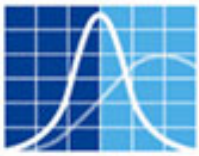

VENTILATOR-ASSOCIATED PNEUMONIA AT A TERTIARY-CARE CENTER IN A DEVELOPING COUNTRY: INCIDENCE, MICROBIOLOGY, AND SUSCEPTIBILITY PATTERNS OF ISOLATED MICROORGANISMS

Zeina A. Kanafani, MD; Layla Kara, PharmD; Shady Hayek, MD; Souha S. Kanj, MD

ABSTRACT

OBJECTIVE: Ventilator-associated pneumonia (VAP) complicates the course of up to 24% of intubated patients. Data from the Middle East are scarce. The objective of this study was to evaluate the incidence, microbiology, and antimicrobial susceptibility patterns of isolated microorganisms in VAP in a developing country.

DESIGN: Prospective observational cohort study.

SETTING: The American University of Beirut Medical Center, a tertiary-care center that serves as a major referral center for Lebanon and neighboring countries.

PATIENTS: All patients admitted to the intensive care and respiratory care units from March to September 2001, and who had been receiving mechanical ventilation for at least 48 hours, were included in the study. Results of samples submitted for culture were recorded and antimicrobial susceptibility testing of isolated pathogens was performed.

RESULTS: Seventy patients were entered into the study. The incidence of VAP was 47%. Gram-negative bacilli accounted for 83% of all isolates. The most commonly identified organism was *Acinetobacter anitratus*, followed by *Pseudomonas aeruginosa*. Fifty percent of all gram-negative bacterial isolates were classified as antibiotic resistant. Compared with patients without VAP, patients with VAP remained intubated for a longer period and stayed in the intensive care unit longer. VAP was not associated with an increased mortality rate.

CONCLUSION: Compared with other studies, the results from this referral center in Lebanon indicate a higher incidence of VAP and a high prevalence of resistant organisms. These data are relevant because they direct the choice of empiric antibiotic therapy for VAP (*Infect Control Hosp Epidemiol* 2003;24:864-869).

Pneumonia is the second most common nosocomial infection in the United States and the leading cause of death from hospital-acquired infections, with a crude mortality rate ranging from 20% to 50%.[1-4] Furthermore, it is the single most common infection acquired in the intensive care unit (ICU).[5] Ventilator-associated pneumonia, denoting nosocomial pneumonia arising 48 hours or more after initiation of mechanical ventilation, complicates the course of up to 24% of intubated patients; in some studies, ventilator-associated pneumonia accounts for almost 90% of infections in patients receiving mechanical ventilation.[6,7]

This was a prospective observational cohort study, the purpose of which was to evaluate the incidence, microbiology, and antimicrobial susceptibility patterns of isolated microorganisms in ventilator-associated pneumonia at the American University of Beirut Medical Center, a tertiary-care center in Lebanon. Currently available data from the United States and Europe do not necessarily reflect the trends in developing countries. Also, infecting organisms and resistance patterns differ widely among various centers[6,8,9]; this has major therapeutic implications. This study helped to discern epidemiologic and microbiological data that might be particular to this part of the world.

METHODS

Study Location

The American University of Beirut Medical Center is one of two tertiary-care centers in Beirut and a major referral center for the country and the region. The medical–surgical ICU and the respiratory care unit (RCU) consist of 8 and 12 beds, respectively. The units are run by a team of house staff officers under the supervision of an intensivist. The nurse-to-patient ratio is 2:1 in the ICU and 3:1 in the RCU. The American University of Beirut Medical Center operates an infection control program. When a nosocomial infection occurs in any unit of the hospital, infection control officers are notified. Data are collected and investigations are initiated in response to outbreaks. The use of broad-spectrum antimicrobial agents requires the approval of an infectious diseases specialist.

Drs. Kanafani and Kanj are from the Department of Medicine, Division of Infectious Diseases, and Dr. Hayek is from the Department of Surgery, American University of Beirut Medical Center; and Ms. Kara is from the School of Pharmacy, Lebanese American University, Beirut, Lebanon.

Address reprint requests to Souha S. Kanj, MD, FACP, Associate Professor of Medicine, Head, Division of Infectious Diseases, Department of Medicine, American University of Beirut Medical Center, P.O. Box 113-6044, Hamra 110 32090, Beirut, Lebanon.

