Legionella as a Cause of Severe Pneumonia

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ABSTRACT ***Legionella pneumophila*** **has been found to be a common cause of community-acquired pneumonia in patients who required intensive care unit (ICU) admission. In many studies, the clinical manifestations for Legionnaires' disease were more severe and the mortality was higher when compared with pneumonias of other etiology. However, this may be due to delay in diagnosis and suboptimal antibiotic therapy, rather than enhanced virulence of** ***L. pneumophila*****. A syndromic approach using high fever, diarrhea, mental status changes, hyponatremia, etc., may be useful in suggesting the correct diagnosis in patients with severe pneumonia, but this remains to be validated. The availability of** ***Legionella*** **diagnostic microbiology testing in-house (rather than being sent to an outside reference laboratory) maximizes the ability to correctly diagnose Legionnaires' disease. All patients with community-acquired pneumonia admitted to an ICU should undergo** ***Legionella*** **testing using the urinary antigen and culture on selective media. Moreover, we recommend routine cultures of the hospital water supply once a year (regardless of whether a case of nosocomial Legionnaires' disease has ever been diagnosed). If** ***Legionella*** **is found in the water supply, all patients with nosocomial pneumonia should undergo diagnostic tests for** ***Legionella*****; empiric anti-*** ***Legionella*** **antibiotics should be administered pending definitive diagnosis.**

Key Words: Legionnaires' disease, ***L. pneumophila,*** **nosocomial pneumonia, community-acquired pneumonia, intensive care unit**

In the past two decades since its discovery at the American Legion Convention in 1976, *Legionella pneumophila* has been found to be a relatively common pulmonary pathogen in community-acquired and nosocomial pneumonia. *L. pneumophila* is a member of the family Legionellaceae, which includes over 40 other species of *Legionella*. *L. pneumophila* is the most frequently implicated species in pneumonia, accounting for about 90% of infections, while *L. micdadei* (Pittsburgh pneumonia

Objectives
Upon completion of this article, the reader will: 1) be familiar with the clinical presentation of Legionnaires' disease; 2) understand the laboratory tests for the diagnosis of Legionnaires' disease; and 3) know the antibiotic therapy for the disease.

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agent), *L. bozemanii, L. dumoffii, L. longbeachae,* and other species together account for the remaining 10%. The collective clinical syndromes resulting from infection by members of the Legionellaceae family is referred to as legionellosis.

Strains of *L. pneumophila* differ in virulence. For example, multiple strains will colonize the water distribution system, but only a few strains will cause disease in patients exposed to that water. Of the 15 serogroups of *L. pneumophila,* serogroups 1, 4, and 6 are responsible for the majority of human infections. The point pertinent to this review is that *L. pneumophila* causes more severe disease than other bacterial pathogens associated with community-acquired pneumonia. For example, patients with community-acquired Legionnaires' disease are more likely to be admitted to intensive care units than patients with other pneumonias. The mortality for Legionnaires' disease is notably higher than the other "atypical" pneumonias in which *L. pneumophila* is included (with *Chlamydia pneumonia* and *Mycoplasma pneumoniae*) and is similar to that of bacteremic pneumococcal pneumonia.

EPIDEMIOLOGY

The incidence of Legionnaires' disease depends on several factors, including the extent of contamination of the water reservoir by the organism, susceptibility of the population exposed to that water, and the degree or intensity of the exposure of the patient to the water reservoir. Furthermore, the experience of the testing laboratory and availability of specialized tests are critical to discovery of the infection and establishment of the diagnosis.

Cigarette smoking, advanced age, chronic lung disease are well-established risk factors in immunocompetent hosts. Immunosuppression including receipt of corticosteroids is a major risk factor. Solid organ transplant recipients are at highest risk for Legionnaires' disease.[1,2]

Legionnaires' disease occurs infrequently in patients with HIV disease, but when it occurs, a complicated course including lung abscesses, bacteremia, and extrapulmonary involvement is common. Finally, legionellosis in immunosuppressed children is increasingly being reported; most cases have been nosocomial, usually acquired in neonatal or pediatric intensive care units (ICUs).[3,4]

