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Diffuse Alveolar Hemorrhage: A Medical Emergency with High Mortality

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1. Introduction

Diffuse alveolar hemorrhage (DAH) is a life - threatening pulmonary complication, originates from the pulmonary microvasculature, including the alveolar capillaries, arterioles, and venules. DAH is characterized by the effusion of blood into the alveoli caused by numerous diseases related to hemoptysis, hypoxemia due to alveolar collapse, anemia, diffuse lung infiltration, acute respiratory failure, and death. DAH is usually diffuse but may also be focal. DAH should be distinguished from another mechanism of pulmonary hemorrhage due to localized pulmonary abnormalities and bronchial circulation. [1–3]Pulmonary hemorrhage can arise from the small, medium, and large pulmonary vessels are typically due to systemic vasculitis, which is one of the most common etiology of DAH. Vasculitis involving the microvasculature is known as pulmonary capillaritis. [2, 4]

DAH can be diagnosed based on clinician assessment combined with laboratory, radiographic, and histopathologic features. Early bronchoscopy with bronchoalveolar lavage (BAL) is commonly needed to confirm the diagnosis of DAH and to exclude the infection causes. Failure to diagnose and treat DAH in the early phases may increase mortality due to acute respiratory failure. [2, 5]Currently, DAH has various etiology, including pulmonary capillaritis, drugs, toxins, allogenic hematopoietic stem cell transplantation (HCT), coagulopathies, and blast lung injury. Despite that, the exact mechanism is not well understood, and the standard management for DAH has not been established. The management of DAH includes supportive care such as maintain hemodynamic stability, correction of coagulopathy, ventilatory support, high - dose corticosteroids, immunosuppressants, and plasmapheresis. Despite early identification and treatment of DAH, the morbidity and mortality rates remain high. [1, 2, 6]

2. Definition

Diffuse alveolar hemorrhage (DAH) is a distinct clinicopathologic syndrome with several immune and nonimmune disorders, usually found with nonspecific pulmonary manifestation; thereby, it is a diagnostic and therapeutic challenge. The underlying mechanism for each DAH syndromes is diffuse bleeding into the lung, including the alveolar capillaries, arterioles, and venules. DAH is usually presented with hemoptysis, anemia, diffuse lung infiltration, and acute respiratory failure. [5–7]
Based on histopathologic findings, DAH is associated with pulmonary capillaritis, bland pulmonary hemorrhage, diffuse alveolar hemorrhage, and miscellaneous histology. The former is the most common finding, consisting of an interstitial neutrophilic predominant infiltration, fibrinoid necrosis of the alveolar and capillary walls, leukocytoclastic due to systemic vasculitis, anti - glomerular basement membrane (GBM) disease, and classic autoimmune disease. Red blood cells (RBCs) accumulated in the alveolar spaces are known to be caused by the disruption of the alveolar - capillary basement membranes. Pulmonary capillaritis is limited to the microvasculature of the lung (alveolar capillaries, arterioles, and venules). In contrast, pulmonary vasculitis is known as an inflammation of the lung vessels of any size. [2, 4]

3. Etiology and Classification

Many diseases can cause DAH, which occurs because of injury to the alveolar microcirculation, either localized to the lung (inhalation injuries, diffuse alveolar damage) or associated with a systemic disease (vasculitis or connective tissue disease). Theoretically, alveolar hemorrhage can occur by any source of injury to the alveolar microcirculation. In general, three typical patterns reflect the nature of the underlying vascular injury listed in **Table 1**. [1, 2, 4]

