ORIGINAL ARTICLE

Ventilator-Associated Pneumonia: Overdiagnosis and Treatment Are Common in Medical and Surgical Intensive Care Units

Veronique Nussenblatt, MD, MHS;[1] Edina Avdic, PharmD, MBA;[2] Sean Berenholtz, MD, MHS;[3,4]
Elizabeth Daugherty, MD, MPH;[5] Eric Hadhazy, MS;[1] Pamela A. Lipsett, MD, MHPE;[3,4]
Lisa L. Maragakis, MD, MPH;[1] Trish M. Perl, MD, MSc;[1] Kathleen Speck, MPH;[3]
Sandra M. Swoboda, RN, MS;[3] Wendy Ziai, MD;[3,6] Sara E. Cosgrove, MD, MS[1]

OBJECTIVE.   Diagnosing ventilator-associated pneumonia (VAP) is difficult, and misdiagnosis can lead to unnecessary and prolonged antibiotic treatment. We sought to quantify and characterize unjustified antimicrobial use for VAP and identify risk factors for continuation of antibiotics in patients without VAP after 3 days.

METHODS.   Patients suspected of having VAP were identified in 6 adult intensive care units (ICUs) over 1 year. A multidisciplinary adjudication committee determined whether the ICU team's VAP diagnosis and therapy were justified, using clinical, microbiologic, and radiographic data at diagnosis and on day 3. Outcomes included the proportion of VAP events misdiagnosed as and treated for VAP on days 1 and 3 and risk factors for the continuation of antibiotics in patients without VAP after day 3.

RESULTS.   Two hundred thirty-one events were identified as possible VAP by the ICUs. On day 1, 135 (58.4%) of them were determined to not have VAP by the committee. Antibiotics were continued for 120 (76%) of 158 events without VAP on day 3. After adjusting for acute physiology and chronic health evaluation II score and requiring vasopressors on day 1, sputum culture collection on day 3 was significantly associated with antibiotic continuation in patients without VAP. Patients without VAP or other infection received 1,183 excess days of antibiotics during the study.

CONCLUSIONS.   Overdiagnosis and treatment of VAP was common in this study and led to 1,183 excess days of antibiotics in patients with no indication for antibiotics. Clinical differences between non-VAP patients who had antibiotics continued or discontinued were minimal, suggesting that clinician preferences and behaviors contribute to unnecessary prescribing.

Infect Control Hosp Epidemiol 2014;35(3):278-284

Ventilator-associated pneumonia (VAP) is a common diagnosis in intensive care units (ICUs), occurring in 9%–27% of intubated patients.[1,2] VAP has been associated with higher mortality, increased length of ICU stay, and greater hospitalization costs.[3-6] Delayed appropriate empiric antimicrobial therapy has been associated with worse outcomes in patients with VAP;[7-10] therefore, aggressive early treatment of these patients is commonly practiced.

Guidelines published by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) recommend the use of clinical signs and quantitative or semiquantitative microbiological data to diagnose and manage VAP.[7] Critically ill patients commonly manifest fever, leukocytosis, infiltrates, and hypoxia that can represent VAP or noninfectious conditions; thus, the diagnosis of VAP is chal-lenging, and its misdiagnosis can lead to unnecessary and prolonged antimicrobial therapy. Because of challenges associated with making the diagnosis of VAP, IDSA/ATS guidelines highlight the importance of reassessing patients after 48–72 hours to determine whether antibiotic therapy for VAP is needed or whether an alternative diagnosis should be pursued. Thus far, most studies have focused on optimizing appropriate antimicrobial choice for VAP;[11-13] however, data examining the excessive use of antibiotics for VAP in patients without VAP are limited. In 1 study, Swoboda et al[14] found that half of the empiric antibiotic use for VAP in 2 surgical ICUs was prescribed for patients without pneumonia.