The most common source for infection is the potable water distribution system. In addition to hospitals, cases have been linked to potable water within hotels, office buildings, work places, apartment buildings, and even private residences.[5,6] It is not well known that aerosol-generating devices are actually uncommon sources of Legionnaires' disease. Cooling towers are now known to be overestimated as the source for community-acquired Legionnaires' disease.[7]

COMMUNITY-ACQUIRED PNEUMONIA

Despite differences in geographic location, patient population, and laboratory methods applied, numerous studies of community-acquired pneumonia over the past 18 years have produced surprisingly consistent results as to the likely etiological agents in the immunocompetent individual. We evaluated 19 prospective studies that reported 6845 cases of community-acquired pneumonia requiring hospitalization (Table 1). As expected, *Streptococcus pneumoniae* was the most common bacterial pathogen identified worldwide (Table 1). *Legionella pneumophila* was ranked among the top five most common causes of community-acquired pneumonia in 12 of 19 studies (Table 1), but if the pneumonia warranted intensive care unit admission, it was among the top five most common causes in 8 of 9 studies (Table 2).

NOSOCOMIAL PNEUMONIA

Nosocomial Legionnaires' disease occurs in the context of a contaminated water supply. Comparative studies of hospital water supplies hospital water supplies have shown that in hospital in which *Legionella* was not present in the water, the incidence of nosocomial Legionnaires' disease was zero.[8–14] On the other hand, for hospitals with a contaminated potable water supply, the incidence of Legionnaires' disease has approached 40% of all nosocomial pneumonias.[8]

Nosocomial Legionnaires' disease is vastly underdiagnosed primarily because cultures on multiple selective media are generally not available in-house. In a survey of 192 hospitals participating in the National Nosocomial Infections Surveillance System, 40% of hospitals had no in-house laboratory testing for *Legionella*.[2] Only 19% of hospitals performed laboratory testing for Legionellosis in those hospitals with transplant and cancer programs—patients in these programs are at high risk for Legionnaires' disease! Incredibly, even for those hospitals experiencing cases of nosocomial Legionnaires' disease, only 21% had routine *Legionella* laboratory testing policies for respiratory specimens.

SEVERE PNEUMONIA

At the current time, no consensus definition of "severe" community-acquired pneumonia has achieved standardization. Ewig and Torres[15] have

Table 1. Microbial Etiology in Prospective Studies of Community-Acquired Pneumonia Requiring Hospitalization

