38. SEVERE LEGIONELLOSIS

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Introduction

Legionnaires' disease is a form of pneumonia, caused by bacteria of the genus *Legionella*. In contrast, Pontiac fever is a self-limited influenza-like illness, without pneumonia, that is associated with *Legionella* spp too. The name of this infection is in reference to an outbreak of pneumonia that affected 221 people and caused 34 deaths during the 58th American Legion Convention celebrated in Philadelphia during the summer of 1976 [1]. Epidemiologically, the Philadelphia outbreak was similar in many aspects to two large outbreaks of febrile disease, one in 1965 (District of Columbia) and the other in 1968 (Pontiac, Michigan). The Columbia outbreak involved patients in a large psychiatric hospital in which there were 81 cases and 12 deaths [2]. The Pontiac outbreak was very different, of the 144 documented cases neither death nor pneumonia were demonstrated. Pontiac fever is an acute febrile illness, self-limited and with minor respiratory symptoms [3]. In reality, the first isolation of this organism (OLDA agent) was made in 1947 by Jackson from a sick guinea pig that had been inoculated with the blood of a patient with a febrile respiratory illness [4].

Today, we know that legionella is a common cause of community-acquired and nosocomial pneumonia. The incidence of legionella as a cause of sporadic community-acquired pneumonia varies, but in studies from Europe and North America, it ranged from 2 to 15 per cent of all community pneumonias that require hospitalization [5]. But the most relevant factor is the role of Legionnaires' disease as a frequent cause of severe community-acquired pneumonia (when shock or acute respiratory failure is present), although this is not a universal finding. In some studies, *Legionella* ranks second, after pneumococcus, in the list of causes of pneumonias that are severe enough to require admittance in ICU and that show a high mortality (Table 1) [6–14]. In the nosocomial setting, legionellosis may also appear sporadically or, sometimes, in real outbreaks. In general, the true prevalence of legionellosis has probably been underestimated, since specific diagnostic methods are not routinely used in the initial diagnostic approach. Then, diagnosis is commonly performed retrospectively and we know that the delay in the initiation of adequate treatment due to diagnostic tardiness negatively influences the prognosis of the disease [15–19].

Etiology

Since the original isolation in 1977 of *L. pneumophila* by McDade [20] the number of different species and serogroups of the Legionellaceae family has been continually increasing. Currently there are more than 34 Legionella species and over 50 distinct serogroups. About half of those species have been proven to be pathogenic for humans [21] (Table 2). *Legionella pneumophila* serogroup 1 is responsible for more than 80% of these infections [22]. In general lines, the other species of the family, of which *Legionella micdadei* is the most frequent, tend to show clinical features and susceptibility patterns to antimicrobial agents similar to those shown by *L. pneumophila* [23].

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TABLE 1. Characteristics of severe community-acquired pneumonia (SCAP) in the literature

Author (Ref)	Pachón (8)	Torres (9)	Rello (10)	Moine (11)	Leroy (12)	Rello (13)	Hirani (14)
Year	1990	1991	1993	1994	1995	1996	1997
Episodes	67	92	58	132	299	95	57
MV* (%)	–	61	72.4	61	48.9	87.3	96.4
Diagnosis of etiology (%)	48	52	60.3	72	65.9	39	67
S. pneumoniae (%)	37.5	15	37.1	45	30.8	29.4	67
Legionella spp (%)	21.8	14	22.8	4.2	0	3.1	16
Rank order Legionella SCAP	3rd	2nd	2nd	7th	–	3rd	2nd
Overall death ratio (%)	20.8	22	22.4	24	28.5	40	56
Legionella Mortality (%)	–	15	20	25	–	66	58

*Mechanical ventilation.

