

# Combination Antibiotics for Gram-negative Bacteria in Patients with Healthcare-associated or Hospital-acquired Pneumonia with Severe Sepsis or Septic Shock

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## Abstract

Guidelines suggest that patients with multiple drug resistance pathogen-related hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP) should initially be prescribed with two empiric antibiotics for gram-negative pathogens. Traditional antibiograms cannot provide information about which combination therapy is the best choice. We therefore conducted this observational study to determine which combination of antibiotics is optimal. From July 2007 to June 2010, patients who were admitted to the medical intensive care unit at Chang Gung Memorial Hospital, Keelung due to HCAP or HAP with severe sepsis or septic shock were screened in this study. The clinical characteristics and antimicrobial resistance profiles were analyzed. A total of 117 patients who met the inclusion and exclusion criteria were enrolled for analysis. The most frequently isolated pathogens were *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Escherichia coli*. In monotherapy, the highest susceptibility to gram-negative bacteria was 76.1% with imipenem/cilastatin. In combination therapy, the highest susceptibility was 82.9% with a 6.8% additional advantage with a base of imipenem/cilastatin with amikacin, gentamicin, ciprofloxacin, or levofloxacin. The secondary highest susceptibility in combination therapy was 76.9% with piperacillin/tazobactam and amikacin. Thus, the first choice of combination therapy in this study was imipenem/cilastatin combined with ciprofloxacin or levofloxacin, which covered the most pathogens. (J Intern Med Taiwan 2016; 27: 89-96)

**Key Words:** Hospital-acquired pneumonia, Healthcare-associated pneumonia, Combination therapy

## Introduction

According to current American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines for the management of adults with hospital-acquired pneumonia (HAP),

ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP), patients with HAP or HCAP should initially be prescribed two empiric antibiotics for gram-negative pathogens<sup>1</sup>. The reasons for combination therapy include: 1) broadening the empiric coverage with a different

spectrum of activity; 2) exploiting the synergistic effect; and 3) preventing or delaying the emergence of resistance during antibiotic therapy<sup>2-4</sup>.

The selection of antibiotics for initial empirical therapy is based on prediction of the most likely pathogens and knowledge of local susceptibility. Bacteriology laboratories in most hospitals provide traditional antibiograms every year to help clinical physicians choose the initial empiric antibiotics. However, traditional antibiograms cannot provide information about which combination therapy is the best choice to treat HAP and HCAP in their hospital. A recent study reported antibiotic susceptibility data in the form of a combination antibiogram, which may be useful for clinical physicians when planning empirical antimicrobial therapy in the intensive care unit (ICU)<sup>5</sup>. However, the data in that study were collected from 1999 to 2005, and the patients enrolled were not HAP or HCAP completely.

Thus, we designed this prospective observational study to determine which combination of antibiotics is optimal to treat critically ill patients with HAP and HCAP.

## Materials and Methods

### Subjects

From July 2007 to June 2010, patients who were admitted to the medical ICU at Chang Gung Memorial Hospital, Keelung due to HCAP or HAP with severe sepsis or septic shock were screened in this study. The ICU is a medical and closed unit in our hospital. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (96-0132B, 97-0121C, 98-1682C). The following patient data were recorded within the first 3 days after admission: age; gender; medical history; respiratory tract sample for semi-quantitative culture; Acute Physiology and Chronic Health Evaluation (APACHE) II score; and adverse events. Samples contaminated by upper airway secretions,

as reflected by a high percentage of squamous epithelial cells, were excluded. Patients with gram-positive pathogens or duplicate isolates were also excluded. Pathogens with intermediate susceptibility were considered as resistant.

HCAP includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic<sup>1</sup>. HAP is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission<sup>1</sup>. Severe sepsis and septic shock were defined according to the criteria established in the Consensus Conference<sup>6</sup>. Systemic inflammatory response syndrome (SIRS) was defined as fulfillment of two or more of the following criteria: (1) body temperature > 38°C or < 36°C; (2) respiratory rate > 24 breaths/minute; (3) heart rate > 90 beats/minute; and (4) white blood count > 12,000/μl or < 4000/μl or >10% bands. Sepsis was defined as SIRS according to a confirmed or suspected microbial etiology. Severe sepsis was defined as sepsis with one or more dysfunctional organs or hypotension. Septic shock was defined as sepsis with hypotension unresponsive to fluid resuscitation, which further required vasopressors to maintain blood pressure during the first 3 days following ICU admission. Disease severity was assessed with the APACHE II score<sup>7</sup>. Survivors were defined as patients who were alive 28 days after ICU admission. Adequate and inadequate antibiotic therapy were defined as initial empiric antibiotic sensitivity and resistance to pathogens in the lower respiratory tract sample culture.

