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Importance of *Legionella pneumophila* in the Etiology of Severe Community-Acquired Pneumonia in Santiago, Chile

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Background: **In US and European literature, *Legionella pneumophila* is reported as an important etiologic agent of severe community-acquired pneumonia (CAP), but in Chile this information is lacking. The aim of this study was to determine the incidence and identify predictors of severe CAP caused by *L pneumophila* in Santiago, Chile.**

Methods: **A multicenter, prospective clinical study lasting 18 months was conducted; it included all adult patients with severe CAP admitted to the ICUs of four hospitals in Santiago. We excluded patients who were immunocompromised, had been hospitalized in the previous 4 weeks, or presented with another disease during their hospitalization. All data for the diagnosis of severe CAP were registered, and urinary antigens for *L pneumophila* serogroup 1 were determined.**

Results: **A total of 104 patients with severe CAP were included (mean ± SD age, 58.3 ± 19.3 years; men, 64.4%; APACHE (Acute Physiology and Chronic Health Evaluation) II score, 16.7 ± 6.3; Sepsis-related Organ Failure Assessment score, 6.1 ± 3.2; Pitt Bacteremia Score, 3.4 ± 2.5; Pao_2/FIO_2, 170.8 ± 87.1). An etiologic agent was identified in 62 patients (59.6%), with the most frequent being *Streptococcus pneumoniae* (27 patients [26%]) and *L pneumophila* (nine patients [8.6%]). Logistic regression analysis showed that a plasma sodium level of ≤ 130 mEq/L was an independent predictor for *L pneumophila* severe CAP (OR, 11.3; 95% CI, 2.5-50.5; *P* = .002). Global mortality was 26% and 33% for *L pneumophila*. The Pitt bacteremia score and pneumonia score index were the best predictors of mortality.**

Conclusions: **We found that in Santiago, *L pneumophila* was second to *S pneumoniae* as the etiologic agent of severe CAP. Severe hyponatremia at admission appears to be an indicator for *L pneumophila* etiology in severe CAP.** ***CHEST 2014; 145(2):290–296***

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CAP = community-acquired pneumonia; PBS = Pitt Bacteremia Score; PSI = Pneumonia Severity Index; SOFA = Sepsis-related Organ Failure Assessment

Community-acquired pneumonia (CAP) is the sixth leading cause of death in the United States[1] and the third in Chile.[2] Between 5% and 15% of hospitalized patients present with severe CAP that must be treated in an ICU. Complications are frequent, hospital stay is prolonged, and mortality varies between 21% and 54%.[3,4]

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The principal agent responsible for CAP, including severe cases, is *Streptococcus pneumoniae*.[3-6] In severe

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CAP, *Legionella pneumophila* is recognized worldwide as another important agent.[7-10]

Geographic and seasonal differences are frequently found in the reported incidence of Legionnaires' disease in CAP, which ranges from 2% to 27%.[11,12] In the United States, it is estimated that the yearly occurrence of CAP is between 8,000 and 18,000 new cases.[13,14] In 2009, the reported number of US legionellosis cases was 3,522.[15]

The diagnosis of legionellosis with bacteriologic isolation of *L pneumophila* is difficult and has low sensitivity; direct immunofluorescence test is operator dependent, and with low sensitivity and seroconversion, it permits only a retrospective diagnosis. The introduction of the urinary antigen test has improved the etiologic diagnosis of legionellosis.[11,13-17]

As information regarding *Legionella* severe CAP in Chile is insufficient, our first aim was to determine through a prospective study the incidence of *L pneumophila* etiology in a general population with severe CAP requiring intensive care. Because prompt diagnosis and specific treatment are expected to reduce mortality from *Legionella* CAP (reported in 21%-40% of patients with CAP),[8,14,18-20] most guidelines, including Chilean consensus, recommend covering both,[3,11,21] but this approach is not universally applied. Therefore, we also looked for clinical or laboratory characteristics present at admission that could be identified as early predictors of *Legionella* etiology, prompting the addition of specific antibiotic therapy.

