**Abstract**

Diffuse alveolar hemorrhage (DAH) refers to a clinical syndrome resulting from injury to the alveolar capillaries, arterioles, and venules leading to red blood cell accumulation in the distal air spaces. It is defined by the clinical triad of hemoptysis, anemia, and progressive hypoxemia. Chest radiographs reveal non-specific patchy or diffuse, bilateral pulmonary infiltrates. The diagnosis requires confirmation of the alveolar hemorrhage by bronchoscopy in which serial bronchoalveolar lavage samples reveal persistently hemorrhagic fluid. A number of conditions are associated with DAH, and underlying disease determines the prognosis and the treatment regimen. While there is no uniformly accepted classification of DAH, it is generally categorized according to the underlying histology.

**Etiology**

A number of conditions have been associated with the clinical syndrome of DAH (table 1). In one study of biopsy-confirmed DAH, Wegener’s granulomatosis (WG) was the most frequent underlying condition, followed by Goodpasture’s syndrome, idiopathic pulmonary hemosiderosis, and collagen vascular diseases. Overall, vasculitis (either WG or microscopic polyangiitis [MAP]) was the most frequent, representing 41% of cases [1].

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**Table 1.** Causes of diffuse alveolar hemorrhage categorized according to underlying histopathologic findings

<table>
<thead>
<tr>
<th>With pulmonary capillaritis:</th>
<th>With bland pulmonary hemorrhage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Idiopathic pulmonary hemosiderosis</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Goodpasture’s syndrome*</td>
</tr>
<tr>
<td>Isolated pulmonary capillaritis</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus*</td>
<td>Acute anhydrides, isocyanates</td>
</tr>
<tr>
<td>Connective tissue diseases*</td>
<td>Penicillamine, amidodarone, nitrofurantoin</td>
</tr>
<tr>
<td>PWCary antiphospholipid syndrome</td>
<td>Pulmonary veno-occlusive disease</td>
</tr>
<tr>
<td>Mixed cryoglobulinemia</td>
<td>Pulmonary capillary hemangiomatosis</td>
</tr>
<tr>
<td>Behçet’s syndrome</td>
<td>Lymphangioleiomyomatosis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Tuberosclerosis</td>
</tr>
<tr>
<td>Goodpasture’s syndrome*</td>
<td>Coagulation disorders</td>
</tr>
<tr>
<td>Puci-immune glomerulonephritis</td>
<td>Systemic lupus erythematosus*</td>
</tr>
<tr>
<td>Immune-complex-associated glomerulonephritis</td>
<td>Diffuse alveolar damage (Including inhalational cocaine use)*</td>
</tr>
</tbody>
</table>

Drug-induced
Acute lung allograft rejection

*These diseases may be associated with either pulmonary capillaritis or bland pulmonary hemorrhage (see text). *Diffuse alveolar damage is a unique histopathologic pattern of lung injury which is the result of a variety of toxic insults (see text).
into the interstitium and alveolar spaces. Fibrin may also be released from the injured capillaries, and true fibrinoid necrosis of the capillary wall and interstitium may be seen (fig. 1b). As neutrophils undergo destruction (leukocyto-clasis) they become fragmented and pyknotic, and nuclear debris accumulates in the interstitium and alveolar spaces. Other histologic features include alveolar capillary thrombosis, type II alveolar epithelial cell hyperplasia, intra-alveolar organizing pneumonia, and mononuclear cell infiltration of the alveolar interstitium [1, 3]. During the resolution phase of DAH, hemosiderin deposits appear in the interstitium and in alveolar macrophages [4].

Other histologic patterns in DAH include bland pulmonary hemorrhage (fig. 2) and diffuse alveolar damage (fig. 3). Bland pulmonary hemorrhage is characterized by hemorrhage in to the alveolar spaces without inflammation or necrosis of the alveolar structures present in pulmonary capillaritis. Histopathologic features include alveoli filled with red blood cells and type II alveolar epithelial cell hyperplasia [5]. After repeated episodes of DAH, interstitial fibrosis may evolve [6]. Diffuse alveolar damage can also result in DAH and is characterized by interstitial and alveolar edema and alveolar hyaline membrane formation [7, 8].

