

clinical investigations in critical care

Antibiotic Utilization and Outcomes for Patients With Clinically Suspected Ventilator-Associated Pneumonia and Negative Quantitative BAL Culture Results*

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Objective: To evaluate antibiotic utilization and clinical outcomes among patients with clinically suspected ventilator-associated pneumonia (VAP) and culture-negative BAL (CNBAL).

Design: Prospective observational cohort study.

Setting: A medical ICU from a university-affiliated urban teaching hospital employing a previously described antibiotic discontinuation guideline for the management of VAP.

Patients: One hundred one patients with a clinical suspicion of VAP and CNBAL were evaluated between July 2002 and December 2004.

Interventions: Prospective patient follow-up and data collection. Antibiotic discontinuation was determined by the clinical guideline and not the results of BAL cultures.

Results: The average age of the patients was 60.4 ± 17.9 years and the mean APACHE II score was 23.2 ± 8.7 (\pm SD). The mean duration of mechanical ventilation prior to clinically suspected VAP was 2.9 ± 1.9 days. Nineteen patients (18.8%) received antibiotics for other indications prior to BAL. Empiric antibiotic therapy for VAP was begun in 65 patients (64.4%) following BAL. The duration of empiric antibiotic treatment following BAL was 2.1 ± 0.8 days. None of these patients received antibiotics for > 3 days (median, 2 days; range, 1 to 3 days). Six patients (5.9%) were treated with antibiotics for a secondary episode of VAP or hospital-acquired pneumonia developing at least 72 h after the CNBAL was performed and discontinuation of the empiric antibiotic therapy prescribed for the initially suspected episode of VAP. Overall, 35 patients (34.7%) died during hospitalization. Two deaths occurred in patients with a secondary episode of VAP following CNBAL and discontinuation of empiric antimicrobial therapy. Neither of these two deaths was attributed to VAP.

Conclusions: Although the decision to discontinue antibiotic treatment was based on clinical criteria and not BAL culture results, this study suggests that patients with a clinical suspicion of VAP and CNBAL can have empiric antimicrobial therapy safely discontinued within 72 h or in some cases withheld altogether. Prospective studies are needed to determine the safety of employing CNBAL as the primary criterion for the discontinuation of empirically begun antibiotic treatment for VAP.

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Key words: antibiotics; clinical outcomes; ICU; ventilator-associated pneumonia

Abbreviations: APACHE = acute physiology and chronic health evaluation; CNBAL = culture-negative BAL; CPIS = clinical pulmonary infection score; FI_{O_2} = fraction of inspired oxygen; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection reported among patients receiving mechanical ventilation.^{1–3} VAP is associated with attributable costs $> \$11,000$ per episode and case fatality rates $> 20\%$ in reported studies.^{4–7} Most episodes of VAP are attributed to potentially antibiotic-resistant bacteria.^{6,8–11} This has resulted in the need to prescribe

broad-spectrum initial antimicrobial therapy to patients with suspected VAP in order to avoid dispensing inappropriate treatment with its associated greater mortality.^{7,12,13} However, patient exposure to antibiotics, especially for ≥ 7 days, has been associated with subsequent emergence of patient colonization and infection with antibiotic-resistant bacteria.^{8,14–17} Therefore, physicians are increasingly

faced with the potentially competing clinical goals of prescribing appropriate initial antibiotic regimens to patients with clinically suspected VAP while avoiding the needless administration of these agents.

We previously demonstrated that clinical guidelines for the treatment of VAP could provide statistically greater administration of appropriate antimicrobial treatment while also reducing the overall duration of antibiotics.^{14,18} To further evaluate strategies aimed at minimizing antibiotic exposure for clinically suspected VAP, we performed an investigation with two main goals. First, we wanted to assess the utilization of antibiotics among patients with clinically suspected VAP and culture-negative BAL (CNBAL) in the setting of our clinical guideline. Antibiotic discontinuation decisions were based on clinical guideline criteria and not BAL culture results. Second, we planned to evaluate the clinical outcomes for this patient population.

MATERIALS AND METHODS

Study Location and Patients

The study was conducted at a university-affiliated urban teaching hospital: Barnes-Jewish Hospital (1,200 beds) in St. Louis, MO. During a 3-year period (January 2002 to December 2004), all patients admitted to the medical ICU (19 beds) were potentially eligible for this investigation. Patients were entered into the study if they were > 18 years of age and had a CNBAL evaluation for clinically suspected VAP. Patients were excluded from participation if they were admitted to the ICU with a diagnosis of community-acquired pneumonia or hospital-acquired pneumonia. Patients were also excluded if they had antibiotic therapy started or modified in the 48-h period prior to having a CNBAL.

