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

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, Paeruginosa, 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 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°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, intensive care unit (ICU) admissions, and results of sputum culture. Currently, there is no validated scoring system in use for HAP. Severity of illness was estimated using the pneumonia severity index (PSI) which helps in the risk stratification of patients with community acquired pneumonia, 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.

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
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. 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. 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. 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 (except lung cancer) | 49 (55.1)                     | 40 (32.3)                       | <0.001  |
| Solid 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, x 10^3/L              | 9.71                          | 10.09                           | 0.954   |
| CRP, mg/dl                 | 5.69                          | 11.49                           | <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.

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                          | 16 (8.2)                            | 3 (1.5)                         |
| Resistance to the regimen      | 1 (0.5)                             | 0 (0)                           |

Note: Data are expressed as number (%). 1Resistant to ceftriaxone and clindamycin (methicillin-resistant S. aureus). 2Resistant 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. 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. 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
ceftiraxone 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

![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.](image)

| 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   |

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

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

**References**

1. Kilic AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of america and the american thoracic society. *Clinical Infectious Diseases*. 2016;63(5):e61-e111.

2. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health-care-associated infections. *N Engl J Med*. 2014;370(13):1198–1208. doi:10.1056/NEJMoa1306801

3. Chawla R. Epidemiology, etiology, and diagnosis of hospital-acquired pneumonia and ventilator-associated pneumonia in Asian countries. *Am J Infect Control*. 2008;36(4 Suppl):S93–100. doi:10.1016/j.ajic.2007.05.011

4. Eber MR, Laxminarayan R, Perencevich EN, Malani A. Clinical and economic outcomes attributable to health care-associated sepsis and pneumonia. *Arch Intern Med*. 2010;170(4):347–353. doi:10.1001/archinternmed.2009.509

5. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med*. 1996;153(5):1711–1725. doi:10.1164/ajrccm.153.5.8630626

6. Song JH. Treatment recommendations of hospital-acquired pneumonia in Asian countries: first consensus report by the Asian HAP Working Group. *Am J Infect Control*. 2008;36(4 Suppl):S8392. doi:10.1016/j.ajic.2007.01.015

7. Montravers P, Harpan A, Guivarch E. Current and future considerations for the treatment of hospital-acquired Pneumonia. *Adv Ther*. 2016;33(2):151–166. doi:10.1007/s12265-016-0293-x

8. Torres A, Ewig S, Lode H, Carlet J. Defining, treating and preventing hospital acquired pneumonia: european perspective. *Intensive Care Med*. 2009;35(1):9–29. doi:10.1007/s00134-008-1336-9

9. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682. doi:10.1093/aje/kwq433

10. Rotstein C, Evans G, Born A, et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. *Canadian J Infectious Diseases Med Microbiol*. 2008;19(1):19–53. doi:10.1158/0008-5932

11. Napolitano LM. Use of severity scoring and stratification factors in clinical trials of hospital-acquired and ventilator-associated pneumonia. *Clinical Infectious Diseases*. 2010;51(Suppl 1):S6780. doi:10.1086/653052

12. Carrabba M, Zanantinello M, Bonara P, et al. Severity assessment of healthcare-associated pneumonia and pneumonia in immunosuppression. *Eur Respir J*. 2012;40(5):1201–1210. doi:10.1183/09031936.00187811

13. Chung DR, Song JH, Kim SH, et al. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am J Respir Crit Care Med*. 2011;184(12):1409–1417. doi:10.1164/rcmm.2011102-0349OC

14. Davis J, Finley E. The breadth of hospital-acquired pneumonia: nonventilated versus ventilated patients in Pennsylvania. 2012.

15. Giuliano KK, Baker D, Quinn B. The epidemiology of nonventilator hospital-acquired pneumonia in the United States. *Am J Infect Control*. 2017.

16. Naidu S, Lasalvia MT, Marcantonio ER, Herzig SJ. The diagnostic yield of noninvasive microbiologic sputum sampling in a cohort of patients with clinically diagnosed hospital-acquired Pneumonia. *J Hosp Med*. 2018;13(1):34–37. doi:10.12788/jhm.2868

17. Hecht DW. Prevalence of antibiotic resistance in anaerobic bacteria: worrisome developments. *Clinical Infectious Diseases*. 2004;39(1):92–97. doi:10.1086/421558

18. Lee Y, Park YJ, Kim MN, Uh Y, Kim MS, Lee K. Multicenter study of antimicrobial susceptibility of anaerobic bacteria in Korea in 2012. *Ann Lab Med*. 2015;35(5):479–486. doi:10.3343/aml.2015.35.5.479

19. Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy. *Infect Dis Clin North Am*. 2013;27(1):149–155. doi:10.1016/j.idc.2012.11.016

20. Maruyama T, Fujisawa T, Ishida T, et al. A therapeutic strategy for all pneumonia patients: a 3-year prospective multicenter- cohort study using risk factors for multidrug resistant pathogens to select initial empiric therapy. *Clinical Infectious Diseases*. 2018.

21. Sopena N, Sabria M. Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest*. 2005;127(1):213–219. doi:10.1378/chest.127.1.213
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