Clinical Assessment and Investigations

The onset is typically abrupt. Most affected individuals seek medical attention within one week from the onset of
symptoms, which include dyspnea, hemoptysis, and cough. Less commonly, fever and nonspecific chest pain are reported. Importantly, up to 33% of patients with DAH do not report hemoptysis even though extensive intra-alveolar hemorrhage may have occurred [9]. In the absence of hemoptysis, diffuse alveolar infiltrates on the chest radiograph (CXR), a low or declining hematocrit, and hemorrhagic fluid on sequential bronchoalveolar lavage support the diagnosis of DAH (fig. 4) [10]. If additional symptoms are present, these may highlight an accompanying systemic disease (table 1). The physical examination may also be supportive of a systemic disease such as palpable purpura, synovitis, or eye involvement (fig. 5). Although nonspecific, the pulmonary examination may reveal inspiratory crackles and signs of pulmonary consolidation [11].

Chest radiographs show nonspecific patchy or diffuse, bilateral alveolar infiltrates (fig. 6). These are, on occasion,
Diffuse Alveolar Hemorrhage

symmetric or unilateral. In cases where DAH is recurrent, an interstitial pattern (representing pulmonary fibrosis) may be present [6]. Kerley B lines can be present in DAH associated with post-capillary pulmonary hypertension as seen in mitral stenosis and pulmonary veno-occlusive disease (fig. 7) [12]. Computed tomography is nonspecific, revealing ground-glass attenuation and patchy consolidation (fig. 8) [13]. Magnetic resonance imaging has been used in idiopathic pulmonary hemosiderosis to detect recurrent pulmonary hemorrhage, which demonstrates a diminished T2 relaxation time [14].

Routine laboratory studies reveal an anemia, due to acute blood loss and/or iron deficiency anemia. Because several causes of DAH also result in renal disease (see below), routine investigations may reveal an elevated creatinine and urinalysis may show an active urine sediment with red blood cells, crenated red blood cells, or red blood cell casts [6].

Hypoxemia is almost always present and in many cases acute respiratory failure requiring mechanical ventilation supervenes [6]. In subacute DAH the diffusing capacity for carbon monoxide is typically elevated, reflecting the high affinity of carbon monoxide for hemoglobin [15]. Recurrent and chronic DAH has been associated with restrictive physiology [16].

Diagnosis

If DAH is suspected, the diagnosis must first be confirmed, and then, identification of an underlying etiology should be sought. Bronchoscopy usually secures the diagnosis; sequential bronchoalveolar lavage samples (from the same location) with an increasing red blood cell count is regarded as diagnostic of DAH (fig. 4) [11]. Surgical lung biopsy confirms the presence of DAH, but usually not the underlying systemic disease [1]. Surgical lung biopsy should be strongly considered in younger patients who have isolated pulmonary hemorrhage without clinical or serological evidence of a systemic disease (table 1). The diagnoses
of specific diseases associated with DAH are discussed below (table 2).

### Natural History, Management, and Prognosis of Specific Diseases Associated with Diffuse Alveolar Hemorrhage and Pulmonary Capillaritis

**Wegener’s Granulomatosis**

WG is a systemic small and medium vessel vasculitis which typically affects the upper and lower respiratory tracts and kidneys. Other organ systems (eyes, skin, central nervous system, and gastrointestinal system) may also be involved. The characteristic lung histopathology is a necrotizing granulomatous vasculitis, and kidney biopsy reveals a focal, segmental necrotizing glomerulonephritis (FSNG) (fig. 9). In patients with classic symptoms, the diagnosis is often confirmed serologically by the presence of antineutrophil cytoplasmic antibodies (c-ANCAs), and further confirmation of the diagnosis requires tissue biopsy in selected cases [17].

DAH due to pulmonary capillaritis in WG may occur after an established diagnosis, but can be the initial manifestation of WG in as many as 10% of patients. In most patients with WG and DAH, lung histology reveals both necrotizing granulomatous vasculitis and pulmonary capillaritis, and renal histology reveals a FSNG [6, 18, 19]. WG with DAH

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**Table 2.** Laboratory findings and potential sites of systemic involvement typically associated with the specific diseases resulting in DAH