The medical ICU is a closed unit where patient medical care, including antibiotic utilization, is determined by a multidisciplinary team supervised by physicians who are board certified in critical care medicine. Routine antibiotic treatment of bacterial infections, including VAP, does not require infectious disease consultation. However, a pharmacist routinely made rounds with the medical ICU team to assist in pharmacologic treatments, including antibiotic therapy. This study was approved by the Washington University School of Medicine Human Studies Committee.

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Study Design and Data Collection

A prospective cohort study was employed evaluating patients with clinically suspected VAP and a CNBAL. The main outcome evaluated was antibiotic utilization. Secondary outcomes assessed included hospital mortality, hospital and ICU lengths of stay, duration of mechanical ventilation, and the subsequent occurrence of VAP or hospital-acquired pneumonia during the same hospitalization.

One of the investigators (M.H.K.) made daily rounds in the medical ICU to identify eligible patients with VAP. Relevant data were recorded from medical charts, bedside flow sheets, computerized bedside nursing stations (EMTEK Health Care Systems; Tempe, AZ), computerized radiographic reports, and reports of microbiologic studies (sputum Gram stains and sputum, blood, and pleural fluid cultures). Study patients were prospectively monitored from the initial suspicion of VAP and performance of the CNBAL until they were discharged from the hospital or until death. Patients could not be entered into the study more than once.

For all study patients, the following characteristics were prospectively recorded at the time of study entry: age; gender; race; primary reason for mechanical ventilation; ratio of PaO₂ to fraction of inspired oxygen (FIO₂); severity of illness based on APACHE (acute physiology and chronic health evaluation) II scores¹⁹; clinical pulmonary infection score (CPIS)¹⁶; premorbid lifestyle score²⁰; presence of COPD requiring treatment with inhaled bronchodilators or systemic corticosteroids; congestive heart failure requiring treatment with afterload reducing agents or inotropic agents; underlying malignancy; immunosuppression; and HIV antibody status. Specific processes of medical care examined during the period of intensive care included the administration of corticosteroids, vasopressors, or inotropes; histamine type-2 receptor antagonists; sucralfate; proton-pump inhibitors; and prior antibiotic therapy during the same hospitalization; reintubation; and tracheostomy.

The VAP Antibiotic Policy

The need for initial empiric antibiotic treatment for clinically suspected VAP was based on the clinical judgment of the treating physicians. The VAP antibiotic discontinuation policy was developed based on our prior clinical experience.^{12,14,15} The predominant bacteria associated with VAP in this ICU are *Staphylococcus aureus* and potentially antibiotic-resistant Gram-negative bacteria.^{6,12,14} The main goals of the policy were to promote the initial administration of appropriate antimicrobial treatment for patients with clinically suspected VAP and to discontinue treatment when clinical evidence of infection had resolved. This was accomplished by recommending initial IV combination antimicrobial treatment for patients with cefepime (1 g q8h) plus/minus vancomycin (15 mg/kg q12h) or linezolid (600 mg q12h) plus/minus either ciprofloxacin (400 mg q12 h) or gentamicin (5 mg/kg qd). The combinations of cefepime and ciprofloxacin or cefepime and gentamicin were selected because they provided appropriate initial treatment for > 90% of Gram-negative bacterial isolates from patients with VAP based on the medical ICU-specific antibiogram.^{14,18} Additionally, all antibiotic administration was adjusted for patients with renal insufficiency to minimize toxicity.

The recommendations to discontinue empiric antibiotic treatment for clinically suspected VAP was promoted by the pharmacist or attending critical care physicians managing these patients during the course of morning patient rounds. Antibiotic treatment was recommended to be discontinued if one of the following two conditions were identified: (1) a noninfectious etiology for the infiltrates was identified not requiring antibiotics (eg, atelectasis, pulmonary edema), or (2) the signs and symptoms

suggesting active infection had resolved (*eg*, temperature $\leq 38.3^{\circ}\text{C}$, circulating leukocyte count $< 10,000/\mu\text{L}$ [$10 \times 10^9/\text{L}$] or decreased by $> 25\%$ from the peak value, improvement or lack of progression on the chest radiograph, absence of purulent sputum, and a $\text{PaO}_2/\text{FIO}_2$ ratio > 250).¹⁵ All of the criteria in the second condition had to be met for the antibiotic discontinuation recommendation to be made.