TABLE 2. *Legionella spp.* that have been linked to well-documented human infection

L. pneumophila	L. oakridgensis
L. bozemanii	L. wadsworthii
L. dumofii	L. birminghamensis
L. micddadei	L. cincinnatiensis
L. longbeache	L. anisa
L. jordanis	L. cherrii
L. gormanii	L. sainthelensi
L. feeleil	L. lansingensis
L. hackeliae	L. parisiensis
L. maceachernii	

Legionella pneumophila is a small, aerobic, non-capsulated, Gram-negative bacilli. They are non-spore-forming, most are motile due to polar or subpolar flagellae, and electron microscopy reveals multiple fimbriae extending from the surface. These, in normal conditions measure 0.5–1 μm in width and 2–4 μm in length. The cell wall of all the species of the family shows a distintive fatty-acid profile and ubiquinone composition, different from other Gram-negative bacilli. Legionella have complex growth requirements and do not grow on standard bacteriologic media. All species require supplementation of growth media with L-cysteine and ferric salts and grow best at pH 6.8 to 7.0. So, in these conditions, the primary medium for isolation of *Legionella* is buffered charcoal yeast extract (BCYE) agar. Isolation of *Legionella* from contaminated specimens is enhanced both by acid pre-treatment and by multiple selective media obtained by the addition of antimicrobial agents [22].

Epidemiology

Legionnaires' disease occurs in sporadic, endemic and epidemic forms. To establish a link between the disease and a presumptive site of infection, an environmental investigation and the presence of clinical and environmental *Legionella* isolates are required.

SOURCES OF INFECTION

Water is the natural habitat of *Legionella*. The bacteria has been consistently isolated from a variety of man-made water reservoirs in most nosocomial outbreaks and in many community-acquired cases. The principal sources of nosocomial [24] and community-acquired [25, 26] Legionnaires' disease are the distribution systems for drinking water. The importance of air conditioning cooling towers, although they are undoubtedly a definitive disseminator at least in some outbreaks [27–29], has pro-

bably been overemphasized. Water temperature exerts a crucial influence on the growth of *Legionella*; it is favored in warm water [30, 31].

MODE OF TRANSMISSION

Legionnaires' disease can be fundamentally acquired by the inhalation of aerosols containing *Legionella*, such as cooling towers [32, 33], evaporative condensers [34], showers [35], faucets [31], whirlpool spa [36], saunas [37], humidifiers [38] and medication nebulizers [39]. Contaminated water may also be a mode of transmission after aspiration [40]. Nasogastric tubes have been implicated in several studies of nosocomial legionellosis; microaspiration of contaminated water was the presumed mode of transmission [41]. The patients with lowered consciousness, head and neck surgery, have a high propensity for aspiration, and these circumstances are risk factors for nosocomial pneumonia due to legionella [42]. Direct infection of surgical wounds after contact with contaminated water is also possible [43]. There is no evidence for person-to-person spread [44].

PATHOGENESIS VIRULENCE

The growth of *Legionella* organisms in water is favored by the fact that some algae may provide nutrients and by the role of amoeba; it preserves them in unfavorable environmental factors [45]. Thus, in infected patients, *Legionella* is an intracellular infectious agent and it replicates within the cells, avoiding intracellular destruction, by sophisticated mechanisms that inhibit phagosome-lysosome fusion [46]. In fact, cell-mediated immunity plays the critical role in the host's defence against this infection. There are many virulence factors involved in the intracellular multiplication of the organism: several genetic loci of *Legionella pneumophila* serogroup 1, the macrophage infectivity potentiator, lipopolysacharide endotoxins, or the "defect in organelle trafficking proteins" [47, 48]. The presence of flagella is also one phenotypic difference between avirulent and virulent strains of *Legionella pneumophila*: isogenic avirulent strains obtained by passage lose their flagella [49].

RISK FACTORS

Clinical diagnosis of the *Legionella* infection is difficult. Usually, the empirical treatment of severe community-acquired pneumonia [50, 51] includes specific antibiotics against *Legionella*, but that is different in nosocomial pneumonia [52]. Therefore, it would be useful to identify risk factors associated with *Legionella* pneumonia.

Virulent *Legionella* organisms are capable of causing pneumonia in a previously healthy individual. At least six per cent of nosocomial *Legionella* pneumonia occurs in previously healthy patients [22]. Cigarette smoking, chronic lung disease, diabetes, alcohol abuse, renal failure, immunosuppression and advanced age have been identified as general risk factors for *Legionella* infection, but also for other non-*Legionella* infections. The immunodepression has been consistently implicated as a risk factor (steroids, cytostatics) [53, 54].

