Infectious Diseases Causing Diffuse Alveolar Hemorrhage in Immunocompetent Patients: A State-of-the-Art Review

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Abstract  Diffuse alveolar hemorrhage (DAH) represents a syndrome that can complicate many clinical conditions and may be life-threatening, requiring prompt treatment. It is recognized by the signs of acute- or subacute-onset cough, hemoptysis, diffuse radiographic pulmonary infiltrates, anemia, and hypoxemic respiratory distress. DAH is characterized by the accumulation of intra-alveolar red blood cells originating most frequently from the alveolar capillaries. It must be distinguished from localized pulmonary hemorrhage, which is most commonly due to chronic bronchitis, bronchiectasis, tumor, or localized infection. Hemoptysis, the major sign of DAH, may develop suddenly or over a period of days to weeks; this sign may also be initially absent, in which case diagnostic suspicion is established after sequential bronchoalveolar lavage reveals worsening red blood cell counts. The causes of DAH can be divided into infectious and noninfectious, the latter of which may affect immunocompetent or immunodeficient patients. Pulmonary infections are rarely reported in association with DAH, but they should be considered in the diagnostic workup because of the obvious therapeutic implications. In immunocompromised patients, the main infectious diseases that cause DAH are cytomegalovirus, adenovirus, invasive aspergillosis, Mycoplasma, Legionella, and Strongyloides. In immunocompetent patients, the infectious diseases that most frequently cause DAH are influenza A (H1N1), dengue, leptospirosis, malaria, and Staphylococcus aureus infection. Based on a search of the PubMed and Scopus databases, we review the infectious diseases that may cause DAH in immunocompetent patients.

Keywords  Diffuse alveolar hemorrhage · Infectious disease · Hemoptysis · Pulmonary disease

Introduction

Diffuse alveolar hemorrhage (DAH) represents a syndrome with various presentations that can complicate many clinical conditions and may be life-threatening, requiring prompt treatment [1]. DAH is recognized by the signs of acute- or subacute-onset cough, hemoptysis, diffuse radiographic pulmonary infiltrates, anemia, and hypoxemic respiratory distress. This clinicopathologic syndrome is characterized by the accumulation of intra-alveolar red blood cells (RBCs) originating most often from the alveolar capillaries and, less frequently, from precapillary arterioles or postcapillary venules [2]. DAH must be distinguished from localized pulmonary hemorrhage, which is most commonly due to chronic bronchitis, bronchiectasis, tumor, or localized infection [3, 4].

The treatment of DAH is directed at establishing the underlying diagnosis, providing respiratory support, and preventing the progression of microcirculation damage, typically with corticosteroids and immunosuppressive agents [1, 5]. However, such treatment is potentially harmful when DAH is due to nonimmune causes such as infection [6]. In immunocompetent patients, pulmonary infections are rarely reported in association with DAH, but they should be considered in the diagnostic workup because of the obvious therapeutic implications [7]. This review presents the infectious diseases that most frequently cause DAH in immunocompetent patients [influenza A (H1N1), dengue,
leptospirosis, malaria, and *Staphylococcus aureus* infection] and summarizes the clinical, pathologic, and imaging features of DAH in infectious diseases. We focus on the primary diseases that cause DAH according to the number of cases described in the literature, determined using the PubMed and Scopus databases.

**Initial Considerations**

**Etiology**

The causes of DAH can be divided into infectious and noninfectious, the latter of which can affect immunocompetent and immunodeficient patients. Pulmonary infections include those caused by viruses, bacteria, fungi, and parasites [1, 8, 9]. In immunocompromised patients, the main infectious diseases that cause DAH are cytomegalovirus (CMV) [10, 11], adenovirus [12], invasive aspergillosis [13], and *Mycoplasma* [14], *Legionella* [15], and *Strongyloides* [16] infections. In immunocompetent patients, the most important infections that cause DAH include influenza A (H1N1), dengue, leptospirosis, malaria, and *S. aureus* infection.

**Clinical Presentation**

Hemoptysis, the major sign of DAH, may develop suddenly or over a period of days to weeks. However, this sign is initially absent in up to one-third of patients, in which case diagnostic suspicion is established after sequential bronchoalveolar lavage (BAL) reveals worsening RBC counts. Some patients present with severe acute respiratory distress requiring mechanical ventilation [1, 4]. DAH may present with a course of variable severity and should always be considered an imminently life-threatening condition. DAH is associated with several clinical entities and histologic subtypes. Its pathophysiology is alveolar microcirculation injury, and the cause might be generalized (as in systemic vasculitis) or lung-specific disease [as in diffuse alveolar damage (DAD) or infection] [17, 18].

**Diagnostic Studies**

DAH may impair oxygen transfer, which might result in hypoxemia. In this setting, the diffusing capacity of the lung for carbon monoxide (DLCO) may be increased, and serial increases in the DLCO may indicate progressive alveolar hemorrhage. After recurrent episodes of DAH, interstitial fibrosis and restrictive changes may develop. Less commonly, patients may exhibit spirometric changes indicating airflow obstruction.

**Histopathology**

The histopathology of DAH is characterized by intra-alveolar RBCs and fibrin, with the eventual accumulation of hemosiderin-laden macrophages (siderophages) [4, 9, 20]. Surgical lung biopsy may be required to establish the cause of DAH if serologic testing and/or clinical history is unrevealing [1]. For lung sections, besides hematoxylin and eosin, Grocott, Brown-Hopps, and Ziehl-Neelsen staining may be performed for the identification of fungi, bacteria, and acid-fast bacilli, respectively. Specific immunostaining should also be performed; it may provide information about possible viral inclusions such as those found in CMV, adenovirus, herpesvirus, influenza, and respiratory syncytial virus. Immunohistochemical techniques, such as immunofluorescence, can provide information about immune deposits, and a polymerase chain reaction (PCR) assay can be performed in doubtful cases [9, 19, 21].