Study Patients

All patients admitted to the ICU and RCU from March to September 2001, and who had been receiving mechanical ventilation for at least 48 hours, were consecutively included in the study. Eligible patients were older than 13 years and had normal findings on chest radiographs at baseline. Exclusion criteria included age younger than 13 years and the diagnosis of pneumonia on admission. For each patient, relevant demographic, clinical, and laboratory data were collected on entry into the study and daily thereafter until extubation, death, or the end of the study period. Patients could be entered into the study more than once if they had another episode of ventilator-associated pneumonia 7 or more days after the first episode with a microorganism different from the one previously isolated. Because this was an observational study, informed consent was not sought. The study was reviewed and approved by the Institutional Review Board of the American University of Beirut Medical Center.

Collection of Specimens and Microbiological Testing

Specimens for microbiological analysis were obtained when suspicion for ventilator-associated pneumonia arose. The microbiology laboratory rejected specimens that were submitted in leaky or nonsterile containers, or specimens received after prolonged delay (more than 2 hours). Qualitative cultures were performed on sputum, deep tracheal aspirate, and bronchoalveolar lavage specimens; results were recorded and antimicrobial susceptibility testing of isolated pathogens was performed. Identification of microorganisms was done according to standard procedures. Susceptibility patterns were determined by the disk-diffusion method according to the guidelines of the National Committee for Clinical Laboratory Standards.[10]

Definitions

The definition of ventilator-associated pneumonia was adapted from that of the Centers for Disease Control and Prevention (CDC).[11] Based on the American Thoracic Society consensus statement, early-onset ventilator-associated pneumonia was defined as pneumonia occurring within the first 4 days of mechanical ventilation and late-onset ventilator-associated pneumonia was defined as pneumonia developing 5 or more days after the initiation of mechanical ventilation.[12] The underlying disease conditions (eg, liver disease or renal insufficiency) were determined based on diagnoses mentioned in the patients' charts. Previous antibiotic use was defined as administration of antimicrobial agents for longer than 48 hours during the same hospital stay. Prophylaxis for stress ulcers was defined as administration of H_2-blockers or proton-pump inhibitors for longer than 48 hours during the hospital stay. Immunosuppression was considered present in patients who had received corticosteroids, chemotherapy, or radiation therapy within 4 weeks of entry into the study, or those who had a leukocyte count below 1,000/mm^3 at the time of inclusion in the study. Antimicrobial resistance among isolated organisms was defined as resistance to at least one class of antibiotics typically used in the treatment of ventilator-associated pneumonia. These classes included aminoglycosides (gentamicin, tobramycin, and amikacin), third-generation cephalosporins (ceftazidime), extended-spectrum penicillins (piperacillin/tazobactam), quinolones (ciprofloxacin), and carbapenems (imipenem).

TABLE 1
CHARACTERISTICS OF PATIENTS IN THE STUDY POPULATION

Characteristic	Patients With VAP (n = 33)	Patients Without VAP (n = 37)	*P*
Mean age, y (range)	59 (20–87)	62 (19–89)	.97
Gender, male:female	18:15	20:17	.97
Underlying disease (%)			
Abdominal surgery	8 (24)	6 (16)	.40
ARDS	2 (6)	2 (5)	.91
Cancer	5 (15)	9 (24)	.34
CHF	2 (6)	3 (8)	.74
Coma	11 (33)	10 (27)	.57
COPD	2 (6)	3 (8)	.74
Diabetes mellitus	8 (24)	11 (30)	.61
Liver disease	3 (9)	0	.06
Renal insufficiency	4 (12)	7 (19)	.44
Sepsis/shock	5 (15)	3 (8)	.36
Thoracic surgery	6 (18)	4 (11)	.38
Previous antibiotic use	28 (85)	31 (84)	.90
Stress ulcer prophylaxis	32 (97)	32 (87)	.12
Immunosuppression	9 (27)	14 (38)	.35

VAP = ventilator-associated pneumonia; ARDS = adult respiratory distress syndrome; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

Statistical Analysis

Probability values were obtained using chi-square. When applicable, the independent samples *t* test was performed. A *P* value of .05 or less was considered statistically significant.

