Severe Pneumonia Caused by *Legionella pneumophila*

Differential Diagnosis and Therapeutic Considerations

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KEYWORDS

- Legionnaire's disease • Severe community-acquired pneumonia
- *Legionella pneumophila* • Pneumonia complications • Hospital-acquired pneumonia
- *Legionella pneumophila* outbreaks

KEY POINTS

- Severe legionella pneumonia poses a diagnostic challenge and requires early intervention.
- Legionnaire's disease can have several presenting signs, symptoms, and laboratory abnormalities that suggest that *Legionella pneumophila* is the pathogen, but none of these are sufficient to distinguish *L pneumophila* pneumonia from other respiratory pathogens.
- *L pneumophila* is primarily an intracellular pathogen and needs treatment with antibiotics that efficiently enter the intracellular space.

Legionnaire's disease is one of the most important nonzoonotic, atypical infections that affect humans. Pneumonia is the predominant clinical manifestation of *Legionella* spp infection in humans. Legionellosis is consistently reported among the top 3 most commonly identified respiratory pathogens in community-acquired pneumonia, in addition to being a reported cause of hospital-acquired pneumonia.[1–4] *Legionella pneumophila* pneumonia is associated with high morbidity, as shown by the high proportion of patients requiring intensive care unit (ICU) admission. However, mortalities for severe *Legionella* spp pneumonia have decreased significantly with the realization that early, targeted therapy that covers this pathogen improves outcome.[4,5] This article focuses on severe legionella pneumonia epidemiology, clinical manifestations, laboratory findings, treatment and outcomes, and the differential diagnostic considerations.

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EPIDEMIOLOGY

Legionella pneumonia accounts for about 2% to 15% of all community-acquired pneumonias that require hospitalization in Europe and North America.[6] Patients with legionnaire's disease are more likely to have severe community-acquired pneumonia (SCAP) than those with most other atypical respiratory pathogens. SCAP is defined by more severely abnormal vital signs, more extensive infiltrates on chest radiography, and the need for admission to the ICU.[7–11] For nosocomial legionella pneumonia, the epidemiology has shifted from large outbreaks in tertiary care centers in the 1980s to sporadic cases in community hospitals in more recent years.[12]

The incidence of nosocomial legionella pneumonia is directly related to the lack of availability of in-house testing and lack of due diligence to carefully monitor for the presence of a contaminated water source in the hospital. These nosocomial infections are preventable by careful environmental management in the hospital setting.[13] A single case of nosocomial legionellosis is a priori evidence of a contaminated water supply within the institution. Such an occurrence should immediately prompt an environmental investigation by infection control and environmental services to identify the contaminated water supply and rectify the source of contamination. Person-to-person transmission does not occur and hospital outbreaks indicate a common source of exposure to contaminated water supplies within the hospital.

Factors that have been associated with high severity and mortality in legionella are extremes of age (infants and old patients), nosocomial acquisition, underlying conditions (eg, chronic lung disease, immunodeficiency, solid organ transplants, human immunodeficiency virus, end-stage renal disease, malignancies, and diabetes mellitus), and delayed initiation of proper antimicrobial therapy.[14] Possible predisposing factors and prognostic factors for severe *L pneumophila* pneumonia are listed in **Table 1**.

CLINICAL MANIFESTATIONS AND LABORATORY DIAGNOSIS

Legionella is one of the most commonly misdiagnosed pathogens as a cause severe community-acquired pneumonia. Multiple studies have shown it to be underdiagnosed and undertreated.[15] *Legionella* spp cause an array of respiratory illnesses but this article focuses on SCAP and nosocomial infections. SCAP is operationally defined as community-acquired pneumonia of sufficient severity to warrant ICU care for ventilatory and/or hemodynamic support. Delayed diagnosis of legionellosis is partly

Table 1 Predisposing factors and prognostic factors	
Predisposing Factors	**Prognostic Indicators**
Extremes of age	Extremes of age
Smoking	Chronic lung disease
Chronic lung disease	Immune compromised states
Immunocompromised states	Multilobar involvement and severe hypoxia
Solid organ transplantation	with need for ventilatory support
Exposure to contaminated water	Delay in appropriate antibiotics
supplies	End-stage kidney disease
Human immunodeficiency virus	Human immunodeficiency virus
Late summer and early autumn	Diabetes
months in northern hemisphere	Septic shock
Male gender	Hyponatremia