Author	Study Years	Site	*N*	Rank Order of Etiology (%)				
				First	Second	Third	Fourth	Fifth
Burman et al.[46]	1982–1984	Umea/Sweden	196	*S. pneumoniae* 32	viral 21	*M. pneumoniae* 9	*H. influenzae* 5	*C. psittaci* 3
Bates et al.[47]	1985	Little Rock/AK	254	Legionella 8	*S. pneumoniae* 5	*C. pneumoniae* 5	*S. aureus* 5	viral 4
Fang et al.[21]	1986–1987	Pittsburgh/PA	359	*S. pneumoniae* 15	*H. influenzae* 11	Legionella 7	*C. pneumoniae* 6	aerobic gnr 6
Kauppinen et al.[48]	1986–1987	Oulu/Finland	125	*S. pneumoniae* 55	*C. pneumoniae* 43	*H. influenzae* 11	viral 8	*M. catarrhalis* 6
Amundson et al.[49]	1987–1989	San Diego/CA	75	*M. pneumoniae* 81	viral 17	*H. influenzae* 16	M. catarrhalis 5	—
Ostergaard et al.[50]	>5 y	Aarhus/Demark	254	*S. pneumoniae* 15	*H. influenzae* 8	*M. pneumoniae* 4	Legionella 3	aerobic gnr 3
Karalus et al.[51]	1988	Hamilton/NZ	92	*S. pneumoniae* 33	*M. pneumoniae* 19	viral 11	*H. influenzae* 5	Legionella 4
Kauppinen et al.[48]	1990	Valencia/Spain	510	*S. pneumoniae* 85	Legionella 14	viral 12	*M. pneumoniae* 4	aerobic gnr 2
Almirall et al.[52]	1990–1991	Barcelona/Spain	105	*C. pneumoniae* 15	*S. pneumoniae* 12	viral 11	*M. pneumoniae* 8	Legionella 3
Mundy et al.[53]	1990–1991	Baltimore/MD	205	*S. pneumonia* 15	*H. influenzae* 7	Viral 7	aerobic gnr 3	Legionella 3
Marston et al.[54]	1991	Columbus/Ohio	2776	*M. pneumoniae* 33	*S. pneumoniae* 13	*C. pneumoniae* 9	viral 7	*H. influenzae* 7
Lieberman et al.[55]	1991–1992	Beer-Sheva/Israel	346	*S. pneumoniae* 43	*M. pneumoniae* 29	*C. pneumoniae* 18	Legionella 16	viral 10
Bohte et al.[56]	1991–1993	Leiden/Netherlands	334	*S. pneumoniae* 27	*H. influenzae* 8	*M. pneumoniae* 6	*C. pneumoniae* 3	Legionella 2
Gomez et al.[57]	1991–1994	Murcia/Spain	100	*S. pneumoniae* 43	*C. pneumoniae* 21	*H. influenzae* 19	*M. pneumoniae* 11	Legionella 5
Vergis et al.[58]	1994–1996	Pittsburgh/PA	149	*S. pneumoniae* 25	Legionella 14	*H. influenzae* 13	*C. pneumoniae* 10	*M. pneumoniae* 9
Ishida et al.[59]	1994–1997	Okyama/Japan	326	*S. pneumoniae* 23	H. influenzae 7	*M. pneumoniae* 5	*K. pneumoniae* 4	*S. millerei* 4
Sopena et al.[30]	1994–1996	Barcelona/Spain	389	*S. pneumoniae* 24	*C. pneumoniae* 14	Legionella 13	*H. influenzae* 2	*P. aeruginosa* 2
Socan et al.[60]	1996–1997	Ljubljana/Slovenia	211	virus 24	*C. pneumoniae* 10	*S. pneumoniae* 6	*M. pneumoniae* 6	Legionella 3
Ruiz et al.[61]	1996–1997	Barcelona/Spain	395	*S. pneumoniae* 29	*H. influenzae* 11	Influenza 10	Legionella 7	*C. pneumoniae* 7

aerobic gnr = aerobic Gram-negative rod.

Table 2. Microbial Etiology of Prospective Studies of Severe Community-Acquired Pneumonia Admitted to Intensive Care Units

Author	Study Years	Site	*N*	Organism Rank, % (cases/total cases)				
				First	Second	Third	Fourth	Fifth
Torres et al.[18]	1984–1987	Barcelona/Spain	92	*S. pneumoniae* 15	Legionella 14	*M. pneumoniae* 6	*P. aeruginosa* 5	aerobic gnr 4
Pachon et al.[22]	1985–1987	Seville/Spain	67	*S. pneumonie* 18	Legionella 10	aerobic gnr 9	fungi 4	*H. influenzae* 3
Fang et al.[21]	1986–1987	Pittsburgh/PA	44	Legionella 25	*S. pneumoniae* 16	*H. influenzae* 15	*C. pneumoniae* 14	aerobic gnr 10
Moine et al.[17]	1987–1989	Garches/France	132	*S. pneumoniae* 33	*H. influenzae* 11	aerobic gnr 10	*Streptococcus* spp 7	virus 5
Falco et al.[25]	1988–1989	Barcelona/Spain	104	*S. pneumoniae* 18	Legionella 14	*C. psittachi* 5	aerobic gnr 5	*H. influenzae* 3
Sorensen et al.[24]		Linkoping/Sweden	36	*S. pneumoniae* 46	Legionella 12	*H. influenzae* 12	*S. aureus* 12	virus 4
Potgieter et al.[23]	1987–1989	Cape Town/ South Africa	95	*S. pneumoniae* 33	*H. influenzae* 13	aerobic gnr 13	*S. aureus* 8	Legionella 5
Rello et al.[19]	1988–1990	Barcelona/Spain	58	*S. pneumoniae* 22	Legionella 14	aerobic gnr 7	*M. tuberculosis* 7	P. carinii 5
Olaechea et al.[20]	1991–1992	Vizcaya/Spain	262	*S. pneumoniae* 11	Legionella 8	*H. influenzae* 4	*S. aureus* 4	*M. pneumoniae* 3

aerobic gnr = aerobic gram rod.