**Influenza A (H1N1)**

Influenza A (H1N1) virus infection causes a broad spectrum of clinical syndromes, ranging from afebrile upper respiratory illness to fulminant viral pneumonia [22]. Most patients presenting for care have a typical influenza-like illness with fever and cough, sometimes accompanied by sore throat, rhinorrhea, and other common systemic viral symptoms [23]. Signs and symptoms such as dyspnea...
(or tachypnea in children), chest pain, hemoptysis or purulent sputum, altered mental status, and manifestations of dehydration indicate progression to more severe disease or complications [24]. Underlying conditions associated with complications from seasonal influenza are also risk factors for complications from influenza A (H1N1) virus infection. Pregnant women, those less than 2 weeks postpartum, and patients with immunosuppression or neurologic disorders have also been overrepresented among those with severe influenza A (H1N1) infection [24]. Several other risk factors for severe or fatal cases of this infection, particularly in patients younger than 5 years and older than 65 years, include severe obesity, cardiovascular disease, diabetes, chronic lung disease, metabolic disorders, chronic renal or hepatic disease, immunosuppression, hemoglobinopathy, a long history of smoking, and long-term aspirin therapy [25]. Several laboratory diagnostic tests can be used to detect the presence of influenza viruses in respiratory specimens, including direct antigen detection tests, virus isolation in cell culture, and detection of influenza-specific RNA by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). RT-PCR has the highest sensitivity and specificity; rapid antigen and immunofluorescence tests, albeit very useful as initial screening tests, are considerably less sensitive [26].

The predominant HRCT findings in influenza A (H1N1) infection consist of bilateral areas of ground-glass opacity and/or consolidation. The crazy-paving pattern has also been described. These abnormalities have a predominantly peripheral and subpleural distribution [27–29]. Although HRCT findings of influenza A (H1N1) pneumonia frequently overlap with those of other diseases, a pattern of extensive or diffuse ground-glass opacities and consolidations with a primarily peribronchovascular or subpleural distribution can be strongly related to influenza A (H1N1) infection [28].

Most reports describing pathologic findings have been related to autopsy series. The most important pathologic finding is focal to extensive DAD, often associated with marked hyaline membrane formation, pulmonary edema, and various degrees of acute pulmonary hemorrhage. Another important finding is focal necrotizing bronchiolitis. Autopsy evidence of acute pneumonia has usually been observed in association with bacteria [21, 30].

Superimposed bacterial infections of the respiratory tract are not only extremely common in severe influenza, but also complicate the histopathologic appearance. A clear distinction between lesions produced by the virus of the epidemic disease and those attributable to complicating organisms may be very difficult [31].

DAH is a serious complication among patients with influenza A (H1N1) with or without other risk factors (Fig. 1). Pulmonary hemorrhage is a known complication of influenza-related pneumonia. Although DAH has been reported in other influenza epidemics [32], in this review we discuss only influenza A (H1N1), which is the viral serotype of influenza currently considered to be related most closely to DAH. Gilbert et al. [30] suspected that severe cases of influenza A (H1N1) pneumonia had a higher incidence of alveolar hemorrhage than previously reported. This suspicion was supported by Mauad et al. [21], who found an intense hemorrhagic component in 5/21 autopsied patients with influenza A (H1N1) infection. These histopathologic features were also reported by other authors, who noted the frequent association of alveolar hemorrhage with DAD in influenza A (H1N1) pneumonia [33–35]. Some other case reports related DAH to influenza A (H1N1) infection, in which HRCT scans showed diffuse bilateral ground-glass opacities [7, 36]. A retrospective chart analysis of 15 fatal cases of influenza A (H1N1) showed that 80% had intra-alveolar hemorrhage; the most common radiologic findings were fluffy infiltrates, followed by confluent opacities [33].

**Dengue**

Dengue fever (DF) is an acute infectious disease caused by the dengue virus, an arthropod-borne RNA virus belonging to the family Flaviviridae with four distinct serotypes (DENV 1–4) [37]. Dengue virus causes disease in humans, including DF and dengue hemorrhagic fever (DHF), in which increased vascular permeability is the main pathology leading to shock [37]. The virus is transmitted to humans by the bite of an infected female mosquito of the genus *Aedes*. Its prevalence has grown dramatically in

![Fig. 1 A 28-year-old woman with influenza A (H1N1) virus-associated pneumonia and diffuse alveolar hemorrhage. High-resolution computed tomography exhibits consolidations and ground-glass opacities in both lower lobes](image-url)
recent decades, and the disease is now endemic in more than 100 countries in Eastern and Western Africa, Central and South America, the Eastern Mediterranean, Southeast Asia, and the Western Pacific [38].

Dengue disease has a wide spectrum of clinical signs and symptoms, ranging from asymptomatic infection to severe and lethal manifestations. DF usually presents as an acute fever with headache, rash, myalgia, arthralgia, retro-orbital pain, prostration, lymphadenopathy, and dry cough. Other findings include petechiae, epistaxis, gingival bleeding, and gastrointestinal bleeding [39]. According to the World Health Organization guidelines, DHF is characterized by four major clinical manifestations: high fever, hemorrhagic phenomena, and often hepatomegaly and circulatory failure. Moderate to marked thrombocytopenia with concurrent hemoconcentration is a hallmark of clinical laboratory findings in DHF [40]. In general, other laboratory findings include neutropenia followed by lymphocytosis, with the presence of atypical lymphocytes [37–40]. The diagnosis is based on serology, RNA detection, and viral isolation in blood specimens. Enzyme-linked immunosorbent assays remain the most widely used technique for serologic diagnosis, but they do not identify the dengue virus serotype responsible for the current infection [8].