RESULTS

Patient Characteristics

A total of 70 consecutive patients receiving mechanical ventilation for more than 48 hours were entered into the study. Thirty-three patients (47%) had one or more episodes of ventilator-associated pneumonia. Baseline demographic information on patients who developed ventilator-associated pneumonia and those without ventilator-associated pneumonia is provided in Table 1. There was no statistically significant difference between the two groups regarding age, gender, underlying disease, previous antibiotic use, stress ulcer prophylaxis, or immunosuppression.

TABLE 2
DISTRIBUTION OF ORGANISMS ISOLATED IN PATIENTS WITH EARLY-ONSET AND LATE-ONSET VENTILATOR-ASSOCIATED PNEUMONIA

Organism	Early-Onset VAP (n = 8)	Late-Onset VAP (n = 38)
Acinetobacter anitratus	1	10
Pseudomonas aeruginosa	1	7
Klebsiella species	1	5
Escherichia coli	0	5
Stenotrophomonas maltophilia	0	3
Enterobacter species	1	1
CNS	2	3
Staphylococcus aureus	2	1
Others	0	3

VAP = ventilator-associated pneumonia; CNS = coagulase-negative staphylococci.

TABLE 3
OUTCOME OF PATIENTS AT THE END OF THE STUDY PERIOD

Outcome	Patients With VAP	Patients Without VAP
Extubated* (%)	13 (39)	25 (68)
Intubated (%)	7 (21)	1 (3)
Deceased (%)	13 (39)	11 (30)
Total mean MV duration,† d (range)	30 (4–108)	9 (2–49)
Mean ICU/RCU stay,‡ d (range)	24 (2–117)	11 (2–54)

VAP = ventilator-associated pneumonia; MV = mechanical ventilation; ICU = intensive care unit; RCU = respiratory care unit.
*P = .006.
†P = .001.
‡P = .013 (comparing ICU/RCU after development of VAP with entire ICU/RCU stay for controls).

Episodes of Ventilator-Associated Pneumonia

We detected 40 episodes of ventilator-associated pneumonia in 33 patients. The incidence density was 30 per 1,000 ventilator-days. Seven (18%) of the episodes were classified as early-onset and 33 (82%) as late-onset ventilator-associated pneumonia. The mean number of days of mechanical ventilation after which patients developed ventilator-associated pneumonia was 12.8 (range, 3 to 92 days). Because some of the patients in the RCU were receiving long-term mechanical ventilation, being comatose or in a vegetative state, the duration of mechanical ventilation ranged from 4 to 108 days in the ventilator-associated pneumonia group and from 2 to 49 days in the group without ventilator-associated pneumonia. The cumulative risk of ventilator-associated pneumonia was 10 episodes per 100 patients by day 4, 37 by day 10, and 57 by day 92 of mechanical ventilation. The characteristics of patients who had early-onset ventilator-associated pneumonia were similar to those of patients who had late-onset ventilator-associated pneumonia.

Microbiology

Cultures were performed in 37 (93%) of the 40 cases. Most specimens were deep tracheal aspirates (28 cases, 70%); other specimens included sputum (2 cases, 5%), bronchoalveolar lavage (5 cases, 13%), and blood (2 cases, 5%). Thirty-three specimens (83%) yielded positive culture results, whereas the remaining 4 failed to grow any organisms. In 13 cases (33%), more than one organism was cultured, and the infection was thus termed polymicrobial. The total number of isolates was 46. Table 2 details the distribution of isolated pathogens categorized according to whether they were identified in the setting of early-onset or late-onset ventilator-associated pneumonia. Thirty-eight isolates of gram-negative bacilli were identified, amounting to 83% of all isolates. The most commonly identified organism was *Acinetobacter anitratus* (n = 11), followed by *Pseudomonas aeruginosa* (n = 8) and *Klebsiella* species (n = 6). Among the gram-positive organisms (17%), *Staphylococcus aureus* accounted for 3 isolates; the remaining isolates were coagulase-negative staphylococci (n = 5).

Susceptibility Patterns

All 11 isolates of *A. anitratus* and 3 isolates of *Stenotrophomonas maltophilia* were susceptible to imipenem, compared with 5 (63%) of the *P. aeruginosa* isolates. Conversely, all 8 isolates of *P. aeruginosa* were susceptible to amikacin and ciprofloxacin. In addition, 2 (33%) of the *Klebsiella* species isolates and 2 (40%) of the *Escherichia coli* isolates were extended-spectrum beta-lactamase producers. Taken together, 19 (50%) of 38 gram-negative bacterial isolates were classified as antibiotic resistant. Regarding *Staphylococcus aureus*, all 3 isolates were methicillin susceptible.