Standard bundle therapies including fluid resuscitation, broad-spectrum antibiotics, drainage, blood transfusion, sedation/paralysis, blood glucose control, hemodialysis, stress ulcer prophylaxis, and

basic support were provided to all patients according to the recommended guidelines<sup>8</sup>. Pneumonia was diagnosed based on a new abnormal infiltration seen on chest radiography. Acute renal failure was diagnosed as a rapidly rising serum creatine level  $\geq 0.5$  mg/dl over the base-line value<sup>9</sup>. Initial broad-spectrum antibiotics were chosen according to the Taiwan Guidelines for Pneumonia Management (2007 version). No empiric aminoglycoside antibiotic was used initially due to high risk of acute kidney injury in these patients. Antibiotic was adjusted after around 3 days according to final culture sensitivity report.

All antimicrobial susceptibility data included in the study were reported by the Chang Gung Memorial Hospital Clinical Microbiology Laboratory at Keelung. The laboratory determines the antimicrobial susceptibility results by disk diffusion in accordance with current accepted standards of the Clinical and Laboratory Standards Institute.

### Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 for Windows (SPSS Inc., Illinois, USA). Differences in continuous variables between the two groups were analyzed using the Mann-Whitney test. Differences in categorical variables between the two groups were compared using the chi-square test. A p value of less than 0.05 was considered to be statistically significant.

### Results

During the study period, 493 patients with severe sepsis and septic shock were screened, and 376 patients were excluded. The reasons for exclusion included non-pneumonia infection, two or more pathogens detected, gram-positive pathogens and no detectable pathogens in lower respiratory tract sample for culture. A total of 117 patients were enrolled for analysis (Figure 1). There were no differences in clinical characteristics between those

