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Legionnaires' Disease, A Rising Occurrence in the United States

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Abstract
Legionella pneumophila, a microscopic bacterium usually responsible for a number of illnesses and fatalities, can eliminate a local population, a region or even a nation. In 1976, L. pneumophila was first discovered due to a number of cases presenting with pneumonia-like symptoms. These cases occurred in an isolated population attending an American Legion convention in Philadelphia, Pennsylvania, therefore lending to the name Legionella. Usually found in aquatic environments such as lakes, streams, cooling towers, air conditioning systems and hot tubs, its ability to thrive in artificial and natural environments makes it an ideal bacterium. L. pneumophila can be transmitted via inhaling aerosols that contain the pathogen. After inhalation, the alveolar macrophages phagocytize the pathogen which then serves as its host. Virulence factors such as lipopolysaccharides (LPS), are one way the pathogen causes infection, however it can also utilize heat shock protein and surface antigens. Usually with Legionnaires' disease the physical symptoms consist of high fever, malaise, muscle aches, rigors, confusion, headache and diarrhea which categorizes this pathogen as causing an atypical pneumonia. Since L. pneumophila may be associated with travel-related infections, it is hard to track and isolate travel-associated incident clusters because the symptoms present themselves after returning from travel. In regard to diagnosis, this disease has five available techniques to confirm that the patient is in fact positive for L. pneumophila. Programs such as the Environmental Legionella Isolation Techniques Evaluation Program (ELITE) have been started by the Centers for Disease Control and Prevention (CDC) in order to decrease outbreak incidences. Additionally, the current recommendations for the management of Legionnaires' disease adapted from the CDC have been summarized into a flow chart which may help clinical decisions in the treatment of this disease.

Key Terms
Centers for Disease Control and Prevention (U.S.); Disease Outbreaks; Legionella; Legionella Pneumophila; Legionellosis; Legionnaires' Disease

Introduction
Legionnaires' disease, or Legionellosis, was first identified in 1976 when an onslaught of pneumonia-like symptoms began in a group of individuals in attendance at an American Legion convention in Philadelphia. Since its first documented manifestation, Legionnaires' disease has remained relatively dormant. Recently, however, the respiratory illness has returned to the spotlight as its abnormal instances of infection have been thoroughly covered by the news to alert the public. In July 2015, an outbreak of Legionnaires' disease in the South Bronx of New York occurred. Investigation of this recent outbreak has allowed scientists to trace the pathogen to its origin at the Opera House Hotel in the South Bronx. The same strain of bacteria responsible for the outbreak of Legionnaires' disease was found on the cooling towers of the hotel. This was an overlooked location for disinfection and may be the reason behind the reoccurrence of the disease.

Potential sources of Legionnaires' disease are often undetected until the disease manifests itself in symptomatic infected individuals. Furthermore, because patients present with fever, cough and diarrhea, symptoms that are common among many conditions, the disease presentation does not often provide a differential diagnosis. Laboratory diagnostics are utilized to confirm a case of Legionnaires' disease. The condition is classified as a notifiable disease by the Centers for Disease Control and Prevention (CDC) and, therefore, is subject to CDC protocol and intervention in the instance of an outbreak. Finally, with a recent increase in Legionnaires' disease, new policies have been set forth by the CDC to control as well as prevent future outbreaks.

Etiology/Transmission
Legionella pneumophila is the causative agent of Legionnaires' disease. The microbe is a small, rod-shaped, gram-negative, aerobic, intracellular bacterium. The variations in antigens that reside on the surface of the bacteria give rise to variations, or serogroups, of the microbe. Serogroup 1 is responsible for approximately 79 percent of infections in humans. Many diagnostic tools utilize the prevalence of serotype 1 as the primary source of infection to determine whether a patient has Legionnaires' disease or another type of respiratory infection. L. pneumophila resides in natural, as well as artificial, aquatic environments such as lakes, streams, cooling towers and air conditioning systems. In a natural environment, the microbes reside as an intracellular parasite within protozoa. The microorganism thrives best in warm temperatures, at an optimal temperature of 35°C, and therefore it is prevalent in human synthesized water environments where this temperature is maintained. The opportunistic, waterborne pathogen is transmitted via inhalation of aerosols. The bacterium is able to contaminate an aerosol, become airborne and easily access the respiratory system of a potential host. Aerosols are common in the form of sprays or mists. For instance, transmission may occur while an individual is showering. This provides an opportunity for accidental inhalation. Likewise, an individual may become infected by inhaling contaminated water. It is also important to note that this particular pathogen is not transmitted from person to person. A droplet expelled from an infected individual in the form of a sneeze or cough will not transmit the
pathogen. Therefore, contact with a patient infected by Legionnaires' disease is not dangerous. Furthermore, most healthy people do not become infected with L. pneumophila after exposure. Risk factors include ages 50 years or older, current or former smokers, having a chronic lung disease, weakened immune system from diseases like cancer, diabetes, or kidney failure, and taking medications that suppress the immune system. The incidence of Legionnaires' disease in the United States has increased greatly since 1998. This may be attributed to a rise in the number of individuals in close proximity to contaminated water sources that have not been properly sanitized. The increase, however, may also be due to greater access to diagnostic testing or an increase in the number of immunocompromised or at-risk individuals. This includes the elderly and those with weakened immune systems or an underlying illness.

