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Original Article

Microbiology Section

Role of Appropriate Therapy in Combating Mortality among the Ventilated Patients

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ABSTRACT

Context: Ventilator associated pneumonia (VAP) is a nosocomial infection prevalent among the intensive care unit (ICU) patients despite proper infection control practices. The diagnosis of VAP still remains controversial and hence the mortality rate is higher among this group of patients.

Aim: The aim of our study was to identify the antibiotic pattern and the appropriateness of treatment followed in the ICU in relation with the clinical pulmonary infection score (CPIS) as a tool to diagnose VAP. This was compared with patients who had an inappropriate treatment in comparison to the CPIS and the clinical outcome.

Results: Out of the 18 VAP patients, 12 (66.7%) received appropriate therapy based on the antibiotic susceptibility pattern of the causative organism, while 1 (5.5%) received partially inappropriate therapy and 5 (27.8%) received totally inappropriate therapy. Nine of the 18 (50%) VAP patients died, while only 5 of the 58 (8.6%) patients without VAP died. 72.2% patients with VAP received appropriate treatment based on the sensitivity of the isolates. The mortality rate in VAP patients receiving inappropriate therapy was 80%, while in those receiving appropriate therapy the mortality rate was 38.5%. The mortality rate among VAP patients with blood culture positivity was 100%, while it was 43.75% among those with negative blood culture.

Conclusion: The mortality rate among the patients receiving inappropriate therapy is high compared to other group of patients. Hence, a proper evaluation and administration of appropriate antibiotics can curb mortality among the ventilated patients.

Keywords: APACHE (acute physiology and chronic health evaluation) II scores, Clinical pulmonary infection score, Endotracheal aspirate, Ventilator associated pneumonia

INTRODUCTION

Ventilator associated Pneumonia (VAP) is a nosocomial infection prevalent among the intensive care unit (ICU) patients despite proper infection control practices [1]. The diagnosis of VAP still remains controversial and hence the mortality rate is higher among this group of patients [2]. The mortality rate ranges from 24-71% [3]. The mortality rate may increase in case of specific pathogens [1]. The common etiological agents isolated from these patients are multidrug resistant and thereby the treatment is cumbersome [4]. Out of factors which determine the outcome of treatment, empirical therapy plays a major role [1]. Though a routine surveillance can predict the organisms and their antibiogram, this approach is not valid for initial antibiotic therapy [5]. There are other factors such as duration of antibiotic treatment which can also alter the treatment outcome. It is shown in a study that early treatment with antibiotics for 3 days with Clinical Pulmonary Infection Score (CPIS) less than six had a better outcome [6]. But empirical treatment with broad spectrum antibiotics can lead to the development of multi drug resistant pathogens. Hence, the choice of antibiotic and its duration remains controversial. The aim of our study was to identify the antibiotic pattern and the appropriateness of treatment followed in the ICU in relation with the CPIS as a tool to diagnose VAP. This was compared with patients who had an inappropriate treatment in comparison to the CPIS and the clinical outcome.

MATERIALS AND METHODS

Study Design

This was a prospective study conducted over a period of 20 months from 2009 to 2011 at Mahatma Ghandi Medical College and Research Institute. Around 76 patients who were mechanically ventilated in the critical care unit were evaluated. All patients who developed VAP were included in the study. The VAP patients were evaluated for their treatment, outcome and mortality. Our study included critically ill patients with both surgical and medical conditions. Proper aseptic precautions were followed while handling the patients as per the hospital infection control guidelines.The study was approved by our institutional ethical committee and informed consent was obtained from patient's relative.

Data Collection

The name, age, sex, provisional diagnosis, date of admission to the hospital and the duration of mechanical ventilation were noted. The patients were followed up for the empirical treatment given and their antibiogram. The change of the antibiotics, following the antibiogram result of the isolated organism, was noted. The patients were followed up till death or discharge from the ICU.

Diagnostic Criteria

VAP was diagnosed in patients fulfilling both the clinical and microbiological criteria. The clinical diagnosis of VAP was made using the modified CPIS [7].

