# Community-Acquired Legionnaires Disease: Implications for Underdiagnosis and Laboratory Testing

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**(See the article by von Baum et al. on pages 1356–64)**

*It is better to be looked over than overlooked.*

—Mae West

Legionnaires disease is an uncommon but not rare cause of pneumonia. Legionnaires disease was considered to be an unusually severe pneumonia, given the mortality rate (29%) at the initial outbreak during the American Legion convention at the Philadelphia, Pennsylvania, hotel and for the patients first reported with nosocomial legionnaires disease (40%) [1]. This impression was solidified when observational studies of patients with community-acquired pneumonia (CAP) admitted to the intensive care unit showed that legionnaires disease was consistently the second-most-common cause of pneumonia (secondary only to pneumococcal pneumonia) [2]. Numerous observational studies of patients with CAP requiring hospitalization have documented that the incidence of legionnaires disease ranges from 2% to 9%.

On the other hand, legionnaires disease has been thought to be rare in ambulatory CAP. In 7 studies of patients with ambulatory CAP, the incidence of legionnaires disease ranged from 0% to 3.6% (mean, 0.8%) [3–9]. Significant weaknesses of these 7 studies were that serologic testing was the only diagnostic modality used, the number of serogroups tested was limited, and convalescent-phase serum samples were not obtained from all patients. Three studies of ambulatory patients with CAP, in which *Legionella* urinary antigen testing, direct fluorescent antibody stain, and/or culture were performed in addition to serologic tests, found a higher incidence—a range of 1.8%–12.5% (mean, 7.5%) [10–12].

Given this background, the study initiated by the German multicenter study of the Competence Network for Community-Acquired Pneumonia (CAPNETZ) [13] is enlightening. A cohort of 2503 patients was prospectively enrolled; 776 of them had ambulatory CAP. Most important, a standardized microbiology protocol using *Legionella* testing was implemented. It should be noted that culture for *Legionella* was part of the protocol—a difficult and often underrepresented diagnostic component of large-scale collaborative studies. The most common identifiable etiologic agent was *Streptococcus pneumoniae* (30%), as expected. However, nearly 100 patients were given the diagnosis of legionnaires disease.

Testing of urine for *Legionella pneumophila* soluble antigen was the basis for diagnosis in 58 of the 94 patients with legionnaires disease. This test has revolutionized the diagnosis of legionnaires disease, given the rapidity of the test and ease of performance, although its sensitivity is 80% and is only effective for *L. pneumophila* serogroup 1 detection [14]. In the CAPNETZ study, the use of PCR uncovered cases of legionnaires disease due to other species and serogroups. The value of PCR as an adjunct diagnostic modality is still uncertain, and its sensitivity and specificity is unknown.

Although the effort to identify *Legionella* was ambitious, the authors conceded that the methods used were not optimal. The culture methodology used in this study was not the most sensitive; 2 selective media plus the application of heat or acid treatment would have increased the yield. Culture of respiratory secretions was also underused. Patients with legionnaires disease frequently have nonpurulent spu-

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tum or insufficient sputum; however, nonpurulent sputum from patients with legionnaires disease, unlike that from patients with pneumococcal pneumonia, can often yield the microorganism in culture. Unlike the other previously cited studies of ambulatory pneumonia, serologic tests, which might have uncovered more cases, were not performed. Finally, testing for *Legionella* urinary antigen is sensitive for only 1 species *(L. pneumophila)* and only for serogroup 1. Thus, as the authors suggested, the actual incidence of legionnaires disease might have been higher than noted.

Regardless, it is noteworthy that the incidence of legionnaires disease among ambulatory patients (3.7%) was essentially identical to that among hospitalized patients (3.8%). Outpatients were younger, had fewer comorbidities, and had a less severe clinical course than did patients who were hospitalized. The authors point out that these patients would have been overlooked had *Legionella* laboratory testing not been performed. Similarly, we have also found that a significant proportion of patients with legionnaires disease had mild to moderate disease and did not have expected comorbidities [15].

Thus, confining *Legionella* laboratory testing to "high-risk" patients will overlook a notable number of cases. So, testing for legionnaires disease is warranted in patients with CAP with broader demographic characteristics than previously appreciated, including outpatients. The CAPNETZ finding supports the practice of placing more emphasis on ascertaining the etiology of pneumonia.