Materials and Methods

From January 1, 2005, to June 31, 2006, we performed a prospective, multicenter clinical study in four hospitals (one university hospital and three from the Public National Health System) in Santiago, Chile. All consecutive inmunocompetent patients aged > 18 years hospitalized for CAP in an ICU in accordance with American Thoracic Society criteria[3] were considered. The diagnosis of CAP was made in the presence of a new infiltrate on chest radiography and at least one of the following criteria: fever (temperature, ≥ 38°C), cough, production of purulent sputum, pleuritic pain, leukocytosis or leukopenia, and no alternative diagnosis made during follow-up. Exclusion criteria were hospitalization during the 28 days preceding the study, inmunosuppression, solid organ or bone marrow transplantation, known HIV infection, neutropenia $< 1 \times 10^9$/L, treatment with steroids with > 20 mg prednisone or equivalent per day for > 2 weeks, and treatment with immunosuppressive drugs.

The following variables were recorded: age; sex; smoking, alcohol, and drug habits; comorbidities; antibiotic treatment before admission; onset of pneumonia; clinical symptoms; vital signs; CBC count; sedimentation rate; plasma electrolyte, BUN, plasma creatinine, C-reactive protein, and lactic dehydrogenase levels; arterial blood gases and pH measurements; and antibiotic regimen initially prescribed. Mechanical ventilation requirements, complications during ICU stay (pulmonary abscess, pleural empyema, nosocomial pneumonia, ARDS, renal insufficiency, septic shock, and multiorgan failure), length of ICU stay, and 28-day mortality rate were also recorded.

Chest radiography findings were classified into one of the following patterns: alveolar, interstitial, or mixed infiltrate. Bilateral or multilobar infiltrates, presence of cavitation or pleural effusion, and progression of infiltrates of ≥ 50% within the first 72 h were recorded. The chest radiograph was evaluated by radiologists, but they were not involved in the study. Assessment of illness severity in these patients was performed according to the following scores: Pneumonia Severity Index (PSI),[22] CURB-65 (confusion of new onset, urea > 7 mmol/L [19 mg/dL], respiratory rate ≥ 30/min, systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg, age ≥ 65 y),[23] APACHE (Acute Physiology and Chronic Health Evaluation) II,[24] Sepsis-related Organ Failure Assessment (SOFA),[25] and Pitt Bacteremia Score (PBS).[26]

Microbiology

The microbiologic evaluation on admission included Gram staining and culture of sputum or tracheobronchial aspirates. Two sets of blood cultures were also taken. The detection of *L pneumophila* serogroup 1 and *S pneumoniae* antigens by means of an immunochromatographic test (BinaxNOW; Alere) in nonconcentrated urine samples was performed. Aspirated nasopharyngeal secretions for detection of respiratory virus antigens were obtained (test to detect influenza A and B, parainfluenza 1-3, adenovirus, and respiratory syncytial virus) and tested with an indirect immunofluorescence assay kit with monoclonal antibodies (Chemicon/EMD Millipore Corporation). Serum IgM antibody detection for *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* was performed (RIDASCREEN; R-Biopharm AG). Bacteriologic study of pleural fluid and BAL and a search for *Mycobacterium tuberculosis* or IgM and IgG for hantavirus was performed according to clinical judgment. The IgM and IgG antibodies for hantavirus were confirmed with enzyme-linked immunosorbent assay according to the guidelines of the Centers for Disease Control and Prevention. The antigens used were Laguna Negra virus, Andes virus, or both for IgM and Sin Nombre virus, Andes virus, or both for IgG. Respiratory samples were considered representative of lower respiratory tract infection and cultured if > 25 leukocytes and < 10 epithelial cells were present.

Definitions

Any antibiotic use within 30 days of admission was considered a previous treatment. Antibiotic treatment used for each patient was labeled as adequate if sensitivity tests for the isolated organism revealed that at least one of the drugs was effective. In the case of *Pseudomonas aeruginosa*, two active drugs were required for treatment. An antimicrobial treatment failure in patients with CAP was defined according to a prior publication.[27] For predictors observed in the patients with severe CAP from *L pneumophila*, clinical and laboratory data were compared with that of patients with non-*Legionella* severe CAP.