Sample Processing

On clean grease free glass slide, smear was prepared from endotracheal aspirate (EA) and was air dried. It was heat fixed and Gram's staining was done [8]. A loopful of EA was inoculated on 5% sheep blood agar and MacConkey agar and a qualitative culture was done [8]. EA was serially diluted in sterile normal saline as 1/10, 1/100, 1/1000 and 0.01 ml of 1/1000 dilution was inoculated on 5% sheep blood agar and quantitative culture was done. If it was more than 10^5 CFU/ ml it was taken as positive [9].

Blood Culture

Five to ten ml of blood, from patients with suspected VAP, was collected in 50 ml brain heart infusion (BHI) broth and sub-cultured on

blood agar and Mac Conkey after 24 h, 48 h and 1 week of aerobic incubation [8]. The organisms isolated from the clinical specimens were identified based on standard bacteriological procedures [8]. The patients fulfilling both the clinical and microbiological criteria were diagnosed to be suffering from VAP. **Clinical criteria:** Modified CPIS>6 **Microbiological criteria:** Positive Gram stain (>10 Polymorphonuclear cells/ high power field and ≥ 1 bacteria/ oil immersion field) and quantitative EA culture showing ≥ 10^5 CFU/ ml. The patients who were on prior antibiotics were excluded from the study. The patients were monitored from the day of mechanical ventilation. The antibiotics given to the patients were noted. The CPIS was calculated from the day of mechanical ventilation. They were followed for the change in antibiotics in relation with the CPIS. The patients were monitored till death or disconnecting the mechanical ventilation.

The patients who received antibiotics based on the antibiogram of all the pathogens were termed as appropriate therapy. Those patients who were not covered with antibiotics for one pathogen were termed as partially appropriate therapy. Those who were not covered with antibiotics for any of the pathogen based on their antibiogram result or received a delayed treatment were termed as inappropriate therapy.

The physicians were intimated with the antibiogram result based on the EA culture. They followed American thoracic society strategy or surveillance report and the knowledge of local organisms and their antibiogram.

Statistical Analysis

Results were expressed as mean± SD. The chi-square test or Fisher's exact test was used to compare patients without VAP to patients with VAP. Univariate analysis was used to compare the variables for the outcome groups of interest (patients with VAP vs patients without VAP). Comparisons were unpaired and all tests of significance were 2-tailed. Continuous variables were compared using Student's t-test for normally distributed variables. We confirmed the results of these tests, with logistic regression analysis, using statistics software (SPSS 16.0, SPSS Inc, Chicago, Illinois). This was necessary to avoid producing spuriously significant results with multiple comparisons. A stepwise approach was used for entering new terms into the model, with 0.05 as the limit for their acceptance or removal. Results of the logistic regression analyses are reported as estimated odd ratios with their 95% confidence intervals. Values were expressed as mean ± SD for continuous variables or as a percentage of the group they were derived from (categorical variables).

RESULTS

Around 18 of our patients developed VAP. Out of the 18 VAP patients, 12 (66.7%) received appropriate therapy based on the antibiotic susceptibility pattern of the causative organism, while 1 (5.5%) received partially inappropriate therapy and 5 (27.8%) received totally inappropriate therapy [Table/Fig-1]. Around 50% VAP patients died, while only 8.6% patients without VAP died [Table/Fig-2]. In this study, 72.2% patients with VAP received appropriate treatment based on the sensitivity of the isolates. The mortality rate in VAP patients receiving inappropriate therapy was higher, while in those receiving appropriate therapy the mortality rate was less [Table/Fig-2]. Blood culture was positive in one patient with *Pseudomonas aeruginosa* infection and other with *Burkholderia pseudomallei* infection. Both these patients died. The mortality rate among VAP patients with blood culture positivity is shown in [Table/Fig-3].

