


Clinical Benefits of Piperacillin/Tazobactam versus a Combination of Ceftriaxone and Clindamycin in the Treatment of Early, Non-Ventilator, Hospital-Acquired Pneumonia in a Community-Based Hospital

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Purpose: There is an increasing prevalence of multidrug-resistant (MDR) organisms worldwide. Therefore, broad-spectrum antibiotics are recommended in the treatment of hospital-acquired pneumonia (HAP). However, it remains controversial whether patients with early onset, non-ventilator HAP (NV-HAP) should also be empirically treated with broad-spectrum antibiotics. We compared the clinical benefit of ceftriaxone plus clindamycin vs piperacillin/tazobactam as the initial empirical treatment of adults with early NV-HAP.

Patients and Methods: Retrospective cohort study was conducted in adult patients who were diagnosed with early, NV-HAP between January 2013 and June 2017 at a community-based tertiary care hospital. Patients were eligible for inclusion if they had received empiric treatment with either ceftriaxone and clindamycin or piperacillin/tazobactam for at least 3 days. Patients with increased risk of MDR pathogens were excluded.

Results: A total of 89 patients were treated with ceftriaxone and clindamycin, while 124 received piperacillin/tazobactam. There were no significant differences between the two antibiotic groups with regard to median age, sex, or risk of pneumonia. The 30-day all-cause mortality did not differ significantly between the ceftriaxone plus clindamycin and piperacillin/tazobactam groups (4.5% vs 1.6%, $P=0.202$, respectively). However, in multivariate analysis, clinical failure was more frequent in the ceftriaxone plus clindamycin group than in the piperacillin/tazobactam group (HR 3.316; 95% CI, 1.589–6918, $P=0.001$).

Conclusion: Treatment with piperacillin/tazobactam was more effective than that with ceftriaxone plus clindamycin in patients with early NV-HAP. This study supports the recent treatment recommendations that patients with early NV-HAP should be treated empirically with broad-spectrum antibiotics.

Keywords: empirical antibiotics, hospital-acquired infection, pneumonia, multiple drug resistance

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Introduction

Hospital-acquired pneumonia (HAP) is one of the most common hospital-acquired infections (HAIs) worldwide, accounting for approximately 1520% of all HAIs.^{1–3} HAP usually occurs in patients with underlying disease and is associated with substantial clinical and economic burdens, including prolonged hospital stays,

high costs of health care, and increased nosocomial morbidity and mortality.⁴ Inappropriate initial antibiotic therapy in HAP may increase its mortality rates. According to the HAP guidelines from the American Thoracic Society (ATS, 2005) and the 2006 European guidelines, the most common causative organisms of non-ventilator HAP (NV-HAP) in patients with no usual risk factors or early onset are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*. Less frequently, NV-HAP is attributable to gram-negative bacteria including *Pseudomonas aeruginosa* or drug-resistant bacteria. The recommendations state that patients with early, NV-HAP may be appropriately treated with second-generation cephalosporins, non-pseudomonal cephalosporins, quinolones, clindamycin, or aztreonam.^{5–8}

However, given the rapidly changing resistance patterns and increasing prevalence of beta lactamase-producing strains of bacteria, the Infectious Diseases Society of America (IDSA) updated its guidelines in 2016. The new guidelines state that patients being treated empirically for NV-HAP ought to receive broad-spectrum antibiotics with activity against *S. aureus*, *P. aeruginosa*, and other drug-resistant gram-negative bacteria. The evidence for these recommendations, however, is largely focused on research on ventilator-associated pneumonia (VAP) rather than on HAP. While risk factors for MDR organisms in HAP have been well reported, there is a paucity of data specific to risk factors for MDR organisms for NV-HAP with regard to the early and late onset of pneumonia. There is also a lack of evidence regarding whether broad-spectrum antibiotics are required in the early treatment of NA-HAP. Treatment guidelines published by an Asian society state that there is no need for broad-spectrum therapy in patients who develop pneumonia within the first four days of hospitalization. Instead, this group recommends limited spectrum antibiotics for such patients.⁶ Our institution is a community-based tertiary care facility. In this study, we empirically prescribed a combination of ceftriaxone and clindamycin or piperacillin/tazobactam in the treatment of early NV-HAP. The aim of this study was to compare the clinical outcomes of these two antibiotic regimens in patients with early NV-HAP.

