Diffuse alveolar hemorrhage: Diagnosing it and finding the cause

ABSTRACT

Diffuse alveolar hemorrhage is an acute, life-threatening event, and repeated episodes can lead to organizing pneumonia, collagen deposition in small airways, and, ultimately, fibrosis. Among the many conditions it can accompany are Wegener granulomatosis, microscopic polyangiitis, Goodpasture syndrome, connective tissue disorders, antiphospholipid antibody syndrome, infectious or toxic exposures, and neoplastic conditions. Its many causes and presentations pose an important challenge to the clinician.

KEY POINTS

Most patients present with dyspnea, cough, hemoptysis, and new alveolar infiltrates. Early bronchoscopy with bronchoalveolar lavage is generally required to confirm the diagnosis; blood in the lavage specimens (with numerous erythrocytes and siderophages) establishes the diagnosis.

Therapy targets both the autoimmune destruction of the alveolar capillary membrane and the underlying condition. Corticosteroids and immunosuppressive agents remain the gold standard.

In patients with diffuse alveolar hemorrhage and renal impairment (pulmonary-renal syndrome), kidney biopsy can be considered to identify the cause and to direct therapy.

DIFFUSE ALVEOLAR HEMORRHAGE can complicate a large number of clinical conditions. It may present in different ways and may be life-threatening, and it poses an important challenge for the clinician.1

Diffuse alveolar hemorrhage is an uncommon condition in which blood floods the alveoli, usually at multiple sites. It is also known as intrapulmonary hemorrhage, diffuse pulmonary hemorrhage, pulmonary alveolar hemorrhage, pulmonary capillary hemorrhage, alveolar bleeding, or microvascular pulmonary hemorrhage.

In this article we review the causes, clinical features, diagnostic criteria, treatment, and prognosis of diffuse alveolar hemorrhage.

CAUSES OF DIFFUSE ALVEOLAR HEMORRHAGE

A number of diseases can cause diffuse alveolar hemorrhage (TABLE 1). Although no prospective study has yet identified which cause is the most common, in a series of 34 cases,2 Wegener granulomatosis accounted for 11 cases, Goodpasture syndrome four cases, idiopathic pulmonary hemosiderosis four, collagen vascular disease four, and microscopic polyangiitis three. In a series of 29 cases of diffuse alveolar hemorrhage associated with capillaritis,3 the most common cause was isolated pauci-immune pulmonary capillaritis (8 cases).

TABLE 2 summarizes the frequency of diffuse alveolar hemorrhage in some conditions in which it can occur, as well as some of the diagnostic features that should prompt consideration of the specific cause.
In general, diffuse alveolar hemorrhage can occur in three characteristic patterns, which reflect the nature of the underlying vascular injury:

**Diffuse alveolar hemorrhage associated with vasculitis or capillaritis.** As described by Spencer a few years ago, pulmonary capillaritis is the most frequent underlying histologic lesion described in diffuse alveolar hemorrhage. Neutrophils infiltrate the interalveolar and peribronchiolar septal vessels (pulmonary interstitium), leading to anatomic disruption of the capillaries (ie, impairment of the alveolocapillary barrier) and to extravasation of red blood cells into the alveoli and interstitium. Neutrophil apoptosis and fragmentation, with

### TABLE 1

**Causes of diffuse alveolar hemorrhage: Three general patterns**

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<th>Vasculitis or capillaritis</th>
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<td>Cryoglobulinemia</td>
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<td>Behçet syndrome</td>
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<td>Acute lung-graft rejection</td>
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<td>Thrombotic thrombocytopenic purpura and idiopathic thrombocytopenic purpura</td>
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‘Bland’ pulmonary hemorrhage (ie, without capillaritis or vasculitis)

| Anticoagulants, antiplatelet agents, or thrombolytics; disseminated intravascular coagulation |
| Mitral stenosis and mitral regurgitation |
| Pulmonary veno-occlusive disease |
| Infection: human immunodeficiency virus infection, infective endocarditis |
| Toxins: trimellitic anhydride, isocyanates, crack cocaine, pesticides, detergents |
| Drugs: propylthiouracil, diphenylhydantoin (Dilanin), amiodarone (Cordarone), mitomycin (Mutamycin), D-penicillamine (Cuprimine, Depen), sirolimus (Rapamune, Rapamycin), methotrexate (Trexall), haloperidol (Haldol), nitrofurantoin (Furadantin, Macrobid, Macrodantin), gold, all-trans-retinoic acid (ATRA, Vesanoind), bleomycin (Blenoxane) (especially with high oxygen concentrations), montelukast (Singulair), zafirlukast (Accolate), infliximab (Remicade) |
| Idiopathic pulmonary hemosiderosis |

