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Original Article

Impact of procalcitonin-guided therapy for hospitalized community-acquired pneumonia on reducing antibiotic consumption and costs in Japan

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ABSTRACT

Background and objective: This study aimed to investigate the usefulness of procalcitonin-guided therapy in hospitalized community-acquired pneumonia patients to reduce antibiotic duration and costs without worsening prognosis.

Methods: 352 hospitalized community-acquired pneumonia patients in an observational cohort study in which procalcitonin was measured three times serially, on admission (Day 1) and 2–3 days (Day 3) and 6–8 days (Day 7) after admission, between October 2010 and February 2016 were reviewed retrospectively. Antibiotics could be stopped if Day 7 procalcitonin was <0.25 ng mL^{-1} or ≤10% of the higher value of procalcitonin on Day 1 or 3. Antibiotic duration and costs and recurrence and mortality rates were evaluated in mild to moderate or severe pneumonia by theoretical procalcitonin guidance for community-acquired pneumonia treatment.

Results: Using theoretical procalcitonin guidance, antibiotic duration could be reduced from 12.6 to 8.6 days ($P < 0.001$), while costs could be reduced from 45,833 to 38,952 yen ($P = 0.005$). Among the patients in whom theoretical procalcitonin guidance could be adopted, recurrence rates (5.6% vs. 8.1%, $P = 0.15$) and mortality rates (0% vs. 5.1%, $P = 0.07$) did not worsen between the group having the same antibiotic durations as with theoretical procalcitonin guidance in actual practice (N = 71) and the group having durations more than 2 days longer in actual practice than in theoretical procalcitonin guidance (N = 198). There was no significant difference in pneumonia severity using A-DROP, CURB-65, and PSI between two groups.

Conclusions: Procalcitonin-guided therapy may be useful in hospitalized community-acquired pneumonia patients to reduce antibiotic duration and costs without worsening the prognosis.

1. Introduction

Community-acquired pneumonia (CAP) is a major cause of hospitalization and mortality [1]. Respiratory tract infections including CAP are the most frequent indications for antibiotic use [2]. Appropriate antibiotic use is important for reducing antibiotic-resistant bacteria and antibiotic-related adverse effects. To achieve this, treating with necessary and sufficient doses of antibiotics and short durations are needed for antimicrobial stewardship. Procalcitonin (PCT) is a biomarker that increases when sepsis or bacterial infection occurs [3]. Previous reports have shown that PCT values on admission in CAP patients are correlated with pneumonia severity and prognosis [4–6], and serial measurements of PCT are also useful for predicting prognosis [7–10]. In addition, there have been some reports that PCT guidance for treating CAP could reduce antibiotic duration without worsening mortality and recurrence rates [11–14]. Recently, it has been reported that PCT-guided

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therapy for CAP could reduce antibiotic costs, including the biomarker measurement cost [15]. However, these previous reports were almost all from Europe, and there have been no reports in Asia, including Japan. This study aimed to investigate whether antibiotic duration and cost could be reduced without worsening outcomes if theoretical PCT guidance were adopted for hospitalized CAP patients in Japan.

2. Patient and methods

2.1. Study population

This study retrospectively analyzed hospitalized CAP patients enrolled in a prospective, observational, cohort study at Kurashiki Central Hospital between October 2010 and February 2016. CAP was diagnosed if the patients had at least one of the following clinical symptoms: cough, sputum, fever, pleuritic chest pain, or dyspnea; plus at least one of the following findings: coarse crackles on auscultation, elevated inflammatory biomarkers, and a new infiltrate shadow on chest radiography. Exclusion criteria were: age ≤15 years, acquired immune deficiency syndrome, hospital-acquired pneumonia, and healthcare-associated pneumonia [16].

This study was performed as part of a clinical study for pneumonia (UMIN000004353) and was approved by the institutional review board of Kurashiki Central Hospital (approval number 1946). All patients gave their informed consent to participate in this study.

2.2. Study design and setting

The severity of pneumonia was assessed in all patients on admission with the A-DROP score (age ≥70 years in men or age ≥75 years in women, blood urea nitrogen ≥21 mg dL^{-1} or dehydration, oxyhemoglobin saturation measured by pulse oximetry ≤90% or partial pressure of oxygen in arterial blood ≤60 Torr, confusion, or systolic blood pressure ≤90 mmHg) [17], CURB-65 score (confusion, urea >7 mmol L^{-1}, respiratory rate ≥30 breaths min^{-1}, low blood pressure (systolic <90 mmHg or diastolic ≤60 mmHg), or age ≥65 years) [18], Pneumonia Severity Index (PSI) score [19], or Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) criteria for severe community-acquired pneumonia (IDSA/ATS severe CAP) [1]. They underwent blood and chest X-ray examinations to assess the effectiveness of the antimicrobials and relapse of pneumonia, as appropriate. PCT measured on admission was defined as PCT D1, that measured within 48–72 h after admission was PCT D3, and that measured within 120–168 h after admission was PCT D7. Patients with all PCT D1, D3, and D7 values available were included in the analysis.

