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Committee Report

Clinical presentation of *Legionella* pneumonia: Evaluation of clinical scoring systems and therapeutic efficacy☆

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ABSTRACT

To evaluate scoring systems to predict *Legionella* pneumonia and therapeutic efficacy against *Legionella* pneumonia, the Japanese Society of Chemotherapy *Legionella* committee has collected data on cases of *Legionella* pneumonia from throughout Japan. We analyzed 176 patients with *Legionella* pneumonia and compared them with 217 patients with *Streptococcus pneumoniae* pneumonia and 202 patients with *Mycoplasma pneumoniae* pneumonia. We evaluated four scoring systems, the Winthrop-University Hospital score, Community-Based Pneumonia Incidence Study Group score, and Japan Respiratory Society score, but they demonstrated limited sensitivity and specificity for predicting *Legionella* pneumonia. Using six clinical and laboratory parameters (high fever, high C-reactive protein, high lactate dehydrogenase, thrombocytopenia, hyponatremia, and unproductive cough) reported by Fiumefreddo and colleagues, only 6% had *Legionnella* pneumonia when less than 2 parameters were present. The efficacy rates of antibiotics at the time of termination were 94.6% for intravenous antibiotics, including ciprofloxacin and pazufloxacin, and 95.5% for oral antibiotics, including ciprofloxacin, levofloxacin, garenoxacin, moxifloxacin, and clarithromycin. Our results suggested that the previously reported clinical scoring systems to predict *Legionnella* pneumonia are not useful, but 6 simple diagnostic score accurately ruled out *Legionnella* pneumonia, which may help to optimize initial empiric therapy. Quinolones and clarithromycin still showed good clinical efficacy against *Legionella* pneumonia.

1. Introduction

Legionellosis is an important cause of community-acquired pneumonia (CAP), nosocomial infection, and respiratory diseases outbreaks [1–4]. Pneumonia due to *Legionella* often presents as rapidly progressive severe form of pneumonia. In addition, *Legionella* CAP has a high mortality rate of about 10%, which may increase up to 27% in patients not receiving adequate antibiotics as part of their empiric treatment on admission [2]. Treatment with routinely used β-lactam or aminoglycoside antibiotics is ineffective against *Legionella* because *Legionella* is an intracellular pathogen, and only those antibiotics that achieve high intracellular penetrations are efficacious. Thus, early identification of *Legionella*

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infection is important because it affects the timing and choice of empiric antibiotic therapy and reduces the risk of adverse outcomes.

Urinary antigen test is the only diagnostic test that is able to simply and rapidly diagnose Legionnaires disease, and numerous studies have reported on its usefulness. The number of patients diagnosed definitively has increased since the introduction of this test. However, a systematic review demonstrated that although the *Legionella* urinary antigen for serotype 1 appears to have excellent specificity is has only modest sensitivity [5]. In addition, other high-quality studies showed lower sensitivity for this test [5]. These results indicated that many *Legionella* cases may be missed in daily clinical setting where only the urinary antigen test is used for the diagnosis of Legionnaires disease. For this reason, several clinical scoring systems to predict *Legionella* pneumonia have been proposed [6–11].

To improving the management of *Legionella* pneumonia, in 2006 the Japan Society of Chemotherapy (JSC) inaugurated a *Legionella* Committee to evaluate diagnosis and treatment of *Legionella* pneumonia. The committee has collected data on cases of *Legionella* pneumonia from throughout Japan. The purpose of the present study was to identify a means of rapidly predicting *Legionella* pneumonia in daily clinical practice when a urinary antigen test was negative. For comparison, we used different CAP pathogens, *Streptococcus pneumoniae*, which is most common bacterial CAP, and *Mycoplasma pneumoniae*, which is most common atypical pneumonia [12]. In addition, this study investigated differences in therapeutic efficacy against *Legionella* pneumonia among quinolones and macrolides.

2. Materials and methods

2.1. Study population

The study was conducted by the JSC between December 2006 and November 2011. During the study period, 176 cases with *Legionella* pneumonia were recorded. A complete list of participating facilities is provided in the appendix. For comparison we used 217 cases of *S. pneumoniae* pneumonia and 202 cases of *M. pneumoniae* pneumonia who were diagnosed during study period. Cases of pneumonia mixed with other microorganisms were excluded from this study. Microbiological tests, cultures, antigen detection test, real-time polymerase chain reaction (PCR), and serological tests were performed as described previously [13]. The study protocol was approved by the Ethics Committee at Kawasaki Medical School and all participating facilities.

