CLINICS IN CHEST MEDICINE

Clin Chest Med 23 (2002) 469–478

Pulmonary complications of leptospirosis

Carlos Roberto Ribeiro Carvalho, MD, PhD [a],
Eduardo P. Bethlem, MD, PhD [b,*]

[a]*Division of Respiratory Diseases, Heart Institute (InCor), University of São Paulo Medical School, Rua Maria Figueiredo 396, Apt. 141, CEP 04002-002, São Paulo, Brazil*
[b]*Division of Pulmonary Medicine, Federal University of Rio de Janeiro State, Rua General Glicério 55, Apt. 604, CEP 22245-120, Rio de Janeiro, Brazil*

Leptospirosis is a widespread zooanthroponosis that is prevalent in tropical regions due to the favorable environmental survival conditions of its etiologic agent. The agent is a pathogenic spirochete of the genus *Leptospira*. *Leptospira* are motile microorganisms, 6 to 20 μm in length and 0.1 to 0.2 μm in diameter, and are obligate aerobes with unique nutritional requirements for long-chain fatty acids [1,2]. There is a pathogenic (*Leptospira interrogans*) and a saprophytic (*Leptoospira biflexa*) strain.

The disease caused by *L interrogans* has a broad spectrum of clinical findings. *L interrogans* is classified in about 25 serotypes and over 210 serovars according to shared major agglutinins. Virulence does not generally correlate with specific serovars, although serovar classifications can be useful epidemiologically to identify common-source outbreaks. The serogroup most frequently found is the icterohaemorrhagiae and the serotype also is icterohaemorrhagiae; others found are the grippotyphosa, panama, canicola, pomona, andamana, wolfii, batavae, and australis. It seems probable that different strains can cause various clinical manifestations [2,3]. More recently, evidence based on DNA sequencing and DNA–DNA homology techniques reveal that the taxonomy of the genus *Leptospira* may be more complex than traditionally thought. At least eight distinct pathogenic species and five nonpathogenic species can be differentiated; however, for practical purposes, the serovar classification continues to be widely used [4].

Weil made the first detailed description of a severe presentation of the disease in 1886; the disorder was therefore called Weil's disease. This presentation is associated with high fever, severe hepatic malfunction, intense jaundice, hemorrhagic diathesis, renal and pulmonary dysfunction, neurological alterations, and cardiovascular collapse. In epidemic studies the great majority of infected persons who are investigated are asymptomatic or oligosymptomatic, however [5,6].

Leptospirosis has a mortality rate of about 5% [7]. The mortality rate for Weil's syndrome is high. Death in severe leptospirosis often results from acute renal failure or, eventually, from irreversible myocardial failure. Myocardiopathy probably occurs more frequently than is recognized, but cardiomyosistis is independent of peripheral myositis. Metabolic disturbances such as hypokalemia may aggravate this condition. Patients who survive these complications usually recover within 6 to 12 weeks. Although hepatic dysfunction is not directly a major cause of death it is associated with a higher incidence of complications and higher mortality. Hemorrhagic phenomena are relatively common in Weil's syndrome, and they may occur in the skin, mucosa, or internal organs. Pulmonary hemorrhages may vary from ordinary hemoptoic sputum to massive pulmonary bleeding [2,8,9].

* Corresponding author.
E-mail address: epbethlem@uol.com.br (E.P. Bethlem).

PII: S0272-5231(01)00010-7

Epidemiology

Leptospirosis is an infection transmitted among animals and occasionally from animals to humans. Asymptomatically infected wild or domestic mammals can harbor *L interrogans* for months in the proximal convoluted tubules of the kidneys. After excretion in urine, the spirochete may survive for months in the environment under favorable conditions such as a temperature of 28°C to 32°C and a neutral or slightly alkaline pH [67].

Rodents, particularly rats (*Rattus norvegicus*), are the great disseminators of the disease all over the world, although many others animals like dogs, livestock (cattle and swine), wild mammals, and cats can be infected with *Leptospira*. These animals seldom get sick but eliminate several *Leptospira* in their urine. As the organisms proliferate in surface water transmission occurs by direct or indirect contact between infected material (water or soil) and abraded skin, exposed mucous membranes, or conjunctiva. Indirect transmission occurs most frequently and comes about through contact with ground or water contaminated with the urine of infected animals. Artificial or natural collection of free water with little flow such as small brooks, ponds, river branches, dams, and marshes are the preferred habitat. In urban areas leptospirosis epidemics are related to floods caused by summer rainstorms [3,5,11–13].

Before 1970 most cases of leptospirosis occurred in occupational settings. Traditional occupational hazards have included farmers, ranchers, rice field workers, veterinarians, miners, abattoir workers, and military personnel. After 1970 the epidemiology shifted to transmission in home and recreational settings. The increase in adventure travel to exotic tropical regions means that hiking, swimming, fishing, hunting, kayaking/canoeing, and riding trail bicycles through puddles must be considered as risk factors [8,14]. In the Netherlands 14% of confirmed cases of leptospirosis reported between 1987 and 1991 were associated with foreign travel. In 1991 an outbreak occurred among five boys who had been swimming in a small pond in rural Illinois, USA. The creek that emptied into the pond drained two cattle pastures. In 1996 35% of a group of American whitewater rafters in Costa Rica met the case definition for leptospirosis, falling ill after their return to the United States. In the summer of 1998 an outbreak occurred among 9% of 110 triathlon participants from 44 states and 8 countries who swam in Lake Springfield, Illinois, USA [8,14].