Patients and Methods

Study Design, Patients, and Definitions

A retrospective cohort study was conducted. We reviewed the electronic medical records of adult patients (age ≥ 18) who were diagnosed with early NV-HAP between

January 2013 and June 2017 at Konkuk University Hospital, a 950-bed, community-based tertiary medical center in Seoul, Republic of Korea. Pneumonia was defined using the following two criteria: i) presence of a new or progressive pulmonary infiltration on chest radiography and ii) at least one of the following signs and symptoms: fever ($>38^{\circ}\text{C}$) or respiratory symptoms (cough, sputum, dyspnea).⁹ Patients were eligible for inclusion if they developed early NV-HAP and were treated empirically with either ceftriaxone plus clindamycin or piperacillin/tazobactam at least three days.

Considering clinical and radiological examinations, we excluded patients who were more likely to have acute exacerbation of asthma or acute heart failure misdiagnosed as pneumonia. Patients who were hospitalized with suspected pneumonia but were newly diagnosed with other structural lung diseases were also excluded. HAP is defined as pneumonia that is not incubating at the time of admission, but occurs at least 48 hours after hospital admission. Patients who developed HAP and were not ventilated were classified as having NV-HAP. We recorded the hospital day on which the pneumonia was diagnosed. Early onset NV-HAP was considered when the NV-HAP occurred within 48 hours to 5 days of hospitalization.⁶

Patients were excluded if they had specific characteristics that increased the likelihood of pneumonia due to *P. aeruginosa* or MDR organisms. The exclusion criteria were based on the American Thoracic Society (ATS) guidelines, taking into account the well-known risk factors of MDR organisms.⁵ Therefore, we excluded patients with chronic obstructive lung disease (COPD) and structural lung disease such as emphysema, interstitial lung disease, or tuberculosis destroyed lung disease,^{10,11} lung cancer and metastatic lung cancer. We also excluded patients being treated with immunosuppressive agents, patients with another infection besides pneumonia, those with a history of recent hospitalization within 30 days, and those with a hematologic malignancy.

The primary outcome was clinical failure, defined as an absence of significant improvement in a patient's signs and symptoms (eg, cough, sputum, dyspnea, pleuritic chest pain, fever and aggravation of consolidation in chest x-ray) within 72 hours of empiric antibiotics use; death due to pneumonia; and recurrent pneumonia within two weeks of antibiotics cessation. No clinical improvement was defined as cases in which clinicians changed the antibiotic regimen due to unstable vital signs or deteriorating radiologic findings according to decision from an

infectious disease consultation. The secondary outcome was 30-day all-cause mortality. Antibiotic-related side effects were defined as clinical events such as cytopenia, *Clostridium difficile* associated diarrhea, liver function abnormalities, or drug eruption.

Data Collection

Data were collected from administrative, pharmaceutical, and laboratory computerized databases maintained by the medical information team at Konkuk University. The clinical records were reviewed and analyzed for potential factors that could affect clinical outcomes. The following information was recorded: age, sex, comorbid conditions, Charlson weighted index (CWI) score,⁹ intensive care unit (ICU) admissions, and results of sputum culture. Currently, there is no validated scoring system in use for HAP.^{10,11} Severity of illness was estimated using the pneumonia severity index (PSI) which helps in the risk stratification of patients with community acquired pneumonia,¹² white blood cell count (WBC), and C-reactive protein (CRP) level. A PSI score of 91 or higher was classified as moderate- to- high-risk group.¹²

Microbiological Assessment

Bacteriological tests were performed at baseline and comprised gram stain and aerobic culture of the sputum or other respiratory secretions before administration of antibiotics. All sputum specimens were gram stained and examined microscopically for the presence of WBCs, epithelial cells, and bacteria. A sputum sample was considered adequate if there were >25 WBCs and <10 squamous epithelial cells.