Thoracic manifestations such as pleural effusion and pneumonitis are uncommon in DHF, and pulmonary hemorrhage is even rarer (Fig. 2). Hemoptysis has been reported in 1.4 % of dengue infections [41, 42]. The pathogenesis of bleeding in patients with DHF is not well understood. It is thought to be a multifactorial process with abnormalities in the coagulation cascade, thrombocytopenia, platelet dysfunction, disseminated intravascular coagulation, and vascular defects. Increased vascular permeability has been thought to be mediated by histamine release [41, 42]. A histopathologic review of 319 adult patients with dengue showed that pulmonary hemorrhage and DAD were the main features of the infection [43]. Morphologic studies of lung tissues revealed interstitial pneumonia associated with focal or diffuse zones of alveolar congestion and hemorrhage, an increased number of alveolar macrophages, and recruiting of platelets, mononuclear cells, and polymorphonuclear cells [44, 45]. DAH in DHF has been rarely described [41, 42]. HRCT findings in DHF causing DAH may present discrete patchy ground-glass opacities in both lungs [41]. Other features are extensive and bilateral areas of consolidation with air bronchogram and ground-glass opacities associated with small pleural effusions [8].

**Leptospirosis**

Leptospirosis is a zoonosis caused by spirochetes from the species *Leptospira interrogans* [46]. It is one of the most widespread zoonoses in the world, occurring mainly in tropical and subtropical regions, and is considered an important public health problem [46]. Humans are infected when mucous membranes or abraded skin come into direct contact with the urine of infected animals (including rats, mice, sheep, cattle, pigs, dogs, raccoons, and goats) or by exposure to contaminated water, soil, or other matter. Clinical manifestations of leptospirosis range from asymptomatic or febrile episodes to severe forms. The clinical findings include fever, muscle tenderness (especially of the calf muscles), headache, conjunctival suffusion, and digestive disorders, with hepatic and renal involvement. Mental status disturbance may also appear [47]. Leptospirosis should be considered in the differential diagnosis of patients with febrile illnesses associated with pneumonitis and respiratory failure, especially when hemoptysis is present [48].

This disease is associated with cardiovascular collapse and significant mortality [47]. Severe disease is estimated to occur in 5–15 % of all human infections, typically
presenting as Weil’s syndrome, a triad of hemorrhagic manifestations and hepatic and renal dysfunction. Severe pulmonary involvement in leptospirosis consists primarily of hemorrhagic pneumonitis. The emergence of severe pulmonary hemorrhage syndrome (SPHS) in leptospirosis may present as acute respiratory distress or massive pulmonary hemorrhage, generally associated with hemoptysis [49, 50]. The diagnosis of leptospirosis is based on clinical findings, a history of direct or indirect exposure to infected animals in endemic areas, and positive serologic tests [51].

Radiographic findings commonly accompany pulmonary symptoms but may occur without them; they consist of nonspecific, diffuse, small opacities, which may be disseminated or coalesce into larger areas of consolidation with increasing severity of symptoms [52]. These infiltrates correspond to areas of intra-alveolar and interstitial hemorrhage [52]. The most frequent HRCT findings are extensive, bilateral, ground-glass opacities involving all lobes (Fig. 3). Areas of consolidation, peripheral airspace nodules, and pleural effusions may be present. The abnormalities involve mainly the peripheral and dorsal lung regions and the lower lung zones [48, 53]. Microscopic examination reveals extensive areas of intra-alveolar and interstitial hemorrhage, but other findings, such as pulmonary edema, fibrin deposition, hyaline membrane formation, and proliferative fibroblastic reactions, are frequent [49].

Bernardi et al. [54] found increased expression of C3aR, toll-like receptor 2, and intercellular and vascular cell adhesion molecules in the lungs of patients who died of leptospirosis. These data indicate that innate immune receptors and adhesion molecules contribute to the pathogenesis of lung hemorrhage in leptospirosis. Croda et al. [55] suggested that the linear deposition of immunoglobulins (IgA, IgG, and IgM) and complements on the alveolar surface may play a role in the pathogenesis of pulmonary hemorrhage in human leptospirosis. Thus, leptospirosis pulmonary hemorrhage syndrome seems to have unique pathologic features not seen in other pulmonary hemorrhagic syndromes. These results are important because no treatment other than supportive respiratory care is currently available for this syndrome. A better understanding of the pathogenesis can contribute to the development of treatment strategies for this devastating manifestation of leptospirosis [54, 55].

Surveillance between 2003 and 2005 identified 47 (10 %) SPHS cases among 474 patients whose diagnosis met the clinical definition of severe leptospirosis [56]. All of these cases presented with the onset of massive hemoptysis, and 24 showed alveolar or interstitial bilateral infiltrates on chest radiographs [56]. In one series, 74 % of 89 fatal cases of leptospirosis had clinically detected pulmonary involvement, which was the strongest risk factor [57]. Autopsies performed on 43 of these patients showed pulmonary hemorrhage in 72 % of cases [57]. The treatment of leptospirosis is based on antibiotics and supportive care. Some studies have reported success in the treatment of DAH caused by leptospirosis using hemostatic agents such as desmopressin [58] and recombinant activated factor VII [59].