Data from Refs.[1–7,11–13,15,16,19]

related to the lack of readily accessible diagnostic tools to help with early identification of legionella infection. The clinical manifestations and radiographic findings are nonspecific and do not accurately distinguish *L pneumophila* from other respiratory pathogens. In addition, typical empiric antibiotic therapy often lacks proper antimicrobial coverage against *Legionella*.[16] Several clinical and laboratory abnormalities have been linked in the past to the diagnosis of legionellosis. These abnormalities include hyponatremia, hypophosphatemia, increased liver enzyme levels, acute mental status changes, headache, diarrhea, early onset of pleuritic pain (sometimes confused with a pulmonary embolus), and acute increase in creatine phosphokinase level. However, follow-up clinical studies have been largely unsuccessful in reliably identifying and verifying clinical and laboratory parameters that are specific for legionella infection. Note that hyponatremia has been a fairly reproducible indictor of severe legionellosis in several studies. Individually, clinical and laboratory abnormalities lack diagnostic specificity. Nonetheless, the specificity of clinical and laboratory findings is increased when those parameters are combined[5] (**Table 2**). Respiratory symptoms tend to be less prominent initially in patients with legionnaire's disease.[17–20]

Legionella pneumonia shares with other intracellular pathogens the propensity to produce relative bradycardia in the presence of fever. This temperature-pulse abnormality with relative bradycardia in response to fever (Faget sign) is uncommon with typical bacterial pneumonia. Pulse rate usually increases by about 15 beats/min for every 1°C increase in body temperature. Faget sign has been frequently described in older adult patients with more severe pneumonia[19] but this finding is not highly specific for legionellosis. Gastrointestinal manifestations such as watery diarrhea and sudden abdominal pain can sometimes be the presenting symptoms in patients with legionella pneumonia. Another clue to the possibility of SCAP from legionellosis is the finding of numerous neutrophils on Gram strain of respiratory specimens with the absence of visible bacteria. Legionella spp are gram-negative pathogens but do not stain well with the standard Gram stain.

Diagnosis is based mainly on the isolation of the pathogen from sputum, bronchoalveolar lavage fluid, pleural fluid, and occasionally from blood cultures. Nonculture, molecular diagnostic methods promise to improve the laboratory diagnosis of

Table 2		
Diagnostic clues to the possibility of legionellosis		
Factor	**Comments**	**Frequency of Occurrence**
Hyponatremia	Fairly reliable in several studies	≥2
Hypophosphatemia	—	≥1
Gastrointestinal symptoms	Diarrhea, abdominal pain, vomiting	≥2
Altered mental status	Confusion, lethargy, head ache	≥1
Increased liver enzyme levels	—	—
Neutrophils on Gram stain with no bacteria identified	Helpful but can be found in viral and mycoplasma pneumonia	≥3
Temperature-pulse dissociation with relative bradycardia	Helpful but not specific	≥3
Acute kidney injury	—	≥1
Nosocomial outbreaks	*Legionella* in hospital water supply	≥2

≥1, uncommon; ≥2, occasionally observed; ≥3, frequently reported.
Data from Refs.[4,5,7,11–13]

legionellosis in the future, but this molecular diagnostic technique has not yet proved sufficiently superior to cultures to supplant the diagnostic accuracy of cultures on standard buffered charcoal yeast extract plates. The urinary antigen is highly specific but primarily detects serotype 1 *L pneumophila* and does not detect other *Legionella* species. Imaging studies, histopathologic findings, and other laboratory methods are of limited use. A 4-fold or greater increase in serum antibody level is useful for epidemiologic purposes but not as a diagnostic test for patients presenting with SCAP. The direct fluorescent antigen test performed on respiratory specimens can be useful in laboratories proficient with the technique and with available reagents.

