Tanaffos (2010) 9(1), 21-27

Ventilator-Associated Pneumonia: Evaluation of Etiology, Microbiology and Resistance Patterns in a Tertiary Respiratory Center

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ABSTRACT

Background: *Ventilator-associated pneumonia (VAP) has been reported as the most common hospital-acquired infection among patients requiring mechanical ventilation. This study aimed to determine the incidence of ventilator-associated pneumonia in a cardiopulmonary tertiary center, and to evaluate its etiology, resistance patterns, and outcome of admitted patients.*

Materials and Methods: *In a retrospective study, patients admitted to the Masih Daneshvari Hospital, a tertiary cardiopulmonary center, were evaluated in a 7-month period. A total of 530 patients were admitted to the ICU out of which, 40 acquired VAP. Overall, 99 patients were evaluated (male= 57, female= 42) including 40 VAP and 59 non-VAP cases. The incidence of VAP was estimated to be 7.5% in this unit. The underlying conditions included respiratory diseases (COPD, asthma, etc), and cardiac problems (post "coronary artery bypass graft" CABG, etc). Also, patients in the thoracic surgery ward and those with renal, gastrointestinal, neurologic and other medical problems were evaluated. The patients were divided into two groups of VAP and non-VAP cases. The micro-organisms were recovered from the patients' bronchoalveolar lavage fluid.*

Results: *The most common micro-organisms recovered were Pseudomonas aeruginosa (17 cases) and Staph. aureus species (15 cases). In VAP patients in whom S. aureus was recovered, 80 percent of species were methicillin-resistant (MRSA) but all were sensitive to Vancomycin. Moreover, resistance to two, three or four antibiotics was seen in 12, 10, and 5 patients, respectively, in whom P. aeruginosa was recovered. The prevalence of S. aureus in patients with respiratory problems was more than other groups (including MRSA species). But the prevalence of recovered P. aeruginosa was the lowest in respiratory patients, compared to other groups. Also the mortality rate in drug resistant S. aureus and P. aeruginosa groups were 42 and 47 percent, respectively. Length of stay for MRSA group was 80% and death rate was 50%. In P. aeruginosa group, there was a positive relationship between resistance to multiple drugs and mortality and also ICU stay.*

Conclusion: *VAP is a common infection in ICU setting and certain interventions may affect its incidence. In our study, P. aeruginosa and S. aureus were more common in ICU patients. Pseudomonas species were associated with the highest mortality rate and were resistant to four antibiotics in the antibiogram testing. S. aureus species were more common in patients with underlying respiratory problems, compared to those with other conditions.* ***(Tanaffos 2010; 9(1): 21-27)***

Key words: *Ventilated-associated pneumonia (VAP), Micro-organisms, Drug-resistance pattern*

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Received: 10 March 2009
Accepted: 30 September 2009

INTRODUCTION

Mechanical ventilation is commonly used as a respiratory support device in modern intensive care units (ICUs) nowadays. Regardless of different underlying conditions, most ICUs have more than one third of their patients on mechanical ventilation every day.

Ventilator-associated pneumonia (VAP) is the most common and important complication in nearly 20% of patients requiring mechanical ventilation in the ICU (1-3). On average, a patient under mechanical ventilation has a 1% chance per day of acquiring VAP during his/ her ICU stay. VAP is among the infections that occur after the first 48 hours of the initiation of mechanical ventilation (4).VAP risk factors include the duration of mechanical ventilation(>48 hours), length of ICU stay, severity of the underlying condition and other organ failures (5). Patients who acquire VAP have a longer ICU stay with higher morbidity and mortality rates of about 15-50%, and more infectious agents are usually involved (6-10).

Increased mortality rate in VAP patients is associated with bacteremia, especially with *Pseudomonas aeruginosa* or Acinetobacter species, medical rather than surgical illness, and ineffective antibiotic therapy (11). The clinical pulmonary infection score (CPIS) is a description to lead us to clinical VAP diagnosis. It includes some criteria to show the severity of pneumonia (12). The clinical evaluation is generally based on the presence of a new radiographic infiltrate, fever, blood leukocytosis, or leukopenia and purulent tracheal secretions (13).

Other studies have demonstrated that relying on the endotracheal aspiration result alone often results in mismatching in classification of VAP (14,15).

Another study tried to compare the results of quantitative culture of bronchoalveolar-lavage fluid and endotracheal aspiration and found more certain diagnoses, less antibiotic prescriptions, and decreased mortality rates (16).

