Early Antibiotic Discontinuation in Patients With Clinically Suspected Ventilator-Associated Pneumonia and Negative Quantitative Bronchoscopy Cultures*

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Objectives: Preliminary data suggest that antibiotic discontinuation in patients with negative quantitative bronchoscopy and symptom resolution will not increase mortality. Because our hospital algorithm for antibiotic discontinuation rules out ventilator-associated pneumonia in the setting of negative quantitative bronchoscopy cultures, we compared antibiotic utilization and mortality in empirically treated, culture-negative ventilator-associated pneumonia patients whose antibiotic discontinuation was early versus late.

Design: Retrospective, observational cohort study.

Setting: Eight hundred sixty-seven bed, tertiary care, teaching hospital in Hartford, CT.

Patients: Eighty-nine patients with clinically suspected ventilator-associated pneumonia and a negative ($<10^4$ colony forming units/mL) quantitative bronchoscopy culture between January 2009 and March 2012. Early discontinuation patients ($n = 40$) were defined as those who had all antibiotic therapy stopped within one day of final negative culture report, whereas late discontinuation patients ($n = 49$) had antibiotics stopped later than one day.

Measurements: Univariate analyses assessed mortality, antibiotic duration, and frequency of superinfections. Multivariate logistic regression was performed to assess the effect of early discontinuation on hospital mortality.

Results: Patients had a mean ± SD Acute Physiology and Chronic Health Evaluation II score of 26.0 ± 6.0. Mortality was not different between early discontinuation (25.0%) and late discontinuation (30.6%) patients ($p = 0.642$). Antibiotic duration (days) was also not different for patients who died vs. those who survived (Median [interquartile range]: 3 [1–7.5] vs. 3 [1.75–6.25], respectively, $p = 0.87$), and when controlling for baseline characteristics and symptom resolution, only Acute Physiology and Chronic Health Evaluation II score was associated with hospital mortality on multivariate analyses. There were fewer superinfections (22.5% vs. 42.9%, $p = 0.008$), respiratory superinfections (10.0% vs. 28.6%, $p = 0.036$), and multidrug resistant superinfections (7.5% vs. 35.7%, $p = 0.003$), in early discontinuation compared with late discontinuation patients.

Conclusions: In this severely ill population with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoalveolar lavage cultures, early discontinuation of antibiotics did not affect mortality and was associated with a lower frequency of MDR superinfections. (*Crit Care Med* 2013; 41:1656–1663)

Key Words: antimicrobial stewardship; bronchoalveolar lavage; quantitative culture; superinfection; ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) occurs in 9% to 27% of all mechanically ventilated patients and is a leading cause of morbidity and mortality in hospitalized patients (1–5). Additionally, VAP places a substantial burden on healthcare spending, adding an average of 7–9 days of hospitalization and over $40,000 of additional cost per patient

*See also p. 1810.

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Supported by a Hartford Hospital Competitive Research Grant Award.

Dr. Nailor received grant support from Merck and payment for lectures from Astellas Forrest. Dr. Kuti received grant support from Forest Pharmaceuticals, Inc., Pfizer, Merck and Company, and ViraPharma. The remaining authors have not disclosed any potential conflicts of interest.

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DOI:10.1097/CCM.0b013e318287f713

(4, 5). The attributable mortality of VAP has been estimated between 33% and 50%, with additional risk of mortality associated with *Pseudomonas aeruginosa* or *Acinetobacter* species, medical illness (rather than surgical conditions), and failure to utilize appropriate antibiotics (6, 7).

Due to the risk for infection with multidrug resistant (MDR) pathogens, including methicillin-resistant *Staphylococcus aureus* and *P. aeruginosa*, VAP is often empirically treated with broad-spectrum antibiotics (1). As a result, recent data suggest that suspected respiratory tract infections account for more than 50% of antibiotics prescribed in the ICU (3). Moreover, many patients are treated for "VAP" despite absence of high suspicion for active infection, identification of a causative pathogen, or even confirmation of pneumonia on chest radiograph. This may lead to the indiscriminate overconsumption of antibiotics and immediate, as well as long-term consequences, which include the development of superinfections such as *Clostridium difficile*, antibiotic-associated adverse events, and the emergence of MDR bacteria at the local and national levels (8). The development of these superinfections has been linked with higher healthcare costs and length of stay (9). Therefore, interventions focused toward reducing unnecessary antibiotic burden are encouraged in ICUs.

