Review Articles

Current Concepts

LEGIONELLOSIS

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LEGIONNAIRES' disease was first recognized during an outbreak of pneumonia involving delegates to the 1976 American Legion convention at a Philadelphia hotel. Full appreciation of its role other than as an exotic pathogen has only come in the past several years. As diagnostic methods have improved and epidemiologic understanding of its reservoir has been exploited, legionella has been found to be a common cause of community-acquired and nosocomial pneumonia. Many excellent reviews have been published,[1-4] so this review will focus on newer findings.

EPIDEMIOLOGY

Community-Acquired Pneumonia

Outbreaks of legionnaires' disease in hotels, cruise ships, and office buildings continue to garner media attention. 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 percent of all community-acquired pneumonias that require hospitalization.[5] Studies in which diagnostic tests for legionella, especially culture, were consistently used showed *Legionella pneumophila* to be among the top three or four microbial causes of community-acquired pneumonia. One large-scale study of community-acquired pneumonia in Ohio suggested that only 3 percent of sporadic cases of legionnaires' disease were correctly diagnosed.[6] We have noted the cyclic nature of legionella as a cause of community-acquired pneumonia in Pittsburgh, with an incidence ranging from 2 to 9 percent over the past 10 years. Patients with community-acquired legionnaires' disease are more likely to have severe community-acquired pneumonia, as defined by more severely abnormal vital signs, more extensive infiltrate on chest radiography, and the need for admission to an intensive care unit.[7-11]

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Nosocomial Pneumonia

The epidemiology of nosocomial legionellosis has gradually shifted. In the 1980s most cases reported to us were associated with outbreaks at tertiary care centers. In the past few years, sporadic nosocomial cases from community hospitals have predominated. The reported incidence of nosocomial pneumonia is directly correlated with two factors: the ready availability of specialized diagnostic tests in-house (especially sputum culture and urinary antigen assay) and the presence of legionella in the hospital water supply.

Risk Factors

Cigarette smoking, chronic lung disease, and immunosuppression (especially that caused by corticosteroid therapy) have been consistently implicated as risk factors.[12,13] Surgery is a major predisposing factor in nosocomial infection, with transplant recipients at the highest risk.[14-18] The incidence of legionnaires' disease in patients with the acquired immunodeficiency syndrome is low.[19] However, the clinical manifestations are more severe; lung abscesses, extrapulmonary infections, and bacteremia have been observed.[20-22] Regional differences in the rates of reported cases in the United States may be due to ecologic factors or to intensified surveillance in some states. For example, in 1994 the number of cases of legionnaires' disease in Allegheny County, Pennsylvania, exceeded that in 36 states.[23] Allegheny County has issued guidelines for legionella surveillance in all hospitals in the county.[24]

Pediatric Legionellosis

Both community-acquired and nosocomial cases of legionellosis are now being seen in children.[25-27] Most children with legionnaires' disease are immunosuppressed. A number of immunocompetent children have acquired legionnaires' disease postoperatively[28] or neonatally.[29] Most cases of legionellosis in neonates occurred in association with hospital-acquired ventilator-associated pneumonias.[30,31] Molecular subtyping of environmental and patient isolates has established that the water-distribution system is generally the source.

Mode of Transmission

Legionnaires' disease can be acquired by the inhalation of aerosols containing legionella or by microaspiration of water contaminated with legionella.[3] Aerosol-generating systems that have been linked to disease transmission include cooling towers, respiratory-therapy equipment, and whirlpool baths.[32,33] One of the more fascinating outbreaks originated from an

ultrasonic mist machine in a grocery store. This machine aerosolized mist over the produce section, and 28 shoppers contracted legionnaires' disease.[34] We have challenged the role of cooling towers as a reservoir for nosocomial legionnaires' disease,[35] but this is controversial.[36]

The role of legionella-contaminated distribution systems for potable water as a source of nosocomial and community-acquired legionnaires' disease has been well established. The British Communicable Disease Surveillance Centre reported that 19 of 20 hospital outbreaks of legionnaires' disease in the United Kingdom from 1980 to 1992 were attributed to such systems.[37] Water-distribution systems in nursing homes, workplaces, and private residences have now been implicated in community-acquired cases.[38-42]

Aspiration has been underrecognized as a mode of transmission.[43-46] Documented episodes of aspiration have been noted in cases of legionella pneumonia.[46,47] Nasogastric tubes have been implicated in several studies of nosocomial legionellosis; microaspiration of contaminated water was the presumed mode of transmission.[43-45] One of the highest reported incidences of nosocomial pneumonia due to legionella (30 percent) was reported among patients who had undergone head and neck surgery — patients with a high propensity for aspiration.[17]