Table 1: Causes of diffuse alveolar hemorrhage

Cause
With pathologic capillaritis
Primary idiopathic small vessel vasculitis
Wegener's granulomatosis
Churg - Strauss syndrome
Microscopic polyangiitis
Isolated pauci - immune pulmonary capillaritis (ANCA positive and negative)
Idiopathic pauci - immune glomerulonephritis
Primary immune complex - mediated vasculitis
Goodpasture's syndrome
Henoch - Schonleinpurpura
Secondary vasculitis
Classic autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Antiphospholipid antibody syndrome
Mixed connective tissue disease
Polymyositis/dermatomyositis
Scleroderma
Essential cryoglobulinemia
Behcet's disease
Acute lung transplantation rejection
Idiopathic pulmonary fibrosis
Autologous bone marrow transplantation
Drug - induced (e. g., chemotherapeutic agents, propylthiouracil)
Without pathologic capillaritis (bland pulmonary hemorrhage)
Idiopathic pulmonary hemosiderosis
Coagulopathy: anticoagulants, anti - platelet, thrombolytics, DIC
Mitral stenosis, pulmonary veno - occlusive disease
Subacute bacterial endocarditis
Toxin or inhalation injury (isocyanates, crack cocaine, retinoic acid)
Goodpasture's syndrome
Systemic Lupus erythematosus

Multiple myeloma Drug - associated disease (amiodarone, penicillamine, nitrofurantoin) Diffuse alveolar damage and other conditions Bone marrow transplantation, inhalation Cytotoxic drug therapy, radiation therapy ARDS Other conditions (infection, malignancy, embolism, etc.)
DIC: disseminated intravascular coagulation; ARDS: acute respiratory distress syndrome.

A study conducted by Prost et al. has demonstrated that immune DAH was the most common etiology, accounting for 35% of all causes. Small vessels vasculitis, predominantly microscopic polyangiitis, and Wegener's granulomatosis, were the main subset of immune DAH (72%). The same study also showed that DAH was the first reason for ICU admission in small - vessel vasculitis cases with an acute life - threatening condition, observed in 37% of cases. [7]Another study has shown that systemic vasculitis was related to the longer mechanical ventilation duration and the ICU mortality was 16% - 31% in patients requiring mechanical ventilation. [8]In bland pulmonary hemorrhage classification, the epithelial lesions are typically microscopic and are scattered geographically, which may lead to the leakage of RBCs into the alveoli without any evidence of inflammation or injuries to the alveolar capillaries, venules, and arterioles. In the last group of DAH, the alveolar hemorrhage occurs due to processes other than pulmonary vascular inflammation or the direct extravasation of RBCs. [2]

3.1 Clinical Presentation, Symptoms, and Signs

DAH can occur at any age and usually with the established associated disease. The typical manifestation of DAH is hemoptysis, which may presents for a few hours to days. Up to 33% of patients do not have hemoptysis in their disease course because of the large total alveolar volume and can absorb a large amount of blood without extending more proximally into the airways. It is unpredictable and has various severity but always should be considered a potentially life - threatening condition. Other clinical presentations of DAH are nonspecific, such as fever, chest pain, cough, and dyspnea, which can accompany the underlying systemic disease. [2, 4, 9]The following conditions should raise the suspicion for DAH based on the patient's clinical history are 1) current infection suggesting Henoch - Schönleinpurpura or cryoglobulinemic vasculitis, 2) use of possibly aggravating drugs such as an anticoagulant, D - penicillamine, nitrofurantoin, amiodarone, propylthiouracil, cocaine, or sirolimus, 3) exposure to toxic agents such as trimellitic anhydride, insecticides, or pesticides, or 4) prior known medical comorbidities such as systemic vasculitis, CVD, mitral valve disease, or solid organ or stem cell transplantation. [2, 10]

3.2 Diagnostic Approach

Because DAH is a life - threatening condition, a careful and precise approach to diagnosing DAH is essential to appropriate management. The diagnosis of DAH depends on the clinician's history taking and physical examination alongside laboratory, radiologic, and pathologic features. The two critical goals of the clinical evaluation are: 1) establishing the diagnosis of DAH and 2) determining the underlying causes. [2, 4]The usual manifestation of DAH is characterized by a triad of clinical presentation with cough, hemoptysis, dyspnea, or blood in bronchoscopy; anemia, which is shown by new hemoglobin declining; and pulmonary infiltrates on chest x - ray. The triad of DAH was only shown in 34% of patients, although most had severe diseases. Thereby, it could be challenging to make a diagnosis of DAH based on clinical and radiologic criteria. [7, 11]A current recommended approach to diagnose DAH is outlined in **Figure 1.** [2]

