (27.7)	12 (30.8)	9 (27.3)	6 (23.1)	4 (28.6)	0.96
Crackles	86 (76.8)	30 (76.9)	27 (81.8)	21 (80.8)	8 (57.1)	0.54
Mechanical ventilation	20 (17.8)	6 (15.4)	6 (18.2)	7 (26.9)	1 (7.1)	0.59
Shock	23 (20.5)	6 (15.4)	11 (33.3)	5 (19.2)	1 (7.1)	0.31
Extra-pulmonary symptoms						
Cutaneous	30 (26.8)	18 (46.1)	7 (21.2)	4 (15.4)	1 (7.1)	0.07
Bone-joint	16 (14.3)	13 (33.3)	2 (6.1)	0 (0.0)	1 (7.1)	0.004
Gastro-intestinal	12 (10.7)	4 (10.2)	4 (12.1)	3 (11.5)	1 (7.1)	0.97
Neurological	24 (21.4)	11 (28.2)	5 (15.1)	6 (23.1)	2 (14.2)	0.68
Nose-ear-throat	26 (23.2)	16 (41.0)	3 (9.0)	1 (3.8)	6 (42.8)	0.007
Ocular	11 (9.8)	7 (17.9)	1 (3.0)	1 (3.8)	2 (14.2)	0.18
Urinalysis reagent strip						
Hematuria	29 (25.9)	25 (64.1)	1 (3.0)	3 (11.5)	0 (0.0)	<0.001
Proteinuria	34 (30.3)	25 (64.1)	4 (12.1)	2 (7.7)	3 (21.4)	<0.001

Data are presented as mean ± SD or median (IQR 25–75) when appropriate, or number (N) and percentage (%). DAH, diffuse alveolar hemorrhage; CHF, Congestive heart failure.

[a] Hypertension ($n = 36$), coronary heart disease ($n = 22$), atrial fibrillation ($n = 13$), oblitering arteriopathy of the lower limbs ($n = 6$), stroke ($n = 3$).

[b] COPD ($n = 9$), respiratory tract infection ($n = 10$), miscellaneous ($n = 8$).

[c] Time elapsed between the first symptom of DAH and hospital admission.

[d] Defined as anemia (hemoglobin level <12 g/dL), pulmonary infiltrates and hemoptysis.

[e] $p < 0.05$ as compared to immune DAH and DAH of miscellaneous causes.

[f] $p < 0.01$ as compared to idiopathic and immune DAH.

[g] $p < 0.001$ as compared to all other DAH.

with MP. Three patients with negative ANCA tests (one WG and two MPs) had a positive diagnosis of necrotizing crescentic glomerulonephritis. Immunofluorescence was available in 16 kidney biopsy samples including seven patients with WG, four with MP and five with ABMAD. Among WG and MP patients, two patients exhibited a granular IgG, IgM, or C_3 staining pattern on the basal membrane compatible with immune complexes, and nine had no significant immune deposit. All five patients with ABMAD exhibited a linear IgG staining on the glomerular basement membrane. Three of those patients did not have circulating anti-glomerular basement membrane antibodies.

Overall, nine lung biopsies were performed and confirmed the presence of DAH but did not diagnose its cause in 8/9 cases. Transbronchial biopsies were performed in six cases and revealed mild fibrosis in three patients with idiopathic DAH, capillaritis in a patient with WG, and did not assist in diagnosis of two patients. Open chest biopsies were performed in three patients with immune DAH: one patient had typical features of WG (*i.e.*, foci of necrosis and granulomatous inflammation), one had mixed connective tissue disease with mild interstitial edema and capillary congestion, and another with MP exhibited marked fibrosis. Immunofluorescence was negative in all cases.

Hospital course and outcome

Upon hospital admission, 77% of the patients required ICU admission (Fig. 3). Twenty patients (18%) underwent

Table 3 Laboratory features of 112 patients with DAH upon hospital admission.