In the United States human leptospirosis predominantly occurs in a sporadic pattern. The true incidence and prevalence are not known. Since 1970 $\sim$40 to 120 cases of leptospirosis have been reported to the Center for Disease Control and Prevention (CDC) annually [15]. The highest reported incidences have been in the South Atlantic, Gulf, and Pacific coastal states. Thirty of 54 cases of leptospirosis reported to the CDC in 1992 and 24 of the 51 cases reported in 1993 occurred in Hawaii [16]. The average annual incidence in the United States as a whole is 0.05 cases per 100,000 population, while the average annual incidence in Hawaii is 1.08 per 100,000 population. Reported incidences represent significant underestimation. Active, as opposed to passive, surveillance for the infection results in a fivefold increase in the incidence of the disease [8,17].

Based on serologic studies, during October and November 1993 an outbreak of acute febrile illness with hemorrhagic manifestation and pulmonary involvement occurred in Diglipur, North Andaman, India. This outbreak was the first description of leptospirosis from India [18].

In Latin America leptospirosis is more common in rural than in urban populations and occurs more frequently in men than in women. Environmental exposition to contaminated water, mainly during rainy season, is the most frequent mode of disease transmission. A high rate of infection has been found among garbage collectors (46.7%), farm workers (25.9%), butchers (24.6%), domestic employees (22.2%), and children (17.2%) [2].

In 1995 in rural Nicaragua leptospirosis was responsible for an epidemic of "hemorrhagic fever" without jaundice or renal involvement. Some patients died due to pulmonary hemorrhage. Case-control studies demonstrated that patients were more likely than controls to have ever walked in creeks (OR: 15.0), have household rodents (OR: 10.4), or own dogs with high titers (>400) of *Leptospira* species (OR: 23.4). This epidemic resulted from exposure to flood waters contaminated by urine from infected animals, particularly dogs [13].

Over the last 5 years in Venezuela the annual morbidity rate for leptospirosis—based on the number of cases confirmed nationally by serology—has ranged between 0.21 and 0.42 per 100,000 inhabitants. A mortality rate of 0.005 to 0.03 per 100,000 inhabitants and a lethality of 2.2% to 6.9% among patients has been observed [2].

In Brazil the incidence is highest during the summer, when heavy rains and floods occur in urban areas. Between 1990 and 1995 the Brazilian government officially reported 2634 new hospitalized cases (range 2396 to 4138) per year and 448 deaths (range 265 to 425) per year [19]. In São

Paulo, a city in Southeast Brazil with more than 15 million people in the metropolitan area, the Central Institute of the Hospital das Clínicas, a tertiary University Hospital with about 950 beds (150 being ICU beds), admitted 264 patients with leptospirosis between January 1991 and June 2001. This population presented the median age of 33 years (minimum 9, maximum 77), 223 being men (85,4%), and a mortality rate of 10.0% (26 patients died). The median duration of stay at the hospital was 10 days (minimum zero, maximum 42 days). About 60% of these patients were admitted to the ICU for at least 1 day and 10% needed mechanical ventilation (CRRC, unpublished data).

In Rio de Janeiro, a Brazilian city with more than 8 million people in the metropolitan area, there was a notification of 2447 cases of leptospirosis between 1996 and 1999. Clinical information was obtained in 599 patients (24.5%). Of these cases, pulmonary involvement was present in 248 (41.4%). The clinical evolution of this group (599) was obtained in 177 patients (30%). The mortality rate was 32.2% (57 patients), 46 of whom had pulmonary involvement (80.7%). These data—despite the large rate of ignored pulmonary involvement and evolution—suggest the severity of this complication in the course of leptospirosis [20].

Pathogenesis

After skin or mucosa penetration *Leptospira* organisms rapidly invade the blood and lymphatic circulation and spread throughout all sites in the body. The survival of the spirochete in the host depends upon local tissue environment (nutrients and pH) and may be influenced by pre-existing specific antibodies from previous exposure. Thus, dissemination is hematogenic. There is an incubation period of 7 to 14 days, when the *Leptospira* disseminate to different organs, especially the liver, kidneys, muscles, and lungs. Experimental data suggest that after gaining access to the bloodstream the leptospires concentrate in the liver, where they reproduce [21]. A corresponding leptospiremia is present and organisms can be recovered from blood, cerebrospinal fluid, and most tissues. Vascular injury, mainly capillary damage and hemorrhagic diathesis, are prominent features in the affected organs. Once a focus of tissue infection has developed, bacterial multiplication begins rapidly [2,22,23].

Pathogenic *Leptospira* organisms are resistant to bactericidal activity of normal serum in the absence of specific antibodies, and they resist either phagocytosis or destruction by macrophages and polymorphonuclear cells [22,24]. Spirochetes adhere to epithelial cells but do not cause any direct injury during penetration. This adherence contributes to the persistence of the microorganism in tissues (eg, kidney) leading to a carrier state [25].

The hemorrhagic diathesis seen in severe cases is not believed to be due to depletion of serum prothrombin or to thrombocytopenia. The hemorrhagic phenomena are attributed to severe vasculitis with endothelial damage, resulting in capillary injury. This lesion is considered to be the characteristic tissue alteration in leptospirosis. During the adherence of the *Leptospira* organism to cell membranes lipids of the bacterial cell wall interact with similar substances of the cell membrane. Metabolization of the host's fatty acids by leptospiral phospholipases enhances cell membrane permeability [26,27]. Toxins and enzymes produced by leptospires may contribute to their pathogenicity. The clinical and pathological features of infection have suggested the presence of an endotoxin, but these substances have not been isolated [8].

The hepatic lesions may be directly mediated or be caused by toxins, and the jaundice mechanism appears to be similar to that of other septicemias. The participation of hemolysis does not appear to play a role in humans. Pathological studies of the liver show only slight or focal hepatocellular necrosis. Results of histochemical studies suggest that the fundamental hepatic lesion is due to a subcellular effect on enzyme systems [8].