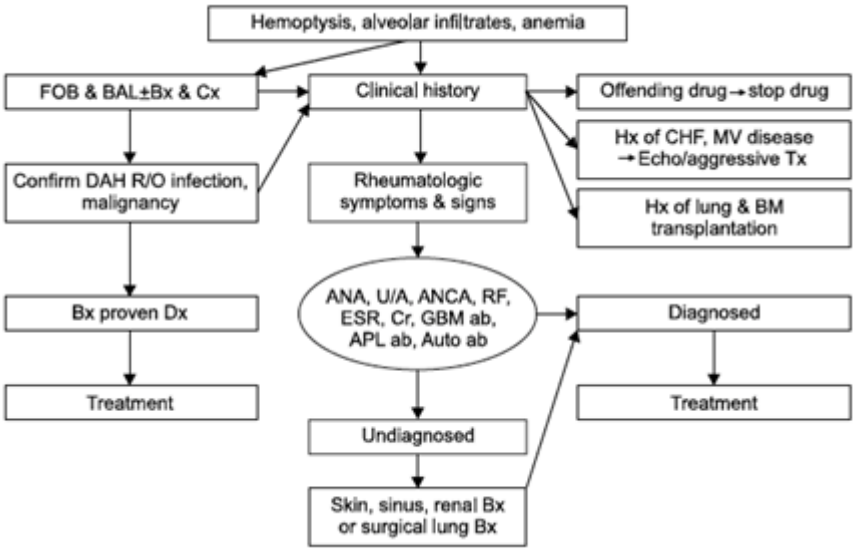

Figure 1: Diagnostic approach in patients with diffuse alveolar hemorrhage. FOB: fiberoptic bronchoscopy; BAL: bronchioloalveolarlavage; Bx: biopsy; Cx: culture; DAH: diffuse alveolar hemorrhage; Dx: diagnosis; Hx: history; CHF: congestiveheart failure; MV: mitral valve; BM: bone marrow; ANA: anti - nuclear antibody; U/A: urinalysis; ANCA: anti - neutrophil cytoplasmicantibodies; RF: rheumatic factor; ESR: erythrocyte sedimentation rate; Cr: creatinine; GBM: glomerularbasementmembrane; APL: anti - phospholipid; Ab: antibody.

1) Careful history taking and physical examination

A detailed history should be taken since DAH can be secondary to numerous immune - mediated disorders, vasculitis, infections, valvular disorders, bone marrow transplantation, and other conditions. A specific drug and occupational history should be obtained. In patients with hemoptysis, focal origins of pulmonary hemorrhage and upper airway and gastrointestinal bleeding should be excluded. [2, 12]Physical examination findings are often nonspecific, including signs related to the underlying systemic vasculitis, such as rash, purpura, eye manifestations, hepatosplenomegaly, or clubbing. DAH may represent the primary manifestation of an underlying systemic vasculitis or collagen vascular diseases (CVDs); thereby, the absence of history or physical examination should not exclude these as a possible mechanism of DAH. [2, 9]

2) Laboratory Studies

Infection should be excluded by obtaining the culture of blood and other affected organs. The other laboratory examination, such as complete blood count, with differential, chemistry, liver tests, blood urea nitrogen, and creatinine, should be taken, although the results are generally nonspecific. There could be an elevated erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) in active vasculitis, but it lacks specificity. In Wegener's granulomatosis and microscopic polyangiitis, proteinuria and microscopic hematuria are commonly found; thereby, urinalysis with microscopic examination should be done in all patients. [2, 12]

Renal abnormalities are usually found in Goodpasture's syndrome and granulomatosis with polyangiitis. If patients present with hematuria or renal impairment suspected of a pulmonary - renal syndrome, then antineutrophil cytoplasmic antibodies (ANCA) should be checked. ANCA is specific for proteins found in the azurophilic granules of polymorphonuclear leukocytes and the peroxidase - positive lysosomes for monocytes. With cytoplasmic distribution (c - ANCA), which is characterized by granular cytoplasmic staining and primarily associated with antibodies directed against proteinase 3 (PR3), it is highly associated with Wegener granulomatosis due to its reasonable specificity. Meanwhile, ANCA with a perinuclear pattern (p - ANCA), associated with antibodies directed against a wide variety of intracellular antigens, with anti - myeloperoxidase specificity, favors the diagnosis of microscopic polyangiitis or Churg - Strauss syndrome. [2, 10, 12, 13]

