

Incidence and Risk Factors for Ventilator-Associated Pneumonia in 4 Multidisciplinary Intensive Care Units in Athens, Greece

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INTRODUCTION: Ventilator-associated pneumonia (VAP) is the most common nosocomial infection among intensive care unit (ICU) patients. **OBJECTIVE:** Prospectively identify the factors associated with development of VAP and examine the incidence of VAP. **SUBJECTS:** Over a 6-month period we had 175 patients who required mechanical ventilation for longer than 24 hours. **RESULTS:** VAP occurred in 56 patients (32%). Stepwise logistic regression analysis identified 5 factors independently associated with VAP ($p < 0.05$): bronchoscopy (adjusted odds ratio [AOR] = 2.95; 95% confidence interval [CI], 1.1–8.3; $p = 0.036$); tube thoracostomy (AOR = 2.78; 95% CI, 1.1–6.6; $p = 0.023$); tracheostomy (AOR = 3.56; 95% CI, 1.7–8.4; $p = 0.002$); Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥ 18 (AOR = 2.33; 95% CI, 1.1–5.1; $p = 0.033$); and enteral feeding (AOR = 2.89; 95% CI, 1.3–7.7; $p = 0.026$). The duration of mechanical ventilation was longer among patients who developed VAP ($p < 0.001$). VAP was not associated with the cause of ICU admission. **CONCLUSIONS:** VAP is a common infection and certain interventions might affect the incidence of VAP. ICU clinicians should be aware of the risk factors for VAP, which could prove useful in identifying patients at high risk for VAP and modifying patient care to minimize the risk of VAP, such as avoiding unnecessary bronchoscopy or modulating enteral feeding. *Key words:* pneumonia, intensive care unit, risk factors, ventilator-associated pneumonia, ICU, VAP. [Respir Care 2003;48(7):681–688. © 2003 Daedalus Enterprises]

Introduction

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection among intensive care unit (ICU) patients.^{1,2} VAP occurs in mechanically ventilated patients,^{3–5} and the incidence of VAP ranges from 6 to 52 cases per 100 patients; it is 6–21 times higher in intubated patients.^{5–10} The risk for VAP rises 1–3% for each day the patient requires mechanical ventilation.^{8,9} VAP is a common problem in ICUs; its clinical diagnosis, microbiological diagnosis, risk factors, preventive measures, and empirical treatment are still under consideration by specialists. The incidence of VAP depends on the population studied,

the type of ICU, and the diagnostic criteria used. Knowledge of the incidence of nosocomial infections and their associated risk factors may be important to allow more effective development and use of preventive measures.^{11,12} Despite improvements in the diagnosis, treatment, and prevention of VAP, it remains an important cause of hospital morbidity and mortality.^{13,14}

We performed a prospective study to determine the incidence of VAP among mechanically ventilated adult patients and to identify the main risk factors for development of VAP in a critically ill ICU population.

Methods

Setting and Subjects

The study was conducted in the ICUs of 4 general, multidisciplinary hospitals in Athens, Greece: KAT Hospital; Geniko Kratiko Athinon; Geniko Kratiko Nikaias; and Evangelismos Hospital. During a 6-month period (March through August 2000), all patients admitted to the

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ICU were potentially eligible for the study. The study population consisted of all patients who required mechanical ventilation for at least 24 hours at any point during their ICU stay. The study protocol was approved by the ethics committee of each hospital.