suggested that a combination of hypotension, multilobar involvement of chest radiograph, arterial hypoxemia, and mechanical ventilator be used to define severe pneumonia. Because few of the published studies explicitly listed all of the above criteria, we applied the commonly used subjective criteria of admission to the ICU to define "severe pneumonia."[16] For this review, we focused on nine studies that reported 890 cases of community-acquired pneumonia in which admission to the ICU was required (Table 2).[17–25]

The most conspicuous finding was that *S. pneumoniae* and *L. pneumophila* were the most frequently identified etiologic agents. Mortality from these cases of severe pneumonia in these nine studies ranged from 8 to 29%. Mortality from severe Legionnaires' disease in this series ranged from 0 to 25%. Aerobic Gram-negative bacilli ranked third overall, although few of these cases could be considered as "definitive" (i.e., confirmed by bacteremia or isolation of Gram-negative bacilli from pleural fluid or lung tissue). Moreover, the precise contribution of patients from nursing homes could not be ascertained in most studies (these patients are more likely to have Gram-negative pneumonias). In these nine studies, the frequency of mechanical ventilation among patients with severe pneumonia ranged from 9 to 91%, and with a mean mortality rate among mechanically ventilated patients of 35% with a range of 31 to 42%. Mortality among mechanically ventilated patients with severe Legionnaires' disease ranged from 0 to 25%.

CLINICAL MANIFESTATIONS

The predominant clinical manifestation of Legionnaires' disease is pneumonia. Classically, patients with atypical pneumonias usually have a relatively nonproductive cough and grossly purulent sputum is uncommon. The Gram's stain of sputum shows numerous polymorphonuclear leukocytes, with very few or no organisms seen. As mentioned previously, the clinical manifestations of Legionnaires' disease are usually more severe than those of the other atypical pneumonias caused by viruses, *C. pneumoniae,* and *M. pneumoniae*. It should be noted that in the early studies of Legionnaires' disease, investigators reported that there was a characteristic syndrome reflecting a pneumonia of unusual clinical severity. Notable clinical manifestations included gastrointestinal symptoms especially diarrhea, relative bradycardia (pulse-temperature defect), and nonspecific neurological symptoms (headache and mental status changes). Laboratory abnormalities included renal dysfunction, hepatic dysfunction, hyponatremia, hypophophatemia, and hematuria.[26,27] Development of respiratory failure and chest radiograph progression were more common in Legionnaires' disease than in pneumonias of other etiology.[25]

In 1982, we published a comparative pneumonia study in which clinical manifestations and laboratory parameters for Legionnaires' disease were compared to those of other bacterial etiologies (mostly aspiration pneumonia, *Streptococcus pneumoniae, Haemophilus influenzae,* aerobic Gram-negative bacilli, *Staphylococcus aureus*).[28] We found that clinical manifestations of Legionnaires' disease was similar to those of other bacterial etiologies. We did confirm that hyponatremia occurred significantly more often in patients with Legionnaire' disease; other investigators have also noted this significant association.[29–31] Since then, more than 10 comparative studies of pneumonia have confirmed that the clinical presentation of Legionnaires' disease is nonspecific. We believe that the earlier studies were biased toward more patients with severe clinical manifestations for two reasons: (1) laboratory diagnostic methods for *Legionella* were rarely ordered by physicians in their first encounter in patients with Legionnaires' disease leading to delay of correct diagnosis, (2) effective anti-*Legionella* antibiotic therapy was rarely given to patients with Legionnaires' disease because beta-lactam antibiotics, especially cephalosporins, were the empiric antibiotics of choice for pneumonia up until the early 1990s.