Anti - glomerular basement membrane (anti - GBM) disease should be screened in all patients with DAH or pulmonary - renal syndrome. The presence of anti - GBM antibodies in serum is an important marker for Goodpasture's syndrome, directed against epitopes in the NC1 domain of the α3 chain of type IV collagen (Goodpasture antigen). [2, 13]Other laboratory studies are complement fractions C3 and C4, anti - double - stranded DNA (ds - DNA), and antiphospholipid antibodies (ANA) levels, should be checked if lupus or antiphospholipid antibody syndrome is suspected. [2, 12, 14]

3) Radiologic findings

Imaging findings are typically consistent with unexplained new infiltrates, commonly diffuse but in the perihilar regions. [14]In the absence of clinically significant symptoms, plain chest x - rays and computed tomography scans (CT scans) are usually helpful in showing several abnormalities (**Fig.2**). [2, 4, 10]Chest x - rays may show patchy or diffuse alveolar opacities. Reticular interstitial opacities because of pulmonary fibroids are usually seen in recurrent episodes of pulmonary hemorrhage, typically with minimal honeycombing. A CT scan examination could show areas of consolidation with areas of ground - glass attenuation and preserved common areas. [2, 9, 12]Cavities, nodules, and diffuse ground - glass opacification with DAH are suspicious of vasculitis. [2, 10]

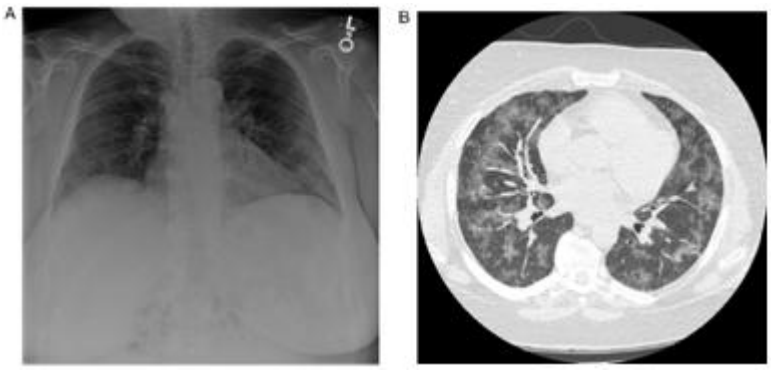

Figure 2: Chest radiograph (A) and chest CT scan (B) showing diffuse nonspecificalveolar infiltrates in a patient with diffusealveolar hemorrhage

The imaging results of DAH are related to its chronicity. The imaging of the lung in the acute condition is usually expected in 20% - 50% of cases. The radiographic features of acute pulmonary hemorrhage could be seen as airspace opacities, predominantly in central and basilar, and sparing the costophrenic angles. The abnormalities correspond to patchy ground - glass opacities on CT scan examination, without significant interlobar septal thickening (**Fig.3A**). Interlobar and intralobular interstitial thickening will be seen in the subacute phase, usually within 48 hours of the disease course. When the septal thickening occurs alongside ground - glass opacities, a crazy - paving pattern will be seen on CT scans examination (**Fig.2B**). Clearing of acute airspace opacities and septal thickening are typically seen within two weeks in a monophasic phase of pulmonary hemorrhage. Pulmonary fibrosis will occur with regions of architectural distortion and areas of lobular sparing when the hemorrhage is chronic and recurrent (**Fig.3C**). [15]