Variables	All patients ($N = 112$)	Immune ($N = 39$)	CHF ($N = 33$)	Miscellaneous ($N = 26$)	Idiopathic ($N = 14$)	P
SAPS II	22 (13–35)	21 (12–37)	25 (17–35)	23 (12–38)	15 (6–24)	0.19
LOD score	3 (0–5)	3 (1–5)[c]	3 (1–4)	3 (0–4)	0 (0–1)	0.027
PaO_2/FiO_2 ratio	264 ± 108	269 ± 110	274 ± 96	222 ± 102	299 ± 127	0.16
Pulmonary infiltrates on CXR	104 (92.8)	36 (92.3)	33 (100)	24 (92.3)	11 (78.6)	0.97
Unilateral infiltrates	13 (11.6)	1 (2.6)	6 (18.2)	5 (19.2)	1 (7.1)	0.17
Bronchoalveolar lavage						
Bloody or pink	94 (83.9)	35 (89.7)	25 (75.7)	24 (92.3)	10 (71.4)	0.92
Total cell count, 10^3/mL[a]	350 (195–640)	295 (115–565)	390 (195–682)	340 (200–912)	365 (224–750)	0.80
Macrophages, %	71 (47–82)	68 (45–75)	74 (47–80)	71 (45–87)	78 (51–88)	0.54
Including siderophages, %	68 (47–99)	60 (50–100)	73 (50–91)	39 (2–85)[f]	100 (83–100)	0.003
Neutrophils, %	15 (4–37)	25 (10–49)	12 (4–25)	12 (4–33)	8 (1–40)	0.18
Lymphocytes, %	5 (2–13)	4 (1–13)	9 (2–19)	5 (1–10)	4 (1–8)	0.25
Eosinophils, %	0 (0–1)	0 (0–4)	0 (0–1)	0 (0–1)	0 (0–1)	0.69
Presence of germs	20 (17.8)	4 (10.2)	6 (18.2)	8 (30.8)	2 (14.3)	0.38
LDH, UNV	1.1 (0.7–1.9)	1.2 (0.7–1.7)	1.2 (0.7–3.1)	1.0 (0.7–2.0)	1.2 (0.7–2.3)	0.93
Glomerular filtration rate, mL/min	65 (40–101)	43 (13–77)[d]	55 (40–88)	90 (64–114)	97 (61–108)	<0.001
Pulmonary-renal syndrome[b]	19 (17.0)	16 (41.0)	3 (9.1)	0 (0.0)	0 (0.0)	<0.001
Hemoglobinemia, g/dL	10.9 ± 3.0	9.0 ± 2.1[e]	11.8 ± 2.5	11.5 ± 3.4	13.0 ± 2.7	<0.001
White blood cells count, $10^3/\mu L$	9.5 (7.0–14.9)	9.6 (6.9–13.0)	11.0 (7.4–16.8)	8.9 (7.0–15.3)	8.3 (6.5–12.6)	0.46
Platelets count, $10^3/\mu L$	285 ± 139	330 ± 149	285 ± 131	226 ± 142[g]	265 ± 81	0.027

Data are presented as mean ± SD or median (IQR 25–75) when appropriate, or number (N) and percentage (%). DAH, diffuse alveolar hemorrhage; CHF, Congestive heart failure; UNV, upper normal value; CXR, chest x-ray.

[a] Cytology was only obtained in 90 patients because the amount of red blood cells in the BAL fluid precluded its analysis in 22 cases.

[b] As defined by the presence of DAH and the following criteria: hematuria on urinalysis reagent strip, proteinuria > 1 g/L, and glomerular filtration rate <60 mL/min.

[c] $p < 0.05$ as compared to idiopathic DAH.

[d] $p < 0.01$ as compared to DAH of idiopathic and miscellaneous causes.

[e] $p < 0.001$ as compared to all other groups.

[f] $p < 0.01$ as compared to idiopathic DAH.

[g] $p < 0.05$ as compared to immune DAH.

