An Early Predictor of the Outcome of Patients with Ventilator-associated Pneumonia

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Background: Ventilator-associated pneumonia (VAP) contributes to high mortality, prolonged intensive care unit (ICU) stay and increased costs of health care. Reports of early predictors of death in patients with VAP are rare. Our study was designed to determine early predictors of poor outcome in patients with VAP.

Methods: A total 838 patients with nosocomial lower respiratory tract infection in a tertiary medical center from January, 2004 to June, 2006 were retrospectively reviewed. Forty-two patients had VAP and were enrolled in the study. The age, sex, underlying diseases, including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, end-stage renal disease, congestive heart failure/coronary artery disease, and collagen vascular disease, diagnosis at admission, Acute Physiological Assessment and Chronic Health Evaluation II score (APACHE II score), Clinical Pulmonary Infection Score (CPIS), time between intubation and ICU admission, time between intubation and development of VAP, risk factors for multi-drug resistant pathogens, time to adequate therapy, initial antibiotics regimen, bacterial cultures, mortality rate from VAP, 28-day mortality rate and in-hospital mortality rate were compared between the mortality group and non-mortality group.

Results: The VAP, 28-day and in-hospital mortality rates were 23.8% (10/42), 40.5% (17/42) and 50% (21/42), respectively. The APACHE II score ($p = 0.002$) and CPIS ($p = 0.048$) at the onset of VAP, inadequate initial antibiotics treatment ($p = 0.007$) and concomitant bacteremia ($p = 0.008$) were the only parameters which were significantly different between groups. The independent risk factors for VAP mortality in multivariable analysis were the APACHE II score at the onset of VAP ($p = 0.018$), inadequate initial antibiotics treatment ($p = 0.032$) and concomitant bacteremia ($p = 0.034$). An APACHE II score > 27 at VAP onset was an independent and early predictor of the mortality. (ROC AUC: 0.841; Sensitivity: 70%; Specificity: 90.6%; $p = 0.001$).

Conclusion: A high APACHE II score (> 27) at VAP onset was an independent and early predictor of mortality due to VAP.

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Key words: ventilator-associated pneumonia (VAP); Clinical Pulmonary Infection Score (CPIS); Acute Physiological Assessment and Chronic Health Evaluation (APACHE) II score

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Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops after endotracheal tube intubation/mechanical ventilation for more than 48 hrs. It is a common nosocomial infection in intensive care units (ICU) and results in high mortality, prolonged ICU stay and increased costs of health care.[1] Early identification of patients at high risk for death may help physicians adjust antibiotic therapy appropriately. Serial determinations of the Clinical Pulmonary Infection Score (CPIS), and serum procalcitonin and C-reactive protein (CRP) levels during the course of VAP could be primary prognostic factors as early as day 3 of therapy.[2-5] The predictors of long-term mortality, infection recurrence and death are known,[6,7] but reports on the early predictors of death at VAP onset are rare. Our study was designed to determine early predictors of poor outcome in patients with VAP and to also assess the mortality rate, 28-day mortality rate and in-hospital mortality rate of patients with VAP.

METHODS

Study design and patients

Patients with nosocomial lower respiratory tract infection reported by the computerized online infectious disease surveillance and control system (COIDSC system) from January, 2004 to June, 2006 in a tertiary center were retrospectively reviewed. Inclusion criteria were: (1) age > 18 years old, (2) respiratory failure with mechanical ventilator support > 48 hrs, (3) systemic inflammatory response syndrome, (4) newly developed infiltrates/consolidation on chest radiographs, and (5) CPIS > 6. Exclusion criteria were: (1) prior history of VAP, (2) acute pulmonary edema, (3) atelectasis, (4) acquired immune deficiency syndrome-defined condition, or (5) neutropenia (< 500 cells/ml) before development of VAP.