Acute renal failure in leptospirosis is the result of tubular damage, frequently in the absence of interstitial inflammation. A pre-renal component due to dehydration, hypovolemia, hypotension, eventual hemorrhages, and low cardiac output (myocarditis or plasma sequestration) may also play a role in renal insufficiency. Histopathological features include tubular epithelial cell necrosis, foci of vasculitis, and lymphocytic infiltrates. Hypoxia secondary to renal ischemia is the fundamental alteration causing nephropathy in patients with leptospirosis. Initially leptospires can be detected in capillary lumen, subsequently reaching the interstitium, causing edema and inflammatory infiltrate. In fatal cases acute tubular necrosis and focal interstitial nephritis can be found [3,8,28].

Pulmonary lesions are primarily hemorrhagic rather than inflammatory. Focal or diffuse areas containing alveoli filled with erythrocytes characterize the pulmonary involvement observed in leptospirosis, but the mechanism of endothelial lesion is not clear. Two principal hypotheses are presented. The

first indicates a direct action of the spirochete on the membrane of parenchymal cells, initially by intact leptospires and then of their granular products of degradation by macrophages. The affinity of the antigenic material for cell membranes suggests an interaction with surface proteins. This action may first cause functional disorders of these membranes, leading only latter to necrosis. Vascular damage may be due to the same process that occurs in endothelial cells [28]. The second hypothesis is related to the undefined leptospiral toxin that causes endothelial damage to pulmonary capillaries, leading to increased permeability [29]. It has been demonstrated that patients with severe leptospiral infection with kidney, liver, and lung involvement have significantly higher levels of circulating tumor necrosis factor-alpha (TNF-α) compared to patients without these complications [21–23,28–31].

There is no clinical, laboratory, or histopathologic evidence for the occurrence of disseminated intravascular coagulation (DIC) in human leptospirosis, and if this phenomenon does occur, it is rare in human disease [28].

Clinical presentation

The disease has two classical forms of presentation: the icteric and anicteric forms. The anicteric form is more common and less severe [32], with >90% of patients having a clinically mild anicteric illness that resolves spontaneously. The jaundice, when present, is more characteristically rubinic with conjunctival congestion associated with intense myalgias, especially in the calves. The clinical manifestations may be extremely variable, ranging from flu-like symptoms with mild constitutional complains like fever, headache, myalgias, and gastrointestinal complaints to a severe presentation with the complete Weil's syndrome and sometimes with acute respiratory distress syndrome (ARDS). The icteric form has a classic biphase presentation. The first phase, also called the septicemic stage, is characterized by a sudden onset of intense symptomatology lasting $\sim$5 days. After an asymptomatic period of 24 to 48 hours a posterior variable immunologic stage develops with the appearance of antileptospira IgM antibodies in the serum and a return of symptomatology during days 7 through 30 days. Aseptic meningitis and a reduction of fever and constitutional symptoms might occur at this stage [3,33].

The true incidence of pulmonary involvement in leptospirosis is not known, but it may range from 20% to 70% [33]. The pulmonary involvement may have two forms: a benign form, in which the patient recovers without sequelae, and a severe form that may be fatal [3]. Pulmonary involvement is usually incidental and mild in the course of the disease, but, on the other hand, it may be a prognostic factor associated with mortality [34–36]. The anicteric form is much more common and less severe, although this does not mean that it is not associated with severe renal and pulmonary compromise [33]. Anicteric cases with severe, frequently fatal hemoptysis have been reported from China with an association with *L icterohaemorrhagiae* serovar *Lai* and pulmonary involvement, but they were not confirmed by Singh et al [37]. The incidence of pulmonary involvement in the icteric and anicteric forms is still a controversial issue [33,38,39].

In Brazil—especially in Rio de Janeiro—after a long period of rainstorms initiated in 1988, epidemic cases became more frequent. Current local practice doctors believed that the disease was changing, with a more frequent and severe pulmonary manifestation (Figs. 1, 2) [40,41].

Diagnosis

The diagnosis of leptospirosis is based on the epidemiologic history, clinical manifestation, and laboratory findings. *Leptospira* identification by dark field microcopy has a low sensibility in much material [3]. Long and helicoidal agents, strongly suggesting leptospires in suspected cases, can be detected by direct examination with dark field methods in bronchoalveolar lavage while screening for nosocomial infection in patients who are mechanically ventilated [41]. Silver impregnation or immunofluorescence can further demonstrate *Leptospira* in tissues. *Leptospira* needs special culture media (Fletcher, Stuart, and Tween 80) and has a slow growth rate. Samples of blood, liquor, and urine are used. Hemocultures should be performed until the seventh day. Because the elimination of *Leptospira* in the urine is intermittent it is advisable to take several samples, even in the immunologic stage of the disease. Serology with macro- or microscopic agglutination is the most common method of diagnosing leptospirosis. Immunoglobulin G (IgG) and ELISA have shown similar results to microagglutination, and the IgM ELISA can be positive from the fifth day onward. Seroconversion in positive cases is observed with at least a fourfold rise in microagglutination titer [2,3,5,43].

