Can Legionnaires Disease Be Diagnosed by Clinical Criteria?

A Critical Review

Legionella is a relatively common cause of pneumonia. In patients with community-acquired pneumonia, the incidence ranges from 2 to 15%. Of pathogens that are of consequence in patients with community-acquired pneumonia, the mortality rate is highest for those with bacteremic pneumococcal pneumonia and Legionnaires disease. Of the atypical pneumonia pathogens, the mortality for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* is low. Consensus guidelines on empiric antibiotic therapy for patients with community-acquired pneumonia recommend that coverage be extended to Legionella in suspicious cases, although the criteria for "suspicious" is not explicitly delineated. Although numerous studies have shown that the clinical manifestations of Legionnaires disease are nonspecific, Burke Cunha[1] from Winthrop University Hospital (WUH) has claimed that Legionnaires disease is a unique clinical syndrome as originally depicted in the early studies (Table 1). Cunha even devised a weighted point system, referred to as the WUH point scale for Legionnaires disease. If the WUH score was valid, then antibiotic selection might be simplified. We sought to assess the utility of the syndromic approach on the management of community-acquired pneumonia and Legionnaires disease.

Table 1—*Classical Clinical Parameters Associated With Legionnaires Disease

Clinical Parameter	American Legion†	Wadsworth VA‡
Underlying disease		
Cardiac	Yes	Yes
Neoplastic	Yes	Yes
Pulmonary	Yes	Yes
Renal	Yes	Yes
Diabetes mellitus	Yes	Yes
Predisposing factor		
Male sex	Yes	Yes
Cigarette smoking	Yes	Yes
Immunosuppression	No	Yes
Symptoms		
Malaise	Yes	Yes
Cough	Yes	Yes
Chest pain	Yes	Yes
Diarrhea	Yes	Yes
Headache	Yes	Yes
Confusion/delirium	Yes	Yes
Signs		
Fever	> 38.9°C	> 39.3°C
Relative bradycardia	Yes	Yes
Neurologic findings	Yes	Yes
Laboratory		
Leukocytosis	Yes	Yes
Hyponatremia	Yes	Yes
Hepatic dysfunction	Yes	Yes
Hypophosphatemia	NR	Yes
Proteinuria	Yes	Yes
Hematuria	Yes	No

*NR = not reported.
†Data are from Tsai et al.[3]
‡Data are from Kirby et al.[4,5]

Review of the Literature

In the original outbreak of Legionnaires disease in 1976, the case fatality rates were highest for the β-lactam antibiotics, aminoglycosides, and chloramphenicol. The case fatality rate was lowest for erythromycin and tetracycline.[2] It was subsequently discovered that Legionella is an intracellular pathogen and that only those antibiotics that achieve high intracellular penetrations would be efficacious. In retrospect, only a minority of patients in the American Legion outbreak received therapy that would be considered efficacious today.

The clinical syndrome of Legionnaires disease was largely defined by early outbreaks, especially the 1976 American Legion outbreak at a hotel[3] and an endemic situation at Wadsworth Veterans Affairs Hospital in the late 1970s.[4,5] The severity of the clinical manifestations was impressive (Table 1), and subsequent case descriptions from other early studies contributed to the image of Legionnaires disease as being a distinct clinical syndrome of unusually severe pneumonia with multisystem dysfunction. Legionnaires disease occurred primarily in elderly male patients with underlying diseases (*eg*, cardiac, pulmonary, or renal) who were cigarette smokers.[3–5] Underlying immunosuppressive illnesses, especially in organ transplant recipients, were common. Symptoms that were prominent included nonproductive cough, chest pain, diarrhea, and confusion/delirium. Signs included temperature ≥ 39°C, relative bradycardia, and neurologic manifestations. Laboratory abnormalities likewise were common (Table 1).

In 1982, we published a study[6] in which all cases of pneumonia, both community-acquired and hospital-acquired, underwent specialized testing for Legionella (*ie*, serology, direct fluorescent antibody tests, and culture on selective media). To our surprise, we found that *Legionella pneumophila* was a relatively common cause of pneumonia. Furthermore, when compared to pneumonias of other bacterial etiologies, the clinical manifestations were similar and generally not distinctive. Since then, numerous large-scale studies of pneumonia have confirmed the nonspecificity of the clinical manifestations of Legionnaires disease.[7–10] We now know that in severe

cases of Legionnaires disease, blood cultures can be positive for *L pneumophila*[11] and that bacteremic pneumonias of any etiology, be they pneumococcal, *Staphylococcus aureus*, or Gram-negative bacilli, can be expected to cause high mortality rates.