Study Design and Data Collection

A group of attending physicians and nurses prospectively collected data on all patients who received mechanical ventilation; they made all observations, identified eligible patients, and recorded relevant data from medical records, bedside flow sheets, computerized radiographic reports, and reports of microbiological studies (sputum, blood, and pleural fluid culture results). Study patients were prospectively followed for the occurrence of VAP until either discharge from the ICU or death. Only the first episode of VAP was evaluated. Each subject had a chest radiograph, a white blood cell count, and a tracheal aspirate specimen culture daily. From each patient the following data were collected at ICU admission: age, sex, concomitant diseases, presence of underlying malignancy, hospital-admission diagnosis, and Acute Physiology and Chronic Health Evaluation (APACHE II) score.¹⁵ Causes of ICU admission were classified as either multiple injury, head injury, respiratory disease, neurologic disorder, cardiovascular disorder, intra-abdominal disorder, poisoning (usually attempted suicide), or miscellaneous. Process of care variables included admission source (ward or emergency room), having had surgery, and having had emergency surgery. Specific medical care processes throughout the ICU stay were examined as potential risk factors for the development of VAP; these included tracheostomy, dialysis, reintubation, tube thoracostomy, sedatives, corticosteroids, inotropic drugs, presence and duration of central venous and arterial catheters, presence of a nasogastric tube, type of nutritional support (parenteral or enteral feeding), duration of mechanical ventilation, and duration of prior use of antibiotics.

The main outcome evaluated was the occurrence of VAP. Secondary outcomes included the length of ICU stay.

Definitions

All definitions were prospectively selected and included in the original study protocol. APACHE II score was calculated based on clinical data available from the first 24 hours of ICU admission. The worst value in the first 24 h was selected for each of the 12 APACHE II variables.

In this study the diagnostic criteria for VAP were modified from the work of Salata et al.¹⁶ A diagnosis of VAP was defined as the occurrence of a new and persistent radiographic infiltrate not otherwise explained, appearing on chest radiograph along with 2 of the following:

1. Body temperature $> 38.3^{\circ}\text{C}$
2. Leukocytosis ($> 10,000$ white blood cells/mL)
3. Purulent tracheal aspirate

A new infiltrate was defined as having occurred more than 48 hours after the onset of mechanical ventilation. Persistence of an infiltrate was defined as the infiltrate being radiographically visible for at least 72 hours. Tracheal aspirates were considered purulent if there were > 25 neutrophils per high power field, using Gram stain.

Bacteremia was diagnosed when at least 2 sets of blood cultures yielded a microorganism.

Prior antibiotic administration was defined as intravenous antibiotic administration for > 24 hours during any part of the patient's hospitalization prior to and during mechanical ventilation.

Statistical Analysis

Results are expressed as mean \pm SD. 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 and the Wilcoxon rank-sum test for nonnormally distributed variables. The chi-square test or Fisher's exact test was used to compare patients without VAP to patients with VAP. We confirmed the results of these tests, while controlling for specific patient characteristics and severity of illness, with multiple logistic regression analysis, using statistics software (SPSS, SPSS Inc, Chicago, Illinois).¹⁷

Multivariate analysis was performed using models that were judged a priori to be clinically sound.¹⁸ 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 adjusted odd ratios with their 95% confidence intervals. Values are expressed as mean \pm SD for continuous variables or as a percentage of the group they were derived from (categorical variables). All *p* values < 0.05 were considered statistically significant and were based on univariate analysis.

Results

Over the 6-month study period (March through August 2000) a total of 205 patients were admitted to the ICUs of the 4 hospitals and were prospectively evaluated. One hundred-seventy-five patients (85.4%) received mechanical ventilation and those patients composed the study cohort. Table 1 shows the baseline demographic data. Of the 175 study patients, 122 were men (70%) and 53 were women

Table 1. Patient Data

	Non-VAP (n = 119)	VAP (n = 56)	p
Age (mean ± SD y)	51.9 ± 21	52.5 ± 18.1	0.959
Sex			
Male	82 (69%)	40 (71%)	0.432
Female	37 (31%)	16 (29%)	
Cause of ICU admission*			
Multiple injury	25 (21%)	16 (29%)	0.181
Head injury	12 (10%)	9 (16%)	0.186
Respiratory failure	23 (19%)	8 (14%)	0.277
Neurological disease	21 (18%)	12 (21%)	0.344
Cardiovascular disease	6 (5%)	3 (5%)	0.594
Intra-abdominal disease	23 (19%)	5 (9%)	0.059
Poisoning†	4 (3%)	0 (0%)	0.210
Miscellaneous	5 (4%)	3 (5%)	0.500
Congestive heart failure	12 (10%)	7 (12%)	0.404
COPD	17 (14%)	7 (12%)	0.475
Underlying malignancy	21 (18%)	10 (18%)	0.564
APACHE II score (mean ± SD)	18.3 ± 7.2	21.8 ± 8	0.004
APS score (mean ± SD)	12.0 ± 5.9	15.6 ± 6.2	< 0.001
Underwent surgery	55 (46%)	20 (36%)	0.126
Thoracoabdominal surgery	21 (18%)	6 (11%)	0.236
Acute renal failure	8 (7%)	4 (7%)	0.573
Bacteremia	8 (7%)	26 (46%)	< 0.001
Admitted to ICU from			
Medical ward	64 (54%)	36 (64%)	0.126
Scheduled surgery	29 (24%)	8 (14%)	0.090
Emergency surgery	26 (22%)	12 (21%)	0.558
Duration of mechanical ventilation (mean ± SD d)	8 ± 6.3	22.5 ± 14.7	< 0.001

