Research Paper

Appropriate Antibiotic Administration in Critically Ill Patients with Pneumonia

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Inappropriate initial antibiotics for pneumonia infection are usually linked to extended intensive care unit stay and are associated with an increased risk of mortality. This study evaluates the impact of inappropriate initial antibiotics on the length of intensive care unit stay, risk of mortality and the co-predictors that influences these outcomes. This retrospective study was conducted in an intensive care unit of a teaching hospital. The types of pneumonia investigated were hospital-acquired pneumonia and ventilator-associated pneumonia. Three different time points were defined as the initiation of appropriate antibiotics at 24 h, between 24 to 48 h and at more than 48 h after obtaining a culture. Patients had either hospital-acquired pneumonia (59.1%) or ventilator-associated pneumonia (40.9%). The length of intensive care unit stay ranged from 1 to 52 days (mean; 9.78±10.02 days). Patients who received appropriate antibiotic agent at 24 h had a significantly shorter length of intensive care unit stay (5.62 d, $P<0.001$). The co-predictors that contributed to an extended intensive care unit stay were the time of availability of susceptibility results and concomitant diseases, namely cancer and sepsis. The only predictor of intensive care unit death was cancer. The results support the need for early appropriate initial antibiotic therapy in hospital-acquired pneumonia and ventilator-associated pneumonia infections.

Key words: Antibiotics, hospital-acquired pneumonia, ventilator-associated pneumonia, critical care

Pneumonia is the most common hospital-acquired infection in critically ill patients with prevalence rates ranging from 10 to 70%[1]. It comprises 15 to 23% of all hospital-acquired infections[2] and is associated with a high risk of mortality[3]. Available data suggest that pneumonia occurs at a rate of between 5 to 10 cases per 1000 hospital admissions with the incidence increasing by as much as 6 to 20-fold in patients who are being ventilated mechanically[3]. Pneumonia acquired in hospital admitted patients are divided into two main types, namely hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP)[3]. It has been reported that HAP increases hospital stay by an average of 7 to 9 d per patient, and produces an excess cost of more than $ 40 000 per patient[3]. VAP has been reported to occur in 9 to 27% of all intubated patients[4].

Organisms associated with nosocomial pneumonia are usually bacterial pathogens that may be polymicrobial, and are rarely due to viral or fungal pathogens[5]. Common pathogens include aerobic gram-negative bacilli such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae* and *Acinetobacter species*. Infections due to gram-positive cocci such as *Staphylococcus aureus* particularly methicillin-resistant *Staphylococcus aureus* (MRSA) have been rapidly emerging in the United States[4,5]. Organisms, namely the *viridans* group, *Streptococci* spp., coagulase-negative *Staphylococci*, *Neisseria* spp. and *Corynebacterium* spp. can produce infection in immunocompromised hosts and some immunocompetent patients[5].

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Pneumonia included in the study was HAP and VAP. Patients that were infected with bacterial pneumonia was selected to fit the purpose of this study. The definitions of HAP and VAP used during the study were as that described by the Infectious Disease Society of America (IDSA)[3]. HAP is defined as pneumonia that occurs 48 h or more after hospital admission and that was not present at the time of admission[3]. VAP refers to pneumonia that occurs 48 h or more after endotracheal intubation[3].

Initial antibiotic therapy was defined as the first antibiotic agent that the patient received. Appropriate initial antibiotic therapy was defined as antibiotic agents that were initially selected empirically based on local guidelines and IDSA[3,6] but later supported by the antibiotic susceptibility tests. In addition to this, appropriate antibiotic therapy should be administered at a correct dose, dosing interval and duration[3,6].