Table 4 ANCA-test results in 28 patients with DAH due to vasculitides.

IIF pattern	ELISA specificity	MP ($N = 16$)	WG ($N = 11$)	CSS ($N = 1$)
p-ANCA	MPO-ANCA	8	2	0
	PR3-ANCA	0	0	0
	Not reported	3	2	0
c-ANCA	MPO-ANCA	0	0	0
	PR3-ANCA	0	1	0
	Not reported	2	4	0
Nonspecific	MPO-ANCA	0	0	0
	PR3-ANCA	0	0	0
	Not reported	0	1	1
Negative		3	1	0

ANCA, anti-neutrophil cytoplasm antibody; IIF, indirect immunofluorescence; MP, microscopic polyangiitis; WG, Wegener's granulomatosis; CSS, Churg and Strauss syndrome; p-ANCA, ANCA with a perinuclear staining; c-ANCA, ANCA with a cytoplasmic staining; MPO-ANCA, ANCA directed against myeloperoxydase; PR3-ANCA, ANCA directed against proteinase-3.

invasive mechanical ventilation within the 24 h of hospital admission and 18 patients (16%) immediate hemodialysis, which was more frequently required in immune DAH patients than in others (36% *vs* 5%; $p < 0.01$).

The median hospital length of stay was 10 days [6–19], tending to be longer for immune DAH patients, as compared to others ($p = 0.09$) (Table 5). Invasive mechanical ventilation and blood transfusion requirement did not differ between etiologic groups. In-hospital mortality was higher for CHF (36.4%) than miscellaneous (26.9%), immune (17.9%) and idiopathic (7.1%) DAH patients, although not of statistical significance (Table 5).

Eighty five patients were discharged alive from hospital and followed up for a median period of nine months [1–48] (Table 6). Pulmonary fibrosis was diagnosed upon a review of histologic section in two patients with idiopathic DAH. Overall, the mortality rate of discharged patients was 14.1% ($n = 12/85$), and was not different between groups.

All-cause mortality over the follow-up period

All-cause mortality rate over the follow-up period was 35% ($n = 39/112$), encompassing both in-hospital mortality and

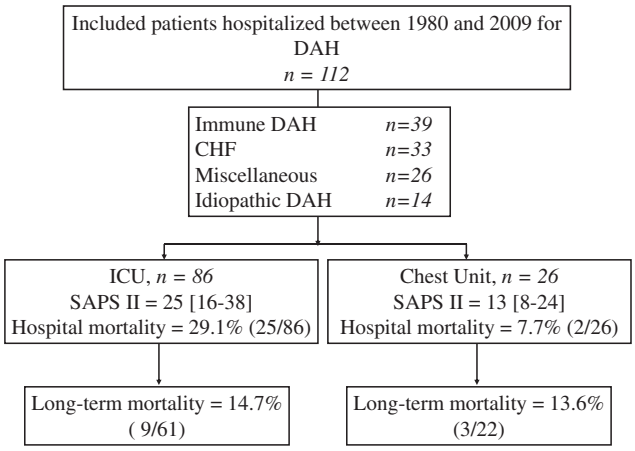

Figure 3 Flow chart of patients hospitalized for suspected diffuse alveolar hemorrhage between 1980 and 2009.

mortality in discharged patients. Although not statistically significant, CHF patients exhibited a higher mortality (45.4%; $n = 15/33$) than miscellaneous (34.6%; $n = 9/26$), immune (30.8%; $n = 12/39$) and idiopathic (21.4%; $n = 3/14$) DAH patients (Fig. 4).

Discussion

Since the comprehensive review published in 1984 by Leatherman et al.,[2] this is the largest series to describe the causes of DAH and their relative frequency and particular presentation in unselected patients. Based on a simple classification of DAH in four groups, the main results of this study are as follows: 1) Patients with immune, CHF, miscellaneous, and idiopathic DAH exhibited distinct clinical and laboratory features; 2) In-hospital mortality was 24.1%, ranging from 7.1% in patients with idiopathic DAH to 36.4% in those with CHF.