DISCUSSION

VAP is a type of nosocomial infection acquired in the ICU. Among 76 patients there were 18 patients diagnosed as VAP. Most of the organisms isolated were Gram negative. The patients had both monomicrobial and polymicrobial infection. In the current study, of the 18 patients with VAP, 50% patients died, while among the remaining 58 patients without VAP only 8.6% patients died. This difference was statistically significant (p-value 0.0004). This denotes that the mortality rate is high among this group of patients. Similar Indian study has also reported a mortality rate of 46.67%

Patient No.	Quantitative culture	Resistance Pattern	Sensitivity Pattern	Antibiotics Given	Treatment	Response
3	*Pseudomonas aeruginosa*	-	Nt, Ac, Cf, I, Ca, Ak, G	Va, Me, Ci	Appropriate	Died
24	*Klebsiella pneumoniae*	Ac, Cf, Ca, Ak, G	Nt, Pt, I	Pt, Ak, Cf, Me	Appropriate	Recovered
35	*Pseudomonas aeruginosa*	-	Nt, Ac, Cf, I, Ca, Ak, G, Pt	Pt	Appropriate	Died
36	*Pseudomonas aeruginosa*	Ac	Nt, Cf, I, Ca, Ak, G, Pt	Ce	Appropriate	Recovered
38	*1) Klebsiella pneumoniae* *2) Proteus mirabilis*	Ac, Ca -	Nt, Cf, I, Ak, G, Pt Nt, Ac, Cf, I, Ca, Ak, G, Pt	Ce, Me, Cf	Appropriate	Recovered
39	*Burkholderia pseudomallei*	Ca, Ak, G	Nt, Ac, Cf, I, Pt	Ca, Va, Me, Cd, M (D3)	Appropriate (Delayed)	Died
40	*Candida albicans*	-	-	Ca, Cd	Inappropriate	Died
48	*Klebsiella pneumoniae*	Ac, Ca, G	Nt, Cf, I, Ak, Pt	Ce, Me, Cf, Ak	Appropriate	Died
50	*Escherichia coli*	Cf, Ca, Ak, G	Nt, Ac, I, Pt	Ak, Cs, Va, Cz	Appropriate	Recovered
53	*Pseudomonas aeruginosa*	Ac	Nt, Cf, I, Ca, Ak, G, Pt	Cd, Ac	Inappropriate	Died
57	*1) Pseudomonas aeruginosa* *2) Klebsiella pneumoniae*	Nt, Cf, Ca, Ak, G Ac, Ca, Ak	Ac, Pt, I Nt, Cf, I, G, Pt	CS, Pt, Me	Appropriate	Died
58	*1) Escherichia coli* *2) Pseudomonas aeruginosa*	Ac, Ca Ac, Ca, Ak	Nt, Cf, I, Ak, G, Pt Nt, Cf, I, G, Pt	Ce, Me, G	Appropriate	Recovered
59	*1) Pseudomonas aeruginosa* *2) Klebsiella pneumoniae*	- Ac, Ca	Nt, Ac, Cf, I, Ca, Ak, G, Pt Nt, Cf, I, Ak, G, Pt	Me, Pt	Appropriate	Died
62	*Candida albicans*	-	-	Ce	Inappropriate	Died
63	*Staphylococcus aureus*	-	Ac, Cf, G, Cd, Va, E, Ox	Va, Cs	Appropriate	Recovered
64	*Staphylococcus aureus*	-	Ac, Cf, G, Cd, Va, E, Ox	Ce	Appropriate	Recovered
68	*Stenotrophomonas maltophilia*	I	Nt, Ac, Cf, Ca, Ak, G, Pt	Cs	Appropriate	Recovered
70	*1) Acinetobacter baumannii* *2) Pseudomonas aeruginosa* *3) Citrobacter koseri*	Ac Ac, Cf, Ca, Ak, G Ac	Nt, Cf, I, Ca, Ak, G, Pt Nt, I, Pt Nt, Cf, I, Ca, Ak, G, Pt	Ci, Ak	Partially inappropriate	Recovered