VAP = ventilator-associated pneumonia
 ICU = intensive care unit
 *Percentage totals differ from 100% because of rounding.
 †Poisoning was usually from attempted suicide.
 COPD = chronic obstructive pulmonary disease
 APACHE = Acute Physiology and Chronic Health Evaluation
 APS = Acute Physiology Score

(30%). The mean ± SD age was 52 ± 20 years (range, 16–92 y). The mean ± SD APACHE II score was 19.5 ± 7.58. The mean ± SD Acute Physiology Score on admission was 13.1 ± 6.2. Seventy-five patients (43%) underwent surgery prior to ICU admission, either scheduled or emergency. Of the 175 patients, 56 (32%) developed VAP during their ICU stay. The most frequent admission diagnosis was multiple injury trauma (23%). The cause of ICU admission did not correspond to the incidence of VAP, although patients who had intra-abdominal disease showed a weak trend toward the occurrence of VAP (p = 0.059).

The duration of mechanical ventilation was longer among patients who suffered VAP (22.5 ± 14.7 d vs 8.0 ± 6.3 d, p < 0.001).

The onset of VAP was more likely to occur during the first 2 weeks of mechanical ventilation (Fig. 1).

In this study the crude mortality rate of patients with VAP was 39.3%. There was no significant difference in mortality between patients with VAP and those without VAP (39.3% vs 33.6%, p = 0.464).

Most cases of VAP were caused by Enterobacteriaceae and *Pseudomonas aeruginosa*, which accounted for 84% of causative organisms. Microorganisms isolated in the tracheal aspirates of patients with VAP were *P. aeruginosa* (n = 17, 30.4%), *Staphylococcus aureus* (n = 9, 16.1%), *Acinetobacter calcoaceticus* (n = 8, 14.3%), *Klebsiella pneumoniae* (n = 6, 10.7%), and *Enterobacter* species (n = 1, 1.8%). *P. aeruginosa* was the most common Gram-negative bacteria associated with VAP and *S. aureus* was the most common Gram-positive bacteria among patients with VAP. VAP was polymicrobial in 15 patients (26.8%).

Patients who developed VAP had significantly longer ICU stays than patients without VAP (27.9 ± 16.7 d vs 10.3 ± 7.4 d, p < 0.001). Patients with VAP had higher APACHE II and Acute Physiology Scores and were more likely to have bacteremia (see Table 1). Univariate analysis indicated that the following were significantly associated with VAP: tracheostomy, tube thoracostomy, bronchoscopy, enteral feeding, duration of mechanical ventilation ≥ 5 days, mean duration of central vein catheterization, APACHE II score ≥ 18 on admission, and acute physiology score ≥ 10 on admission (Table 2). Table 3 shows the variables that were not significantly associated with VAP.

Bronchoscopy was performed in 27 patients, 16 of whom developed VAP following bronchoscopy. The main indication for bronchoscopy was pulmonary atelectasis or removal of respiratory secretions (therapeutic bronchoscopy). Diagnostic bronchoscopy was performed in only 4 patients who had chest radiograph abnormalities that did not fulfill the criteria for the diagnosis of VAP, and 2 of them developed VAP in the following days. VAP developed 2–6 days after bronchoscopy (Fig. 2).