Outcome

Patient outcomes are listed in Table 3. At the end of the study period, 13 patients (39%) in the ventilator-associated pneumonia group were extubated and 7 (21%) were still receiving mechanical ventilation, whereas among those who did not develop ventilator-associated pneumonia, 25 (68%) were extubated and 1 (3%) was still intubated (P = .006). Patients without ventilator-associated pneumonia were more likely to be extubated at the end of the study than were patients with ventilator-associated pneumonia (odds ratio, 13.5; 95% confidence interval, 1.5 to 121.5). For patients with ventilator-associated pneumonia, the mean total duration of mechanical ventilation was 30 days, compared with 9 days for patients without ventilator-associated pneumonia (P = .001). The mean duration of ICU or RCU stay was longer for patients with ventilator-associated pneumonia than for patients without ventilator-associated pneumonia (24.5 and 11.3 days, respectively; P = .013). Thirteen patients with ventilator-associated pneumonia died (39%), compared with 11 patients without ventilator-associated pneumonia (30%). The difference in mortality between the two groups was not statistically sig-

nificant ($P = .40$). Among patients who developed ventilator-associated pneumonia, the likelihood of remaining intubated at the end of the study and the risk of death were both independent of the time of onset of pneumonia ($P = .60$ and 0.41, respectively).

DISCUSSION

Standardized criteria for the diagnosis of ventilator-associated pneumonia are still lacking. Numerous definitions have been formulated based on clinical, radiographic, and bronchoscopic criteria, none of which is universally accepted.[13] Even definitions based on histopathologic findings at autopsy have not proved to be flawless.[8,12,14-20] Such controversy has made the accurate diagnosis of ventilator-associated pneumonia difficult, especially in the setting of an underlying pulmonary process such as adult respiratory distress syndrome.[5,6] In this study, we adapted the CDC definition of nosocomial pneumonia that relies on data procured from the combination of clinical, radiographic, microbiological, and pathologic examinations.[11]

The incidence of ventilator-associated pneumonia in our patient population was 47%, which is clearly among the highest figures reported in the literature. A study of 1,014 patients receiving mechanical ventilation admitted to 16 ICUs in Canada quoted an incidence rate of 15.5%.[7] On the other hand, the European Prevalence of Infection in Intensive Care study found that 46.9% of 2,046 patients receiving mechanical ventilation developed pneumonia.[21] Weighing our results against data from other developing countries, we observed an incidence density of ventilator-associated pneumonia of 30 per 1,000 ventilator-days, compared with 23.9 in Jordan, 16.8 in Saudi Arabia, and 20 in Israel.[22-24] In the United States, the National Nosocomial Infections Surveillance System of the CDC reports an incidence density for ventilator-associated pneumonia of 10.5 per 1,000 ventilator-days in medical–surgical ICUs at major teaching centers.[25] These results raise key questions about infection control practices in our center. The small sample size in our study compared with the aforementioned studies probably contributed to this disparity. Intensive efforts are currently being made for the training of ICU and RCU staff in the prevention of nosocomial infections, and great attention is being focused on meticulously implementing these guidelines.

Most culture specimens in this study were obtained through deep tracheal aspiration rather than via bronchoscopy. Several studies have shown the superiority of invasive sampling of respiratory secretions over noninvasive techniques, with more antibiotic-free days and a lower mortality rate in the invasive management group.[26] However, other studies have failed to reproduce this favorable impact on outcome and have argued against the routine use of bronchoscopy for the diagnosis of ventilator-associated pneumonia.[27] We performed only qualitative cultures on respiratory specimens. False-positive results are therefore a concern in the setting of colonization of the upper airways. Some studies have used quantitative culture techniques, with 10^6 colony-forming units/mL of respiratory secretions as the cutoff point for the diagnosis of pneumonia. Sensitivity becomes an issue, however, because many patients with pneumonia may not be identified using this threshold.[28,29]

