Legionnaires' Disease, or Legion fever, a form of legionellosis

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Etiologic agent: *Legionella pneumophila*

Transmission: *Legionella pneumophila* is transmitted to humans through inhalation of organism-rich water droplets as mist or aerosol. It can be breathed in wherever conditions allow for water from its reservoirs to be vaporized, including water in showers, hot tubs, cooling systems which evaporate and condense, potable water systems, fountains, humidifiers, and misters (14). It can also enter the respiratory system through aspiration of water containing the bacteria or more commonly amoebas harboring the bacteria. These bacteria have been documented in surgical wounds exposed to water containing the organism (19). Legionnaires' Disease is not transmitted from person to person by either direct or indirect contact (4).

Reservoirs: *Legionella pneumophila* is prevalent in surface freshwater and ground water, especially in areas with stagnant water or warm, humid conditions and significant precipitation (17). This organism is often present in drinking water distribution systems, even those that are chlorinated. It can be isolated from running water, recirculating water, and biofilms in plumbing and water fixtures, cooling towers, grocery mist machines, and fountains (14). Water systems in hospitals, hotels, public buildings, and cruise ships are often contaminated with large numbers of these bacteria. *Legionella* especially thrive at water temperatures between 20 and 50 degrees celcius, and are thought to exist in approximately 80% of freshwater locations (2, 9). These bacteria have also been found in moist soil. They most commonly exist as parasites inside the cells of amoebas and some other protozoa and slime molds (2).

General characteristics of microorganism: *Legionella pneumophila* are Gamma Proteobacteria of the family *Legionellaceae*. They are strictly aerobic, Gram-negative, fimbriated bacilli, each with one polar flagellum (19). These organisms replicate within other cells such as amoebas or the macrophages in mammalian lungs. When isolated from tissue samples, the bacterial cells are about 3-5 micrometers long, yet in spite of being considered fastidious in culture, they grow to 10-25 micrometers on appropriate nutrient media. There are 16 serotypes of this species, serogroup 1 being the causative agent of 79% of known cases of Legionnaires' Disease(10, 2). Other bacteria from the *Legionella* genus, of which there are 52 species, can cause a less serious flu-like illness called Pontiac Fever (9, 16).

Key tests for identification: When a patient presents signs and symptoms of pneumonia, Legionnaires' disease may be suspected, especially if alveolar infiltrates are evident in X-ray images of the lungs (2). *L. pneumophila* is a pathogenic bacterium that is not part of humans' normal flora (19). The most definitive identification comes from cultures grown of the organism isolated from lung biopsies, bronchiol brushing, or sputum (12, 5). *Legionella pneumophila* is seemingly ubiquitous in the environment, but requires specific selective and differential media in laboratory culture, where it often produces long, filamentous cells. These media, which mimic the nutrients available in protozoan cells
and in slime molds, consist of agar with buffered charcoal yeast extract, sometimes including either polymixin B, vancomycin, and anisomycin or polymixin B, cefamandole, and anisomycin (12). Direct fluorescent antibody staining can aid in recognition of this organism. Serology tests for immunoglobulins can be done with confirmation following a titer of 128 on a recovery blood sample, representing a 400% increase in antibodies over a sample taken during illness. This is helpful for epidemiology and case reporting, not for disease treatment (5). Quicker tests that can identify serotype 1 of this bacterium are urine antigen assays such as the enzyme-linked immunoassay and the faster paper chromatography based assay (2). Organisms from water samples are confirmed as Legionella using polymerase chain reactions and monoclonal antibody identification (14).

Signs and symptoms of disease, risk factors: Legionnaires' disease has an incubation period of 2-14 days following infection with L. pneumophila (9). Pneumonia, often acute, always characterizes this disease, and may be accompanied by high fevers up to 41 degrees celcius, dry cough, chest pain, confusion, headache, and muscular pain (10). These symptoms may last weeks to months, and this disease is fatal in up to 30% of cases (1). Smokers, people with chronic lung diseases, people older than 50 years, and among these especially men, are at greater risk of contracting Legionnaires' disease than the general population. The danger is also greater for people who are immunocompromised as a result of disease or transplant recipients who require immunosuppressive drugs (7). Healthy people exposed to L. pneumophila often develop antibodies to its antigens without presenting any disease symptoms (2).