Statistical Analysis

Results are expressed as mean ± SD. Continuous variables were compared by Student *t* test and categorical variables by χ^2 or Fisher exact test. To identify factors associated with the presence of *L pneumophila* severe CAP, we used a logistic regression model with categorized variables and stepwise forward selection. Variables were included in a multivariate analysis when a univariate analysis yielded a level of significance of $P < .10$. The following variables were tested: APACHE II score, SOFA score, and hyponatremia, pH, creatinine, and BUN levels. Results of multivariate analysis are reported as ORs. All tests of significance were two tailed, and α was set at 0.05. All analyses were performed with SPSS, version 12.0 (IBM Corporation) software.

The four hospitals used the same criteria and methods, and their ethics committee approved the study (Hospital del Tórax, 1707/02, and University of Chile, 67/04). Because no intervention was performed, informed consent was waived by institutional review boards.

Results

Of 120 patients with severe CAP, 104 were included in the study. The reasons for exclusion from the analyses were as follows: HIV infection (n = 4), cardiac insufficiency (n = 3), alveolar hemorrhage (n = 2), bronchiolitis obliterans organizing pneumonia (n = 2), high-dose corticosteroids (n = 2), pulmonary embolism (n = 1), atelectasis (n = 1), and previous hospitalization (n = 1).

The mean age was 58.2 years (range, 19-89 years); 64.4% were men. Eighty patients (76.9%) had preexisting medical conditions, including pulmonary disease in 44 (42.3%), diabetes in 21 (20.4%), alcohol abuse in 19 (18.4%), and congestive heart failure in 17 (16.5%). The clinical characteristics of the population analyzed are summarized in Table 1.

Microbiology

A microbiologic diagnosis of pneumonia was established in 62 patients (59.6%). The top seven most frequently identified pathogens were *S pneumoniae* (26%), *L pneumophila* (8.6%), *M pneumoniae* (6%), *C pneumoniae* (4%), gram-negative bacilli (3%), influenza A (3%), and *Staphylococcus aureus* (3%). In four patients, two concomitant pathogens were isolated (*S pneumoniae* plus *M pneumoniae*, *S pneumoniae* plus *Haemophilus* species, *S pneumoniae* plus *S aureus*, and *S pneumoniae* plus influenza A), and in one patient, four bacteria were present (*Streptococcus viridans* plus three anaerobic bacilli). Table 2 shows the diagnostic procedures used to identify the different microorganisms.

Table 1—*General Characteristics of Patients With Severe CAP*

Characteristic	Value
No. patients	104
Age, y	58.3 ± 19.6
Male sex	67 (64.4)
Pulmonary comorbidity	44 (42.3)
COPD	21 (20.4)
Asthma	9 (8.7)
Diabetes mellitus	21 (20.4)
Congestive heart failure	17 (16.5)
Current smokers	42 (40.4)
Alcoholism	19 (18.4)
Two or more comorbid conditions	42 (40.4)
Prior antibiotic use	30 (29.2)
Onset of pneumonia, d	5.6 ± 4.5
PSI[22]	
I-II	12 (11.5)
III	14 (13.5)
IV	30 (28.8)
V	48 (46.2)
CURB-65 score[23]	
0-1	28 (27)
2	26 (25)
3-5	50 (48)
APACHE II score[24]	16.7 ± 6.3
SOFA score[25]	6.1 ± 3.2
PBS[26]	3.4 ± 2.5

Data are presented as mean ± SD or No. (%). APACHE = Acute Physiology and Chronic Health Evaluation; CAP = community-acquired pneumonia; CURB-65 = confusion of new onset, urea > 7 mmol/L [19 mg/dL], respiratory rate ≥ 30/min, systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg, age ≥ 65 y; PBS = Pitt Bacteremia Score; PSI = Pneumonia Severity Index; SOFA = Sepsis-related Organ Failure Assessment.

In 14 patients, a pleural empyema developed, and in six of them (43%), the etiology was identified (*S pneumoniae* in four, β-hemolytic *Streptococcus* in one, and *S viridans* plus anaerobes in one). All isolated strains of *S pneumoniae* from six blood cultures were susceptible to penicillin.

Determination of urinary antigens of *L pneumophila* and *S pneumoniae* was performed in 104 (100%) and 69 patients (66%), respectively. The urine antigen was obtained 0.72 ± 1.5 days after ICU admission. The urinary antigens allowed for the identification of etiology in 26.9% of the patients, improving diagnostic yield over other techniques from 32.7% to 59.6%. A more extensive use of this test for *S pneumoniae* could lead to a higher diagnostic yield.