Statistical Analysis

The Mann–Whitney U-test was used to compare continuous variables. Chi-square and Fisher's exact tests were used for categorical variables. Kaplan–Meier curve was used to evaluate the time to clinical failure according to the antibiotics group; the log rank test was applied for between-antibiotics group comparisons. The Cox proportional hazard model was used to examine the association of the empiric antibiotic regimens with clinical failure by adjusting for potential confounding factors. All collected clinical variables with any relevance to prognosis were evaluated for confounding in univariate analysis. In addition to the empirical antibiotic regimen, age, PSI score, and variables with statistical significance in the univariate analyses were included in the multivariate analysis. All

P-values were two-tailed, and those <0.05 were considered statistically significant. IBM SPSS Statistics version 20.0 for Windows (IBM, Armonk, NY, USA) was used for all statistical analyses. The present study was approved by Institutional review board of Konkuk University of Medical center. Informed consent was waived since the electronic medical record was reviewed retrospectively with de-personalized identification number.

Results

Study Population, Baseline Characteristics, and Clinical Outcomes

A total of 279 patients were empirically treated with either ceftriaxone plus clindamycin or piperacillin/tazobactam for early NV-HAP. Of these, 66 patients were excluded. The remaining 213 patients were classified according to empirical antibiotic regimen (Figure 1). Eighty-nine patients were treated with ceftriaxone and clindamycin, while 124 patients received piperacillin/tazobactam. The demographic and clinical patient characteristics are shown in Table 1. There were no significant differences between the groups with regard to median age, sex, and laboratory findings. Neurologic disease was more frequently seen in the ceftriaxone and clindamycin group than in the piperacillin/tazobactam group (55.1% vs 32.3%; $P < 0.001$). Solid cancer, with the exception of lung cancer, was more prevalent in the piperacillin/tazobactam group than in the ceftriaxone and clindamycin group (2.2% vs 21%; $P < 0.001$). Admissions to the ICU were more prevalent in the ceftriaxone and clindamycin group than in the piperacillin/tazobactam group (69.7 vs 50%; $P = 0.004$). Clinical outcomes according to the antibiotic group are presented in Table 1. Clinical failure occurred in 26 patients in the ceftriaxone plus clindamycin group and in 10 patients in the piperacillin/tazobactam group (29.2% vs 8.1%, $P < 0.001$). Overall, there were 6 deaths (2.8%), 4 patients in the ceftriaxone plus clindamycin group and 2 patients in the piperacillin/tazobactam group (4.5% vs 1.6%, $P = 0.202$). Antibiotic-related side effects occurred in only 2 patients (0.93%), both of whom were in the ceftriaxone and clindamycin group.

Microbiological Studies

Sputum culture was performed in 195 patients. A bacterial etiology was identified in 33 patients (16.9%), 6 of whom had >1 bacterial species identified. The most frequently identified pathogen was *S. aureus* (9.7%), followed by