In endemic areas bronchoalveolar lavage can be useful for an early diagnosis of pulmonary hem-

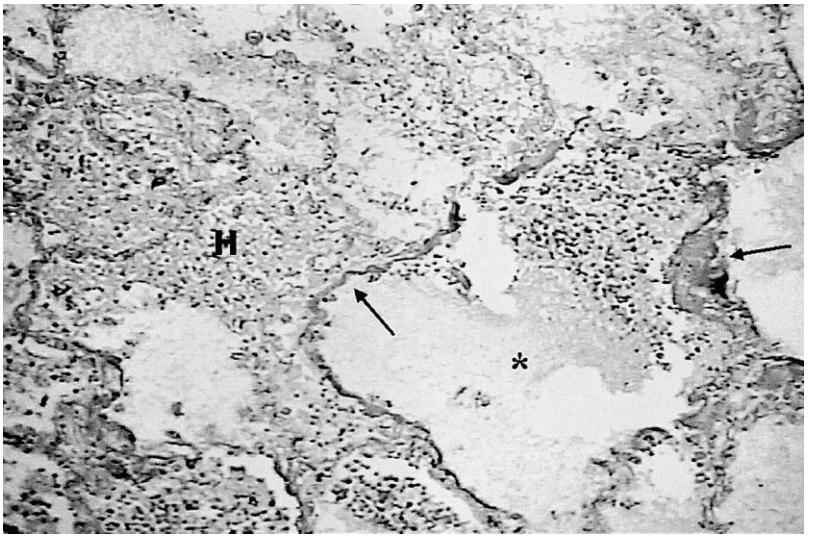

Fig. 1. Necropsy specimen of lung parenchyma with alveolar hemorrhage (**H**) and diffuse alveolar damage characterized by alveolar edema (*) and hyaline membrane (*arrows*) of a patient who died of ARDS associated with leptospirosis. (Courtesy of Marisa Dohlnikoff, Department of Pathology, University of São Paulo, Brazil.)

orrhage in individuals with a positive epidemiologic history for leptospirosis, during an investigation of community acquired pneumonia, and in patients with acute renal failure who presenting with or without jaundice. Besides the hemorrhagic aspect of the lavage, the presence of a high number of siderophages may be useful for the diagnosis [42,44].

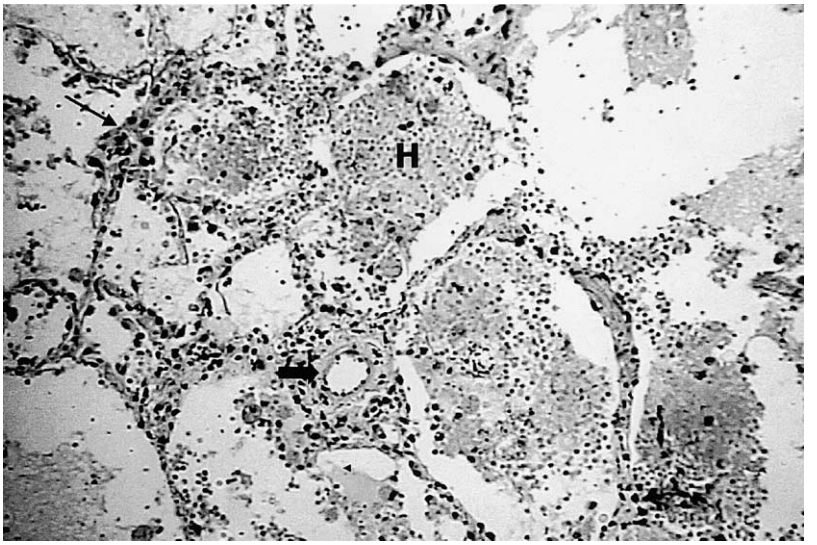

Fig. 2. Necropsy specimen of lung parenchyma with alveolar hemorrhage (**H**) and capillaritis. Observe the presence of inflammatory cells within alveolar septa (*thin arrow*), and surrounding a small arteriole (*thick arrow*) in a patient who died of alveolar hemorrhage secondary to leptospirosis. (Courtesy of Marisa Dohlnikoff, Department of Pathology, University of São Paulo, Brazil.)

Lung involvement

The first publication of lung involvement in leptospirosis is attributed to Moeschlin in 1943. There is a large spectrum of pulmonary manifestations ranging from mild respiratory symptoms to the presence of ARDS. Cough (either dry or productive of bloodstained sputum), hemoptysis, and different grades of dyspnea are the most common pulmonary symptoms, although they are not always correlated with the radiograph involvement [1,3,33,38,39,45].

Pulmonary examination may be normal or reveal the presence of rales at the bases or dyspnea, which is more often found in association with significant hemoptysis and extensive pulmonary involvement possibly associated with cyanosis [33]. With a good evolution most patients are asymptomatic in 15 days, but patients with severe pulmonary involvement and major hemoptysis can die in less than 24 hours.

Alveolar hemorrhage is a common finding, possibly secondary to capillary endothelium damage with different grades of interstitial and alveolar hemorrhage. While performing bronchoalveolar lavage Du Couedic and colleagues found that alveolar hemorrhage was present in all patients with signs of pulmonary involvement and in 7 of 10 patients without any respiratory symptoms [42]. There is an absence of significant inflammation in areas of hemorrhage [30,46,47]. Moreover, in a study in Nicaragua pulmonary hemorrhage was described with no renal failure or jaundice [13].

Sometimes pulmonary edema, which is probably secondary to myocarditis, might be found [48]. Lung involvement might not be due to hypervolemia consequent to oliguric acute renal failure since no association was found between oliguria and pulmonary rales in a recent study [35].

Yersin and colleagues concluded that pulmonary hemorrhage was a main cause of death in hospitalized patients with leptospirosis in Seychelles [49].

Martinez-Garcia and colleagues have shown that cigarette smoking is a risk factor for the development of pulmonary involvement in human leptospirosis [50].