Routine VAP prevention measures were applied to all patients in the medical ICU. These included maintaining a semirecumbent body position, discontinuation of mechanical ventilation using an ICU-specific weaning protocol, avoidance of gastric distension by monitoring residual volumes following feedings, and routine inspection of ventilator circuits to remove condensate.²¹

Definitions

All definitions were selected prospectively as part of the original study design. APACHE II scores were calculated based on clinical data available from the first 24 h of ICU admission.¹⁹ Immunosuppression was defined as patients receiving corticosteroids, having a positive HIV antibody, having received chemotherapy within the past 45 days, having neutropenia (absolute neutrophil count $< 1.0 \times 10^9/\text{L}$) resulting from the administration of chemotherapy, or recipients of an organ transplant (renal, liver, heart, or bone marrow) requiring immunosuppressive agents. The premorbid lifestyle score was used as previously defined²⁰: 0 = patient was employed without restriction; 1 = patient was independent, fully ambulatory, not employed, or employed with restriction; 2 = patient had restricted activities, could live alone and get out of the house to do basic necessities, or had severely limited exercise ability; 3 = patient was house bound, could not get out of the house unassisted, could not live alone, or could not do heavy chores; and 4 = patient was bed bound or chair bound.

Clinical suspicion of VAP was based on clinical criteria modified from those established by the American College of Chest Physicians.²² These criteria require the occurrence of new and persistent radiographic infiltrates in conjunction with two of the following: fever, leukocytosis, and purulent tracheal aspirate or sputum. Persistence of an infiltrate was defined as having the infiltrate present radiographically for > 24 h. Fever was defined as an increase in the core temperature of $\geq 1^{\circ}\text{C}$ and a core temperature $> 38.3^{\circ}\text{C}$. Leukocytosis was defined as a 25% increase in the circulating leukocytes from the baseline admission value and a value $> 10,000 \mu\text{L}$ ($10 \times 10^9/\text{L}$). Tracheal aspirates were considered purulent if abundant neutrophils were present per high-power field using Gram stain (*ie*, > 25 neutrophils per high-power field). The CPIS was calculated as a modified score as outlined by Singh and coworkers.¹⁶

In addition to the clinical criteria for VAP, BAL culture specimens with appropriate quantitative thresholds were obtained bronchoscopically to support the diagnosis of VAP.^{7,22} Quantitative thresholds $\geq 10^4$ cfu/mL for a pathogenic microorganism were employed to support a diagnosis of VAP. Quantitative cultures $< 10^4$ cfu/mL were considered equivocal, and the absence of growth of potentially pathogenic microorganisms was considered to be a CNBAL. A secondary episode of VAP was considered to have occurred if it was diagnosed at least 72 h after CNBAL was performed and discontinuation of the empiric antibiotic treatment prescribed for the initial episode of clinically suspected VAP. Hospital mortality was defined as those patient deaths occurring during the initial hospital admission during which they were studied.

All patients were prospectively screened to exclude the following possible alternative causes for fever and radiographic chest densities. The presence of atelectasis was defined by the com-

plete disappearance of radiographic densities within 48 h of evaluation. Congestive heart failure with pulmonary edema was defined by a suggestive hemodynamic profile on pulmonary artery catheterization or transesophageal Doppler echocardiographic imaging (*ie*, increased pulmonary artery occlusion pressure or corrected flow time) and resolution of the pulmonary infiltrates following diuresis. Alveolar hemorrhage was defined by progressively bloodier return of BAL fluid and at least 20% hemosiderin-laden macrophages. Finally, pulmonary embolism was defined by the presence of at least two segmental or larger mismatched perfusion abnormalities on a ventilation-perfusion scan or suggestive radiographic findings on pulmonary angiography and spiral CT.

Statistical Analysis

Univariate analysis was used to compare variables. Comparisons were unpaired, and all tests of significance were two tailed. Continuous variables were compared using Student *t* test for normally distributed variables and the Mann-Whitney *U* test for nonnormally distributed variables. The χ^2 statistic or Fisher Exact Test were used to compare categorical variables. All values are presented as means and their SDs.

