Legionnaire's disease – a subject review

Ana Martins

Abstract

Legionnaires' Disease was initially described during a pneumonia outbreak among delegates of an American Legion convention in 1976. Its true importance only became evident years later. As diagnostic tests evolved enabling a better understanding of this infection epidemiology, Legionella became progressively recognized as an important cause of community-acquired as well as nosocomial pneumonia.

Key words: Legionella, legionellosis, nosocomial, pneumonia, prophylaxis.

HISTORICAL INTRODUCTION

In the summer 1976, 182 members of the American Legion developed acute respiratory infections of variable clinical severity; twenty-nine of them died. Epidemiological and microbiological studies were conducted within six months of the outbreak. The origin of the disease remained unclear, given the lack of laboratory support for environmental investigations at that time.[1]

In four of the fatal cases, a bacterium known as *Legionella pneumophila* (*LP*) was later isolated in samples of lung tissue. Through the epidemiological and clinical description, this agent was retrospectively associated with other outbreaks of pneumonia,[2] like those that occurred in a meat packing plant in Minnesota in 1957,[3] and at the St. Elizabeth Hospital in 1965.[1]

Thus, LP pneumonia was historically linked to the 58th Annual Congress of the American Legion, held at the Bellevue-Stratford Hotel in Philadelphia in 1976.[2,4,5]

Portugal is part of the European Working Group for Legionella Infections Study (known by its acronym EWGLI) established in 1986, which seeks to ensure the surveillance of the Legionnaires' disease in Europe.[6] In 1987, the EWGLI founded the European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET).[7]

Fonseca Ferreira Unit, São Bernardo Hospital
Centro Hospitalar de Setúbal E.P.E.

Received for publication on the 8th January 2008
Accepted for publication on the 30th September 2008

The LP bacterium can cause two distinct diseases: Pontiac fever, a febrile disease of benign and self-limited course, and Legionnaire's disease,[2,8,9] which we shall discuss in this review.

MICROBIOLOGY

Legionella is a gram negative, aerobic, catalase-positive and weakly oxidase-positive bacterium.

It does not grow anaerobically or in the usual media, but requires a treated medium called BCYEA (buffered charcoal yeast extract agar) in order to grow under conditions of aerobiosis.[2]

The Legionellaceae family consists of 42 species, constituting 64 serogroups.[2,4] Less than half of these species cause diseases in humans.[4] *Legionella pneumophila (LP)* is the most pathogenic of the species, causing 90% of cases of legionellosis, followed by *L.micdadei, L. bozemanii, L. dumoffii* and *L. longbeachae*.[2,4,10]

We identified more than 14 serogroups of *LP*, with serogroups 1, 4 and 6 being the main cause of diseases in humans.[2, 4, 10]

The serogroup 1 accounts for 80% of cases of legionellosis caused by LP.[2,5] There is a difference between strains in terms of the degree of aggressiveness, and one of the aspects that leads to increased aggressiveness is the presence of a flagellum, which enables it to adhere to the pulmonary cells.[2-4]

The main reservoir of *Legionella* in the environment is water. It can infect and reproduce within protozoa, such as species of *Acanthamoeba* and *Hartmanella*, amoebae that are found in natural and artificial aquatic environments.[2-4] These amoebae, in addition to acting as a reservoir, increase the resistance of *Legionella* in adverse conditions, such as in hot water systems.[3]

Legionella parasitised these amoebas, avoiding the endosomal pathway and reproducing inside the phagosome. It uses the same mechanism in macrophages and monocytes when infecting humans.[2,3]

RESERVOIR

Legionella can be found in natural aquatic environments (lakes, rivers) and artificial aquatic environments (water supply systems, air conditioning and aerosol devices).[6,8]

The favorable environment for the growth of this microorganism is a stagnate aquatic environment, with temperatures of between 25-42ºC and nutrients and amoebae capable of supporting intracellular reproduction.[2,6,9]

It can colonize water storage tanks, pipes, showers, cooling towers of air conditioning systems, etc. It colonizes approximately 1-30% of regular hot water systems.[9]

A species of *Legionella*, – *L. longbeachae* – has been isolated in soil.[8,9,11]

EPIDEMIOLOGY

Infection by *Legionella spp* is an important cause of community-acquired pneumonia and nosocomial pneumonia, and may occur sporadically or in outbreaks. It is estimated to be one of the two leading causes of community-acquired pneumonia and is isolated in about 40% of nosocomial pneumonias. Only about 2% to 10% of cases are reported.[12]