Alveolar bleeding associated with another process or condition

| Diffuse alveolar damage |
| Pulmonary embolism |
| Sarcoidosis |
| High-altitude pulmonary edema, barotrauma |
| Infection: invasive aspergillosis, cytomegalovirus infection, legionellosis, herpes simplex virus infection, mycoplasmosis, hantavirus infection, leptospirosis, other bacterial pneumoniae |
| Malignant conditions (pulmonary angiosarcoma, Kaposi sarcoma, multiple myeloma, acute promyelocytic leukemia) |
| Lymphangioleiomyomatosis |
| Tuberous sclerosis |
| Pulmonary capillary hemangiomatosis |
| Lymphangiography |

**Three Characteristic Patterns**

In general, diffuse alveolar hemorrhage can occur in three characteristic patterns, which reflect the nature of the underlying vascular injury:
subsequent release of the intracellular proteolytic enzymes and reactive oxygen species, beget more inflammation, intra-alveolar neutrophilic nuclear dust, fibrin and inflammatory exudate, and fibrinoid necrosis of the interstitium.6,7

‘Bland’ pulmonary hemorrhage (ie, without capillaritis or vasculitis). In this pattern, red blood cells leak into the alveoli without any evidence of inflammation or destruction of the alveolar capillaries, venules, and arterioles. The epithelial lesions are usually microscopic and are scattered geographically.

Diffuse alveolar hemorrhage associated with another process or condition (eg, diffuse

<table>
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<td><strong>SPECIFIC CAUSE</strong></td>
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ANCA = antineutrophil cytoplasmic antibody; ANA = antinuclear antibody; dsDNA = double-stranded DNA; c-ANCA = ANCA type C; p-ANCA = ANCA type P
alveolar damage, lymphangioleiomyomatosis, drug-induced lung injury, metastatic tumor to the lungs, mitral stenosis). Diffuse alveolar damage is the main underlying lesion of the acute respiratory distress syndrome and is characterized by formation of an intra-alveolar hyaline membrane, by interstitial edema with minimal inflammation, and, at times, by "secondary" diffuse alveolar hemorrhage. In this third category of diffuse alveolar hemorrhage, the underlying process causes alveolar hemorrhage by processes other than pulmonary vascular inflammation or direct extravasation of red cells.

**THE CLINICAL PRESENTATION**

The clinical presentation of diffuse alveolar hemorrhage may reflect either alveolar bleeding alone or features of the underlying cause (eg, hematuria in Wegener granulomatosis, arthritis in systemic lupus erythematosus). Hence, its recognition requires a high degree of suspicion.

Some patients present with severe acute respiratory distress requiring mechanical ventilation. However, dyspnea, cough, and fever are the common initial symptoms and are most often acute or subacute (ie, present for less than a week). The fever is usually due to the underlying cause, such as lupus.

Hemoptysis may be absent at the time of presentation in up to a third of patients because the total alveolar volume is large and can absorb large amounts of blood, without extending more proximally into the airways. Apparent hemoptysis, if present, must be differentiated from hematemesis or pseudo-hemoptysis (alveolar flooding with fluid that resembles blood, as in *Serratia marcescens* pneumonia, in which the reddish hue of the infecting organism can create the impression of alveolar bleeding).

**DIAGNOSTIC EVALUATION**

Generally speaking, dyspnea, cough, hemoptysis, and new alveolar infiltrates in conjunction with bloody bronchoalveolar lavage specimens (with numerous erythrocytes and siderophages) establish the diagnosis of diffuse alveolar hemorrhage. Surgical biopsy from the lung or another organ involved by an underlying condition is often necessary.

**Physical examination**

The physical findings are nonspecific and may reflect the underlying systemic vasculitis or collagen vascular disorder (eg, with accompanying rash, purpura, eye lesions, hepatosplenomegaly, or clubbing).

**Imaging studies**

Radiography may show new or old or both new and old patchy or diffuse alveolar opacities. Recurrent episodes of hemorrhage may lead to reticular interstitial opacities due to pulmonary fibrosis, usually with minimal (if any) honeycombing. Kerley B lines suggest mitral valve disease or pulmonary veno-occlusive disease as the cause of the hemorrhage.

Computed tomography may show areas of consolidation interspersed with areas of ground-glass attenuation and preserved, normal areas.