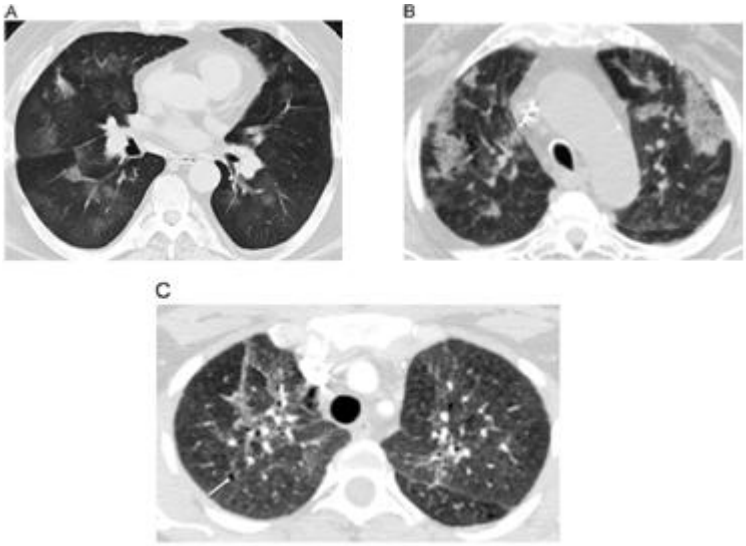

Figure 3: Axial CT image (A) shows bilateral patchy ground - glass opacities, typical in acute pulmonary hemorrhage. Axial CT image (B) shows bilateral ground - glass opacities with superimposed interlobular septal thickening in this patient with subacute pulmonary hemorrhage. Axial CT image (C) shows bilateral upper lobe linear opacities with associated traction bronchiectasis (arrow), indicating fibrosis in this patient with Goodpasture syndrome and chronic pulmonary hemorrhage

4) Bronchoscopy

In most patients with suspicion of DAH, early bronchoscopy with bronchoalveolar lavage (BAL) is indicated. This examination is typically used to look for alveolar hemorrhage and rule out the infection or other alveolar - filling processes such as alveolar proteinosis. A study conducted by Prost et al. has shown that 84% of DAH could be confirmed immediately by a bloody or pink BAL macroscopically (**Fig.4**). [2, 7, 15]Hemoptysis is not seen in up to 33% of patients with DAH; thereby, DAH is confirmed by increasing RBC count in sequential BAL aliquots from the same sites. In addition to that, a declining hematocrit level should alert the clinician to the possibility of DAH. [2, 4]

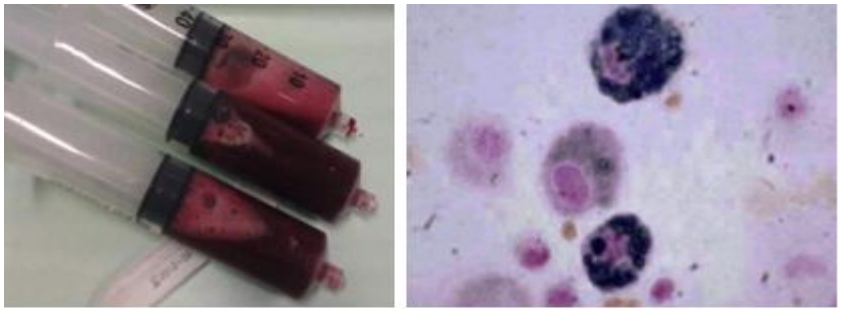

Figure 4: (Left) Macroscopically bloody BAL specimen. An increasing RBC count in sequential BAL aliquots from the same location is considered as a diagnostic tool of DAH; (right) BAL stained by Perl's Prussian blud method, showing deep blue throughout the cytoplasm of two alveolar hemosiderin - laden macrophages

Based on cases with non - massive hemoptysis but not specifically diffuse alveolar hemorrhage, the diagnostic value of bronchoscopy is higher if performed within the first 48 hours of symptoms rather than later. In subacute or recurrent episodes of DAH, the diagnosis could be confirmed by counting the hemosiderin - laden macrophages (siderophages) as shown by Prussian blue staining of a pooled BAL specimen centrifuge (**Fig.4**). [7, 9, 12]BAL specimens should be sent for routine bacterial cultures and fungal, viral, and Pneumocystis carinii when indicated. [1, 2]

In chronic and mild DAH, usually can be diagnosed using a score (e. g., Golde score), alternatively, which assigned a rank to the semiquantitative hemosiderin content based on a subjective estimate after identifying 200 alveolar macrophages. [7, 16]The hemosiderin score was determined based on the grading of blue coloration, which indicates the presence of iron deposits in the cytoplasm of alveolar macrophages as listed in Table 2**.** [17]In order to obtain a hemosiderin score for a mean of 100 alveolar macrophages, the total score from 200 cells was divided by 2. A Golde score of >100 was considered as severe DAH, while a score of 20 - 100 was considered as mild - to - moderate DAH. [16]

