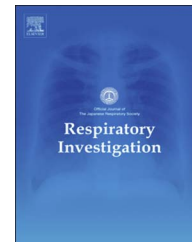




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## Original article

## Guidelines-concordant empiric antimicrobial therapy and mortality in patients with severe community-acquired pneumonia requiring mechanical ventilation

Yukiyo Sakamoto, MD<sup>a</sup>, Yasuhiro Yamauchi, MD, PhD<sup>a,\*</sup>, Hideo Yasunaga, MD, PhD<sup>b</sup>, Hideyuki Takeshima, MD<sup>a</sup>, Wakae Hasegawa, MD<sup>a</sup>, Taisuke Jo, MD, PhD<sup>a,c</sup>, Hiroki Matsui, MPH<sup>b</sup>, Kiyohide Fushimi, MD, PhD<sup>d</sup>, Takahide Nagase, MD, PhD<sup>a</sup>

<sup>a</sup>Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

<sup>b</sup>Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

<sup>c</sup>Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

<sup>d</sup>Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan

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## ABSTRACT

**Background:** Community-acquired pneumonia (CAP) has high morbidity and mortality among adults. Several clinical guidelines recommend prompt administration of combined antimicrobial therapy. However, the association between guidelines concordance and mortality in patients with severe pneumonia remains unclear. The present study aimed to examine the impact of guidelines-concordant empiric antimicrobial therapy on 7-day mortality in patients with extremely severe pneumonia who required mechanical ventilation at admission, using a nationwide inpatient database in Japan.

**Methods:** Data of CAP patients aged over 20 years who required mechanical ventilation at admission between April 2012 and March 2014 were retrospectively analyzed. Multi-variable logistic regression analysis was performed to examine the association between guidelines-concordant empiric antimicrobial therapy and all-cause 7-day mortality, with adjustment for patient backgrounds and pneumonia severity.

**Results:** There were a total of 3719 eligible patients, 836 (22.5%) of whom received guidelines-concordant combination therapy. Overall, 7-day mortality was 29.5%. Higher 7-day mortality was associated with advanced age, confusion, lower systolic blood pressure, malignant tumor or immunocompromised state, and C-reactive protein  $\geq 20$  mg/dl or infiltration occupying two-thirds of one lung on chest radiography. After adjustment for these variables, guidelines-concordant combined antimicrobial therapy was associated with significantly lower 7-day mortality (odds ratio: 0.78; 95% confidence interval: 0.65–0.95;  $P=0.013$ ).

**Conclusions:** Adherence to initial empiric treatment as recommended by the guidelines was associated with better short-term prognosis in patients with extremely severe pneumonia who required mechanical ventilation on hospital admission.

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## 1. Introduction

Community-acquired pneumonia (CAP) has a high morbidity and mortality among adults. The annual incidence of CAP in the United States was recently reported as 25 cases per 10,000 adults [1]. Lower respiratory system infection is a leading cause of death [2]; in fact, it was the fourth most common cause (3.1 million deaths) worldwide in 2012 [3].

Some academic societies, such as the British Thoracic Society, the Infectious Diseases Society of America (IDSA), and the Japanese Respiratory Society (JRS), have developed guidelines for management of CAP [4–6]. These guidelines recommend stratifying patients according to CAP severity and the risk of mortality using scoring systems such as CURB-65 (Confusion-Urea-Respiratory rate-Blood pressure-age  $\geq$  65 years), the Pneumonia Severity Index and A-DROP (Age-Dehydration-Respiratory failure-Orientation disturbance-blood Pressure) and administering initial appropriate antimicrobial empirically. Patients in the highest score groups often require hospital admission, including intensive care unit (ICU) admission, and prompt administration of combined antimicrobial therapy, because they are assumed to have higher risk of death.

Although a previous study described IDSA guidelines-concordant antimicrobial therapy and prognostic factors of patients with severe CAP who were admitted to the ICU [7], little is known about the impact of adherence to JRS or IDSA guidelines and prognosis in patients with extremely severe CAP who require intubation/mechanical ventilation at admission.

Therefore, this study evaluated the effectiveness of initial empirical antimicrobial treatment as recommended by JRS or IDSA guidelines in patients with extremely severe CAP who required mechanical ventilation at admission, using a nationwide inpatient database in Japan.