Data collection included patient characteristics, underlying co-morbidity, diagnosis at admission, time between intubation and ICU admission, time between intubation and development of VAP, Acute Physiological Assessment and Chronic Health Evaluation II (APACHE II) score on the day of ICU admission and at onset of VAP, CPIS, risk factors for multi-drug resistant pathogens (MDR-pathogens), adequate/inadequate treatment according to endotracheal aspiration cultures and guidelines of the American Thoracic Society (ATS guidelines), bacterial etiology and culture results, and initial antibiotics regimen.

Definitions

VAP

VAP is pneumonia that develops after endotracheal intubation/mechanical ventilation for more than 48 hrs. Early-onset and late-onset VAP are defined as occurring within the first 4 days and more than 4 days, after intubation, respectively.

Systemic inflammatory response syndrome

This is a syndrome that fulfills at least two of the following criteria: (a) body temperature ≧ 38°C or < 36°C; (b) heart rate > 90 beats/min; (c) respiratory rate > 20 breaths/min or PaCO2< 32 mmHg; (d) WBCs > 12,000/mL or < 4,000/mL or > 10% immature bands.

CPIS

CPIS is a score for calculated variables which was originally standardized by Pugin et al.[8] In this study, we used the modified CPIS which was published by Fartoukh et al.[9]

Adequate antibiotics treatment according to the endotracheal aspiration culture

This is defined as coverage of all the pathogens isolated by at least one antibiotic administered at initial therapy, determined by the susceptibility pattern in the antibiogram.

Adequate antibiotics treatment according to ATS guidelines

The antibiotics therapy was reviewed by two chest physicians and was defined as adequate if both physicians considered the initial antibiotics compatible with the recommendations of ATS guidelines for VAP.[10] The risk factors for MDR-pathogens were also determined according to ATS guidelines.

COIDSC system

This system is designed for surveillance of the etiology and antibiotic treatment of infectious diseases in this center. When a physician prescribes antibiotics, the system asks the physician to report the etiology of the infectious disease immediately,

such as community/nosocomial lower respiratory infection, intra-abdominal infection, urinary tract infection and soft tissue infection.

Mortality due to VAP

This was determined when Patients died after a diagnosis of VAP and the attending physician recorded the pneumonia as the leading cause of death in the records. Causes of death other than VAP were not assessed in the mortality rate for VAP.

28-day mortality and in-hospital mortality

The total number of deaths within 28 days after onset of VAP and during hospitalization were defined as 28-day mortality and in-hospital mortality.

Delay in ICU admission

This was reported for patients who were not admitted to the ICU within 48 hrs after intubation/ventilator support.

Outcome criteria

Outcomes included mortality due to VAP, 28-day mortality and in-hospital mortality.

Statistical analysis

Categorical variables were analyzed using the chi-square test or Fisher's exact test where appropriate, and continuous variables were compared using the Student t test or Mann-Whitney U test. Multivariate logistic regression analyses were performed to identify independent risk factors for VAP mortality. The goodness-of-fit was assessed with the Hosmer-Lemeshow test. The cutoff values of the APACHE II score and VAP mortality were analyzed using receiver operating characteristic (ROC) curves. Cumulative mortality was estimated by Kaplan–Meier analysis comparing participants below and above the optimal APACHE II cut-off level found by ROC curve analysis. Differences in survival were calculated according to log-rank statistics.

Results are presented as absolute number (percentage), mean (± standard deviation) or median (interquartile range). Odd ratios and 95% confidence intervals (CIs) are reported for logistic regression analysis. A two-tailed p value < 0.05 was considered significant. All statistical analyses were performed using the SPSS 14.0 software package (SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

Forty-two of the 838 patients with nosocomial lower respiratory tract infection reported by the COIDSC system were identified as having VAP. The incidence rate of VAP was 5.0%. Three of these 42 patients patients had early-onset VAP. The mortality rate was not significantly different between those with early-onset and late-onset VAP (33.3% vs. 23.1%; $p = 0.688$).

Ten patients died due to VAP. The mortality rate for VAP, 28-day mortality rate and in-hospital mortality rate were 23.8% (10/42), 40.5% (17/42) and 50% (21/42), respectively.