2.3. PCT measurements

Serum PCT levels were determined by Elecsys B·R·A·H·M·S® PCT automated immunoassays (Roche Diagnostics GmbH, Mannheim, Germany). The PCT assay has a detection limit of 0.02 ng mL^{-1}.

2.4. Criteria for theoretical PCT-guided therapy

All patients were administered antimicrobials based on the decision of the attending physician in accordance with the recommendations of the CAP guidelines of the Japanese Respiratory Society [17], and the duration of antibiotic therapy was also decided by the attending physician regardless of PCT values. Each attending physician stopped antimicrobials referring to the CAP guidelines published by IDSA/ATS in 2007 [1]: afebrile for 48–72 h and meet all or all with one exception of the CAP-associated signs of clinical stability (temperature ≤37.8 °C, heart rate ≤100 beats/min, respiratory rate ≤24 breaths/min, systolic blood pressure ≥90 mmHg, arterial oxygen saturation ≥90% or pO2 ≥60 mmHg on room air, ability to maintain oral intake, normal mental status). To assess the usefulness of theoretical PCT-guided therapy (t-PCT-guided therapy), t-PCT-guided therapy was defined such that antibiotics for CAP could be stopped if PCT D7 was <0.25 ng mL^{-1} or ≤10% of the higher of PCT D1 or D3. These criteria were developed based on previous reports [12].

2.5. Theoretical PCT-guided therapy and pneumonia severity

Patients whose actual duration of antibiotic therapy as prescribed was the same as that for t-PCT-guided therapy (a difference of ±1 day was permitted) were placed into Group A (t-PCT-guided therapy-compliant). Patients whose actual duration of antibiotic use was different from that of t-PCT-guided therapy were divided into Group B (≥2 days longer than t-PCT-guided therapy; t-PCT-guided therapy non-compliant) and Group C (≥2 days shorter than t-PCT-guided therapy). Patients to whom t-PCT-guided therapy could not be applied were allocated to Group C (≥2 days shorter than t-PCT-guided therapy) or D (continued antibiotics according to t-PCT-guided therapy). Group D patients' antibiotic therapy periods were decided by the attending physicians, and therefore differed among the patients. Pneumonia severity was evaluated by A-DROP, CURB-65, PSI, and IDSA/ATS severe CAP in all four groups.

2.6. Calculation of antibiotic and biomarker costs

The antibiotic costs were calculated as multiple one-day costs of each antibiotic over the antibiotic prescription period, both in the case of t-PCT-guided therapy and the actual prescriptions. In Japan, the current one-time cost of measuring PCT is 3200 yen. In this study, because PCT was measured three times for t-PCT-guided therapy, the biomarker cost increased by 9600 yen compared to daily practice. These biomarker costs were added to antibiotic costs to assess net benefit.

2.7. Theoretical PCT-guided therapy and clinical outcomes

This study investigated the usefulness of PCT-guided therapy using t-PCT-guided therapy criteria and was not an interventional study of PCT-guided therapy. When the criteria for t-PCT-guided therapy were applied to all hospitalized CAP patients, whether the duration and cost of antibiotic therapy could be reduced without worsening mortality or relapse rates was evaluated. The mortality and relapse rates were compared between groups A and B to determine whether patients' prognosis would be worse if PCT-guided therapy were adopted in CAP.

2.8. Statistical analysis

Continuous variables are expressed as means and standard deviation (SD), and categorical variables are expressed as counts (percentages), as appropriate. Categorical variables were compared using Fisher's exact test, and continuous variables were tested by Student's *t*-test. Analysis of variance was used to compare the four groups. To evaluate whether the duration and cost of antibiotics could be reduced by t-PCT-guided therapy in CAP patients, the duration and cost of actual practice were compared to the duration and cost if t-PCT guided therapy were adopted for all patients. Whether the patients' prognosis would be worse using PCT-guided therapy was also evaluated by comparing the t-PCT-guided therapy-compliant group (group A) to a non-compliant group