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Testing and treatment of community-acquired pneumonia caused by *Streptococcus pneumoniae* or *Legionella pneumophila*

Pneumonia is a leading cause of death in all age groups worldwide.[1,2] In affected patients, the air sacs of the lungs fill with fluid or pus, hindering oxygen exchange. There are dozens of reported infectious agents, including bacteria, fungi, and viruses.[3,4] Additionally, non-infectious causes such as aspiration of foreign substances or inhalation of chemicals or other irritants have been reported.[5,6] Diagnosis and subsequent appropriate treatment can be challenging since symptoms are similar irrespective of the causative agent and include fever, chest pain, cough, abnormal breathing, and rapid heart rate.

Classification of Pneumonia: CAP, HAP, and VAP

Pneumonia is often classified by site of acquisition: community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). CAP is the most common and, in the United States, accounts for more than 1.5 million visits annually to emergency departments.[7] While symptoms of all classifications are similar, the causative agents are notably different. Antibiotic resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) are more commonly observed in HAP and VAP patients,[8] while *Streptococcus pneumoniae* is found in 33-50% of CAP infections in adults and is the most frequently identified organism in specimens taken from patients with CAP.[9] Globally, pneumonia is the leading cause of death in children under 5 years old, with an estimated 672,000 deaths annually,[10] and the fifth leading cause of death in adults over 70, with an estimated 1.23 million deaths per year.[11] If diagnosis of pneumonia caused by *S. pneumoniae* (pneumococcal pneumonia) is delayed or inaccurate, *S. pneumoniae* can enter the blood stream, cross the blood-brain barrier, or infect the heart and joints, manifesting as bacteremia, meningitis, pericarditis or arthritis.[12]

Legionellosis, caused by *Legionella pneumophila*, is another significant cause of CAP.[13] Legionellosis is subdivided into non-pneumonic (Pontiac fever) and pneumonic (Legionnaires' disease.) Pontiac fever is an acute, self-limiting influenza-like illness, usually lasting 2–5 days with symptoms of fever, chills, headache, malaise, and muscle pain occurring within 72 hours of exposure. Legionnaires' disease has an incubation period of 2 to 10 days (but up to 19 days has been recorded in some outbreaks) and presents initially with symptoms of fever, loss of appetite, headache, malaise, and lethargy.

Legionnaires' Disease

Legionnaires' Disease was discovered following an outbreak at an American Legion meeting held in Philadelphia, PA in July 1976. By mid-August, 221 individuals had been ill, and 34 deaths were attributed to the unknown disease. 72 cases were not involved with the meeting but had been inside or walked past the hotel where the meeting was held.

On January 18, 1977, the CDC announced *Legionella pneumophila* as the cause and was traced to the cooling towers connected to the air conditioning of the hotel.

Pontiac Fever

In July 1968, 144 visitors and employees of the Health Department in Pontiac, MI developed a mild illness, Pontiac fever, with no cause determined.

Serum from the affected individuals tested contained antibodies to *L. pneumophila*.

The source was traced to a leak in the air duct which allowed water from the air conditioning system to enter the building.