Historical information: It is probable that the pneumonia now known as Legionnaires' disease has been affecting humans worldwide for centuries, but it was not recognized as a specific illness until 1976. In July of that year, in celebration of the American Bicentennial, members of the Pennsylvania chapter of the American Legion, a veteran's organization, gathered to hold a convention in Philadelphia. Many of the attendees were older men, veterans who were smokers and/or had chronic health problems. They stayed in the Bellevue Stratford Hotel, and 182 people were infected with a mysterious pneumonia-causing agent. Of these, 29 died. A Pennsylvania doctor, Ernest Campbell, became suspicious that something unusual was happening when three of his patients presented similar pneumonia symptoms, and he learned that they had all been at the American Legion convention in the hotel (15). The largest number of disease investigators ever deployed from the Centers for Disease Control in Atlanta rushed to Pennsylvania to collect data, samples, and histories from these patients as well as alert other people who may have been exposed. Researchers hurried to find treatments and isolate an etiologic agent. The progress of the disease and of its investigation were widely reported in the media, and there was public speculation that the "Philly Killer" might have been the result of bioterrorism. It became known as Legionnaires' disease, and Bob Dylan wrote a song about it, rhyming the name with "it came out of the trees". More than half a year later, Dr. Joseph McDade of the CDC isolated the causative bacterium, and it was given the name Legionella pneumophila (6). More research was necessary to determine that the water supply in the Bellevue Stratford Hotel was a reservoir for the organism, and that it was most likely contracted when guests breathed in water droplets while taking showers or using the hot tub. In 2006, Veterans' Administration officials "destroyed, without warning, more than 11,000 unique microbes--including specimens of bacteria that caused the original outbreak of Legionellosis" at the Special Pathogens Laboratory of the Veterans' Administration Infectious Disease Section in Pittsburgh (1).
This act caused the loss of three decades worth of invaluable research involving human pathogens by Dr. Victor Yu and Dr. Janet Stout, who pioneered the investigations into transmission and effective antibiotic treatments for Legionnaire's disease. This episode, decried by scientists worldwide, was determined by a congressional subcommittee to have been motivated by personal differences between the researchers affected and new administrators at the facility (1).

Virulence factors: The risk of Legionnaires' disease development in humans seems to increase in correlation with the concentration of infecting organisms (12). *L. pneumophila* exist in watery environments as parasites of protozoa that eat bacteria, especially *Acanthamoeba, Hartmanella*, and *Naegleria* species. Inhaled amoebas containing large numbers of bacteria can provide the critical mass of pathogens associated with disease (9). Adherence to target cells is facilitated by Type IV pili, and these organisms are motile by means of flagella. The gene rtxA, whose name indicates repeats in structural toxins, codes for a toxin that helps *L. pneumophila* adhere and enter into host cells, both protozoan cells and human alveolar monocytes, and form pores in them. The bacteria also display complement C3b in order to attract phagocytes (18). This organism turns the defense of opsonization against its human host, because it is only through coiling phagocytosis that the bacteria can be taken into the cells where they replicate in nature (20). Chemical products of the bacteria prevent the phagosome from combining with a lysosome, and convert it into a replication vacuole. The pathogen injects its own proteins through a tube-like secretion system into the host cytoplasm, commandeering cellular processes for its own replication. Eventually, the infected monocyte lyases, releasing bacteria to infect other cells and provoking an immune response that causes the air space in the lungs to become inflamed and fill with fluids and fibrin (19). It is thought that some of *L. pneumophila's* eukaryote-like proteins that increase virulence in humans may have been gained over time by association with their protozoan hosts. An example is the Mip, or macrophage infectivity potentiator, which provides some of the antibiotic resistance characteristic of *Legionella*. These bacteria also produce a lipopolysaccharide endotoxin.