Malaria

Malaria remains a significant global public health problem, especially in tropical and subtropical regions where temperature and rainfall are most suitable for the development of the malaria agent, the Plasmodium parasite, in Anopheles mosquitoes, which transmit malaria through their bites. Malaria has a devastating socioeconomic impact on
affected countries. More than two billion people are exposed to the risk of acquiring malaria [60].

Whereas patients with uncomplicated malaria usually present with fever and nonspecific symptoms, severe and complicated malaria is characterized by multiorgan involvement, including acute lung injury and acute respiratory distress syndrome (ARDS). Pulmonary symptoms such as cough with or without expectoration and dyspnea have been described in patients with malaria [60, 61]. The clinical manifestations of malaria have shown a paradigm shift in the last two decades; multiorgan failure is encountered much more frequently than previously, likely due to the high transmission rate of falciparum malaria and drug resistance to commonly used antimalarial agents [62]. In patients living or having traveled in endemic areas, malaria should be considered as a possible cause of ARDS of obscure etiology. ARDS is increasingly reported in falciparum malaria and malaria caused by species formerly considered benign (*Plasmodium vivax*, *P. ovale*, and *P. malariae*) [60]. Parasites can be detected on thick and thin peripheral blood smears. Thick smear examination facilitates the quantification of parasitemia [60, 61].

ARDS is considered to be the most severe form of lung injury in malaria and is frequently associated with cerebral malaria. In patients with falciparum malaria, ARDS can develop at the time of initial presentation or after several days of treatment, when patients appear to be improving and parasitemia is reduced [60, 61]. Pregnant women with severe falciparum malaria are particularly prone to the development of ARDS and have a high rate of mortality [61]. Adequate supportive management is considered to be an essential component of treatment to reduce mortality in patients with severe complicated malaria, and the early administration of specific antimalarial treatment can be lifesaving [60–62].

General radiographic and HRCT findings in malaria are consistent with noncardiogenic pulmonary edema. Pleural effusion, diffuse interstitial edema, and lobar consolidation may also be seen [63].

Malaria causing DAH may show progressive refractory hypoxemia and diffuse infiltrates on radiographs and pathologic findings of scattered hemorrhage and alveolar septal thickening, leading this complication to resemble ARDS [64]. Corne et al. [65] reported the occurrence of intra-alveolar hemorrhage during *P. falciparum* malarial crisis. Brooks et al. [66] described five patients who developed fatal pulmonary edema with normal central venous pressure in which histopathologic specimens showed alveolar hemorrhage and hyaline membrane formation. Autopsy studies in patients with severe falciparum malaria revealed heavy edematous lungs, congested pulmonary capillaries, thickened alveolar septa, intra-alveolar hemorrhage, hyaline membrane formation, and serous pleural and pericardial effusions [60].

**Staphylococcus aureus Pneumonia**

*Staphylococcus aureus* is recognized as an extremely successful human pathogen that may colonize patients in the hospital or community, potentially causing a variety of clinical entities such as cutaneous infections, pneumonia, and sepsis [67]. *Staphylococcus aureus* is estimated to cause 1–10% of community-acquired pneumonias and 20–50% of nosocomial pneumonias [68]. Pneumonia often occurs after influenza infection, particularly in elderly patients with preexisting chronic diseases such as chronic obstructive pulmonary disease and cardiovascular diseases. It has an abrupt clinical scenario, with pleural chest pain, cough, purulent sputum, and sometimes hemoptysis. The prevalence of methicillin-resistant *S. aureus* (MRSA) is well known as a cause of hospital-acquired infections, and the frequency of community-onset MRSA (CO-MRSA) infections has increased substantially in the past decade [69]. Methicillin resistance is determined by the presence of a penicillin-binding protein with decreased affinity to penicillin [56]. Methicillin-sensitive *S. aureus* (MSSA) and MRSA may produce Panton-Valentine leukocidin (PVL) and cause necrotic hemorrhagic pneumonia, but the majority of publications have been related to CO-MRSA or mixed patient groups [70, 71]. Whether methicillin resistance plays a role in the pathogenesis of CO-MRSA has not been well established. One study compared outcomes between MSSA and MRSA strains and found no significant difference. Mortality rates are not higher among patients with MRSA-related PVL-positive pneumonia than among those with MSSA-related PVL-positive pneumonia [71].

The main feature of *S. aureus* pneumonia on HRCT is bronchopneumonia with segmental consolidations, which tend to be multilobar and typically affect the lower lobes. Nodular opacities can also be seen on radiographs or HRCT. Lung abscesses are present in about 15–30% of patients; they are usually solitary, but may be multiple. Pneumatoceles occur in ~50% of children and 15% of adults, generally in the first week of pneumonia, and often disappear spontaneously within weeks or months. Pleural effusions are found in 30–50% of patients [72].

The role of CO-MRSA infection as a causative agent of serious pneumonia in children and healthy young adults was previously reported. Frank hemoptysis occurs in about one-third of patients and the outcome is fatal in about 50%, illustrating the lethal potential of CO-MRSA pneumonia [69, 70, 73, 74]. In one series, hemoptysis was found in 6/16 (38%) patients with severe pneumonia associated with *S. aureus* strains carrying PVL genes compared with 1/33 (3%) PVL-negative patients [70]. Lina et al. [75] screened 23 cases of CO-MRSA pneumonia with PVL genes; 14 (61%) of these cases were fatal, and autopsies revealed diffuse, bilateral necrotic
hemorrhagic pneumonia. Moreover, Francis et al. [69] reported four cases of severe necrotizing MRSA pneumonia in previously healthy patients, which presented as an influenza or influenza-like prodrome. Two of the patients had evidence of concomitant influenza A infection. The association between influenza and severe staphylococcal pneumonia is well recognized [69]. In a cohort of 112 patients with criteria for DAH, the most infectious cause was *S. aureus*, which was present in five cases, including two methicillin-resistant and three PVL-producing strains [6].