VIRULENCE

Pathogens that are able to survive in the environment for extended periods tend to be relatively virulent.[48] Bacteria and protozoa found naturally in water systems can promote the replication of legionella. *L. pneumophila* can infect and replicate within various protozoa found in soil and water.[49] The virulence of legionella may be increased by replication in amoeba.[50] As mentioned previously, *L. pneumophila* appears to cause more severe disease than most common bacterial pathogens associated with community-acquired pneumonia. The various strains of *L. pneumophila* clearly differ in virulence. Multiple strains may colonize water-distribution systems, but only a few strains will cause disease in patients exposed to the water. Although 40 different legionella species have been identified, less than half of these have been linked to disease in humans. *L. pneumophila* is the most pathogenic, accounting for 90 percent of the cases of legionellosis, followed by *L. micdadei* (the Pittsburgh pneumonia agent). Although more than 14 serogroups of *L. pneumophila* have been identified, serogroup 1 accounts for more than 80 percent of the reported cases of legionellosis caused by *L. pneumophila*.[20]

One phenotypic difference between avirulent and virulent *L. pneumophila* is the presence of flagella; isogeneic avirulent strains obtained by passage lose their flagella.[51] A surface antigen of *L. pneumophila* serogroup 1 that is recognized by one particular monoclonal antibody may be associated with virulence.[52] Several genetic loci appear to direct intracellular infection and thus govern virulence.[53-55]

CLINICAL MANIFESTATIONS

As legionellosis has become increasingly recognized, less severely ill patients are seen earlier in the course of the disease. Thus, clinical manifestations of unusual severity once considered distinctive of legionnaires' disease are now known to be nonspecific. Pneumonia is the predominant clinical syndrome. The disease presents with a broad spectrum of illness, ranging from a mild cough and low-grade fever to stupor, respiratory failure, and multiorgan failure. Early in the illness, patients have nonspecific symptoms including fever, malaise, myalgias, anorexia, and headache. The temperature often exceeds 40°C. The cough is only slightly productive. Chest pain, occasionally pleuritic, can be prominent and, when coupled with hemoptysis, may mistakenly suggest pulmonary emboli. Gastrointestinal symptoms are prominent, especially diarrhea, which occurs in 20 to 40 percent of cases. The stool is watery rather than bloody. The physical findings are those of pneumonia. Relative bradycardia has been overemphasized as a diagnostic finding but can often be seen in elderly patients with advanced pneumonia. Hyponatremia (serum sodium concentration, $\leq$130 mmol per liter) occurs more frequently in legionnaires' disease than in other types of pneumonia.

Extrapulmonary legionellosis is rare, but the clinical manifestations are often dramatic.[56] Since the index of suspicion is low, these infections can easily be overlooked. Legionella have been implicated in cases of sinusitis, cellulitis, pancreatitis, peritonitis, and pyelonephritis. Dissemination apparently occurs through bacteremia.[57] The most common extrapulmonary site is the heart, with numerous reports of myocarditis, pericarditis, postcardiotomy syndrome, and prosthetic-valve endocarditis.[58,59] Most such cases were acquired in the hospital. Interestingly, in many cases there was no overt pneumonia; the cardiac infections may have been caused by the entry of contaminated water into a postoperative sternal wound or a mediastinal-tube insertion site.[60] Legionella wound infections developed in several patients after cardiothoracic surgery; foreign bodies such as sutures or drainage tubes may have promoted the development of infection.[60] One patient had superinfection of a hip wound with *L. pneumophila* postoperatively after immersion in a Hubbard tank whose faucets were colonized with *L. pneumophila*.

The chest radiograph cannot be used to distinguish legionnaires' disease from other pneumonias. In a few cases of nosocomial disease, fever and respiratory tract symptoms preceded the appearance of the infiltrate on the chest radiograph. Pleural effusion can be seen in one third of patients. In immu-

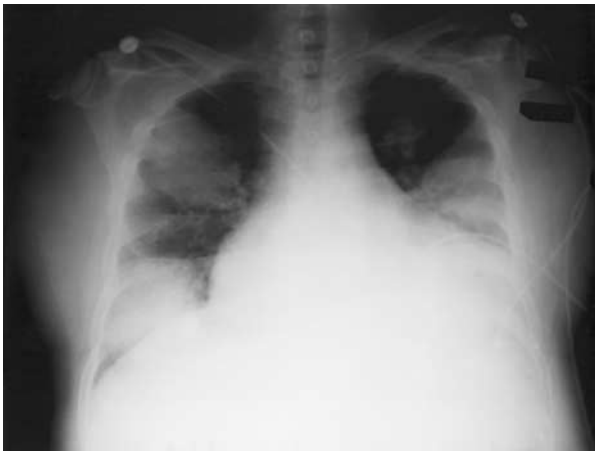

Figure 1. Chest Radiograph of an Immunosuppressed Patient with Legionnaires' Disease, Showing Rounded Nodular Opacities at Presentation (Courtesy of Feng-Yee Chang, M.D.).

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TABLE 1. USEFULNESS OF SPECIALIZED LABORATORY TESTS FOR THE DIAGNOSIS OF LEGIONNAIRES' DISEASE.

TEST	SENSITIVITY	SPECIFICITY
	percent	
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 microorganisms 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 a single titer of ≥1:256 or a fourfold increase in antibody titer is considered definitive evidence.

nosuppressed patients, especially those receiving corticosteroids, distinctive bilateral nodular opacities may be seen, which may expand and cavitate[61] (Fig. 1). Progression of infiltrates on chest radiographs despite appropriate antibiotic therapy is common, and radiographic improvement lags several days behind clinical improvement. Complete clearing of infiltrates on chest radiographs requires one to four months.

LABORATORY DIAGNOSIS

Specialized laboratory tests are necessary to establish the diagnosis (Table 1). These tests must be specifically requested from the clinical-microbiology laboratory because they are not routinely performed. The definitive method for the diagnosis of legionellosis is culture of the organism; however, legionella does not grow on standard microbiologic medium. The investigation of the original American Legion outbreak was hampered by this fact. Investigators at the Centers for Disease Control ultimately grew legionella on 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. In a 1989 survey conducted by the College of American Pathologists, only 32 percent of laboratories identified *L. pneumophila* correctly from a simulated lung biopsy.[3] For maximal sensitivity, several types of dye-containing selective mediums with acid or heat pretreatment to minimize overgrowth of competing microorganisms must be used. Sputum from patients suspected of having legionnaires' disease should be cultured regardless of quality, since in one study specimens that had more than 25 squamous epithelial cells and fewer than 25 leukocytes per low-power field often yielded the organism.[62]

Direct fluorescent-antibody staining is a rapid diagnostic test. Its sensitivity is less than that of culture because large numbers of organisms need to be present before they can be readily visualized. For detecting *L. pneumophila* in respiratory specimens, we have found the monoclonal-antibody direct fluorescent-antibody reagent (Genetic Systems, Sanofi Diagnostics Pasteur, Chaska, Minn.) to be superior to polyclonal reagents because there is less background fluorescence. In addition, false positive results due to cross reactions with nonlegionella bacteria do not occur.

The legionella urinary antigen test is a relatively inexpensive, rapid test that detects antigens of *L. pneumophila* in urine. This test is commercially available as both a radioimmunoassay and an enzyme immunoassay (Binax, Portland, Me.) and has a sensitivity of 70 percent and a specificity that approaches 100 percent.[63] Sensitivity can be further improved if the urine is concentrated by ultrafiltration.[64] 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,[65] we found that less than 10 percent 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.

Serologic tests are useful for epidemiologic studies but are less valuable to physicians, given the requirement for a measurement during convalescence. The diagnosis is based on a fourfold increase in the antibody titer to 1:128 or more. Serum samples from

both the acute and convalescent phases are required because an antibody response may not be detectable until one to three months after the onset of the illness. Single titers of 1:256 or more during convalescence in a patient with pneumonia are suggestive of legionellosis. Antibody screening should include both IgG and IgM because some patients will only have an IgM response.

Assays based on the polymerase chain reaction (PCR) have been used to detect legionella in urine samples,[66] bronchoalveolar-lavage fluid,[67,68] and serum.[69] Although PCR-based assays for the detection of legionella in clinical samples are highly specific, they are not more sensitive than culture.[66,68] Further limitations of the test include the presence of inhibitors of PCR in sputum and some blood samples. The primary advantage of this technique is the ability to detect legionella rapidly and to detect species other than *L. pneumophila*.

The sensitivity of culture and direct fluorescent-antibody staining of specimens obtained by bronchoscopy is approximately the same as that for sputum; bronchoalveolar lavage gives higher yields than bronchial-wash specimens. Pleural fluid, if present, should be evaluated by both culture and the radioimmunoassay used for urinary antigen.[70]

Since the clinical and radiologic presentation of legionnaires' disease is generally nonspecific (although a temperature of up to 40°C, the presence of diarrhea and abdominal signs, and hyponatremia can be clues) and since numerous studies have established legionella as a common pathogen, we recommend that all patients hospitalized for community-acquired pneumonia be routinely evaluated for legionnaires' disease. A Gram's stain may immediately suggest the diagnosis: a finding of leukocytes with a paucity of microorganisms should raise the possibility of an atypical pneumonia. One rapid test for legionella would be ideal, and currently, we would recommend that the urinary antigen assay be available in every clinical microbiology laboratory.

THERAPY

Delay in instituting appropriate therapy for legionella pneumonia significantly increases mortality.[71] Therefore, empirical antilegionella therapy should be included in the treatment of severe community-acquired pneumonia.[72] Erythromycin has historically been the drug of choice, but the newer macrolides, especially azithromycin, have superior in vitro activity and greater intracellular and lung-tissue penetration. The gastrointestinal intolerance, the requirement for the administration of large volumes of fluid, and ototoxicity related to the 4-g dose of erythromycin[73] have made this drug less attractive. Azithromycin, clarithromycin, josamycin, and roxithromycin have been efficacious in anecdotal reports.[74-76] With the intravenous formulation of azithromycin now available, it may displace erythromycin as the drug of choice.

TABLE 2. ANTIBIOTIC THERAPY FOR LEGIONELLA INFECTION.

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
Ofloxacin	400 mg orally or intravenously every 12 hr
Doxycycline	100 mg† orally or intravenously every 12 hr
Minocycline	100 mg† orally or intravenously every 12 hr
Tetracycline	500 mg orally or intravenously every 6 hr
Trimethoprim–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.

‡The intravenous route is investigational in the United States.

§This drug is investigational in the United States.

Quinolones also have greater in vitro activity and better intracellular penetration than the macrolides.[77-79] Numerous anecdotal successes with the quinolones, especially ciprofloxacin, have been reported. Given the pharmacologic interaction of the macrolides and rifampin with the immunosuppressive medications used after transplantation, we recommend ciprofloxacin or levofloxacin for transplant recipients with legionnaires' disease. Rifampin is highly active in vitro and in vivo against legionella[80,81] and is recommended as part of combination therapy (with a macrolide or a quinolone) for patients who are severely ill. Tetracycline proved efficacious in the original American Legion outbreak, and successes with minocycline and doxycycline have also been documented. Imipenem, trimethoprim–sulfamethoxazole, ofloxacin, and clindamycin have proved efficacious in isolated reports.[79]

Parenteral therapy should be given until there is an objective clinical response; most patients become afebrile within three days. Then, oral therapy can be substituted. The total duration of therapy is 10 to 14 days,[75,76,82] but a 21-day course has been recommended for immunosuppressed patients or those with extensive evidence of disease on chest radiographs. Five to 10 days of azithromycin therapy is sufficient. The dosages of the various drugs are shown in Table 2.

A newer macrolide may be the antibiotic of choice for immunocompetent patients with community-acquired pneumonia, since such an agent would cover both the typical bacterial pathogens (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxel-*

la catarrhalis, and *Staphylococcus aureus*) and atypical pathogens (*Chlamydia pneumoniae, Mycoplasma pneumoniae,* and *L. pneumophila*). If an undiagnosed pneumonia is severe enough to warrant admission to the intensive care unit, empirical coverage for legionella is warranted.

PREVENTION

One approach to preventing legionnaires' disease is to identify the environmental source and then eradicate the organism. Allegheny County, Pennsylvania, has formulated guidelines for routine culturing of the water supply for legionella in all hospitals in the county.[24] The guidelines recommend an annual environmental survey of all hospitals, including those with no known cases of legionellosis. All hospitals were included because hospital-acquired legionellosis can easily be overlooked unless specialized laboratory tests are readily available.[83,84] A minimum of 10 distal sites (faucets and showerheads) and all hot-water tanks are cultured. If the organism is found, then physicians should have a high index of suspicion for legionella in hospital-acquired pneumonias, and specialized laboratory tests should also be made available for patients with nosocomial pneumonia. Disinfection should be considered on the basis of the number of positive culture sites and prior experience with hospital-acquired cases.

Over the past 13 years, numerous methods of disinfection have been tried with variable success.[85,86] Three methods are now being used, but no method is ideal[87]: superheating the water to 70 to 80°C, with flushing of the distal sites; installing copper–silver ionization units (Liquitech, Willowbrook, Ill.; Pan-Ionic, High Wycombe, Buckinghamshire, United Kingdom); and hyperchlorinating the water (chlorine concentration, 2 to 6 ppm). The advantage of the first approach is that it can be instituted quickly to halt an outbreak. The long-term efficacy of both superheating and hyperchlorination has been problematic. Copper–silver units have proved cost effective for hospitals whose plumbing systems have been damaged by years of hyperchlorination.

In summary, legionnaires' disease has been insightfully characterized as a disease that is overtreated and underdiagnosed.[4] With the introduction of rapid diagnostic tests into hospital laboratories, especially the urinary antigen assay and PCR, this trend may be reversed.

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