VAP is most often diagnosed similarly to other lower respiratory tract infections, utilizing nonspecific clinical signs and symptoms, radiographic findings, and microbiologic cultures (1). The use of quantitative cultures from bronchoalveolar lavage (BAL) has been suggested as a mechanism for improving the diagnosis of VAP and streamlining antimicrobial utilization (10–18). Some studies have suggested discontinuation of antibiotics in the setting of negative (i.e., below a certain threshold, usually $<10^4$ colony forming units [CFU]/mL) quantitative respiratory cultures, whereas others have recommended de-escalation to narrower spectrum agents (10–14, 19, 20). Two prospective studies have supported discontinuation of antibiotics in the setting of negative bronchoscopic cultures and resolution of clinical symptoms of VAP (21, 22). Investigators at Barnes-Jewish Hospital reported the safety of discontinuing antibiotics in the setting of complete clinical resolution (mortality 32.0% with early discontinuation vs. 37.1% with standard therapy, $p = 0.357$) (23). They went on to further validate the safety of antibiotic discontinuation in asymptomatic patients with $<10^4$ CFU/mL of pathogenic organism in BAL fluid, finding similar mortality rates (34.7%) as their prior studies including prolonged therapy (21, 23). Discontinuation of antibiotics based on negative quantitative cultures alone, however, is still a hotly debated topic (24–26).

At our tertiary care hospital, VAP is typically treated with broad-spectrum antibiotics, and the majority of patients with suspected VAP have quantitative cultures ordered from a BAL or mini-BAL; however, there is no specific protocol for discontinuation of antibiotics based on the results of these cultures or based on resolution of any clinical signs or symptoms of VAP. Healthcare providers are instead encouraged to investigate alternative diagnoses and to consider antibiotic discontinuation in this setting. Because many patients at our hospital do not have their antibiotic therapy stopped despite the presence of a negative bronchoscopy, this study sought to evaluate the relationship between antibiotic discontinuation within 1 day of negative BAL report and mortality in patients who were treated for suspected VAP across several ICU settings.

METHODS

Study Design

This study was approved by the Hartford Hospital Institutional Review Board. The study was a single-center, retrospective cohort study performed at Hartford Hospital, Hartford, CT, over a 3-year period (January 2009 to March 2012). All adults (age ≥18 yr) admitted to one of five ICUs (medical ICU, cardiac ICU, neurotrauma ICU, surgical ICU, and cardiothoracic surgical ICU) having a quantitative BAL or mini-BAL culture performed were eligible for inclusion. Records of patients were included if the first quantitative BAL or mini-BAL culture of their admission grew $<10^4$ CFU/mL. Antibiotic administration within one calendar day of the BAL combined with at least one clinical sign or symptom of pneumonia was required for inclusion to demonstrate clinical suspicion of VAP. Patients were excluded if they received antibiotics for another indication prior to the BAL, and their antibiotics were not changed within 1 day of the BAL, or if there was no documentation supporting suspicion of a new pulmonary infection. Patients were also excluded if the only antibiotics received within 1 day of the BAL were for surgical prophylaxis. Two investigators (K.R., M.D.N.) independently and jointly assessed the medical record for the prescriber's inclination of a new pulmonary process.

Data Collection

Data on included patients were collected using medical charts, nursing flowsheets, computerized radiology reports, computerized microbiology reports, and computerized laboratory data (Eclipsys, Sunrise Enterprise 5.5, Atlanta, GA). For all patients, investigators recorded baseline demographics including age, sex, race, and comorbidities, reason for hospital admission and ICU admission, duration of care (including duration of hospitalization, ICU care, and ventilation), antibiotic utilization, microbiologic findings, markers of clinical status, and death at end-of-hospitalization. Severity of illness was calculated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sepsis-related Organ Failure Assessment (SOFA) score (27, 28). The likelihood for the presence of pneumonia was assessed as a clinical pulmonary infection score (CPIS) greater than 6 (29). Notably, the APACHE II, SOFA, and CPIS scores were calculated for research purposes using data from the date of bronchoscopy and are not used routinely in clinical care at Hartford Hospital.