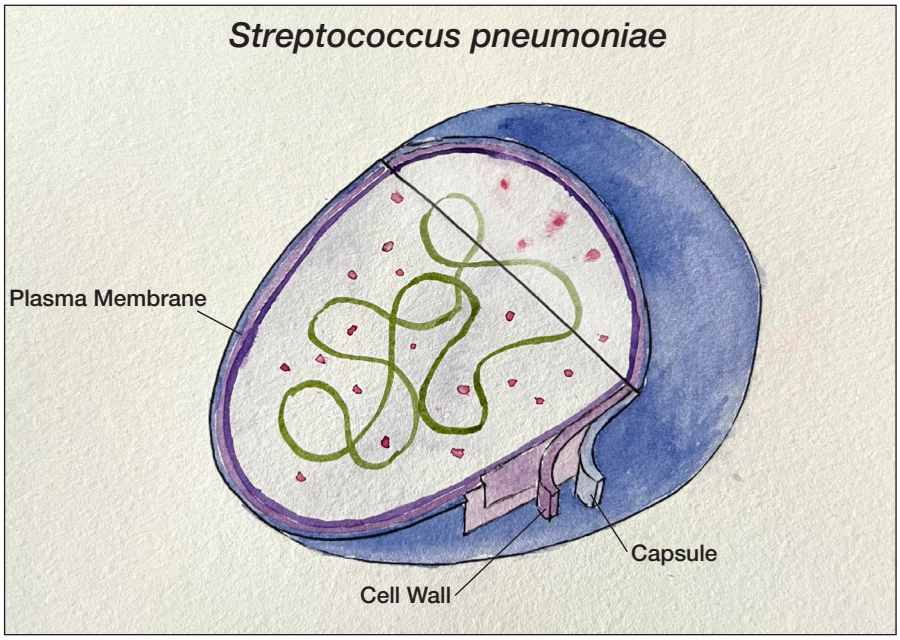
Some patients may also experience muscle pain, diarrhea, and confusion. The severity of Legionnaires' disease ranges from a mild cough to a rapidly fatal pneumonia, with death occurring through progressive pneumonia with respiratory failure and/or shock and multi-organ failure. In 2018, there were nearly 10,000 cases of Legionnaires' disease in the United States,[14] – the most in U.S. history, though this number is likely an underestimate. Legionnaires' Disease is underdiagnosed largely due to the difficulty in distinguishing Legionnaires' disease from other types of pneumonia. The incidence rate is likely 1.8-2.7 times higher than what is reported with a mortality rate of about 10%.[15]

Microbiology

Streptococcus pneumoniae

S. pneumoniae bacteria are facultative anaerobic, Gram-positive, lancet-shaped organisms (Figure 1). Typically seen in pairs, or diplococci, they can also occur singularly or in short chains. Most pneumococci are encapsulated, with an outer surface covered by a layer of complex polysaccharides. The polysaccharide capsule is a central virulence factor as well as a major protective antigen of *S. pneumoniae* and protects the bacterial cell wall from host antibodies and complement in the bloodstream.[16,17]

Figure 1. ***Streptococcus pneumoniae***



Capsular polysaccharides vary between different pneumococci and the organism can be classified by type-specific antisera (SSI Diagnostica, Denmark). By 2020, over one hundred genotypes had been recognized.[17] Although most serotypes are known to infect humans, a smaller subset of serotypes cause most illnesses.[17] Importantly, antibodies specific to the capsular polysaccharide of a serotype are protective against pneumonia caused by that serotype.[17] Despite being protective against opsonization by host antibodies in the blood, *S. pneumoniae* bacteria rapidly shed the capsule when they encounter innate antimicrobial peptides that are present on the respiratory epithelium.[19] The de-capsulated bacteria can then attach and invade the epithelial cell more easily and may also be less subject to anti-capsular immunity. Thus, the role of the capsule as a protector or a discardable cover can vary depending on the locality (bloodstream or mucosal surface).[18] The protective role in the bloodstream comes at the price of being a target for antibodies, especially in immunized individuals. The interplay of capsule serotype with infectivity complicates vaccine development and challenges our understanding of how serotype replacements occur after successful vaccine introductions. Serotyping in addition to whole genome sequencing provides critical information for effective vaccine development.

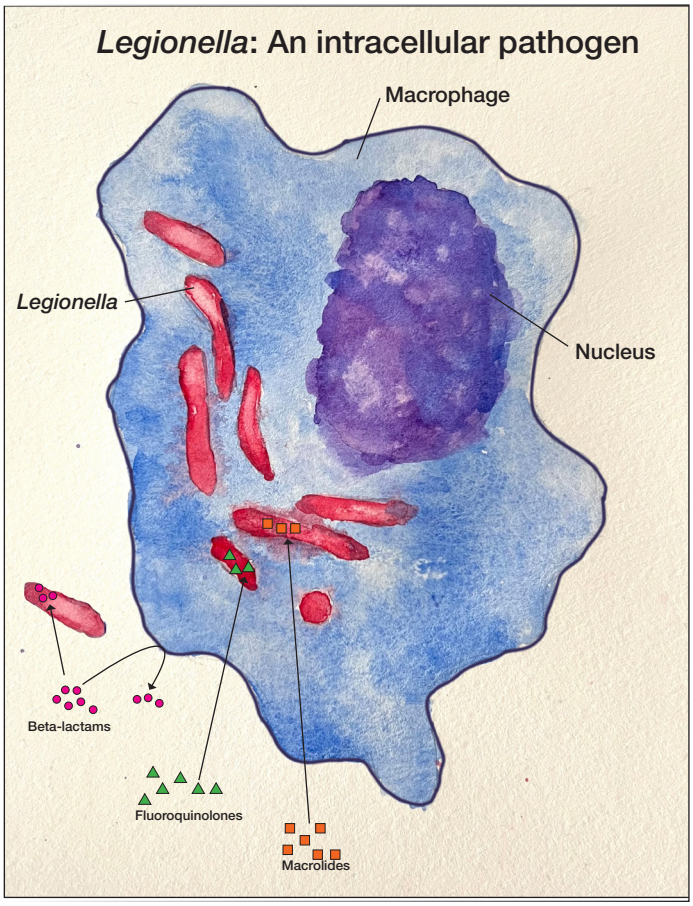
Many serotypes of *S. pneumoniae* organisms are harbored in the nasopharynx.[16] Long term carriage of pneumococci in healthy people is common and numerous studies have found that bacteria can be isolated in up to 90% of healthy individuals.[16] This location enables easy airborne transmission of bacteria to uninfected