Control/Treatment: Legionnaires' disease is nationally notifiable in the United States and many other countries, so that reservoirs and patterns of outbreak can be identified (11). It is sometimes considered a traveler's disease, because it is often contracted during stays away from one's habitual environment, and because large facilities like hotels are more likely to have some contaminated components in their water delivery systems. A large proportion of Legionnaires' illnesses are nosocomial infections, due to the high populations of immune-compromised hosts among hospital patients. The Johns Hopkins hospital attempted to stem the spread of hospital pathogens as well as save water by installing hands-free water taps with electronic motion sensors. An unfortunate and unexpected result of this measure was an increase in Legionella infections. The lesser volume of flowing water, combined with more complicated, harder-to-clean plumbing valves caused the numbers of *L. pneumophila* in the water system to skyrocket to as many as 3,000 colony forming units per milliliter of water supplied. The hospital has gone back to traditional plumbing fixtures in patient care areas (3). There is some protection from overgrowth of *Legionella* provided by the use of copper pipes, and this benefit must be weighed in long term care facilities against a possible connection between physiologic accumulations of trace copper and Alzheimer's disease. Regular flushing of pipes with superheated water can help control this pathogen (19). Disinfection
of water systems with free chlorine has proven inadequate to control the amplification of *L. pneumophila* in plumbing. Monochloramine, which kills organisms residing in biofilms, is much more effective when used in municipal water disinfection and may prevent some community-acquired cases of Legionnaires' disease as well as up to 70% of nosocomial cases (2, 17). Legionnaires' disease is most effectively treated if timely diagnosis is made, because treatments for other kinds of pneumonia are usually ineffective. The fluoroquinolone Levofloxacin and Azithromycin are the most effective antimicrobials against *L. pneumophila*, followed by the more commonly used erythromycin (2).

Prevention/Vaccine information: Recommendations have been made by the CDC, and protocols have been established by state health agencies regarding surveillance of water supplies, especially in hospitals. Treatment of pathogen-affected water supplies and plumbing systems by monochlorination, cleaning, superheating, and UV light are effective measures to prevent Legionnaires' disease. Educating people at high risk about the potential dangers of traveling and staying in places with untested water supplies can help raise awareness and encourage patients to seek medical care earlier if Legionellosis is suspected (12). It may also behoove high-risk patients to refrain from using hot tubs and avoid environments with aerosolized droplets from freshwater or system sources. Immunization of laboratory animals has been accomplished and is in development for humans (19). There is currently no vaccine against *L. pneumophila* (8).

Local cases or outbreaks: In 1998, of 15 Texas hospitals tested, 73% had water systems contaminated with *L. pneumophila*. Nosocomial cases of Legionnaires' disease, with about a 40% mortality rate, are twice as likely to be fatal as community-acquired cases. In 1999, a task force on Legionellosis comprised of health care professionals in Texas was organized in response to several diagnosed cases in San Antonio hospitals. Confirmed cases of Legionnaires' disease represent a small number of probable cases, because patients who recover do not often return to provide a second blood sample for paired sera testing. There were 227 confirmed cases in Texas from 1990 to 1999, with the estimate of true cases being more than four times as many. In the past 25 years, there have been three documented outbreaks in Texas, each involving between 3 and 20 patients. In the United States, the probable number of Legionnaires' cases is between 8,000 and 18,000 per year, although many fewer cases are reported (12). This is because not every state requires reporting, and definitive tests are not always done to discover the etiologic agents of pneumonia. The cause of disease is also missed because cases often occur only singly or in small clusters. There is some noticeable increase in community incidence in the summer and early autumn when cooling towers for air-conditioning are in use, but otherwise no clear trends have been identified (2). Between 2002 and 2005, there has been a dramatic increase in incidence of Legionnaires' disease in the United States, with 4% of pneumonias being diagnosed as such. It is unclear whether this represents a true increase, or merely more correct diagnoses being made as a result of widespread use of the urine antigen tests (17).

Global cases or outbreaks: In the ten years between 1995 and 2005, 600 outbreaks of Legionnaires' disease encompassing 32,000 patients occurred worldwide. Each year, there are about 75 cases in Canada (10). In 2001, the largest confirmed outbreak of Legionnaires' disease occurred in Murcia, Spain, with 449 cases. Six of these patients died. The reservoir of *L. pneumophila* in this case was determined to be an industrial
cooling tower (1, 15). Between 2000 and 2009, 271 cases of Legionnaires' disease were confirmed in Singapore, with 33 of these cases originating from travel to other locations (16). A current outbreak in Portugal that began in November, 2014, involves 302 confirmed cases, with 5 deaths. Medical investigators are trying to find the environmental source of this outbreak (13).

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