In a prospective cohort study over 4 years (1994 to 1997) 690 patients (81% male) with leptospirosis were hospitalized. Forty-two consecutive patients with acute lung injury who were mechanically ventilated were analyzed. Fresh blood specimens were aspirated from endotracheal tubes in all patients after intubation. These patients were older than the group without respiratory failure. Nineteen patients (45%) survived and 23 (55%) died, 21 due to multiple organ failure and massive pulmonary hemorrhage. The other two died of nosocomial infections. Multivariate analysis revealed that three variables were independently associated with mortality: hemodynamic disturbance (OR: 6.0, 95% CI = 0.9–38.8, $P = 0.047$), serum creatinine level >265.2 μmol/L (OR: 10.6, CI = 0.9–123.7, $P = 0.026$), and serum potassium level >4.0 mmol/L (OR: 19.9, CI = 1.2–342.8, $P = 0.009$). These observations can be used to identify factors associated with mortality early in the course of severe respiratory failure in leptospirosis [51].

Radiographic abnormalities are more common at the bases and lung periphery [33]. Involvement of apices and hilar areas are uncommon [38,39,47]. The radiographic pattern is similar of those of other pulmonary hemorrhagic syndromes, with a patchy alveolar infiltration that can conglomerate in evolution, especially in patients who have severe pulmonary hemorrhage with massive hemoptysis (Fig. 3) [38,47]. Accentuated marking of the lungs is also a common radiographic finding [47], but others patterns like interstitial infiltration, ground glass appearance, and pleural effusion are not commonly reported [33,38]. The radiographic manifestation is almost always bilateral, but an unusual case of unilateral leptospiral pneumonia in a 5-year-old girl was described recently [52]. The radiographic manifestation may be seen as early as the first 24 hours, during the septicemic stage of the disease, but *Leptospira* are only occasionally identified in lung tissues [42,46] or in the bronchoalveolar lavage fluid [44]. This may indicate a different pathogenesis of organ injury [37]. Acute respiratory failure (ARF) and ARDS have also been reported [40,41,53–56].

ARDS and alveolar hemorrhage are two of the most fatal conditions in leptospirosis (Figs. 1, 2). This association has been recognized in the last 20 years [56,57], but the etiology of ARDS has not been entirely explained and the neutrophil-mediated mechanism is less probabe given the lack of inflammation noted in pathologic studies [33]. The possibility of a Jarisch–Herxheimer reaction must be considered [29]. ARDS and severe hemoptysis are both important causes of death today in Brazil, although they were infrequent before 1988 [2].

Others forms of pulmonary edema, like those secondary to myocarditis, renal failure, and overrehydration for resuscitation have also been reported and must be differentiated [23,33,48,58–60]. It is also important to make a differential diagnosis with the pulmonary Hantavirus syndrome [41].

Some abnormalities found in lung function tests are intra-pulmonary shunt, hypoxemia, hyperventilation with hypocarbia, and normal steady-state dif-

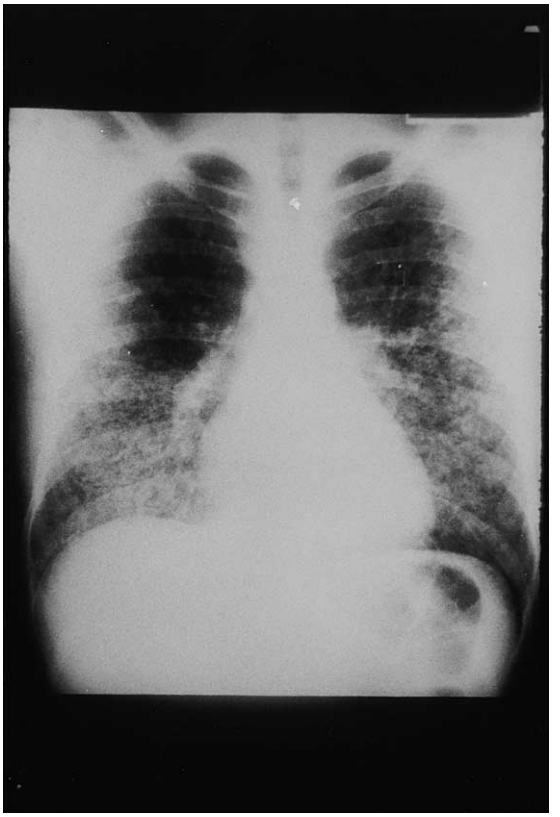

Fig. 3. Chest radiograph showing bilateral alveolar pulmonary infiltration in a patient with leptospirosis (pulmonary hemorrhage).

fusion capacity of carbon monoxide, which is consistent with intra-alveolar hemorrhage [57].

Treatment

The great majority of cases need no specific treatment once the disease recovers spontaneously. The prompt correction of dehydration, hypovolemia, hypotension, and electrolyte abnormalities are extremely important. The correct treatment of severe manifestations with renal and hepatic dysfunction or ARF (or both) may decrease the mortality rate. The use of antibiotics is controvertible. Most authorities agree that if antibiotics are not started early in the disease (up to the fourth day) they do not change the course of the illness. At this early time, the specific diagnosis may be difficult and therefore antibiotics end up not being used very frequently. On the other hand, some studies show good results even in the immunologic stage of the disease [5,61]. Penicillin G 100,000 U/kg/24 hours (given in divided doses every 3 to 4 hours) or tetracycline 25 to 40 mg/kg/day (given in divided doses every six hours) or, preferentially, doxycycline at a dosage of 100 mg orally, twice daily over 7 days is the most effective drug regimen [2,62].

Recently a systematic review from the Cochrane Foundation was presented that was based on randomized clinical trials (RCT) evaluating the effectiveness and safety of antibiotics versus placebo or other antibiotic regimens in treating leptospirosis. Only three studies met the inclusion criteria. Of the patients enrolled, 75 were treated with placebo and 75 with antibiotics, 61 (81.3%) with penicillin and 14 (18.6%) with doxycycline [10,61]. Despite the absence of RCTs that compared each antibiotic regimen to other antibiotic regimens the reviewers concluded that there is insufficient evidence to provide clear guidelines for administration of an antibiotic regimen for the treatment of leptospirosis. The randomized trials suggest that the use of antibiotics (penicillin and doxycycline) for the treatment of leptospirosis could be useful, causing more good

than harm, although the indication for general use of these antibiotics is uncertain [63].