Chest radiographic features have been touted as characteristic for Legionnaires disease. These features have included pleural effusions, pleural-based infiltrates that mimicked pulmonary embolism, and circumscribed peripheral densities. The tendency for radiographic abnormalities to progress while the patient is receiving antibiotic therapy has been widely noted, and earlier studies[12–15] have suggested that such progression is more frequent in patients with Legionnaires disease than in those with other types of pneumonia. In a study[16] of hospital-acquired Legionnaires disease, 29% of patients showed progression of a unilateral infiltrate that spread to other lobes despite receiving erythromycin. Similarly, in a study[17] of community-acquired Legionnaires disease, 65% of patients had a worsening of radiologic findings in the first week. Keep in mind that in earlier studies, specific antibiotic therapy against *L pneumophila* was likely to have been delayed more often than in cases of bacterial pneumonias of other etiologies.[18] Pleural effusions are common but are of small volume. Tan et al[17] found pleural effusions in 28% of patients with community-acquired Legionnaires disease on hospital admission, but the number of patients with pleural effusions increased to 63% during the hospital course. Nevertheless, when comparative studies[5,13,17,19–23] have been performed, the chest radiographic findings also have been shown to be nonspecific.

In this issue of *CHEST*, Gupta et al (see page 1064) evaluated the syndromic approach in patients with community-acquired pneumonia from the University of Indiana and found distinctive features for Legionnaires disease. Given their results, we reevaluated the issue of whether Legionnaires disease could be characterized as a distinct clinical syndrome by reviewing comparative studies of Legionella vs other causes of pneumonia. Most studies have used serology as a criterion for the diagnosis of Legionnaires disease, but since the specificity of this test is uncertain at individual hospitals, we confined our analyses only to those studies that used a second confirmatory test, either urinary antigen, direct fluorescent antibody, or culture. We found 13 studies[6–8,10,12,14,15,22,24–28] of community-acquired pneumonia that had sufficient clinical details for evaluation and that fulfilled our laboratory criteria for Legionnaires disease (Table 2). The study by Fang et al[28] used all four diagnostic tests (*ie*, serology, direct fluorescent antibody, urinary antigen, and culture). Numerous clinical manifestations attained statistical significance (*ie*, headache, diarrhea, arthralgias or myalgias, neurologic symptoms including confusion, fever to 39°C, purulent sputum, hyponatremia, hepatic dysfunction, creatine phosphokinase [CPK] elevation, hypophosphatemia, proteinuria, and hematuria). In at least 2 of the 13 studies, the following parameters occurred significantly more often in patients with Legionnaires disease than in those with other etiologies of community-acquired pneumonia: receipt of prior antibiotics; diarrhea; neurologic signs, especially confusion; temperature > 39°C; hyponatremia; and hepatic dysfunction (*ie*, transaminase and bilirubin elevations) [Table 3]. Hematuria also was found to be significant in the Gupta study. Relative bradycardia was evaluated in two studies[6,25] and was not found to be useful. The mortality rate ranged from 0% in three studies[7,26,27] to 46%,[6] with a median of 15%. Most studies showed a trend toward higher mortality for Legionnaires disease (Table 2), but only one study[12] showed a significantly greater mortality rate for Legionnaires disease compared to *M pneumoniae*.

Roig et al[29] have cautioned that statistical significance is not synonymous with clinical significance. For example, in one study[22] in which the presence of diarrhea and increased CPK level was significantly higher in patients with Legionnaires disease than in those with community-acquired pneumonia due to other pathogens, 75% of patients with Legionnaires disease did not experience diarrhea and 68% had normal CPK levels.

Critique of the Syndromic Approach

Gupta and colleagues evaluated the ability of the WUH criteria to identify Legionnaires disease in patients with community-acquired pneumonia who required hospital admission. Patients with bacteremic pneumococcal pneumonia were the negative control group. The ability of the WUH criteria to distinguish only two causative agents of community-acquired pneumonia might be justified on the grounds that the mortality rate is notable for these two microorganisms in patients with community-acquired pneumonia. In contrast, the mortality rate among patients with *Haemophilus influenzae*, *M pneumoniae*, and *C pneumoniae* was $< 5\%$. Gupta et al found, somewhat to their surprise (and ours), that the sensitivity for the WUH score in diagnosing Legionnaires disease was 78 to 87%. The adjusted negative predictive value was 92%. On the other hand, the specificity was only 50 to 65%. An unpublished study by De Caroles et al also found the WUH score to be sensitive, but also nonspecific (De Car-

Table 2—*Assessment of Clinical Parameters Favoring the Diagnosis of Legionnaires Disease in 13 Comparative Studies*