RESULTS

Patients and BAL Results

One hundred one consecutive patients with clinically suspected VAP and CNBAL specimens were evaluated. This included all patients having a CNBAL during the study period. The mean age of the patients was 60.4 ± 17.9 years (range, 23 to 95 years); 47 patients (46.5%) were men and 54 patients (53.5%) were women. The mean APACHE II score for all 101 patients comprising the entire study cohort was 23.2 ± 8.7 (range, 4 to 50), and the mean CPIS for this group was 6.3 ± 0.7 (range, 4 to 9). Baseline characteristics at entry into the study and the medical care process-of-care variables examined are present in Tables 1, 2. Seventy-eight patients (77.2%) had bilateral radiographic infiltrates and 23 patients (22.8%) had unilateral infiltrates present on the chest radiographs obtained on the day the CNBALs were performed. The mean duration of mechanical ventilation prior to clinically suspected VAP and performance of BAL was 2.9 ± 1.9 days. None of the 101 patients had growth of a pathogenic microorganism in their BAL cultures.

The percentage of neutrophils for the BAL specimens of the 69 specimens having this performed is demonstrated in Figure 1. The mean percentage of neutrophils was 27.1 ± 14.1 (range, 8 to 79%) for all specimens. The mean percentage of alveolar macrophages and lymphocytes was 62.4 ± 14.3 (range, 8 to 82%) and 7.3 ± 4.3 (range, 2 to 22%), respectively.

Antimicrobial Utilization

Nineteen patients (18.8%) were receiving antibiotics for other indications prior to having a clinical

Table 1—Baseline Characteristics of Patients at Entry Into the Study*

Characteristics	Data
Patients, No.	101
Age, yr	60.4 ± 17.9
Male/female gender, No.	47/54
Race	
White	64 (63.4)
Black	37 (36.6)
Reason for mechanical ventilation	
Acute lung injury/ARDS	5 (5.0)
COPD/asthma	22 (21.8)
GI hemorrhage	9 (8.9)
Hydrostatic pulmonary edema	26 (25.7)
Nonpulmonary sepsis	13 (12.9)
Mixed respiratory failure	26 (25.7)
COPD	32 (31.7)
Congestive heart failure	32 (31.7)
Underlying malignancy	23 (22.8)
Immunosuppressed	20 (19.8)
Positive serum HIV antibody	3 (3.0)
PaO ₂ /FIO ₂ ratio	229 ± 128
APACHE II score	23.2 ± 8.7
Lifestyle score	1.7 ± 1.1
CPIS	6.3 ± 0.7

*Data are presented as mean ± SD or No. (%) unless otherwise indicated.

suspicion for VAP and their BAL samples obtained (Fig 2). Sixteen of these patients (84.2%) were receiving antibiotics for nonpulmonary causes of sepsis (pancreatitis, urinary tract infection, biliary tract infection, GI tract infection), and 3 patients (15.8%) were receiving antibiotics empirically for an exacerbation of COPD. All patients underwent BAL within 12 h of having initial suspicion for VAP, based on the chest radiograph or clinical signs suggestive of VAP. Additionally, all patients had BAL performed

Table 2—Process-of-Care Variables*

Variables	Data
Patients, No.	101
Corticosteroids	15 (14.9)
Vasopressors or inotropes	40 (39.6)
GI hemorrhage prophylaxis	92 (91.1)
Reintubation	16 (15.8)
Tracheostomy	17 (16.8)
Prior antibiotics†	19 (18.8)
Prior antibiotic type	
Vancomycin alone	0 (0)
Broad-spectrum Gram-negative drug alone	3 (15.8)
Vancomycin and broad-spectrum Gram-negative drug	14 (73.7)
Other	2 (10.5)

*Data are presented as No. (%) unless otherwise indicated.

†Antibiotics administered during the 48 h prior to BAL.