Treatment of pneumonia is largely successful with appropriate antibiotics. Nonetheless, there are various factors involved in successful antibiotic treatment such as time of initiation, drug concentration and time of exposure[4,5]. Antibiotic resistant gram-negative bacteria and methicillin resistant *Staphylococcus aureus* often arise due to inappropriate use of initial antibiotic therapy[5]. As such, in-hospital mortality is substantially higher among patients receiving inappropriate initial antibiotic therapy, which accounts for 52% compared to 12% of those treated appropriately[4]. Inappropriate initial antibiotic therapy has also been demonstrated to extend the length of intensive care unit (ICU) stay[7]. To that end, appropriate use of initial antibiotic therapy is vital to reduce mortality rate and length of ICU stay[5]. Despite extensive work demonstrating the need for appropriate antibiotic treatment, there is still a lack of urgency in ensuring adequate treatment is given at the recommended times[4,5]. Furthermore, the lack of local data proves the need for investigating the use of appropriate antibiotics in admitted patients. Thus, this study was conducted to evaluate the impact of appropriate administration of antibiotics as well as other predictors on the length of ICU stay and mortality in a local tertiary teaching hospital.

MATERIALS AND METHODS

This retrospective study was conducted in a 17-bed general ICU of a local teaching hospital that provides tertiary care services located in the capital city of Malaysia. Patients admitted to the ICU from 2008 to 2009 with pneumonia (HAP or VAP) were identified from the ICU records. The demographic profile of selected patients namely age, gender, type of pneumonia, type of causative organism, concomitant diseases, time of availability of susceptibility result, initiation time point of appropriate initial antibiotic therapy, length of ICU stay and the outcome on mortality upon discharge from the ICU were collected. A positive culture from tracheal aspirate, bronchoalveolar lavage fluid or blood was required for inclusion in the study. Ethical approval was obtained from the local medical research and ethics committee (ID: 10-523-6-12).

In this study, the impact of three different initiation time points of appropriate initial antibiotic therapy on the length of ICU stay and mortality were assessed. The three different time points were defined as the initiation of appropriate antibiotic therapy at 24 h after the culture was obtained, between 24 and 48 h after the culture was obtained, and at more than 48 h after the culture was obtained. The numbers of patient-days was measured at the point of initiation of initial antibiotic therapy for pneumonia. Patients who died in the hospital were excluded from the length of stay comparisons since their ICU stay was shortened by death. Mortality meant that the patient died in the ICU due to either pneumonia infection itself or other complications that were related to the concomitant diseases of the patient. The diagnosis of pneumonia was based on the diagnosis by the physician. Patients were excluded from the study if there were absent or incomplete susceptibility results, incomplete medication record and incomplete administration record.

Data analysis:

Data analysis of this study was conducted using statistical package for social sciences (SPSS) for Windows version 16.0.1 (2008, SPSS Inc, Chicago, IL, USA). Kruskal-Wallis and Mann-Whitney U tests were used to compare means for nonparametric variables. Co-predictors of the increase in ICU stay and mortality was analysed using multiple regression. All variables with a *P*-value of <0.05 in the univariate analysis of logistic regression and linear regression were considered for inclusion in the final multivariate regression modelling. Appropriate initial antibiotic therapy was included in all multivariate analysis since

it was a primary variable of interest in this study. The odds ratios (OR) derived from the multivariate logistic regression were estimated to test the significance of appropriate initial antibiotic therapy together with the influence of co-predictors in predicting the likelihood of ICU length of stay and mortality. All tests of significance with *P*-values of <0.05 were considered significant.

RESULTS

Patient demographics:

During the study period, a total of 44 patients matched the inclusion criteria. Majority of the patients involved in this study were male (n=28, 63.6%, Table 1). The age of the 44 patients ranged from 20 to 84 y old with a mean age of 58.2±15.9 y. Out of these 44 patients, 38.6% (n=17) were elderly patients, aged 65 y old and above. Pneumonia occurred after 5.0±4.87 d of ICU stay with the majority of the patients diagnosed with HAP (59.1%) and VAP (40.9%). In this study, organisms were isolated from three different sites namely tracheal aspirate (65.9%), bronchoalveolar lavage (15.9%) and blood (18.2%). The mean time for availability of susceptibility result in this study was 3.36±0.917 d. The three most common microorganisms identified were *Klebsiella* spp. (28.8%), *Acinetobacter* spp. (28.8%) and *Pseudomonas* spp. (21.2%). *Acinetobacter* spp. and *Klebsiella* spp. were isolated with the highest proportion from the bronchoalveolar lavage compared to tracheal aspirate and blood (44.4% vs 30.3% vs 12.5% and 33.3% vs 30.3% vs 25%, respectively). On the other hand, *Pseudomonas aeruginosa* was the most common organism isolated from tracheal aspirate and blood samples (27.27 and 25%). During admission to the ICU, a number of patients were also diagnosed with other concomitant diseases. Analysis of treatment outcomes has shown that length of ICU stay and mortality with patient demographics demonstrated no significant findings when compared with age and gender.

TABLE 1: CHARACTERISTICS OF PATIENTS ADMITTED IN THE ICU FOR PNEUMONIA (N-44) DURING THE STUDY DURATION

Patient characteristics	No. of patients (n=44)	
	Survived (n=40) n (%)	Died (n=4) n (%)
Gender		
Male	25 (89.3)	3 (10.7)
Female	15 (93.75)	1 (6.25)
Age		
≤64	26 (96.3)	1 (3.7)
≥65	14 (82.4)	3 (17.6)
Appropriate initial antibiotic therapy		
At 24 h	21 (95.5)	1 (4.5)
Within 24-48 h	4 (66.7)	2 (33.3)
At >48 h	15 (93.75)	1 (6.25)
Concomitant disease		
Sepsis	16 (94.1)	1 (5.9)
Cancer	2 (50)	2 (50)
Cancer and sepsis	2 (66.7)	1 (33.3)
Non-cancer/-sepsis	20 (100)	0 (0)
Causative organsims		
Klebsiella spp.	11 (100)	0 (0)
Acinetobacter spp.	9 (90)	1 (10)
Pseudomonas spp.	9 (81.8)	2 (18.2)
Methicillin-resistant *Staph. aureus*	2 (66.7)	1 (33.3)
Others	4 (100)	0 (0)
Polymicrobial	5 (100)	0 (0)
Type of nosocomial pneumonia		
Hospital-acquired pneumonia (HAP)	23 (92)	2 (8)
Ventilator-acquired pneumonia (VAP)	17 (89.5)	2 (10.5)
Time of availability of susceptibility results		
≤3 days	25 (89.3)	3 (10.7)
≥3 days	15 (93.75)	1 (6.25)

HAP is hospital-acquired pneumonia, VAP is ventilator-associated pneumonia

Appropriate administration of antibiotics:

Appropriate antibiotics were given based on three different initiation time points as 24 h after a culture was obtained, 24 to 48 h and after 48 h. Approximately half of the patients (n=22) were given antibiotics within 24 h of a culture. A total of 13.6% (n=6) of patients were given antibiotics between 24 to 48 h after a culture was obtained. The remaining patients (n=16, 36.4%) received antibiotics more than 48 h after a culture was obtained. The lengths of ICU stay ranged from 1 to 52 d with the mean length of stay of 9.78±10.02 d (median; 7 d). Patients receiving appropriate antibiotics within 24 h after a culture was obtained had a significantly shorter length of ICU stay (5.62 d; $P<0.001$; Kruskal-Wallis test) compared to patients that received antibiotics between 24 to 48 h (9 d), and more than 48 h (15.8 d) after a culture was obtained.

The overall mortality rate in this study was 9.1% (n=4). From this, one patient received appropriate initial antibiotics within 24 h of obtaining a culture, two patients received antibiotics between 24 to 48 h after a culture was obtained, and the remaining one patient received appropriate antibiotics more than 48 h after a culture was obtained. Nevertheless, the

univariate logistic regression showed no significant difference in mortality rate between the three different initiation time points of appropriate initial antibiotic therapy after controlling other clinically significant mortality risk factors [$X^2(2)=3.553$; $P=0.169$].