**Pathophysiology**

Once inhaled, the pathogen is phagocytized by alveolar macrophages. Attachment and entrance into the immune cells is thought to be complement independent and facilitated by the presence of pili. The microbe possesses the ability to escape an immune response by preventing the formation of the phagolysosome utilizing a type 4 secretion system. Therefore, the immune function of the macrophage is disabled. The intracellular bacterium then replicates depending on iron levels and the success of its various virulence factors.

The virulence factors contributing to the body's response to a L. pneumophila infection are key elements in the bacterium's ability to enact an immune response. For example, lipopolysaccharide (LPS), heat-shock proteins as well as other surface proteins serve as antigens, which are common to all gram-negative bacteria. Lipopolysaccharide is an endotoxin that signals the macrophage to release different pro-inflammatory cytokines that produce an immune response. The cytokines that trigger the inflammatory response include tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1). T-lymphocytes target heat-shock proteins and produce antibodies in response to their presence to promote the immune response. Furthermore, fluid extravasation is a characteristic of this immune response. When the response is signaled within the lung, fluid can occupy the air spaces thus causing pneumonia in progressive cases of Legionnaires' disease. Finally, once the bacterium has completed its replication process, it can initiate apoptosis or necrosis of the macrophage. New bacteria are then released to infect other cells of the immune system to further its infective process.

**Signs/Symptoms**

L. pneumophila is classified as an atypical pneumonia. Presented symptoms, radiograph or x-ray results, and response to certain antibiotics may differ from typical bacteria that cause pneumonia by Streptococcus pneumoniae. Physical symptoms that are commonly observed in patients include high fever, malaise, muscle aches, rigors, confusion, headache and diarrhea. These symptoms may be followed by a nonproductive cough and shortness of breath. Symptoms usually present two to 10 days following exposure to the bacteria. However, patients should still be monitored for two weeks following exposure. Legionnaires' disease is also usually associated with hospital-acquired pneumonia and travel. Association with travel has been reported during the incubation period for more than 20 percent of cases reported to the CDC. Symptoms often do not present until after the person has returned from traveling from the source of infection, which makes detection of travel-associated clusters difficult.

**Diagnosis**

If an individual is suspected of having Legionnaires' disease, confirmation should be made with diagnostic testing. There are five available techniques for the diagnosis of Legionnaires' disease. A urine antigen assay along with a culture of respiratory secretions is the preferred diagnosis method because both tests are 100 percent specific. Urine antigen assay allows for rapid, same day results but only tests for L. pneumophila serogroup 1. Respiratory cultures can take more than five days to provide a result but allow for comparison of clinical and environmental samples. Cultures may be affected by antibiotic therapies and must be obtained as soon as possible after a suspected diagnosis. Additionally, cultures detect all species and serogroups of the bacteria. The following chart adapted from the CDC classifies the advantages and disadvantages for each diagnostic test (Table 1).

After confirmation of Legionnaires' disease, steps must be taken to find the source of infection and inform the proper officials. Figure 1 provides a breakdown of the steps to diagnose a case of Legionnaires' disease.

**Recent Outbreaks**

The World Health Organization (WHO) defines a disease outbreak as an 'occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season.' These occurrences may be confined to one area or may span entire countries while lasting anywhere from days to several years. The CDC mentions that when two or more L. pneumophila exposed individuals occur at the same time and place and become sick as a result, a Legionellosis outbreak has occurred. In 2008, there were eight confirmed cases of a Legionnaires' disease outbreak at Saint Peter's University Hospital in New Jersey, resulting in three fatalities. All those infected had other underlying diseases that made them more susceptible to the L. pneumophila that was traced back to the hospital's water system.

The Veteran Affairs Pittsburgh Healthcare System reported another L. pneumophila outbreak in October 2012. The CDC identified a total of 21 cases of Legionnaires' disease in this outbreak. This total was broken down into five definite and 16 probable health care-associated cases. There were five fatalities resulting from this outbreak, all within 30 days of a positive diagnostic test.
Table 1. Diagnostic Tests for Legionnaires' Disease.\textsuperscript{1, 2}