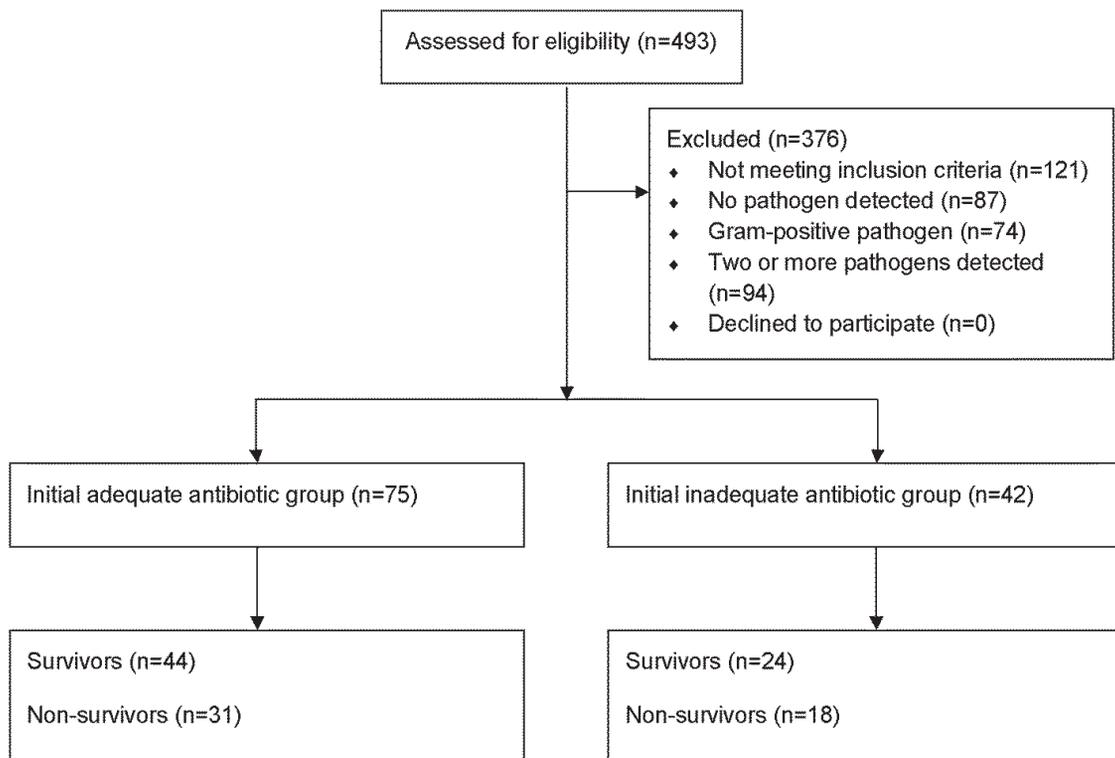


Figure 1. Enrollment of patients.

Table 1. Clinical characteristics of the patients with severe pneumonia under adequate or inadequate treatment

	All (N=117)	Adequate (N=75)	Inadequate (N=42)	p value
Age, years*	75.6 ± 11.1	75.2 ± 11.5	76.2 ± 10.4	0.838
APACHE II score*	26.2 ± 7.1	26.9 ± 6.7	25.0 ± 7.8	0.178
Gender, No. (%)				
Male	81 (69)	51 (68)	30 (71)	0.700
History, No. (%)				
COPD	29 (25)	20 (27)	9 (21)	0.529
CHF	11 (9)	8 (11)	3 (7)	0.744
Hypertension	48 (41)	29 (39)	19 (45)	0.488
Liver cirrhosis	7 (6)	5 (7)	2 (5)	1.000
Chronic renal failure	9 (8)	4 (5)	5 (12)	0.279
Diabetes mellitus	33 (28)	21 (28)	12 (29)	0.947
Adverse events, No. (%)				
GI bleeding	15 (13)	13 (17)	2 (5)	0.081
Shock	48 (41)	35 (47)	13 (31)	0.097
New arrhythmia	9 (8)	4 (5)	5 (12)	0.279
Acute renal failure	50 (43)	36 (48)	14 (33)	0.124
Jaundice	11 (9)	6 (8)	5 (12)	0.488
Thrombocytopenia	44 (38)	26 (35)	18 (43)	0.380
28-day mortality, No. (%)	49 (42)	31 (41)	18 (43)	0.873
Duration of MV (Days)*	19.6 ± 21.0	21.0 ± 22.3	17.2 ± 18.3	0.695
ICU and RCC stay (Days)*	20.0 ± 19.7	21.0 ± 20.5	18.3 ± 18.3	0.623

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; GI = gastrointestinal; MV = mechanical ventilation; ICU = intensive care unit; RCC = respiratory care center.

\*Data are shown as mean ± standard deviation.

who initially received adequate and inadequate antibiotic treatment (Table 1). Overall, approximately 40% of the patients had septic shock, acute renal failure, and thrombocytopenia. There was no difference in 28-day mortality between adequate and inadequate antibiotic treatment in all and different pathogens (data not shown). Table 2 shows the isolated pathogens in the adequate antibiotic group, inadequate antibiotic group and the patients overall. The most frequently isolated pathogens, in decreasing order, were *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*,

and *Escherichia coli*. Most of the patients received adequate antibiotic therapy, except for patients with *Acinetobacter baumannii* infection. All *Acinetobacter baumannii* in the inadequate antibiotic group were multidrug-resistant. The cause of high percentage of inadequate antibiotic therapy for *Acinetobacter baumannii* infection is that guideline do not suggest initially empiric colistin use to cover multidrug-resistant *Acinetobacter baumannii* infection.