The sex, age, underlying disease, diagnosis at admission, emergency surgical intervention, delay in ICU admission, APACHE II score at ICU admission, risk factors for MDR-pathogens, and days on the mechanical ventilator prior to VAP onset were not significantly different between the mortality and non-mortality groups (Table 1). The APACHE II score and CPIS at the time of VAP diagnosis were significantly higher in the mortality group (Table 1).

Psudomonas aeruginosa, Acinetobacter baumannii, and *Staphylococcus aureus* were the three most common nosocomial pathogens (Table 2). Fourteen patients had concomitant bacteremia and seven died (Table 2).

The initial antibiotics were not associated with mortality ($p = 0.123$) (Fig. 1). The initial antibiotics treatment according to the endotracheal aspiration culture and ATS guidelines was adequate in 24 and 19 patients, respectively. The number of patients receiving inadequate therapy according to endotracheal tube aspiration culture was greater in the mortality group, but was not different between groups according to ATS guidelines (Table 3).

Multivariable analysis showed that the APACHE II score at VAP onset, inadequate initial antibiotics treatment, and concomitant bacteremia were independent risk factors of VAP mortality (Table 4). An APACHE II score > 27 determined at VAP diagnosis was an independent and early predictor of mortality (Fig. 2). Patients with high APACHE II scores at VAP onset had poor outcomes (Fig. 3).

Table 1. Basic Characteristics of 42 Patients with VAP

	All (n = 42)	Non-mortality (n = 32)	Mortality (n = 10)	*p* value
Sex				0.451
Male	28 (66.7%)	20 (62.5%)	8 (80%)	
Female	14 (33.3%)	12 (37.5%)	2 (20%)	
Age				0.460
Median	69.5	69.5	70.5	
Interquartile range	(54.25~79.25)	(46.75~79.75)	(64.25~78.75)	
Underlying diseases				
HTN	12 (28.6%)	10 (31.3%)	2 (20%)	0.696
DM	11 (26.2%)	9 (28.1%)	2 (20%)	> 0.999
COPD	7 (16.7%)	7 (21.9%)	0	0.168
ESRD/CRI	6 (14.3%)	3 (9.4%)	3 (30%)	0.135
CHF/CAD	4 (9.5%)	4 (12.5%)	0	0.557
Adrenal insufficiency	4 (9.5%)	3 (9.4%)	1 (10%)	> 0.999
Collagen vascular disease	3 (7.1%)	3 (9.4%)	0	> 0.999
Old TB	2 (4.8%)	1 (3.1%)	1 (10%)	0.424
GU	2 (4.8%)	2 (6.3%)	0	> 0.999
Cancer	2 (4.8%)	1 (3.1%)	1 (10%)	0.424
Others	11 (26.2%)	8 (25%)	3 (30%)	> 0.999
Diagnosis at admission				0.117
Trauma	7 (16.7%)	7 (21.9%)	0	
Neurogenic	12 (28.6%)	8 (25%)	4 (40%)	
Sepsis	4 (9.5%)	2 (6.3%)	2 (20%)	
COPD with AE	4 (9.5%)	4 (12.5%)	0	
GI bleeding	4 (9.5%)	3 (9.4%)	1 (10%)	
Pneumonia	2 (4.8%)	2 (6.3%)	0	
Cardiogenic	2 (4.8%)	2 (6.3%)	0	
Cancer	1 (2.4%)	0	1 (10%)	
Other infection	3 (7.1%)	3 (9.4%)	0	
Others	3 (7.1%)	1 (3.1%)	2 (20%)	
Emergency op before VAP	7 (16.7%)	6 (18.8%)	1 (10%)	> 0.999
Risk factors for MDR pathogens				0.714
Yes	17 (40.5%)	12 (37.5%)	5 (50%)	
No	25 (59.5%)	20 (62.5%)	5 (50%)	
Delay in ICU admission				> 0.999
Yes	11 (26.2%)	8 (25%)	3 (30%)	
No	31 (73.8%)	24 (75%)	7 (70%)	
APACHE II at ICU admission				0.408
Mean (SD)	23.67 (6.99)	23.13 (7.17)	25.4 (6.38)	
APACHE II at VAP onset				0.002
Mean (SD)	23.19 (5.93)	21.66 (5.60)	28.10 (4.12)	
CPIS at VAP onset				0.048
Median	8	8	9	
Interquartile range	(7~9)	(7~8.5)	(7.75~10)	
Mechanical ventilator days prior to VAP onset				0.919
Median	11	10	11.5	
Interquartile range	(7~16)	(6.25~19)	(7~15.25)	