Antimicrobial Therapy

Of the 104 patients studied, 29% received antibiotic treatment before admission. Five of these patients with *L pneumophila* received antibiotic treatment, but the therapy covered the pathogen in only one patient. In this group, the yield of blood cultures was low compared with that of patients without previous antibiotics (4.2% vs 10.7%).

Antibiotic therapies were started at hospital admission (0.11 ± 0.37 days). Among all patients with severe CAP, the initial treatment covered atypical pathogens in only 56%. However, initial antibiotic therapy was adequate in 84% of patients with an ultimately established etiology and in eight of nine patients (89%) with *L pneumophila.* The most frequent regimens were β-lactam plus fluoroquinolones (n = 50 [48%]); β-lactams as monotherapy (n = 19 [18.2%]), β-lactam plus clindamycin (n = 18 [17.3%]), and β-lactam plus macrolides (n = 6 [5.8%]).

Overall, 42 patients (40%) had antimicrobial treatment failure. Causes were primary infection (n = 5), definite persistent infection (n = 8), nosocomial infection (n = 7), noninfectious causes (n = 2), and pleural empyema (n = 14).

Severe CAP From L pneumophila *Compared With Other Causes of CAP*

When comparing patients with severe CAP from *L pneumophila* with that from other causes, no differences were detected in age, symptoms, physical signs, or chest radiographic findings. APACHE II and

Table 2—*Microbiologic Findings in 104 Patients With Severe CAP*

Variable	Sputum	TBA	BAL	Blood Culture	IFA	Urinary Antigen for *Legionella pneumophila* and *Streptococcus pneumoniae*	Pleural Fluid	Serology	Total
Samples	42	41	9	81	60	104[a]/69[b]	21	83	…
Positive findings	7	4	2	7	5	9[a]/21[b]	…	…	…
S pneumoniae	1	2	…	6	…	21	…	…	27
L pneumophila	…	…	…	…	…	9	…		9
Mycoplasma pneumoniae	…	…	…	…	…	…	…	6	6
Chlamydophila pneumoniae	…	…	…	…	…	…	…	4	4
GNB	2	1	…	…	…	…	…	…	3
Influenza A	…	…	…	…	3	…	…	…	3
Staphylococcus aureus	1	1	…	1	…	…	…	…	3
Haemophilus species	2	…	…	…	…	…	…	…	2
RSV	…	…	…	…	2	…	…	…	2
Mycobacterium tuberculosis	1	…	1	…	…	…	…	…	2
Hantavirus	…	…	…	…	…	…	…	2	2
Others[c]	…	…	1	…	…	…	5	…	6

Data are presented as counts. GNB = gram-negative bacteria; IFA = indirect inmunofluorescence assay on a nasopharyngeal sample; RSV = respiratory syncytial virus; TBA = tracheobronchial aspirate. See Table 1 legend for expansion of other abbreviation.

[a]For *L pneumophila*.

[b]For *S pneumoniae*.

[c]Others include β-hemolytic streptococcus (n = 1), *Streptococcus viridans* (n = 1), anaerobes (n = 3), *Pneumocystis jiroveci* (n = 1).

PSI scores were higher in *L pneumophila* cases, but the difference was not significant (18.4 ± 3.3 vs 16.6 ± 6.5 and 147 ± 34 vs 126 ± 48, respectively). In contrast, SOFA scores were significantly higher for *L pneumophila* (8.4 ± 2.4 vs 5.9 ± 3.2, $P = .024$). Levels of BUN, creatinine, and plasma sodium ≤ 130 mEq/L on admission showed significant differences between *L pneumophila* and other pneumonias (Table 3).

All *L pneumophila* cases were associated with acute respiratory failure, and all required invasive mechanical ventilation, whereas only 39% of the rest did ($P < .0001$). Shock (eight of nine vs 45 of 95 patients, $P = .031$), acute renal failure (eight of nine vs 34 of 95 patients, $P = .003$), and multiple organ failure (six of nine vs 16 of 95 patients, $P = .003$) were also more frequent in *L pneumophila* severe CAP (Table 4). Three *L pneumophila* cases required dialysis, but only four in all the other pneumonias did ($P = .003$).