Selected risk factors were entered into a logistic regression model to perform the multivariate analysis, which revealed that the independent risk factors for VAP were bronchoscopy, tube thoracostomy, tracheostomy, APACHE II score ≥ 18, and enteral feeding (Table 4).

Discussion

VAP is a common problem among ICU patients. Our data indicate that VAP is associated with longer ICU stay. The crude mortality rate of VAP patients in this study was 39.3%. Prospective, randomized, controlled trials have reported similar outcomes for patients with VAP and without VAP.^{19,20}

P. aeruginosa and *S. aureus* were the most common VAP pathogens in tracheal aspirate cultures.

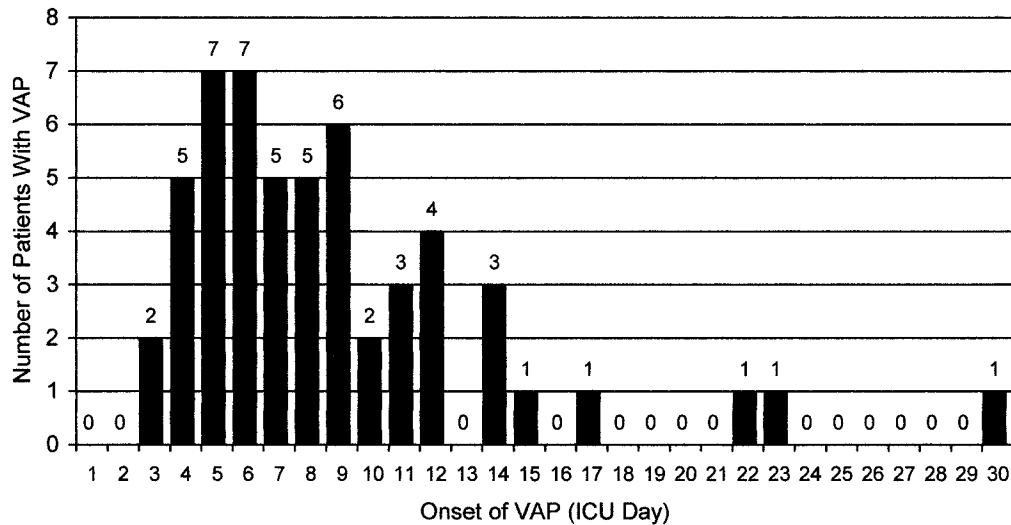


Fig. 1. Day of onset of ventilator-associated pneumonia (VAP) after intensive care unit (ICU) admission.

It has been reported that VAP is caused by multiple organisms in 30–50% of cases, but the rates differ by method of diagnosis.^{4,8,21} VAP was polymicrobial in 27% of our cases.

Independent factors associated with VAP included bronchoscopy, tube thoracostomy, tracheostomy, APACHE II score ≥ 18 on admission, and enteral feeding. Those risk factors could prove useful in identifying patients at high risk for VAP as well as in developing preventive measures such as avoiding unnecessary bronchoscopy or modulating enteral feeding.

We found that VAP was more likely to begin during the first 2 weeks of mechanical ventilation. The etiology is not obvious, but it is tempting to hypothesize that the initial period in the ICU involves the interaction of several risk factors that can put the patient at higher risk. Alternatively,

one would postulate that the “exhaustion” of the most vulnerable patients during the first 2 weeks leads to the decline in the incidence of VAP.

We also found that patients who developed VAP had longer ICU stays than those who did not, which is consistent with other reports.²²

Our study is the first to identify tube thoracostomy as an independent risk factor for VAP. This suggests that interventions near the lung parenchyma may play a role in the development of VAP. Tube thoracostomy was applied in cases of pneumothorax or large pleural effusions that required placement of a chest tube. Interestingly, in all patients who underwent tube thoracostomy VAP involved at least the lateral lung. That would support the hypothesis that the cause that leads to tube thoracostomy influences the lateral lung’s ventilation, which in turn may lead to

Table 2. Variables Significantly Associated With Ventilator-Associated Pneumonia, by Univariate Analysis