Abbreviations: VAP: ventilator associated pneumonia; HTN: hypertension; DM: Diabetes mellitus; COPD with AE: Chronic obstructive pulmonary disease with acute exacerbation; ESRD/CRI: end-stage renal disease/chronic renal insufficiency; CHF/CAD: congestive heart failure/coronary artery disease; TB: tuberculosis; GU: Gastric ulcer; GI bleeding: Gastrointestinal tract bleeding; op: operation; MDR: Muti-drug resistant; APACHE II: Acute Physiological Assessment and Chronic Health Evaluation II score; CPIS: Clinical Pulmonary Infection Score.

Table 2. Microorganism Studies

	All (n = 42)	Non-mortality (n = 32)	Mortality (n = 10)	*p* value
Blood culture positive	14 (33.3%)	7 (21.9%)	7 (70%)	0.008
Gram stain positive endotracheal aspiration				> 0.999
GNB	5 (11.9%)	4 (12.5%)	1 (10%)	
GPC	1 (2.4%)	1 (3.1%)	0	
Endotracheal aspiration culture				
AB	11 (26.2%)	8 (25%)	3 (30%)	> 0.999
Ps. aeruginosa	13 (31.0%)	11 (34.4%)	2 (20%)	0.466
ORSA/OSSA	9 (21.4%)	7 (21.9%)	2 (20%)	> 0.999
KP	4 (9.5%)	4 (12.5%)	0	0.557
Enterobacter cloacae	3 (7.1%)	1 (3.1%)	2 (20%)	0.136
Corynebacterium	2 (4.7%)	2 (6.3%)	0	> 0.999
Streptoccocus	1 (2.3%)	1 (3.1%)	0	> 0.999
E coli	1 (2.3%)	1 (3.1%)	0	> 0.999
Serratia marcescens	1 (2.3%)	1 (3.1%)	0	> 0.999
No growth	6 (14.3%)	3 (9.4%)	3 (30%)	> 0.135

Abbreviations: GNB: Gram negative bacilli; GPC: Gram positive cocci; AB: *Acinetobacter baumannii; Ps. Aeruginosa: Psudomonas aeruginosa;* ORSA/OSSA: Oxacillin resistant *Staphylococcus aureus*/*Oxacillin susceptible Staphylococcus aureus;* KP: *Klebsiella pneumoniae; E coli: Escherichia coli*.