persons. From the nasopharynx, *S. pneumoniae* can easily infect the middle ear or lungs. Although *S. pneumoniae* can cause disease directly, the major source of illness is the severe inflammation that the bacteria trigger. The seriousness of pneumococcal disease correlates with the strength of the inflammatory reaction.

Legionella pneumophila

Legionella bacteria are aerobic, unencapsulated, Gram-negative, rod-shaped, intracellular pathogens (Figure 2). Although occurring naturally in small amounts in freshwater environments such as streams and lakes, *Legionella* poses a health risk when found in water distribution systems of public buildings such as hospitals and hotels. *Legionella* is also resistant to standard water disinfection procedures and can be found in treated potable water, hot tubs and nearly any water storage device. These environments allow for *Legionella* proliferation and the organisms are then transmitted to humans via aerosolization or aspiration of the contaminated water. There are more than 50 *Legionella* species described in the literature, and 18 of the species have been associated with human infections. *Legionella pneumophila* is the cause of more than 90% of all cases of Legionnaires' disease. *L. pneumophila* is divided into 15 serogroups, with serogroup 1 causing more than 84% of global reported cases of *L. pneumophila* legionellosis, though this figure is complicated by the fact that some tests only detect serogroup 1 and serogrouping is not routinely performed in many localities.[20]

Figure 2. *Legionella pneumophila*
Fluoroquinolones and macrolides are capable of penetrating mammalian cell membranes to kill intracellular Legionella. *Beta-lactams cannot penetrate the cell membrane and kill only extracellular* Legionella.



Testing

Culture

The gold standard for diagnosis remains traditional culture-based methods, using respiratory samples or blood cultures. The most clear-cut advantage of culture is that positive results provide strong confirmation of organism, which can then be serogrouped or tested for antibiotic resistance. However, obtaining high quality sputum samples is a common limitation,[21] such that negative results are typically not informative, particularly in Legionellosis, where less than 50% of patients produce sputum.[22-25] Additionally, samples should be collected from the lower airway as upper airway samples can be contaminated.

Blood cultures from patients with pneumonia identify a bacterial pathogen in only 5-16% of cases. This finding is reasonable as not all patients with pneumonia are bacteremic. *S. pneumoniae* is detected in one third of positive blood cultures.[26] Culture results will also be negative for viral pathogens, which appear to cause 30-50% of cases.[26] The recent Guidelines of the ATS/IDSA do not recommend blood cultures for adults with nonsevere CAP who are managed as outpatients.[21]

Prompt initiation of appropriate antibiotic therapy is a goal of treatment for pneumonia illnesses. Culture requires more than 24 hours to identify an organism, or as long as 3-5 days for *Legionella*, and a further 1-2 days to provide information on its antibiotic sensitivity.[27] If antibiotics have been started prior to specimen collection, culture becomes further compromised.