The incidence of Legionnaire's disease depends on several factors, such as the degree of contamination of the reservoir, the susceptibility of the exposed population, and the intensity of the exposure.[8,10] The experience of the laboratory and the availability of additional methods of diagnosis can be added to these factors.[10]

In most cases, infection by LP takes the form of pneumonia, which may be community-acquired or nosocomial.[3,4]

Community-Acquired Pneumonia (Cap)

Legionnaire's disease often occurs in localized outbreaks, in hotels, office buildings, cruise ships, etc. About 2% to 15% of cases are sporadic.[2,4,11] Technical improvements in diagnostic methods in recent years have certainly contributed to the fact that LP is now considered to be a common cause of CAP.[3]

Patients with Legionnaire's disease acquired in the community are more likely to have severe pneumonia, with a higher number of vital signs affected, increased infiltration on chest x-ray, or the need for hospitalization in an intensive care unit.[4]

The incidence rate in Portugal in 2004 was 0.49 per 100,000 inhabitants,[13] which certainly reflects a high degree of underreported cases.[12]

Nosocomial Pneumonia

Nosocomial Legionnaire's disease is invariably associated with contamination of the water supply system.[3,10] It is vastly underdiagnosed, given the low degree of suspicion and the failure to request appropriate culture media. It is estimated to be the cause of about 40% of cases of nosocomial pneumonia.[3]

The epidemiology of nosocomial Legionnaires' disease has changed in recent years. While in the 1980s it was associated with outbreaks in tertiary healthcare centers, it is now mainly associated with sporadic cases in hospitals.[4]

Infection in hospitals is related to contamination of the supply system, but there are other causes. The incidence of the infection depends on many complex factors, including the susceptibility of patients, the "virulence" of the *Legionella* species, the methods used to disinfect breathing apparatus, the concentration of bacteria in the water, and the frequency of appropriate tests for detecting the agent among patients with nosocomial pneumonia.[14] The risk of nosocomial transmission depends more on the number of sources of infection than the concentration of *Legionella* (CFU/mL) in the positive samples.[14,15]

Early diagnosis of the Legionnaire's disease in hospitals can save lives. This is not only based on the association between the early start of antibiotic therapy and a better prognosis, but also because the diagnosis of a case should lead to measures to detect the sources of infection and prevent new cases.[15]

RISK FACTORS

The main risk factors for Legionnaire's disease are: age over 50 years, smoking, chronic lung disease and immunosuppression.[3,4,8,10,11] Other chronic diseases are also associated with increased risk of infection, such as diabetes mellitus, chronic renal failure, and haematologic neoplasms.[2,8,9] Surgery, especially transplant surgery, is an important predisposing factor for nosocomial infection.[3,4,10,11] The incidence among HIV-infected patients is low, but the severity is high-

er.[4,10] An increasing number of immunosuppressed children infected in hospitals has been observed.[10]

TRANSMISSION

Legionella is not transmitted from person to person; it is always acquired in the environment.[9] Almost all outbreaks reported, in which a single source of infection was isolated, were due to inhalation of contaminated aerosols.[9] Therefore, the microorganism is mostly transmitted by aerosol inhalation or microaspiration and contaminated water supply, contaminated aerosol devices, contaminated cooling towers for air conditioning, showers and saunas [2,4,5,9] and to a lesser extent, by aspiration or direct contamination of wounds.[4,9]

The disease has a higher incidence in warmer months, probably due to the increased use of air conditioning.[2]

With regard to nosocomial transmission, it also seems to be associated with the inhalation of droplets through aerosol devices and direct infection of wounds.[2]

Nevertheless, despite the belief that the disease cannot be transmitted from person to person, some opinions support the respiratory isolation of infected patients.[16]

CLINICAL MANIFESTATIONS

Legionnaire's disease is manifested as progressive and severe pneumonia.[9]

The incubation period is 2-10 days, followed by a prodrome within about 10 days, characterized by nonspecific malaise with myalgias, headache and fever,[2,3,5,11] Symptoms that are indicative of upper respiratory infection, such as, runny nose, rhinitis or sore throat, are less common in the Legionnaire's disease than in CAP caused by other microorganisms.[11,16]

The main clinical syndrome is pneumonia with a wide spectrum of severity, ranging from slight symptoms, such as cough and mild fever, to respiratory and multi-organ failure.[3,4,11]