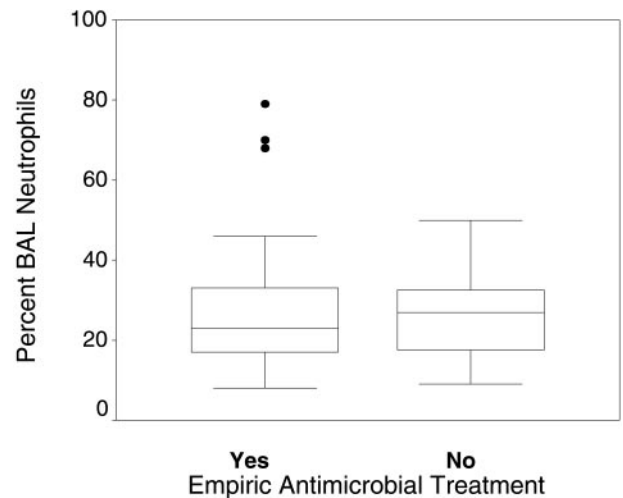


FIGURE 1. Box plots depicting the percentage of neutrophils in the BAL specimens of patients treated with empiric antimicrobial treatment (n = 45) and those not receiving empiric treatment (n = 24). The boxes represent 25th to 75th percentiles, with the 50th percentile shown as a solid line within the boxes. The 10th and 90th are shown as capped bars, and outliers are shown as black circles.

for clinically suspected VAP prior to the administration of empiric antibiotic treatment for VAP.

Sixty-five patients (64.4%) had empiric antibiotic therapy for VAP started after BAL sampling (Fig 2). The CPIS for the 65 patients begun on empiric antibiotic therapy for VAP after BAL sampling was statistically greater compared to the 36 patients not treated with empiric antibiotics for VAP following BAL sampling (6.5 ± 0.9 vs 5.8 ± 0.7 , $p < 0.001$). All other comparisons were not significantly different between patients treated with empiric antibiotics and those not receiving antibiotics following BAL sampling. Empiric antibiotic therapy for VAP consisted of cefepime plus/minus vancomycin or linezolid plus/minus ciprofloxacin or gentamicin in 63 of the treated patients (96.9%). The mean duration of antibiotic treatment following a CNBAL was 2.1 ± 0.8 days. None of the patients treated with empiric antibiotics received therapy for > 3 days (median, 2 days; range, 1 to 3 days). All decisions to discontinue antibiotic treatment were based on clinical criteria as outlined in the “Materials and Methods” section.

Forty-three patients (66.1%) empirically treated with antibiotics had specific noninfectious alternative etiologies identified for their radiographic infiltrates (atelectasis [n = 16], hydrostatic pulmonary edema [n = 13], nonhydrostatic pulmonary edema [n = 8], pulmonary embolism [n = 4], alveolar hemorrhage [n = 2]). Twenty-five patients (69.4%) not receiving empiric antibiotics had specific noninfectious alternative etiologies identified for their radiographic

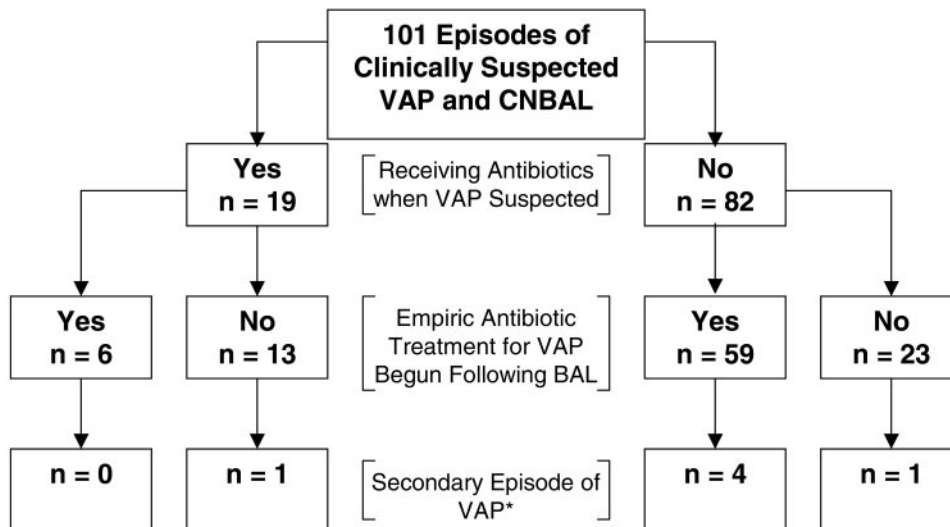


FIGURE 2. Algorithm detailing antibiotic management in 101 patients with CNBAL. *Episodes of secondary VAP occurred at least 72 h after CNBAL was performed and discontinuation of the empiric antibiotic therapy prescribed for the initially suspected episode of VAP.

infiltrates (atelectasis [n = 9], hydrostatic pulmonary edema [n = 8], nonhydrostatic pulmonary edema [n = 4], pulmonary fibrosis [n = 2], pulmonary embolism [n = 1], alveolar hemorrhage [n = 1]). The remaining patients had no specific alternative diagnoses established for their radiographic infiltrates.

