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

**Felipe Mussi von Ranke · Gláucia Zanetti ·
Bruno Hochhegger · Edson Marchiori**

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.

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,

F. M. von Ranke · G. Zanetti · B. Hochhegger ·
E. Marchiori (✉)
Department of Radiology, Federal University of Rio de Janeiro,
438 Rua Thomaz Cameron, Valparaiso, Petrópolis,
RJ CEP 25685.120, Brazil
e-mail: edmarchiori@gmail.com

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.

Diagnostic imaging consists primarily of chest radiography showing diffuse alveolar opacities, but recurrent episodes of hemorrhage may produce reticular interstitial opacities due to pulmonary fibrosis [1, 4]. High-resolution computed tomography (HRCT) findings are nonspecific and consist of bilateral areas of ground-glass opacity and/or consolidation [1, 4].

Once the diagnosis of DAH is made, the underlying cause must be established in order to initiate treatment [4]. In addition to the patient's history, other data useful for establishing the underlying diagnosis can be collected by physical examination; flexible bronchoscopy with BAL fluid analysis; chest imaging; routine laboratory studies (to detect anti-neutrophil cytoplasmic antibodies, among others); directed serologic testing for connective tissue disease, systemic vasculitis, and infectious diseases; and biopsy with histologic and immunofluorescence analyses [1, 19]. An exhaustive search should be performed for signs of systemic disease such as sinusitis, cutaneous leukocytoclastic vasculitis, iridocyclitis, synovitis, and glomerulonephritis [9]. BAL specimens should be subjected to routine stains and cultures for bacterial, mycobacterial, fungal, and viral organisms [1].

Histopathology

The histopathology of DAH is characterized by intraalveolar 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 post-partum, 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
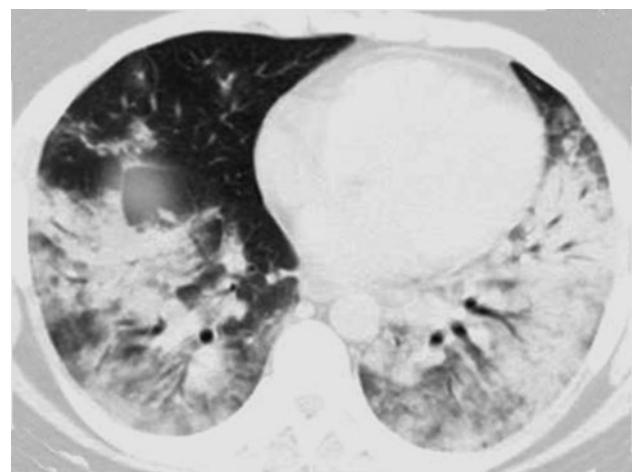
Fig. 1 A 28-year-old woman with influenza A (H1N1) virus–associated pneumonia and diffuse alveolar hemorrhage. High-resolution computed tomography exhibits consolidations and ground-glass opacities in both lower lobes

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
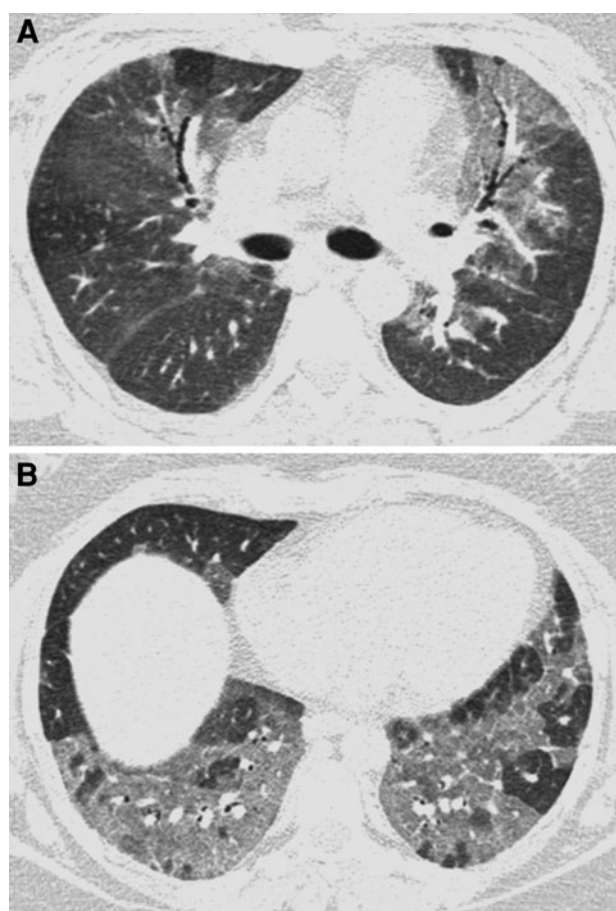
Fig. 2 A 59-year-old man with dengue hemorrhagic fever and diffuse alveolar hemorrhage. High-resolution computed tomography at the levels of the carina (**a**) and lower lobes (**b**) shows extensive areas of ground-glass opacities in both lungs