On the other hand, Cunha[32] has advocated for a syndromic approach and has even devised an elaborate point system for the diagnosis of Legionnaires' disease. Points were assigned for lethargy, diarrhea, abdominal pain, relative bradycardia for temperature ≥102°F. Points were deducted for productive cough, sore throat, ear pain, and hoarseness. The higher the number of points, the more likely the diagnosis of Legionnaires' disease. Interestingly, in a preliminary study, De Carolis et al[33] have found this point system to be relatively sensitive in the diagnosis of Legionnaires' disease, but not specific. In a prospective comparative study of pneumococcal pneumonia versus Legionnaires' disease, Falco et al[25] found that gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea) and neurological symptoms (headache, confusion, delirium) were significantly more frequent in Legionnaires' disease. In contrast, upper respiratory tract symptoms, productive cough with purulent sputum, and pleuritic chest pain were significantly more frequent in pneumococcal pneumonia. Similarly, hepatic enzymes and serum creatinine were more likely to be elevated in Legionnaires' disease. In this study, 30 patients had Legionnaires' disease, and 67% were culture-proven. Sopena et al[30] found diarrhea and headache to be significantly more frequent in 48 patients with Legionnaires' disease than in pneumonias

of other etiology. Productive cough and chest pain were seen more commonly in pneumonias of other etiology. Serum creatinine phosphokinase was also significantly higher in Legionnaires' disease. Investigators from the Community-Based Pneumonia Incidence Study Group also suggested a syndromic approach based on a multivariate analysis of patients hospitalized for community-acquired pneumonia; 53 patients had Legionnaires' disease. They found that fever ≥ 102°F, headache, elevated serum lactate dehydrogenase (LDH) > 700 U/L, and hyponatremia were significantly more likely to occur in Legionnaires' disease.[34] Finally, Blatter et al[35] suggested that temperature ≥ 39°C and presence of cough without purulent sputum were more likely in a study in which 18 patients had Legionnaires' disease.

We remain skeptical of the utility of the syndromic approach in a setting in which physician index of suspicion is high for Legionnaires' disease and laboratory testing for *Legionella* is available. In such a scenario, cases of Legionnaires' disease will be diagnosed earlier, such that the severe clinical manifestations associated with a syndromic approach will be muted. On the other hand, in patients who present to the physician late in the course of disease, or in patients in whom the diagnosis of Legionnaires' disease is mistakenly overlooked by the physician, application of the syndromic approach may suggest the correct diagnosis. Therefore, we recommend that for patients with pneumonia of sufficient severity to be admitted to the ICU, application of the syndromic approach warrants evaluation in a validation cohort. If a trend favoring the utility of the syndromic approach can be documented, such an approach may be useful to clinicians in increasing the index of suspicion for Legionnaires' disease.

In any case, the following clinical observations should heighten clinical suspicion of Legionnaires' disease: (1) fever exceeding 39°C; (2) presence of diarrhea, (3) Gram's stain of sputum with presence of neutrophils, but few, if any, organisms are visible; (4) hyponatremia (serum sodium ≤ 130 meg/L), (5) failure of a therapeutic response to β-lactam (penicillin or cephalosporin) or aminoglycoside antimicrobial agent; and (6) occurrence in a setting of known contamination of the potable water supply with *Legionella.*

RADIOLOGICAL MANIFESTATIONS

Abnormalities in the chest radiograph are generally nonspecific. However, progression of infiltrates despite appropriate antibiotic therapy, presence of pleural effusions, evidence of pleural-based infiltrates that clinically mimic pulmonary embolism, and circumscribed peripheral densities are suggestive of pneumonia caused by Legionella.[36] The initial radiographic finding is a unilateral alveolar infiltrate that may progress to lobar consolidation. Radiographic abnormalities are seen by the third day of the illness in virtually all the patients. Patchy and diffuse infiltrates, or segmental or lobar infiltrates may be seen at presentation. Multilobar involvement may become evident despite antibiotic therapy.[37]

Circumscribed peripheral densities and nodules are typically seen in immunosuppressed patients. These can rapidly progress with a tendency to cavitate. Cavitation and abscess formation are uncommon features of Legionnaires' disease in the immunocompetent patient, but can be quite impressive in patients receiving corticosteroids.[38] Cavitary disease may develop up to 14 days after initial presentation despite appropriate antibiotic therapy. Pleural effusions are evident in one third of patients with Legionnaires' disease and may herald the pulmonary infiltrate. Empyema and pericardial effusion have been described. The degree of radiographic abnormalities does not necessarily correlate with the clinical severity or outcome. Radiographic improvement in patients with Legionnaires' disease often lags behind clinical response, and several weeks to months may pass before the infiltrates resolve completely.[37]