Other Infections Rarely Presenting with DAH in Immunocompetent Patients

CMV is considered a member of the family Herpesviridae and can cause severe symptomatic and life-threatening pulmonary disease in immunocompromised patients [76]. Although CMV infections are prevalent in the general population, symptomatic pneumonia in immunocompetent hosts is rarely reported [77]. In severe cases, massive hemorrhage with frank hemoptysis may occur [78]. Magro et al. [10] described four previously healthy adults who developed subacute onset of respiratory symptoms temporally associated with serologic or culture evidence indicative of acute CMV infection. Biopsies showed vascular injury involving the lungs or other organs. Open lung biopsies showed extensive hemorrhage and hemosiderin deposition. Another report [11] described a fulminant lethal case of DAH in an immunocompetent patient with CMV pneumonia, whose HRCT demonstrated bilateral perihilar consolidation with air bronchograms. In patients with CMV pneumonia, the diagnostic histologic feature is cellular enlargement combined with intranuclear and intracytoplasmic inclusions [79].

Humans are infected by hantaviruses after inhalation of aerosolized virus particles from rodent urine, saliva, or dried excreta [80, 81]. Several antigenically distinct viruses throughout the world have been found to cause two clinical symptom complexes: hantavirus hemorrhagic fever with renal syndrome and hantavirus fever with pulmonary and cardiovascular syndrome [82]. Hantavirus pulmonary syndrome (HPS) has a high case-fatality rate and characteristically presents as respiratory distress from noncardiogenic edema, although alveolar hemorrhage may be present [83, 84]. The pathogenesis of HPS is believed to be related to the immune response to the virus, which is responsible for increased capillary permeability leading to pulmonary edema. Although the virus antigen is present in microvascular endothelial cells, the disturbance is basically functional and no alveolar damage occurs in most patients [85]. Based on clinical suspicion and epidemiologic history, the etiologic diagnosis is made by serologic tests and detection of the viral genome by RT-PCR [85].

Radiographically, HPS presents as interstitial edema with or without rapid progression to airspace disease; the distribution is central or bibasilar and lacks the peripheral pattern usually seen in the acute phase of ARDS [86]. On HRCT, HPS may present with bilateral areas of ground-glass attenuation, thickened interlobular septa, poorly defined small nodules, and bronchial wall thickening. These findings are nonspecific and the differential diagnosis should consider other pulmonary infectious and noninfectious diseases [87]. Histopathologic examination of the lungs may reveal interstitial and alveolar edema, alveolar hemorrhage, and mild interstitial pneumonia characterized by infiltrates of immunoblasts and mononuclear cells [88].

Although pulmonary tuberculosis (TB) is a very common infectious disease, it is rarely associated with DAH. TB is usually diagnosed using Ziehl-Neelsen staining for acid-fast bacilli, which is nonspecific, or by culture. Keung et al. [89] reported a fatal case of pulmonary TB infection masquerading as DAH after autologous stem cell transplantation. Marruchella et al. [90] reported a case of culture-proven pulmonary TB presenting as DAH in an immunocompetent man. HRCT showed bilateral areas of ground-glass opacity, focal areas of consolidation, and scattered nodules. Traditional findings of pulmonary TB, such as upper-lobe nodules or cavities, were not found. BAL showed a progressively bloodier return, and its culture revealed *Mycobacterium tuberculosis*. The patient showed progressive clinical improvement after receiving a drug regimen to treat TB.

A fatal case of miliary TB causing DAH has also described [91]. Radiography and HRCT showed bilateral pulmonary infiltration and diffuse ground-glass opacities, but disseminated nodules were not identified. BAL was bloody, leading to the suspicion of DAH, and its culture revealed *M. tuberculosis*. An autopsy showed abundant necrotizing epithelioid granulomas in both lungs and other organs. Marked alveolar hemorrhage and hyaline membrane were also found in both lungs [91].

Conclusions

In conclusion, infectious diseases should be considered in the differential diagnosis of DAH syndrome because early, adequate, targeted therapy in combination with supportive treatment and, possibly, corticotherapy will improve survival. The most frequent infections causing DAH in immunocompetent patients are influenza A (H1N1), dengue, leptospirosis, malaria, and *S. aureus* pneumonia. Hantaviruses, CMV, and TB may also cause DAH, although such cases are rare.
Conflict of interest None.