Diagnosis of DAH

The typical presentation of DAH is a triad of anemia, pulmonary infiltrates on chest x-ray, and hemoptysis.[2] In the current series, this triad was only present in 34% of patients, although most had severe diseases. Therefore, to make a diagnosis of DAH on the basis of clinical and radiologic criteria could be challenging.

Early bronchoscopy with bronchoalveolar lavage is indicated in most of patients suspected of having DAH in order to confirm the diagnosis and to rule out infection.[1,3] Indeed, we found that DAH could be confirmed immediately by a macroscopically bloody or pink BAL in 84% of cases. Alternatively, usually in chronic and mild DAH, it can be diagnosed using a score (*i.e.*, the Golde score) based on the semiquantitative hemosiderin content of alveolar macrophages.[19,40]

Etiologies of DAH and their relative frequency

More than 100 causes of DAH have been described (Table 1 of the online supplement). Yet, the most common etiology is still unknown. In the present series, we identified 24 causes, which were classified into four groups based on their relative frequency: immune, CHF, miscellaneous, and idiopathic DAH.

Immune DAH was the largest etiologic group, accounting for 35% of all causes. Small-vessel vasculitides, predominantly MP and WG, were the main subset of immune DAH (72%). Among 34 cases of DAH, Travis et al. initially reported 14 vasculitides, including 11 cases of WG and three cases of systemic necrotizing vasculitis.[12] Our study confirms that ANCA-associated diseases are now the main subset of immune DAH with a small proportion of WG. Indeed, DAH was the first cause of ICU admission, observed in 37% of cases, in patients with small-vessel vasculitis having acute life-threatening manifestations.[41] Five patients had ABMAD, accounting for 13% of immune and 4% of all DAH. In contrast, Leatherman et al. reported 10 cases of ABMAD out of 26 patients, and likely overestimated the frequency of this disease, as their cohort was based on a combination of literature review and analysis of cases encountered by the authors.[2] Finally, four of six patients with connective tissue disorder-associated DAH had systemic lupus erythematosus (SLE). DAH is associated with SLE in about four percent of cases and represents about 22% of respiratory complications. In a previous series of patients with SLE-related DAH, the diagnosis of SLE was established before the onset of DAH in 80% of cases allowing for early targeted management.[6]

CHF affected 29% of all patients and was the most frequent diagnosis among patients with non-immune DAH. Those patients exhibited overt DAH, as opposed to usual cardiogenic pulmonary edemas, as attested by a macroscopically bloody/pink BAL in 76% of cases and high

Table 5 Hospital course of 112 patients with DAH.

Variables	All patients ($N = 112$)	Immune ($N = 39$)	CHF ($N = 33$)	Miscellaneous ($N = 26$)	Idiopathic ($N = 14$)	*P*
Hospital LOS, days	10 (6–19)	16 (7–24)	8 (6–18)	8 (4–15)	9 (7–15)	0.09
Mechanical ventilation	30 (26.8)	11 (28.2)	11 (33.3)	7 (26.9)	1 (7.1)	0.51
Hemodialysis	18 (16.1)	14 (35.9)	2 (6.1)	2 (7.7)	0 (0.0)	0.006
Blood transfusion	48 (42.8)	24 (61.5)	10 (30.3)	10 (38.5)	4 (28.6)	0.32
In-hospital mortality	27 (24.1)	7 (17.9)	12 (36.4)	7 (26.9)	1 (7.1)	0.30

Data are presented as median (IQR 25–75) or number (N) and percentage (%). DAH, diffuse alveolar hemorrhage; CHF, Congestive heart failure; LOS, length of stay.

Table 6 Outcome of discharged patients ($N = 85$) over the follow-up period.

