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Research Article

Incidence, risk factors, and outcome of ventilator-associated Pneumonia in 18 hospitals of Iran.

Running title: ventilator-associated pneumonia in Iran

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ABSTRACT

Ventilator-Associated Pneumonia is the second most common nosocomial infection and the first most common infection in Intensive Care Units .The present study was conducted to investigate the Epidemiology of ventilator-associated pneumonia in intensive care units of hospitals affiliated to Mazandaran University of Medical Sciences. The present descriptive-analytical study was conducted in ICU patients in hospitals in Mazandaran province over a period of 14 months. The research setting consisted of the ICUs of hospitals in Mazandaran province in Iran. The study population consisted of patients over the age of 18 hospitalized in these units and connection to mechanical ventilation. The patients' data were collected on a daily basis by the hospital infection control staff. The statistical analysis of the data was carried out in SPSS version 20

Results: Of the total of 562 patients examined (5965 days), 205 developed VAP (36.5%).The incidence of VAP was reported as 34.367% per each 1000 days of tracheal intubation. The incidence of VAP was directly correlated with re-intubation, age, the duration of ventilation, the Glasgow coma score, nasogastric intubation, the use of stress ulcer *prophylaxis*, the use of mouthwash and tracheostomy.

Conclusion: The incidence of VAP was almost twice the global rate in this study. Gram-negative bacteria were the most common cause of VAP and multi-antibiotic resistance was also perceived among the participants. This problem can be solved if changes are made to the empirical treatment of patients based on the careful assessment of multi-antibiotic resistant organisms.

Keywords: Ventilator associated pneumonia, risk factors, intensive care units, antibiotic resistance, microorganisms

[I] INTRODUCTION

Nosocomial infections account for an annual of 44-100 thousand deaths and cost 17 to 29 billion dollars of treatment in the United States [1]. Ventilator-associated pneumonia (VAP) occurs 48

to 72 hours after intubation [2] and is the second most common nosocomial infection **[**3,4] and the first most common ICU infection [5]. VAP is the most important nosocomial infection across the world that increases hospital stays, health care costs and mortality rates [6-8]. The incidence of VAP has been reported as 8-68% [9]; however, providing a reliable estimation of the mortality rate associated with the condition is difficult, as this infection tends to affect the most vulnerable and critically-ill patients in hospitals [10]. Nevertheless, its crude death ratehas been reported as 30-70% [11]. VAP is worthy of attention because it presents a high rate of mortality and is associated with high healthcare costs and also given the antibiotic resistance in bacteria [12]. In Iran, it is estimated that an annual of approximately 600,000 people are affected by a variety of nosocomial infections. Different studies have reported different rates of VAP. In one study, the incidence of VAP was reported as 31.52% [13], while in another study, it was reported as 28% [14]. Although VAP is a significant cause of mortality and morbidity, it is often misdiagnosed and underestimated.

Intubated patients are at risk for aspiration of or pharyngeal pathogens, contamination of the ventilator components, such as the nebulizer, the humidifier and the ventilator tubes, immobility and increased secretion, pharyngealdamage and inflammationfollowing tracheotomy, tracheal intubation and bacterial accumulation, gastric pathogens following treatment with gastric acid inhibitors, mucosal damage following the insertion of the suction catheter, mucous plaques and the obstruction of the bronchioles, the lack of natural protective mechanisms such as cough and sneeze reflexes and mucus function and contamination of the hands of hospital staff or the tracheal tube. Other risk factors of VAP include tracheostomy, bronchoscopy, enteral feeding, prolonged intubation, and an APACHE score of 18 or higher upon admission, long-term central venous catheter, the use of sedatives and corticosteroids [15] and emergency intubation [16]. According to previous studies, Acinetobacters [17,18] are the gram-negative bacteria [19] responsible for VAP and include mainly Klebsiella, Acinetobacter and Staphylococcus aureus [20]. Local studies should be conducted on this subject due to the disparity of findings on the order of prevalence assigned to the causes of VAP.

According to the databases available, no epidemiological studies have yet been conducted on this subject in Mazandaran province. The present study therefore examines the incidence of VAP and its risk factors in the ICUs of hospitals affiliated to Mazandaran University of Medical Sciences so as to compare the results with foreign reports and to learn of any deficiencies in the national healthcare system and to provide reasonable solutions for resolving the problem.