References

1. Ioachimescu OC, Stoller JK (2008) Diffuse alveolar hemorrhage: diagnosing it and finding the cause. Cleve Clin J Med 75:258–265
2. Fontenot AP, Schwarz MI (2003) Diffuse alveolar hemorrhage. Interstitial Lung Dis 3:632–656
3. Primack SL, Miller RR, Muller NL (1995) Diffuse pulmonary hemorrhage: clinical, pathologic and imaging features. AJR Am J Roentgenol 164:295–300
4. Lara AR, Schwartz MI (2010) Diffuse alveolar hemorrhage. Chest 137:1164–1171
5. Ioachimescu OC (2006) Alveolar hemorrhage. In: Laurent GL, Shapiro SD (eds) Encyclopedia of respiratory medicine. Academic Press, Amsterdam, pp 92–100
6. de Prost N, Parrot A, Cuquemelle E, Picard C, Antoine M, Fleury-Feith J, Mayaud C, Boffa JF, Fartoukh M, Cadranel J (2007) Diffuse alveolar hemorrhage in immunocompetent patients: etiologies and prognosis revisited. Respir Med 106:1021–1032
7. Marchiori E, Zanetti G, Hochhegger B (2011) Diffuse alveolar hemorrhage in infectious diseases. Chest 139:228
8. Marchiori E, Ferreira JL, Bittencourt CN, de Araújo Neto CA, Zanetti G, Mano CM, Santos AA, Vianna AD (2009) Pulmonary hemorrhage syndrome associated with dengue fever, high-resolution computed tomography findings: a case report. Orphanet J Rare Dis 4:8
9. Gómez-Román JJ (2008) Diffuse alveolar hemorrhage. Arch Bronconeumol 44:428–436
10. Magro C, Ali N, Williams JD, Allen JN, Ross PJ (2005) Cyto-megalovirus-associated pulmonary septal capillary injury sine inclusion body change: a distinctive cause of occult or macroscopic pulmonary hemorrhage in the immunocompetent host. Appl Immunohistochem Mol Morphol 13:268–272
11. Ciledag A, Karnak D, Kayacan O (2010) A butterfly shaped alveolar hemorrhage caused by cytomegalovirus. Southeast Asian J Trop Med Public Health 41:900–903
12. Mayeur N, Srairi M, Guilbeau Frugier C, Fourcade O, Dahan M (2012) Lethal hemorrhagic alveolitis after adenovirus pneumonia in a lung transplant recipient. Heart Lung 41:401–403
13. Agusti C, Ramírez J, Picado C, Xaubet A, Carreras E, Ballester E, Torres A, Battochia C, Rodríguez-Roisin R (1995) Diffuse alveolar hemorrhage in allogeneic bone marrow transplantation. A postmortem study. Am J Respir Crit Care Med 151:1006–1010
14. Kane JR, Shenepl JL, Krance RA, Hurwitz CA (1994) Diffuse alveolar hemorrhage associated with Mycoplasma hominis respiratory tract infection in a bone marrow transplant recipient. Chest 105:1891–1892
15. Sundar KM, Pearce MJ (2004) Diffuse alveolar hemorrhage due to Legionella pneumonia. Sarcoïdosis Vasc Diffuse Lung Dis 21:158–159
16. Agarwal VK, Khurana HS, Le HK, Mathisen G, Kamangar N (2009) 30-year-old HIV-positive female with diffuse alveolar hemorrhage. J Intensive Care Med 24:200–204
17. Collard HR, Schwarz MI (2004) Diffuse alveolar hemorrhage. Clin Chest Med 25:583–592
18. Travis WD, Colby TV, Lombard C, Carpenter HA (1990) A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 14:1112–1125
19. Specks U (2001) Diffuse alveolar hemorrhage syndromes. Curr Opin Rheumatol 13(1):12–17
20. Sherman JM, Winnie G, Thomassen MJ, Abdul-Karim FW, Boat TF (1984) Time course of hemosiderin production and clearance by human pulmonary macrophages. Chest 86:409–411
21. Mauad T, Hajar LA, Callegari GD, da Silva LF, Schout D, Galas FR, Alves VA, Malheiro DM, Auler JO Jr, Ferreira AF, Borsato MR, Bezerra SM, Gutierrez PS, Căldăru ET, Pasqualucci CA, Dolnikhoff M, Saldiva PH (2010) Lung pathology in fatal novel human influenza A (H1N1) infection. Am J Respir Crit Care Med 181:72–79
22. Cao B, Li XW, Yao Y, Wang J, Lu HZ, Chen YS, Liang ZA, Liang L, Zhang SJ, Zhang B, Gu L, Lu LH, Wang DY, Wang C, A National Influenza Pandemic (H1N1) 2009 Clinical Features and Patient Management Group of China (2009) Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 361:2507–2517
23. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, Gubareva LV, Xu X, Bridges CB, Uyeki TM, Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team (2009) Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 360:2605–2615
24. Louie JK, Acosta M, Winter K, Jean C, Gavaller S, Schechter R, Vugia D, Harriman K, Matyas B, Glaser CA, Samuel MC, Rosenberg J, Talarico J, Hatch D, California Pandemic (H1N1) Working Group (2009) Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 302:1896–1902
25. London Health Protection Agency (HPA) (2009) Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave. Available at http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1258560552857. Accessed 27 February 2012
26. Centers for Disease Control, Guidance for clinicians on the use of rapid influenza diagnostic tests for the 2010–2011 influenza season, CDC guideline, Available at http://www.cdc.gov/flu/pdf/professionals/diagnosis/clinician_guidance_ridt.pdf. Accessed 21 August 2012