Predictors of increased ICU stay:

Analysis of other predictors of ICU stay was tested (Table 2). Other variables included in this work were concomitant diseases, causative organisms for pneumonia, type of pneumonia that the subjects were diagnosed with, time of availability of susceptibility results and the demographic factors, namely age and gender. It was demonstrated that there was a significant difference in the length of stay in patients with concomitant disease ($P=0.038$) and time of availability of culture results ($P=0.008$).

A univariate linear regression analysis was carried out on these variables to determine independent predictors of increased ICU stay. Of the six predictors, only two were associated with an increase in ICU stay. The independent predictors of ICU stay were concomitant diseases ($F(1,38)=12.041$; $P=0.001$) and time of availability of culture results ($F(1,38)=9.967$; $P=0.003$). Concomitant diseases that were included for analysis on the length of ICU stay were sepsis ($F(1,38)=4.814$; $P=0.034$) and cancer ($F(1,38)=6.012$; $P=0.019$). No significant findings were demonstrated with other concomitant diseases such as cardiovascular ($F(1,38)=0.089$; $P=0.766$), diabetes ($F(1,38)=0.464$; $P=0.5$), asthma/COPD ($F(1,38)=0.335$; $P=0.566$), renal disease ($F(1,38)=0.089$; $P=0.766$) and liver disease ($F(1,38)=0.432$; $P=0.515$). The three variables, time of antibiotic administration, concomitant diseases and time of availability of culture results were then included in the multivariate model to evaluate their relationship with the length of ICU stay. The result demonstrated a significant impact of those variables on the length of ICU stay ($F(3,36)=13.129$; $P<0.001$). All three variables were found to be dependent predictors of length of ICU stay.

Predictors of mortality:

Predictors of mortality in ICU patients were also tested (Table 3). A univariate analysis identified concomitant diseases and its association with mortality in this group of patients ($X^2(3)=9.837$, $P=0.02$). Concomitant diseases tested for likelihood of ICU mortality were cancer ($X^2(1)=8.053$; $P=0.005$), sepsis ($X^2(1)=0.037$; $P=0.848$), cardiovascular ($X^2(1)=0.365$; $P=0.546$), diabetes ($X^2(1)=0.782$; $P=0.376$), asthma/COPD ($X^2(1)=0.999$; $P=0.318$), renal disease ($X^2(1)=3.499$; $P=0.061$) and liver disease ($X^2(1)=0.411$; $P=0.522$). In particular, cancer was found to be the most significant independent predictor of mortality with a 27-fold likelihood to cause mortality than in noncancerous patients (OR=27, CI=2.244–324.9). Both concomitant diseases and appropriate antibiotic administration were included in the multivariate model to evaluate their relationship with ICU mortality. The likelihood ratio of the multivariate logistic regression demonstrated a significant relationship between both variables on ICU mortality ($X^2(3)=10.335$, $P=0.016$). However, only concomitant disease (cancer) was a dependent predictor of ICU mortality ($X^2(1)=5.633$; $P=0.018$, Table 4).

DISCUSSION

Pneumonia is a common occurrence in the hospital setting. The risk of acquiring infection increases with the number of hospitalization d. In the Malaysian ICU setting, the rate of pneumonia has been previously reported to be approximately 18%[8]. This was similar to the finding of this present study, which reported an incidence rate of 19.4% attributed to pneumonia. The average length of ICU stay found in previous work was 10.0±4.85 d[8], which was also similar to current findings. Although age was not found to be related to an increase in ICU stay or mortality, complications

TABLE 2: UNIVARIATE AND MULTIVARIATE REGRESSION ANALYSIS ON THE INFLUENCE OF PREDICTORS ON THE LENGTH OF ICU STAY (*N*=44)