[II] **MATERIAL AND METHODS**

The present descriptive- analytical study was conducted in the ICUs of hospitals in Mazandaran province from March 2014 to May 2015. The research setting consisted of the ICUs, BICUs and CCUs of 18 hospitals in Mazandaran province with a total of 256 beds. The study population consisted of patients over 18 hospitalized in the units and connecting to mechanical ventilation.

VAP was diagnosed in this study based on the induction of infiltration within 48 hours of the first mechanical ventilation as per the radiography and a temperature higher than 38.3°C and the detection of leukocytosis (WBC>10,000); [21]. The study exclusion criteria consisted of having fever and showing signs of infection within the first 48 hours after hospital admission.

A checklist was used to record the demographic data and clinical symptoms of each eligible patient. The other variables studied included age, gender, the cause of hospitalization, the duration of ventilation, re-intubation, the Glasgow coma score, nasogastric intubation, the use of stress ulcer prophylaxis, the use of antibacterial mouthwash at least twice a day, a history of lung disease, the administration of antibiotics before

intubation, performing tracheostomy from the beginning for patients expected to be intubated for more than 10 days, the type of pathogen, the type of antibiotic and the rate of mortality.

A culture and the anti bigram were performed based on microbiological [22,23] and CLSI [24] standards. The specific clinical and laboratory protocols defined in these standards for the detection of nosocomial infections determined the final diagnosis made in this study. Several studies have used this questionnaire in the past [25-28]. An assistant researcher evaluated and recorded the data on a daily basis and after controlling their accuracy and, if necessary, by following up with the patient and reviewing their medical records. The data obtained were analyzed in SPSS version 20 using descriptive statistics, including the mean, frequency and percentage, as well as inferential statistics including the Chi-Square and t test.

[III] **RESULTS**

Of the total of 562 patients examined (5965 days of tracheal intubation), 205 cases (36.5%) developed VAP. The incidence of VAP was 34.367 per each 1000 days of tracheal intubation. The mean age of the study participants with and without VAP was 64.785±16.775 and 60.263±19.126, in respective order. The *t*-test showed a significant difference between age and the incidence of VAP (p=0.004). The mean time of ventilation in participants with and without VAP was 14.336 ± 23.319 and 9.36 ± 10.828 respectively. The *t*-test showed a significant difference between the time of ventilation and the incidence of VAP (p= 0.006). The mean GCS in participants with and without VAP was 8.099 ± 3.362 and 8.937 ±3.862 respectively. The *t*-test showed a significant difference GCS and the incidence of VAP (p= 0.008)The leading causes of hospitalization included stroke, multiple trauma, loss of consciousness and head trauma, by order of prevalence. The results showed that the incidence of VAP had a direct relationship with re-intubation, the duration of ventilation, the Glasgow coma score, nasogastric intubation and the use of stress ulcer prophylaxis. A total of 91.8% of the patients in this study used mouthwash at least twice a day .Chlorhexidine mouth wash was the most frequent type used(n=235 and 41.8%).There was a statistically significant relationship between the use of mouthwash and the incidence of VAP, as the use of mouthwash reduced the incidence of VAP. The results showed that performing tracheostomy from the beginning for patients expected to be intubated for more than 10 days reduces the incidence of VAP. The incidence of VAP was found to not be significantly related to the history of lung disease (p=0.994) and antibiotic administration before intubation (p=0.221); (Table 1).

According to the laboratory results, the most common gram-negative pathogens responsible for VAP were Acinetobacter (29.9%), Klebsiella (21.3%), and Pseudomonas (14%). Staphylococcus aureus was the most common gram-positive bacteria causing the infection (11.5%). Other pathogens were responsible for 23.3% of the infections. The results showed that Acinetobacter was resistant to Cephalosporins, Carbapenems and Aminoglycosides. Table 2 presents the antibiotic resistance pattern in some of the VAP pathogens.