The incidence of *Legionella* infections in patients with acquired immunodeficiency syndrome is low, and normally it doesn't occur among persons receiving prophylactic therapy with trimethoprim-sulfamethoxazole, and the clinical manifestations are more severe [55] but, usually they respond well to treatment. Surgery is a major predisposing factor in nosocomial infection, with transplant recipients at the highest risk [16, 56, 57]. Regional and seasonal differences in reported cases may be due to ecological factors [53].

Clinical Manifestations

Two clinical forms of *Legionella* infection have been described: Pontiac fever and Legionnaires' disease.

Pontiac fever is a non-pneumonic, usually self-limited, nonfatal influenza-like disease, with

a short incubation period (36 h) and high attack rate (up to 95 per cent). Normally, it is caused by *L. pneumophila*, as well as other *Legionella spp.* It has recently been recognized that severe encephalopathy, due to acute disseminated encephalomyelitis, may rarely follow an allegedly benign Pontiac fever [58].

Pneumonia is the predominant clinical syndrome of Legionnaires' disease. The clinical manifestations of *Legionella* pneumonia are nonspecific. It is not possible to distinguish between Legionnaires' disease and other common causes of pneumonia on the basis of clinical findings [22, 59–61]. Demographic, clinical, laboratory, radiological and outcome data in nosocomial and community-acquired Legionella pneumonia are quite similar [62]. The disease presents itself with a broad spectrum of illness, ranging from a mild respiratory illness to a severe respiratory failure and multiorgan failure with fulminating course. Mild pneumonia generally occurs in young patients and those without underlying disease.

Initially, the patients present non-specific symptoms, including fever, malaise, myalgias, anorexia and headache. Although Legionellosis may behave as a multisystemic disease, fever (often exceeding 40°C) and non-specific respiratory manifestations are usually predominant. The frequency of cough, sputum production or purulence is variable. Chest pain, occasionally pleuritic, can be prominent. Progressive respiratory failure is the most common cause of death in Legionellosis [53, 63, 64].

Gastrointestinal symptoms are prominent, especially diarrhoea, which occurs in 20 to 40 per cent of cases [60, 65]. Neurologic symptoms are relatively common in Legionellosis, ranging from mild headache to severe encephalopathy [66].

The physical findings are those of pneumonia. Hyponatremia [63], elevated levels of serum transaminase and creatinine phosphokinase [65] are the most common types of non-specific laboratory abnormalities associated with Legionnaires' disease.

The chest radiograph of Legionellosis has been described in many reports [67–69]. Although some attempted to describe those which are specific for *Legionella*, chest radiographic findings are also non diagnostic. Initial focal infiltrates are the most frequent radiographic finding. The infiltrates often spread to contiguous lobes, eventually becoming bilateral. Recently, some authors have written that radiological findings are related to the outcome of Legionnaires disease. Thus, rapid progression of radiological infiltrates or multilobar lung involvement is an indication for admission in a critical care unit [50, 51]. Early, appropriate treatment against Legionella seems to decrease the incidence of radiological progression in about 30 per cent of cases [70]. Likewise, radiographic improvement is related to a better outcome [71].

The incidence of pleural effusions is about 30%, less frequent than other causes of severe pneumonia; and usually of moderate volume. Empiema is a rare complication of Legionellosis. Cavitation is a rare event, whereas, the immunocompromised host has a marked tendency to cavitation. Hiliar adenopathy is also seen in this subset of patients [68, 69]. A prolonged resolution phase of up four or six months is common in severe Legiontonaires' disease.

EXTRAPULMONARY LEGIONELLOSIS

Extrapulmonary *Legionella* infections are rare and normally occur through bacteremia. Bacteremia appears in the 20 per cent of severe legionnaires' disease. The extrapulmonary manifestations can be concomitant with the pulmonary infection or can become manifest weeks after the successful treatment of pneumonia. These are often dramatic [59, 60]. Most extrapulmonary infections develop in immunosuppressed patients [72].