It begins with nonspecific symptoms, including which is fever, which is often high, above 40°C.[2,4,5,11] The cough is usually not very productive, but can become productive over the course of the disease. Like other manifestations, chest pain can be observed, occasionally pleuritic pain, and haemoptysis. [4,5,11] Gastrointestinal symptoms are also prominent, including diarrhea in 20%-40% of cases, nausea and vomiting.[2,4,5,11] Another manifestation reported is relative bradycardia.[4,5,11] Extrapulmonary legionellosis is rare and may occur in the form of sinusitis, pancreatitis, cellulites, pyelonephritis and peritonitis. The most frequently affected extra-pulmonary organ is the heart, in the form of myocarditis, pericarditis, prosthetic valve endocarditis and postcardiotomy syndrome.[2-4]

In a quarter of patients, alterations in the central nervous system are observed. The most common alterations are confusion and disorientation, agitation, hallucinations, mental confusion, and less commonly, altered focal signs or neuropathy.[16]

DIFFERENTIAL DIAGNOSIS

Given the wide range of clinical manifestations, a differential diagnosis is made between Legionnaire's disease and pneumonia caused by other pathogens, whether bacteria, viral or fungal,[2,5] and between Legionnaire's and other types of infections, such as gastroenteritis and meningitis.[5]

ADDITIONAL DIAGNOSTIC METHODS

Usually, nonspecific laboratory tests can be conducted, such as leukocytosis with neutrophilia, elevated transaminases, elevated CPK and LDH, hyponatraemia and hypophosphataemia, proteinuria and hematuria. Changes due to complications of the disease itself can also be observed.[2,3,5]

The radiological signs observed in the chest x-ray are indistinguishable from the characteristic signs of pneumonia caused by other agents.[2,4,10] Between days 1 and 3, alveolar infiltrates appear,[2,4,10,11] which are usually unilateral and located in the lower lobes. One third of patients have pleural effusion.[2,4,10] In immunosuppressed patients, nodular opacities may occur, which expand and cavitate. Radiological progression is common despite adequate treatment with antibiotics, and these signs regress after clinical improvement within several days, with complete resolution only within 1 to 4 months.[2,4,10,11]

DIAGNOSIS

The definitive method of diagnosing Legionnaire's disease is the isolation of biological samples in culture (bronchial secretions, bronchoalveolar lavage, pleural fluid, serum). The LP does not grow in normal culture media, but only in media containing charcoal (BCYE - buffered charcoal yeast extract

agar), which must be requested by the laboratory.[2-4,8,10] Three to five days may elapse until visible colonies are seen. The sensitivity of this method for bronchial secretions is 80%, with specificity of 100%.[2,10] An increase in sensitivity is observed for culture of the bronchoalveolar lavage, and a decrease to less than 20% in the blood serum.[2]

Gram staining in samples of bronchial secretions indicates suspected Legionnaire's disease when there is a high leukocyte count, and few or no microorganisms are identified.[2,10,11] Where these microorganisms are visible, they are poorly-stained gram negatives.[2]

Direct immunofluorescence, using labeled antibodies, is a rapid diagnostic test (2 to 4 hours), with lower sensitivity that of the culture, as it requires a high number of microorganisms to be positive.[2,4,10] The use of monoclonal antibodies seems to be superior to the use of polyclonal antibodies.[2,4,8] The former has a sensitivity of 33-70% and specificity of 96-99%.[2,10] With the appropriate antibiotic therapy, it becomes negative within 4 to 6 days. Attention should be paid to false positives from cross-reaction with other gram negative microorganisms.[2,3,8]

The urinary antigen test for LP is a quick and inexpensive method for detecting the presence of LP antigens in the urine, by radio-immunoassay or ELISA.[2,4,10] It has sensitivity of 70% and specificity of approximately 100%. The sensitivity can be increased with a higher urine concentration.[4] Its main disadvantage is that it only detects LP serogroup 1, although this is the serogroup that causes the majority - about 90% - of cases of Legionnaire's disease. Unlike the culture test, the urinary antigen test for LP remains positive for several weeks, even though the patient has been medicated with the appropriate antibiotic therapy.[2,4,10]

Serology tests are useful in epidemiological studies, but not in clinical practice.[2,4,11] The diagnosis is based on a four-fold increase in antibody titers, to values equal to or higher than 128. Samples are needed in the acute and convalescent phase, since the humoral activity may remain undetectable until one to three months after the onset of the disease. Isolated titers equal to or higher than 256 during convalescence are suggestive of Legionnaire's disease, but do not constitute a diagnosis.[2,4,10] Some patients have IgM activity only; therefore, IgG and IgM assay should always be requested.[4,10] Sensitivity for these tests is 46-60% and specificity is 96-99%.[2,10]

The method of polymerase-chain-reaction (PCR) has been used to detect *Legionella* in urine, serum and BAL samples. It is a very specific test, but is more sensitive than the culture test. Its main advantage is the fact it provides rapid results, and its capacity to detect species other than the LP.[2,4,8,10]

