Outcome Analysis of Patients Requiring Mechanical Ventilation with Severe Community-Acquired Pneumonia and Identified Bacterial Pathogens

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Background: Severe community-acquired pneumonia (CAP) is associated with high mortality. The choice of antibiotics should be guided by the distribution of bacterial pathogens. The purpose of this study was to analyze the causative bacteria and outcomes of patients with severe CAP in a medical intensive care unit (MICU) in Taiwan. The results may provide a basis of guidance for future empirical antibiotic treatments.

Methods: We enrolled patients with severe CAP who were intubated and who required mechanical ventilation in an MICU in 2001. Only patients with identified bacterial pathogens were included. The bacterial distribution was determined, while differences in age, acute physiology and chronic health evaluation (APACHE) II scores, and initial PaO_2/FiO_2 ratio between surviving and expired patients were compared.

Results: Fifty-nine patients were enrolled and 75 isolates were obtained. *Klebsiella pneumoniae* was the most common bacteria (21.3%), followed by *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Staphylococcus aureus* (8%) was the most-commonly isolated gram-positive organism, and half of its isolates were oxacillin-resistant (ORSA). The overall mortality was 55.9%. Multiple logistic regression analysis revealed that survivors had a significantly younger age and lower APACHE II scores.

Conclusions: Gram-negative bacilli were the most-common causative pathogens among patients with severe CAP requiring mechanical ventilation. Antipseudomonal antibiotics or a carbapenem should be considered to cover Pseudomonas species, extended-spectrum β-lactamase-producing strains, and Acinetobacter species. If the isolated bacteria are gram-positive, care should be taken to cover the possibility of ORSA. Old age and higher APACHE II scores were associated with higher mortality.

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Key words: severe community-acquired pneumonia, gram-negative bacilli, APACHE II.

Pneumonia was the eighth leading cause of death in Taiwan in 2001, at more than 3700 fatalities.[1] Pneumonia is classified into community-acquired pneumonia (CAP) and hospital-acquired pneumonia

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(HAP) according to the source of the infection. CAP and HAP have different causative pathogens, clinical courses, and management.

The majority of CAP patients are managed at outpatient clinics, and approximately 20% of them require hospitalization.[2] Furthermore, about 10% of hospitalized patients need intensive care.[3] The overall mortality of CAP is less than 5%, but severe CAP that requires intensive care is associated with higher mortality rates of up to 20%~50%.[4-8] The mortality rate might be even higher among intubated patients.[8] Empirical therapy with broad-spectrum antibiotics is still the mainstay of treatment for severe CAP. Many studies have emphasized the importance of adequate empirical therapy to improve outcomes and decrease the length of hospital and intensive care unit (ICU) stays. The mortality rate can be lowered to 10% if the initial therapy for severe CAP is adequate and patients improve within the first 3 days. In contrast, the mortality rate can be as high as 60% if the initial therapy is inadequate.[8]

The choice of empirical antibiotics is often guided by consensus guidelines developed according to local surveillance data.[9,10] Therefore, the choice of antibiotics varies in different areas. It is important to discern patterns of causative pathogens and antibiotic susceptibilities, which can provide guidance for the initial treatment of CAP, especially severe CAP. Therefore, we retrospectively reviewed the bacterial pathogens and patterns of drug susceptibility in patients with severe CAP admitted to a medical ICU of a medical center in northern Taiwan in 2001. The outcomes of these severe CAP patients were also analyzed.

METHODS

This was a retrospective study performed at a 20-bed adult medical ICU of a medical center in northern Taiwan. From January to December 2001, consecutive patients admitted to the ICU, either from the emergency room or ward, with a diagnosis of severe CAP and respiratory failure were included. Only patients with identified bacterial pathogens were enrolled in the study. Patients coming from nursing homes, those who had been admitted to another hospital, or who were discharged within fewer than 7 days prior to this admission were excluded. Patients who were admitted to the ward with a diagnosis of CAP but were transferred to the ICU within 24 h because of respiratory failure were also included. Because this was an ICU-based study, patients fulfilling the criteria of severe CAP but who were not associated with respiratory failure or were not admitted to the ICU were not included.