A variety of locations of extrapulmonary Legionellosis have been reported. The most common site is the heart, especially pericarditis [73]. There are also described cases of myocarditis, post-cardiotomy syndrome and prosthetic-

valve endocarditis [74, 75]. Some cardiac infections have been caused by direct contact with contaminated water, and normally were acquired in the hospital; there are reported cases of valvular infections, and thoracic aortic graft infection, usually it is through wound infection and is favoured by foreign bodies [43, 76].

Although neurologic symptoms are relatively common in legionellosis, CT shows no abnormality that can account for the symptoms; proving that neurologic infection is rare. A few brain abscesses have been reported [77]. Digestive legionella infections are not frequent; some reports have described perirectal abscess [78], peritonitis [79] and pancreatitis [80, 81]. Renal involvement is usually caused by hypotension and rhabdomyolisis [82]. Pyelonephritis with abscess formation is also described [83]. Other unusual clinical presentations of *Legionella* are: wound infections (hip, cardiothoracic surgery), sinusitis [84], hemodialysis fistula infections [85], and cellulitis [86].

Laboratory Diagnosis

It must be emphasized that prospective, well-designed comparative studies between Legionnaires' disease and those pneumonias that are caused by non-Legionella aerobic organisms have shown that a definite differential diagnosis based on clinical, analytical, and radiological signs is not possible [53, 63, 65, 87]. For this reason, specialized laboratory tests are necessary to establish the diagnosis (Tables 3 and 4). These tests must be specifically requested from the clinical microbiology laboratory because they are not routinely performed.

A variety of stains have been used to visualize the organisms in clinical samples, but they are not specific. Gimenez stain is a rapid and more effective technique than Gram stain and Dieterle silver-impregnation stain permits visualization in paraffin-fixed tissues [88].

Isolation of *Legionella* in culture is the definitive method for the diagnosis of legionellosis; however, *Legionella* does not grow on standard microbiologic medium [22, 59]. Investigators at the Centers for Disease Control ultimately grew legionella on a charcoal-containing medium (buffered-charcoal yeast-extract agar), which is the base formulation of the medium used today. Unfortunately, many laboratories either do not culture for legionella or do so inadequately. Anyway, *Legionella* usually takes three to five days to grow. Cultures should be held for many days so as not to miss some delayed isolations [64, 89, 90]. For maximal sensitivity, several types of dye-containing selective mediums with

TABLE 3. Usefulness of specialized laboratory test for the diagnosis of Legionnaires' disease

Test	Sensitivity (%)	Specificity (%)
Sputum culture*	80	100
Direct fluorescent-antibody stain of sputum	33–70	96–99
Urinary antigen assay**	70	100
Serologic tests for antibody***	40–60	96–99

*Multiple selective mediums that contain dyes and have been pretreated with acid or heat to minimize overgrowth of competing microorganims should be used.

**This test is useful only for L. Pneumophila serogroup 1.

***This approach requires IgG and IgM testing of serum samples obtained during both the acute phase and convalescence. A single titer of ≥1 : 128 in a patient with pneumonia is considered presumptive evidence of infection, and single titer of ≥1 : 256 or a fourfold increase in antibody titer is considered definitive evidence.

From: Stout JE, Yu VL. Legionellosis. New Engl J Med 337:682, 1997. (with permission).

TABLE 4. Laboratory criteria for diagnosis of Legionellosis

- Isolation of *Legionella* from respiratory secretions, lung tissue, pleural fluid, or other normally sterile fluids, or
- Demonstration of a fourfold or greater rise in the reciprocal immunofluorescence antibody (IFA) titer to greater than or equal to 128 against *Legionella pneumophila* serogroup 1 between paired acute- and convalescent-phase serum specimens, or
- Detection of *Legionella pneumophila* serogroup 1 in respiratory secretions, lung tissue, or pleural fluid by direct fluorescent antibody testing, or
- Demonstration of *Legionella pneumophila* serogroup 1 antigens in urine by radioimmunoasssay or enzyme-linked immunosorbent assay