Currently, nuclear imaging such as gallium or tagged red blood cell studies have little role in evaluating diffuse alveolar hemorrhage. Other nuclear studies, geared to reveal breakdown of the microcirculatory integrity and extravasation of red blood cells out of the vessels, have also not been proven useful.

**Evaluating pulmonary function**

Diffuse alveolar hemorrhage may cause impairment of oxygen transfer and hypoxemia. In addition, it can cause several other abnormalities of pulmonary function.

**Increased diffusing capacity.** Because blood in the lungs can absorb inhaled carbon monoxide, the diffusing capacity for carbon monoxide (DLCO) may be distinctively increased. Serial increases in the DLCO may indicate progressive alveolar hemorrhage. However, the clinical instability of patients experiencing active alveolar bleeding precludes performing the DLCO measurement maneuvers, rendering the DLCO test relatively impractical.

**Restrictive changes.** Because recurrent episodes of diffuse alveolar hemorrhage can lead to interstitial fibrosis, restrictive changes—ie, decreased total lung capacity, decreased forced vital capacity (FVC), and
preserved ratio of the forced expiratory volume in 1 second (FEV\textsubscript{1}) to the FVC—may characterize diffuse alveolar hemorrhage.

**Obstructive changes (less common).** Less commonly, patients with diffuse alveolar hemorrhage may have spirometric changes indicating airflow obstruction—ie, decreased FEV\textsubscript{1} and decreased ratio of FEV\textsubscript{1} to FVC—possibly because neutrophilic infiltration from blood extravasation into the alveolar sacs causes release of reactive oxygen species and proteolytic enzymes, which in turn may cause small airway and parenchymal damage such as bronchiolitis and emphysema. A pattern of obstructive lung disease associated with recurrent diffuse alveolar hemorrhage should prompt consideration of an underlying condition that can cause airflow obstruction, such as sarcoidosis, microscopic polyangiitis, or Wegener granulomatosis, or, less commonly, lymphangioleiomyomatosis, histiocytosis X, pulmonary capillaritis, or sometimes idiopathic pulmonary hemosiderosis.

As an example of an unusual circumstance, we have described elsewhere a case of a woman with idiopathic pulmonary hemosiderosis with multiple episodes of diffuse alveolar hemorrhage and resultant emphysema.\textsuperscript{8} Radiographic images showed several very large cysts, one of which herniated through the incision site of an open lung biopsy.

**Decreased exhaled nitric oxide.** Though currently unavailable in most clinical pulmonary function laboratories, evaluation of exhaled gas or condensate may have value in diagnosing diffuse alveolar hemorrhage.\textsuperscript{9} Specifically, because increased intra-alveolar hemoglobin binds nitric oxide, as it does carbon monoxide, levels of exhaled nitric oxide may be decreased in diffuse alveolar hemorrhage. In contrast to the difficulty of measuring DLCO in patients with active alveolar bleeding or hemoptysis, analysis of exhaled gas is clinically feasible, making this a promising diagnostic test.

**Laboratory evaluation**

Hematologic assessment in patients with diffuse alveolar hemorrhage generally reveals:

- Acute or chronic anemia
- Leukocytosis
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein level (particularly in patients whose alveolar hemorrhage is due to systemic disease or vasculitis, or both).

Renal abnormalities such as elevated blood urea nitrogen and serum creatinine or abnormal findings on urinalysis (with hematuria, proteinuria, and red blood cell casts indicating glomerulonephritis) can also occur, as diffuse alveolar hemorrhage may complicate several pulmonary-renal syndromes such as Goodpasture syndrome and Wegener granulomatosis.

**Bronchoscopy**

The diagnostic evaluation in diffuse alveolar hemorrhage usually includes bronchoscopic examination,\textsuperscript{10} which serves two purposes:

- To document alveolar hemorrhage by bronchoalveolar lavage and to exclude airway sources of bleeding by visual inspection
- To exclude an associated infection.

Based on experience with nonmassive hemoptysis of all causes (but not exclusively diffuse alveolar hemorrhage), the diagnostic yield of bronchoscopy is higher if the procedure is performed within the first 48 hours of symptoms rather than later. Evidence supporting diffuse alveolar hemorrhage is persistent (or even increasing) blood on three sequential lavage aliquots from a single affected area of the lung.