Antimicrobial resistance continues to be a threat in the ICU, and studies are needed to identify areas of antimicrobial management that can be optimized in order to decrease un-
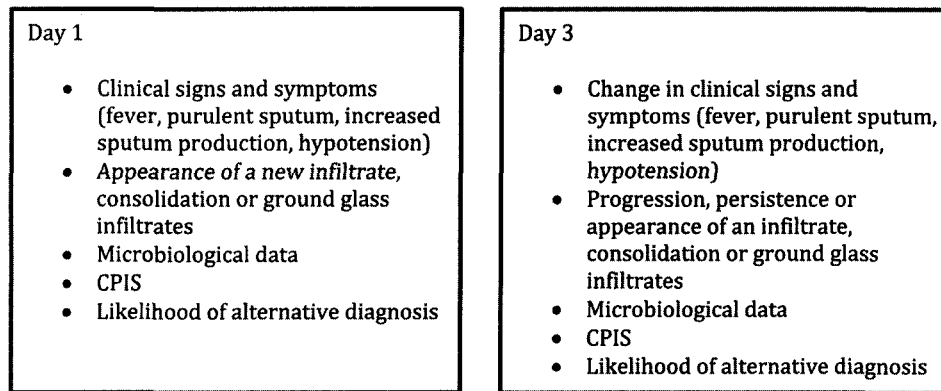
FIGURE 1.   Criteria used by the adjudication committee for the diagnosis of ventilator-associated pneumonia (VAP). All criteria were considered by the adjudication committee in making the diagnosis of VAP. Clinical pulmonary infection score (CPIS) was used as a clinical tool to determine the likelihood of VAP in conjunction with other criteria, but a low score did not outweigh other criteria suggesting a likely diagnosis of VAP.

necessary antibiotic use without compromising patient outcomes. In this study, we sought to quantify and characterize justified and unjustified antimicrobial use for VAP and identify risk factors for the continuation of antibiotics in patients without VAP after 3 days.

METHODS

Study Population

Mechanically ventilated patients suspected of having VAP by their ICU teams were prospectively identified in 6 adult ICUs between February 2009 and February 2010 at Johns Hopkins Hospital, a 913-bed academic tertiary care center in Baltimore, Maryland. Patients were excluded from the study if they died prior to receiving at least 3 days of antibiotics.

Data Collection

Study staff identified ICU patients administered antibiotics daily, using an electronic database (Theradoc). If the indication for antibiotics were unclear from the chart, indication was confirmed with ICU staff.

The same database and electronic medical records were used to collect clinical data, including microbiological and radiographic information, antibiotic therapy, and clinical course. Other infectious processes requiring antibiotic treatment were recorded. In-hospital mortality was defined as death occurring for any reason during the hospitalization in which the VAP occurred. *Clostridium difficile* infection was recorded if it occurred within 30 days of receiving antibiotics for VAP. Baseline severity of illness was measured using the acute physiology and chronic health evaluation (APACHE) II[15] 24 hours before the patient was identified as having VAP by the ICU team. The clinical pulmonary infection score (CPIS)[16] was calculated by the research team at diagnosis and on day 3 after the ICU VAP diagnosis. Multiple episodes of VAP in a single patient were included in the total number of

VAP events if appropriate treatment for the first event was completed and associated with clinical improvement prior to the subsequent VAP event.

Adjudication Methods

VAP events were reviewed by a multidisciplinary adjudication committee consisting of surgery, anesthesia, pulmonary and critical care medicine, pharmacy, and infectious diseases specialists to determine whether the ICU team's VAP diagnosis and antimicrobial therapy were justified. Committee members were selected because of their expertise caring for critically ill patients with pneumonia. The committee used clinical, microbiologic, and radiographic data including the CPIS on the day of diagnosis and day 3, with reviewers blinded to later events, to adjudicate the cases (Figure 1). Each case was reviewed by at least 2 members independently. If there were disagreement between reviewers, the committee erred on the side of the most lenient reviewer. Unjustified antibiotic use was defined as the prescription of antibiotics for a patient with VAP diagnosed by the ICU clinicians but adjudicated not to have VAP (Clin+/Adj−).

Data Analysis

Data were analyzed using STATA (ver. 12.0; STATACorp). Student t test and 2-group test of proportions were used to compare continuous and dichotomous characteristics, respectively, of patients with Clin+/Adj− VAP on day 3 whose antibiotics were continued past or discontinued on day 3. Multiple logistic regression models were used to obtain adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the same associations adjusted for potential confounding variables. We used a robust variance estimator to account for patient-level clustering, since patients could contribute more than 1 VAP event. Covariates were included in the multiple logistic regression model if the associated P value were less

than .05 in the univariate model, if they changed the association of primary interest by at least 20%, if they had previously been identified as a potential confounder in the literature, or if it were biologically plausible that they could confound the association of interest. Explanatory variables were added in a stepwise fashion to assess the effect of the addition of each variable on other covariates.

