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Diffuse alveolar hemorrhage: a narrative review

Abstract

This review discusses clinical presentation of DAH, diagnosis of the underlying histology's, treatment options, as well as morbidity and mortality rates. Diffuse alveolar hemorrhage (DAH) is considered a life-threatening pulmonary complication in patients with systemic autoimmune disorders, hematologic malignancies, and coagulation disorders. DAH is distinguished by acute onset of hypoxia and alveolar infiltrates that may lead to progressive alveolar bleeding. Early diagnosis and recognition are crucial for survival. Treatment for DAH involves treating both the underlying condition and the autoimmune damage of the alveolar capillary membrane. The gold standard is immunosuppressive agents and corticosteroids. Despite early recognition and proper treatment DAH mortality rates remain high.

Keywords: diffuse alveolar hemorrhage, corticosteroids, hemoptysis, hypoxia, diffuse lung infiltrates, systemic auto immune diseases, hematopoietic stem cell transplant

Volume 9 Issue 3 - 2022

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Received: October 23, 2022 | **Published:** November 03, 2022

Introduction

DAH is an unfortunate clinical syndrome that may lead to respiratory failure. DAH is caused by a range of the following disorders: diffuse lung infiltrates, anemia, hemoptysis, and acute respiratory failure. Majority of DAH cases originate via capillaritis corresponding with systemic autoimmune diseases such as: systemic lupus erythematosus, anti-glomerular basement membrane disease, and antineutrophil cytoplasmic anti-body associated vasculitis. However, DAH may also originate via coagulation disorders, inhaled toxins, drugs, or stem cell transplantation. DAH recognition requires bronchial alveolar lavage via bronchoscopy and pulmonary function may be done in patients who meet criteria.[1] Radiographic imaging is also non-specific due to it may represent other acute alveolar processes. The main clinical symptom is hemoptysis and may not be present in one-third of patients.[2–7] Once DAH diagnosis has been established, the underlying cause should be recognized to initiate proper treatment. Early recognition is critical due to immediate recognition and treatment are required for survival. Despite advances in recognition and management of DAH, it remains an unfortunate clinical syndrome with high morbidity and mortality rates. This review discusses clinical presentation of DAH, diagnosis of the underlying histology's, treatment options, as well as morbidity and mortality rates (Table 1).

Table 1 Causes of diffuse alveolar hemorrhage

Disorders
diffuse lung infiltrates
anemia
hemoptysis
acute respiratory failure
Auto immune diseases
systemic lupus erythematosus
anti-glomerular basement membrane disease
antineutrophil cytoplasmic anti-body associated vasculitis
Coagulation disorders
inhaled toxins
drugs
stem cell transplant

Clinical presentation, signs, and symptoms

DAH may be determined via the clinical presentation of hemoptysis, dyspnea, fever, cough, decrease in hematocrit, diffuse alveolar infiltrates. Several patients present with hypoxemic respiratory failure, which may lead to death.[1–7] Hemoptysis may be present for as little as a few hours leading to a few days, approximately one third of patients do not present with hemoptysis.[1,2] Clinical presentation of DAH may be repetitive, acute, or subacute, and severity level may vary.[1] Consequently, DAH should be contemplated in patients who present unexplained alveolar infiltrates. Underlying systemic symptoms may or may not be present but occur within one of the following categories: DAH without systemic symptoms and signs or DAH with associated signs and systemic symptoms. In situations when DAH is considered but no suggestive findings are present, the following conditions should be considered: pulmonary limited MPA, anti-GBM disease, idiopathic pulmonary hemosiderosis, pauci-immune isolated pulmonary capillaritis.[1,2] In cases of DAH with associated signs and systemic symptoms, the following indications from the patient's clinical history should intensify suspicion of DAH: acute glomerulonephritis, recent infection suggestive of vasculitis, particular use of offending drugs such as D-penicillamine, anticoagulants, cocaine, nitrofurantoin, amiodarone, propylthiouracil, or sirolimus, systemic vasculitis, mitral valve disease, CVD, and stem cell or organ transplant.[1–7]

Diagnosis

Early recognition via bronchoscopy and bronchial alveolar lavage (BAL) is typically required to confirm diagnosis. Recognition of DAH may be extremely difficult due to the clinical presentation of the underlying disease process.[1–5] A thorough approach in the diagnosis of DAH is critical to determine appropriate management. DAH is diagnosed via clinician recognition in conjunction with specific laboratory, clinical, pathologic, and radiologic features.[1,2] It is of high importance to first and foremost establish the diagnosis of DAH and secondly identify the underlying cause. The recommended approach may vary per patient however, the following outline should be followed: thorough physical exam and patient history, laboratory studies, chest radiograph findings, bronchoscopy to include diagnostic biopsy as indicated.[1–3,7] Laboratory studies such as blood culture, CBC with differential, chemistry, BUN, liver test, and creatine should be obtained.[1,2] During active vasculitis elevation of C-reactive protein and erythrocyte sedimentation are noted.[1] Chest radiograph findings include patchy or diffuse opacities. Nodules, cavities, and ground glass opacities in conjunction with DAH is indictive of vasculitis.[1]