In a US Centers for Disease Control and Prevention (CDC) report from 2001, only 35 of the first 1000 cases of sporadic legionella pneumonia reported to the CDC were confirmed by culture, and only 19 from specimens obtained before death.[21] Culturing for *Legionella* spp is the single most important laboratory test. This test should be routinely available in all clinical microbiology laboratories given the frequency of *Legionella* as a causative organism. Increased procalcitonin level was found to be a potentially useful biomarker for severity of illness from legionella infection.[22,23]

There is no specific radiological finding that can help identify legionella pneumonia on chest imaging. *Legionella* is typically associated with rapidly worsening infiltrates on chest radiography that may continue to worsen despite antimicrobial treatment.[24,25]

L pneumophila serotype 1 accounts for about 90% of all *Legionella* spp. Infections with serotypes 1, 4, and 6 are the most common isolates from patients with severe community-acquired pneumonia. Other *Legionella* spp, such as *Legionella micdadei*, *Legionella bozemanae*, *Legionella longbeachae*, *and Legionella dumoffii*, account for the remaining 10% of human cases of legionella pneumonia.

DIFFERENTIAL DIAGNOSIS CONSIDERATIONS
Mycoplasma pneumoniae

Mycoplasma pneumonia is typically a disease of gradual onset with persistent cough for several days to weeks. Patients characteristically do not appear toxic, despite having significant disease infiltrates on chest radiography, hence the walking pneumonia appellation. Mild pharyngeal injection with minimal or no cervical adenopathy can be seen with mycoplasma pneumonia, but upper respiratory tract symptoms are not common with legionella infections. *Mycoplasma pneumoniae* has long been associated with bullous myringitis, but recent literature has disproved this association.[26] Similar to legionella pneumonia, atypical pneumonia with mycoplasma can be associated with extrapulmonary symptoms such as myalgia, abdominal pain, and diarrhea. Mycoplasma is frequently associated with additional cardiovascular abnormalities such as myocarditis, pericarditis, and heart block.[27] Such cardiac manifestations are not commonly seen in legionella infections. Mycoplasma infection has been associated with several skin manifestations, including erythema multiforme, macular and vesicular exanthems, urticaria, erythema nodosum, and Stevens-Johnson syndrome.[28] Dermatologic findings are uncommon in legionella pneumonia.

Although not exclusive to mycoplasma infection, increased cold agglutinin titers of 1:64 or higher are highly associated with community-acquired pneumonia from *Mycoplasma*. The cold agglutinin titers occur early in presentation (day 1–3). Rarely, meningoencephalitis from *M pneumoniae* can be seen, and is usually associated with very high agglutinin titers (1:1052 or higher).[29] If untreated, mycoplasma pneumonia can lead to the development of asthma in nonasthmatic patients, or an asthma

exacerbation in known asthmatics.[30,31] Electrolyte abnormalities are not usually seen in cases of *M pneumoniae* disease.

Streptococcus pneumoniae

Streptococcus pneumoniae is the most common bacterial cause of community-acquired pneumonia. *S pneumoniae* can cause a wide variety of clinical symptoms because of its ability to cause disease by either direct extension from the nasopharynx into surrounding anatomic structures or vascular invasion and hematogenous spread. It can result in meningitis, bacteremia, otitis media, sinusitis, septic arthritis, osteomyelitis, peritonitis, and endocarditis.

Pneumococcal pneumonia typically presents with an acute onset of high fever, rigors, productive cough, and dyspnea. Respiratory symptoms dominate the presentation in cases of *S pneumoniae* infection. Unlike in legionella, extrapulmonary symptoms are uncommon in pneumococcal pneumonia. Patients are typically very sick looking. Patients have rales and dullness to percussion on examination. Concomitant pleural effusion is the most common complication with *S pneumoniae*, but pleural effusions can be seen in many other microorganisms causing pneumonia. The characteristic chest radiography finding in pneumococcal pneumonia is lobar consolidation, whereas sharply marinated peribronchial consolidations within ground-glass opacities are more specific finding with *Legionella*.[32] To differentiate legionella from *S pneumoniae* community-acquired pneumonia, cardiac, hepatic, and renal abnormalities are helpful because they are expected to be normal with *S pneumoniae* but frequently abnormal in legionnaire's disease.