Excess days of antibiotics were calculated for individual antibiotics as the number of days an antibiotic was given past 3 days for patients with Clin+/Adj− VAP. For Clin+/Adj− VAP patients thought to have an alternative diagnosis of ventilator-associated tracheobronchitis at day 3, treatment past 5 days was considered excessive. If a patient with Clin+/Adj+ VAP had clinical improvement by day 8 (eg, was extubated, discharged from ICU, required minimal ventilator settings), therapy past day 8 was considered excessive. If not, antibiotic therapy was considered appropriate until day 14, after which antibiotics were considered excessive if no other workup were performed to rule out alternative diagnoses. Treatment duration for patients with Clin+/Adj+ VAP with *Staphylococcus aureus*, *Pseudomons*, *Acinetobacter*, and multidrug-resistant gram-negative organisms was not considered excessive until

after 14 days. Antibiotic days were normalized by dividing the total excess antibiotic days by the total number of VAP cases in each ICU.

RESULTS

VAP Rates on Days 1 and 3

A total of 231 events were identified as VAP by the ICU teams in 203 patients: 34 (14.7%), 137 (59.3%), and 60 (26%) in the medical, surgical subspeciality, and general surgery ICUs, respectively. On day 1, 135 of the ICU-diagnosed VAP events (58.4%) were determined to be Clin+/Adj−. On day 3, 158 events (68.4%) were adjudicated to be Clin+/Adj−. The most frequent alternative diagnoses for Clin+/Adj− VAP on day 3 included VAT ($n = 13$), pulmonary edema ($n = 22$), atelectasis ($n = 5$), and cardiogenic shock ($n = 4$).

Differences between Patients with Clin+/Adj− and Clin+/Adj+ VAP on Day 3

Time from intubation to diagnosis of VAP was 3 days or fewer for 22 patients with Clin+/Adj+ VAP on day 3. One of these patients was extubated at the time of diagnosis. The

TABLE 1. Demographic and Clinical Characteristics for Patients without Ventilator-Associated Pneumonia (VAP; $n = 155$) on Day 3

Characteristic	Antibiotics discontinued ($n = 35$)	Antibiotics continued ($n = 120$)	P
Age, mean ± SD, years	60.7 ± 11.4	62.2 ± 14.4	.55
Sex, female	18	35	.055
Underlying lung disease[a]	40	30	.26
WBC count, mean ± SD	13,378.6 ± 7,590.7	14,803.9 ± 8,050.9	.35
Decrease in WBC count[b]	58	49	.35
New infiltrate on imaging	24	25	1.00
Febrile on day 3	32	33	.84
Vasopressors			
Day 1	61	43	.058
Day 3	50	36	.31
Change in character of sputum	12	27	.076
Purulent secretions	60	69	.34
Sputum culture obtained			
Day 1	95	78	<.03
Day 3	16	39	<.01
Positive Gram stain			
Day 1	68	61	.49
Day 3	50	43	.73
Positive sputum culture on day 1	14	31	.045
CPIS >6	17	15	.76
APACHE score, mean ± SD[c]	25.3 ± 7.6	22.7 ± 7.0	.055
Still intubated at day 3	86	86	.99
Days to clinician-diagnosed VAP	9.45 ± 13.9	8.7 ± 9.6	.70
Other source infection	45	33	.20

NOTE. Data are %, unless otherwise indicated. APACHE, acute physiology and chronic health evaluation; COPD, chronic obstructive pulmonary disease; CPIS, clinical pulmonary infection score; SD, standard deviation; WBC, white blood cell.
[a] Includes COPD, emphysema, and idiopathic lung fibrosis.
[b] Decrease in WBC count from day 1 to day 3.
[c] Twenty-four hours prior to VAP diagnosis.