This study aimed to determine the incidence of ventilator-associated pneumonia in a cardio-pulmonary tertiary center, its risk factors and underlying condition of admitted patients, and also to establish an association between acquired species, their anti-microbial resistance pattern and the above mentioned variables.

MATERIALS AND METHODS

A retrospective case-control study was conducted to estimate the incidence of VAP, identify its risk factors, and also to ascertain the relationship between patients' outcome and the type of cultured species and their antimicrobial resistance pattern. This study was performed on patients who were admitted to the Intensive Care Unit of Masih-Daneshvari Hospital between September 2006 and March 2007.

We studied 99 cases with respiratory (COPD, asthma, etc), and cardiac underlying diseases (post CABG, etc), patients in the thoracic surgery ward and those with renal, gastrointestinal, neurologic and other medical problems. We divided patients into case group (n=40) and control group (n=59) which included VAP and non-VAP patients, respectively. VAP cases were defined as patients with hospital-acquired pneumonia diagnoses occurring>24 h following intubation (based on ATS/IDSA criteria for diagnosis of nosocomial pneumonia) (11).The presence of pneumonia was defined as a new lung infiltrate plus clinical signs that the infiltrate was infectious in origin. These clinical evidences included fever greater than 38 ˚C, leukocytosis (WBC count greater than $11.0x10^3$) or leukopenia (leukocyte count less than 3,500 per cubic milliliter), purulent endotracheal secretions, recovery of potentially pathogenic bacteria from endotracheal aspirate, and increasing oxygen requirements (17). Control subjects consisted of patients who did not have clinical and microbiologic criteria for VAP diagnosis according to ATS/ IDSA criteria. The exclusion criteria were age under 18 years old,

underlying malignancy or immunosuppression, and patients with positive HIV tests.

To evaluate outcomes of VAP, cases were matched with at least one control subject based on these variables: duration of mechanical ventilation (control subjects had to be intubated for at least as long as cases prior to the onset of VAP), and type of hospital admission (medical [including respiratory and other medical conditions], surgical, and cardiac).

We collected patients' data including gender, age and duration of hospital stay. Also, clinical pulmonary infection score (CPIS) was used to detect VAP group in clinical setting. Criteria for diagnosis of ventilator-associated pneumonia were compatible with ATS/IDSA 2005 guidelines (11). For each patient, bronchial washings were taken and the accumulated fluid was sent for microbiologic analysis to find out the frequency of offending organisms. Finally, the patients were evaluated during their ICU stay and number of discharged patients as well as number of those who passed away was reported.

RESULTS

Ninety nine patients were studied in the intensive care unit of Masih Daneshvari Hospital. Statistical analysis was performed using SPSS version 16.0 software. From a total of 99 cases, 40(40%) were diagnosed as VAP .We divided our patients into two groups: VAP and non-VAP (Table1). The mean age of patients was 55.68±20.25 yrs. in cases and 52.68±21.68 yrs. in controls which showed no significant difference between the two groups ($p>5.0$).

Among our patients, 22(55%) of cases were females and 18(45%) were males. Among controls, there were 20(33.9%) females and 39(66.1%) males ($p<0.05$).

Table 1. Demographic findings of the patients

Characteristics	VAP(40)	Non-VAP(59)	Total (99)
Age-Yr	55.68±20.25	52.68±21.68	53.99±2.14
Male sex-number of patients (%)	18(45%)	39(66.1%)	57(59.6%)
Female sex-number of patients (%)	22(52.4%)	20(33.9%)	42(40.4%)

We measured PaO_2/FIO_2 in both case and control groups. The relationship between underlying diseases and VAP is shown in table 2. We discovered a significant correlation between VAP and gasterointestinal disorders ($p<0.05$).

Table 2. Correlation of underlying diseases and VAP

Underlying diseases	VAP	Non-VAP	P Value	Odds ratio(95% CI)
Tracheal stenosis	7(17.5%)	4(6.8%)	0.096	2.971 (0.724-0.793)
COPD *	1(5.2%)	8(13.6%)	0.060	0.163(0.020-1.362)
Chronic pulmonary infection	0	1(1.7%)	0.408	1.017(0.984-1.025)
Sepsis	6(15%)	4(6.8%)	0.183	2.426(0.638-9.225)
Trauma	6(15%)	3(5.1%)	0.092	3.294(0.773-14.042)
Post operation	1(2.5%)	3(5.1%)	0.522	0.497(0.048-4.773)
Cardio-vascular disease	10(25%)	16(27.2%)	0.814	0.896(0.358-2.242)
Neurological disorders	4(10%)	7(11.9%)	0.772	0.825(0.225_3.028)
Gasterointestinal disorders	7(17.5%)	0	0.024	1.135(1.033-1.246)
Renal disorders	1(2.5%)	7(11.9%)	0.093	0.19(0.022-1.613)
CABG **	3(7.5%)	2(3.4%)	0.359	2.311(0.368-14.494)