As *Legionella* is a very common pathogen, it is recommended that all hospitalized patients with CAP be tested for infection by this organism, because Legionnaire's disease is very nonspecific. Gram staining can be suggestive of the disease and indicate the need for additional exams. The ideal test would be one that is rapid, like the urinary antigen test, which is available in almost all microbiology laboratories, only more sensitive.[4] The importance of diagnosis is also evident in cases of nosocomial infection, not only at an individual level, allowing early and appropriate treatment with antibiotics, but also at endemic level, allowing the identification of a focus of infection.[15]

According to the additional methods of diagnosis and due to epidemiological characterization, cases of Legionnaire's disease can be classified as "confirmed" or "probable", according to the definitions of the General Board of Health,[17] as follows:

A confirmed case when one or more of the following are present:

• Isolation of *Legionella spp* from cultures of sputum, bronchial secretions, BAL, pleural fluid, lung biopsy or blood.

• An increase in the titer of LP serogroup 1 antibodies by at least four times in two blood samples collected at least 10 days apart (seroconversion) by indirect immunofluorescence, with a second titer with value equal to or above 128.

• Detection of LP serogroup 1 antigen in the urine.

A probable case when one or more of the following are present:

• An increase in the titer of non-LP serogroup 1 LP spp antibodies by at least four times, in two blood samples collected at least 10 days apart, by indirect immunofluorescence, with a second titer with value equal to or above 128.

• A single antibody titer greater than or equal to 256.

• Detection of specific *Legionella spp* antigen or staining with monoclonal antibodies marked by immunofluorescence.

• Detection of *Legionella spp* nucleic acid by the PCR technique.

THERAPY

Given the frequency and potential severity of Legionnaire's disease, antibiotic therapy appropriate for LP is indicated for the empirical treatment of CAP. This indication is also supported by the evidence of increased mortality associated with a delay in initiating appropriate antibiotic treatment.[2-4,8,10]

Most patients with Legionnaire's disease require hospitalization and start of intravenous therapy.[2]

Erythromycin is historically associated with Legionnaire's disease, but has now been replaced with new macrolides and fluoroquinolones, due to their superior performance and intracellular and lung tissue penetration, observed *in vitro*.[2-4,10,11,18]

Other antibiotics, such as tetracyclines and co-trimoxazole, are also effective.[4,18]

Of the macrolides, azithromycin appears to be the most effective.[18] Fluoroquinolones are associated with more rapid clinical improvement, but no data exist to support a reduction in mortality.[19] *Table 1* describes the recommended antibiotics and doses.

Quinolones and azithromycin can be used in association, in more severe cases.[18]

Most patients have a clinical response between the 1st and 4th days of antibiotic treatment. The therapy should be administered intravenously until a clinical response is achieved, at which point it can be changed to oral administration. The period of antibiotherapy should be 10 to 14 days[2,3] or 5 to 10 days in the case of azithromycin.[3,4] In immunosuppressed patients with underlying disease, including renal and heart insufficiency, or with severe Legionnaire's disease, 21 days of antibiotic treatment are recommended.[2,3]

TABLE I

Recommended antibiotherapy

Azithromycin	500 mg* by mouth or iv every 24h
Clarithromycin	500 mg by mouth or iv every 12h
Levofloxacin	500 mg* by mouth or iv every 24h
Ciprofloxacin	400 mg by mouth or iv every 8h or 750 mg by mouth or iv every 12h
Oxofloxacin	400 mg by mouth or iv every 12h
Doxycycline	100 mg* by mouth or iv every 24h
Co-trimoxazole	960 mg iv every 8h or 960 mg by mouth or iv every 12h

*It is recommended that double the indicated dose be administered in the first administration. Adapted from Stout JE et al. Legionellosis. N Engl J Med 1997.

PREVENTION

Given the problem Legionnaire's disease represents for public health, and the clear cause-effect relationship between the colonization of water supply systems and the disease, a Practical Guide was issued in 2001 by the General Board of Health and General Board of Tourism, outlining control procedures for tourism resorts.(6) This guide provides instructions on the design, construction and maintenance of different water systems, and also gives guidance on prophylaxis.

Primary prophylaxis

- Do not use construction materials for water systems that enable adherence of microorganisms;
- Keep systems clean, to ensure there are no deposits of sediments and nutrients;
- Prevent the cold water temperature from exceeding 21°C, and hot water reservoirs from falling below 60°C; also the circulating hot water should be maintained at between 50°C and 55°C;
- Have a monitoring and inspection program in place for all equipment and systems;
- Establish cleaning and disinfection procedures;
- Control water quality, regularly carrying out tests for the *Legionella* bacteria in the most sensitive points of the system;

Secondary prophylaxis

There are two methods available:

- Chemical disinfection (usually used for cold water systems);
- Thermal treatment (usually used for hot water systems).