A diagnosis of pneumonia was based on the following criteria: (1) new chest radiographic infiltration which was compatible with pneumonia, (2) a body temperature of > 38°C or < 35°C, (3) purulent productive sputum, and (4) a white blood cell count of > 12,000/ml or < 3000/ml. Severe CAP was defined according to the American Thoracic Society definition published in 2001.[9] The major criteria are (1) a need for mechanical ventilation and (2) the presence of septic shock. Minor criteria are (1) a systolic blood pressure of < 90 mmHg, (2) multilobar disease, and (3) a PaO_2/FiO_2 ratio of < 250. Patients fulfilling at least 1 major or 2 minor criteria were defined as having severe CAP.

Medical records were reviewed in detail by 2 of the authors to obtain the following information: age, gender, acute physiology and chronic health evaluation (APACHE) II score, initial PaO_2/FiO_2 ratio after intubation, length of mechanical ventilator usage, length of ICU stay, and length of hospital stay. Chest radiographs were separately reviewed by 2 pulmonologists to confirm the diagnosis of pneumonia. We also collected the results of cultures and susceptibility tests yielded from blood sampling, transtracheal aspirations before initiation or change of antibiotic treatment, or bronchoalveolar lavage or pleural effusions within 24 h after admission. Viral and mycobacterial infections were excluded because of limited available data. Atypical pneumonia was not included because seral tests were not routinely carried out. Adequate antibiotic therapy was defined if the isolated pathogen was susceptible to at least 1 of the initial agents in the ICU with correct dosage, timing, and route of administration.[8]

Data are expressed as the mean ± standard deviation for continuous variables and the number with percentage for categorical data. All analyses were performed using SPSS software. The difference between surviving and expired patients was compared with t-test for continuous variables and χ^2 test or Fisher's exact test for categorical data, where applicable. Stepwise multiple logistic regression analysis was performed using whether or not a

patient survived as the dependent variable. A p value of < 0.05 was considered significant for all analyses.

RESULTS

There were 706 patients admitted to this ICU during the study period. In total, 169 patients fulfilled the definition of severe CAP, 36 of whom were from the ward and the others from the emergency room. Fifty-nine patients (59/169, 34.9%; 48 men and 11 women) with positive microbiological results were included in the analysis, with an age (mean ± SD) of 67.7 ± 16.3 years, APACHE II score of 23.1 ± 6.0, and initial PaO_2/FiO_2 ratio of 172.1 ± 65.6.

Seventy-five pathogens were isolated from these 59 patients. Forty-four patients had a single pathogen, and 14 patients had 2 pathogens. Most of the pathogens were obtained from transtracheal aspirations (n = 44, 44/59), among which only 1 was polymicrobial. Others were obtained from bronchoalveolar lavage (n = 11), blood culture (n = 2), pleural effusion (n = 1), and protected sheath brushing (PSB, n = 1). The identified bacteria are summarized in Table 1. The most-common pathogens were *Klebsiella pneumoniae* (21.3%), *Pseudomonas aeruginosa* (17.3%), and *Acinetobacter baumannii* (10.7%). These 3 pathogens comprised nearly 1/2 of all bacterial pathogens. Those 8 patients infected with *A. baumannii* were all hospitalized between April and August. *Streptococcus pneumoniae* and *Hemophilus influenzae* were less frequently seen in the present study. Only 5.3% of isolates were *S. pneumoniae* and 6.7% were *H. influenzae*.

The overall mortality was 55.9% (n = 33), and the characteristics of surviving and expired patients are summarized in Table 2. There was no gender difference by Fisher's exact test. The survivors had a lower mean age (61.7 ± 17.8 vs. 72.4 ± 13.5, $p < 0.05$) and lower mean APACHE II scores (20.9 ± 5.0 vs. 24.8 ± 6.2, $p < 0.05$). In patients older than 74 years, the mortality rate was 76%, while that of the other younger patients was 41.2%. The patients with