Clinical Course

The peak body temperature and WBC count and the lowest value for PaO₂/FIO₂ ratio measured during a 24-h period are shown in Figures 3–5, respectively. There were no statistically significant differences in body temperature, WBC count, or PaO₂/FIO₂ ratio among all possible comparisons for the data obtained on the day of BAL and data obtained 3 days, 7 days, 10 days, and 14 days following BAL.

Secondary Outcomes

Secondary outcomes are presented in Table 3. Six patients were treated with a subsequent course of antibiotics for a suspected secondary episode of VAP (n = 5) or hospital-acquired pneumonia (n = 1). These episodes occurred 4, 6, 6, 7, 8, and 9 days after the initial CNBAL was performed and discontinuation of the initially prescribed course of empiric antibiotic treatment. Five of these patients had a positive respiratory culture finding (BAL [n = 2], tracheal aspirates [n = 3]) identifying a potential etiologic agent (methicillin-resistant *S aureus* [n = 3], Enterobacter species [n = 1], and *Pseudomonas aeruginosa* [n = 1]).

Overall, 35 patients (34.9%) died during hospitalization. Two deaths occurred in patients with a secondary episode of VAP. Neither of these two deaths was attributed to VAP. One patient died of diffusely metastatic melanoma, and one patient died from multiorgan dysfunction. The latter patient had an autopsy without evidence of acute pneumonia. Among the remaining 33 patient deaths, none were attributed to VAP. Six patients in this group had

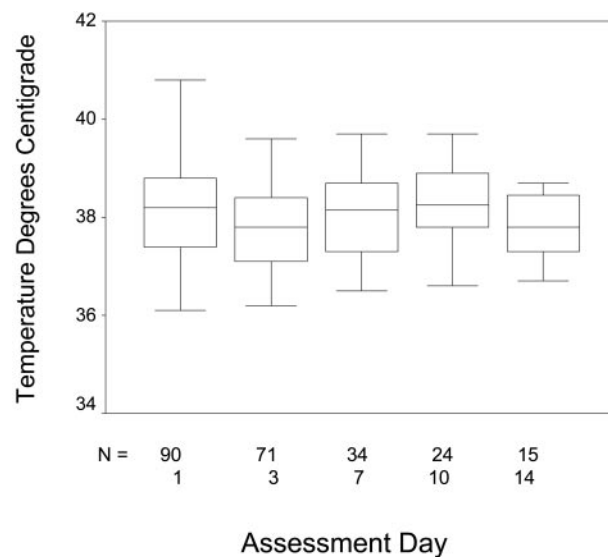


FIGURE 3. Box plots depicting body temperature for days 1, 3, 7, 10, and 14 as related to the collection of the BAL specimen. The boxes represent 25th to 75th percentiles, with the 50th shown as a solid line within the boxes. The 10th and 90th percentiles are shown as capped bars.

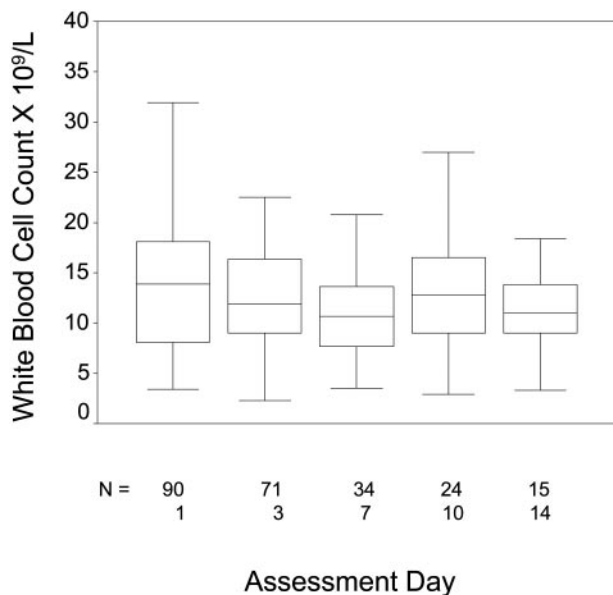


FIGURE 4. Box plots depicting WBC count for days 1, 3, 7, 10, and 14 as related to the collection of the BAL specimen. The boxes represent 25th to 75th percentiles, with the 50th percentile shown as a solid line within the boxes. The 10th and 90th percentiles are shown as capped bars.

autopsies, with one showing focal areas of pneumonia. The hospital mortality was similar for the 65 patients treated with empiric antibiotics following BAL sampling and the 36 patients not treated with antibiotics following BAL sampling (33.8% vs 36.1%, $p = 0.830$).