<table>
<thead>
<tr>
<th>Disease</th>
<th>ANCA</th>
<th>ANA</th>
<th>RF</th>
<th>Complement levels</th>
<th>ABMA</th>
<th>Sites of systemic involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis</td>
<td>+C-ANCA</td>
<td>+/−</td>
<td>+/−</td>
<td>normal</td>
<td>no</td>
<td>renal</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>+P-ANCA</td>
<td>+/−</td>
<td>+/−</td>
<td>normal</td>
<td>no</td>
<td>renal</td>
</tr>
<tr>
<td>Isolated pulmonary capillaritis</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>normal</td>
<td>no</td>
<td>none</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>low</td>
<td>no</td>
<td>renal</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>+/−</td>
<td>no</td>
<td>no</td>
<td>normal</td>
<td>no</td>
<td>renal</td>
</tr>
<tr>
<td>Goodpasture’s syndrome (ABMA)</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>normal</td>
<td>yes</td>
<td>renal</td>
</tr>
<tr>
<td>Idiopathic pulmonary hemosiderosis</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>normal</td>
<td>no</td>
<td>none</td>
</tr>
</tbody>
</table>

ABMA = Anti-basement membrane antibody; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; RF = rheumatoid factor.

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[Fig. 9. Photomicrograph of a renal biopsy with a focal segmental necrotizing glomerulonephritis. Original magnification ×40.](#)
may be clinically indistinguishable from microscopic polyangiitis (MAP) if the lung biopsy reveals only pulmonary capillaritis [10]. In this scenario, the presence of serum c-ANCA positivity supports the diagnosis of WG while serum p-ANCA positivity (see next paragraph) suggests a diagnosis of MAP. However, there are reports of serum p-ANCA positive WG, and serum c-ANCA positive MAP [20, 21]. In this situation, the diagnosis of WG may be delayed months or years until more typical clinical manifestations of WG develop [22].

On immunofluorescence staining of ethanol-fixed neutrophils, c-ANCA positivity is determined by a pattern of diffuse staining of the cytoplasm whereas p-ANCA positivity is defined by a pattern of perinuclear staining. The cytoplasmic antibodies are most often directed against proteinase 3 (PR3), and the perinuclear antibodies are often directed against myeloperoxidase (MPO) antibodies. These specific antibodies to PR3 and MPO may be tested by enzyme-linked immunosassays (ELISAs) [23].

Recommended therapy for DAH associated with WG includes high-dose corticosteroids and cyclophosphamide. In patients who require mechanical ventilation, intravenous methylprednisolone (250–1,000 mg/day for 3–5 days) and intravenous cyclophosphamide is recommended (1 g/m²). For those patients who do not require mechanical ventilation, oral prednisone (1 mg/kg/day) and cyclophosphamide (2 mg/kg/day) is the mainstay of treatment. Once a therapeutic response is achieved (clinical improvement, normalization of gas exchange abnormalities, and clearing of radiographic infiltrates), corticosteroids are tapered over the following 2–6 months, while cyclophosphamide is continued for 6–12 months. Due to the high incidence of *Pneumocystis jiroveci* with this regimen, trimethoprim-sulfamethoxazole prophylaxis is also recommended [24]. Although data are limited, azathioprine and methotrexate have be used in patients who do not tolerate cyclophosphamide therapy [24–26]. In persistent disease, intravenous immunoglobulin has shown some benefit in persistent disease [25].

As with WG, treatment is initiated with corticosteroids and cyclophosphamide, and substitution of cyclophosphamide with azathioprine is appropriate once the disease is in remission [25]. Additionally, intravenous immunoglobulin has shown some benefit in persistent disease [25]. In one case, life-threatening DAH was successfully treated with recombinant factor VIIa [31]. In patients with MAP and DAH, the early mortality reaches 30% [29]. Recurrences are common, may be lethal, and have been associated with the development of both obstructive lung disease and pulmonary fibrosis [28, 32, 33]. The 5-year survival is approximately 65% [28, 29].

### Isolated Pulmonary Capillaritis

Isolated pulmonary capillaritis is a lung-limited small vessel vasculitis in which there is no evidence of an accompanying systemic disease. Although most patients diagnosed with isolated pulmonary capillaritis have negative serologies, there are reports of patients with isolated pulmonary capillaritis with positivity of serum p-ANCA [34, 35], suggesting that at least some cases may represent a lung-limited form of microscopic polyangiitis [10, 36]. Since isolated pulmonary capillaritis is a lung specific disease, it must be distinguished from idiopathic pulmonary hemosiderosis, and therefore, a lung biopsy is required.

In retrospective review of 8 patients with isolated pulmonary capillaritis, the clinical presentation included symptoms of dyspnea, cough, pleuritic chest pain, fever, and hemoptysis [36]. Over half the patients had symptoms suggestive of an upper respiratory tract infection prior to Diffuse Alveolar Hemorrhage 255