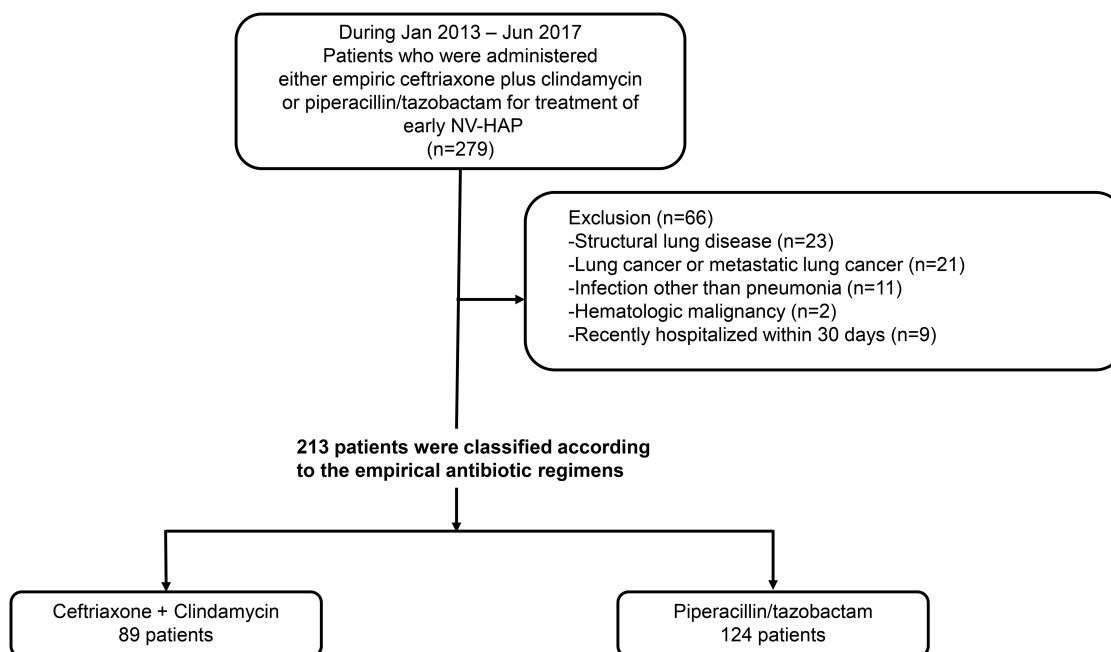


Figure 1 Flowchart of study population among patients with early, non-ventilator hospital-acquired pneumonia.

Enterobacteriaceae (6.6%) (Table 2). Only 1 patient (0.5%) was found to harbor *P. aeruginosa*. Two patients in the ceftriaxone and clindamycin group were not susceptible to these antibiotics. Only one patient in the piperacillin/tazobactam group was not susceptible to this antibiotic. There was no difference in the detection rates of drug-resistant bacteria between the ceftriaxone plus clindamycin and piperacillin/tazobactam group (9.1% vs 9.1%, $P=0.748$). The other identified bacteria were susceptible to most antimicrobial agents.

Multivariate Analysis of Clinical Failure and 30-Day All-Cause Mortality

In the univariate analysis, the following parameters were significantly associated with clinical failure: empiric ceftriaxone and clindamycin (HR 4.261; 95% CI 2.049–8.822, $P<0.001$), neurologic disease (HR 2.695; 95% CI 1.365–5.322, $P=0.004$), and ICU stays (HR 4.990; 95% CI 1.940–12.639, $P=0.001$) (Supplementary Table S1). In log rank test, the piperacillin/tazobactam group tended to have a better clinical outcome than the ceftriaxone and clindamycin group (Log rank $P<0.001$) (Figure 2). Likewise, in multivariate analysis, the independent risk factors for clinical failure were empiric treatment with ceftriaxone and clindamycin (HR 3.316; 95% CI, 1.589–6.918, $P=0.001$), neurologic disease (HR 2.137; 95% CI 1.075–4.250,

$P=0.030$) and ICU stays (HR 3.729; 95% CI, 1.436–9.680, $P=0.007$) (Table 3). Despite a relatively high odds ratio of treatment with ceftriaxone and clindamycin, there was no statistically significant difference in the multivariate analysis of 30-day all-cause mortality (HR 2.542; 95% CI, 0.432–14.594, $P=0.302$) (Table 3).

