



Legionnaires' disease: Seek and ye shall find

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■ ABSTRACT

Legionella pneumophila is among the top three or four microbial causes of community-acquired pneumonia, yet is often misdiagnosed and inadequately treated. New laboratory tests should simplify the diagnosis. Also, contrary to common perception, the disease is usually spread via aspiration of water from contaminated hot water distribution systems, not from air conditioning systems. The treatment of choice has shifted from erythromycin to the newer macrolides and quinolones. Routine culturing of the hospital water supply is a requisite first step in preventing hospital-acquired Legionnaires' disease.

OFTEN THOUGHT TO BE UNUSUAL AND rare, Legionnaires' disease actually accounts for 2% to 15% of cases of community-acquired pneumonia that require hospitalization.¹ *Legionella pneumophila* also accounts for many cases of nosocomial pneumonia. Extrapulmonary infections including nosocomial wound infection, endocarditis, and pericarditis have been reported.^{2,3}

Unfortunately, most cases of Legionnaires' disease are misdiagnosed and inadequately treated. The Centers for Disease Control and Prevention (CDC) estimates that only 3% of cases of community-acquired Legionnaires' pneumonia are correctly identified.⁴

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This will change. With new, convenient diagnostic tests and improved understanding, physicians will recognize many more cases of Legionnaires' disease that have been under our noses the whole time. The key, however, is to suspect it in the first place

■ PATIENTS AT RISK

Particularly at risk of infection are patients weakened by underlying disease: those with chronic obstructive pulmonary disease, transplant recipients, patients receiving corticosteroids, patients with chronic lung abscesses, neonatal intensive care patients, and immunosuppressed children.

■ NEW UNDERSTANDING OF HOW THE DISEASE IS TRANSMITTED

Although air conditioners were implicated in the first outbreak of Legionnaires' disease (in Philadelphia in 1976),⁵ more recent data show that the *Legionella* bacterium is actually found in water distribution systems in large buildings, such as hospitals, workplaces, and nursing homes.⁶⁻¹⁰ Other habitats include private residences, whirlpool spas, hot springs, and mist machines.^{5,9,11} Optimal growth conditions for the bacterium are in water temperatures of 100° to 120°F.

Aspiration of contaminated water is now considered the major mode of transmission. Inhaling aerosols containing the bacterium is another, less frequent mode.^{5,12} Patients with compromised lung conditions, such as smokers and ill patients, are particularly at risk of acquiring the disease through aspiration because of impaired action of the cilia, which allows bacteria to more easily get into the respiratory tract.⁵ A study of patients who under-

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TABLE 1

Specialized laboratory tests for Legionnaires' disease

Sputum culture

Uses multiple selective media that contain dyes and are pretreated with acid or heat to minimize overgrowth of competing microorganisms
Sputum of patients with suspected Legionnaires' disease should have culture studies regardless of quality

Direct fluorescent-antibody stain of sputum

Rapid test that requires the presence of a large number of organisms to be readily visualized

Urinary antigen assay

Inexpensive and rapid
Detects antigens of *L pneumophila* in urine
Unlike cultures, the test results remain positive for weeks even after antibiotic therapy
Only detects *L pneumophila* serogroup 1; however, serogroup 1 accounts for most cases of Legionnaires' disease

Serologic tests for antibody

Requires IgG and IgM testing of serum samples obtained during both the acute phase and convalescence
Evidence of infection is considered suspicious in a patient with pneumonia who has a single titer of $\geq 1:128$
Evidence of infection is considered presumptive in a patient with a single titer of $> 1:256$ or definitive with a fourfold increase in antibody titer
Test is more useful for epidemiological studies than it is for individual persons because of the measurement required during convalescence

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Hyponatremia and nonresponse to treatment are diagnostic clues

went head and neck surgery reported one of the highest incidences (30%) of hospital-acquired pneumonia due to *Legionella*; these patients experienced chronic aspiration.¹³

CLINICAL SIGNS

Pneumonia is the main clinical presentation, with symptoms that can include fever (often higher than 103°F), cough, chest pain, diarrhea (watery stool), stupor, respiratory failure, and multiorgan failure.¹² Low-grade fever, malaise, anorexia, headaches, and myalgias are common symptoms in the early stages.¹²