Zoonotic Atypical Pneumonias

Chlamydophila psittaci (psittacosis), *Francisella tularensis* (tularemia), and *Coxiella burnetii* (Q fever), are 3 zoonotic pathogens that can cause atypical pneumonia in humans. Acquisition of these zoonotic infections can only occur with direct contact with animal hosts or laboratory exposure. Therefore, zoonotic pneumonias can be eliminated from diagnostic consideration with a negative contact history. In *C burnetii*, cattle, sheep, and goats are the primary reservoirs. Transmission to humans occurs primarily through inhalation of aerosols from soil contaminated with animal waste. Psittacosis is usually an occupational disease seen in zoo and pet-shop employees, ranchers, and poultry farmers. Human-to-human transmission has been reported but is very rare. Tularemia pneumonia is an uncommon condition that may develop in laboratory workers. It is rarely acquired naturally nowadays and its occurrence should suggest the possibility of a bioterrorist event.

Atypical pneumonia from Q fever and psittacosis are probably underdiagnosed because patients with mild cases may not seek medical attention or may not be reported because pneumonia can sometimes be an incidental finding. It often presents with dry cough, pleuritic chest pain, and dyspnea. The incubation period varies from 2 to 6 weeks.[32] Symptoms are more abrupt in pneumonic tularemia and tend to be more severe. Rash and pharyngitis can be part of the presentation. Association with gastrointestinal symptoms and hepatitis presenting with pain and mild transaminitis can be seen with Q fever and psittacosis. Unlike legionella, no diarrhea is often associated with zoonotic pneumonias. Relative bradycardia in zoonotic community-acquired pneumonia should suggest Q fever or psittacosis but not tularemia.

Leukopenia can sometimes be seen in psittacosis. All zoonotic pneumonias can result in hyponatremia. Transaminitis can be seen with either Q fever or psittacosis. Chest radiology can show bilateral hilar adenopathy and lobar infiltrates or

round/oval densities in pneumonic tularemia. Psittacosis and Q fever tend to be associated with patchy consolidation on chest imaging.[33]

Viral Pneumonia

Because of improved diagnostic techniques, the reported incidence of viral pneumonia has increased during the past decade. Recent studies have shown viruses to cause 13% to 50% of pathogen-identified community-acquired pneumonia as sole pathogens and around 8% to 27% of cases as mixed bacterial-viral infections.[34–37] Several viruses have been identified as causes of pneumonia. Among those viruses are influenza virus types A and B (accounting for more than 50% of all viral pneumonias), parainfluenza virus (2%–3%), respiratory syncytial virus (RSV; 1%–4%), coronavirus (1%–14%), adenovirus (1% to 4%), and human metapneumovirus (hMPV; 0%–4%).[34–36,38] Viral pneumonias show seasonal variations and outbreaks can be identified by possible exposure to sick contacts.

Viral pneumonias usually present with nonspecific constitutional symptoms such as fever, chills, rhinitis, dry cough, myalgia, fatigue, and headaches. Later, patients might develop dyspnea and productive cough. Hoarseness of voice and diffuse wheezes are frequent findings on examination in cases of viral pneumonia (especially with RSV and hMPV),[37] findings that are not seen with legionella pneumonia. Chest pain and rigors are not common with viral pneumonias. Extrapulmonary symptoms are not commonly seen in viral pneumonia, with the exception of nausea, vomiting, and diarrhea, which can be seen with adenovirus. Secondary bacterial pneumonia can happen in cases of viral pneumonia, especially with influenza pneumonia. It is characterized by the relapse of high fever, with purulent sputum and cough. This relapse usually occurs after initial improvement.

TREATMENT CONSIDERATIONS
Macrolides, Quinolones, Rifampin, Combinations, Steroids?

Legionella pneumonia should be treated in most patients with a respiratory quinolone and/or a macrolide such as azithromycin (**Table 3**). No randomized controlled trials have directly compared fluoroquinolones versus macrolides in treating legionellosis. A retrospective study has suggested that the use of azithromycin alone or a quinolone alone was associated with a similar mortality and length of stay.[39] However, quicker defervescence and fewer complications were observed with quinolone treatment.[40–44] As a result, levofloxacin is thought to be the empiric drug of choice in severe pneumonia with suspected *Legionella* spp as well as in nosocomial cases.