Sputum culture is the acknowledged reference standard for diagnosis of *Legionella* infection. All tertiary care hospitals in Pittsburgh, Pennsylvania, have access to *Legionella* culture on selective media, as do most community hospitals. Thus, it is probably not happenstance that the yearly incidence of legionnaires disease in Pittsburgh exceeds that of 40 American states [16]. In addition, many review articles have commented on the geographic predilection of legionnaires disease for Pittsburgh. Similarly, culture for *Legionella* has been widely used in numerous studies from Spain. As the CAPNETZ authors point out, in Europe, legionnaires disease is often referred to as a "Mediterranean disease," because Spain has the highest incidence of legionnaires disease in Europe.

In 2 studies of patients hospitalized with CAP, investigators made a concerted attempt to uncover cases of legionnaires disease [17, 18]. Testing for *Legionella* urinary antigen, specialized cultures for *Legionella,* and *Legionella* serologic tests were all performed. The incidence of legionnaires disease among hospitalized patients was the highest ever recorded: 12.5% of patients in Spain [17] and 14% of patients in the United States [18]. These data plus the CAPNETZ study suggest that the incidence of legionnaires disease in a given community varies with the index of suspicion of the physicians who order tests for it.

The Infectious Diseases Society of America/American Thoracic Society consensus guidelines on CAP do not favor routine laboratory testing for legionnaires disease unless the patient is admitted to the intensive care unit [19]. Broad-spectrum empirical therapy is recommended instead. In addition, $\beta$-lactam agents are often used to treat ambulatory pneumonia, especially in Europe. The Infectious Diseases Society of America/American Thoracic Society guidelines recommend the use of *Legionella* laboratory tests in 3 specific situations: for patients with enigmatic pneumonia, for patients who do not respond to $\beta$-lactam treatment, and in the presence of an epidemic [19].

The clinical manifestations considered characteristic of legionnaires disease in the early 1980s included high fever, diarrhea, confusion, hyponatremia, and high mortality. Thus, *Legionella* testing is often confined to patients with severe pneumonia and less likely to be ordered for patients who are not severely ill. The CAPNETZ authors confirm that clinical manifestations are not useful in predicting the likelihood of legionnaires disease [20], so enigmatic pneumonia will remain enigmatic unless *Legionella* testing is applied. This has implications for the management of CAP, given the fact that legionnaires disease and pneumococcal pneumonia have the highest mortality rates.

The CAPNETZ authors [13] make an articulate and reasoned critique of the current Infectious Diseases Society of America/American Thoracic Society guidelines [19]. We agree that greater focus should be placed on diagnosis of etiology—a basic principle of infectious disease treatment practice. Administering specialized *Legionella* laboratory testing as the patient's condition is deteriorating while being treated with $\beta$-lactam antibiotics is unpalatable to both physicians and patients. Survival rates of patients with legionnaires disease improves with expedient administration of active antibiotics. Four patients received discordant antibiotic therapy in the CAPNETZ study and died. Finally, although epidemics were the original presenting scenario for legionnaires disease in the early 1980s, most cases are now known to be sporadic. The CAPNETZ authors suggest the selective use of urinary antigen testing for *L. pneumophila* and *S. pneumoniae.* We would apply both tests simultaneously for all patients with CAP. The urinary antigen tests are rapid tests that are easy to perform. If either test yielded positive results, targeted therapy with a potent antibiotic could be initiated immediately. The break points for penicillin and *S. pneumoniae* will be modified by the US Food and Drug Administration and Clinical Laboratory Standards Institute such that penicillin may remain the drug of choice for pneumococcal pneumonia [21]. Prior break points for nonsusceptibility to penicillin were misleading and led to the widespread use of broad-spectrum antibiotics, including quinolones [22, 23].

In summary, the results from the CAPNETZ study support basic infectious disease principles: use a rapid laboratory test for determining the etiology of the pneu-

monia, and target the identified pathogen with specific antibiotic therapy rather than reflexly initiating empirical broad-spectrum antibiotic therapy [24].

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