[IV] **DISCUSSION**

Ventilator-associated pneumonia is one of the most common problems among patients admitted to special healthcare facilities, especially ICUs. The present study found the incidence of VAP to be 34.367 per each 1000 days of tracheal intubation. Different studies have reported different rates of VAP. According to a study conducted in Iran, the incidence of VAP was reported as 32.2% [21] and 10.2% [22], while other studies have reported it as 21.87% [19] ,46% [29] and 28.9% [30], indicating a high rate of infection. Nevertheless, the rates reported in different studies cannot be compared with each other due to the lack of similar diagnostic procedures for VAP, the differences in the

patients' ICU stays and the lack of proper systems for comparing disease severities [15].

In this study, men were found to be at a greater risk of VAP than women. Jaimes et al. also reported men to be at a greater risk of VAP compared to women, although the difference was not statistically significant [31]. Contrary to the present findings, another study found that gender had no effect on the incidence of nosocomial infections [32].

In the present study, re-intubation was associated with an increased risk of pneumonia, which is consistent with the results obtained by Joseph [16] and Rit [19]. Re-intubation is one of the risk factors of VAP. The main cause of the incidence of VAP is the aspiration of gastric contents. Gastric contents are aspirated during re-intubation [33]. Re-intubation can also increase the incidence of VAP by transferring organisms from the upper to the lower respiratory tract [34]. The risk factors of VAP presenting with re-intubation include subglottic dysfunction and the loss of consciousness in mechanically-ventilated patients [35].In this study, the duration of intubation increased the risk of pneumonia. Saravu et al. also reported that prolonged intubation increases the incidence of VAP [34]. Prolonged intubation is also associated with drug-resistant pathogens and increases the risk of developing Pseudomonas and MRSA [36]. Prolonged ventilation also increases bacterial colonization [35.]The present study also found the Glasgow coma score to be a risk factor of VAP. Disease severity was also found to contribute to the incidence of VAP. Apostolopoulou et al. reported patients with higher APACHE scores to be at a greater risk of VAP, although they measured this score during the patients' hospitalization [15]. It appears that, the patients' loss of consciousness due to impaired cough reflex can make them vulnerable to VAP [16].

A significant relationship was also observed in this study between nasogastric intubation and increased risk of VAP. In line with the present findings, Joseph et al. also reported nasogastric intubation to be associated with an increased risk of pneumonia [16]. Apostolopoulou et al. also reported similar findings in their study on the risk factors of VAP in hospitals in Greece and concluded that enteral feeding affects the incidence of VAP [15]. Enteral feeding increases gastric PH and bacterial colonization and can lead to lower respiratory tract aspiration and the incidence of VAP as a result [35]. In the present study, most of the patients received the same stress ulcer prophylaxis, which contained aproton pump and H2 antagonists. Another study conducted in Iran revealed Ranitidine to be the most widely-used drug among ventilated patients [37].

The results of the present study showed that the use of stress ulcer prophylaxis does not reduce the incidence of VAP. According to different studies, most patients under ventilation use a type of stress ulcer prophylaxis, most of which tend to increase gastric PH [38]. Increased gastric PH can accelerate the overgrowth of bacteria. Nasogastric intubation can also accelerate the movement of these bacteria to the pharynx and thus increase the incidence of VAP [39]. According to Yildizdas et al., no differences were observed in the incidence of VAP with the use of ranitidine, Omeprazole or Sucralfate [40] H2 blockers and antacids have been reported as some of the independent causes of VAP. Moreover, the administration of Sucralfate for gastric ulcer prophylaxis does not increase gastric volume without reducing gastric acidity [41]. If necessary, using stress ulcer prophylaxis should be carried out after a careful study of its advantages and disadvantages.

The results obtained showed that the use of mouthwash reduced the incidence of VAP. In the present study, most of the patients used mouthwash. In one study, Munro et al. compared the effect of 0.12% Chlorhexidine and tooth brushing on the incidence of VAP and found that, compared to tooth brushing, using chlorhexidine can reduce early VAP in patients withoutpneumonia [42]. Tantipong also compared the effect of 2% chlorhexidine with normal saline

and found that the incidence of VAP was lower in the chlorhexidine group than in the normal saline group [43]. Oropharyngeal flora aspiration in patients under ventilation is the main mechanism for the development of VAP [44]. Chlorhexidine is an antibacterial agent that affects a wide range of bacteria. However, the role of chlorhexidine in preventing respiratory tract infections in ICU patients is still a controversial issue. In certain concentrations, chlorhexidine can partially inhibit microbial proliferation and delay but not prevent respiratory tract infection [45].