Some laboratory studies and case reports have suggested possible therapeutic benefits with the combination of antimicrobial therapy with a quinolone plus azithromycin or rifampin. However, clinical observational studies of antimicrobial therapies for legionella have yet to validate the benefits of combination treatment compared with monotherapy. Combination therapy of a quinolone plus azithromycin can be considered in critically ill patients as well as in extrapulmonary legionellosis. One review article suggested considering rifampin therapy for patients with severe disease or significant comorbid conditions and immunocompromised hosts who are refractory to conventional monotherapy regimens.[45]

Despite comparative bioavailability in oral and parenteral treatment, the latter is recommended initially for all patients with severe legionella pneumonia. Vomiting, impaired gastric mobility, nasogastric suctioning, and alkalization of the gastrointestinal tract for stress-ulcer prophylaxis are all factors that can result in compromised absorption of these medications in critical care settings.[46–49]

Table 3		
Therapeutic options for adult patients with severe pneumonia from *Legionella pneumophila*		
Therapy	**Normal Adult Dose**	**Comments**
Macrolides	Azithromycin 500 mg IV every 24 h or clarithromycin 500 mg IV every 12 h	Preferred regimen in most settings, or a fluoroquinolone
Fluoroquinolones	Levofloxacin (500 mg IV/d) or moxifloxacin 400 mg IV once daily	Generally well tolerated and effective
Rifampin	300–600 mg IV every 12 h	Multiple drug interactions, including warfarin, opiates, cyclosporine, antiretroviral protease inhibitors; used with a macrolide or quinolone
Doxycycline	200-mg IV loading dose followed by 100 mg IV every 12 h	Limited clinical experience shows activity
Combinations	Levofloxacin (500 mg IV/d) or another fluoroquinolone + azithromycin (500 mg IV every 24 h); consider adding rifampin to monotherapy despite many drug interactions	No clear evidence of efficacy of combination therapy compared with monotherapy; often used in SCAP with extensive disease in high-risk patients failing monotherapy
Corticosteroids	0.5–1 mg/kg/d	No clinical evidence of benefit at present in patients with SCAP from legionellosis; awaiting clinical trial evidence

Abbreviation: IV, intravenous.
Data from Refs.[11–13,40–55]

In contrast with the 5-day course of atypical coverage in empiric regimens for community-acquired pneumonia, confirmed cases of legionella require longer courses of treatment. Levofloxacin or azithromycin for 7 to 10 days are recommended in cases of moderate to severe legionella pneumonia. For immunocompromised hosts, a 21-day course of levofloxacin is usually recommended.

A recent randomized controlled study found that low-dose corticosteroid therapy was effective in treating community-acquired pneumonia.[50] A series of recent systematic reviews and meta-analyses have appeared in the literature recently that indicate that steroids might be of some benefit in community-acquired pneumonia.[51–54] However, there are no specific data for the effect of corticosteroids in legionella pneumonia. One case study reported that using high-dose corticosteroid is effective for treating severe legionella pneumonia,[55] but sufficient data are not available to validate the use of corticosteroids in the treatment of SCAP caused by *Legionella* spp. Further observational studies, or preferably controlled trials, will be needed to justify the use of glucocorticoids, with their attendant risks, in this clinical setting.

OUTCOMES/MORTALITY

In one study, mortality in cases of legionella pneumonia admitted to the ICU was around 33%. In another study, SAPS (Simplified Acute Physiology Score) II score higher than 46, duration of symptoms before ICU admission longer than 5 days, and intubation were associated with increased mortality.[56] The same study also suggested

that early initiation of fluoroquinolone therapy within 8 hours of ICU admission reduces mortality. With early initiation of appropriate antibiotics, mortality decreases to less than 5%.[14] Delay in initiation of appropriate antibiotics is associated with a worse prognosis.[57] Treatment failure tends to occur in patients with severe disease at the time of admission[41] or in immune compromised patients.[58] Legionellosis can leave patients with long-term adverse health effects and morbidity. In one study, survivors of severe legionella pneumonia reported persisting fatigue (75%), neurologic symptoms (66%), and neuromuscular symptoms (63%) at 17 months' follow-up.[59] The same study also reported that health-related quality of life (HRQL) was impaired in 7 of the 8 dimensions assessed by the HRQL questionnaire, and 15% of patients reported symptoms of PTSD.

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