Adjudicated VAP n=71
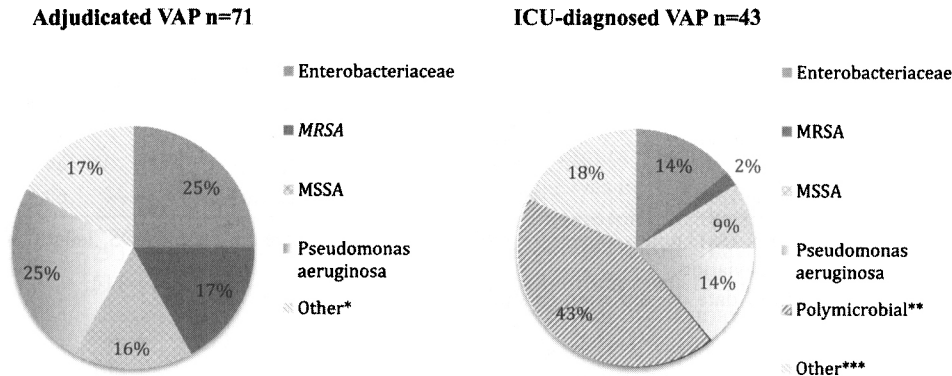
ICU-diagnosed VAP n=43

FIGURE 2. Culture results for adjudicated and intensive care unit (ICU)–diagnosed ventilator-associated pneumonia (VAP). One asterisk: *Acinetobacter baumannii* ($n = 3$), *Stenotrophomonas maltophilia* ($n = 2$), *Streptococcus* spp. ($n = 5$), *Haemophilus influenza* ($n = 2$). Two asterisks: methicillin-resistant *Staphylococcus aureus* (MRSA; $n = 4$), *Pseudomonas aeruginosa* ($n = 6$), methicillin-sensitive *S. aureus* (MSSA; $n = 2$), and Enterobacteriaceae ($n = 7$) were recovered from polymicrobial cultures. Three asterisks: *Streptococcus* spp. ($n = 1$), *Enterococcus faecalis* ($n = 2$), *Haemophilus influenza* ($n = 2$), yeast ($n = 3$).

mean age of patients with Clin+/Adj+ VAP on day 3 was 54.2 ± 17.4 years compared with 61.9 ± 13.7 years for those with Clin+/Adj− VAP ($P < .01$). Ninety-two percent of patients with Clin+/Adj+ VAP on day 3 had progression, persistence, or appearance of an infiltrate compared with 25% of patients with Clin+/Adj− VAP ($P < .01$). Five Clin+/Adj+ VAP patients had no infiltrate on day 3. Of these, 3 had one on day 1, and their clinical course suggested VAP despite no infiltrate on day 3. One patient had questionable imaging, purulent secretions, and significant oxygen requirements and was too ill to be considered to have VAT, and 1 patient was bacteremic with the same organism recovered in the sputum. Ninety-seven percent of patients with Clin+/Adj+ VAP were still intubated on day 3 compared with 86% of patients with Clin+/Adj−VAP ($P < .01$). Mean CPIS on days 1 and 3 were 7.5 ± 2.2 and 6.9 ± 1.8 for those with Clin+/Adj+ VAP and 4.9 ± 2.0 and 4.5 ± 2.0 for those with Clin+/Adj− VAP ($P < .001$).

Differences between Patients with Clin+/Adj− VAP Whose Antibiotics Were Continued or Discontinued Past Day 3

Antibiotics were continued in 120 (76%) of the 158 Clin+/Adj− events on day 3. Characteristics for events with Clin+/Adj− VAP whose antibiotics were discontinued at day 3 or continued beyond day 3 are shown in Table 1. Patients whose antibiotics were discontinued at day 3 had higher illness severity than those whose antibiotics were continued; they were more likely to require vasopressors on day 1 (61% vs 43%; $P = .058$) and day 3 (50% vs 36%; $P = .31$) and had higher mean APACHE II scores (25.3 ± 7.6) than patients whose antibiotics were continued past day 3 (22.7 ± 7.0; $P = .055$). Among patients whose antibiotics were continued past day 3, a smaller proportion had a sputum sample sent for culture on day 1 compared with those whose antibiotics were discontinued (78% vs 95%; $P < .03$), but a larger proportion

had one sent on day 3 (39% vs 16%; $P < .02$). Overall, a small proportion of patients with Clin+/Adj−VAP on day 3 had positive sputum cultures on day 1 (26%), and patients whose antibiotics were continued had a greater proportion of positive sputum cultures on day 1 (31%) compared with those whose antibiotics were discontinued (14%; $P = .045$). The mean CPIS score for both groups combined was 5.3 ± 0.1, with 17% and 15% of patients having a CPIS score greater than 6 on day 3 among those whose antibiotics were discontinued and continued, respectively ($P = .71$). Among patients with Clin+/Adj− VAP on day 3 and no other source of infection requiring antibiotics, purulent sputum was present for 66% of the patients whose antibiotics were continued past day 3, compared with 36% in those who had them discontinued ($P = .04$). Otherwise, there were no other significant differences in the characteristics listed in Table 1 between these 2 groups. Among patients with VAT, antibiotics were discontinued by day 3 in 3 patients.