Variables	All patients ($N = 85$)	Immune ($N = 32$)	CHF ($N = 21$)	Miscellaneous ($N = 19$)	Idiopathic ($N = 13$)	*P*
Clinical relapse of DAH	19 (22.3)	10 (31.2)	2 (9.5)	3 (15.8)	4 (30.8)	0.18
LTOT	5 (5.9)	1 (3.1)	0 (0.0)	1 (5.3)	3 (23.1)	0.026
End stage renal disease	7 (8.2)	7 (21.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.008
Follow-up period duration, months	9 (1—48)	16 (1—48)	3 (1—25)**	13 (1—88)	70 (5—157)	0.015
Mortality	12 (14.1)	5 (15.6)	3 (14.3)	2 (10.5)	2 (15.4)	0.90

Data are presented as median (IQR 25—75) or number (N) and percentage (%). DAH, diffuse alveolar hemorrhage; CHF, Congestive heart failure; LTOT, long-term oxygen therapy; **$p < 0.01$ as compared to idiopathic DAH.

percentages of BAL siderophages. Interestingly, only four of those patients had mitral stenosis, which was formerly considered to be the main cause of CHF-related DAH.[1,42] Instead, most of those patients had congestive heart failure due to systolic or diastolic dysfunction of the left ventricle. This finding is in keeping with the increasing incidence and prevalence in chronic heart failure, likely related to the increase in life span and effective treatment of hypertension and coronary artery disease.[43]

There were 13 causes of miscellaneous DAH in 26 patients. Although most of those causes had already been reported (Table 1 of the online supplement), our study allows for the assessment of the proportion of frequent causes of DAH, as opposed to rare and anecdotal ones. Indeed, infections, barotraumas, and clotting disorders accounted for 77% of the diagnoses within this etiologic group.

Infection

The pathogen retrieved in most of the infectious causes was *Staphylococcus aureus* ($n = 5$), including two methicillin-resistant and three Panton-Valentine leukocidin (PVL) producing strains. This is consistent with previous reports emphasizing the hemorrhagic presentation of pneumonia involving those strains and confirms that *S. aureus* is prevalent among DAH patients presenting signs of acute infection.[44—46] One patient, with recent travel history to the French Antilles, had a leptospirosis, frequently underestimated in the setting of DAH.[21] Although it is mainly endemic in tropical areas,[47] it can occur worldwide. One patient, who had recently traveled to Democratic Republic of the Congo, had a DAH related to pulmonary filariasis. *Dirofilaria immitis*, often referred to as the canine heartworm, is a vascular parasite that is prevalent in dogs in the United States,[48] and in South America.[49] This parasite is usually transmitted to humans by mosquito bites and causes pulmonary and subcutaneous nodules,[50] and eosinophilia. To the best of our knowledge, there is no previously published case of *D. immitis* infection revealed by DAH.

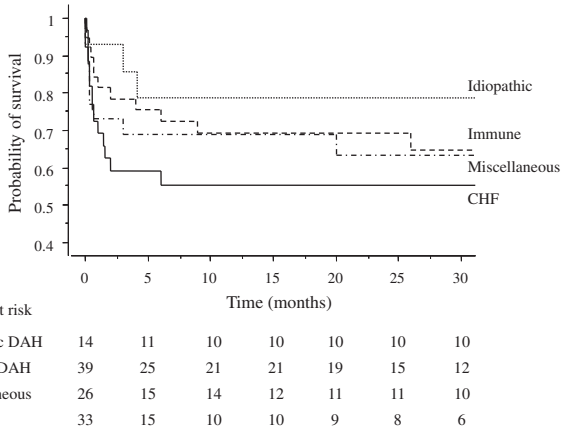

Figure 4 Kaplan—Meier curve of survival probability over time for idiopathic (dotted line), immune (dashed line), miscellaneous (dotted/dashed line), and congestive heart failure-related (CHF, continuous line) diffuse alveolar hemorrhage (DAH). Overall, there was no statistical difference between groups ($p = 0.25$ by the log-rank test).