In monotherapy, the highest susceptibility to gram-negative bacteria was 76.1% with imipenem/cilastatin (Table 3). In combination therapy, the

Table 2. Pathogens in the patients with severe pneumonia who were adequately and inadequately treated with antibiotics

Pathogens	Total N (% of pathogens)	Adequate N (% of total)	Inadequate N (% of total)	p value
<i>Pseudomonas aeruginosa</i>	40 (34)	35 (88)	5 (12)	<0.001
<i>Acinetobacter baumannii</i>	29 (25)	9 (31)	20 (69)	<0.001
<i>Klebsiella pneumoniae</i>	26 (22)	17 (65)	9 (35)	0.877
<i>Escherichia coli</i>	14 (12)	10 (71)	4 (29)	0.768
<i>Stenotrophomonas maltophilia</i>	3 (2.5)	2 (67)	1 (33)	1.000
<i>Enterobacter</i>	2 (2)	1 (50)	1 (50)	1.000
<i>Citrobacter</i>	3 (2.5)	1 (33)	2 (67)	0.292

Table 3. Combination antibiograms for gram-negative bacteria in patients with severe healthcare-associated and hospital-acquired pneumonia

	Susceptibility by antibiotic, %					
	Monotherapy	Amikacin	Gentamicin	Ciprofloxacin	Levofloxacin	Moxifloxacin
Cefepime	55.6	71.8	67.5	65.8	65.8	62.4
Imipenem/Cilastatin	76.1	82.9	82.9	82.9	82.9	79.5
Piperacillin/Tazobactam	62.4	76.9	73.5	71.8	71.8	68.4
Amikacin	71.8	--	--	--	--	--
Gentamicin	59.8	--	--	--	--	--
Ciprofloxacin	54.7	--	--	--	--	--
Levofloxacin	54.7	--	--	--	--	--
Moxifloxacin	27.4	--	--	--	--	--

highest susceptibility was 82.9% with a 6.8% additional advantage with a base of imipenem/cilastatin with amikacin, gentamicin, ciprofloxacin, or levofloxacin. With a base of cefepime, a combination with amikacin achieved a maximum susceptibility of 71.8% with a 16.2% additional advantage. Similarly, a combination with amikacin achieved a maximum susceptibility of 76.9% with a 14.5% additional advantage with the base of piperacillin/tazobactam.

## Discussion

The pathogens found in our study cohort are commonly found in most Asian countries<sup>10</sup>. Our findings are also similar to those of Pogue et al., in which combining antipseudomonal  $\beta$ -lactam with

amikacin was the most optimal combination therapy for gram-negative bacteria<sup>11</sup>. Many hospitals only provide antibiograms but not combination antibiograms of susceptibilities to each pathogen as they only consider monotherapy when treating patients. Most clinical physicians use antibiograms to select the antibiotics for critically ill patients which target *Pseudomonas aeruginosa* according to the ATS/IDSA guidelines. However, selecting empiric antibiotic targeting *Pseudomonas aeruginosa* without considering other gram-negative bacteria may not provide optimal empiric coverage<sup>11</sup>. Thus, clinical laboratories should consider providing combination antibiograms including susceptibility to all gram-negative bacteria so that physicians can select the most appropriate empiric combination therapy for

critically ill patients with HCAP/HAP.

In this study, amikacin provided more additional coverage than quinolones, which is similar to the study of Bhat et al., who found that compared with ciprofloxacin, antipseudomonal  $\beta$ -lactam in combination with amikacin provided a higher likelihood of adequate therapy (96% vs. 87%, respectively) for patients in the ICU with *Pseudomonas aeruginosa* infection<sup>12</sup>. This suggests that  $\beta$ -lactam-resistant isolates are frequently cross-resistant to quinolones.

Traditionally, aminoglycoside is thought to have higher nephrotoxicity and ototoxicity than quinolones. A systematic review and meta-analysis that compared  $\beta$ -lactam monotherapy with  $\beta$ -lactam-aminoglycoside combination therapy for severe infections found that nephrotoxicity was significantly more common in the combination group with an average number needed to harm of 15<sup>13</sup>. In addition, Moore et al. found that prolonged therapy for 10 or more days, preexisting renal impairment, and prior treatment with aminoglycosides were risk factors for ototoxicity for treatment of suspected gram-negative infections with aminoglycosides<sup>14</sup>. However, the number needed to result in nephrotoxicity for  $\beta$ -lactam-aminoglycoside combination therapy was around 15, meaning that the risk of nephrotoxicity was not very high<sup>13</sup>. Aminoglycosides can still be considered for combination treatment in patients who are not at risk of acute kidney injury.