Table 1. Main Pathogens Identified in Severe CAP Patients

Organism	Surviving	Expired	Total (n = 75)	Mortality rate
G(+) bacteria			11 (14.6)	
S. pneumoniae	3	1	4 (5.3)	25%
OSSA	2	1	3 (4)	33.3%
ORSA	1	2	3 (4)	66.7%
Corynebacterium spp.	1	0	1 (1.3)	0%
G(-) bacteria			64 (85.4)	
K. pneumoniae	10	6	16 (21.3)	37.5%
P. aeruginosa	3	10	13 (17.3)	76.9%
A. baumannii	3	5	8 (10.7)	62.5%
H. influenzae	1	4	5 (6.7)	80%
E. coli	2	2	4 (5.3)	50%
Enterobacter cloacae	0	3	3 (4)	100%
E. coli-ESBL	0	2	2 (2.7)	100%
K. pneumoniae-ESBL	1	1	2 (2.7)	50%
Serratia marcescens	1	1	2 (2.7)	50%
Branhamella catarrhalis	1	1	2 (2.7)	50%
Stenotrophomonas	0	1	1 (1.3)	100%
Proteus mirabilis	1	0	1 (1.3)	0%
Pseudomonas spp.	1	0	1 (1.3)	0%
Bacillus	0	1	1 (1.3)	100%
Neisseria meningitis	1	0	1 (1.3)	0%
Citrobacter diversus	1	0	1 (1.3)	0%
Pneumocystis carinii	1	0	1 (1.3)	0%

Abbreviations: OSSA: oxacillin-sensitive *Staphylococcus aureus*; ORSA: oxacillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum β-lactamase-inducing strains.
Data are presented as the no. (%).

Table 2. Comparison between Surviving and Expired Patients with Severe CAP

Characteristics	Surviving (n = 26)	Expired (n = 33)	Total (n = 59)	*p* Value
Male: Female	20 : 6	28 : 5	48 : 11	NS†
Age (mean ±SD)	61.7 ±17.8	72.4 ±13.5	67.6 ±16.3	< 0.05*
Underlying disease				
COPD	3	3	6	
Diabetes mellitus	5	5	10	
Malignancy	1	8	9	
Liver cirrhosis		2	2	
ESRD		1	1	
APACHE II score (mean ±SD)	20.9 ± 4.9	24.8 ± 6.2	23.1 ± 6	< 0.05*
PaO_2/FiO_2 (mean ± SD)	183.2 ±67.2	163.8 ±64.1	172.1 ±65.6	NS*

Abbreviations: COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; APACHE II: acute physiology and chronic health evaluation scoring system, version II; PaO_2/FiO_2: arterial oxygen pressure/fraction of inspiratory oxygen; NS: non significant.
* Compared by *t*-test.
† Compared by Fisher's exact test.

lower APACHE II score (≤23) also had lower mortality (40.0% vs. 72.4%). The mortality rate was higher for those with *P. aeruginosa* (76.9%), *H. influenzae* (80%), and *A. baumannii* (62.5%) infections. Comparatively, those patients infected with *S. pneumoniae* or *K. pneumoniae* had lower survival rates (25% and 38.8%, respectively). In patients infected with *K. pneumoniae*, a higher percentage of patients expired if it was an extended-spectrum beta-lactamase (ESBL)-producing strain. However, the percentage was not subjected to statistical analysis due to the small case numbers involved. As for comorbidity, both groups had similar percentages of chronic obstructive pulmonary disease and diabetes mellitus, but expired patients had more-malignant disease. The initial PaO_2/FiO_2 ratio was higher among survivors (183.2 vs. 163.8), but the difference was not statistically significant.

The initial empiric antibiotic regimen was adequate in 25 patients, 16 of whom died (64%). Comparatively, the mortality in the inadequate treatment group was 50%, without a significant difference between these 2 groups ($p = 0.211$). Patients who received adequate initial antibiotic treatment were older (71.6 ±13.6 vs. 64.8 ±17.7 years, $p = 0.05$) than those who received inadequate treatment. No statistical difference was found in APACHE II scores and PaO_2/FiO_2 ratios between these 2 groups.

In the surviving group, the mean duration of intubation was 7.3 days, the length of the ICU stay was 10.3 days, and the length of the hospital stay was 24 days. In the expired group, the mean length of the ICU stay (equal to the length of the hospital stay) was 11.8 days. The length of the ICU stay did not significantly differ between these 2 groups when compared using the *t*-test.