	Non-VAP (n = 119)	VAP (n = 56)	AOR	p
Tracheostomy	20 (17%)	29 (52%)	5.32	< 0.001
Bronchoscopy	11 (9%)	16 (29%)	3.93	0.002
Tube thoracostomy	20 (17%)	18 (32%)	2.35	0.024
Enteral feeding	67 (56%)	48 (86%)	4.65	< 0.001
Duration of mechanical ventilation (d) prior to VAP ≥ 5 d	81 \pm 68.1	49 \pm 87.5	3.28	0.008
Duration of central vein catheterization (mean \pm SD d)	9.3 \pm 7.3	26.2 \pm 16.2	1.15	< 0.001
APACHE II score ≥ 18 on admission	57 (48%)	38 (68%)	2.30	0.014
APS ≥ 10 on admission	73 (61%)	47 (84%)	3.29	0.004

VAP = ventilator-associated pneumonia

AOR = adjusted odds ratio

APACHE = Acute Physiology and Chronic Health Evaluation

APS = Acute Physiology Score

INCIDENCE AND RISK FACTORS FOR VENTILATOR-ASSOCIATED PNEUMONIA

Table 3. Variables Not Significantly Associated with Ventilator-Associated Pneumonia, by Univariate Analysis

	Non-VAP (n = 119)	VAP (n = 56)	P
Dialysis	3 (2%)	3 (5%)	0.291
Reintubation	11 (9%)	7 (12%)	0.339
Sedatives	43 (36%)	28 (50%)	0.058
Inotropic drugs	27 (23%)	13 (23%)	0.541
Corticosteroids	7 (6%)	2 (4%)	0.406
Inhaled medication	30 (25%)	13 (23%)	0.466
Duration of antibiotic treatment (mean ± SD d)	9.8 ± 6.8	9.5 ± 6.5	0.795
Nasogastric tube	113 (95%)	56 (100%)	0.095

VAP = ventilator-associated pneumonia

retention of secretions and possibly to development of VAP. Alternatively, the lung parenchyma injury caused by pneumothorax or hemothorax may play a role in the development of VAP.

In our study bronchoscopy was mainly performed in cases of pulmonary atelectasis or to remove secretions. It was used for diagnostic purposes in only 4 patients who had chest radiograph abnormalities that did not fulfill the criteria for diagnosis of VAP. We observed no complications in the subjects who underwent bronchoscopy, with the exception of 2 patients who developed fever almost 12 hours after bronchoscopy. However, the fever subsided the following day. Another study identified recent bronchoscopy as an independent risk factor for VAP.¹⁹ Bronchoscopy is frequently performed in mechanically ventilated patients for diagnostic or therapeutic purposes. Therapeutic bronchoscopy performed for respiratory toilet is a preventable risk factor not emphasized in earlier studies. Many authors have reported the infectious complications of bronchoscopy, but their findings supported the rarity of this complication.^{23,24} Advanced age and the endoscopic find-

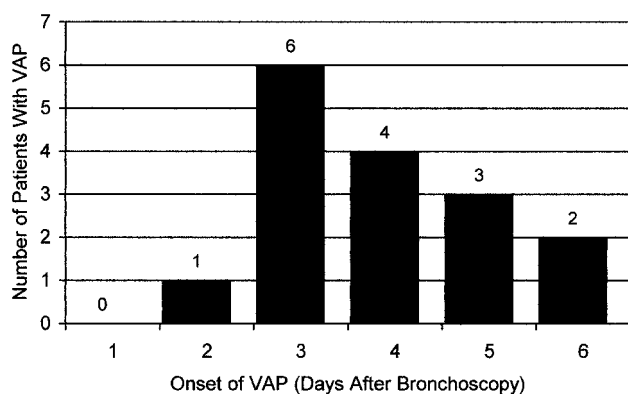


Fig. 2. Day of onset of ventilator-associated pneumonia (VAP) after bronchoscopy.

Table 4. Variables Independently Associated with Ventilator-Associated Pneumonia, by Logistic Regression Analysis

Variable	AOR	95% CI	p
Bronchoscopy	2.954	1.089–8.270	0.036
Tube thoracostomy	2.777	1.137–6.596	0.023
Tracheostomy	3.556	1.734–8.363	0.002
APACHE II score ≥ 18	2.332	1.076–5.074	0.033
Enteral feeding	2.894	1.257–7.737	0.026

AOR = adjusted odds ratio

CI = confidence interval

APACHE = Acute Physiology and Chronic Health Evaluation

ing of an abnormality were noted as possible predisposing factors.^{25,26}

To our knowledge there are few data on the infectious complications of therapeutic bronchoscopy, but it has been suggested that bronchoscopy may predispose to VAP in mechanically ventilated patients, possibly by introducing bacteria or dislodging biofilm-encased bacteria into the lower airway. Moreover, the introduction of a large volume of bronchoalveolar lavage fluid may decrease bacterial clearance.^{19,27}

In our study bronchoscopy was an independent risk factor for VAP, and with our patients bronchoscopy was mainly therapeutic. Diagnostic bronchoscopy was performed in 4 patients and 2 of them developed VAP afterwards. Those few cases do not prove a causal relationship between bronchoscopy and VAP, but if bronchoscopy introduces bacteria to the lower airways (either by dislodging biofilm-encased bacteria or introducing bacteria not previously present), then VAP may be related to both diagnostic and therapeutic bronchoscopy. Possibly bronchoscopy is overlooked as a predisposing factor for VAP, since these patients are perceived as being at high risk independent of the procedure. It is possible that the common indications for which bronchoscopy is performed (increased respiratory secretions or pulmonary atelectasis) place these patients at high risk of VAP independent of bronchoscopy. The relationship between bronchoscopy and VAP merits further investigation. If a causal relationship is confirmed, the risks and benefits of bronchoscopy may need to be re-evaluated, since therapeutic bronchoscopy may be an avoidable risk factor.

We found that APACHE II score ≥ 18 at ICU admission is an independent risk factor for VAP. However, we did not examine APACHE II score throughout the duration of mechanical ventilation as a potential risk factor for VAP. Many studies have identified severity of illness as an important risk factor for VAP, which suggests that VAP can be decreased only to a certain level.^{5,22,28,29}

Tracheostomy has been reported as a risk factor for VAP.³ This suggests that aspiration may contribute to the

development of VAP in some patients. Leakage around the endotracheal tube cuff enables pooled secretions to enter the trachea, increasing tracheal colonization and leading to VAP.³⁰ Late tracheotomy was performed in all subjects included in our study cohort, whereas subjects who had already had tracheotomy were excluded.

Enteral feeding has also been found to be a risk factor for VAP, alone or in combination with supine body position.^{31,32} In our study enteral feeding was initiated on the first ICU day unless contraindicated. We used gastric intermittent feeding, with the patient's head elevated $> 30^\circ$ from the horizontal plane. However, head positioning was monitored only during the first 24 hours of mechanical ventilation because of the need for repeated direct examinations by the investigators to verify positioning. Enteral feeding may predispose to VAP by elevating gastric pH, leading to gastric colonization and causing gastric distention, thus increasing the risk of reflux and aspiration.³³⁻³⁵ If enteral feeding is a risk factor for VAP, it would support the theory that the esophagus is an important source of pulmonary bacterial colonization, and therefore a primary cause of VAP. Hence, modulating enteral feeding might limit gastropulmonary colonization and thus reduce the incidence of VAP. This is very important, because the provision of adequate nutritional support to patients receiving mechanical ventilation is believed to prevent VAP.³⁶

We did not find any significant difference in the occurrence of VAP among different ICU populations originating from medical wards, scheduled surgery, or emergency surgery. This finding is in accordance with Torres et al, who found that the type of ICU population did not influence the occurrence of VAP.⁷

Previous studies have used similar multivariate methods, and those studies found the following as independent risk factors for VAP: reintubation, gastric aspiration, patient age, supine head positioning during the first 24 hours of mechanical ventilation, the number of organ system derangements, the presence of chronic obstructive pulmonary disease, intracranial pressure monitoring, and the use of cimetidine.^{3,5,7,21,37-40} These factors did not emerge as statistically significant in our study. One possible explanation may be that our study was performed in 4 multidisciplinary ICUs in different hospitals, so it is not assured that the prophylactic measures for VAP were uniformly applied with all the patients. However, we were particularly careful that the diagnostic criteria were fulfilled.

Our statistical methods are sound and generally accepted, but may sometimes produce invalid estimates at identifying risk factors.⁴¹⁻⁴³

In this study we used a clinical diagnosis of VAP, and the presence of VAP was established without invasive diagnostic procedures. As a result some cases with non-infectious etiologies for pulmonary infiltrates may have

been misclassified as VAP. Many investigators have claimed that the incidence of VAP may be overestimated when clinical criteria alone are used.⁴⁴⁻⁴⁶ This may account for the higher incidence of VAP in our study than in other studies that employed bronchoscopic methods for the diagnosis of VAP. In a recent postmortem study the combination of infiltrates on the chest radiographs and at least 2 of 3 clinical criteria (fever, leukocytosis, purulent secretions) had a sensitivity of 69% and a specificity of 75% for diagnosing VAP.⁴⁷ Moreover, there have been studies that demonstrated a similar diagnostic yield with invasive and noninvasive techniques and similar patient outcomes in terms of mortality, ICU stay, and duration of mechanical ventilation.^{27,48,49} However, the VAP rates in the various studies cannot be compared because of differences in survey methods, lack of uniform diagnosis criteria, different lengths of ICU stay, and the lack of an adequate system to compare illness severity and invasive diagnostic or therapeutic procedures.

Prior antibiotic exposure is also a risk factor for VAP.^{5,7,30,50} Almost all of our patients were receiving antibiotics, so we could not evaluate this variable as a potential risk factor. The use of antibiotics may partly explain the higher incidence of VAP in our study; this highlights the importance of cautious selection of patients for antibiotic treatment. The prophylactic use of antibiotics is not recommended, and exposure to antibiotics is a significant risk factor for colonization and infection with nosocomial multidrug-resistant pathogens.^{5,7,30,50} The judicious use of appropriate antibiotics may reduce patient colonization and subsequent infections with multidrug-resistant bacteria.

Our subgroup analyses may not have the power to identify all important VAP risk factors in this study population.

Despite those limitations, our findings indicate the importance of VAP in mechanically ventilated patients. Risk factors identified in this study need further validation. Additional studies of VAP risk factors, combined with knowledge of the causative pathogens, may lead to more effective VAP prevention and treatment strategies.

Conclusions

VAP is a common infection and certain interventions might affect the incidence of VAP. ICU clinicians should be aware of the risk factors for VAP, which could prove useful in identifying patients at high risk for VAP and modifying patient care to minimize the risk of VAP, such as avoiding unnecessary bronchoscopy or modulating enteral feeding.

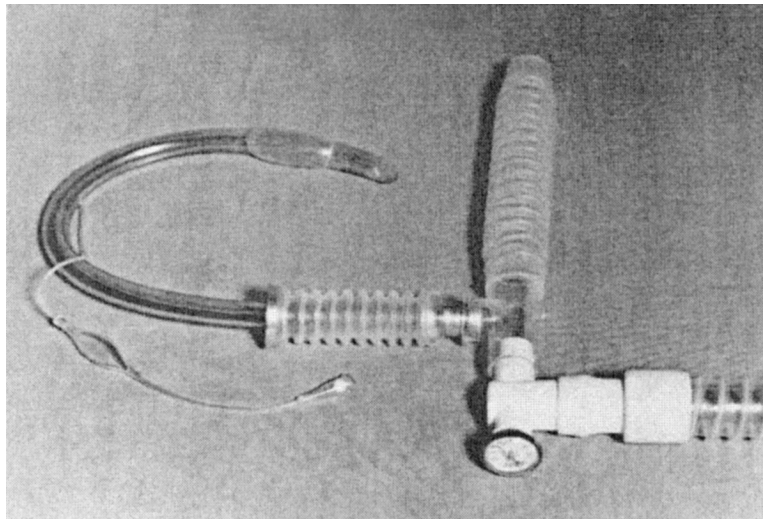
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