CDC, Case Definitions for Infectious Conditions Under Public Health Surveillance. MMWR 46 (No.RR–10):20, 1997.

acid or heat pre-treatment to minimize overgrowth of competing microorganisms must be used. In patients with severe Legionellosis which have a productive cough, sputum is a good non-invasive sample for isolating the organism. Interestingly, sputum from patients suspected of having Legionnaires' disease should be cultured regardless of quality, since in one study specimens that did not meet the classical criteria of Murray and Washington and had more than 25 squamous epithelial cells and fewer than 25 leukocytes per low-power field often yielded the organism [64, 91]. Sputum culture sensitivity estimates increase in parallel with the severity of the disease by about 60% in severe community-acquired pneumonia due to *Legionella pneumophila* [64]. The isolation rate increases slightly when combining cultures from both sputum and other respiratory specimens obtained from more invasive methods [64].

Direct fluorescent-antibody (DFA) staining is a rapid diagnostic test that permits a quick diagnosis of severe legionellosis but requires skilled microbiology technicians to interpret the test [92]. Its sensitivity, regardless of the type of respiratory sample, is less than that of culture because large numbers of organisms need to be present before they can be readily visualized [22, 59]. The specificity has been determined to be about 95% [22]. For detecting *L. pneumophila* in respiratory specimens, it has been found that the monoclonal-antibody direct fluorescent-antibody reagent (Genetic Systems, Sanofi Diagnostics Pasteur, Chaska, Minn.) is superior to polyclonal reagents because there is less background fluorescence [59]. In addition, false positive results due to cross-reactions with nonlegionella bacteria do not occur. The average time for the DFA test to become negative is after four to six days of appropriate antibiotic therapy [89, 93].

In severe legionellosis, serologic tests are only useful for epidemiologic studies and are less valuable to physicians, given the requirement for measurement during convalescence [22, 59]. Immunofluorescent antibody (IFA) detection, ELISA, and microagglutination are the most commonly used serologic tests [92]. The IFA test is the most sensitive and widely employed serologic method. The diagnosis is based on a four-fold increase in the antibody titer to 1:128 or more. The period of time needed to obtain a four-fold rise in the antibody titer usually ranges from four to eight weeks after the onset of the illness. However, seroconversion may even take many months, specially in the elderly [94] and about 30% of patients suffering from Legionnaires' disease will never develop an antibody increase [89]. Single titers of 1:256 or more during convalescence in a patient with pneumonia are suggestive of Legionellosis. To improve the sensitivity, antibody screening should include both IgG and IgM because some patients will only have an IgM response [22, 59]. A high specificity of 95% is restricted to *L. pneumophila* serogroup 1 infection. When other *Legionella* species antigens are used, the IFA test clearly decreases its specificity [22, 59, 95].

The legionella urinary antigen test is a rapid test that detects antigens of *L. pneumophila* in urine. This test is commercially available as both a radioimmunoassay and an enzyme immunoassay, has a sensitivity of 56 per cent and a speci-

ficity that approaches 100 per cent [96]. Sensitivity can be further improved if the urine is concentrated by ultrafiltration [97], and today the new EIA test, (Biotest AG, Dreieich, Germany; Binax, Portland, Marine) can offer sensitivity in non-concentrated and concentrated urine of more than 83 per cent with a specificity of 100% [98, 99]. More recently, a novel 15 minute rapid *Legionella* urinary antigen test (Binax Now, Portland, Maine) has been presented with very high specificity and sensitivity [100]. Radioimmunoassay (RIA) does not seem to show any advantage over the more simple, non-isotopic, enzyme immunoassay (EIA) tests [101]. Moreover, it is often easier to obtain a urine sample than an adequate sputum specimen, since many patients have a nonproductive cough. Finally, unlike culture, the test results will remain positive for weeks despite antibiotic therapy. Although *Legionella* antigen has been reported to persist in a patient's urine for as long as one year [102], less than 10 per cent of culture-confirmed cases were positive for urinary antigen more than 60 days after the onset of disease. The chief drawback is that this test detects only *L. pneumophila* serogroup 1. However, serogroup 1 accounts for the large majority of cases of legionnaires' disease.