Multiple stepwise logistic regression analysis was performed with survival or expiration as the dependent variable. Several independent variables were entered, including age, gender, coma scale, creatinine level, platelet count, albumin level, whether initial treatment was adequate or not, the PaO_2/FiO_2 ratio, and the APACHE II score. As the result, only age and the APACHE II score were significant independent variables. In the final model, the odds ratio for the group aged ≥ 75 years was 3.71 (95% confidence interval: 1.13~12.18, $p = 0.03$) and that of patients with APACHE II scores of > 23 was 3.18 (95% confidence interval: 1.01~10.01, $p = 0.048$).

DISCUSSION

Severe community-acquired pneumonia is associated with high mortality, exceeding 60% if patients require intubation and mechanical ventilation support.[11] Another meta-analysis showed an average mortality of 36.5% for patients admitted to the ICU, with a range of 21.7%~57.3%.[12] The overall mortality of our patients with identifiable bacterial pathogens was 55.9%, which was high but similar to those of previous studies.

Several studies have reported that the initial antibiotics used had a significant impact on final outcomes.[5,8,13] If the initial antibiotic regimen was inad-

equate, then the mortality increased. Physicians should be knowledgeable about the spectrum of pathogens in their local area so that treatment can focus on possible target organisms.

The prevalence of organisms is variable in different areas. In most studies, *S. pneumoniae* is the most-common pathogen, ranging from 15% to 46% of isolates.[5,7,13,14] Other organisms such as *H. influenzae*, Staphylococcus spp., Legionella spp., and gram-negative bacilli are also common causative agents. Ruiz and coworkers reported that gram-negative bacilli caused 11% of severe CAP cases.[15] Lee et al. found that 47% of the causative pathogens of severe CAP were gram-negative bacilli, and in their study, *K. pneumoniae* was the most-common organism (15%) which also produced higher mortality.[11] In the present study, *K. pneumoniae* accounted for 27.1% of severe CAP cases with a mortality of 37.5%, which was lower than that due to other pathogens.

The roles of *P. aeruginosa* and *A. baumannii* in severe CAP are unclear.[16] Almirall et al. isolated *P. aeruginosa* in 6% of patients with CAP.[17] Torres et al. isolated *P. aeruginosa* in 5% patients with CAP and found that severe pneumonia caused by *P. aeruginosa* was associated with 100% mortality.[13] In our study, *P. aeruginosa* was isolated in 17.3% of patients, and the mortality was high (76.9%). In general, *A. baumannii* was more prevalent with nosocomial infections. Rudin et al. described 6 cases of CAP caused by Acinetobacter spp.[18] Chen et al. also reported 13 cases of severe CAP caused by *A. baumannii*, with a mortality of 62%,[19] which is similar to our results (60%). *Acinetobacter baumannii* is more active in warm and humid seasons,[19] and this is therefore compatible with our findings that all infections with *A. baumannii* we noted occurred in the period of April to August.

Staphylococcus aureus is also an important organism responsible for severe CAP. Its incidence has been increasing in recent years, ranging from 12% to 22%, as reported in several patient series.[7,13,14,20] Woodhead et al. analyzed 61 cases of *S. aureus*-related CAP, and nearly 1/2 of them had underlying systematic disease.[21] According to our results, 3 had diabetes, 1 had chronic renal failure and was undergoing hemodialysis, and 1 had decompensated liver cirrhosis. In addition, the percentage of *S. aureus* was even higher than that of *S. pneumoniae*. Half of them were ORSA, and 2/3 of patients with ORSA infection died.

Patients with severe CAP are usually associated with a major systematic disease, including chronic obstructive pulmonary disease, diabetes mellitus, and alcoholism.[22] Fine et al. reported independent predictors of mortality to be neoplastic disease, corticosteroid use, and alcohol abuse.[23] Torres et al. noted that chronic respiratory disease was not associated with higher mortality.[13] In our study, the surviving and expired patients had similar proportions of comorbidities, except for a higher malignancy rate in the expired group.

Elderly populations are more susceptible to severe CAP and have more-adverse outcomes. Woodhead et al. found that the mortality was 90% in patients older than 70 years with pneumonia.[24] Another multivariate analysis showed that being aged older than 60 years was independently associated with death.[25] On the contrary, Riquelme et al. reported that age was not a significant factor related to the prognosis.[26] In our study, the mortality rate in patients of 75 years or older was 76.0%; which was higher than the mean mortality. In addition, the surviving group was younger than the expired group (61.7 ± 17.8 vs. 72.4 ± 13.5 years, respectively, $p < 0.05$). This reveals that increasing age had a negative impact on outcomes.

