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.

With new tests, we will recognize many more cases

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]

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 ≥ 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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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 and nonresponse to treatment are diagnostic clues

- Hyponatremia (serum sodium concentration ≤ 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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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*

Consider empiric treatment for Legionnaires' if undiagnosed pneumonia requires hospitalization

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.

Give antibiotics intravenously for the first 3 days

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]

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