The present study found that performing tracheostomy in patients expected to be intubated for more than 10 days reduces the incidence of VAP. Tracheostomy is often recommended to patients with acute respiratory failure requiring long-term ventilation. Since prolonged intubation causes damage to the larynx and leads to tracheal stenosis [46], tracheostomy can prevent these complications in patients with prolonged intubation. Contrary to the results of the present study, Ferrer et al. (2003) reported that tracheostomy is associated with an increased risk of VAP in intubated patients [47]. Pre-tracheostomy airway colonization may be a risk factor for VAP after tracheostomy, particularly in the case of fever and if sedation is required after the surgery [35]. Aseptic techniques must therefore be used when performing tracheostomy.

In the present study, 68.8% of the patients received antibiotic prophylaxis, most commonly Keflin(18.6%) andCeftriaxone (18.3%). Never the less, pre-intubation antibiotic administration did not reduce the incidence of VAP. Rit et al. (2014) examined the risk factors of VAP and found that antibiotic treatment does reduce the incidence of VAP, which is inconsistent with the present findings [19]. Another study also examined the effect of Ceftazidime antibiotic prophylaxis using the aerosol method on the incidence of VAP in trauma patients. The results showed that the use of aerosol reduced the incidence of VAP [48]. The disparity of results can be attributed to the patients' inaccurate reporting of their use of prophylaxis. Nevertheless, these studies do not recommend the preventive use of antibiotic prophylaxis, as it can lead to bacterial resistance. Antibiotics should be selected and used with caution so as to reduce colonization and the incidence of VAP [49]. The best choice may be made if antibiotics are used after performing a culture and evaluating the sensitivity test results [50].

This study found no significant relationships between the history of chronic pulmonary disease and the incidence of VAP. In their study of ICUs in India, Saravu et al. also found no relationships between chronic pulmonary diseases and the incidence of VAP [34], which is in line with the results of the present study. Tejerina et al. (2005), however, reported that patients with acute or chronic pulmonary disease are at a greater risk of VAP [51]. Old age, increased airway colonization, mucosal dysfunction due to smoking and impaired cough reflex can increase the incidence of VAP in patients with lung disease [35]. In the present study, the number of patients with chronic lung disease was limited in both groups (i.e. in the group with and the group without VAP), which explains why no significant relationships were observed between this disease and VAP. Another study is recommended to be conducted to examine the incidence of VAP in a greater number of patients with COPD.

In the present study, the rate of mortality due to VAP was 16.5% , which is consistent with the result obtained by Jaimes et al. (2007) [31]. Given the importance of awareness about the risk factors of VAP and the nurses' little knowledge about the non-pharmacological methods of its prevention in Iran [52], continuing education targeting this subject is required for nurses.

Similar to in other studies [18,19] this study also found acinetobacter to be the most common pathogen of VAP, while the other pathogens causing VAP included Klebsiella, Pseudomonas and S. aureus, by order of prevalence. In one study, Nadi et al. reported gram-negative bacteria to be the main cause of VAP [20]. In another

study, reported Klebsiella, Acinetobacter and S. aureusto be the most common pathogens, by order of prevalence [21]. Acinetobacter was found to be resistant to Cephalosporins, Carbapenems and Aminoglycosides in the present study, thus appearing tobe a multidrug-resistant pathogen. Another study conducted in Iran reported Acinetobacterto be resistant to Cephalosporins, particularly to Cefotaxime [21]. However, a study conducted in Turkey showed that Acinetobacter is highly sensitive to Imipenem [53]. Another study conducted in Iran revealed all the 16 Acinetobacter strains studied to have 100% resistance to all the antibiotics examined, including different types of Cephalosporins, Aminoglycosides and Imipenem [54].

The present study also found Acinetobacterto be a potential cause of multidrug-resistant VAP in the region and effective treatments should be selected based on the local antibiotic resistance pattern of this pathogen.

In this study, Klebsiella was reported to be highly resistant to third-generation Cephalosporins such as Ceftriaxone and Ceftizoxime. Klebsiellais also highly sensitivity to aminoglycosides. A case study conducted on a patient with acute endocarditis caused by Carbapenem-resistant Klebsiella revealed a combination regimen of Gentamicin and Colistin to be helpful in the treatment of this condition [55].