Early bronchoscopy is suggested in patients who are suspected to have DAH. Primarily utilization of bronchoscopy is to rule out infection and to document DAH. In the presence of DAH, lavage fluid becomes increasingly hemorrhagic in consecutive BAL aliquots obtained from the same location.[1–7] Diagnostic biopsy remains crucial to diagnosis of DAH. In the event of a diagnostic biopsy tissue may be obtained from upper airway lesions or skin.[1] Surgical biopsy may be obtained in patients whose DAH diagnosis is still unclear post thorough evaluation.[1] Further serologic testing may be done to determine underlying disorders, in which the following serologic test may be conducted for verification: anti-double stranded DNA (anti-dsDNA), antinuclear antibody, antineutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (anti-GBM) antibodies, and antiphospholipid antibody.[2]

Histology

DAH is an unfortunate clinical syndrome that may result from several disorders associated with diffuse lung infiltration, anemia, hemoptysis, and respiratory failure.[1–4,7] DAH generates via pulmonary microcirculation: arterioles, alveolar capillaries, venules, and is typically diffuse but may be focal.[1] DAH should be differentiated from other causes of pulmonary hemorrhage which result from bronchial circulation and localized pulmonary abnormalities.[1] The most common cause of DAH is systemic vasculitis which may be pathologically established by the presentation of tissue necrosis, vessel destruction, cellular inflammation, and organ dysfunction.[1,2] Clinical situations suggestive of vasculitis: ulcerating or deformed upper airway disease, acute glomerulonephritis, pulmonary renal syndrome, acute glomerulonephritis, palpable purpura, nodule on chest radiograph, multisystem disease, DAH, and mononeuritis multiplex.[1,2]

Alveolar hemorrhage transpiring in hematopoietic stem cell transplant patients with no identifiable infection indicates DAH.[5] DAH emerges via pulmonary microvasculature and is suggested in response to alveolar injury. Although the exact etiology of DAH post hematopoietic stem cell transplant (HSCT) is unknown, factors such as radiation therapy and chemotherapy cause inflammation and vascular damage, as well as immune mediated events to include graft vs. host disease, are indicated in its pathophysiology.[5,7]

Treatment

Therapy for DAH involves treating the both the underlying condition and the autoimmune damage of the alveolar capillary membrane.[1–3,5] The gold standard is immunosuppressive agents and corticosteroids.[1–3,5,7] Other immunosuppressive drugs such as rituximab, methotrexate, azathioprine, and cyclophosphamide may be used to treat DAH, particularly in severe cases refractory to corticosteroids.[1,2] Plasmapheresis is indicated for treatment of Goodpasture syndrome and may also be used to treat other vasculitic processes in which immune complexes and pathogenic immunoglobulins are elevated.[1,2] Several studies have shown Recombinant-activated human factor VII to be a promising new therapy however, at this time further evaluation is required.[1,2] A crucial aspect of therapy for vasculitis is early recognition followed by immediate disease control via immunosuppression. The initial treatment for vasculitis varies based upon severity of disease as well as risk of complication.[1] Treatment is divided into two phases: "remission- induction" phase thus targeting active disease and a "maintenance" phase, that consist of less intense therapy, sustains disease remission, which in turn decreases the risk of adverse events.[1] Treatment recommendations correlate with severity of disease which is measured via presence of DAH, organ systems involved, and severity of renal disease. The patient's disease process is categorized into the following categories: active, generalized, limited, early, generalized, refractory, or severe. Proper treatment options vary per category. Patients who are categorized into the refractory category typically receive experimental agents.[1,5]

Morbidity and mortality

DAH is considered a fatal pulmonary complication of systemic lupus erythematosus (SLE) with high mortality rates between 70-90%.[6] The mortality rate for DAH in systemic vasculitis is 75% pre corticosteroids, post corticosteroids mortality rate decreased to 50%. Although corticosteroids improved the mortality rate in vasculitis, the rate remained at 50%, the breakthrough occurred once cyclophosphamide was initiated. The mortality rate decreased from 50% to 12% thus improving overall mortality rate.[1] DAH is a vital complication of hematopoietic stem cell transplant which contributes to high morbidity and mortality. Majority of HSCT recipients require mechanical ventilator support due to respiratory failure, with a mortality rate greater than 70-80%.[3–5,7]

Conclusion

DAH remains an unfortunate clinical syndrome as a result of many disorders and is considered a life-threatening event. Common causes of DAH are diffuse lung infiltrates, anemia, hemoptysis, acute respiratory failure, systemic lupus erythematosus, anti-glomerular basement membrane disease, anti-neutrophil cytoplasmic anti-body associated vasculitis, inhaled toxins, drugs, and stem cell transplant. DAH should be suspected in patients with hemoptysis, infiltrates on chest radiograph, and hypoxia. Physical exam, medical history, and laboratory evaluation are utilized to declare the underlying cause. Immediate recognition and confirmation via bronchoscopy and BAL followed by appropriate treatment is crucial for survival. Despite advances in recognition and management of DAH, it remains an unfortunate clinical syndrome with high morbidity and mortality rates. More research is indicated to determine pathogenesis and etiology of DAH in HSCT recipients.

Acknowledgments

None.

Conflict of interest

There are no conflicting interests declared by the authors.

Funding

None.

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Citation: Lopez SA. Diffuse alveolar hemorrhage: a narrative review. *J Lung Pulm Respir Res*. 2022;9(3):75–77.
DOI: 10.15406/jlprr.2022.09.00284