Table 2: Alveolar macrophage hemosiderin score grading system

Grade	Description
0	Absence of blue coloration in the cytoplasm
1	Faint blue staining in the cytoplasm
2	Dense blue color in a minor portion of the cytoplasm or medium color intensity throughout the cell
3	Deep blue staining in most of the cytoplasm
4	Cell filled with hemosiderin, dark blue throughout the cytoplasm

5) Diagnostic Biopsy

Although BAL findings are diagnostic for progressive hemorrhage, it does not diagnose the underlying etiology of hemorrhage. In order to do that, a transbronchial or surgical biopsy may be required to determine the etiology if serologic examination or clinical history is unclear. [4, 15]Transbronchial biopsy (TBB) is usually controversial in patients with suspected DAH. It is rarely used in determining the etiology of DAH due to the small size of the specimens and the mechanical disruption of tissue architecture that usually occurs. [2, 4]Although the diagnosis of DAH usually could be made without tissue biopsy, diagnostic biopsy procedure remains critical in diagnosing DAH, which may be obtained from easily accessible sites, such as the skin or upper airway lesions. [2]

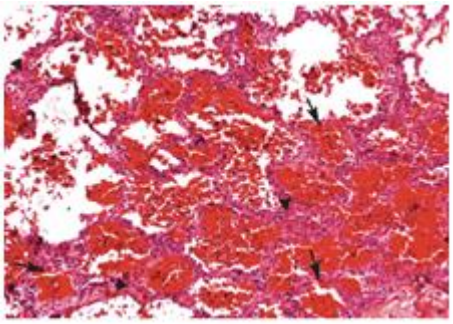

Figure 5: This biopsy specimen shows blood - filled alveolar spaces and hemosiderin - laden macrophages (arrows). Alveolar septae show widening due to a chronic inflammatory infiltrate of lymphocytes and plasma cells (arrowheads). (Hematoxylin and eosin stain, × 4)

The histologic appearance of DAH is relatively uniform, despite the underlying cause (**Fig.5**). [9]Changes of acute or chronic organizing hemorrhage, occasionally with hyaline alveolar membranes, may be seen alongside small vessel vasculitis or changes related to the underlying pathology, such as granulomatous vasculitis in Wegener granulomatosis. Renal biopsy should be obtained immediately if systemic vasculitis, Goodpasture's syndrome, or CVD is suspected. A renal biopsy with immunofluorescence (IF) is usually helpful in laboratory abnormalities suggestive of renal insufficiency or glomerulonephritis. [2, 9]

6) Treatment and Management

Management of DAH includes treating both the autoimmune damage of the alveolar - capillary membrane and the underlying cause. Currently, corticosteroids (CS) and immunosuppressive agents remain the gold standard for most cases. [2, 9]DAH, especially in acute macroscopic hemorrhage, requires prompt and aggressive multidisciplinary management due to its relatively high mortality rate. Management of DAH involves three significant disciplines: (1) supportive care including hemodynamic management, transfusion, and ventilator support, ranging from oxygen supplementation to mechanical ventilation; (2) treatment of underlying cause including intensive immunosuppressive treatments to control disease progressivity, plasmapheresis to remove autoantibodies, and antivirals or antibiotics for infection - related; and (3) rapid and effective local hemostasis. [1, 18]

High - dose CS is recommended to start early alongside the treatment for the underlying disease to control the inflammatory activity by reducing acute inflammatory response such as lung alveolar epithelial swelling, thrombotic microangiopathy, and elevating inflammatory cells and cytokines. Based on recent studies, the drug of choice for DAH management is systemic high - dose CS using intravenous methylprednisolone at 500 mg to 2 g/day or 30 mg/kg/day for 3–5 days followed by gradual tapering over four weeks. [1, 2, 18]A study in infant patients, the first - line treatment was also with oral CS, which have been reported to correlate with decreased pulmonary bleeding relapses and progression of pulmonary fibrosis, as well as with higher survival rates. [19]