In mild and moderate forms of the illness patients must receive symptomatic therapy, mainly intravenous hydration. In the most severe forms of the illness patients must be admitted to the ICU to undergo respiratory, hemodynamic, and renal assistance or other life-supporting measures.

Today lung involvement is responsible for the most fatal conditions. Pulmonary hemorrhage and ARDS are the main causes of death in the most recently presented cases [28,34,40,41,49,50,53,55, 64]. Recently, the use of mechanical ventilation applying lung protective strategies based on the use of low tidal volumes demonstrated a significant reduction in mortality among ARDS patients [53,65,66]. In a prospective randomized study conducted in Brazil, the use of high levels of positive-end expiratory pressure, according to the inflection point of the pressure $\times$ volume curve of the respiratory system (associated with small tidal volumes), demonstrated very good results. This trial compared two different modes of mechanical ventilation, conventional and lung-protective strategies. The authors described 8 patients with leptospirosis associated with ARDS. Four patients were treated in a conventional method with a high tidal volume and a positive-end expiratory pressure level high enough to maintain an inspired oxygen fraction $< 60\%$; all patients died. Another four patients were ventilated in a protected strategy with small tidal volumes (≤ 6 mL/kg) and high positive-end expiratory pressure levels (>15 cm H_2O). Only one patient died, due to CNS bleeding [53,67]. In spite of the permissive hypercapnia and the high mean airway pressure observed, because high positive-end expiratory pressure was applied no deleterious hemodynamic compromise occurred, demonstrating a safety of this strategy [66].

The successful use of others strategies have been described recently, like nitric oxide inhalation and hemofiltration in a patient with massive pulmonary hemorrhage and respiratory failure [68]. This strategy and new forms of management of pulmonary involvement must be tested in the future to obtain better control of this fatal complication of leptospirosis.

Prophylaxis

Prophylaxis for leptospirosis is a difficult task. Good sanitary measures and special recommendations about some specific professional activities may be useful. Animal and humans vaccination studies are still underway. In certain special circumstances, chemoprophylaxis may be used [3].

Doxycycline is widely used for prevention in clinical practice. A systematic review was performed recently by the Cochrane Foundation to evaluate the effectiveness and safety of any antibiotic regimen versus placebo or other antibiotic regimens in the prophylaxis of leptospirosis. All RCTs were evaluated, but only two were selected according to the inclusion criteria. Both compared doxycycline with placebo. The number of patients enrolled were 1022; 509 were treated with doxycycline and 513 were treated with placebo. In one trial 940 participants were soldiers. The randomized trials suggest that prophylaxis of leptospirosis may be achieved by administrating doxycycline to soldiers training in endemic areas with a high risk of exposure to *Leptospira*. Whether these findings apply to other scenarios remains to be proven [7].

Summary

Leptospirosis is a worldwide disease. In this time of globalization knowledge about leptospirosis is important. Although pulmonary involvement has an incidence varying from 20% to 70% and its exteriorization may vary from mild to severe, The severe form appears to be becoming more prevalent (at least in Brazil) and may be associated with higher mortality.

Acknowledgments

We would like to thank Professor Om P. Sharma for his kindly invitation and review of the manuscript, and Dr. Suelene A. Franca for her helpful comments.

References

[1] Farrar WE. Leptospira species. In: Mandell GL, Douglas RG Jr, Bennett JE, editors. Principles and practice of infectious diseases. 2nd edition. New York: John Wiley and Sons; 1985. p. 1338–41.
[2] Lomar AV, Diament D, Torres JR. Leptospirosis in Latin America. Infect Dis Clin N Am 2000;14:23–39.
[3] Bethlem N, Lemle A, Pereira NG. Leptospirosis. Semin Respir Med 1991;12:58–67.
[4] Zuerner RL, Bolin CA. Differentiation of Leptospira interrogans isolates by IS1500 hybridization and PCR assays. J Clin Microbiol 1997;35:2612–7.
[5] Bethlem EP, Carvalho CRR. Pulmonary leptospirosis. Curr Opin Pulm Med 2000;6:436–41.
[6] Weil A. Veber eine eigenthumliche, milmilztumor,