Clinical Parameter	Trend	Significant ($p < 0.05$)
Demographics		
Male gender	Miller[14]; Helms et al[12]; Granados et al[10]; Falco et al[15]; Sopena et al[22]	
Cigarette smoking	Miller[14]; Helms et al[12]; Granados et al[10]; Fang et al[28]; Sopena et al[22]	Falco et al[15]
Chronic alcoholism	Sopena et al[22]	Falco et al[15]
Underlying disease		
Chronic lung disease	Miller[14]; Helms et al[12]; Falco et al[15]	
Predisposing factor		
Prior antibiotic therapy		Falco et al[15]; Granados et al[10]
Prior surgery	Fang et al[28]	
Prior hospitalization	Fang et al[28]; Sopena et al[22]	
Symptoms		
Headache	Sopena et al[22]	Falco et al[15]
Diarrhea	Fang et al[28]; Miller[14]	Sopena et al[22]; Falco et al[15]
Arthralgias/myalgias	Granados et al[10]	
Confusion, neurologic symptoms	Sopena et al[22]	Falco et al[15]; Miller[14]; Helms et al[12]; Woodhead and MacFarlane[24]
Signs		
Fever > 38.9°C	Miller[14]; Ostergaard and Andersen[26]; Mundy et al[27]	Woodhead and MacFarlane[24]; Fang et al[28]
Purulent sputum		Olaechea et al[25]
Laboratory		
Hyponatremia		Miller[14]; Yu et al[6]; Olaechea et al[25]; Sopena et al[22]; Woodhead and MacFarlane[24]
Hepatic dysfunction		Miller[14]; Helms et al[12]; Granados et al[10]; Sopena et al[22]; Falco et al[15]; Woodhead and MacFarlane[24]
Leukocytosis	Ruiz et al[7]	
Creatine phosphokinase elevation		Sopena et al[22]
Hypophosphatemia		Olaechea et al[25]
Proteinuria		Helms et al[12]
Hematuria		Helms et al[12]
Serum creatinine elevation		Falco et al[15]
Mortality	Granados et al[10]; Fang et al[28]; Falco et al[15]	Helms et al[12]

oles; personal communication, 1999). Other unpublished studies have utilized syndromic approaches for the diagnosis of Legionnaires disease. In the Community-Based Pneumonia Incidence Study,[30] high fever, elevated lactate dehydrogenase, and hyponatremia were distinctive, and in a small study[31] of 18 patients, high fever and nonproductive cough were distinctive. One potentially fatal flaw of the study by Gupta et al is that the authors conceded that a sizable number of patients had not undergone any testing for Legionella. If Legionella testing was skewed to patients who were severely ill or if tests were ordered primarily for those patients with the classic clinical manifestations listed in Table 2, an overwhelming bias with circular reasoning would have confounded the study results.

Table 3—*Classic Clinical Manifestations of Legionnaires Disease Confirmed by at Least Two Comparative Studies*

Symptoms	Signs	Laboratory Testing
Diarrhea	Fever > 39°C	Hyponatremia
Neurologic findings including confusion		Hepatic dysfunction
		Hematuria*

*Helms et al[12] and Gupta et al.

Given the results of this review, can the use of clinical criteria be useful in the management of this disease? Although sensitivity was relatively high, 13 to 22% of patients with Legionnaires disease were missed by the WUH score in the Gupta study. Given the high mortality rate, the authors correctly point out that the WUH score cannot be used to focus antibiotic therapy (*eg*, using a β-lactam agent only on those patients who do not fulfill the criteria). Since the specificity was low (50 to 65%), the application of the WUH score also could lead to unnecessarily broad coverage.

Despite the knowledge that Legionella can be

widespread in the community, most hospitals currently do not have diagnostic laboratory tests available for Legionella testing. The rationale is that the disease is relatively rare and that the application of an expensive test would be of low yield. This leads to a "catch-22" situation, in that the diagnosis cannot be made unless tests are available. And while we believe that the urinary antigen test for Legionella (Binax; S Portland, ME) should be performed for all community-acquired pneumonia patients requiring hospital admission, this has not been recommended by the consensus guidelines for community-acquired pneumonia of either the American Thoracic Society or the Infectious Diseases Society of America, with expense cited as one reason.[32,33] The latter organization's guidelines recommend that Legionella testing be performed if "clinical features are supportive of the disease."[33] The WUH score might be used to screen patients for specialized Legionella testing. If the WUH score were fulfilled, the patient could receive anti-Legionella antibiotics as empiric therapy without Legionella laboratory testing. But, if the criteria were not fulfilled, Legionella testing could be performed on these patients to cover the 13 to 22% of patients who do not have the classical syndrome.