27. Marchiori E, Zanetti G, Hochhegger B, Rodrigues RS, Fontes CA, Nobre LF, Mançoan AD, Meirelles GS, Iran KL (2010) High-resolution computed tomography findings from adult patients with Influenza A (H1N1) virus-associated pneumonia. Eur J Radiol 74:93–98
28. Aflan AM, Quiney B, Nicolau S, Müller NL (2009) Swine-origin influenza A (H1N1) viral infection: radiographic and CT findings. AJR Am J Roentgenol 193:1494–1499
29. Agarwal PP, Cinti S, Kazerooni EA (2009) Chest radiographic and CT findings in novel swine-origin influenza A (H1N1) virus (S-OIV) infection. AJR Am J Roentgenol 193:1488–1493
30. Gilbert CR, Vipul K, Baram M (2010) Novel H1N1 influenza A viral infection complicated by alveolar hemorrhage. Respir Care 55:623–625
31. Taubenberger JK, Morens DM (2008) The pathology of influenza virus infections. Annu Rev Pathol 3:499–522
32. Laver WG (2004) Hunting the 1918 flu: one scientist’s search for a killer virus. N Engl J Med 350:523–524
33. Prasad HB, Puranik SC, Kadam DB, Sangle SA, Borse RT, Basavraj A, Umarji PB, Mave V, Ghopade SV, Bhadrawaj R, Jamkar AV, Mishra AC (2011) Retrospective analysis of necropsy findings in patients of H1N1 and their correlation to the clinical features. J Assoc Physicians India 59:498–500
34. Nakajima N, Sato Y, Katano H, Hasegawa H, Kumasaka T, Hata S, Tanaka S, Amano T, Kasai T, Chong JM, Izuoka T, Nakazato I, Hino Y, Hamamatsu A, Horiguchi H, Tanaka S, Hasegawa A, Kanaya Y, Oka R, Oya T, Sata T (2012) Histopathological and immunohistochemical findings of 20 autopsy cases with 2009 H1N1 virus infection. Mod Pathol 25:1–13
35. Rose NG, Lopez AE, Anzalone ML, Wolf DA, Derrick SM, Florez LF, Gonsoulin ML, Hines MO 3rd, Mitchell RA, Phatak DR, Haden-Pinneri K, Sanchez LA (2010) Postmortem findings in eight cases of influenza A/H1N1. Mod Pathol 23:1449–1457
36. Rhee H, Song SH, Lee YJ, Choi HJ, Ahn JH, Seong EY, Lee SB, Kwak IS (2011) Pandemic H1N1 influenza A viral infection complicated by atypical hemolytic uremic syndrome and diffuse alveolar hemorrhage. Clin Exp Nephrol 15:948–952
37. Balmaseda A, Hammond SN, Pérez L, Tellez Y, Saborio SI, Mercado JC, Cuadra R, Rocha J, Pérez MA, Silva S, Rocha C, Harris E (2006) Sero-type-specific differences in clinical manifestations of dengue. Am J Trop Med Hyg 74:449–456
38. Chaturvedi UC (2006) The curse of dengue. Indian J Med Res 124:467–470
39. Tavakoli NP, Tobin EH, Wong SJ, Dupuis AP 2nd, Glasehen B, Kramer LD, Bernard KA (2007) Identification of dengue virus in respiratory specimens from a patient who had recently traveled from a region where dengue virus infection is endemic. J Clin Microbiol 45:1523–1527
40. World Health Organization (1997) Leptospirosis. Clin Infect Dis 21:1–8
41. Castro JR, Salaberry SR, Souza MA, Lima-Ribeiro AM (2011) Immune receptors and adhesion molecules in human pulmonary leptospirosis. Hum Pathol 43(10):1601–1610
42. Croda J, Neto AN, Brasil RA, Pagliari C, Nicodemo AC, Duarte MI (2010) Leptospirosis pulmonary haemorrhage syndrome is associated with linear deposition of immunoglobulin and complement on the alveolar surface. Clin Microbiol Infect 16(6):593–599
43. Gouveia EL, Metcalfe J, de Carvalho AL, Aires TS, Villasboas-Bisneto JC, Queiroz A, Santos AC, Salgado K, Reis MG, Ko AI (2008) Leptospirosis-associated severe pulmonary hemorrhagic syndrome, Salvador, Brazil. Emerg Infect Dis 14:505–508
44. Spichler AS, Vilaça PJ, Athanazio DA, Albuquerque JO, Buzzar M, Castro B, Seguro A, Vinetz JM (2008) Predictors of lethality in severe leptospirosis in urban Brazil. Am J Trop Med Hyg 79:911–914
45. Pea L, Roda L, Boussaoud V, Lonjon B (2003) Desmopressin therapy for massive hemoptysis associated with severe leptospirosis. Am J Respir Crit Care Med 167:726–728
46. Tatopoulos A, Herbsin D, Kazmirczak C, Bollaert PE, Gibot S (2010) Parenteral refeeding of recombinant activated factor VII during diffuse alveolar hemorrhage secondary toleptospirosis. Intensive Care Med 36:555–556
47. Greenwood BM, Fidock DA, Kyle DE, Kappe SH, Collins FH, Duffy PE (2008) Malaria: progress, perils, and prospects for eradication. J Clin Invest 118:1266–1276
48. Taylor WR, Cañon V, White NJ (2006) Pulmonary manifestations of malaria: recognition and management. Treat Respir Med 5:419–428
49. Mishra SK, Mohanty S, Mohanty A, Das BS (2006) Management of severe and complicated malaria. J Postgrad Med 52:281–287
50. Taylor WR, White NJ (2002) Malaria and the lung. Clin Chest Med 23:457–468
51. Heineman HS (1972) The clinical syndrome of malaria in the United States. Arch Intern Med 129:607–616
52. Coma P, Landreau L, Moulare V, Jonquet O (2001) Intra-alveolar hemorrhage during Plasmodium falciparum malaria crisis. Presse Med 30:1499
53. Brooks MH, Kiel FW, Sheehy TW, Barry KG (1968) Acute pulmonary edema in falciparum malaria. N Engl J Med 279:732–737