Legionnaires' disease is easily mistaken for other types of pneumonia, such as pneumonia due to *Streptococcus pneumoniae* or *Mycoplasma pneumoniae*. Although the diagnosis cannot be made by a physical examination alone, clinical clues include:

- Hyponatremia (serum sodium concentra-

tion ≤ 130 mmol/L), which is found significantly more often in patients with Legionnaires' disease than in patients with other types of pneumonia

- Presence of gastrointestinal symptoms, especially diarrhea.
- Nonresponse to the typical antibiotics, particularly the beta lactam agents and aminoglycosides, used for severe pneumonia or sepsis.¹²

TEST ALL PATIENTS HOSPITALIZED WITH COMMUNITY-ACQUIRED PNEUMONIA

I recommend that all patients hospitalized for community-acquired pneumonia be tested for Legionnaires' disease.

The diagnosis depends on testing the microbiology of the disease. An immediate diagnosis may be suggested by a Gram stain that shows leukocytes with few microorganisms, as seen in "atypical" pneumonia.

**TABLE 2****Antibiotic treatment for Legionnaires' disease based on clinical experience**

AGENT	DOSE	ADMINISTRATION
Macrolides		
Azithromycin	500 mg*	Orally or intravenously every 24 hours
Clarithromycin	500 mg	Orally or intravenously [†] every 12 hours
Roxithromycin	300 mg	Orally every 12 hours
Erythromycin	1 g	Intravenously every 6 hours
	500 mg	Orally every 6 hours
Quinolones		
Ciprofloxacin	400 mg	Intravenously every 8 hours
	750 mg	Orally every 12 hours
Levofloxacin	500 mg*	Orally or intravenously every 24 hours
Ofloxacin	400 mg	Orally or intravenously every 12 hours
Other antimicrobial agents		
Doxycycline	100 mg*	Orally or intravenously every 12 hours
Minocycline	100 mg*	Orally or intravenously every 12 hours
Tetracycline	500 mg	Orally or intravenously every 6 hours
Trimethoprim-sulfamethoxazole	160 and 800 mg	Intravenously every 8 hours
	160 and 800 mg	Orally every 12 hours
Rifampin	300 to 600 mg	Orally or intravenously every 12 hours

*Doubling the first dose is recommended

[†]Intravenous administration is investigational in the United States

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Consider empiric treatment for Legionnaires' if undiagnosed pneumonia requires hospitalization

Several specialized laboratory tests are available (TABLE 1), although, unfortunately, they are not routinely performed for patients presenting with pneumonia. Ideally, one rapid test should be available in every clinical microbiology laboratory. I recommend the new urinary antigen assay because of its high specificity (100%) and fairly high sensitivity (70%), along with its rapid detection and low cost.¹²

Culture of respiratory secretions is the ideal method and should be available in every tertiary care hospital.

ANTIBIOTIC THERAPY: EARLY TREATMENT IS IMPERATIVE

Early appropriate treatment is imperative to prevent death. Erythromycin was once the drug of choice, but newer antibiotics are now proving to be more effective with fewer side effects.¹² Newer macrolides (particularly

azithromycin) and quinolones (particularly levofloxacin and ciprofloxacin) are the best classes of antibiotics to treat Legionnaires' disease.^{5,12} Specific drugs are recommended on the basis of particular risk factors:

- Ciprofloxacin or levofloxacin for transplant patients
- A macrolide or quinolone combined with rifampin for severely ill patients.¹²

Other antibiotic agents reported to be effective include tetracycline, minocycline, doxycycline, imipenem, trimethoprim-sulfamethoxazole, ofloxacin, and clindamycin.^{12,14}

A patient who presents with an undiagnosed pneumonia severe enough to require hospitalization should be empirically treated for *Legionella*. The treatment of choice for such a patient may be a new macrolide because it covers typical pathogens (*Hemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Staphylococcus*



aureus) as well as atypical pathogens (*L pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*)¹²

Antibiotics are usually started intravenously until a clinical response is noted, often about 3 days. Oral therapy can then be substituted for about 10 to 14 days.^{15–17} For patients with suppressed immune systems or evidence of extensive disease on chest x-rays, 21 days of therapy is recommended.¹² Typical dosage schedules are shown in TABLE 2.