Barotrauma

Barotrauma-related DAH have been previously described in various situations associated with high transpulmonary pressures such as scuba diving,[16] upper airway obstruction,[51] and mechanical ventilation with major patient-ventilator asynchronies, usually following general anesthesia.[17]

Iatrogenic and toxic

Anticoagulant treatments were associated with other causes in about 15% of the cases and were likely to have triggered or aggravated DAH in these cases, especially if overdosed or when associated with anti-platelet treatments. We only reported three cases of toxic- and drug-induced DAH, and surprisingly no case of DAH related to cocaine smoking or inhalation, a common cause of DAH.[52] Current and past drug intake is crucial in the evaluation of DAH patients, as withdrawal of the culprit drug or toxic can reverse a life-threatening situation.[38]

Finally, idiopathic DAH is a rare condition with an unknown incidence and prevalence in the population. In the current series, it accounted for 12% of the DAH. There are more than 500 cases of idiopathic DAH published in the literature. However, many patients previously reported to have idiopathic DAH were likely misdiagnosed, having DAH of other origins.[53] They would currently be categorized differently with the advent of newer diagnostic tools.[54]

Presentation and diagnosis of the underlying causes of DAH

Classification of DAH in four etiologic groups allowed us to depict specific clinical and laboratory patterns.

Clinical patterns

Patients having immune DAH exhibited more extra-pulmonary symptoms, such as cutaneous, bone-joint, and ear-nose- throat symptoms, more urinary sediment abnormalities, and worse renal function than others upon hospital admission. Pulmonary-renal syndrome was associated with a high specificity (96%), but a low sensitivity (41%) for the diagnosis of immune DAH. Except for SLE-related DAH, which was previously shown to have an abrupt presentation,[6] the onset of immune DAH was usually subacute, with a median duration of 18 days between the first respiratory symptom and hospital admission. This might have contributed to more important blood spoliation and thus deeper anemia in patients with immune DAH as compared to others. Miscellaneous DAH patients had shorter onset of initial respiratory symptoms from time of hospital admission than others. As a result, they had less BAL siderophages, as hemosiderin appears at least 48 h after bleeding.[55] Most of barotrauma-related DAH occurred after a short period of general anesthesia in healthy subjects ($n = 4/6$), as previously described.[17,51,56]

Idiopathic DAH patients tended to exhibit lower LOD scores and required less frequent invasive mechanical ventilation than others. Those patients had more BAL siderophages than others, suggesting that they had experienced chronic/latent alveolar hemorrhage before admission. Indeed, most patients with idiopathic DAH experience recurrent episodes of DAH over life, frequently starting during childhood.[53,54]

Specific laboratory tests and histological approach

Since the ANCA era, routine serological screening for ANCA allowed using a less invasive diagnostic strategy in a majority of patients.[57] Indeed, only 34% of our patients underwent lung or kidney biopsies, which were more frequently performed in patients with immune than in those with non-immune DAH (30/39 *vs* 8/73; $p < 0.001$). The indications and the diagnostic yield of kidney and lung biopsies in the setting of DAH are however distinct. A renal biopsy is indicated in presence of rapidly progressive renal function decline associated with hematuria and/or proteinuria. Renal histology contributes in the diagnosis, particularly when ANCA test is negative, but also in the decision of immunosuppressive therapy and in renal prognosis.[58] In contrast, the benefit/risk ratio associated with lung biopsy is not clear, particularly in patients with acute respiratory failure. The interest of lung biopsy for diagnosing the cause of DAH was weak in previous studies.[12] If the underlying cause of DAH remains elusive after a thorough clinical evaluation, then, a biopsy approach might be required. A surgical lung biopsy should be considered when the level of suspicion for extra-pulmonary lesions (*e.g.*, kidney or skin) is low.[3] In such cases, specimens should be processed for immunofluorescence staining and bacterial culture.[57]

Complications and outcome of DAH

The reported mortality of DAH syndromes is high, ranging generally from 20% to 50%.[4–6,13,59] However, the outcome varies depending on the cause. For instance, in a series of 28 cases of ABMAD with DAH, all patients were discharged alive from hospital.[14] In contrast, DAH related to SLE exhibited particularly poor outcome with mortality rates over 50%.[6] In the current series, in-hospital mortality rates dramatically differed among the different etiologic groups, ranging from 7.1% in idiopathic DAH to 36.4% in CHF.