The treatment approach depends on the accurate identification of disease severity. Although disease severity and prognosis are related to various factors, the most critical seems to be the number of organs involved measured, the degree of renal involvement, and the presence of DAH. According to this correlation, the European Vasculitis Study Group (EUVAS) has classified a clinically helpful grading system (Table 3) in which the patient's status is categorized as (1) limited; (2) early, generalized; (3) active, generalized; (4) severe; or (5) refractory. [2]In chronic cases of DAH with inadequate responses to CS, or cases related to systemic disease, other immunosuppressive agents, including cyclophosphamide (CYC), azathioprine (AZA), methotrexate (MTX), mycophenolatemofetil (MMF), and etanercept may be given to the DAH patients, especially in severe cases refractory to the first - line regimen with CS. In DAH related to Goodpasture's syndrome or other vasculitis processes, plasmapheresis (PE) is indicated, in which the titers of pathogenic immunoglobulins and immune complexes are surprisingly high. CS therapy alone could improve mortality rates, but unfortunately, the 5 - year mortality remained at 50%. [1, 2]

Table 3: The severity of vasculitis and treatment options according to European vasculitis (EVUS) grading

Clinical class	End organ involvement	Constitutional symptoms	Renal function	Threatened vital organ function	Treatment options
Limited	No, only upper airway	No	Cr < 120 µmol/L (1, 4 mg/dL)	No	CS or MTX or AZA
Early generalized	Yes, but no functional impairment	Yes	Cr < 120 µmol/L (1, 4 mg/dL)	No	CS + CYC or MTX
Active generalized	Yes, with significant impairment	Yes	Cr < 500 µmol/L (5, 7 mg/dL)	Yes	CS + CYC or RIT
Severe	Yes, immediate threat to organ failure. DAH, CHF	Yes	Cr > 500 µmol/L (5, 7 mg/dL)	Yes	CS + CYC or RIT + PE
Refractory	Failed to respond conventional therapy	Yes	Any	Yes	Consider investigational agents

EUVAS: European Vasculitis Study Group; Cr: creatinine; CS: corticosteroid; MTX: methotrexate; AZA: azathioprine; CYC: cyclophosphamide; RIT: rituximab; DAH; diffuse alveolar hemorrhage; CHF: congestive heart failure; PE: plasma exchange

Recombinant - activated human factor VII (rFVIIa) seems a promising therapy, but further studies are needed. A study conducted by Alabed have demonstrated the administration of rFVIIa at a dose of 75 µg/kg via BAL and reportedly had a significant hemostatic effect. Immunosuppressive agents are still the treatment of choice for DAH, primarily if associated with systemic or pulmonary vasculitis, Goodpasture's syndrome, or CVDs. [2, 20]Another alternative regimen is rituximab (RIT), a specific anti - CD20 antigen B - cell antibody that has been described with reported favorable outcomes. A randomized trial conducted by Stone et al. has compared the impact of glucocorticoid in combination with RIT (375 mg/m2 once weekly for four weeks) and glucocorticoid plus CYC (2 mg/kg/day) for the remission induction in severe AAV. [1, 14, 21]Maintenance therapy used to maintain control of the disease activity require less immunosuppression and should be related with fewer and less severe adverse effects. Patients usually convert to AZA or MTX after the initiation of clinical remission agents. Additional agents that have currently been used including MMF, leflunomide, and cyclosporine. In the absence of disease flare, maintenance therapy generally continued for 12 to 18 months. [2]

4. Conclusion

DAH is a clinicopathologic syndrome caused by various disorders and should be considered a life - threatening and medical emergency condition. Common etiologies for DAH are systemic vasculitides such as Wegener granulomatosis, Churg - Strauss syndrome, microscopic polyangiitis, Goodpasture's syndrome, CVD, bone marrow transplantation, drugs, and idiopathic causes. DAH usually comes with a triad of clinical manifestation with cough, hemoptysis, dyspnea, blood in bronchoscopy, anemia, and pulmonary infiltrates on chest radiographs. Patients suspected to have DAH should generally undergo bronchoscopy and BAL. A multidisciplinary approach should be made to early identification, the establishment of diagnosis, and aggressive treatment to decrease the morbidity and mortality rates associated with DAH.