* Chronic Obstructive Pulmonary Disease

** Coronary artery bypass graft

Length of ICU stay, extracted from available patients` registry revealed that 82.5% of cases and 59.3% of controls had prolonged ICU stay for more than seven days. Also, there was a history of ICU or ward admission within 90 days in 44(44.4%) patients including 23(57.5%) of VAP and 21(36.2%) of non-VAP groups ($p < 0.05$).

Mortality rate in VAP patients was 45%, compared to 38% in non-VAP individuals.

A comparison was made between the most common species recovered (*P. aeruginosa* and *S. aureus*). In general, 17 patients were infected by *P. aeruginosa* and 15 by *S. aureus*.

Moreover, we studied the drug resistance in these two groups. In *P. aeruginosa* group, the studied antibiotics were amikacin, ceftazidime, ciprofloxacin, imipenem and piperacillin (Table 3). We divided P. aeruginosa patients into five groups to find out which antibiotics they are resistant to. For example, in group one we studied the resistance to one antibiotic, in group 2 resistance to two antibiotics was evaluated, and so on were the other groups, correspondingly.

Table 3. Drug sensitivity patterns of P. aeruginosa among VAP patients

Antibiogram	Resistant	Sensitive	Total
Amikacin	7(41.2%)	10(58.8%)	17
Ceftazidime	10(58.8%)	7(41.2%)	17
Ciprofloxacin	6(35.3%)	11(64.7%)	17
Imipenem	8(47.1%)	9(52.9%)	17
Piperacillin	10(58.8%)	7(41.2%)	17

The first and fifth groups which included P. aeruginosa resistant to 1 and 5 antibiotics, respectively, had no members.

In the second group with a pathogen resistant to 2 antibiotics, we had 12 patients including 5 females and 7 males, 10 cases and 2 controls. Ten patients had more than seven days of hospitalization in ICU, and also, we had 41% (n=5) mortality rate.

The 3rd group comprised of 10 patients among whom 7 were men and 3 were women. Nine of them had prolonged ICU hospitalization for ≥ 7 days and 4 passed away.

Group four, consisted of 3 cases and 2 controls. Out of which, 4 were males and 1 was female. The morbidity rate among those with more than 7 days of ICU stay was 80% (4 cases). Moreover, we had 60% (3 cases) mortality outcome (Figure 1).

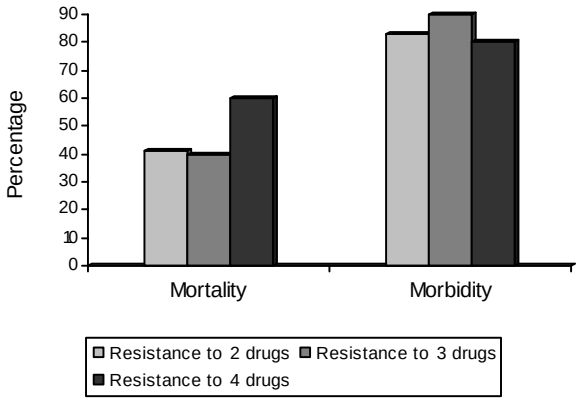

Figure 1. Morbidity and mortality rates in *P. aeruginosa* resistance groups.

In the *Staph. aureus* group, resistance to methicillin and vancomycin was compared (Table 4). Among antibiogram reports, 12 out of 15 belonged to methicillin resistant group (80%). Also, all cases were reported to be sensitive to vancomycin. The results showed a significant difference between these two groups ($p<0.001$).

Table 4. Drug resistance patterns of S. aureus among VAP patients

Antibiogram	Resistant (%)	Sensitive (%)	Total
Methicillin	12(80%)	3(20%)	15
Vancomycin	-	15(100%)	15

Length of ICU stay in 14 patients in S. aureus group was≥7 days. The mortality rate among S. aureus group was 40%.

In MRSA group, 6 patients out of 12 were females (50%), there were 11 cases and one control, 11 patients remained in ICU for more than 7 days and 6 cases passed away.