CHF-related DAH mortality is likely related to older age and associated cardiovascular comorbidity. Previous cardiovascular disease was present in 72.7% of patients with CHF, suggesting that DAH was related to acute heart failure that frequently complicated an underlying chronic heart disease. The overall mortality rate of this subgroup of patients was 45.4% over the follow-up period, suggesting that DAH is a sign of end stage chronic heart failure, as previously discussed.[10]

Although all patients with barotrauma-related DAH were treated successfully, seven patients with miscellaneous causes, mainly infection and cancer, died. Three of those had a *S. aureus* infection, including two PVL-producing strains. Previous series of patients hospitalized for community-acquired pneumonias due to PVL-producing *S. aureus* reported mortality rates between 56 and 75%.[46,60]

In-hospital mortality of patients with immune DAH was 17.9% in our series, which is lower than in previous series.[5,6,13,59] Patients with immune DAH exhibited severe acute illnesses related to pulmonary-renal syndromes. The relatively good outcome, as compared to previous series of immune DAH and DAH of other causes, illustrates the sensitivity of immune DAH to early aggressive immunosuppressive treatment.[2,5,13,61] Moreover, renal recovery in patients presenting with acute renal failure is maximized in patients receiving early adequate treatment.[8,62] In this series, end stage renal disease occurred in seven out of 24 patients who had documented necrotizing glomerulonephritis. In patients who required immediate hemodialysis, renal death was avoided in 50% of cases, a stark contrast to a previous study reporting no renal survival in this subgroup of patients.[8]

Patients with idiopathic DAH had a good prognosis. In-hospital mortality rate was 7.1%, and two patients died over the follow-up period. Many reports emphasized the better prognosis of adult onset diseases,[54] compared to children.[63] For instance, Chryssanthopoulos et al. reported a mortality rate of 60% associated with a mean survival time of three years in a series of 30 children.[63] Steroid treatment is commonly used, particularly in the acute phase of the disease.[54,64] Currently, there are no codified long-term treatment strategies to prevent recurrence of disease and progressive pulmonary fibrosis leading to deterioration of lung function.

While immunological tests and organ biopsy results are pending, deciding whether to initiate an immunosuppressive treatment or not is challenging. Ideally, immune DAH patients should receive such treatment as soon as possible, as it is life- and renal function-saving. In contrast, immunosuppressive treatment could be deleterious for non-immune DAH patients. Differences in the clinical presentation of patients with immune and non-immune DAH recently allowed our group to build a predictive clinical scale in order to help clinicians in the initial steps of DAH patients management.[65]

Limitations

Several limitations of the current series must be acknowledged. First, this is a retrospective study conducted over a 30-year period, during which diagnostic procedures, patients management and global quality of care may have varied. Missing data were however limited by excluding patients who had incomplete medical charts ($n = 10$). Second, it is a single-center study with a limited number of patients included in each subgroup, which limits the potential generalization of our conclusions. Third, some ($n = 98$) of the patients included in the current study were also included in a previously published one.[10] However, the methods and data presented in these two studies are different. Our previous study aimed at identifying factors associated with hospital and long-term mortality of DAH patients[10] while the current one not only focused on the differential presentation of four etiologic groups, but also provided a detailed description of diagnostic strategies and outcomes.

In conclusion, we report a large series of unselected patients hospitalized for DAH. The underlying causes of DAH were classified into four etiologic groups that exhibited distinct and easily identifiable clinical and laboratory features, thus making easier early identification by clinicians. In-hospital mortality varied between 7.1% in patients having idiopathic DAH to 36.4% in patients with DAH related to CHF.

Conflict of interest

None declared.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2012.03.015.

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