In subacute or recurrent episodes of diffuse alveolar hemorrhage, counting the hemosiderin-laden macrophages (siderophages) as demonstrated by Prussian blue staining of a pooled lavage specimen centrifugate may be useful for diagnosis. Bronchoalveolar lavage specimens should be sent for routine bacterial, mycobacterial, fungal, and viral stains and cultures, as well as for Pneumocystis stains.

Transbronchial biopsy is unlikely to establish a diagnosis of diffuse alveolar hemorrhage because the specimens are small. Thus, transbronchial biopsy should be reserved for situations in which the alternative cause that is being considered (eg, sarcoid) actually can be diagnosed by this method.

The histologic appearance of diffuse alveolar hemorrhage (FIGURES 1–3) is relatively uniform, whatever the underlying cause.
Changes of acute or chronic organizing hemor-
Rhage, sometimes with hyaline alveolar mem-
bane membranes, may accompany findings of
small-vessel vasculitis or changes associated
with the underlying pathology, such as gran-
ulomatous vasculitis in Wegener granulo-
matosis (TABLE 1).

FIGURE 1. This biopsy specimen shows blood-
filled alveolar spaces and hemosiderin-laden
macrophages (arrows). Alveolar septae show
widening due to a chronic inflammatory
infiltrate of lymphocytes and plasma cells
(arrowheads). (Hematoxylin and eosin stain, × 4)

FIGURE 2. Hemosiderin pigment is visible
in both alveolar macrophages (arrows, AM)
and within connective tissue of alveolar
septae (arrowheads, CT). (Hematoxylin and
eosin stain, × 10)

FIGURE 3. A stain for iron highlights
hemosiderin within the alveolar macrophages
in the alveolar spaces (Prussian blue stain × 20).

A history of exposure to toxic agents raises suspicion of diffuse alveolar hemorrhage

Finding the Underlying Cause

Once the diagnosis of diffuse alveolar hem-
orrhage is established, the clinician must
ascertain whether an underlying cause is present. Serologic studies may prove impor-
tant, although the results are generally not
available in a manner timely enough to
guide immediate management.

When a pulmonary-renal syndrome is sug-
gested by accompanying hematuria or renal
dysfunction, antiglomerular basement mem-
brane antibody and antineutrophil cytoplas-
mic antibody (ANCA) levels should be
checked. Tests for complement fractions C3
and C4, anti-double-stranded DNA, and
antiphospholipid antibodies should be ordered
if an underlying condition such as lupus or
antiphospholipid antibody syndrome is sus-
pected (TABLE 2).11

If the underlying cause remains elusive
after a thorough clinical evaluation that
includes imaging studies, serologic studies,
and bronchoscopy, then surgical biopsy
should be considered.1 Which organ to biop-
sy (eg, lung, sinus, kidney) depends on the
level of suspicion for a specific cause. For
example, suspicion of Wegener granulomato-
sis with hematuria or renal dysfunction might
prompt renal biopsy. However, lung biopsy
often needs to be performed with video-
assisted thoracoscopy, especially when dis-
ease is confined to the lung (as in idiopathic
pulmonary hemosiderosis or pauci-immune
pulmonary capillaritis). Renal biopsy speci-
mens should also undergo immunofluores-
cence staining, which may reveal linear
deposition of immunoglobulins and immune
complexes along the basement membrane in
patients with Goodpasture syndrome, or of
granular deposits in patients with systemic
lupus erythematosus.
TABLE 2 offers a guide to diagnosis for most common causes of diffuse alveolar hemorrhage, while TABLE 3 outlines the differential diagnosis of underlying conditions.12–62

### TWO GENERAL CLINICAL SCENARIOS

In general, the clinician will be confronted by one of two scenarios: a patient with diffuse alveolar hemorrhage and associated systemic findings, or a patient with hemorrhage and no associated systemic findings.

#### Hemorrhage with associated systemic findings

Certain clues from the history raise suspicion of diffuse alveolar hemorrhage:
- Recent infection suggests Henoch-Schönlein purpura or cryoglobulinemic vasculitis
- Use of a possibly offending drug such as an anticoagulant, D-penicillamine (Cuprimine, Depen), nitrofurantoin (Furadantin, Macrodant, Macrodantin), amiodarone (Cordarone), propylthiouracil, cocaine, or sirolimus (Rapamune, Rapamycin)
- Exposure to toxic agents such as trimellitic anhydride, insecticides, and pesticides
- A known comorbid condition such as vasculitis, connective tissue disease, mitral valve disease, or solid organ or stem cell transplantation.