Discussion

Increasing antimicrobial resistance can contribute to antibiotic failure and poor clinical outcomes in patients with HAP.¹³ HAP includes two distinct subgroups: NV-HAP and ventilator-associated pneumonia (VAP). Of all patients diagnosed with HAP, 60.9% were classified as NV-HAP. However, most studies regarding the epidemiology, etiology, risk factors, and treatment choice of HAP have focused primarily on VAP because it is an easily identifiable and measurable event based on the standardized surveillance case definition from the National Center for Disease Control and Prevention.^{14,15} For this reason, the treatment recommendations for NV-HAP have been determined based on indirect evidence from research on VAP. There was limited direct data or evidence supporting regarding whether patients with NV-HAP should be treated empirically for *P. aeruginosa* and other MDR gram-negative bacilli.¹ Our study is based a community tertiary care medical center. Considering the hospital characteristics and previous guidelines, we treated NV-HAP with

Table 1 Demographics and Clinical Outcomes of Patients with Early, Non-Ventilator Hospital-Acquired Pneumonia in the Ceftriaxone Plus Clindamycin Group Vs Piperacillin/Tazobactam Group

Variables	Ceftriaxone Clindamycin (n=89)	Piperacillin Tazobactam (n=124)	P value
Sex, male	56 (62.9)	61 (65.3)	0.718
Age (years)	70.67 (54.25–80.63)	64.43 (54.33–74.43)	0.093
Patients with any comorbidity			
Diabetes mellitus	19 (21.3)	31 (25)	0.535
Cardiovascular disease	42 (47.2)	73 (58.9)	0.092
Liver disease	14 (15.7)	16 (12.9)	0.559
Renal disease	4 (4.5)	9 (7.2)	0.406
Neurologic disease	49 (55.1)	40 (32.3)	<0.001
Solid cancer (except lung cancer)	2 (2.2)	26 (21)	<0.001
Connective tissue disease	0 (0)	10 (8.1)	0.006
CWI score	1 (0–1)	2 (1–2)	0.002
Severity variables at admission			
PSI score ≥91 (high risk)	42 (47.2)	53 (42.7)	0.519
PSI score	89 (71.5–104)	86.5 (71–104)	0.651
ICU stays	62 (69.7)	62 (50)	0.004
WBC, × 10 ³ /uL	9.71 (7.43–12.535)	10.09 (7.95–12.625)	0.954
CRP, mg/dl	5.69 (2.37–10.14)	11.49 (6.24–17.04)	<0.001
Clinical outcomes			
Clinical failure	26 (29.2)	10 (8.1)	<0.001
30 days mortality	4 (4.5)	2 (1.6)	0.202
Any side effects of antibiotics	2 (2.1)	0 (0)	0.173
Antibiotics duration	7 (5–11)	10 (8–13) _–	<0.046

Note: Data are expressed as number (%) of patients or median (IQR)

Abbreviations: CWI, Charlson weighted index; PSI, pneumonia severity index; ICU, intensive care units; WBC, white blood cells; CRP, C-reactive protein.

either a relatively narrow spectrum antibiotics: combination of ceftriaxone and clindamycin or with piperacillin/tazobactam. There was no difference in the detection rates of drug-resistant bacteria between the two antibiotic groups. The piperacillin/tazobactam group had a higher mean CWI score than did the ceftriaxone and clindamycin group. However, overall, piperacillin/tazobactam was associated with less clinical failure than ceftriaxone and clindamycin in the treatment of patients with early NV-HAP. We were unable to show a statistically significant difference in the multivariate analysis of 30-day all-cause mortality. This result is likely due to a small number of deaths in our study. Considering the lack of prior research

Table 2 Distribution of Single and Multiple Pathogens in 33 Patients with Positive Results of Sputum Culture Among 195 Patients Underwent Sputum Culture