Predictors	Patient's outcome (length of ICU stay)							
	Linear regression (Univariate)				Multiple regression[a] (Multivariate)			
	F	*P* value	t	*P* value	F	*P* value	t	*P* value
Appropriate initial antibiotic therapy	11.314	0.002	3.364	0.002	13.129	<0.001	2.850	0.007
Concomitant disease[b]	12.041	0.001	3.470	0.001			3.716	0.001
Time of availability of susceptibility results	9.967	0.003	3.157	0.003			2.665	0.011

[a]Represents that only variables with values of p<0.05 were included in multivariate analysis, [b]refers to cancer and sepsis

TABLE 3: UNIVARIATE LOGISTIC REGRESSION OF VARIABLES INVOLVED IN PREDICTING THE LIKELIHOOD OF ICU MORTALITY (N=44)

Predictors	Patient's outcome (ICU mortality)		
	Odds ratio (95% CI)	Wald test	Likelihood ratio
Appropriate initial antibiotic therapy			
At 24 h	0.714 (0.041-12.347)	X^2 (2)=3.787	X^2 (2)=3.553
Within 24-48 h	7.5 (0.534-105.279)	*P*=0.151	*P*=0.169
At>48 h[a]	1.0		
Concomitant disease			
Sepsis	1×10^8	X^2 (3)=3.938	X^2 (3)=9.837
Cancer	1.6×10^9	*P*=0.268	*P*=0.02
Cancer and sepsis	8.1×10^8		
None[a]	1.0		
Cancer vs non-cancer	27 (2.244-324.9)	X^2 (1)=6.742	X^2 (1)=8.053
		P=0.009	*P*=0.005
Sepsis vs non-sepsis	1.222 (0.156-9.557)	X^2 (1)=0.037	X^2 (1)=0.037
		P=0.848	*P*=0.848

CI stands for confidence interval, [a]represents the reference category

TABLE 4: MULTIPLE LOGISTIC REGRESSION OF VARIABLES INVOLVED IN PREDICTING THE LIKELIHOOD OF ICU MORTALITY (N=44)

Predictors	Patient's outcome (ICU mortality)[a]		
	Odds ratio (95% CI)	Wald test	Likelihood ratio
Concomitant disease			
Cancer	25.601 (1.759-372.543)	X^2 (1)=5.633	X^2 (4)=11.670
Non-cancer[c]	1.0	*P*=0.018	*P*=0.016
Appropriate initial antibiotic therapy[b]			
At 24 h	0.614 (0.026-14.442)	X^2 (2)=2.180	
Within 24-48 h	6.1 (0.244-152.470)	*P*=0.336	
At>48 h[c]	1.0		

CI stands for confidence interval, [a]represents that only variables with values of p<0.05 were included in multivariate analysis, [b]this variable is included as it is a primary variable of interest in this study, [c]represents the reference category

can potentially lead to a downward trajectory of illness particularly in elderly patients[9]. Physiological and anatomical changes in the elderly may alter the patient's response to infection particularly due to a decline in cellular immune response and subsequently may lead to an increased morbidity and mortality[10]. However, the association between advanced age and the risk of mortality attributable to pneumonia was not demonstrated in this current work comparable to previous data[11].

Appropriate antibiotic treatment in patients diagnosed with pneumonia has been an important factor in patient management. Indeed, there was a significant increase in the length of ICU stay in patients who were delayed treatment with appropriate initial antibiotics for pneumonia infection. This is in line with previous work[12]. Secondary modifications of an initially failing antibiotic regimen do not substantially shorten length of stay for critically ill patients. Thus, the best approach that may be performed to reduce the length of ICU stay seems to be the initiation of an adequate and broad-spectrum initial antibiotic therapy which should be modified in a de-escalating strategy when the susceptibility results are available in order to avoid prolonged use of a broader spectrum antibiotic therapy[13]. One great concern about the widespread use of broad-spectrum empiric therapy in the ICU is the fear of the emergence of multidrug-resistant pathogens. However, if empiric therapy is administered in a timely manner by using highly effective agents that lead to rapid bacterial killing, the emergence of resistance could theoretically be minimized[14]. Besides a de-escalation approach, the optimisation of initial antibiotic therapy should also be stressed on. Through this approach, antibiotics selected should provide coverage of the key pathogens including resistant strain. Treatment should also be initiated in a timely manner using the correct dose, duration and route of administration to ensure sufficient antibiotic concentrations are achieved at the site of infection[14]. This may simultaneously reduce the risk of the development of resistance. In the current work, antibiotics were considered