LABORATORY TESTING

Specialized laboratory testing is required to make the diagnosis of Legionnaires' disease since the clinical and radiographic presentation is nonspecific (Table 3). Five specialized tests have been used for diagnosis of Legionnaires' disease: serology, culture, direct fluorescent antibody (DFA) stain, culture on selective media, and polymerase chain reaction (PCR). Three of the tests are applied to respiratory secretions (direct fluorescent antibody [DFA], culture, PCR), and two of the tests use blood (serology) or urine specimens (urinary antigen). Three of the tests are considered "rapid" tests, that is, results are available within hours of test performance; they are the urinary antigen, DFA, and PCR. We recommend that the urinary antigen for *Legionella* and culture on selective media be available in-house in every hospital laboratory.

GRAM STAIN

Gram's staining of pleural fluid or lung tissue may allow visualization of small, pleomorphic, faint Gram-negative bacilli that is characteristic of Legionella. The organism is not easily seen in sputum. *Legionella micdadei* are occasionally seen on modified acid-fast stains.

Table 3. Usefulness of Specialized Laboratory Tests 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 media that contain dyes and have been pretreated with acid to minimize overgrowth of competing microorganism.
†This test is useful only for *L. pneumophila* serogroup 1.
‡This approach requires IgG and IgM testing of serum samples obtained during the acute phase and convalescence. A single titer of > 1:256 in a patient with pneumonia is considered presumptive evidence of infection, and a fourfold increase in antibody titer is considered definitive evidence.

CULTURE

Recovery of the organism from respiratory secretions on buffered charcoal yeast extract (BCYE) culture media is the definitive method of diagnosis. Standard bacteriological media do not support the growth of *Legionella.* Three media need to be used for maximal sensitivity: (1) BCYE media, (2) BCYE supplemented with polymyxin, anisomycin, vancomycin and dyes, (3) BCYE supplemented with polymyxin, anisomycin, and cefamandole.[39] Acid wash pretreatment of sputum is also necessary to reduce overgrowth of competing microflora. Specimens obtained by bronchoscopy are not necessarily superior to expectorated sputum. Macroscopically visible colonies appear after 3 to 5 days of growth. Nonpurulent sputum with few polymorphonuclear leukocytes and numerous squamous epithelial cells are traditionally considered to be inadequate specimens for cultures; however, many such specimens have yielded *L. pneumophila* by culture.[25,40]

DFA STAIN

DFA stain is a rapid test that allows direct visualization of *Legionella* in clinical specimens. Positive results with this staining method depends on a large burden of organisms and is more likely to be positive if there is extensive pulmonary disease on chest radiograph at presentation.[37] False-positive results are usually due to improper laboratory technique or contamination.

ANTIBODY DETECTION

Serological detection of antibodies directed against Legionella is made by either indirect fluorescent antibody or enzyme-linked immunosorbent assays (ELISA). Diagnosis requires that acute and convalescent sera demonstrate a fourfold rise in antibody titer to 1:128. Both IgM and IgG antibody titers should be performed. A single titer of 1:256 in a patient with pneumonia has been considered as presumptive evidence of Legionnaires' disease, although Plouffe et al[41] found this cutoff to be insensitive. Titers may be elevated in 25 to 40% of patients during the first week of illness. Convalescent sera at three different time points are needed for maximal sensitivity: at the time of presentation, 4 to 6 weeks later, and 3 to 6 months later. Serology is used primarily for epidemiological studies or to verify a suspected diagnosis. It cannot be used for decision-making on antibiotic therapy because it may take weeks to obtain a result.

URINARY ANTIGEN

A new, rapid immunochromatographic assay (NOW, Binax, S. Portland, ME) is an improvement over previous radioimmunoassay and ELISA tests with respect to ease of performance. Urine is often easier to obtain than sputum and results are not affected by antibiotics. The test is available only for *L. pneumophila* serogroup 1, although this serogroup accounts for at least 90% of *Legionella* infections.

POLYMERASE CHAIN REACTIONS

This rapid method has been used to detect *Legionella* in urine samples, bronchoalveolar lavage fluid, and serum. Current assays have not proven more sensitive than culture, such that technical improvements are required before PCR can be widely applied.