Genus-specific hybridation of *Legionella* spp. by a commercially available radiolabeled DNA probe test (Gen Prove Inc., San Diego, California) can be performed in a few hours. Once more, a good correlation between *Legionella* organism concentration and DNA probe activity has been observed. In contrast with the DFA test, the DNA probe does not depend on the operator's skill. The test may remain positive in the respiratory secretions for up to eight days after beginning proper therapy [103, 104]. Again, the sensitivity is less than that of culture and quite similar to that of the DFA test and specificity approaches 99% [22].

Several molecular systems have been developed for the detection of *Legionella* species using the polymerase chain reaction (PCR). Assays based on the PCR have been used to detect *Legionella* on clinical specimens, such as bronchoalveolar lavage fluid (BAL) [105–108], intratracheal aspirates [109], sputum [108], urine [110, 111], throat swabs [112] and serum [111, 113]. Although PCR-based assays for the detection of *Legionella* in clinical samples are highly specific (approach 99%), they show a clearly lower sensitivity than that of culture [107, 110]. However, a recent study has shown a better than usual sensitivity of 73% if testing was restricted to urine and/or serum samples taken within four days of the onset of the symptoms [111]. The advantages of PCR in urine and serum over conventional methods for the detection of *Legionella* DNA are evident. Urine and serum samples are readily obtainable and can be processed within a single working day, thereby providing a rapid result for the clinician. In one more recent study with respiratory specimens, such as sputum and BAL, the sentitivity of PCR was near to 100%, when the PCR inhibition that produces the group hem of the hemoglobin [114] was eliminated by the inclusion of a preliminary wash and centrifugation step in distilled water [108]. Finally, another important factor is that PCR of *Legionella* is not restricted to specific serogroups or species [59].

Finally, it is obvious that if Legionellosis is suspected in a critically ill patient, clinicians have to give priority to the laboratory diagnostic techniques that confirm, in a simple, fast, and reliable way, that *Legionella* is the etiology agent of the pneumonia. Along these lines, the last generation test for detection of urinary antigen and/or the news assays based on the polimerase chain reaction, seem to be the most important future diagnostic options.

Treatment

Since *Legionella pneumophila* is an intracellular pathogen, only antimicrobial agents that are concentrated in cells are effective. These agents must maintain biological activity against *Legionella*. Standard *in vitro* susceptibility testing is not reliable for study of antibiotic activity,

as it does not measure the ability of the drug in the intracellular compartment. This fact can explain the *in vitro-in vivo* dichotomy (i.e. with imipenem or amoxicillin-clavulanic acid). Susceptibility of *Legionella* agents to new antimicrobial drugs is based on the intracellular infection and experimental guinea pig infection models. It has been postulated that the guinea pig is the animal model that offers the most similarities with Legionnaires' disease in humans [115]. In spite of this, conclusions derived from an animal model cannot be directly extrapolated to humans [22].

The most effective therapy in Legionnaires' disease must combine the highest activity against *Legionella* spp., the ability to enter and concentrate within phagocytic cells, and the ability to achieve high concentrations in lung tissue and alveolar exudate.

Normally, the best utility of extracellular susceptibility testing is as a screening test to determine which drugs are inactive. There are exceptions; β-lactam antibiotics are active against extracellular *Legionella*, but they have no activity against the intracellular bacterium. However, some antibiotics are less active in extracellular testing than they are in animal models and intracellular testing (doxicycline, azithromycin).

As expected, in most acute lung infections, early appropriate treatment usually implies the best outcome. Mortality of Legionnaires' disease is correlated with both delay in the initiation of specific treatment and the total delay in starting of specific treatment [19]. In endemic areas, the non-specific presentation of Legionnaires' disease obliges clinicians to include effective treatment against Legionellosis in all episodes of pneumonia, in which diagnosis remains uncertain. Specific treatment against *Legionella* infections is recommended by different guidelines on severe community-acquired pneumonia [50, 51, 116]. The recommendations for nosocomial pneumonia are highly dependent on every hospital epidemiology (water colonization) [52].