References

[1] Park JA. Treatment of Diffuse Alveolar Hemorrhage: Controlling Inflammation and Obtaining Rapid and Effective Hemostasis. Int J Mol Sci.2021 Jan 14; 22 (2): 793.
[2] Park MS. Diffuse Alveolar Hemorrhage. Tuberc Respir Dis.2013; 74 (4): 151.
[3] Kusunoki M, Umegaki T, Shoji T, Nishimoto K, Anada N, Ando A, et al. Severe Progressive Diffuse Alveolar Hemorrhage in a Patient with Systemic Lupus Erythematosus. Case Rep Crit Care.2018 Jun 7; 2018: e9790459.
[4] Lara AR, Schwarz MI. Diffuse Alveolar Hemorrhage. CHEST.2010 May 1; 137 (5): 1164–71.
[5] de Prost N, Parrot A, Picard C, Ancel PY, Mayaud C, Fartoukh M, et al. Diffuse alveolar haemorrhage: factors associated with in - hospital and long - term mortality. Eur Respir J.2010 Jun 1; 35 (6): 1303–11.
[6] Park JA. Diffuse alveolar hemorrhage and recombinant factor VIIa treatment in pediatric patients. Korean J Pediatr.2016 Mar 31; 59 (3): 105–13.
[7] Diffuse alveolar hemorrhage in immunocompetent patients: Etiologies and prognosis revisited. Respir Med.2012 Jul 1; 106 (7): 1021–32.
[8] Mirouse A, Parrot A, Audigier V, Demoule A, Mayaux J, Géri G, et al. Severe diffuse alveolar hemorrhage related to autoimmune disease: a multicenter study. Crit Care.2020 May 18; 24 (1): 231.
[9] Ioachimescu OC, Stoller JK. Diffuse alveolar hemorrhage: Diagnosing it and finding the cause. Cleve Clin J Med.2008 Apr 1; 75 (4): 258–80.
[10] Brown KK. Pulmonary Vasculitis. Proc Am Thorac Soc.2006 Mar; 3 (1): 48–57.
[11] Kliewer B, Hull C, Yasmer J. Diffuse alveolar hemorrhage.
[12] Panikkath D, Gadwala S, Mills B, Panikkath R. Diffuse alveolar hemorrhage. Southwest Respir Crit Care Chron.2015 Jan 11; 3 (9): 19–27.
[13] Gómez - Román JJ. [Diffuse alveolar hemorrhage]. Arch Bronconeumol.2008 Aug; 44 (8): 428–36.
[14] Abdalla AO, Al - Khafaji J, Akella PM, Taha M. A fatal case of diffuse alveolar hemorrhage as the initial presentation of systemic lupus erythematosus: A case report and literature review. Respir Med Case Rep.2018 Apr 13; 24: 55–7.
[15] Diffuse Pulmonary Hemorrhage: Clues to the Diagnosis. Curr Probl Diagn Radiol.2014 May 1; 43 (3): 128–39.
[16] Maldonado F, Parambil JG, Yi ES, Decker PA, Ryu JH. Haemosiderin - laden macrophages in the bronchoalveolar lavage fluid of patients with diffuse alveolar damage. Eur Respir J.2009 Jun 1; 33 (6): 1361–6.
[17] Doucet MY, Viel L. Alveolar Macrophage Graded Hemosiderin Score from Bronchoalveolar Lavage in Horses with Exercise - Induced Pulmonary Hemorrhage and Controls. J Vet Intern Med.2002; 16 (3): 281–6.
[18] The Bleeding Pneumonia — A Review of Diffuse Alveolar Hemorrhage. US Respir Pulm Dis.2018 Sep 18;
[19] Gkogkou E, Broux I, Kempeneers C, Boboli H, Viellevoye R, Janssen A, et al. Diffuse alveolar hemorrhage in infants: Report of five cases. Respir Med Case Rep.2020 Jun 11; 31: 101121.
[20] Alabed IB. Treatment of Diffuse Alveolar Hemorrhage in Systemic Lupus Erythematosus Patient With Local Pulmonary Administration of Factor VIIa (rFVIIa): A Case Report. Medicine (Baltimore).2014 Sep; 93 (14): e72.
[21] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus Cyclophosphamide for ANCA - Associated Vasculitis. N Engl J Med.2010 Jul 15; 363 (3): 221–32.