Chemical disinfection involves hyperchlorinating the water in the reservoir, reaching an amount of residual chlorine of 20 to 50 mg/l. This chlorinated water is then recirculated throughout the system.

Thermal disinfection usually involves increasing the temperature in the thermal accumulators or hot water tanks to values close to 70°C, and at the same time, circulating the water throughout the system.

Other methods of disinfection are described in the literature, including UV radiation and localized areas of copper-silver ionization.[2]

PROGNOSIS AND MORTALITY

When adequate therapy is not administered, the

disease usually evolves to aggravation of symptoms within the first week. Still, some patients with less serious conditions recover without treatment, with a prolonged period of convalescence.[16]

The factors associated with poor prognosis are old age, male, nosocomial infection, renal failure, neoplasm, immunosuppression and isolation of the LP serogroup 6.[20]

The mortality is influenced not only by antibiotic therapy, but also by the existence of chronic diseases, with rates of about 80% among immunosuppressed, untreated patients. The overall mortality rate is 15-20%,[16,21] and can exceed 30% in outbreaks of nosocomial infection.[14] Between 30% and 50% of patients require hospitalization in an intensive care unit.[21]

References

1. Winn WC et al. Legionnaires Disease: Historical Perspective. Clin Microbial Rev 1988; 1: 60-81.

2. Sullivan L MD et al. Legionellosis. www.emedicine.com/med/topic1273.htm

3. Schulz D et al. Doença dos Legionários: uma Revisão. RBAC 2005; 37 (4): 251-255.

4. Stout JE et al. Legionellosis. N Engl J Med 1997; 337 (10): 682-687.

5. Smeek F MD et al. Legionnaires Disease. www.emedicine.com/emerg/topic295.htm

6. Ricketts KD et al. Legionnaires' Disease in Europe 2003-2004. Eurosurveillance 2005; 10: 256-259.

7. Fields BS et al. Legionella and Legionnaires' Disease : 25 years of investigation. Cli Micro Reviews 2002; 15: 506-526.

8. Louisiana Office of Public Health – Infectious Disease Epidemiology Section. Legionella Infections - Infectious Disease Control Manual 2004.

9. Vergis EN e tal. Legionella as a cause of severe pneumonia. Seminars in respiratory and critical care medicine 2000; 21 (4): 295-304.

10. Direcção Geral de Saúde e Direcção Geral do Turismo. Doença dos Legionários – procedimentos de controlo nos empreendimentos turísticos 2001.

11. H Akbas E MD et al. Legionnaires' disease and pneumonia – beware the temptation to underestimate this "exotic" cause of infection. Postgraduate Medicine 2001; 109 (5): 135-147.

12. Sabrià M et al. Legionnaires' Disease: Update on Epidemiology and Management Options. American Journal of Respiratory Medicine 2003; 2 (3); 235-243.

13. Pina APB e Silva FC. www.saudepublica.web.pt/04-PrevencaoDoenca/DTDOmanual/inf.legionelose.htm

14. Kool JL MD et al. Hospital characteristics associated with colonization of water systems by Legionella and risk of nosocomial Legionnaires' disease: a cohort study of 15 hospitals Infect Cont Hosp Epid 1999; 20:798 - 805.

15. Stout JE et al. Hospital-acquired Legionnaires' disease: new developments. Curr Opin Infect Dis 2003; 16: 337-341.

16. H Edelstein PH et al. Legionnaires' disease. A review. Chest 1984;85;114-120.

17. Direcção Geral de Saúde. Programa de vigilância epidemiológica integrada da Doença dos Legionários: Investigação Epidemiológica 2004.

18. Dedicoat M et al. The treatment of Legionnaires' disease. Journal of Antimicrobial Chemotherapy 1999: 43; 747-752.

19. Sabrià M MD et al. Fluoroquinolones vs macrolides in the treatment of Legionnaires' disease. Chest 2005; 128 (3); 1401-1405.

20. Marston BJ et al. Surveillance for Legionnaires' disease. Risk factors for morbidity and mortality. Archives of Internal Medicine 1994; 154: 2417–2422.

21. Lettinga KD et al. Legionnaires' Disease at a Dutch Flower Show: Prognostic Factors and Impact of Therapy. Emerging Infectious Diseases 2002; 8 (12): 1448-1454.