Multivariate Analysis of Factors Associated with Antibiotic Continuation in Patients with Clin+/Adj− VAP after 3 Days

After adjusting for APACHE II score and requiring vasopressors on day 1, sputum culture collection on day 3 was associated with a 3.2 times higher odds of having antibiotics continued compared with those who did not have sputum sent for culture ($P < .03$) among patients with Clin+/Adj− VAP. This association appeared to be driven mainly by a surgical subspecialty ICU, although this association was seen across ICUs. In this model, requiring vasopressors on day 1 was associated with a decreased odds of antibiotic continuation for patients with Clin+/Adj− VAP (OR, 0.44; $P = .04$), and APACHE score was no longer associated with antibiotic continuation (OR, 1.0; $P > .05$).

TABLE 2. Clinical Outcomes for Patients without Ventilator-Associated Pneumonia on Day 3

Outcome	Antibiotics discontinued (n = 38)	Antibiotics continued (n = 120)	P
Death	14 (37)	26 (22)	.061
Clostridium difficile infection[a]	0 (0)	9 (7.5)	.82
ICU LOS, mean ± SD, days	20.7 ± 17.7	22.8 ± 16.3	.49
Developed multidrug resistance	4 (10.5)	10 (8.3)	.68

NOTE. Data are no. (%), unless otherwise indicated. ICU, intensive care unit; LOS, length of stay; SD, standard deviation.
[a] Within 1 month of date of admission to study.

Microbiology Results for Clin+/Adj+ VAP and Clin+/Adj− VAP Events

The most common organisms recovered in patients with Clin+/Adj+ VAP were *Pseudomonas aeruginosa* (25%), methicillin-resistant *S. aureus* (17%), and methicillin-sensitive *S. aureus* (16%; Figure 2). Among patients with Clin+/Adj− VAP, 50% of the cultures were polymicrobial. Bronchoscopy was used infrequently for the diagnosis of VAP in this cohort; 36 (16%) patients had bronchoscopy with bronchoalveolar lavage performed on day 1 and 7 (3%) on day 3.

Clinical Outcomes for Patients with Clin+/Adj− VAP on Day 3 Whose Antibiotics Were Continued or Discontinued

Among patients with Clin+/Adj− VAP on day 3, 13 (37%) and 26 (22%) deaths occurred in patients whose antibiotics were discontinued and continued past day 3, respectively (P = .063). The all-cause mortality rate among patients with Clin+/Adj+ VAP on day 3 was 31.5%. Two deaths were due to VAP; 4 additional deaths were possibly related to VAP in conjunction with other causes. In a multiple logistic regression model for patients with Clin+/Adj− VAP, the continuation of antibiotics past day 3 was not significantly associated with mortality (OR, 0.78; P = .60) after adjusting for APACHE score and need for vasopressors at day 1. Higher APACHE score (OR, 1.17; P < .001) and need for vasopressors (OR, 3.70; P < .01) were both associated with higher odds of death in the same model. ICU length of stay and *Clostridium difficile* colitis rates were not significantly different between groups (Table 2).

Excess Days of Antibiotics Attributed to Unjustified Antibiotic Use

Patients with Clin+/Adj+ VAP on day 3 received 374 excess days of antibiotics, mainly as a result of prolonged therapy beyond 8 days despite clinical improvement or resolution. Patients with Clin+/Adj− VAP and no other source of infection requiring antibiotic treatment received 1,183 excess days of antibiotic during the duration of the study. Excess days of antibiotics/case are listed by ICU in Table 3.

DISCUSSION

This study demonstrates that antibiotics are continued for a large proportion of patients without VAP beyond 3 days after a diagnosis of possible VAP (77.4%) and that clinical differences between patients without VAP who had antibiotics continued or discontinued after 3 days of treatment were minimal, suggesting that clinician practices and preferences contribute to unnecessary prescribing. Over the year of the study, overdiagnosis and treatment of VAP resulted in a cumulative 1,183 excess days of antibiotics in adult ICU patients with Clin+/Adj− VAP and no other indication for antibiotics. Among patients with Clin+/Adj+ VAP, prolonged VAP treatment beyond the recommended duration led to an additional 374 excess days of antibiotics. These findings highlight the need for interventions to reduce antibiotic misuse for VAP.