icterus and nephritis einhergehende, acute infection-skrankheit. Dtsch Arch Klin Med 1886;39:209 [article in German].
[7] Guidugli F, Castro AA, Atallah NA. Antibiotics for preventing leptospirosis (Cochrane Review). In: The Cochrane Library. Issue 3. Oxford: Update Software; 2001.
[8] Farr RW. Leptospirosis. Clin Infect Dis 1995;21:1–8.
[9] Feigin RD, Anderson DC. Human leptospirosis. Crit Rev Clin Lab Sci 1975;5:413–65.
[10] Guidugli F, Castro AA, Atallah NA. Antibiotics for leptospirosis (Cochrane Review). In: The Cochrane Library. Issue 3. Oxford: Update Software; 2001.
[11] Andrade J, Brandão AP. Contribuição ao conhecimento da epidemiologia da leptospirose humana com especial referência ao Grande Rio, Brasil, de 1970 a 1982. Mem Inst Oswaldo Cruz 1987;82:91 [article in Portuguese].
[12] Feigin RD, Anderson DC. Leptospirosis. In: Feigin RD, Cherry JD, editors. Textbook of pediatrics infectious disease, 2nd edition. Philadelphia: WB Saunders, 1987, p. 1190.
[13] Trevejo RT, Rigau-Pérez JG, Ashford DA, McClure EM, Jarquín-González C, Amador JJ, et al. Epidemic leptospirosis associated with pulmonary hemorrhage—Nicaragua, 1995. J Infect Dis 1998;178:1457–63.
[14] Freedman DO, Woodall J. Emerging infectious diseases and risk to the traveler. Med Clin North Am 1999;83:865–83.
[15] Centers for Disease Control and Prevention. Graphs and maps for selected notifiable diseases in the United States. MMWR Morb Mortal Wkly Rep 1994;42:13–64.
[16] Centers for Disease Control and Prevention. Graphs and maps for selected notifiable diseases in the United States, 1993. MMWR Morb Mortal Wkly Rep 1994;42:1–12.
[17] Sasaki DM, Pang L, Minette HP. Active surveillance and risk factors for leptospirosis in Hawaii. Am J Trop Med Hyg 1993;48:35–43.
[18] Sehgal SC, Murhekar MV, Sugunan AP. Outbreak of leptospirosis with pulmonary involvement in north Andaman. Indian J Med Res 1995;102:9–12.
[19] DATASUS. Ministério da Saúde. Sistema Único de Saúde (SUS). Sistema de Informação Hospitalar, 1998. Available at: http://www.datasus.gov.br. November 2001.
[20] SINAN–SUS/RJ. Sistema Nacional de Notificação—Sistema Único de Saúde/Rio de Janeiro. Secretaria Municipal de Saúde: notificação dos casos de leptospirose. 2000.
[21] DeBrito T, Bohm GM, Yasuda PH. Vascular damage in acute experimental leptospirosis of the guinea pig. J Pathol 1979;128:177–82.
[22] Arean VM, Sarasin G, Green JH. The pathogenesis of leptospirosis: toxin productions by Leptospira icterohaemorrhagiae. Am J Vet Res 1964;25:836–43.
[23] DeBrito T, Morais CF, Yasuda PH, Lancelloti CP, Shimizu S, Yamashiro E, et al. Cardiovascular involvement in human and experimental leptospirosis: pathologic findings and immunohistochemical detection of leptospiral antigen. Ann Trop Med Parasitol 1987;81:207–14.
[24] Cinco M, Banfi E, Soranzo MR. Studies on the interactions between macrophages and leptospires. J Gen Microbiol 1981;124:409–13.
[25] Vihn T, Adler B, Faine S. Glycolipoprotein cytotoxin from Leptospira interrogans serovar copenhageni. J Gen Microbiol 1984;18:73–85.
[26] Alves VAF, Gayotto LCC, Yasuda PH. Leptospiral antigen in the kidney of experimentally infected guinea pigs and their relation to the pathogenesis of renal injury. Exp Pathol 1991;42:81–93.
[27] Volina EG, Levina LF, Soboleva GL. Phospholipase activity and virulence of pathogenic leptospirae. J Hyg Epid Microb Im 1986;2:163–9.
[28] Nicodemo AC, Duarte MIS, Alves VAF, Takakura CFH, Santos RTM, Nicodemo EL. Lung lesions in human leptospirosis: microscopic, immunohistochemical, and ultrastructural features related to thrombocytopenia. Am J Trop Med Hyg 1997;56:181–7.
[29] Emmanouilides CE, Kohn OF, Garibaldi R. Leptospirosis complicated by a Jarisch–Herxheimer reaction and adult respiratory distress syndrome: case report. Clin Infect Dis 1994;18:1004–6.
[30] Edwards G, Domm BM. Human leptospirosis. Medicine (Baltimore) 1960;39:117–56.
[31] Pereira MM, Andrade J, Marchevsky RS, Ribeiros dos Santos R. Morphological characterization of lung and kidney lesions in C3H/HeJ mice infected with Leptospira interrogans serovar icterohaemorrhagiae: defect of CD4+ and CD8+ T-cells are prognosticators of the disease progression. Exp Toxicol Pathol 1998;50:191–8.
[32] Vieira A, Barros MS, Valente C, Trindade L, Faria MJ, Freitas F. Leptospirose humana. Breves considerações a propósito de uma casuística. Acta Med Port 1999;12:331–40 [article in Spanish].
[33] O'Neil KM, Rickman LS, Lazarus AA. Pulmonary manifestations of leptospirosis. Rev Infect Dis 1991;13:705–9.
[34] Coutin JP, Di Francia M, Du Couedic L, Poubeau P, Mahe C, Bapteste J, et al. Respiratory manifestations of leptospirosis. A retrospective study of 91 cases (1978–1984). Rev Pneumol Clin 1998;54:382–92.
[35] Daher E, Zanetta DM, Cavalcante MB, Abdulkader RC. Risk factors for death and changing patterns in leptospirosis acute renal failure. Am J Trop Med Hyg 1999;61:630–4.
[36] Dupont H, Dupont-Perdrizet D, Perie JL, Zehner-Hansen S, Jarrige B, Daijardin JB. Leptospirosis: prognostic factors associated with mortality. Clin Infect Dis 1977;25:720–4.
[37] Singh SS, Vijayachari P, Sinha A, Sugunan AP, Rasheed MA, Sehgal SC. Clinico-epidemiological study of hospitalized cases of severe leptospirosis. Indian J Med Res 1999;109:94–9.
[38] Im JG, Yeon KM, Han MC, Kim CW, Webb WR, Lee JS, et al. Leptospirosis of the lung: radiographic findings in 58 patients. Am J Roentgenol 1989;152:955–9.