54. Charlebois ED, Perdreau-Remington F, Kreiswirth B, Bangsberg DR, Ciccione D, Diep BA, Ng VL, Chansky K, Edlin BR, Chambers BF (2004) Origins of community strains of methicillin-resistant Staphylococcus aureus. Clin Infect Dis 39:47–54
55. Howard LS, Sillis M, Pasteur MC, Kamath AV, Harrison BD (2005) Microbiological profile of community-acquired pneumonia in adults over the last 20 years. J Infect 50:107–113
56. Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T, Cai M, Hansel NN, Perl T, Ticehurst JR, Carroll K, Thomas DL, Nuenrberger E, Bartlett JG (2005) Severe community-onset pneumonia in healthy adults caused by methicillin-resistant Staphylococcus aureus carrying the Panton-Valentine leucocidin genes. Clin Infect Dis 40:100–107
57. Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, Vandenec F, Piémont Y, Brousse N, Fliotot D, Etienne J (2002) Association between Staphylococcus aureus strains carrying gene for Panton-Valentine leucokin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359:753–759
58. Vardakas KZ, Matthaiou DK, Falagas ME (2009) Comparison of community-acquired pneumonia due to methicillin-resistant and methicillin-susceptible Staphylococcus aureus producing the Panton-Valentine leucokin. J Infect Dis Lung Dis 13:1476–1485
72. Santos JW, Nascimento DZ, Guerra VA, da Rigo VS, Michel GT, Dalcin CT (2008) Community-acquired staphylococcal pneumonia. J Bras Pneumol 34:683–689
73. Gorak EJ, Yamada SM, Brown JD (1999) Community-acquired methicillin-resistant Staphylococcus aureus in hospitalized adults and children without known risk factors. Clin Infect Dis 29:797–800
74. Boussaud V, Parrot A, Mayaud C, Wislez M, Antoine M, Picard C, Delisle F, Etienne J, Cadranel J (2003) Life-threatening hemoptysis in adults with community-acquired pneumonia due to Panton-Valentine leukocidin-secreting Staphylococcus aureus. Intensive Care Med 29:1840–1843
75. Lina G, Pienmont Y, Godail-Gamot F, Bes M, Peter MO, Gauduchon V, Vandenesch F, Etienne J (1999) Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia. Clin Infect Dis 29:1128–1132
76. Crumpacker CS (2000) Cytomegalovirus. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Douglas and Bennett’s principles and practice of infectious diseases. Churchill Livingstone, Philadelphia, pp 1586–1599
77. Salomon N, Perlman DC (1999) Cytomegalovirus pneumonia. Semin Respir Infect 14:353–358
78. Tsushima K, Koyama S, Takematsu H, Okada K, Hata S, Ichiyoshi T, Seyama K, Kubo K (1999) Massive pulmonary hemorrhage due to cytomegalovirus infection in a Japanese patient with alpha-1-antitrypsin-deficient emphysema. Respiration 66:373–376
79. Katzenstein ALA (1997) Katzenstein and Askin’s surgical pathology of non-neoplastic lung disease, 3rd edn. Saunders, Philadelphia
80. Khan AS, Khabbaz RF, Armstrong LR, Holman RC, Bauer SP, Graber J, Strine T, Miller G, Reef S, Tappero J, Rollin PE, Nichol ST, Zaki SR, Bryant RT, Chapman LE, Peters CJ, Ksiazek TG (1996) Hantavirus pulmonary syndrome: the first 100 US cases. J Infect Dis 173:1297–1303
81. Fabbri M, Maslow MJ (2001) Hantavirus pulmonary syndrome in the United States. Curr Infect Dis Rep 3:258–265
82. Peters CJ (1998) Hantavirus pulmonary syndrome in the Americas. In: Scheld WM, Craig WA, Hughes JM (eds) Emerging infections 2. ASM Press, Washington DC, pp 17–64
83. Butler JC, Peters CJ (1994) Hantaviruses and hantavirus pulmonary syndrome. Clin Infect Dis 19:387–394
84. Moolenaar RL, Breiman RF, Peters CJ (1997) Hantavirus pulmonary syndrome. Semin Respir Infect 12:31–39
85. Lee KS, Kim HJ, Chun YH, Choi HS, Lee DS, Moon J (1988) Thoracic manifestations in hemorrhagic fever with renal syndrome. J Korean Radiol Soc 24:541–545
86. Kim EA, Lee KS, Primack SL, Yoon HK, Byun HS, Kim TS, Suh GY, Kwon OJ, Han J (2002) Viral pneumonias in adults: radiologic and pathologic findings. Radiographics 22:S137–S149
87. Gasparetto EL, Davaus T, Escurriato DL, Marchiori E (2007) Hantavirus pulmonary syndrome: high-resolution CT findings in one patient. Br J Radiol 80:e21–e23
88. Ferreira MS, Nishioka S, Santos TL, Santos RP, Santos PS, Rocha A (2000) Hantavirus pulmonary syndrome in Brazil: clinical aspects of three new cases. Rev Inst Med Trop Sao Paulo 42:41–46
89. Keung YK, Nugent K, Jumper C, Cobos E (1999) Mycobacterium tuberculosis infection masquerading as diffuse alveolar hemorrhage after autologous stem cell transplant. Bone Marrow Transplant 23:737–738
90. Marruchella A, Corpolongo A, Tommasi C, Lauria FN, Narciso P (2010) A case of pulmonary tuberculosis presenting as diffuse alveolar hemorrhage: is there a role for anticardiolipin antibodies? BMC Infect Dis 10:33
91. Nakamura S, Kamioka E, Tokuda A, Tabeta H (2011) A case of miliary tuberculosis showing diffuse alveolar hemorrhage. Nihon Kokyuki Gakkai Zasshi 49:548–552