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Research Article

ANTIMICROBIAL THERAPY IN CRITICALLY ILL PATIENTS WITH NOSOCOMIAL INFECTIONS

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ABSTRACT

Nosocomial infections in critically ill patients are associated with higher risk of mortality. Effective antimicrobial treatment is important to ensure a better overall outcome for the patients. This study evaluated the effect of initial antimicrobial therapy on the outcome of critically ill patients with nosocomial pneumonia and bloodstream infections. Data was collected retrospectively from patients who were admitted in 2007 in an intensive care unit (ICU) of a tertiary care Malaysian hospital. The mean age of the study cohort was 50.8 ± 21.8 years. The subjects had either nosocomial pneumonia (72%) or bloodstream infections (28%). Three common microorganisms isolated from the tracheal aspirate and blood samples were *Acinetobacter spp*., *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Appropriate initial antimicrobial agents were given to 60% of the subjects. Advanced age was associated with the less desirable treatment outcomes ($p < 0.05$). The percentage of subjects who survived from nosocomial pneumonia and nosocomial bloodstream infections was 65.1% and 41.7%, respectively. Overall, the survival rate was higher in patients who received appropriate initial antimicrobial therapy (97% *versus* 50%; $p < 0.001$). The results support the need for early appropriate antimicrobial treatment in critically ill patients with nosocomial infections.

Keywords: Antimicrobials, Nosocomial, Critical care

INTRODUCTION

Nosocomial infections are frequently documented in patients who are critically ill[1]. Throughout the Asian region, the 4 to 43% of infection cases are nosocomial infections[2]. The majority of these patients developed either nosocomial pneumonia or bloodstream infections. In the intensive care units (ICUs), these infections are commonly caused by aerobic gram-negative organisms such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebseilla pneumonia*, and *Acinetobacter spp*., and gram-positive cocci bacteria such as *Staphylococcus aureus*[3]. Invasive medical device usage, patient clinical conditions and the ward environment affect the risk for nosocomial infections[4]. The level of influence of these factors may vary from ICU to ICU. Therefore, each intensive care setting may have a specific microbiology pattern and may require individualised antimicrobial treatment guidelines.

In practice, empirical therapy of antimicrobial agent is started as early as possible when a critically ill patient shows evidence of infection. It is important for this patient to receive an appropriate antimicrobial agent as early as possible to avoid an adverse outcome. Studies from the United State have demonstrated that appropriate choice of antimicrobial agent in empirical therapy significantly reduced infection-related mortality and hospital stay[5,6]. Improper usage of antimicrobial agents is believed to be associated with bacterial resistance to antimicrobial agent[3] and the emergence of antimicrobial resistance has been suggested to be one of the important variables that influence patients' treatment outcome[7]. The percentage of inappropriate empirical antimicrobial therapy was reported at 43.7%[8].

Choice of antimicrobial agent for empirical therapy is commonly based on local or international antibiotic guidelines, and the physician's experience. However, the efficacy of an antimicrobial agent can vary, as it can be affected by local infection and antimicrobial resistance patterns[7]. A correct choice of antimicrobial agent at the initial stage of treatment is vital to prevent delays in resolution of the infection and to improve patient's overall outcome. This study was conducted to evaluate the outcome of antimicrobial therapy in critically ill patients with nosocomial infections and its relationship with appropriate use of antimicrobial agents.

METHODS

This retrospective study was conducted in the 12-bed ICU of a tertiary hospital located on the North East of Peninsular Malaysia. Patients admitted to the unit in 2007 were identified from the admission book and the demographic profile of the selected patient, such as age and gender were collected as well as type of infection, treatment and the outcome.

The approval to conduct this study was obtained from the Ministry of Health Malaysia (Registration ID: NMRR-08-716-1871).

For the purpose of this study, nosocomial infection was defined as infections that occur after 48 hours admission to the ICU. The types of nosocomial infections that were selected only include pneumonia and bloodstream infections. Both types of infections were chosen based on their significant effect on patient mortality risk[9].

Antimicrobial therapy was defined as appropriate when the prescribed antimicrobial agent was in agreement with the results of antimicrobial sensitivity test. This definition includes antimicrobial agents that were initially selected empirically but later supported by the antimicrobial sensitivity tests. On the other hand, antimicrobial therapy was defined as inappropriate when the antimicrobial agent used in the empirical therapy was not supported by the antimicrobial sensitivity results and thus there is usually a delay in the use of appropriate antimicrobial agent. The outcome of treatment was either survival or mortality. Survival meant that the patient's nosocomial infection achieved resolution based on clinical evidence such as negative culture results, afebrile, normalization of the white-cell count and no other signs and symptoms of infection, or being discharged from the ICU. Mortality meant that the patient died in the ICU due to either the infection itself or its complications. Clinical problems of the physiological system were described as being present when the related laboratory results showed 2-fold or more increase or decrease from the normal range. Severity of each patient condition was evaluated using the organ dysfunction and infection (ODIN) score[10].

Appropriate contingency table test (X^2 test or Fisher's Exact test) at a confidence interval of 95% was used to evaluate the association between variables and outcome. A $p < 0.05$ was considered significant.