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,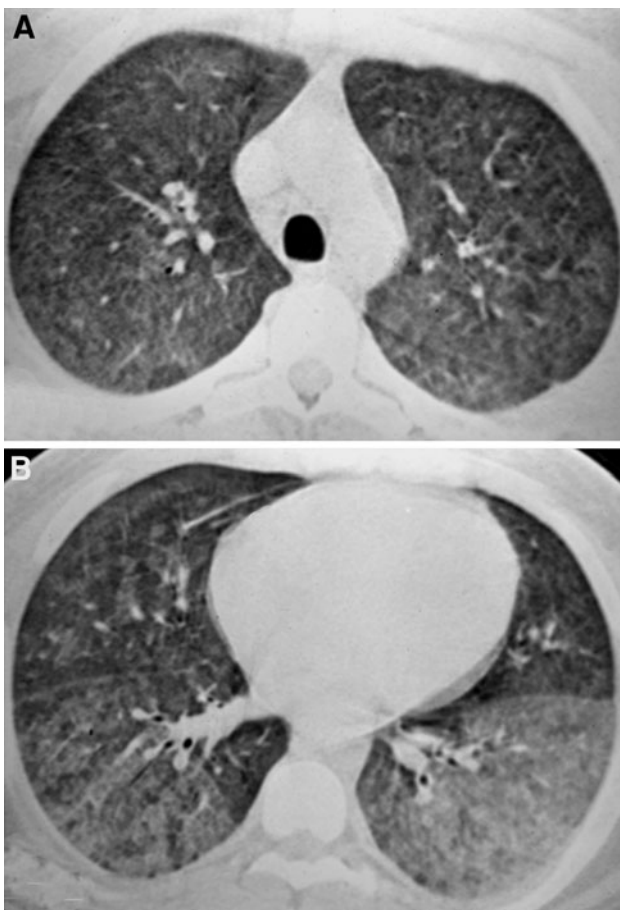 ground-glass opacities involving all lobes (Fig. 3). Areas of consolidation, peripheral airspace nodules, and pleural effusions may be present. The abnormalities involve mainly the peripheral and dorsal lung regions and the lower lung zones [48, 53]. Microscopic examination reveals extensive areas of 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].

Fig. 3 A 41-year-old man with leptospirosis and diffuse alveolar hemorrhage. High-resolution computed tomography at the levels of the upper (**a**) and lower (**b**) lobes shows bilateral ground-glass opacities in both lungs

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.

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, Schwars 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 JJ, Fartoukh M, Cadranel J (2012) 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) Cytomegalovirus-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, Tetu L, 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. Agustí C, Ramírez J, Picado C, Xaubet A, Carreras E, Ballester E, Torres A, Battochia C, Rodriguez-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, Shenep 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*. Sarcoidosis Vasc Diffuse Lung Dis 21:158–159

16. Agarwal VK, Khurana HS, Le HX, 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, Hajjar LA, Callegari GD, da Silva LF, Schout D, Galas FR, Alves VA, Malheiros DM, Auler JO Jr, Ferreira AF, Borsato MR, Bezerra SM, Gutierrez PS, Caldini ET, Pasqualucci CA, Dolhnikoff 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, Mao 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 Investigation 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, Gavali 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/webc/HPAwebFile/HPAweb_C/1258560 552857. 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, Mançano AD, Meirelles GS, Irion KL (2010) High-resolution computed tomography findings from adult patients with Influenza A (H1N1) virus-associated pneumonia. Eur J Radiol 74:93–98

28. Ajlan AM, Quiney B, Nicolaou 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, Ghorpade SV, Bharadwaj 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, Iizuka T, Nakazato I, Hino Y, Hamamatsu A, Horiguchi H, Tanaka T, Hasegawa A, Kanaya Y, Oku 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. Rosen DG, 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, Saborío 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, Glasheen 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) Dengue haemorrhagic fever: diagnosis, treatment, prevention and control, 2nd ed. Geneva: WHO Library Cataloguing in Publication Data. Available at http://www.who.int/csr/resources/publications/dengue/Dengue publication/en/. Accessed 14 March 2012

41. Sharma SK, Gupta BS, Devpura G, Agarwal A, Anand S (2007) Pulmonary haemorrhage syndrome associated with dengue haemorrhagic fever. J Assoc Physicians India 55:729–730

42. Setlik RF, Ouellette D, Morgan J, McAllister CK, Dorsey D, Agan BK, Horvath L, Zimmerman MK, Purcell B (2004) Pulmonary hemorrhage syndrome associated with an autochthonous case of dengue hemorrhagic fever. South Med J 97:688–691

43. Weerakoon KG, Kularatne SA, Edussuriya DH, Kodikara SK, Gunatilake LP, Pinto VG, Seneviratne AB, Gunasena S (2011) Histopathological diagnosis of myocarditis in a dengue outbreak in Sri Lanka, 2009. BMC Res Notes 4:268

44. Barreto DF, Takiya CM, Schatzmayr HG, Nogueira RM, Farias-Filho Jda C, Barth OM (2007) Histopathological and ultrastructural aspects of mice lungs experimentally infected with dengue virus serotype 2. Mem Inst Oswaldo Cruz 102:175–182