ANTIBIOTIC CHOICE

Erythromycin has historically been the drug of choice [22, 59, 117]. A number of clinical studies have proven that it is highly effective against *Legionella* spp. The intravenous route in severe pneumonia is recommended. The optimal dose is 4 g/d. Gastrointestinal intolerance, volume overload and ototoxicity have made this drug less attractive. Other side effects less well-known are prolongation of the Q-T interval and "torsades de pointes". Erythromycin can rarely be arrythmogenic, especially when given rapidly intravenously or to patients with a myocardial infarction. The existence of metabolic interactions between erythromycin and cyclosporine, at the cytochrome P-450 level, makes close monitoring of serum cyclosporine levels mandatory to avoid toxicity in organ transplantation recipients.

Many clinical and bacteriologic failures of erythromycin treatment have been reported, as might be expected by the fatality rates of 10%–40% reported in retrospective studies. In none of these instances "*in vitro*" resistance to erythromycin was demonstrated [118]. The accumulated clinical experience in favour of erythromycin as the treatment of choice for Legionnaires' disease has to be balanced against the appearance of new antibiotics that offer many theoretical and practical advantages. These new antibiotics, are especially the new macrolides (clarithromycin and azithromycin), and more recently third and fourth generation fluoroquinolones. These antibiotics have greater *in vitro* activity and better intracellular penetration than erythromycin [119]. There are studies which support the effectiveness or clarithromycin in severely ill patients with chest infections due to *Legionella pneumophila*. Azithromycin has been efficacious in some reports [120]; it offers advantages over the other macrolides due to its unique pharmacokinetics, high and sustained tissue penetration, and spectrum of activity [121]; with its intravenous formulation now available in some countries, it may

displace erythromycin as the macrolide of choice [59].

As a class, fluoroquinolone antimicrobials have the greatest activity against *L. pneumophila* in experimental models and animal studies [118]. The bactericidal activity of the new quinolones (ciprofloxacin, levofloxacin and trovafloxacin) could make them the most effective treatment in the severest cases. Some guidelines have recommended quinolones as alternative therapy (as sole therapy) in severe community-acquired pneumonia [50]. In contrast with erythromycin, relatively little is known about these new drugs in large series of severely ill patients. These are the treatments of choice for *Legionella* infections in immunocompromised patients, based on the lack of pharmacologic interactions in this special group of patients. Probably these are the antibiotics of choice for severe Legionnaires' disease [122]; this affirmation needs future clinical studies for its confirmation. Rifampicin is highly active *in vitro* and *in vivo* against *Legionella* spp. [123, 124]. Its induction of rifampicin-resistant mutants argues against its use as sole therapy [117]. It can be added to the treatment regimen with macrolides in cases of more severe disease.

More recently, combination of macrolides with quinolones has shown promising preliminary results [125]. That must be confirmed with future clinical trials. At the moment no good clinical data exists confirming the superiority of combination therapy over single-antibiotic treatment. Some of these combination therapies can be selected if a lack of clinical response is observed after 3–5 days of therapy, in an attempt to obtain synergy.

Trimethroprim-sulfamethoxazole has generally appeared inactive against extracellular *L. pneumophila*. It has been effective in the treatment of *legionella* pneumonia and *legionella* peritonitis in guinea pigs [126]. There is relatively little information regarding the clinical outcome for patients with Legionnaires' disease who have been treated with co-thrimoxazole. Again on the basis of a few uncontrolled studies, it has been suggested that it could be especially effective against *L. micdadei* [23].