DISCUSSION

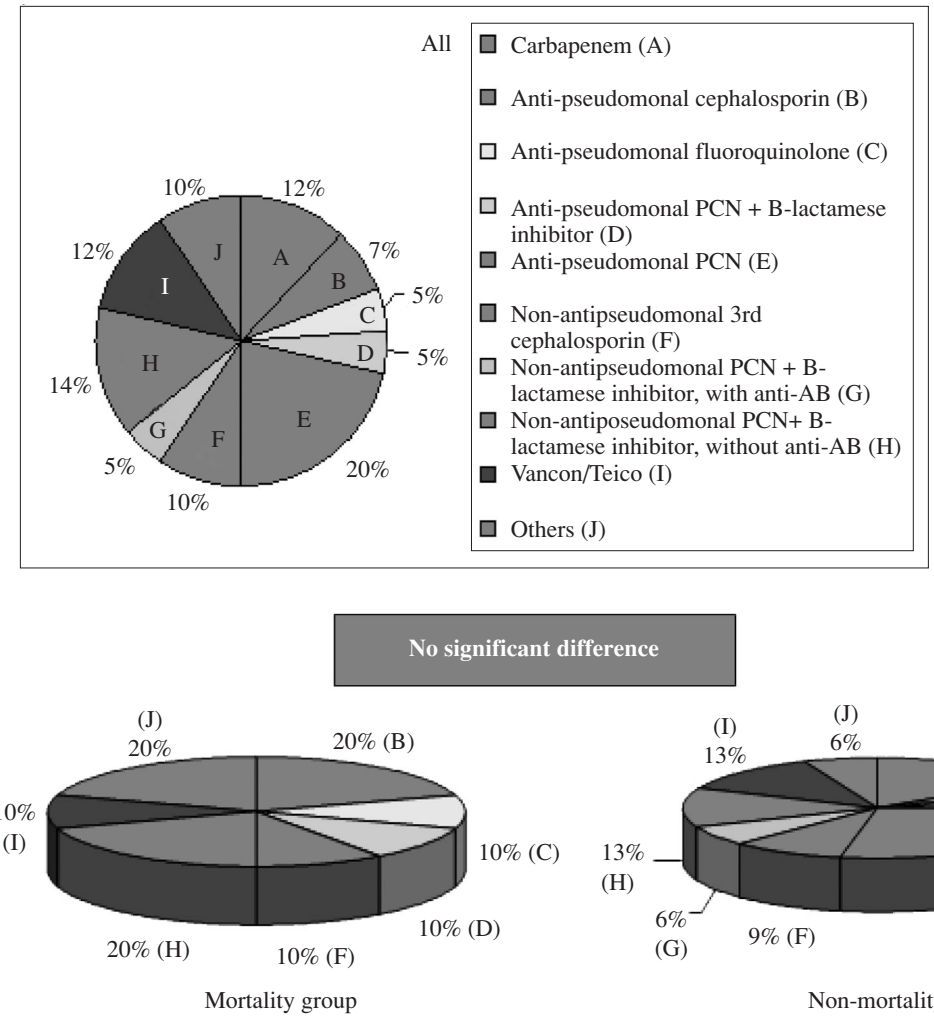
Despite the ready availablilty of ATS guidelines for the management of VAP[10] and recent advances in critical care medicine, the mortality rate from VAP is still high. In our study, the VAP, 28-day and in-hospital mortality rates were 23.8%, 40.5% and 50%, respectively. Initial antibiotic therapy was adequate in 19 patients according to ATS guidelines, but the mortality rate did not decrease (Table 3).

Michel et al. found that EA-pre (endotracheal aspiration culture performed just before suspicion of VAP) identified the same microorganisms as a bronchoalveolar lavage (BAL) culture in 83% of patients,[11] and adequate therapy was provided in 95% of patients who were later diagnosed with VAP. Our data showed improvement in the outcomes in patients who received adequate therapy according to endotracheal aspiration culture.

Psudomonas aeruginosa, Acinetobacter baumannii, and *Staphylococcus aureus* were the three most common nosocomial pathogens in our data and in other studies.[6,12,13] *Acinetobacter baumannii* contributed to significantly higher mortality than other pathogens in one study of patients with nosocomial pneumonia.[12] It was also the pathogen associated with the highest death rate in patients with VAP in another study.[13] However, we did not observe this result in our study in VAP patients, similar to the study of Ranes et al.[6]

Studies have reported that about 8%~20% of nosocomial pneumonia cases are bacteremic,[14,15] and bacteremic VAP also contributes to high mortality.[6,16] Among our patients, the incidence and mortality rates of bacteremic VAP were 33.3% and 50% respectively.

Kollef et al. performed a prospective,[13] observational, cohort study of 398 patients in twenty ICUs in the United States. They found the mortality rates were similar among patients treated with carbapenem (31.1%), cefepime (30.6%), ureidopenicillin/monobactum (25.2%), and quinolone (26.7%) initially, but were significantly lower among patients initially treated with other or no antibiotics, which included those treated with vancomycin (19.1%). The result may be biased because there were more than 100 different antibiotic regimens/combinations prescribed as initial therapy in these ICUs. In our study, we did not observe any antibiotic regimen that could improve the outcome ($p = 0.123$) (Fig. 1).