Multivariate Analysis

Regression logistic analysis showed that plasma sodium concentration ≤ 130 mEq/L on admission was an independent predictor for *L pneumophila* etiology in severe CAP (OR, 11.3; 95% CI, 2.5-50.5; $P = .001$).

Outcome

Stay in the ICU was significantly longer for *L pneumophila* (13.38 ± 9.1 days vs 3.7 ± 5.4 days, $P = .02$) as was hospital stay, but this was not significant (23.3 ± 9.9 days vs 15.3 ± 11.3 days, $P = .057$). Global mortality at 28 days in severe CAP was 25% and that of *L pneumophila* was 33.3% (three of nine cases), but the difference was not significant with non-*Legionella* severe CAP mortality (33% vs 24.5%; $P = .55$). PBS and PSI were better predictors of mortality (Table 5). It must be pointed out that the *L pneumophila* cases occurred sporadically and were not part of a cluster or outbreaks.

Discussion

The main findings in this study of severe CAP are that (1) in Santiago, Chile, the incidence of *L pneumophila* in the ICU as the etiologic agent was 8.6%,

Table 3—*Univariate Analysis of Predictive Factors at Hospital Admission*

Variable	*L pneumophila*	Other Pneumonias	OR (95% CI)	*P* Value
BUN ≥ 30 mg/dL	8/9	31/94	16.5 (1.9-137.9)	.002
Creatinine ≥ 2.0	4/9	11/92	7.4 (1.6-33.7)	.017
Plasma Na ≤ 130 mEq/L	6/9	14/93	11.3 (2.5-50.5)	.002
pH ≤ 7.35	6/9	36/90	4.5 (0.9-23.5)	.071
APACHE II score ≥ 14	8/9	63/95	4.1 (0.48-33.9)	.16
SOFA score ≥ 7[23]	7/9	36/94	11.5 (1.4-97.1)	.009

See Table 1 and 2 legends for expansion of abbreviations.

Table 4—*Acute Complications in 104 Patients With Severe CAP From* Legionella *and Other Etiologies*

Complication	*L pneumophila*	Other Pneumonias	OR (95% CI)	*P* Value
Mechanical ventilation	9/9	37/95	…	< .0001
ARDS	7/9	22/95	11.6 (2.3-60.0)	.002
Septic shock	8/9	45/95	8.9 (1.1-73.9)	.031
Dialysis	3/9	4/94	13.5 (2.4-77.4)	.01
MOF	6/9	16/95	9.9 (2.2-43.7)	.003

MOF = multiple organ failure. See Table 1 and 2 legends for expansion of other abbreviations.

second only to *S pneumoniae*, and (2) severe hyponatremia at admission is an independent predictor of *L pneumophila* etiology. To our knowledge, this study is the first to examine the incidence of *L pneumophila* in severe CAP in Chile. The incidence of *Legionella* species as a cause of sporadic CAP reported in the literature shows differences in the severity of clinical presentation and population considered and different geographical and seasonal data. But the most frequent level has been around 3% to 6%,[12,28-30] and in severe CAP, the incidence is greater (5%-24%).[31] The incidence of *L pneumophila* severe CAP found in the present study is similar to other reports in the literature.[32] These results seem to be generalizable to other countries.[33] The problem of *Legionella* is that if one does not search specifically for it, its existence is neglected. However, we do not know whether this incidence is the same in countries with climates much colder than Chile. A study by the German Competence Network for Community Acquired Pneumonia[30] found an incidence of 3.8%. It is important that all countries have good epidemiologic data of *Legionella* to release guidelines and treatment recommendations.

In a national study in Santiago that used diagnostic techniques other than the urinary antigen test, Trucco et al[34] reported an 8.5% incidence of *L pneumophila* in 140 hospitalized patients with CAP. In a retrospective study, Cabello et al[35] reported eight cases of severe CAP as a result of *L pneumophila*. Díaz et al[36] did not identify *L pneumophila* in any of 113 cases of severe CAP in their study, but urinary antigens were measured in only 11% of the patients.