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Culture</td>
<td>• Clinical and environmental isolates can be compared&lt;br&gt;• Detects all species and serogroups&lt;br&gt;• 100% specific</td>
<td>• Technically difficult&lt;br&gt;• Slow (&gt;5 days to grow)&lt;br&gt;• Sensitivity high dependent on technical skill&lt;br&gt;• May be affected by antibiotic treatment</td>
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<tr>
<td>Urine Antigen</td>
<td>• Rapid (same day results)</td>
<td>• Only 100% specific for \textit{L. pneumophila} serogroup 1 (Lp1)&lt;br&gt;Lp1 may account for up to 80% of cases&lt;br&gt;• Does not allow for molecular comparison to environmental isolates</td>
</tr>
<tr>
<td>Serology</td>
<td>• Less affected by antibiotic treatment&lt;br&gt;• 80-90% sensitive; 99% specific</td>
<td>• Must have paired sera&lt;br&gt;• 5-10% of population has titer $1 &gt; 256$ (no discrimination between cases of Legionnaires' disease and other causes of community-acquired pneumonia)</td>
</tr>
<tr>
<td>Direct Fluorescent Antibody (DFA)</td>
<td>• Can be performed on pathologic specimens&lt;br&gt;• &gt; 95% specific</td>
<td>• 25-75% sensitive</td>
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<tr>
<td>Polymerase Chain Reaction (PCR)</td>
<td>• Rapid</td>
<td>• Assays vary by laboratory and are not FDA-approved</td>
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Figure 1. Process for Suspected Cases of Legionnaires' Disease.\textsuperscript{14}
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One of the largest outbreaks occurred in July 2015 in the South Bronx in New York City. The source of contamination was found to be a cooling tower located on top of the Opera House Hotel. In this outbreak, 120 people were infected resulting in 12 deaths.

The most recent cases occurred in August 2015. The Illinois Department of Veterans' Affairs announced eight confirmed cases with no related fatalities. In this same time period, an outbreak also occurred in the San Quentin State Prison located in California where there were six confirmed cases. Furthermore, a woman died after diagnosis in University Hospitals Case Medical Center in Cleveland, Ohio. A month later in Cleveland, Ohio, an employee at the NASA Glenn Research Center was diagnosed with Legionnaires' disease. Although there was no direct CDC response in these cases, the respective state health departments were involved. However, in some situations the CDC protocols for treating L. pneumophila were used.

Response from Centers for Disease Control and Prevention

In response to numerous outbreaks of L. pneumophila, the CDC started the Environmental L. pneumophila Isolation Techniques Evaluation Program (ELITE). Its goal is to certify labs that are collecting and testing water samples for Legionella. However, even with the ELITE certification, a lab is not automatically certified to eliminate the bacteria from the water. The CDC recommends that every outbreak should be treated independent from other cases.

The CDC has kept a close eye on areas of natural disaster or warfare. These events lead to water systems becoming stagnant at room temperature. Since L. pneumophila bacterial growth thrives in temperatures of 35°C, these water systems become the ideal areas for Legionnaires' disease. The CDC has teamed up with the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE®) to compile guidelines for treating and eradicating affected water systems. The final report, “ASHRAE Guideline 12-2000—Minimizing the Risk of Legionellosis Associated with Building Water Systems,” has served as the standard to eradicate L. pneumophila in affected water systems.

Management of Disease

Current general recommendations for the management of Legionnaires' disease have been outlined in the flowchart in Figure 2. These include the early diagnosis, prompt treatment with appropriate antibiotics and management of any of the possible respiratory, renal or CNS complications. This is key in identifying and managing Legionnaires' disease effectively to predict the best patient outcomes. Patients presenting with community-acquired pneumonia (CAP) should be tested for Legionnaires' disease if they have failed a course of antibiotics for CAP, have severe symptoms requiring intensive care, are immunocompromised, are from an environment with a Legionella outbreak or have a travel history within two weeks of the onset of symptoms.

In cases of community-acquired pneumonia, the treatment guidelines are established via the Infectious Diseases Society of America and American Thoracic Society. These consensus guidelines provide information on the diagnosis, empirical therapy and focused management of both inpatient and outpatient situations. For patients who are in the ICU, recommendations for empiric antibiotics are a beta-lactam in addition to azithromycin or respiratory fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin). Once the L. pneumophila is confirmed, the beta-lactam is no longer needed. Most patients recover from fever within three to five days, but therapy is continued for 10 to 14 days (five to 10 days for azithromycin), based on clinical stability (Table 2). In immunocompromised patients, therapy may be continued for as long as 21 days.

Conclusion

Legionnaires' disease management, treatment and eradication come to the spotlight when outbreaks occur. Recent outbreaks throughout the United States have prompted the scientific community to learn more about how to earlier identify and fight Legionnaires' disease. With the use of programs like ELITE from the CDC and effective treatment protocols, health care professionals can effectively eradicate Legionnaires' disease while providing the best care to their patients.

Figure 2. General Recommendations for Legionellosis Management.
Table 2. Criteria for Clinical Stability

<table>
<thead>
<tr>
<th>Patients should have no more than one of the following before discontinuation of antibiotics:</th>
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<tbody>
<tr>
<td>• Temperature ≤ 37.8° C</td>
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<tr>
<td>• Heart rate ≤ 100 beats/min</td>
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<tr>
<td>• Respiratory rate ≤ 24 breaths/min</td>
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<tr>
<td>• Systolic blood pressure ≥ 90mm Hg</td>
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<tr>
<td>• Arterial oxygen saturation 90% or pO2 60mm Hg on room air</td>
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<td>• Normal mental status</td>
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</table>

References