Abbreviations used: PCN: penicilline; AB: *Acinetobacter baumanii*.

Fig. 1 Initial antibiotics for VAP.

Table 3. Adequacy of Antibiotics Therapy

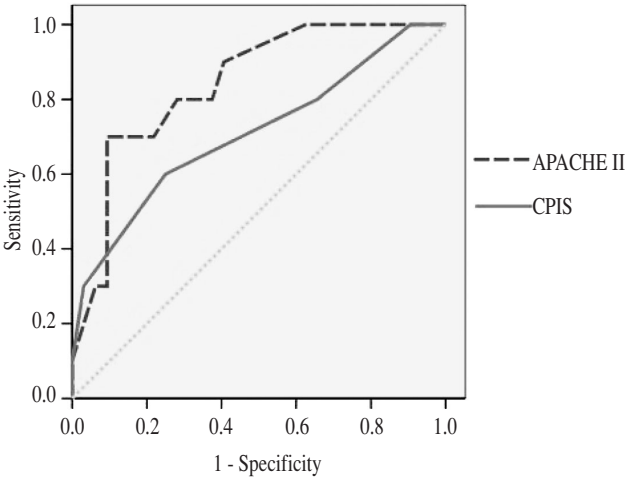
	All (n = 42)	Non-mortality (n = 32)	Mortality (n = 10)	*p* value
ETT aspiration culture				0.010
Adequate	24 (57.14%)	22 (68.8%)	2 (20%)	
Inadequate	18 (42.9%)	10 (31.3%)	8 (80%)	
ATS guidelines				> 0.999
Adequate	19 (45.2%)	14 (43.8%)	5 (50%)	
Inadequate	23 (54.8%)	18 (56.3%)	5 (50%)	

Abbreviations: ETT: Endotracheal tube; ATS: American Thoracic Society.

Table 4. Independent Risk Factors in Multivariate Analysis

Variables	Adjusted odds ratio (95% CI)	*p*-value
APACHE II	1.94 (1.12 ~ 3.36)	0.018
CPIS	1.13 (0.22 ~ 5.72)	0.886
Positive blood culture	179.73 (1.48 ~ 21696.19)	0.034
Inadequate antibiotics therapy according to ETT aspiration culture	840 (1.80 ~ 391174)	0.032

Abbreviations: APACHE II: Acute Physiological Assessment and Chronic Health Evaluation II score; CPIS: Clinical Pulmonary Infectious Score; ETT: Endotracheal tube.



	Cutoff Value	Sensitivity	Specificity	AUC	*p*-value
APACHE II	27	70%	90.60%	0.841	0.001
CPIS	8	60%	75%	0.708	0.050

Fig. 2 ROC curves for APACHE II and CPIS scores

Initial antibiotics therapy is a key factor influencing VAP outcome. Lee et al found that the mortality rate was significantly higher in those patients with inappropriate initial empiric antibiotics therapy even when the subsequent antibiotics therapy was appropriate.[12] Early identification of patients at high risk for death may help physicians choose initial antibiotics more appropriately.

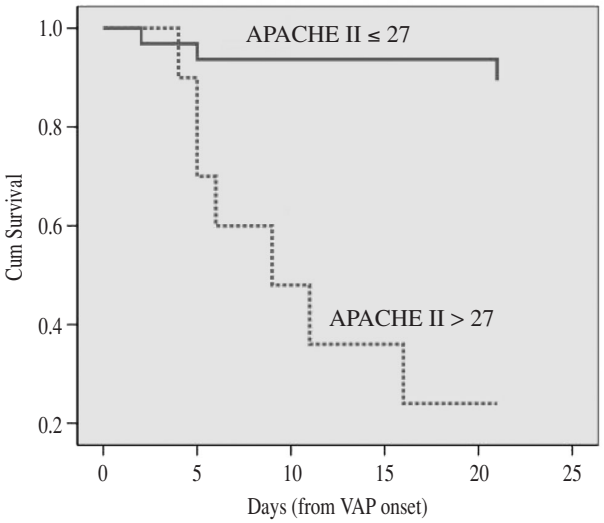


Fig. 3 Kaplan-Meier survival curves for APACHE II scores (> 27 vs. ≤ 27). The *p* value < 0.001. The median survival for patients with an APACHE II score > 27 was 8.83 days.