[39] Lee REJ, Terry SI, Walker TM, Urquhart AE. The chest radiograph in leptospirosis in Jamaica. Br J Radiol 1981;54:939–43.
[40] Gonçalves AJR, Carvalho JEM, Silva JBG, Rozembaum R, Vieira ARM. Hemoptises e síndrome de angústia respiratória do adulto como causas de morte na leptospirose. Mudanças de padrões clínicos e anatomopatológicos. Rev Soc Bras Med Trop 1992;25:261–70 [article in Spanish].
[41] Carvalho JEM, Marchiori ES, Silva JBG, Souza Netto BA, Tavares W, Paula AV. Comprometimento pulmonar na leptospirose. Rev Soc Brazil Med Trop 1992;25: 21–30 [article in Spanish].
[42] Du Couedic L, Courtin JP, Poubeau P, Tanguy B, Di Francia M, Arvin-Berod C. Comprometimento pulmonar na leptospirose. Rev Soc Brasil Med Trop 1992;25: 21–30 [article in Spanish].
[43] Cumberland P, Everard COR, Levett PN. Assessment of the efficacy of an IgM-Elisa and microscopic agglutination test (MAT) in the diagnosis of acute leptospirosis. American Society of Tropical Medicine and Hygiene 1999;61:731–4.
[44] Paganin F, Gauzere BA, Lugagne N, Blanc P, Roblin X. Bronchoalveolar lavage in rapid diagnosis of leptospirosis. Lancet 1996;347:1483–4.
[45] Poh SC, Soh CS. Lung manifestations in leptospirosis. Thorax 1970;25:751–5.
[46] Silverstein CM. Pulmonary manifestations of leptospirosis. Radiology 1953;61:327–34.
[47] Wang CP, Chi CW, Lu FL. Studies on anicteric leptospirosis. III. Roentgenologic observations of pulmonary changes. Chin Med J (Engl) 1965;84:298–306.
[48] Ramachandran S, Perera MVF. Cardiac and pulmonary involvement in leptospirosis. Trans R Soc Trop Med Hyg 1977;71:56–9.
[49] Yersin C, Bovet P, Mérien F, Clément J, Laille M, Ranst MV. Pulmonary haemorrhage as a predominant cause of death in leptospirosis in Seychelles. Trans R Soc Trop Med Hyg 2000;94:71–6.
[50] Martinez-García MA. Pulmonary involvement in leptospirosis. Eur J Clin Microbiol Infect Dis 2000;19: 471–4.
[51] Marotto PC, Nascimento CMR, Eluf-Neto J, Marotto MS, Andrade L, Sztajnbok J, et al. Acute lung injury in leptospirosis: clinical and laboratory features, outcome, and factors associated with mortality. Cin Infect Dis 1999;29:1561–3.
[52] Bowsher B, Callaham CW, Pearson DA, Ruess L. Unilateral leptospiral pneumonia and cold agglutinin disease. Chest 1999;116:830–2.
[53] Amato MBP, Barbas CSV, Medeiros DM, Magaldi RB, Schettino GPP, Lorenzi-Filho G, et al. Effect of a lung protective approach on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–54.
[54] Chee HD, Ossenkoppele GJ, Bronsveld W, Thijs LG. Adult respiratory distress syndrome in Leptospira icterohaemorrhagiae infection. Intensive Care Med 1985; 11:254–6.
[55] Kiatboonsri S, Vathesatogit P, Charoenpan P. Adult respiratory distress syndrome in Thai medical patients. Southeast Asian J Trop Med Public Health 1995;26: 774–80.
[56] Zaltzman M, Kallenbach JM, Goss GD, Lewis M, Zwi S, Gear JHS. Adult respiratory distress syndrome in Leptospira canicola infection. BMJ 1981;283:519–20.
[57] Nery LE, De Paula AB, Nakatani J, dos Santos ML, Ratto OR. Clinical, radiological and functional pulmonary manifestations in patients with leptospirosis. Rev Inst Med Trop Sao Paulo 1977;19:366–73.
[58] Guivarch G, LeGall JR, Regnier B, Jardin F. Etats de choc au cours des Leptospiroses ictero-hemorragiques. Quatre observations. Nouv Press Med 1982;11:837–9 [article in French].
[59] Lee MG, Shar G, Diansumba S, Prussia P. Cardiac involvement in severe leptospirosis. West Indian Med J 1986;35:295–300.
[60] Lin C, Ma TL, Chen YC, Cheng WJ. Studies on anicteric leptospirosis. II. Observations on electrocardiograms. Chin Med J (Engl) 1965;84:291–8.
[61] Klein NC, Cunha BA. New uses of older antibiotics. Med Clin North Am 2001;85:125–32.
[62] Shieh WJ, Greer P, Ferebee T, Goldsmith C, Guarner J, Zali SR. The role of pathology in studies of emerging infectious diseases associated with acute respiratory distress syndrome. Int Conf Emerg Infect Dis 1998; 75:8–11.
[63] Amato MBP, Barbas CSV, Carvalho CRR. Protective ventilation for the acute respiratory distress syndrome. N Engl J Med 1998;339:196–9.
[64] The Acute Respiratory Distress Syndrome Networork. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. New Engl J Med 2000;342:1301–8.
[65] Amato MBP, Barbas CSV, Medeiros RB, Schettino GPP, Lorenzi-Filho G, Kairalla RA, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med 1995;152:1835–46.
[66] Carvalho CRR, Barbas CV, Medeiros DM, Magaldi RB, Lorenzi-Filho G, Kairalla RA, et al. Temporal hemodynamic effects of permissive hypercapnia associated with "ideal PEEP" in ARDS. Am J Respir Crit Care Med 1997; 156:1458–66.
[67] Borer A, Metz I, Gilad J, Riesenberg K, Weksler N, Weber G, et al. Massive pulmonary haemorrhage caused by leptospirosis succesfully treated with nitric oxide inhalation and haemofiltration. J Infect 1999;38: 42–5.
[68] Watt G. Current opinion in infectious disease 1992; 5:659–63.