The diagnosis of VAP is complicated by cardiorespiratory comorbidities that are common in critically ill patients. Furthermore, the presence of individual clinical manifestations are nonspecific for VAP.[18-21] In a meta-analysis by Klompas et al,[22] the only clinical factor to substantively predict the probability of the infection was the absence of a new infiltrate on a plain radiograph, which lowered the likelihood of VAP. In our study, only 25% of patients with Clin+/Adj− VAP had progression, appearance, or persistence of an infiltrate on imaging, suggesting that radiographic findings did not drive the ICU's decision to treat for VAP. Reasons for this may be that physicians may interpret terms such as "less likely" or "possible" in the radiology report as having diagnostic certainty or that practitioners may be using their own imaging read as opposed to the radiologists' report.

Half of the cases with Clin+/Adj− had polymicrobial cultures, suggesting that cultures representing colonization of patients with potential pathogens were frequently viewed as true pathogens by the ICUs. Targeting antimicrobial stewardship interventions to educate ICU staff about differentiating between true pathogens and colonizing organisms may help decrease antimicrobial use in patients without VAP.

There are several possible reasons for the high rate of antibiotic prescribing beyond 3 days for patients with Clin+/Adj− VAP in our study. The first is that physicians may not

TABLE 3. Excess Days of Antibiotics Attributed to Patients Who Had No Other Source of Infection and Did Not Have Ventilator-Associated Pneumonia on Day 3

Intensive care unit	Excess days	Events	Excess days/event
Medical			
A	87	10	8.7
B	34	4	8.5
Surgical subspecialty			
C	293	27	10.9
D	515	36	14.3
General surgical			
E	146	12	12.2
F	108	9	12
Total	1,183	98	12.1

actively reassess the need for antibiotics in patients with suspected VAP. Insufficient microbiological data available on day 3 may prevent physicians from discontinuing antibiotics in some patients, highlighting the importance of obtaining sputum cultures early. A larger proportion of these patients had sputum cultures on day 3, possibly indicating the ICUs continued to attempt to solidify a diagnosis. In our study, patients whose antibiotics were discontinued after 3 days of treatment were sicker and may have had apparent alternative etiologies for their critical illness, leading to the cessation of antibiotics.

Convincing providers to stop therapy once a patient has stabilized is difficult because of the perception that the antibiotic contributed to the patient's improvement. Although debate continues regarding the diagnostic validity of the CPIS for VAP,[19,23] results from the trial by Singh et al[24] demonstrated that the CPIS can be an effective clinical tool to determine which patients with initially low CPIS may have their antibiotics discontinued after 3 days. Although some Clin+/Adj− patients had high CPIS scores in our study, the overall low CPIS scores in these patients indicate that use of the score may have been useful in this cohort.

Several studies have demonstrated that shorter courses of antimicrobial therapy for VAP are safe.[17,25-27] Chastre et al[17] reported that mortality and VAP recurrence did not differ between patients who received 8 versus 15 days of antibiotics. Ibrahim et al[26] reported that in-hospital mortality was similar for patients with VAP before and after the introduction of a clinical guideline reducing the mean number of antibiotic days for VAP from 14.8 to 8.6. In our study, mortality was higher in the Clin+/Adj− patients whose antibiotics were discontinued; however, this is consistent with these patients being sicker at baseline. Incorporating evidence-based recommendations for treatment duration for VAP in hospital guidelines is likely to encourage adherence to shorter courses of antibiotics.

Our study has limitations. Antibiotic use for Clin+/Adj− VAP was so prevalent across ICUs that we may not have been able to capture true differences between groups. The adjudication process was based on expert opinion, and some clin-

ical factors influencing antibiotic prescribing for VAP might be captured only at the bedside; both could have resulted in an over- or underestimation of antibiotic use for VAP. This was an observational study, so we cannot extrapolate with certainty that early discontinuation in patients without confirmation of VAP is safe. Bronchoscopy with bronchoalveolar lavage was not used frequently to obtain quantitative cultures in our hospital at the time of the study. Invasive techniques to obtain cultures have been associated with alterations in antibiotic management,[28,29] so the amount of antibiotic overuse in our study may not be representative of practices in ICUs where invasive testing is routinely used. Also, awareness of recent changes to the VAP surveillance definition by the Centers for Disease Control's National Healthcare Safety Network[30] may have changed prescribing practices in ICUs compared with when the study took place.