DISCUSSION

VAP is a common complication in intensive care patients. In our study, 40 out of 99 patients had a diagnosis of VAP (40.4%). Rello et al. in a global US study reported that the incidence of VAP among their ICU patients was 9.3% (18). It seems that the prevalence of VAP among our patients was more than similar reports. The reason may be the significant referral rate of VAP patients with multi-drug resistance (MDR) pathogens to our hospital and also poorer infection control in our ICU compared to developed countries. This may also result in a more difficult weaning and other complications which can potentially increase the length of ICU stay and even mortality rate.

Moreover, this study revealed a crude mortality rate of 50 percent in VAP patients. There was a significant difference in the mortality rate between cases and controls (50% versus 40.4%). Besides, VAP was not associated with longer ICU stay.

In a prospective study, Apostolopoulou showed that VAP was associated with increased length of ICU stay but not necessarily with patients' mortality rate (19).

Furthermore, in the current study, female gender and gastrointestinal disorders were identified as risk factors associated with VAP. Although risk factors for the development of VAP in intensive care setting have been determined in multiple studies, results are usually controversial mostly due to methodological differences. In his multicenter study, Rello found male gender, trauma, and severity of illness as potential risk factors (18).

In their systematic review, Cook and Kollef demonstrated that most risk factors associated with VAP either predisposed patients to colonization of the aero-digestive tract with pathogenic bacteria (e.g. prior to the use of antibiotics, treatment with histamine type 2 receptor antagonists) or aspiration (e.g. supine position, patient's transport out of intensive care unit)(20).

In our study, some risk factors were associated with VAP (e.g. tracheal stenosis, COPD, trauma and renal disorders), although the correlations were not significant. The reason may be the insufficient number of VAP patients. Further prospective case-control studies are required to evaluate these underlying conditions and risk factors.

Drug sensitivity/ Resistance patterns

In this study the etiology of VAP in our ICU setting was evaluated. The most frequent organisms isolated were *P. aeruginosa* and *S. aureus*. The other frequently isolated bacteria were Acinetobacter species, *Klebsiella. pneumoniae*, coagulase-negative streptococci, *Candida albicans*, *E. coli*, and Enterobacter species.

Shorr et al. showed that S. aureus was the most frequent organism isolated in patients with a confirmed diagnosis of VAP, followed by *P. aeruginosa* (21%), *Haemophilus influenzae* (12%), *Klebsiella pneumoniae* (8%), and *Escherichia coli* (6%) (21).

In this study, 17.2% of VAP patients showed *P. aeruginosa* in their antibiogram results. Parker et al. reported that in 6.4% of their VAP patients, the recovered organism was *P. aeruginosa* (22).

Our data suggested that isolation of multi-drug resistant species increased length of ICU stay and mortality of our patients. In his study, Parker proposed that the isolation of MDR organisms or Pseudomonas from respiratory specimens obtained from patients with suspected VAP was associated with worse clinical outcomes, including longer duration of mechanical ventilation, longer ICU and hospital LOS (length of stay), and increased mortality rate (22-24).

Furthermore, in the S. aureus group, 93% of cases had prolonged ICU stay for more than 7 days and the mortality rate for this group was 40%. Kollef

and coworkers observed that S. aureus was a major pathogen in hospital settings and pneumonia due to this microorganism was associated with greater LOS and increased cost compared with community-acquired pneumonia with S. aureus which was found to be the only pathogen that correlated with mortality after adjusting for confounding factors (25).

Noskin and colleagues reported that S. aureus infection increased the average hospital LOS by three folds, and five times the risk for in-hospital mortality compared with inpatients without S. aureus infection (26).

Moreover, LOS for MRSA group was 80% with 50% mortality rate. Our data revealed an increased mortality rate among MRSA group compared to overall S. aureus group, although the LOS showed a slight decline. Shorr et al. found that MRSA-related VAP was associated with significantly increased overall hospital LOS, ICU LOS, and attributable LOS (21).

Our study had several limitations. First, the retrospective design is associated with a number of limitations, and the present study is a subject to these limitations. Second, our main problem was the limited number of cases which caused uncertainty and limited our findings.

In conclusion, VAP is a common infection in ICU setting and certain interventions may affect its incidence. Intensivists should be aware of the risk factors for VAP. In our study, *P. aeruginosa* and *S. aureus* were more common in ICU patients. Moreover, there was a positive relationship between drug resistance patterns and morbidity and mortality rates of our patients. Despite the limitations outlined above, this study provided clinical, epidemiologic, and paraclinical data regarding VAP in an ICU setting. Besides, our study was a basic research to determine what kind of broad-spectrum antibiotics should be initiated in cases with suspected VAP (de-escalating therapy) in the ICU.

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