We used a standardized questionnaire for collecting clinical information. Information on patient background, clinical signs, symptoms, laboratory data, and clinical course after admission to hospital were collected. The severity of pneumonia was assessed with the use of a clinical severity scale, the Pneumonia Severity Index, published by the Infectious Diseases Society of America [14].

2.2. Clinical prediction rule

The Winthrop-University Hospital (WUH) point scoring scale was published by Cunha based on clinical criteria [6]. The system uses 15 clinical findings (headache, confusion/encephalopathy, lethargy, ear pain, nonproductive cough/sore throat, hoarseness, purulent sputum, mild-to-moderate hemoptysis, pleuritic chest pain, loose stools/diarrhea, abdominal pain without diarrhea, abdominal pain with diarrhea, relative bradycardia, no response to β-lactam therapy, and acute renal failure) and seven laboratory data (hyponatremia, hypophosphatemia, increased serum transaminases, total serum bilirubin, increased cold agglutinin titer, increased creatinine, and microscopic hematuria) to identify patients with *Legionella* pneumonia. A score of: ≥10 indicates legionellosis is highly probable, a score from 5 to 9 indicates a diagnosis probable, and a score of ≤4 indicates that legionellosis is unlikely.

The Community-Based Pneumonia Incidence Study (CBPIS) Group score was created using the results of multivariate analysis from a large prospective CAP incidence study [8]. The system uses four clinical findings (headache and vomiting with current illness, maximum temperature within 24 h of onset, and smoking within 1 month of illness onset) and three laboratory data (serum creatinine, lactate dehydrogenase, and serum sodium concentration) to identify patients with *Legionella* pneumonia. The score ranges from 0 (minimum) to 17 (maximum). Three categories of probability of *Legionella* pneumonia diagnosis were derived from the scores: ≥10 points, high; 5–9 points, moderate; and ≤4 points low.

Fiumefreddo et al. proposed a predictive score for the probability of *Legionella* in patients with pneumonia using 6 dichotomized, routine clinical and laboratory variables, namely high fever >39.4 °C, high C-reactive protein >187 mg/L, high lactate dehydrogenase >225 mmol/L, thrombocytopenia $<171 \times 10^9$/L, hyponatremia (sodium) < 133 mmoL/L, and unproductive cough [10]. Using this score, Haubitz et al. demonstrated a high negative predictive value of 99% for patients with less than 2 parameters present [11].

The Japan Respiratory Society (JRS) CAP guidelines were selected to allow easy differentiation of CAP without special examinations [12]. We extracted six parameters from frequently observed background factors, clinical symptoms, and laboratory findings of patients with atypical pneumonia. These parameters are; 1) <60 years of age, 2) no or minor co-morbid illness, 3) the patient has stubborn cough, 4) the patient has poor chest auscultatory findings, 5) no sputum or identified etiological agent by rapid diagnostic tests (Gram staining and urinary antigen tests), and 6) a peripheral white blood cell (WBC) count $<10{,}000/mm^3$. When there is a correlation of more than four out of all parameters or of more than three out of five parameters excluding laboratory data (parameter 6), then the guidelines suspected atypical pneumonia [12,13].

2.3. Antibiotic therapy

The antibiotic selection was made by the attending physicians. Intravenous ciprofloxacin and pazufloxacin were administered twice daily at doses of 300 mg and 500 mg, respectively. Oral levofloxacin, garenoxacin, and moxifloxacin were administered once daily at doses of 500 mg, 400 mg, and 400 mg, respectively. Oral ciprofloxacin and clarithromycin were administered twice daily at doses of 300 mg and 200 mg, respectively.

The clinical efficacy and bacteriological efficacy (prevalence of bacteria) were examined. Clinical efficacy was assessed at the termination of antibiotic therapy and was classified as “effective”, “ineffective”, or “evaluation not possible” according to clinical efficacy criteria [15]. Bacteriological efficacy was classified as bacterial “eradication” or “persistence” according to bacterial efficacy criteria [15] on the basis of bacteriological examination results before and after antibiotic therapy.

2.4. Statistical analysis

Discrete variables are expressed as counts (percentage) and continuous variables as median and interquartile ranges (IQR). Frequency comparison was done using Fisher's exact test. Two-group comparison of normally distributed data was performed using Students t-test. For data not normally distributed, Mann–Whitney's U test was used.