■ WAYS TO PREVENT OUTBREAKS

Eradication of the *Legionella* organism by identifying the environmental source is one way to prevent Legionnaires' disease. Guidelines for this approach, provided by the Allegheny

County Health Department and the State of Maryland, recommend routine evaluation for *Legionella* in all hospital water distribution systems.^{18–20}

If *Legionella* is found, disinfection of the water supply may be required based on the frequency of the bacterium found. Several methods of disinfection have been tried, with two methods now commonly in use:

- Heating the water to 70° to 80°C and flushing the distal sites
- Installing copper-silver ionization units.¹²

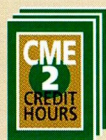
The first method is good for immediately halting an outbreak, but its effectiveness is problematic over time. Currently, more than 75 hospitals in the United States have copper-silver ionization systems.¹⁹ This method is cost-effective for many hospitals.¹²

■ REFERENCES

1. Muder RR, Yu VL, Fang GD. Community-acquired Legionnaires' disease. *Semin Respir Infect* 1989; 4:32–39.
2. Nelson D, Rensimer E, Raffin T. *Legionella pneumophila* pericarditis without pneumonia. *Arch Intern Med* 1985; 145:926.
3. Tompkins LS, Roessler BJ, Redd SC, Markowitz LE, Cohen ML. *Legionella* prosthetic-valve endocarditis. *N Engl J Med* 1988; 318:530–535.
4. Marston BJ, Plouffe JF, Breiman RF, et al. Preliminary findings of a community-based pneumonia incidence study. In: Barbaree JM, Breiman RF, Dufour AP, editors. *Legionella: current status and emerging perspectives*. Washington, D.C.: American Society of Microbiology, 1993:36–37.
5. University of Pittsburgh and VA Special Pathogens Laboratory. www.Legionella.org.
6. Joseph CA, Watson JM, Harrison TG, Bartlett CLR. Nosocomial Legionnaires' disease in England and Wales, 1980–92. *Epidemiol Infect* 1994; 112:329–345.
7. Loeb M, Simor AE, Mandell L, et al. Two nursing home outbreaks of respiratory infections with *Legionella sainthelensi*. *J Am Geriatric Soc* 1999; 47:547–552.
8. Leverstein-van HM, Verbon A, Huisman MV, Kuijper EJ, Dankert J. Reinfection with *Legionella pneumophila* documented by pulsed-field gel electrophoresis. *Clin Infect Dis* 1994; 19:1147–1149.
9. Stout JE, Yu VL, Muraca P, Joly J, Troup N, Tompkins LS. Potable water as a cause of sporadic cases of community-acquired legionnaires' disease. *N Engl J Med* 1992; 326:151–155.
10. Muraca PW, Stout JE, Yu VL, Yee YC. Legionnaires' disease in the work environment: implications for environmental health. *Am Ind Hyg Assoc J* 1988; 49:584–590.
11. Straus WL, Plouffe JF, File TM Jr, et al. Risk factors for domestic acquisition of legionnaires disease. *Arch Intern Med* 1996;156:1685–1692.
12. Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997; 337:682–687.
13. Johnson JT, Yu VL, Best MG, et al. Nosocomial legionellosis in patients with head-and-neck cancer: implications for epidemiological reservoir and mode of transmission. *Lancet* 1985; 2:298–300.
14. Edelstein PH. Antimicrobial chemotherapy for legionnaires' disease: a review. *Clin Infect Dis* 1995; 21(Suppl 3):5265–5276.
15. Vergis EN, Yu VL. *Legionella* species. In Yu VL, Merigan TC, Barriere SL, editors. *Antimicrobial Therapy and Vaccines*. New York: Williams and Wilkins, 1998.
16. Kuzman I, Soldo I, Schonwald S, et al. Azithromycin for treatment of community acquired pneumonia caused by *Legionella pneumophila*: a retrospective study. *Scan J Infect Dis* 1995; 27:503–505.
17. Bartlett CLR, Macrae AD, MacFarlane JT. *Legionella* infections. London: Edward Arnold, 1986.
18. Allegheny County Health Department. Approaches to prevention and control of *Legionella* infection in Allegheny County health care facilities. Allegheny County Health Department: Pittsburgh, 1997. Available at www.Legionella.org.
19. Yu VL. Resolving the controversy on environmental cultures for *Legionella*: a modest proposal [editorial]. *Infection Control and Hospital Environment* 1998; 19:893–897.
20. Maryland State Department of Health. www.dhmd.state.md.us/html/legionella.htm.

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