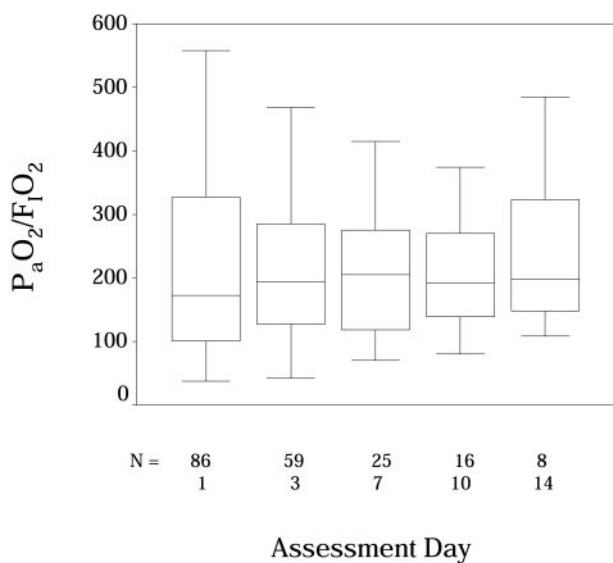


FIGURE 5. Box plots depicting P_{aO_2}/F_{iO_2} ratio for days 1, 3, 7, 10, and 14 as related to the collection of the BAL specimen. The boxes represent 25th to 75th percentiles, with the 50th percentile shown as a solid line within the boxes. The 10th and 90th percentiles are shown as capped bars.

DISCUSSION

We demonstrated that in a clinical setting employing a VAP antibiotic utilization policy, patients with clinically suspected VAP and a CNBAL specimen could have empiric antibiotics safely discontinued within 72 h or completely withheld in some cases. A small percentage of patients (5.9%) had secondary episode of VAP at least 72 h after having CNBAL performed and discontinuation of the empiric antibiotics prescribed to treat VAP. Patients with clinically suspected VAP and CNBAL specimens also had stable clinical markers of pulmonary infection (*eg*, body temperature, WBC count, and P_{aO_2}/F_{iO_2} ratio) for the 14 days following the initial suspicion of VAP.

Clinicians practicing in the ICU environment are often faced with competing concerns regarding their treatment decisions. The administration of appropriate initial antibiotic therapy for VAP and other potentially life-threatening infections has been associated with statistically improved survival compared to antibiotic therapy that is found to be ineffective against the pathogen(s) associated with infection.^{12,13} Several studies^{23–25} suggest that the administration of inappropriate initial antibiotic therapy results in greater hospital mortality due to the temporal delays in achieving treatment with antibiotics to which the pathogens are susceptible. Increasingly, patients in the ICU setting have risk factors for infection due to antibiotic-resistant bacteria (*eg*, prior antibiotic treatment during the same hospitalization, hospitalization for ≥ 5 days, admission from a nursing home or extended-care facility, home wound, or infusion therapy).^{8,26} Therefore, this patient population requires initial empiric treatment with broad-spectrum antibiotics in order to maximize the likelihood of providing appropriate initial treatment.^{7,15}

Competing with the need to administer appropriate initial antibiotic therapy is the necessity to prevent further antibiotic resistance. One of the most effective methods for preventing the emergence of antibiotic-resistant bacteria is the avoidance of unnecessary antibiotic use. Dennesen et al¹⁷ demonstrated that continuing appropriate antibiotic ther-

Table 3—Clinical Outcome Measures*

Variables	Data
Patients, No.	101
Hospital mortality	35 (34.7)
Hospital length of stay, d	15.9 ± 18.2
ICU length of stay, d	7.3 ± 7.7
Duration of ventilation, d	6.1 ± 7.3
Secondary episode of VAP	6 (5.9)

*Data are presented as No. (%) or mean \pm SD unless otherwise indicated.

apy beyond 7 days for VAP increased airway colonization with potentially antibiotic-resistant bacteria. Other investigators have shown that clinical efforts aimed at reducing the duration of empiric antibiotic therapy for VAP can be associated with reductions in the subsequent emergence of antibiotic resistant bacteria. Singh et al¹⁶ found that limiting the duration of empiric antibiotic therapy to 3 days for patients with clinically suspected VAP, and a CPIS of ≤ 6 statistically reduced subsequent colonization or infection with antibiotic-resistant bacteria. Similarly, Ibrahim et al¹⁴ demonstrated that the application of a clinical guideline for the treatment of VAP increased the initial administration of appropriate antimicrobial treatment and decreased the overall duration of antibiotics with fewer secondary infections due to antibiotic-resistant organisms.