Serial determinations of the CPIS, and serum procalcitonin and CRP levels during the course of VAP could be the prognostic factors as early as day 3 of therapy,[2-5] but these measurements may not predict the outcome of VAP at VAP onset.

Studies showed that a high SAPS II (Simplified Acute Physiology Score II) was one of the three independent risk factors for mortality from nosocomial pneumonia,[12] and also one of the early predictors for infection recurrence and death in VAP patients.[7] In our hospital, a tertiary center in southern Taiwan, we used the APACHE II score rather than the SAPS II to determine the severity of clinical illness at ICU admission. Gursel et al found an APACHE II score > 16 was an independent predictor of mortality and treatment failure in VAP patients.[17,18] However, the average APACHE II score at ICU admission was more than 20 in our ICUs, and we could not use a score over 16 as a predictor to determine the VAP outcome.

We found that bacteremia, inadequate initial antibiotic therapy according to the endotracheal aspiration culture, a high CPIS and a high APACHE II score at VAP onset were associated with high mortality. The independent risk factors were bacteremia, inadequate initial antibiotic therapy according to endotracheal aspiration culture, and high APACHE II score at VAP onset (Table 4). Among these factors,

only the APACHE II score at VAP onset could predict a poor outcome early (Fig. 2, 3).

Our study was limited by the study design (retrospective study), data base (*COIDSC system*) and the small case number. The incidence of VAP in our data was 5% which was smaller than in previous reports.[10] This may have occurred because some patients had other concomitant sources of infection and the physicians may not have reported nosocomial lower respiratory tract infection in the *COIDSC system*. Further prospective study is necessary.

Conclusions

High APACHE II scores determined at VAP onset, bacteremia, and inadequate initial antibiotics therapy contributed to the poor outcome of VAP patients. The disease severity (APACHE II > 27) at VAP diagnosis could be an independent and early predictor of mortality in patients with VAP. Physicians should use adequate initial antibiotics according to the underlying comorbidity, ATS guidelines, EA-pre and local surveillance data, and should escalate or deescalate antibiotics appropriately according to the EA, BAL, and blood cultures. Antibiotics should be chosen carefully in patients with high APACHE II scores (> 27) at VAP onset.

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“呼吸器相關性肺炎”預後的早期預測指標

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背 景：“呼吸器相關性肺炎”會造成高死亡率、延長病患住加護病房天數並造成大筆醫療支出。目前其病患預後的早期預測指標仍未明。故本研究之目的爲找出“呼吸器相關性肺炎”病患預後的早期預測指標。

方 法：本研究爲回溯性病歷研究。收集 2004 年 1 月至 2006 年 6 月間，於本院感控線上通報系統通報爲院內下呼吸道感染之病患，從中篩選出符合“呼吸器相關性肺炎”診斷之病患，收集各項有關之臨床資料 (包括診斷“呼吸器相關性肺炎”時病患臨床肺部感染分數、APACHE II 分數及當時使用之抗生素等) 加以統計分析。

結 果：本院感控線上通報系統通報爲院內下呼吸道感染之病患共有 838 人，從中篩選出符合“呼吸器相關性肺炎”診斷之病患共有 42 人。“呼吸器相關性肺炎”死亡率、住院第 28 天死亡率及住院中死亡率分別爲 23.8%、40.5% 及 50%。經由多變項統計分析，我們發現診斷“呼吸器相關性肺炎”時，病患 APACHE II 分數大於 27 分爲病患預後的早期預測指標。

結 論：診斷“呼吸器相關性肺炎”時，高 APACHE II 分數 (大於 27 分) 爲病患預後的早期預測指標。

(長庚醫誌 2010;33:274-82)

關鍵詞：呼吸器相關性肺炎，臨床肺部感染分數，APACHE II 分數

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