In Latin America, we have little information on the epidemiology of *Legionella*. The incidence of *L pneumophila* in Argentina[37] has been 3.5% and in Brazil,[38] 5.1%. We believe that the present study could be of interest in the region and contributes to the knowledge of the epidemiology of *L pneumophila*.

In other international studies,[7-10,39-43] *L pneumophila* is, as in the present study, an important agent for severe CAP after *S pneumoniae.* Real incidence of this agent is probably greater with use of the urinary antigen test. In a systematic review and meta-analysis, Shimada et al[44] found that *Legionella* urinary antigen for serotype 1 appears to have excellent specificity (0.991) but a moderate sensitivity (0.74). In addition, *Legionella* urinary antigen only identifies serogroup 1, which represents 50% to 90% of the *Legionella* species.[14,30,45]

These patients presented with different combinations of the clinical manifestations reported for Legionnaires' disease.[18,46,47] We could not find any clinical or radiologic variables reported in the literature that differentiated *Legionella* from other agents in severe CAP.[8,29,31] Nevertheless, multivariate analysis showed that severe hyponatremia was an independent predictor of *Legionella* etiology, which agrees with literature reporting that hyponatremia occurs more frequently in Legionnaires' disease than in other types of pneumonia.[28,30,46,47] We believe that this finding is clinically useful in the sense that hyponatremia on admission for severe CAP warrants a prompt search for *Legionella* etiology with the best available diagnostic methods or, at least, starting the patient on *Legionella*-active antibiotics.

L pneumophila appears to cause more severe disease with multisystem dysfunction than most common bacterial pathogens associated with CAP.[47] Respiratory failure, particularly when the patient requires intubation and invasive mechanical ventilation, has been

Table 5—*Comparison of Severity of Illness Scoring Systems Related to 28-d Mortality in Patients With Severe CAP*

Variable	Severity	Survival Group	Mortality Group	OR (95% CI)	*P* Value
APACHE II[24]	≥ 14	47/77 (61)	23/26 (88.5)	4.9 (1.3-17.7)	.01
SOFA[25]	≥ 7	27/76 (35.5)	16/26 (61.5)	2.9 (1.2-7.3)	.02
PSI[22]	IV-V	52/76 (68.4)	24/26 (92.3)	5.5 (1.21-25.3)	.016
CURB-65[23]	4-5	15/74 (20.3)	10/25 (40)	2.6 (0.9-7.0)	.05
PBS[26]	≥ 5	12/77 (15.6)	19/26 (73.1)	14.7 (5.1-42.6)	< .0001

Data are presented as proportion (%) unless otherwise indicated. See Table 1 legend for expansion of abbreviations.

associated with increased mortality.[48] In the present study, clinical evolution of *L pneumophila* CAP was more severe than the other etiologies. Rapidly progressive respiratory failure and the need for invasive mechanical ventilation were observed in all the patients. Acute renal insufficiency needing hemodialysis was frequent, and SOFA score was high, indicating more involved organs. Similar to other reports, mortality from *L pneumophila* was higher.[8,18,20,48]

As a secondary result, we observed that use of the urinary antigen test meant a better diagnostic yield than other usual diagnostic methods and had the advantages of not being invasive, being easy to perform, and yielding rapid results, thus, improving the specificity of treatment. Additionally, the test for *L pneumophila* remains positive for weeks and is useful in patients who received previous antibiotic therapy.

Prompt diagnosis of Legionnaires' disease as well as initiation of appropriate therapy can decrease length of stay and the mortality rate.[14,49] A delay in starting appropriate therapy for *Legionella* pneumonia significantly increases mortality.[50]

The limitations of this study were that it covers the population of only two of the four zones of Santiago and that we used only one diagnostic technique for identifying *L pneumophila* serogroup 1. Thus, it is possible that the incidence was higher.

In summary, this prospective multicenter study reveals that *L pneumophila*, with an incidence of 8.6%, is second only to *S pneumoniae* as an agent for serious CAP in Santiago, Chile, and that hyponatremia is a useful independent predictor for this etiology. Thus, these findings confirm the guideline that atypical pathogens, particularly *L pneumophila*, should be covered in addition to pneumococcus by empirical therapy.

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Dr Cortes: contributed to the study design, data analysis and interpretation, and manuscript revision.
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