Molecular Panel Assays of Respiratory Pathogens

Multiplex molecular panels target many pathogens, typically from invasive sampling like bronchial lavage, tracheal suction, or sputum samples from lower airways. Inherent broad coverage of pathogens increases the likelihood that an infecting organism will be identified. Panels also incorporate viral pathogens that culture cannot detect and can also include antibiotic resistance genes. Molecular assays are rapid (<2 hours) and highly sensitive. This is useful for infection control in patient settings and outbreak investigations.[27]

However, the benefits of comprehensive inclusion and high sensitivity are partially offset because both viral and bacterial pathogens can colonize respiratory sites without causing illness.[27] Asymptomatic colonization makes it difficult to clinically assign responsibility and adopt or abandon antibiotic measures for the correct organism, necessitating confirmatory testing.[28] Because of the difficulty in obtaining a suitable patient sample and due to the high cost of multiplex panels, these tools are often reserved for the most acutely ill patients.

Urinary Antigen Testing

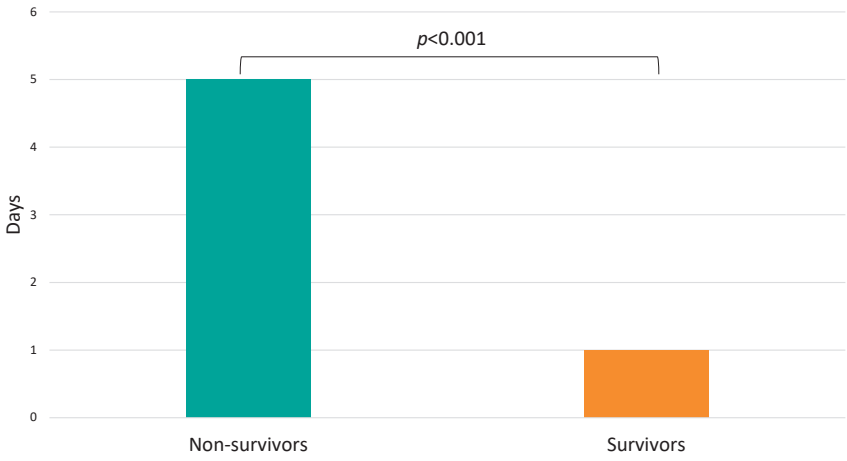
It may seem counter-intuitive to use a urine sample to detect a respiratory illness, but antigens shed from *S. pneumoniae* and *L. pneumophila* can be filtered and concentrated by the kidneys before excretion.[29,30] In 1945 Chr. R. Roesgaard wrote a doctoral thesis, “Pneumococcal carbohydrates in urine”, which showed that it was possible to detect pneumococcal antigens in the urine. The first commercial assay became available in 1997. Urinary antigen testing (UAT) detects the antigen in the urine sample, without the need for invasive sampling of the lower respiratory tract site of actual pneumococcal and/or *Legionella* infection. While *L. pneumophila* serogroup 1 is responsible for most infections, other serogroups are also pathogenic and not all currently available UAT kits detect non-serogroup 1 cases. It is also important to note that the organism is not itself present in the urine and cannot be cultured from the sample or detected by PCR. Detection of urine antigen is especially useful if antibiotic therapy has already been started.[31] Culture of blood or respiratory samples from antibiotic-treated patients will (hopefully) give negative results while antigen is detectable in urine for a longer period of time.[29,32] Multiple studies reported that, due to initiation of antibiotic therapy and general culture insufficiencies, culture recovered a pathogen in less than 30% of blood cultures and less than 50% of sputum cultures[33], but a sample produced a positive urine antigen result in as many as 20% of culture-negative patients.[29] Such antigen test results should be carefully examined as potential true positives if clinical suspicion and symptoms of pneumonia are present.[30,34,35]

Urinary antigen testing is non-invasive and offers the simplicity of urine collection and transport. Results can facilitate early diagnosis and help support appropriate treatment, while also potentially providing a pathway to step down from broad-spectrum antibiotic therapies. The simplicity of urine collection and transport, and the accuracy of results supports the early diagnosis and tailored antibiotic treatment of *S. pneumoniae* and Legionellosis infections. National guidance recommendations have been introduced in some countries to include UAT for both *S. pneumoniae* and *Legionella* in addition to X-ray and culture.[36,37] A positive test result gives physicians confidence to quickly switch from initial broad-spectrum antibiotic therapy to appropriate, targeted treatment in patients with pneumonia.[5,33]