RESULTS

The mean age of the 55-strong study cohort was 50.8 ± 21.8 years and 29.1% of the subjects were more than 65-year old. Majority (67.3%) of the subjects were male. Most of the subjects (72%) had nosocomial pneumonia and the rest (28%) had nosocomial bloodstream infections. The bloodstream infections include bacteremia and septicaemia. The 3 most common microorganisms isolated from the tracheal aspirate and blood samples were *Acinetobacter spp*. (46.5% and 8.3%, respectively), *Pseudomonas aeruginosa* (23.3% and 8.3%, respectively) and multiresistant staphylococci (18.6% and 54.4%, respectively). Overall, the most common antibiotics prescribed were cefepime (34.5%) and meropenem (20%). The nosocomial infections occurred after 9.4 ±

7.8 days of the ICU stay. On the day the nosocomial infection was diagnosed, a number of the subjects also experienced other clinical problems or organ dysfunctions as shown in Table 1. The average ODIN score for patients who received appropriate (43.1%) and inappropriate antimicrobial (53.6%) was not significantly different ($p<0.05$) Appropriate antimicrobial agents were given to 78% of the subjects. Mortality was 21.8% among the subjects with nosocomial infections.

Table 1 shows the percentage of patients with concomitant physiological or clinical problems at the time nosocomial infection was diagnosed

Problem associated with	Number of subjects (% from 55 patients)
Cardiovascular function	29 (52.7)
Respiratory function	55 (100)
Renal function	26 (47.2)
Haematological system	15 (27.3)
Neurological function	7 (12.7)
Liver function	3 (5.4)

Analysis of patients' demographic factors and treatment outcome showed that subjects aged less than 65 years old (72.5%) had a better outcome as compared to more advanced aged group (26.7%; $p < 0.05$). There was no difference in survival rates between the genders ($p > 0.05$). The percentage of subjects who survived nosocomial pneumonia and nosocomial bloodstream infections was 65.1% and 41.7%, respectively ($p > 0.05$). The overall percentage of subjects who survived from nosocomial infections was 78.2%. A significant association was observed between appropriateness of antimicrobial agent given to the subjects and the overall outcomes ($p < 0.001$; Table 2).

Table 2 shows the association between appropriateness of initial antimicrobial agent and the patient overall outcome

Antimicrobial choice for initial therapy	Patient's Outcome	
	Survival, n (%)	*Mortality, n (%)*
Appropriate	32 (97.0))	1 (3.0)
Inappropriate	11 (50.0)	11 (50.0)

* Fisher's Exact Test, $p < 0.001$.

DISCUSSION

The association between age and the risk of developing nosocomial infection was demonstrated in this study cohort also as in previously published data[11]. It is believed that patients with advanced age have an impaired immune systems and prone to multiple organ failure. In the intensive care setting, the usage of intravenous drug delivery and use of ventilators further increase the risk of infection. All of these factors exposed the patients to be infected by the microorganisms from the hospital environment. Nosocomial infection in elderly patients also increases the risk of mortality in intensive care[11]. Nevertheless, mortality in critically ill patients is usual associated with the severe complications of infection such as respiratory failure and shock. Physiological system malfunction has also been identified as an important factor contributed to higher mortality rates, for example, failure of the hepatic, hematologic and renal systems[12]. However, the current study did not evaluate the effect of these factors on the patients' outcome.

The prevalence of nosocomial pneumonia and bloodstream infections detected in this study was comparable with previously published local data[13]. Although bloodstream infections represent a smaller percentage of nosocomial infections, they were associated with a higher risk of mortality particularly in critically ill patients[9]. Additionally, the incidence of nosocomial bloodstream infections is increasingly associated with multiresistant organisms such as staphylococci, *Acinetobacter spp.*, *Pseudomonas aeruginosa* and candida[9,14,15]. The indiscriminate use of antimicrobials and excessively long duration of antimicrobial treatments can lead to the emergence of multiresistant microorganisms[3]. As such, choosing a correct antimicrobial agent is vital in reducing the risk of the development of resistance.

Empirical therapy is defined as an antimicrobial treatment received by the patient before culture and antibiotic susceptibility testing results are available[16]. Commonly, the choice of antimicrobial agent for this type of therapy will be based on previous microbiology culture patterns and the physicians' experience. Thus, the antimicrobial compound used may include a narrow spectrum agent. It has been suggested that to ensure optimal coverage of potentially high resistant bacteria, broad spectrum antimicrobial agents to be used in the treatment of nosocomial infections[17]. The major drawback of broad spectrum antimicrobial agents is their cost. In addition, no one broad spectrum antimicrobial agent can effectively cover all microorganisms that are known to be involved in nosocomial infections. Thus, comprehensive evaluation of the patient's nosocomial infection should be carried-out to ensure appropriate choice of antimicrobial agent.

In this study, majority of patients (60%) has received appropriate initial antimicrobial treatment. Consequently, most of the patients survived from the infection. A higher survival rate with appropriate antimicrobial treatment was also demonstrated in cases of ventilator-related pneumonia and bacteraemia[5,18]. In this study, for a number of patients, the empirical therapy was found to be inappropriate due to the presence of antimicrobial-resistant. In actual practice, this resulted in delay in the initiation of appropriate antimicrobial agent by up to 4 days as the culture and sensitivity test results are only obtained 2 to 3 days after microbiological sampling. Previously, Kang et al. reported a mean duration of delay in starting effective antimicrobial agent around 3.5 days (19)[19]. It has been estimated that delay in receiving appropriate antimicrobial agent for as little as 24 hours is associated with a higher risk of mortality[20]. Early initiation of appropriate antimicrobial therapy is thus vital.

The retrospective nature of the data collection and 1-year duration studied may have affected the sample size. In addition to this, a study from a single centre may limit generalisation of the findings. Nevertheless, the current study results were similar to previously published data from different geographical region, which together support the need for appropriate initial antimicrobial treatment in critically ill patients with nosocomial infections. These findings also indirectly suggest the importance of complete clinical and laboratory investigation results, which will be useful in the initiation of empirical antimicrobial therapy.

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