TREATMENT

The newer macrolides, especially azithromycin, have displaced erythromycin as the antibiotic of choice. Azithromycin, roxithromycin, clarithromycin have superior lung tissue penetration and more potent intracellular and in vitro activity than erythromycin.

The quinolones (levofloxacin, ciprofloxacin, moxifloxacin, gemifloxacin, trovafloxacin) also demonstrate superior in vitro activity and improved pharmacokinetics such that once-daily dosing is feasible. In vitro, all the quinolones are more potent than azithromycin, the current macrolide of choice. Moreover, clinical trials have confirmed the efficacy of levofloxacin and ciprofloxacin for cases of culture-confirmed Legionnaires' disease. Therapy with the fluroquinolones, especially levofloxacin or ciprofloxacin, is recommended for organ transplant recipients with Legionnaires' disease. The macrolides

(but not azithromycin) interact with tacrolimus and cyclosporin—immunosuppressive drugs used following organ transplantation.

There is no data on the utility of combination therapy, although we have used combination therapy in seriously ill patients with confirmed Legionnaires' disease; this might include immunosuppressed patients with multilobar disease or patients with respiratory failure. The most common combination therapy that we have used is levofloxacin plus azithromycin. Rifampin has also been used in combination therapies. Rifampin interacts with tacrolimus and cyclosporin, which may result in marked reductions in the levels of the immunosuppressive drugs so that its use in transplant patients should be limited.

The dosages of the various drugs are shown in Table 4. Duration of therapy of 10 to 14 days is usually sufficient; however, a 21-day course of therapy has been recommended for immunosuppressed patients or for those with extensive pulmonary disease as evidenced by radiographic abnormalities.

Delay in administration of appropriate antibiotic therapy for Legionnaires' disease significantly increases mortality.[25,42] Because of the high incidence of Legionnaires' disease in cases of severe pneumonia (Table 2), empiric therapy for Legionellosis should be included in every patient admitted to the ICU with undiagnosed pneumonia. We recommend that immunocompetent patients with severe pneumonia of uncertain etiology be given one of two empiric regimens at outset: (1) ceftriaxone plus azithromycin or (2) levofloxacin, moxifloxacin, or gemifloxacin as monotherapy. Both of the above regimens would provide coverage for *Legionella,* penicillin-resistant pneumococci, and aerobic Gram-negative bacilli—problem pathogens in patients admitted to the ICU. Adjunctive therapy with extracorporeal membrane oxygenation for severe Legionnaires' disease has been reported to be effective in patients with acute respiratory failure.[43]

Table 4. Antibiotic Therapy for Legionella Infections

Antimicrobial Agent	Dosage
Azithromycin	500 mg* orally or intravenously every 24 hr
Clarithromycin	500 mg orally or intravenously every 12 hr
Roxithromycin	300 mg orally every 12 hr
Erythromycin	1 g intravenously every 6 hr 500 mg orally every 6 hr
Levofloxacin	500 mg* orally or intravenously every 24 hr
Ciprofloxacin	400 mg intravenously every 8 hr 750 mg orally every 12 hr
Doxycycline	100 mg* orally or intravenously every 12 hr
Minocycline	100 mg* orally or intravenously every 12 hr
Timethoprim-sulfamethoxazole	160 and 800 mg intravenously every 8 hr 160 and 800 mg orally every 12 hr
Rifampin	300 to 600 mg orally or intravenously every 12 hr

The doses are based on clinical experience and not on controlled trials.
*We recommend doubling the first dose.

PREVENTION

We recommend routine environmental cultures of the hospital water supply regardless of whether nosocomial Legionnaires' disease has been diagnosed.[44] If *Legionella* is isolated, culture on selective media should be made available in-house rather than being sent to reference laboratories. The Centers for Disease Control and Prevention have opposed this approach claiming that the cost efficacy of routine environmental cultures in the absence of known nosocomial Legionnaires' disease is uncertain. However, health departments in several states in the United States and national communicable disease centers in Europe are now formulating guidelines mandating routine environmental cultures for *Legionella.* Disinfection modalities can be applied to the water distribution system if necessary. Super-heat-and-flush can be applied immediately to terminate an outbreak.[45] Copper-silver ionization systems can be installed for long-term disinfection. Hyperchlorination is no longer recommended.

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