45. Basílio-de-Oliveira CA, Aguiar GR, Baldanza MS, Barth OM, Eyer-Silva WA, Paes MV (2005) Pathologic study of a fatal case of dengue-3 virus infection in Rio de Janeiro, Brazil. Braz J Infect Dis 9:341–347

46. Farr RW (1995) Leptospirosis. Clin Infect Dis 21:1–8

47. Luks AM, Lakshminarayanan S, Hirschmann JV (2003) Leptospirosis presenting as diffuse alveolar hemorrhage: case report and literature review. Chest 123:639–643

48. Marchiori E, Lourenço S, Setúbal S, Zanetti G, Gasparetto TD, Hochhegger B (2011) Clinical and imaging manifestations of hemorrhagic pulmonary leptospirosis: a state-of-the-art review. Lung 189:1–9

49. Arean VM (1962) The pathologic anatomy and pathogenesis of fatal human leptospirosis (Weil's disease). Am J Pathol 40:393–423

50. Dursun B, Bostan F, Artac M, Varan HI, Suleymanlar G (2007) Severe pulmonary haemorrhage accompanying hepatorenal failure in fulminant leptospirosis. Int J Clin Pract 61:164–167

51. Castro JR, Salaberry SR, Souza MA, Lima-Ribeiro AM (2011) Predominant Leptospira spp. serovars in serological diagnosis of canines and humans in the City of Uberlândia, State of Minas Gerais, Brazil. Rev Soc Bras Med Trop 44:217–222

52. Dolhnikoff M, Mauad T, Bethlem EP, Carvalho CR (2007) Pathology and pathophysiology of pulmonary manifestations in leptospirosis. Braz J Infect Dis 11:142–148

53. Marchiori E, Muller NL (2002) Leptospirosis of the lung: high-resolution computed tomography findings in five patients. J Thorac Imaging 17:151–153

54. Del Carlo Bernardi F, Ctenas B, da Silva LF, Nicodemo AC, Saldiva PH, Dolhnikoff M, Mauad T (2012) Immune receptors and adhesion molecules in human pulmonary leptospirosis. Hum Pathol 43(10):1601–1610

55. 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

56. Gouveia EL, Metcalfe J, de Carvalho AL, Aires TS, Villasboas-Bisneto JC, Queirroz A, Santos AC, Salgado K, Reis MG, Ko AI (2008) Leptospirosis-associated severe pulmonary hemorrhagic syndrome, Salvador, Brazil. Emerg Infect Dis 14:505–508

57. 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

58. Pea L, Roda L, Boussaud V, Lonjon B (2003) Desmopressin therapy for massive hemoptysis associated with severe leptospirosis. Am J Respir Crit Care Med 167:726–728

59. Tatopoulos A, Herbain D, Kazmierczak C, Bollaert PE, Gibot S (2010) Parenteral use of recombinant activated factor VII during diffuse alveolar hemorrhage secondary toleptospirosis. Intensive Care Med 36:555–556

60. Greenwood BM, Fidock DA, Kyle DE, Kappe SH, Alonso PL, Collins FH, Duffy PE (2008) Malaria: progress, perils, and prospects for eradication. J Clin Invest 118:1266–1276

61. Taylor WR, Cañon V, White NJ (2006) Pulmonary manifestations of malaria: recognition and management. Treat Respir Med 5:419–428

62. Mishral SK, Mohanty S, Mohanty A, Das BS (2006) Management of severe and complicated malaria. J Postgrad Med 52:281–287

63. Taylor WR, White NJ (2002) Malaria and the lung. Clin Chest Med 23:457–468

64. Heineman HS (1972) The clinical syndrome of malaria in the United States. Arch Intern Med 129:607–616

65. Corne P, Landreau L, Moulaire V, Jonquet O (2001) Intra-alveolar hemorrhage during Plasmodium falciparum malarial crisis. Presse Med 30:1499

66. Brooks MH, Kiel FW, Sheehy TW, Barry KG (1968) Acute pulmonary edema in falciparum malaria. N Engl J Med 279:732–737

67. Charlebois ED, Perdreau-Remington F, Kreiswirth B, Bangsberg DR, Ciccarone D, Diep BA, Ng VL, Chansky K, Edlin BR, Chambers HF (2004) Origins of community strains of methicillin-resistant Staphylococcus aureus. Clin Infect Dis 39:47–54

68. 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

69. Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T, Cai M, Hansel NN, Perl T, Ticehurst JR, Carroll K, Thomas DL, Nuermberger E, Bartlett JG (2005) Severe community-onset pneumonia in healthy adults caused by methicillin-resistant Staphylococcus aureus carrying the Panton-Valentine leukocidin genes. Clin Infect Dis 40:100–107

70. Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, Vandenesch F, Piémont Y, Brousse N, Floret D, Etienne J (2002) Association between Staphylococcus aureus strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359:753–759

71. 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 leukocidin. Int J Tuberc 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, Piemont 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, Bryan 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 JS (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, Escuissato 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 haemorrhage: 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