appropriate when there was a susceptibility match, appropriate choice, dose, dosing interval and duration of therapy, parallel to an optimised approach.

The length of ICU stay was also significantly related to pneumonia patients with both cancer and sepsis compared to patients concomitantly diagnosed with sepsis or cancer alone. The length of ICU stay for patients with pneumonia, cancer and sepsis was almost three times higher than patients with pneumonia and sepsis alone, and five times higher than patients with pneumonia and cancer alone, similar to previous work[15]. Patients with cancer are prone to be linked with infection namely pneumonia and sepsis due to their immunocompromised condition and prolonged repeated contact to the hospital environment[15]. Cancer patients may be immunocompromised due to multiple factors such as chemotherapy, radiotherapy, impairment of normal leukocyte function or the use of corticosteroids. The causative organisms pertaining to cancer patient in this present work were *Pseudomonas* spp*., Acinetobacter* spp., MRSA and *Staphylococcus* spp. As these organisms are highly associated with resistance[13], the use of adequate and broader spectrum initial antibiotics in cancer patients is vital to prevent the emergence of multi-resistant strains.

The time a susceptibility result becomes available was another factor in increasing the length of ICU stay. Delay in receiving susceptibility results (more than 3 d) caused a significantly longer ICU stay. The rationale could be due to the continuing use of inappropriate initial antibiotic therapy following the delay in receiving susceptibility results, which consecutively leads to a longer duration of ICU stay. This further supports the need to ensure appropriate antibiotics are administered as soon as possible.

The rate of mortality was found to be significantly lower than previously reported[4]. Failure to initiate prompt appropriate and adequate therapy has been a consistent factor associated with increased mortality[4]. However, this study did not show any significant trend towards increased mortality in patients who were delayed treatment with initial antibiotic therapy. This is in line with previous work which utilized broad-spectrum empiric therapy for pneumonia with no negative effect on mortality[16]. Changing antibiotics once culture results are available may not reduce the excess risk of hospital mortality associated with inappropriate initial antibiotic therapy treatment[17]. Nonetheless, there have been conflicting results that show a reduction in mortality rate in patients who receive early appropriate antibiotic treatment[18]. It should however be noted that the selection of appropriate initial antibiotic therapy is vital in critically ill patients with pneumonia in order to reduce the length of ICU stay and hence reduce risks associated with prolonged hospitalization.

The predictor of mortality found in this study was cancer. Patients with cancer who require admission into the ICU is known to have an increased risk for serious infections[19]. A high mortality rate is demonstrated in cancer patient with pneumonia due to complications associated with initial respiratory failure[20]. In most instances highly resistant gram negative bacilli such as *Pseudomonas* spp. and *Acinetobacter* spp. as well as MRSA are the predominant microorganisms causing excess mortality in this group of patients[13].

The limitation of the study however was the small number of patients identified as having pneumonia with a positive culture in the ICU. Although generalization of results should be done cautiously, the significant findings provide an insight on the outcome of patients treated with antibiotics for HAP and VAP in the ICU setting. To the end, the present work was able to demonstrate the importance of administering appropriate antibiotic within 24 h of a culture. Predictors of length of ICU stay were found to be time of appropriate antibiotic treatment, concomitant diagnosis of cancer and sepsis, and availability of susceptibility tests. More importantly is the urgency in providing appropriate treatment in patients with pneumonia and cancer in order to reduce the risk of mortality.

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There are no conflicts of interest.

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