Despite these limitations, our study has important implications. Excess use of antibiotics is associated with increased health costs, risk of adverse reactions, selection of drug-resistant organisms, and an increase in morbidity and mortality.[18-20] Difficulties in correctly diagnosing VAP in critically ill patients lead to unnecessary empiric antibiotic use. In our study, antibiotics were frequently continued in patients who did not have VAP at day 3, and the decision to continue antibiotics did not appear to be related to patient clinical parameters. Larger studies are needed to study physician beliefs and practices about diagnosing and treating VAP so that interventions can be developed to decrease excess antibiotic use for these patients.

Address correspondence to Sara Cosgrove, MD, MS, Hospital Epidemiology and Infection Control and Antimicrobial Stewardship Program, Johns Hopkins Hospital, 600 North Wolfe Street, Osler 425, Baltimore, MD 21287 (scosgro1@jhmi.edu).

REFERENCES

1. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165:867–903.
2. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002;122:2115–2121.
3. Safdar N, Dezfulian C, Collard HR, et al. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005;33:2184–93.
4. Warren DK, Shukla SJ, Olsen MA, et al. Outcome and attributable cost of ventilator-associated pneumonia among intensive

care unit patients in a suburban medical center. *Crit Care Med* 2003;31:1312–1317.

5. Heyland DK, Cook DJ, Griffith L, et al. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. *Am J Respir Crit Care Med* 1999;159:1249–1256.

6. Bercault N, Boulain T. Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. *Crit Care Med* 2001;29: 2303–2309.

7. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.

8. Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 2002;122:262–268.

9. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest* 1997;111:676–685.

10. Fowler RA, Flavin KE, Barr J, et al. Variability in antibiotic prescribing patterns and outcomes in patients with clinically suspected ventilator-associated pneumonia. *Chest* 2003;123:835–844.

11. Eachempati SR, Hydo LJ, Shou J, et al. Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? *J Trauma* 2009;66:1343–1348.

12. Leone M, Garcin F, Bouvenot J, et al. Ventilator-associated pneumonia: breaking the vicious circle of antibiotic overuse. *Crit Care Med* 2007;35:379–385.

13. Wilde AM, Nailor MD, Nicolau DP, et al. Inappropriate antibiotic use due to decreased compliance with a ventilator-associated pneumonia computerized clinical pathway: implications for continuing education and prospective feedback. *Pharmacotherapy* 2012;32:755–763.

14. Swoboda SM, Dixon T, Lipsett PA. Can the clinical pulmonary infection score impact ICU antibiotic days? *Surg Infect* 2006;7: 331–339.

15. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–829.

16. Fagon JY, Chastre J, Hance AJ, et al. Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest* 1993;103:547–553.

17. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290:2588–2598.

18. Chastre J, Viau F, Brun P, et al. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. *Am Rev Respir Dis* 1984;130:924–929.

19. Fabregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax* 1999;54: 867–873.

20. Wunderink RG, Woldenberg LS, Zeiss J, et al. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. *Chest* 1992;101:458–463.

21. Balthazar AB, Von Nowakonski A, De Capitani EM, et al. Diagnostic investigation of ventilator-associated pneumonia using bronchoalveolar lavage: comparative study with a postmortem lung biopsy. *Braz J Med Biol Res* 2001;34:993–1001.

22. Klompas M. Does this patient have ventilator-associated pneumonia? *JAMA* 2007;297:1583–1593.

23. Fartoukh M, Maitre B, Honore S, et al. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. *Am J Respir Crit Care Med* 2003;168:173–179.

24. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000;162:505–511.

25. Raman K, Nailor MD, Nicolau DP, et al. Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med* 2013;41:1656–1663.

26. Ibrahim EH, Ward S, Sherman G, et al. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001;29:1109–1115.

27. Micek ST, Ward S, Fraser VJ, et al. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004;125:1791–1799.

28. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: a randomized trial. *Ann Intern Med* 2000;132:621–30.

29. Shorr AF, Sherner JH, Jackson WL, et al. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. *Crit Care Med* 2005;33:46–53.

30. Centers for Disease Control and Prevention. *CDC/NHSN Surveillance Definitions for Specific Types of Infections.* Atlanta: Centers for Disease Control and Prevention, 2014. http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf.