LEGIONELLA: AN OVERVIEW

Stephen A. Weirich, M.D.
NASA Lewis Research Center

History

During the summer of 1976, at an American Legion Convention held at the Bellevue-Stratford Hotel in Philadelphia, 221 participants became mysteriously ill with a fulminant pneumonia. Thirty-four people died. Within six months, the Centers for Disease Control (CDC) had isolated the causative agent: a newly discovered bacteria which was aptly named *Legionella*, and the fulminant pneumonia it caused was called Legionnaires' Disease.

In retrospect, a similar episode had occurred at the same Philadelphia hotel in 1974 where 20 guests became ill with severe pneumonia but no one succumbed. Also in July 1968 at a Health Department building in Pontiac, Michigan, 144 employees and visitors developed a self-limited, flu-like illness which had been blamed on a cryptic "virus." Eight and a half years later, the CDC determined it was actually *Legionella* that had caused this minor epidemic in Pontiac, but the resultant disease was not as virulent as Legionnaires' Disease and was subsequently named Pontiac Fever.

Today, *Legionella* and the infections it can cause are notorious but probably under-diagnosed. Now more than 25 species of *Legionella* have been recognized, with 18 of them having been implicated in causing human disease. The bacteria responsible for the outbreak at the American Legion Convention has been identified as *Legionella pneumophila*, with 14 recognized serotypes. Serotype 1 was specifically responsible for the Legionnaires' Disease outbreak in 1976, and is believed to account for about 50 percent of human disease from *Legionella* species. "Legionellosis" is the term used to refer to the spectrum of disease caused by any species of *Legionella*.

Bacteriology, Ecology and Transmission

Legionella are gram-negative, aerobic bacilli which are ubiquitous in the natural environment, particularly found in mud, frozen streams, hot springs, and stagnant lakes

and ponds. They are small in size, measuring 0.3 to 0.9 microns by 2 to 5 microns. Human disease occurs when a sufficient environmental inoculum is aerosolized and inhaled by a human host. Because of the small size of the bacteria, if inhaled it can easily reach the terminal bronchioles and alveoli of the lung where infection can occur. The course of subsequent disease is determined by the virulence of the bacterium, the immune competence of the human host, and the inoculum size. Immunocompetent individuals develop Pontiac Fever, whereas people that are relatively immunocompromised may develop Legionnaires' Disease.

The growth of *Legionella* is amplified under certain conditions, many of which can be easily found in man-made water supplies -- specifically cooling towers, air conditioning systems, humidifiers, whirlpool baths, respiratory nebulizers, showers, vaporizers, and forced-air heating systems. The air conditioning system of the Bellevue-Stratford Hotel in Philadelphia was determined to have been contaminated with *L. pneumophila*.

Legionella can grow when the ambient water/air temperature is between 20°-70°C, but, in particular, the bacteria proliferate in a warm environment between 35°-43°C. Growth of *Legionella* is further promoted in the presence of low concentrations of iron, zinc, potassium (typical corrosion products in many plumbing systems), and low levels of other competing microorganisms.

If water from man-made water sources contaminated with *Legionella* is aerosolized, the bacteria are readily inhaled. In addition, dusts generated from construction and landscaping activities can aerosolize virulent *Legionella*. Aerosolized *L. pneumophila* can survive for more than two hours, and have been isolated more than one mile downwind of an infected cooling tower. Other routes of entry into human hosts include microaspiration and dermal exposure through wounds that are cleaned with *Legionella*-infected water causing wound infections. While *Legionella* has been isolated in potable drinking water, infection does <u>not</u> occur following ingestion of contaminated water. Furthermore, once infection has occurred, person-to-person transmission does not exist.

Epidemiology

Legionella is probably responsible for 1 to 3 percent of community-acquired pneumonias, and up to 25 percent of "atypical" community-acquired pneumonias. In absolute numbers, *Legionella* is believed to cause 50,000 to 60,000 cases of community-acquired pneumonia each year, and is responsible for an additional 200,000 cases of nosocomial (or hospital-acquired) pneumonia each year. At least 4 percent of the American population demonstrate serologic evidence of prior exposure to at least one *Legionella* species, indicating past infection. Despite these impressive numbers, as of November 2, 1992, only 1,094 cases of *Legionella* had been reported to the CDC so far this year even though Legionellosis is a reportable disease, indicating that this disease is either under-reported or under-diagnosed, or both.

Clinical Manifestations

Legionellosis describes a spectrum of disease, with the now-recognized Legionnaires' Disease (pneumonia) and Pontiac Fever at opposite ends of this spectrum.

Legionnaires' Disease (Legionella pneumonia) is characterized by an abrupt prodrome of malaise, headache, myalgia, and weakness. Within 24 hours the patient develops a fever (exceeding 40°C in half of the patients), rigors, nonproductive cough that can become eventually productive with some blood-tinged sputum, pleuritic chest pain, and dyspnea. Gastrointestinal complaints of diarrhea, nausea, vomiting, and abdominal pain are common, and frequently there is a change in mental status. Unusual clinical signs and laboratory hallmarks of Legionnaires' Disease besides a marked leukocytosis include a relative bradycardia given the patient's temperature elevation, elevated liver function tests (specifically alkaline phosphatase, and transaminase levels), hyponatremia, hypophosphatemia, and rapidly progressive asymmetrical pulmonary infiltrates on chest X-ray.

If an individual is exposed to *Legionella*, the risk of developing pneumonia is 1 to 7 percent. The incubation period is 2 to 12 days. The development of pneumonia is primarily dependent on the presence of specific risk factors, most of which render the host relatively immunocompromised. These risk factors include:

1. **Immunosuppression** (especially individuals with compromised cell-mediated immunity, as in renal transplant recipients).
2. **Concomitant Chronic Disease**, especially diabetes mellitus or COPD.
3. Age Greater than 50 Years Old.
4. Heavy alcohol use.
5. Cigarette smoking.
6. Male (men:women incidence is 3:1).

The overall fatality from *Legionella* pneumonia is 15 percent. In immunocompromised hosts, if untreated, the fatality rates have exceeded 80 percent. Even in immunocompetent hosts who are appropriately treated, the fatality rate is upwards of 7 percent. If the patient survives the infection, there has been no reported sequelae, and if the patient is immunocompetent, the infection renders them immune to reinfection from the same strain of *Legionella*.

Pontiac Fever, as previously mentioned, is an acute, self-limited, flu-like illness that develops within 24 to 48 hours after exposure to the *Legionella* bacterium. If an individual receives a sufficient inoculum of bacteria, the chances of contracting Pontiac Fever approach 95 to 100 percent, regardless of the person's immune status. Symptoms include malaise, myalgia, and headache initially, with the eventual development of fever, chills, cough, coryza, and sore throat. Diarrhea, nausea, dizziness, and mild photophobia may develop. Symptoms typically last 2 to 5 days and resolve with or without antibiotics, with no sequelae, and the condition is never fatal. Unlike the pneumonia, there are no recognized risk factors for the development of Pontiac Fever. Given the non-specificity of the disease's symptoms, frequently this condition is misdiagnosed as a "short-lived viral syndrome."

Diagnosis

There are no good, reliable, and rapid tests to confirm the presence of *Legionella* species, which certainly contributes to the under-reporting of Legionellosis. Proper diagnosis and expedient treatment is dependent on a high index of suspicion on the part of the health care provider.

Legionella can be cultured from induced sputum samples or transtracheal aspirates (because if the patient has a cough it is usually nonproductive). However, the bacteria require a special culture media for adequate in vitro growth, called buffered charcoal yeast extract agar with alpha-ketoglutarate, which must be specifically ordered by the clinician. Typically it takes 2 to 5 days to properly identify the organism.

There are several commercially available urine antigen tests that utilize an enzyme-linked immunosorbent assay, a radioimmune assay, or latex agglutination to detect the presence of antigen in the patient's urine. While these tests are relatively rapid and accurate, they are expensive. Their main disadvantage is that antigenuria may persist for months following an infection with *Legionella*, which can obscure the distinction between acute and past infection.

The most widely used diagnostic test is a serum antibody test. Commercially available tests identify antibodies against six serotypes of *L. pneumophila* and seven other *Legionella* species. Diagnosis of *Legionella* infection is confirmed if there is a four-fold rise in the antibody titer between the acute and convalescent sera, which are typically drawn three to four weeks apart. Convalescent titers must be positive to at least a 1:128 dilution. A single titer that is positive at 1:256 dilution, or greater, is considered diagnostic for *Legionella* infection. Besides the disadvantage of having to wait 3 to 4 weeks to confirm the diagnosis of Legionellosis, only 80 percent of patients will have seroconverted even 10 weeks after the acute infection.

Treatment

Legionella is an intracellular parasite. Only antibiotics that can penetrate cells are effective in treating Legionellosis. These drugs include erythromycin (and the newer macrolides: azithromycin and clarithromycin), rifampin, tetracyclines, and quinolones. Recommended dosages for the treatment of *Legionella* pneumonia are Erythromycin 1 gram IV Q6H, or Doxycycline 200 mg IV Q12H. Parenteral administration is preferred given the frequent gastrointestinal symptoms patients have with the pneumonia. Clinical response is frequently seen within 5 days, at which point the antibiotics can be given orally (Erythromycin 500 mg po Q6H, or Doxycycline 100 mg po Q12H). If there is no significant clinical response to the original parenteral administration of antibiotics, Rifampin 600 mg IV Q12H should be added to the regimen.

Prevention

Unlike other common microbial agents that cause pneumonia, *Legionella* has a source that is extrinsic to the host, and thus the disease can be prevented (at least in theory) by control measures directed at the environmental source. Control of *Legionella* growth can be accomplished by:

1. Preventing the accumulation of stagnant water in an indoor environment.

2. Preventing the dispersal of cooling tower effluent into the indoor environment.

3. Maintaining adequate temperature and/or chlorination of hot water systems, and even periodically elevating the water temperature above 60 to 70°C and flushing the system through distal sites (e.g., faucets, shower heads).

In the absence of diagnosed disease from *Legionella*, routine monitoring of water systems for the presence of the bacteria is not recommended. Given the ubiquity of this organism in the environment, it is frequently found in man-made water systems. The development of human disease is dependent not only on the presence of the bacteria, but the virulence of the particular strain of the bacteria and the bioavailability of the bacteria in a form that can be inhaled by the human host. Therefore, routine testing for *Legionella* should not replace sound engineering practices combined with a regular maintenance and cleaning program of indoor water systems.

References

1. Burge, H., and Platts-Miller, T. Indoor Air-Assessment: Indoor Biologic Pollutants. January 1992: 4-8 to 4-10.

2. Health Department, Victoria, Australia. Guidelines for the Control of Legionnaires' Disease. 1989: 1-7.

3. U.S. Environmental Protection Agency, U.S. Public Health Service, National Environmental Health Association. Introduction to Indoor Air Quality. July, 1991: 103-104.

4. Fang, G. Legionellosis (Legionnaires' Disease, Pontiac Fever). *Current Therapy 1991*: 165-167.

5. Bernstein, M.S., and Locksley, R.M. Legionella Infections. *Harrison's Principles of Internal Medicine, 12th Edition.* 634-637.

6. Lowry, P.W. et al. A Cluster of Legionella Sternal-Wound Infections Due to Postoperative Topical Exposure to Contaminated Tap Water. *NEJM* 1991; 324(2):109-113.

7. Stout, J.E., et al. Potable Water as a Cause of Sporadic Cases of Community-Acquired Legionnaires' Disease. *NEJM* 1992; 326(3):151-155.

8. Addiss, D.G., and Davis, J.P. Sporadic Cases of Legionnaires' Disease. *NEJM* 1992; 326(25):1699.

9. Cunha, B.A. Legionnaires' Disease: Case Studies in Infectious Disease. *Emergency Medicine* 1992; 24(5):227-234.

10. Goldsmith, M.F. New Forms and New Needs May Make Macrolides Antibiotics of the Decade. *JAMA* 1992; 267(7):903-904.