In the present study, Pseudomonas showed resistance to Aminoglycosides, Ceftriaxone, Ceftizoxim and Ciprofloxacin. Another study conducted in Iran revealed ceftriaxone and ciprofloxacinto be the most resistant to Pseudomonas [54] Namiduru et al. also reported Pseudomonas to be highly resistant to third-generation Cephalosporins, including Cefepime, Gentamicin, Ciprofloxacin and Imipenem; however, the highest Pseudomonas-sensitivity pertained to Cefoperazone- Sulbactam and Amikacin [53].

The examination of the antibiotic resistance pattern of S. aureus revealed the S. aureus isolated from the patients in this study to be limited, indicating the lower rate of infection with S. aureus among VAP patients.In line with the present study, also reported S.aurous to be less prevalent compared to other microbial pathogens [21]. The results of the present study showed that most of the samples were resistant to Vancomycin and Methicillin, which may indicate the emergence of Vancomycin-resistant S. aureus strains. Contrary to the present study, another study found S.aureus to be the most sensitive to Vancomycin and thus reported no Vancomycin-resistance among these strains. This study reported most of the S.aureus strains to be resistant to methicillin [53]. Another study conducted in Iran reported the S.aureus strains isolated from the nose of hemodialysis patients to have the highest resistance to Amoxicillin and Penicillin [56]. Another local study conducted in Iran reported S.aureus strains to be the most sensitive to Clindamycin and Amikacin and the least to methicillin [57]. In the present study, S. aureus was not sensitive to Cefazolin and methicillin. In addition to Vancomycin-resistance, Methicillin-resistance may also be an issue in the case of S. aureus. Further studies should therefore be conducted on the antibiotic resistance of this pathogen. It is also crucial to examine the administration of antibiotics so as to make the best choices for the treatment of patients and so that antibiotic resistance can be minimized [58].

[V] **CONCLUSIONS**

The present study found the incidence of VAP to be almost twice the global rate. The most frequent pathogens causing VAP in this study were gram-negative bacteria. Multi-antibiotic resistance was also observed among the patients. This problem can be solved if changes are made to the empirical treatment of patients based on the careful assessment of multi-antibiotic resistant organisms.

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Table 1: Affecting factors on the incidence of ventilator associated pneumonia

Variable	ventilator associated pneumonia	*p* value
Gender		
men	118(36.9%)	*p*=0.822
women	87(36%)	
Reintubation		p<0.001
Yes	84(15.2%)	
No	121(21.8%)	
Use of NG tube		*p*= 0.003
Yes	175(34.3%)	
No	17(3.3%)	
Stress ulcer prophylaxis		*p*= 0.002
Yes	141(2703%)	
No	55(10.7%)	
Use of mouthwash		*p*= 0.001
Yes	193(38.5%)	
No	3(0.6%)	
Tracheostomy		*p*= 0.001
Yes	21(5.8%)	
No	126(34.8%)	
History of lung disease		*p*= 0.573
Yes	11(2.6%)	
No	159(38%)	
Use of antibiotic before intubation		*p*= 0.221
Yes	133(35%)	
No	65(13.3%)	
Death rate		*p*= 0.228
Yes	88(16.5%)	
No	111(21.6%)	

Susceptibility Antibiotic	Acinntrobacter		*Klebsiella pneumonia*		*Pseudomonas aeruginosa*		*Staphylococcus*aureus	
	R	**S**	**R**	**S**	**R**	**S**	**R**	**S**
Amikacin	9	3	3	9	4	5	1	-
Carbapenems	24	1	14	14	5	6	7	3
Gentamicin	23	6	8	13	9	10	3	1
Ceftizoxim	32	1	12	4	11	4	1	-
Ceftriaxon	31	3	16	7	8	7	-	3
Ciprofloxacin/	28	3	11	12	9	8	1	-
Co- trimoxazole	24	-	7	2	9	3	2	-
Ampi/sul	5	-	11	-	7	-	1	-
Cefazolin	6	1	9	-	4	3	2	
Vancomycin	-		-	-	-	-	7	-

Table 2 Antibiotic resistance patterns of bacterial strains isolated from sputum in intensive care units in northern Iran