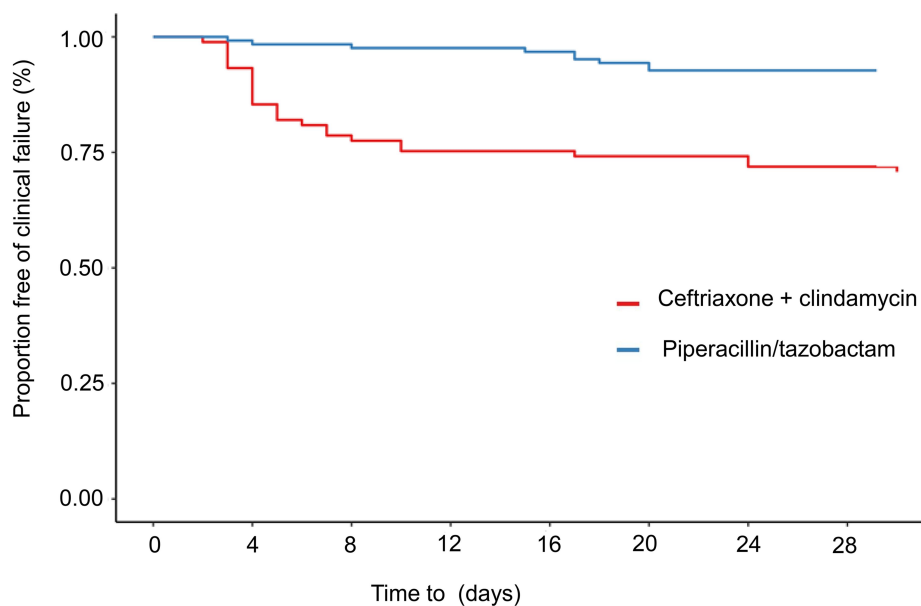
Pathogens	Ceftriaxone Plus Clindamycin (n=22)		Piperacillin/Tazobactam (n=11)	
	Total	Resistance to the regimen	Total	Resistance to the regimen
<i>Staphylococcus aureus</i>	16 (8.2)	1 ^a (0.5)	3 (1.5)	1 ^b (0.5)
<i>Streptococcus pneumoniae</i>	3 (1.5)	0 (0)	1 (0.5)	0 (0)
<i>Klebsiella pneumoniae</i>	1 (0.5)	0 (0)	7 (3.6)	0 (0)
<i>Escherichia coli</i>	0 (0)	0 (0)	1 (0.5)	0 (0)
<i>Enterobacter spp.</i>	2 (1)	0 (0)	1 (0.5)	0 (0)
<i>Serratia marcescens</i>	0 (0)	0 (0)	1 (0.5)	0 (0)
<i>Pseudomonas aeruginosa</i>	1 (0.5)	1 (0.5)	0 (0)	0 (0)
<i>Branhamella catarrhalis</i>	1 (0.5)	0 (0)	0 (0)	0 (0)

Notes: Data are expressed as number (%) of patients. ^aResistant to ceftriaxone and clindamycin (methicillin-resistance *S. aureus*). ^bResistant to oxacillin.

regarding the appropriate empiric treatment of NA-HAP, we believe that our results would be helpful to establish treatment guidelines for NV-HAP.

Two factors may have contributed to our results. It is well known that culture methods in pneumonia may identify a pathogen in only 10–30% of patients with pneumonia.¹⁶ In addition, clinical judgment should be applied to determine whether any identified bacteria are true pathogens. Therefore, the exact prevalence of MDR pathogens is unknown, as additional work-up (such as broncho-alveolar lavage) could not be performed in patients without an identified bacterium. The possible presence of these undetected pathogens may have accounted for the increased efficacy seen with piperacillin/tazobactam compared to that with ceftriaxone and clindamycin.