If asthma, eosinophilia, pulmonary infiltrates, and diffuse alveolar hemorrhage coexist, consideration should be given to Churg-Strauss syndrome. If sinus disease, skin manifestations, pulmonary parenchymal nodules, and cavitary lesions coexist with positivity for antiproteinase 3 c-ANCA and biopsy-proven granulomata, then Wegener granulomatosis should be considered. Similarly, diffuse alveolar hemorrhage with glomerulonephritis and skin manifestations, positivity for p-ANCA, and necrotizing nongranulomatous lesions on end-organ biopsy may lead to a diagnosis of microscopic polyangiitis. In a young smoker with glomeru-
lonephritis and diffuse alveolar hemorrhage presenting as either bland alveolar hemorrhage or pulmonary capillaritis, Goodpasture syndrome or antiglomerular basement membrane antibody disease should be considered.

**Hemorrhage with no associated systemic findings**

When the above conditions have been considered but no suggestive findings are found, the following four conditions should be considered:

- **Antiglomerular basement membrane antibody disease in limited pulmonary form or onset**: positivity to the antibody with linear deposits in the lungs would be diagnostic in such a case
- **Pulmonary-limited microscopic polyangiitis positive for p-ANCA** (a positive anti-myeloperoxidase p-ANCA test makes the diagnosis)
- **Pauci-immune isolated pulmonary capillaritis**, when the biopsy shows evidence of neutrophilic pulmonary capillaritis
- **Idiopathic pulmonary hemosiderosis**, a diagnosis of exclusion, when the biopsy shows evidence of acute, subacute, and chronic bland diffuse alveolar hemorrhage and no evidence of vasculitis.

### TREATMENT OF DIFFUSE ALVEOLAR HEMORRHAGE

Therapy for diffuse alveolar hemorrhage consists of treating both the autoimmune destruction of the alveolar capillary membrane and the underlying condition. Corticosteroids and immunosuppressive agents remain the gold standard for most patients. Recombinant-activated human factor VII shows promise in treating diffuse alveolar hemorrhage.

In patients with pulmonary-renal syndrome, therapy should be started as soon as possible to prevent irreversible renal failure.

Besides corticosteroids, other immunosuppressive drugs such as cyclophosphamide (Cytoxan), azathioprine (Imuran), mycophenolate mofetil (CellCept), and etanercept (Enbrel) may be used in diffuse alveolar hemorrhage, especially when the condition is severe, when first-line therapy with corticosteroids has proven ineffective (generally not advised, unless the condition is mild) or when specific underlying causes are present (eg, Wegener granulomatosis, Goodpasture syndrome, systemic lupus erythematosus). Intravenous cyclophosphamide (2 mg/kg/day, adjusted to renal function) is generally the preferred adjunctive immunosuppressive drug and may be continued for several weeks or until adverse effects occur, such as blood marrow suppression, infection, or hematuria. Thereafter, most clinicians switch to consolidative or maintenance therapy with methotrexate or another agent.

Plasmapheresis is indicated for diffuse alveolar hemorrhage associated with Goodpasture syndrome or with other vasculitic processes in which the titers of pathogenetic immunoglobulins and immune complexes are very high: for example, ANCA-associated vasculitis with overwhelming endothelial injury and a hypercoagulable state. However, the merits of plasmapheresis in diffuse alveolar hemorrhage associated with conditions other than Goodpasture syndrome has not been evaluated in prospective studies.

It remains unclear whether intravenous immunoglobulin therapy adds to the treatment of diffuse alveolar hemorrhage due to vasculitis or other connective tissue disease.

Several case reports have reported successful use of recombinant activated human factor VII in treating diffuse alveolar hemorrhage due to alloimmune hematopoietic stem cell transplantation, ANCA-associated vasculitis, systemic lupus erythematosus, or antiphospholipid syndrome. If borne out by larger experience, recombinant activated human factor VII may gain more widespread use in diffuse alveolar hemorrhage.

Other possible management measures include supplemental oxygen, bronchodilators, reversal of any coagulopathy, intubation.
with bronchial tamponade, protective strategies for the less involved lung, and mechanical ventilation.

**PROGNOSIS**

The prognosis for diffuse alveolar hemorrhage depends on the underlying cause (TABLE 3).

Recurrent episodes may lead to various degrees of interstitial fibrosis, especially in patients with underlying Wegener granulomatosis, mitral stenosis, long-standing and severe mitral regurgitation, and idiopathic pulmonary hemosiderosis. Obstructive lung disease may also complicate microscopic polyangiitis and idiopathic pulmonary hemosiderosis.

**REFERENCES**


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