CHEST

Original Research

CHEST INFECTIONS

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

Francisco Arancibia, MD; Claudia P. Cortes, MD; Marcelo Valdés, MD; Javier Cerda, MD; Antonio Hernández, MD; Luis Soto, MD; and Antoni Torres, MD

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]

For editorial comment see page 202

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

Manuscript received January 21, 2013; revision accepted May 8, 2013.

Affiliations: From the Instituto Nacional del Tórax (Drs Arancibia, Valdés, and Soto), Santiago, Chile; Clínica Santa María (Drs Arancibia and Valdés), Santiago, Chile; School of Medicine (Dr Cortes), University of Chile, Santiago, Chile; Hospital Militar de Santiago (Drs Cerda and Hernández), Santiago, Chile; Hospital San Borja-Arriarán (Dr Cerda), Santiago, Chile; Servei de Pneumologia (Dr Torres), Institut del Tórax, Hospital Clínic, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; and Centro de Investigación Biomedica En Red-Enfermedades Respiratorias (CibeRes, CB06/06/0028)-Instituto de Salud Carlos III (Dr Torres), Madrid, Spain.

Funding/Support: The authors have reported to *CHEST* that no funding was received for this study.

Correspondence to: Francisco Arancibia, MD, Instituto Nacional del Tórax, José Manuel Infante 717, Providencia, Santiago, Chile; e-mail: fearancibia@gmail.com

DOI: 10.1378/chest.13-0162

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.