It is difficult to detect anaerobic bacteria by routine technique of sputum culture. However, these bacteria may play a large role in clinical pneumonias. Among non-bacteroides anaerobes, which can cause pneumonia, resistance to clindamycin is generally often lower than 10%. However, longitudinal survey data is limited, as anaerobic susceptibility testing is not routinely performed at individual hospitals.¹⁷ A multicenter study of antimicrobial susceptibilities of anaerobic bacteria in Korea presented that the susceptibility to clindamycin among non-bacteroides anaerobes was 85–89%. Piperacillin/tazobactam and carbapenems were also highly active agents against most anaerobes. Considering the relatively large number of patients with neurologic disease in the



Ceftriaxone + clindamycin	89	83	70	67	67	66	66	64
Piperacillin/tazobactam	124	123	122	121	120	117	115	115

Number of patients with clinical improvement

Figure 2 The Kaplan–Meier curve for clinical improvement analysis for patients with early, non-ventilator hospital-acquired pneumonia, categorized by ceftriaxone plus clindamycin and piperacillin/tazobactam treatment.

ceftriaxone plus clindamycin group (55.1%), it could be possible that the occurrence of anaerobic-induced HAP may account for more disease than would be expected, leading to the clinical failure.¹⁸ Superior anaerobic coverage with piperacillin/tazobactam may have added to the improved therapeutic outcomes seen with piperacillin/tazobactam.^{17,19}

Our study has several limitations. First, it was a retrospective analysis performed at a single center. We were only able to control for confounders that we collected. Local microbiology of NV-HAP pathogens may vary from institution to institution. For this reason, applying the findings of this study may not be appropriate for another institutions, regions and countries. In addition, we

only investigated the etiologies of pneumonia cases that were determined by sputum examination. As patients with early NV-HAP had been enrolled, there was a limited number of patients who underwent further invasive examinations (eg, bronchoalveolar lavage). A third limitation is that primary and secondary endpoints are potentially subjective and vague. The observer-induced bias could occur in situations in the setting of these endpoints. A fourth limitation is that we did not exclude all high-risk patients with the possibility of obtaining MDR organisms based on the guidelines and other articles.²⁰ However, the exclusion criteria were adjusted according to the clinical situation of our hospital. Fifth, it is possible that patients in the

Table 3 Multivariate Analysis of Association Between Baseline Characteristics of Patients and Clinical Outcomes

Variables	Clinical Failure		30-Day All-Cause Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex, male	1.747 (0.816–3.737))	0.026	0.566 (0.112–2.859)	0.491
Ceftriaxone plus clindamycin	3.316 (1.589–6.918)	0.001	2.542 (0.432–14.954)	0.302
Neurologic disease	2.137 (1.075–4.250)	0.030	2.320 (0.394–13.66)	0.352
PSI score ≥ 91	1.380 (0.697–2.732)	0.355	0.843 (0.169–4.202)	0.835
ICU stays	3.729 (1.436–9.680)	0.007	0.566 (0.112–2.859)	0.491

Abbreviations: CWI, Charlson weighted index; PSI, pneumonia severity index; ICU, intensive care unit.

ceftriaxone and clindamycin group experienced more aggressive antibiotic changes when clinical failure was suspected than piperacillin/tazobactam group. However, our hospital strictly controls antibiotic escalation through an antibiotics stewardship program. There were no cases of suspected unreasonable escalation of antibiotics based on chart review. Because of disproportionate number of patients in the ceftriaxone plus clindamycin group who had neurologic disease, it is possible that neurologic disease is the underlying factor driving worse outcomes in the group. For removing the influence of these differences, neurologic disease as a potential confounding factor was evaluated in multivariate analysis. In addition, the high proportion of neurological diseases could not rule out the occurrence of HAP by aspiration. However, since this is a retrospective study, the distinction between HAP and aspiration pneumonia was virtually impossible. A final limitation is that the 2.8% mortality rate in this study was lower than expected for patients with early NV-HAP. This result likely reflects our exclusion of patients who had risk factors for *Pseudomonas* and other MDR pathogens.^{14,21} It is noteworthy, however, that significant clinical failure was observed in patients with low mortality.

Conclusion

In this retrospective cohort study, there were significantly fewer clinical failures in the piperacillin/tazobactam group than in the ceftriaxone plus clindamycin group in patients with early NV-HAP. This study could support the recent treatment recommendation that patients with early NV-HAP should be treated empirically with broad-spectrum antibiotics.

Disclosure

The authors report no conflicts of interest in this work.

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