Journal of Infection (2016) 73, 314–325

BIAM British Infection Association

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# De-escalation versus continuation of empirical antimicrobial therapy in community-acquired pneumonia

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Accepted 1 July 2016
Available online 7 July 2016

**KEYWORDS**
Bacterial pneumonia;
Anti-infective agents;
Drug resistance

**Summary** *Objectives:* To compare mortality between de-escalation and continued empirical treatment in patients with community-acquired pneumonia.
*Methods:* Using a nationwide administrative database, we identified adult patients with community-acquired pneumonia caused by *Streptococcus pneumoniae*, other streptococci, *Haemophilus influenzae*, *Klebsiella pneumoniae*, or *Escherichia coli* (n = 10,231) or of unknown etiology (n = 8247), discharged between July 2010 and March 2013. De-escalation was determined by the spectrum and number of antimicrobials at day 4. We used propensity score matching to obtain 489 pairs of de-escalation and continuation groups among pathogen-identified patients and 278 pairs among culture-negative patients to compare mortalities.
*Results:* In the pathogen-identified patients, de-escalation was noninferior to continuation in 15-day mortality [5.3% in de-escalation *versus* 4.3% in continuation, a difference of 1.0% (95% confidence interval, −1.7% to 3.7%)] and in-hospital mortality [8.0% in de-escalation *versus* 8.8% in continuation, a difference of −0.8% (95% confidence interval, −4.3% to 2.7%)]. In the culture-negative cases, de-escalation was noninferior to continuation in terms of 15-day mortality but not in terms of in-hospital mortality.
*Conclusions:* Among patients with community-acquired pneumonia of specific etiology,

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http://dx.doi.org/10.1016/j.jinf.2016.07.001

de-escalation was noninferior to continuation of empirical treatment, suggesting that de-escalation is a safe strategy and supporting current recommendations. Safety of de-escalation in culture-negative cases is questionable.


De-escalation of empirical antimicrobial treatment is an important element in antimicrobial stewardship.[1] In critically ill patients with infectious diseases, prompt and adequate antimicrobial therapy is associated with lower mortality rates.[2–5] Broad-spectrum antimicrobials are administered empirically because the causative pathogen is often not identified upon treatment initiation. However, the overuse of broad-spectrum antimicrobials may result in the emergence of bacterial resistance.[6–9] De-escalation is a clinical approach that attempts to provide appropriate initial antimicrobial treatment while limiting unnecessary antimicrobial exposure. De-escalation consists of narrowing the spectrum of antimicrobial therapy based on culture and drug susceptibility test results.[10–12] Guidelines for the treatment of sepsis,[13] ventilator-associated pneumonia,[14] and community-acquired pneumonia (CAP)[15] recommend the implementation of a de-escalation strategy.

Although de-escalation is theoretically appropriate, its safety has been confirmed in a limited number of studies. Observational studies of patients with sepsis,[16,17] ventilator-associated pneumonia,[18,19] and bacteremic pneumonia,[20] and patients in intensive care units (ICUs)[21] have reported similar mortality rates for both de-escalation and continuation of initial broad-spectrum antimicrobials. In one randomized control trial of ICU patients with severe sepsis, de-escalation was noninferior to continuation of empirical treatment in terms of mortality and duration of ICU stay.[22]

One study into the clinical practice of CAP management in Europe reported that de-escalation was implemented in 5.1% of cases.[23] However, no study has evaluated the safety of de-escalation in CAP patients. CAP is a common, serious infectious disease and is one of the leading causes of deaths worldwide.[15,24] Its treatment demands optimization of clinical outcomes and judicious use of antimicrobials.

The objective of the present study was to compare the mortality between de-escalation and continuation of empirical treatment in CAP patients toward evaluating the safety of de-escalation in CAP treatment.

## Methods

This study was approved by the Institutional Review Board of The University of Tokyo (approval number: 3501). Because of the anonymous nature of the data, the need for informed consent was waived.

### Data source

The Diagnosis Procedure Combination database is a national administrative database of acute-care inpatients in Japan. Participation in the database is mandatory for academic hospitals (all 82 hospitals) and voluntary for community hospitals. Participating hospitals provide administrative claims and abstract discharge data for all their acute-care inpatients. In 2012, there were approximately 1000 participating hospitals with 7 million admissions recorded annually, representing 50% of all acute-care hospitalizations in Japan. The database includes the following information: hospital identification code; patient demographic and clinical information; admission and discharge status; main and subcategorized secondary diagnoses; surgeries and procedures performed; medication; and special reimbursements for specific conditions. Diagnoses are coded using International Classification of Diseases, Tenth Revision (ICD-10). Suspected diagnoses are allowed to be recorded, in which case they are designated as such. Surgeries, drugs, procedures, and special reimbursements are coded according to the Japanese fee schedule for reimbursement,[25] and their daily use or application is recorded.

### Patient selection

The present study examined the data of patients discharged between July 1, 2010 and March 31, 2013. We defined inclusion and exclusion criteria similarly to a previous study of CAP using the same database.[26] The inclusion criteria were as follows: age $\geq$18 years; main diagnosis of bacterial pneumonia (ICD-10 codes: J13, J14, J15.x)[27]; intravenous antimicrobial therapy initiated on the day of admission and continued until at least day 4; and bacterial culture and drug susceptibility test performed on the day of admission. The exclusion criteria were as follows: pregnancy; major surgery (under general anesthesia) performed by day 4; HIV infection; and hospitalization in the same hospital within the preceding 90 days.

As in previous studies,[18,19,22] we defined the ranks of intravenous β-lactam antimicrobials according to their spectra as follows: rank 5, carbapenem; rank 4, antipseudomonal β-lactam; rank 3, third-generation cephem; rank 2, ampicillin with β-lactamase inhibitor; and rank 1, other β-lactam. Details of the antimicrobials in each rank—along with other intravenous drugs examined in the study—are presented in Supplementary Table 1.

For each patient, we identified an antimicrobial rank for each day of admission. When a patient was administered multiple β-lactams, we selected the highest rank. By comparing the ranks of antimicrobials between days 1 and 4, we identified elevated, lowered, and unchanged ranks. Further, we counted the number of antimicrobials used for each patient for each day of admission. By comparing the numbers of antimicrobials between days 1 and 4, we determined increased, decreased, and unchanged numbers. We defined escalation as either elevated antimicrobial rank or increased number of antimicrobials and continuation as both unchanged rank and number. De-escalation included unchanged rank and decreased number; lowered rank and unchanged number; and lowered rank and decreased number.