Not all patients benefit from empiric combination therapy. A combination of aminoglycosides with  $\beta$ -lactams for gram-negative bacteremia has been shown to be an independent protective factor only in patients with septic shock and neutropenia after multivariate analysis<sup>15</sup>. However, Cochrane Reviews have not identified any survival benefit with the addition of an aminoglycoside to  $\beta$ -lactams for sepsis<sup>16</sup>. Another study on pediatric patients also reported no survival benefits when

evaluating 10-day mortality for severely ill (pediatric risk of mortality III score  $\geq 15$ ) or profoundly neutropenic (absolute neutrophil count  $\leq 100$  cells/mL) patients receiving the routine addition of an aminoglycoside to a  $\beta$ -lactam as empirical therapy<sup>17</sup>. However, a survival benefit was observed when empirical combination therapy was prescribed for children with multidrug-resistant gram-negative pathogens in blood cultures. Thus, a survival advantage cannot be ruled out in patients presenting with shock or neutropenia with empiric combination therapy followed by de-escalation of therapy when susceptibility results are known.

In our study cohort, the patients with adequate empiric antibiotic treatment did not have a lower mortality rate, however the cohort may not be representative of the general population. On the other hand, this may indicate the importance of bundle care for severe sepsis. In an observational study, the mortality rate decreased from 19.9% to 12.2% in patients with septic shock, and all-or-none total bundle compliance increased from 7.0% to 60.0%<sup>18</sup>. The treatment effects of recombinant human activated protein C and goal-directed fluid resuscitation were not shown in recent studies<sup>19-21</sup>, and patients survived with usual care and more compliance to bundle therapy. Another possible cause that resulted in no difference in the mortality between adequate and inadequate empiric antibiotic therapy was early shift in empiric antibiotic to adequate target antibiotic. In our hospital, clinical laboratory usually provides antibiogram including susceptibility within 3 days. Thus, combined bundle therapy for severe sepsis and early shift to target antibiotic may result in similar mortality rate between patients with adequate and inadequate empiric antibiotic therapy.

There are two limitations in this study. First, the sample size is relatively small and patients were collected in a single hospital. The results might not be applied to general Taiwan patients. Second, pathogen populations and sensitivity results might be dif-

ferent between medical and surgical ICUs. A large scale multi-center study to collect data in medical and surgical ICUs is necessary.

## Conclusions

This study provides additional information about how to choose empiric combinations of antibiotics for patients with HCAP and HAP with severe sepsis in Taiwan. In our patients, the most effective combination was imipenem/cilastatin combined with ciprofloxacin or levofloxacin, which covered the most pathogens and involved the least nephrotoxicity. When considering emerging carbapenem-resistant pathogens, piperacillin/tazobactam combined with amikacin is an alternative choice with a potentially high risk of nephrotoxicity.

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# 嚴重革蘭氏陰性病菌健康照護相關／ 院內肺炎病人的聯合抗生素使用

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## 摘 要

治療指引建議一開始經驗性使用兩種抗生素治療院內及健康照護相關肺炎。傳統抗菌圖譜無法提供適當訊息，告訴我們最佳合併治療藥物。因此我們做了一個觀察性的研究來探討哪種合併治療是適當的。從2007年七月到2010年六月，因為健康照護相關肺炎或院內肺炎合併嚴重敗血症，而入住基隆長庚醫院內科加護病房的病人，都會被此研究收進來篩檢。病患的臨床特徵及病菌藥物敏感結果都會被記錄。一共有117位病患符合收錄及排除條件。最常被採檢到的病菌是綠膿桿菌、鮑氏不動桿菌、肺炎克雷伯氏菌及大腸桿菌。以單一抗生素治療來說，對革蘭氏陰性病菌藥物敏感度最高的是泰寧®，76.1%有效。以合併抗生素治療來說，藥物敏感度最高的組合是以泰寧®為基礎，合併阿米卡星、慶大霉素、速博新或可樂必妥®，敏感度增加6.8%達到82.9%；藥物敏感度第二高的組合是特治星®加上阿米卡星，有76.9%。因此，在這個研究中，合併抗生素治療最佳選擇是泰寧®加上速博新或可樂必妥®，因為可以涵蓋最多革蘭氏陰性病原菌。