Recently, the results of a large randomized trial¹⁵ comparing 8 days of appropriate antibiotic therapy for VAP to 15 days of treatment were reported. Despite similar efficacy, the longer course of antibiotic therapy was associated with statistically greater emergence of multiply resistant bacteria. Given the compelling findings supporting the link between the duration of antibiotic therapy and the emergence of antibiotic resistance, how should clinicians working in the ICU environment proceed? The above studies suggest that the development and implementation of local antibiotic discontinuation policies can be an effective strategy for reducing unnecessary antibiotic therapy in patients with clinically suspected VAP.^{14–16,18} These criteria should include specific recommendations regarding when antibiotic treatment can be discontinued based on the results of clinical or microbiologic criteria. Croce et al²⁷ demonstrated that severely injured patients with clinical criteria for VAP and a quantitative BAL culture with $< 10^5$ cfu/mL could safely have their antibiotics immediately discontinued. Overall, the false-negative rate using this threshold was 3%. Most false-negative results were associated with infection due to *P aeruginosa* and *Acinetobacter* species. Similarly, Timsit et al²⁸ showed that direct examination of BAL Gram stains could avoid unnecessary treatment in patients without VAP. Our study⁷ suggests that a CNBAL can also be safely employed as a criteria for discontinuing antimicrobial treatment in patients with clinically suspected VAP.

Our investigation has several important limitations. First, it was performed within a single ICU and the results may not be generalizable to other treatment settings including surgery or trauma patients and patients evaluated microbiologically using other diagnostic techniques. However, other studies^{14–16,27,29} have shown that empiric antibiotic treatment for clinically suspected VAP could be reduced in dura-

tion without adverse consequences. Second, our observational study was performed in a clinical setting employing an antibiotic treatment guideline, including criteria for the discontinuation of empiric antibiotics begun for clinically suspected VAP. The decision to discontinue antibiotic treatment was based on the clinical criteria in our guideline and not the results of the BAL cultures. Therefore, this study does not prove that CNBAL can solely be used as criteria to discontinue antibiotic treatment in patients with suspected VAP. Third, our patients had relatively low values for the CPIS. It is possible that these patients could have had their antimicrobial treatment discontinued simply based on persistently low CPIS scores as demonstrated by Singh and coworkers.¹⁶

The relatively low CPIS values we observed in this patient cohort also suggest that a potential sampling bias may have occurred. Patients at greater risk for VAP as determined by higher values for the CPIS may have been begun on empiric antibiotic therapy without undergoing BAL. Therefore, our study cohort may represent a group of patients at very low risk for VAP. Additionally, although the CPIS values were statistically lower for the patients we examined not begun on empiric antibiotics, our study design did not allow us to determine the clinicians' exact reasoning regarding whether or not to begin empiric antibiotic treatment for VAP. Nevertheless, the lower CPIS values suggest that patients at low risk for VAP did not have antibiotic therapy begun.

Another important limitation of this study is that we did not compare patients with CNBAL to those with positive or indeterminate BAL culture results. Therefore, we cannot compare the relative importance of CNBAL and clinical criteria for making antibiotic treatment decisions, nor can we compare the outcomes for these groups. There is also the possibility that some of the patients with a secondary episode of VAP represented initial treatment failures due to the premature discontinuation of antibiotics. This seems unlikely given the relatively small number of patients (5.9%) requiring such therapy and the absence of any patient deaths attributed to VAP. Additionally, the results of randomized trials examining early discontinuation of empiric antibiotic therapy for clinically suspected VAP have failed to identify differences in secondary episodes of VAP linked to the duration of initial antibiotic treatment.^{16,18} However, large prospective clinical studies are needed to confirm this observation, to assess the optimal approach for the antibiotic management of clinically suspected VAP, and to determine if CNBAL can be used as a primary criterion for the discontinuation of empirically started antibiotics.

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