TABLE 5. Recommended antibiotic dosage for severe Legionellosis

Erythromycin	1 g every 6 hours
Clarithromycin	500 mg every 12 hours
Azithromycin	500 mg every 24 hours
Ciprofloxacin	400 mg every 8 hours
Levofloxacin	500 mg every 12 hours
Trovafloxacin	200 mg every 12 hours
Rifampicin	600 mg every 12 hours
Trimetoprim/ Sulfamethoxazole	160/800 mg every 8 hours

Tetracycline therapy was apparently as effective as erythromycin therapy in the epidemic of Legionnaires' disease in Philadelphia in 1976 [1]. Tetracycline has apparently been effective as treatment for patients for whom erythromycin therapy failed [127]. Successes with minocycline and doxycicline have also been documented [59].

Several streptogramin drugs have been shown to be active *in vitro* against *L. pneumophila*. There is no clinical experience with these antibiotics for the treatment of *legionella* infections [118]. There is no good evidence that any of the β-lactam or aminoglycoside antimicrobials are effective treatments for Legionnaires' disease. Imipenem and clindamycin have proved efficacious in isolated reports. The recommended dosage of the different antibiotics for severe Legionellosis is shown in Table 5.

DURATION OF TREATMENT

Parenteral therapy should be given until there is an objective clinical response; normally within 3–5 days of treatment. This can then be switched to oral therapy. It is recommended that a full three week course of treatment be given to patients who are immunocompromised hosts, and patients with serious underlying disease, in severe cases of Legionnaires' disease. A recrudescence of the disease has been reported

in patients with shorter courses of therapy [128].

OTHER MEASURES

Respiratory failure with progressive hypoxemia is the most important mechanism of death. Marked increases in intrapulmonary shunt combined with mild to moderate ventilation-perfusion inequalities are the predominant mechanisms of abnormal gas exchange in patients with pneumonia [129]. In addition, hypoxic pulmonary vasoconstriction is associated with an adaptative response. Recent studies have evaluated new strategies to improve oxygenation, including the administration of inhaled nitric oxide or body position changes. Elevated positive end-expiratory pressure (PEEP) with low tidal volume protect the lung in ARDS. FiO_2 should be minimized to target an acceptable SaO_2 (usually ≥90%).

The failure to improve survival rates in humans using a variety of adjunctive immunologic therapies, such as monoclonal antibodies directed against bacterial endotoxin or cytokins, means that current therapeutic options are based on standard supportive therapy with vasoactive drugs. Hemodynamic control is a priority when Legionnaires' disease evolves with severe sepsis or septic shock. Renal failure can be present, can be secondary to rhabdomyolysis; controlled treatment with fluids and electrolytes is very important, in this case. An optimal management of shock and renal failure may improve outcome [71, 82].

In purulent collection due to *Legionella* infection, drainage is required. Thus, prosthetic heart valve replacement is reguired in endocarditis.

Prognostic Factors and Mortality

The mortality rate of patients with *L. pneumophila* pneumonia who require admission to ICUs is 25–30% [71]. Delay in appropriate therapy of *Legionella* pneumonia is associated with increased mortality [19, 22, 59, 71]. Our group defined the prognostic factors in 84 cases of severe *Legionella* pneumonia [71]. Logistic regression analysis suggested that an initial APACHE II score greater than 15 and/or serum sodium level less than 136 mEq/l were the only independent factors related to death. Univariate analysis of the data also identified additional comorbid diseases and acute biochemical abnormalities, including renal failure, as significant contributors to mortality. The triad of *L. pneumophila* pneumonia, rhabdomyolysis, and renal failure is associated with a 40% mortality [130]. Bilateral chest x-ray involvement, ARDS, the need for mechanical ventilation, development of pulmonary complications (cavitation, lung abscess and pleural effusion), advanced age and septic shock, are major factors influencing outcome.

The majority of studies support hospital acquisition of Legionellosis as a factor that increases the likelihood of a fatal outcome [53].

Summary

L. pneumophila is an important cause of severe community- and hospital-acquired pneumonia, with a high mortality rate. The clinical and radiological presentations are not specific. These are the reasons for including an effective treatment against *Legionella* empirically in SCAP. The new macrolides and new quinolones have a relevant role in *Legionella* pneumonia treatment. We need new diagnostic methods, more sensitive, more specific and with quicker results. Currently, detection of urinary antigen and/or PCR are the most important diagnostic tools.

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