The spectrum of pathogens that caused pneumonia in our patients was in accordance with what has been described in many reports, in that most isolates consisted of gram-negative bacilli.[30-33] However, recent studies have referred to *Staphylococcus aureus* as an increasingly common pathogen in ventilator-associated pneumonia.[34] Polymicrobial infection was common in our patients (35%), which is also in line with the literature.[6,35] On categorizing the isolated organisms according to onset of ventilator-associated pneumonia, we noted that, similar to other studies,[9,12,36] *Staphylococcus aureus* isolates, all of which were methicillin susceptible, were more predominant in early-onset ventilator-associated pneumonia. Although *Acinetobacter* species, *P. aeruginosa*, and *Stenotrophomonas maltophilia* are classically more likely to play a role in late-onset ventilator-associated pneumonia, our results did not permit drawing such conclusions, as the number of isolates in each category was small. In this study, no molecular typing was done on the *Acinetobacter* species isolates. However, the different susceptibility patterns suggest that horizontal spread was not responsible for the transmission of this organism in all cases. Although coagulase-negative staphylococci are not regarded as typical respiratory pathogens and are often considered insignificant when isolated from respiratory specimens, the recovery of these organisms in pure growth in patients who fulfilled the criteria for ventilator-associated pneumonia suggests that they might be playing a role in the pathogenesis of pneumonia in these patients.

The emergence of antibiotic-resistant microorganisms in critically ill patients represents a challenge that intensive care and infectious diseases physicians in various parts of the world are facing.[37-39] Some studies have experimented with rotation and restricted use of antibiotics in an attempt to decrease the incidence of ventilator-associated pneumonia caused by multidrug-resistant bacteria.[40,41] All endeavors to decrease antimicrobial resistance notwithstanding, resistant bacteria still comprise a sizable portion of pathogens isolated in ventilator-associated pneumonia.[42] In this study, resistance in gram-negative bacterial isolates was calculated at 50%; this figure draws near to the rates of 42.2% and 48.8% reported in the literature.[40,41] As for *Staphylococcus aureus*, all isolates were methicillin susceptible. Previous antimicrobial therapy has been incriminated in increasing the risk of ventilator-associated pneumonia, selecting for resistant pathogens, and imparting a higher mortality rate.[30,34,36,43-47] However, this effect could not be explored in our study because in excess of 80% of patients had received antibiotics prior to developing ventilator-associated pneumonia. The widespread use of antimicrobial agents in our center is probably responsible for the high rate of resistant pathogens.

There is accumulating evidence that ventilator-associated pneumonia is a major cause of morbidity and increased cost of healthcare. For instance, one study found that ventilator-associated pneumonia prolonged the duration of mechanical ventilation from 10 to 32 days.[48] Another study reported that patients with ventilator-associated pneumonia stayed in the ICU 4.3 days longer than did control subjects.[49] Our results support this evidence: patients with ventilator-associated pneumonia remained intubated for a longer period, stayed in the ICU longer, and were 13.5 times more likely to be intubated at the end of the study period than patients without ventilator-associated pneumonia.

Ventilator-associated pneumonia as a cause of death has been a more controversial issue. Conflicting evidence exists as to how much ventilator-associated pneumonia contributes to the mortality of afflicted patients. Papazian et al. found that after controlling for other determinants of outcome, such as the Acute Physiology and Chronic Health Evaluation II score, ventilator-associated pneumonia was not a major cause of adverse outcome.[31] More recently, another study found similar results through multivariate analysis that showed renal failure, bone marrow failure, and treatment with corticosteroids, but not ventilator-associated pneumonia itself, to be independent risk factors for death in patients receiving mechanical ventilation.[50] Pneumonia caused by certain microorganisms, such as *Acinetobacter* species, *P. aeruginosa*, and *Stenotrophomonas maltophilia*, has been more firmly associated with increased mortality in such patients.[51]

In our study, we found no difference between patients with ventilator-associated pneumonia and those without ventilator-associated pneumonia regarding mortality rate. Also, whether the onset of ventilator-associated pneumonia was early or late did not affect outcome (intubation status and mortality). This is not consistent with evidence suggesting that early-onset ventilator-associated pneumonia is a less severe disease with a better prognosis than late-onset ventilator-associated pneumonia.[12] On the other hand, our study was likely underpowered to detect a true difference in mortality between patients with and patients without ventilator-associated pneumonia, or between patients with early-onset and patients with late-onset ventilator-associated pneumonia.

The main limitation of this study was the relatively small sample size. Also, Acute Physiology and Chronic Health Evaluation II scores, which would have been helpful in assessing the severity of the illness, were not calculated. Future studies should involve several centers from Lebanon, with the purpose of generating epidemiologic information that is representative of the whole country.

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