## 2. Patients and methods

### 2.1. Data source

This study used data from the Diagnosis Procedure Combination (DPC) database, a nationwide administrative inpatient database in Japan. The DPC database includes administrative claims data and discharge abstract data. The main diagnosis and the primary diagnosis on admission are recorded using International Classification of Disease and Related Health Problems Tenth Revision codes and by text data in Japanese. The database also contains the following patient details: type of hospital (academic or non-academic), age, sex, body height and weight, grade of activities of daily life on admission (the Barthel Index) [8], level of consciousness, severity of pneumonia based on the A-DROP score

(Supplementary Appendix A), 'blood urea nitrogen  $\geq$  21 mg/mL or dehydration', 'malignant tumor or immunocompromised state', 'C-reactive protein (CRP)  $\geq$  20 mg/dL or infiltration covering at least two-thirds of one lung on chest radiography', mechanical ventilation, cardiac massage, defibrillation, discharge status including in-hospital death, and medication use during hospitalization. We defined an academic hospital as a hospital that the Ministry of Health, Labor, and Welfare approved as an advanced treatment hospital.

This study was approved by the Institutional Review Board of The University of Tokyo (No. 3501). The Board waived the requirement for patient informed consent because of the anonymous nature of the data.

### 2.2. Patient selection

The DPC database was searched to identify patients aged over 20 years who were admitted to participating hospitals with a primary diagnosis of pneumonia and who were discharged between 1 April 2012 and 31 March 2014. Patients who were diagnosed with CAP, had an A-DROP score of 4 or 5, and underwent mechanical ventilation on the day of admission or the following day were included in the analysis. Patients who received cardiac massage or defibrillation on admission were excluded, because such patients had a high probability of death before receiving antimicrobials.

### 2.3. Antimicrobials

For extremely severe CAP patients who require ICU admission, the JRS guidelines recommend use of combined Group 1 and Group 2 antimicrobials. Group 1 includes carbapenems, third or fourth generation cepheems plus clindamycin, monobactam plus clindamycin, and glycopeptides plus aminoglycoside. Group 2 includes new quinolones, macrolides, and tetracyclines [4]. The IDSA guidelines also recommend combined antimicrobial therapy, though the recommended antimicrobials are slightly different from those in the JRS guidelines. Specifically, the IDSA-recommended combination includes a beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone. To treat *Pseudomonas* infection, the IDSA guidelines recommend an anti-pneumococcal, an anti-pseudomonal beta-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin, levofloxacin, an aminoglycoside and azithromycin, or an aminoglycoside and an anti-pneumococcal fluoroquinolone [5].

Therapy using of one of the above recommended combinations was defined as guidelines-concordant combined antimicrobial therapy.

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CAP, community-acquired pneumonia; CRP, C-reactive protein; CURB-65, Confusion-Urea-Respiratory rate-Blood pressure-65; A-DROP, Age-Dehydration-Respiratory failure-Orientation disturbance-blood Pressure; DPC, Diagnosis Procedure Combination; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; JRS, Japanese Respiratory Society; SD, standard deviation

\*Corresponding author. Fax: +81 3 3815 5954.

E-mail addresses: [ysakamoto-tmd@umin.ac.jp](mailto:ysakamoto-tmd@umin.ac.jp) (Y. Sakamoto), [YAMAUCHIY-INT@h.u-tokyo.ac.jp](mailto:YAMAUCHIY-INT@h.u-tokyo.ac.jp) (Y. Yamauchi), [yasunagah-ky@umin.ac.jp](mailto:yasunagah-ky@umin.ac.jp) (H. Yasunaga), [Htakeshima-ky@umin.ac.jp](mailto:Htakeshima-ky@umin.ac.jp) (H. Takeshima), [w-hasegawa@umin.ac.jp](mailto:w-hasegawa@umin.ac.jp) (W. Hasegawa), [jo-taisuke@umin.ac.jp](mailto:jo-taisuke@umin.ac.jp) (T. Jo), [ptmatsui-ky@umin.ac.jp](mailto:ptmatsui-ky@umin.ac.jp) (H. Matsui), [kfushimi.hci@tmd.ac.jp](mailto:kfushimi.hci@tmd.ac.jp) (K. Fushimi), [takahide-ky@umin.ac.jp](mailto:takahide-ky@umin.ac.jp) (T. Nagase).

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