Treatment

The mainstay for treatment of bacterial pneumonia and of viral pneumonia in patients at elevated risk for bacterial co-infection remains antibiotics. The most recent Clinical Practice ATS/IDSA Guidelines published in 2019 outline treatment recommendations for community-acquired pneumonia (CAP). These guidelines offer several worthwhile updates because of changes in antibiotic resistance of bacterial pathogens. Viral causes of pneumonia are now widely recognized, and the guidelines note that patients often have viral and bacterial infections simultaneously.[21] The recommendations for either type of pneumonia continue to emphasize initial empiric treatment for possible bacterial (co)infection, especially in adult patients with clinical symptoms and radiographic confirmation of pneumonia. Empiric antibiotics are generally successful for patients with mild CAP, and diagnostic testing to identify a specific pathogen does not usually change treatment or outcomes (Figure 3). Of note, standard empiric therapy for severe CAP now favors beta-lactam/macrolide combinations.[21] A new avenue for limiting antibiotic treatment is the use of biomarker tests. Procalcitonin assays can distinguish with about 70% accuracy a viral pneumonia (where antibiotics are not useful and can be discontinued early) from bacterial pneumonia.[38]

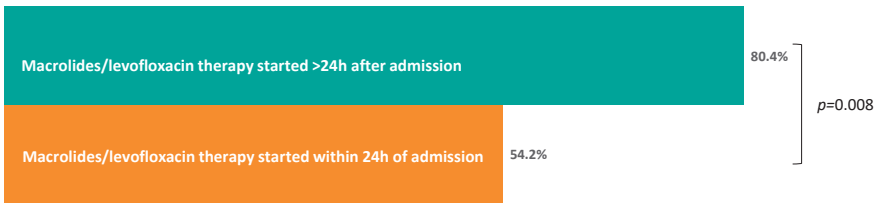
Figure 3. Median delay before starting therapy following pneumonia diagnosis



In a retrospective study, the median delay in therapy initiation was found to be 1 day in survivors, compared to 5 days in non-survivors.[41]

Empiric use of antibiotics, however, is not without risk. A study of the adequacy of initial ceftriaxone antibiotic therapy for CAP found an increased risk of in-hospital death if unnecessarily broad-spectrum antibiotics were used for initial treatment.[39] In contrast, inadequate or inappropriate treatment of patients with antibiotic resistant bacteria also carries a risk of mortality.[40] While many bacterial pneumonias are treated with penicillin, this antibiotic is not effective against *L. pneumophila* as it is an intracellular pathogen. Instead, macrolides or quinolones, which can penetrate infected host cells, can be used.[41] It is important to identify Legionnaires' disease and begin treatment as soon as possible, as delay in initiation of antibiotic therapy is a factor associated with higher mortality (Figure 4).

Figure 4. Frequency of ICU admission for *Legionella pneumophila* patients



Delayed macrolide/levofloxacin therapy in patients with identified *L. pneumophila* results in increased risk of ICU admissions.[41]

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Summary

- *S. pneumoniae* and *L. pneumophila* are serious pathogens that can cause community-acquired pneumonia (CAP) and it is important to differentiate the cause so that appropriate treatment and effective antibiotics can begin quickly.
- Guidelines of the ATS/IDSA do not recommend blood cultures for adults with nonsevere CAP due to concerns that traditional culture of respiratory or blood samples can fail to identify a bacterial pathogen.
- Multiplex molecular panels provide broad coverage of pathogens, incorporate viral pathogens that culture cannot detect and also include antibiotic resistance genes. Detection of sub-clinical colonizing pathogens, difficulty obtaining a suitable sample, and cost reduce the utility of these tests.
- Urinary antigen testing (UAT) detects *S. pneumoniae* and *L. pneumophila* antigens shed into urine rather than requiring invasive respiratory samples and can detect the antigens after antibiotics have been started, increasing the detection of illnesses that culture misses to support the early diagnosis and tailored antibiotic treatment of *S. pneumoniae* infections.
- Emerging serotypes of *S. pneumoniae* show reduced susceptibility to both antibiotics and current vaccines. This worrying combination may lead to a rebound in disease.
- Beta-lactams such as penicillin are not clinically effective when treating *Legionella*, so antibiotics capable of penetrating host cells, such as macrolides and quinolones, must be used to treat pneumonia caused by *L. pneumophila*.

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