If Legionella testing (especially culture or selective media and urinary antigen testing) becomes routinely available for patients with pneumonia, we suspect that the syndromic approach for clinical suspicion of Legionnaires disease will be less useful, because Legionnaires disease will be diagnosed earlier and the manifestations of severe pneumonia will be muted. On the other hand, in patients who present for medical care late in the course of the disease or in patients in whom the diagnosis of Legionnaires disease is overlooked by the physician, the application of the syndromic approach may suggest the correct diagnosis. Also, the WUH score may allow the targeting of patients for longer duration of therapy and the administration of more active therapy (such as quinolones and rifampin). In future comparative studies of community-acquired pneumonia etiology,[34] Legionella laboratory testing should be performed on all patients; testing for Legionella with serology as the sole test is inadequate. Until then, the current approach of using empiric anti-Legionella therapy (*ie*, macrolides or quinolones) for all patients with community-acquired pneumonia requiring hospitalization should prevail.[32,33,35] A pathogen-directed approach using the syndromic approach is not recommended. Further studies focusing on the application of the WUH score to assess its utility, if any, are necessary.

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References

1 Cunha BA. Clinical features of Legionnaires disease. Semin Respir Infect 1998; 13:116–127
2 Fraser DW, Wachsmuth IK, Bopp C, et al. Antibiotic treatment of guinea-pigs infected with agent of Legionnaires disease. Lancet 1978; 1:175–178
3 Tsai TF, Finn DR, Pilikaytis B. Clinical features of the epidemic in Philadelphia. Ann Intern Med 1979; 90:509–517
4 Kirby BD, Snyder KM, Meyer RD, et al. Legionnaires disease: clinical features of 24 cases. Ann Intern Med 1978; 89:297–309
5 Kirby BD, Snyder K, Meyer R, et al. Legionnaires disease: report of 65 nosocomially acquired cases and a review of the literature. Medicine 1980; 59:188–205
6 Yu VL, Kroboth FJ, Shonnard J, et al. Legionnaires disease: new clinical perspective from a prospective pneumonia study. Am J Med 1982; 73:357–361
7 Ruiz M, Ewig S, Marcos MA, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med 1999; 160:397–405
8 Torres A, Sera-Batilles J, Ferrer A, et al. Severe community acquired pneumonia: epidemiology and prognostic factors. Am Rev Respir Dis 1991; 144:312–318
9 Roig J, Aguilar X, Ruiz J, et al. Comparative study of *Legionella pneumophila* and other nosocomial-acquired pneumonias. Chest 1991; 99:344–350
10 Granados A, Podzamczer D, Gudiol F, et al. Pneumonia due to *L. pneumophila* and pneumococcal pneumonia: similarities and differences on presentation. Eur Respir J 1989; 2:130–134
11 Rihs JD, Yu VL, Zuravleff JJ, et al. Isolation of *Legionella pneumophila* from blood using the BACTEC: a prospective study yielding positive results. J Clin Microbiol 1985; 22:422–424
12 Helms CM, Viner JR, Sturm RH, et al. Comparative features of pneumococcal, mycoplasmal and Legionnaires disease pneumonia. Ann Intern Med 1979; 90:543–547
13 MacFarlane JT, Miller AC, Smith RWH. Comparative radiographic features of community acquired Legionnaires disease, pneumococcal pneumonia, mycoplasma pneumonia, and psittacosis. Thorax 1984; 39:28–33
14 Miller AC. Early clinical differentiation between Legionnaires disease and other sporadic pneumonias. Ann Intern Med 2001; 90:526–528
15 Falco V, Fernandez de Sevilla T, Alegre J, et al. *Legionella pneumophila*: a cause of severe community acquired pneumonias. Chest 1991; 100:1007–1011
16 Domingo C, Roig J, Planas F, et al. Radiographic appearance of nosocomial Legionnaires disease after erythromycin treatment. Thorax 1991; 46:633–666