[Table/Fig-1]: Treatment of the VAP cases in relation to the antibiotic susceptibilities of the isolates
Ak - amikacin, Ac – amoxicillin-clavulanic acid, Ca – ceftazidime, Cf – ciprofloxacin, G – gentamicin, M – meropenem, Pt – pipercillin-tazobactam, Me – metronidazole, Ox – oxacillin, E – erythromycin, Ce – cefotaxime, Cs – cefoperazone-sulbactam, Nt – Netilmicin, I – Imipenem, Ci – Ceftriaxone, Va – Vancomycin

Parameter	Died	Alive	p-value
VAP	9 (50%)	9 (50%)	0.0004
Non-VAP	5 (8.6%)	53 (91.4%)	
Inappropriate therapy among VAP	4 (80%)	1(38.5%)	0.2941
Appropriate therapy among VAP	5(38.5%)	8(61.5%)	

[Table/Fig-2]: Outcome of patients with VAP receiving appropriate and inappropriate therapy

Parameter	Outcome		Total	p-value
	Died	Recovered		
Blood culture positive	2 (100%)	0	2	0.4706
Blood culture negative	7 (43.75%)	9	16	
Total	9	9	18	

[Table/Fig-3]: Effect of blood culture positivity on the outcome

among patients with VAP [10]. VAP is an important infection which increases the mortality among the critically ill patients. In addition to the primary illness VAP increases the mortality among the ventilated patients in the ICU. Moreover, mortality in VAP patients is generally the consequence of a complex interaction between the adequacy of host defence, virulence of the pathogen, and adequacy of antibiotic therapy. However, in a similar study bacteraemia, compromised immune system, higher APACHE (acute physiology and chronic health evaluation) II scores, and older age were identified as independent predictors of hospital mortality among VAP patients [11]. The treatment outcome of VAP is based on various factors. It includes lack of proper diagnostic criteria for VAP, the inability to differentiate colonization from infection and the lack of proper sampling method to isolate the organism [1]. In addition to this most of the strains isolated in the ICU are resistant. In order to curb this antibiotic resistance rotational antibiotic therapy and empirical therapy is mandatory [2]. Though most of the ICU settings follow empirical treatment, it has to be altered based on the sensitivity pattern at the earliest without time delay [12]. If the initial treatment misses out the pathogens, mortality rate in these patients who receive inappropriate therapy increases [12]. The duration of antibiotics can also alter the course of treatment. A short course of seven days therapy is associated with reduction in multidrug resistant pathogen and the duration of antibiotics except for non-fermenting Gram negative bacilli [13]. In our study the mortality rate in VAP patients receiving inappropriate therapy was 80%, while in those receiving appropriate therapy the mortality rate was 38.5% respectively. This clearly denotes that adequate treatment is an important prognostic factor for VAP.This is comparable to a similar study which shows that the mortality rate was 29.2%, for adequate therapy whereas it was 63.5% for those receiving inadequate therapy [6]. A retrospective study conducted in Turkey states that mortality among VAP patients with adequate therapy was 72.7% and those with inadequate therapy was 65.1%. But this difference was not statistically significant [14]. The mortality among these patients who received appropriate therapy could be due to other co- morbid conditions, late instillation of these antibiotics or the nature of the organism the patient harboured.

CONCLUSION

Ventilator associated pneumonia is a type of nosocomial pneumonia which is associated with increased mortality. An appropriate therapy based on the early ET aspirate report can reduce the mortality and cost in managing this group of patients.

The mortality rate associated with the critically ill patients receiving inappropriate therapy is high. Hence, knowledge of appropriate therapy and early administration of antibiotics based on antibiogram can reduce mortality among the ventilated patients. Though our study showed higher mortality rate, it has limitations that it was conducted in a single centre. We have not analysed the risk factors which are associated with inappropriate therapy among the ventilated patients. A multi-centered study involving risk factors associated with inappropriate therapy among these patients will enlighten our knowledge to curb the mortality among these patients.

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