Marik et al. reported that APACHE II scores were an independent predictor of mortality.[27] We found that patients with lower APACHE II scores (≤ 23) had a lower mortality rate, which is similar to previous data. Although the PaO_2/FiO_2 ratio was higher in the surviving group, the difference was not significant. Other factors also indicated no positive results.

Adequate initial antibiotic treatment is important and may reduce the mortality rate. In our study, the mortality rates in the adequate and inadequate initial antibiotic treatment groups were 64% and 50%, respectively, but the difference was not statistically significant. The cause of the opposite result may have been due to the small sample size. The mean age of our patients who received adequate initial antibiotic treatment was higher, which might partially explain the higher associated mortality. This also revealed that age might be another risk factor in addition to antibiotics in the prognosis.

There are several limitations to our study. First, because of its retrospective nature, admission criteria

and methods of specimen collection were not standardized. Second, we excluded other atypical pathogens such as viruses and mycoplasma because we did not routinely order serological studies, and this may have affected the results of the pathogen distribution. Third, because only patients in the ICU were enrolled, patients with severe CAP who were not treated in ICU were not included. This resulted in a small sample size and may also have affected the pathogen distribution.

In summary, we have established a database for the local spectrum of bacteria in patients with severe CAP who require mechanical ventilation. Empirical antibiotic treatment should be guided by the possible bacterial distribution in our area. According to our results, gram-negative bacillus infection should be considered in intubated patients, and *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* were common pathogens among these patients. For patients possibly infected with these bacteria, antipseudomonal agents or carbapenem agents might be needed. If gram-positive cocci are found, *S. pneumoniae*, ORSA, and oxacillin-sensitive *S. aureus* (OSSA) should all be considered. In our study, *S. aureus* was even more commonly seen than *S. pneumoniae*. Initial antibiotic treatment should cover possible ORSA because it is associated with a high mortality rate. Furthermore, higher age and APACHE II score were independent risk factors of death. Although the beneficial effect of adequate initial antibiotic treatment might have been masked by the older age of that group in our study, it is still reasonable to choose adequate empirical antibiotics to cover the possible spectrum of pathogens found locally. A prospective, larger-scale study is necessary in order to make more-precise statistical comparisons.

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需使用呼吸器的嚴重社區型肺炎之致病菌及預後分析

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背 景： 肺炎至目前爲止，仍然是重要且致命的感染性疾病，嚴重社區型肺炎的死亡率更高。治療上一般以廣效性抗生素爲主，再根據細菌培養結果更改藥物。本研究之目的在於分析本區的細菌分布，以作爲抗生素選擇的參考，並分析這群病患死亡之危險因子。

方 法： 我們收集 2001 年 1 月至 2001 年 12 月間因嚴重社區型肺炎而插管送進北台灣某醫學中心內科加護病房的患者。我們回顧他們的醫療紀錄，其中 59 位細菌培養有結果，比較存活者和死亡者的年齡，住院時 APACHE II 分數及 PaO_2/FiO_2 比值的差異。

結 果： 59 位病患（48 位男性，11 位女性），平均年齡爲 67.7±16.3 歲。培養的細菌中以克雷白氏菌最多（佔 21.3%），其次爲綠膿桿菌（佔 17.3）。在格蘭氏陽性細菌中以金黃色葡萄球菌最多（佔 8%）。此群患者之平均死亡率爲 55.9%。經由多變項邏輯斯締迴歸 (multiple logistic regression) 分析，年齡大於 75 歲以及 APACHE II 大於 23 者有顯著較高的風險比。

結 論： 格蘭氏陰性桿菌在需使用呼吸器的嚴重社區型肺炎爲重要的致病菌。我們在抗生素的選擇上，應使用更廣泛、更強效的藥物，有時甚至要用到抗綠膿桿菌類的抗生素或 Carbapenem 類之藥物。若格蘭氏陽性菌出現時，要小心抗 Oxacilline 類之金黃色葡萄球菌。在整個治療過程中，年齡及 APACHE II 分數高者有較高的死亡率。
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關鍵字： 嚴重社區型肺炎，格蘭氏陰性桿菌，APACHE II。

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