17 Tan MJ, Tan JS, Hamor R, et al. The radiologic manifestations of Legionnaire's disease: the Ohio Community-Based Pneumonia Incidence Study Group. Chest 2000; 117:398–403
18 Roig J, Martinez-Benazet J, Salvador J. Radiologic features of legionellosis. Curr Topics Radiol 1998; 1:101–105
19 Kroboth FJ, Yu VL, Reddy S, et al. Clinicoradiographic correlations with the extent of Legionnaires disease. AJR Am J Roentgenol 1983; 141:263–268
20 Dietrich P, Johnson R, Fairbank J, et al. The chest radiograph in Legionnaires disease. Radiology 1978; 127:577–582
21 Lieberman D, Porath A, Schlaeffer F, et al. Legionella species in community-acquired pneumonia: a review of 56 hospitalized adult patients. Chest 1996; 109:1243–1249
22 Sopena N, Sabria-Leal M, Pedro-Botet ML, et al. Comparative study of the clinical presentation of Legionella pneumonia and other community-acquired pneumonias. Chest 1998; 113:1195–1200
23 Muder RR, Yu VL, Parry M. Radiology of Legionella pneumonia. Semin Respir Infect 1987; 2:242–254
24 Woodhead MA, MacFarlane JT. Comparative clinical and laboratory features of Legionella with pneumococcal and mycoplasma pneumonias. Br J Dis Chest 1987; 81:133–139
25 Olaechea PM, Quintana MM, Gallardo MS, et al. A predictive model for the treatment approach to community-acquired pneumonia in patients needing ICU admission. Intensive Care Med 1996; 22:1294–1300
26 Ostergaard L, Andersen PL. Etiology of community-acquired pneumonia: evaluation by transtracheal aspiration, blood culture, or serology. Chest 1993; 104:1400–1407
27 Mundy LM, Oldach D, Auwaerter PG, et al. Implications for macrolide treatment in community-acquired pneumonia. Chest 1998; 113:1201–1206
28 Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. Medicine (Baltimore) 1990; 69:307–316
29 Roig J, Rello J, Yu VL. Legionnaires disease. J Respir Dis 2001 (in press)
30 Keller DW, Lipman HB, Marston BJ, et al. Clinical diagnosis of Legionnaires disease using a multivariate model. In: Proceedings of the 35th Interscience Conference of Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, CA
31 Blatter M, Frei R, Widmer AI. Clinical predictors for culture-proven *L. pneumophila* pneumonia: a matched case control study. Paper presented at: the European Congress of Clinical Microbiology and Infectious Diseases, Lausanne, Switzerland, 1997
32 Niederman M, Mandell LA. Guidelines for the initial management of adults with community-acquired respiratory infections: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163:1730–1754
33 Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for management of community-acquired pneumonia. Clin Infect Dis 2000; 31:347–382
34 Vergis EN, Yu VL. New directions for future studies of community-acquired pneumonia optimising impact on patient care. Eur J Clin Microbiol Infect Dis 1999; 18:847–851
35 The Canadian Community-Acquired Pneumonia Working Group. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Clin Infect Dis 2000; 31:383–421

Severe Community-Acquired Pneumonia

The Need To Customize Empiric Therapy

Even with extensive diagnostic regimens, most studies of community-acquired pneumonia (CAP) fail to determine the etiology in ≥ 50% of cases. In usual clinical practice, the diagnostic rate is closer to 15%, which results in most patients with CAP receiving an empiric antibiotic regimen rather than individualized therapy. The choice of empiric antibiotic agents is often guided by consensus guidelines.[1,2] These guidelines are in turn based on covering the majority of pathogens identified in published findings from groups of patients with CAP.

Empiric therapy that does not cover the infecting pathogen is an independent predictor of poor outcome,[3–5] and patients with subsequent changes in antibiotic therapy based on culture results still have a significant mortality.[6,7] The adverse implications for inadequate empiric therapy make it imperative that the antibiotic regimen chosen has as few "holes" as possible, especially in patients with severe CAP, where the mortality is ≥ 20%. As the study by Chen and colleagues in this edition of *CHEST* demonstrates (see page 1072), significant holes in antibiotic coverage may result when the local etiology of CAP differs from the etiology in "standard" populations (predominantly North American and Western European) on which the guidelines are based. To achieve the best outcome, physicians need to have knowledge of local variations in the etiology of CAP, and they must be aware of which pathogens may not be covered by standard empiric regimens, and the risk factors for infection with these pathogens.

Deficiencies in empiric antibiotic coverage can result from either unexpected antibiotic resistance in the common pathogens or because unusual pathogens are the cause of CAP. The impact of antibiotic resistance is dependent on the empiric antibiotic regimen used. In the case of penicillin-resistant *Streptococcus pneumoniae* infection, the impact is relatively small because empiric regimens in areas with a high prevalence of penicillin resistance are designed to cover this eventuality. Conversely, while *Staphylococcus aureus* is not an unexpected pathogen, the presence of methicillin resistance in community-acquired infections is increasing[8] and the inadequacy of usual empiric regimens may significantly impact outcome.[4]

The occurrence of etiologies other than the usual pathogens, *S pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae,* Legionella spp, and respi-