Definitions

The following definitions were applied a priori. A quantitative BAL or mini-BAL was defined as negative if there was

less than 10^4 CFU/mL of growth from the culture. Patients were partitioned by discontinuation of antibiotics within one calendar day after culture report finalization (early discontinuation [E-DC]) or discontinuation of antibiotics greater than one calendar day after culture report finalization (late discontinuation [L-DC]). An antibiotic day was defined as a calendar day in which any antibiotic was administered. The date of antibiotic discontinuation was defined as the date that no further antibiotics were administered to the patient for suspected VAP. Mortality was defined as death due to any cause at the end of hospitalization. Clinical VAP was defined according to the America Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines as a radiographic finding suggestive of a pulmonary infection plus two of the three following signs: temperature >101°F or <96°F, WBC count >11 or $< 4 \times 10^3$ cells/μL, and visually mucopurulent tracheal secretions (1). Immunosuppressed patients were defined as having received systemic corticosteroids (>40 mg prednisone equivalent for >5 days in the prior 30 days), received chemotherapy in the prior 45 days, diagnosis of HIV, neutropenia (absolute neutrophil count <500 cells/mL), or history of organ transplantation. Superinfections were identified by the presence of a positive microbiologic culture collected due to suspicion of additional infection within 28 days of the negative BAL. Positive cultures within 3 days of the BAL being performed (within 1 day of BAL culture finalization) were excluded, as they were considered concomitant infections rather than subsequent infections and may have influenced decisions to discontinue antibiotics early. Superinfections were considered to be MDR if they were resistant to three or more classes of antibiotics, were documented as an extended spectrum beta-lactamase producing isolate, or were classified as methicillin-resistant *S. aureus* (9).

Statistical Analyses

The primary endpoint was mortality of groups categorized by E-DC vs. L-DC as described above. Secondary endpoints were assessments of the relationship between early antibiotic discontinuation and clinical resolution, and independently the development of superinfections. Data were analyzed using Sigma Stat v 2.0 (SPSS, Chicago, IL). Continuous data were analyzed using Student *t* tests for normally distributed data and Mann-Whitney tests for non-normal data. Categorical data were analyzed using Fisher exact tests. Quantification of superinfection was performed by counting the number of patients experiencing superinfections rather than the number of positive cultures. Time to superinfection was determined by the time to first positive culture. Two post hoc subgroup analyses were performed in a cohort of patients who met the ATS/IDSA definition of clinical VAP and in a cohort excluding patients with concomitant infections.

Univariate analyses were conducted to identify variables associated with mortality, so they could be controlled in a multivariate logistic regression. Variables with *p* values less than 0.20 were included in multivariate logistic regression analyses. All results yielding a *p* value less than 0.05 were determined to be statistically significant.

RESULTS

Baseline Characteristics

Over the study period, quantitative BALs were performed on 617 unique patients, of which 172 had less than 10^4 CFU/mL. Eighty-three patients were excluded because they were not started on antibiotics or were previously on antibiotics without modification due presumably to low suspicion of VAP. This left 89 patients for inclusion in this study. Of the patients included, 40 (45%) had all of their antibiotics discontinued within one calendar day of the final BAL report and thus made up the E-DC cohort, whereas the remaining 49 (55%) made up the L-DC cohort. Baseline characteristics were generally similar between the two groups (**Table 1**); however, L-DC patients had more cardiovascular disease and a greater prevalence of immunosuppression ($p = 0.001$) but were less likely to be admitted to the ICU for a neurologic condition ($p = 0.004$) and have a mini-BAL performed ($p = 0.014$). In general, patients were critically ill with relatively high APACHE II (26.0 ± 6.0) and SOFA scores (9.2 ± 2.7). The majority (89.9%) of included patients met the ATS/IDSA definition for clinical VAP. CPIS was less than 6 in 40.4% of patients, and 37.1% of patients had a CPIS of 5 or 6.

Antibiotic Utilization

Duration of antibiotics and timing of de-escalation and discontinuation are provided in **Table 2**. In line with the definition of E-DC, patients had shorter antibiotic courses in this group. Some patients had multiple changes to antibiotic therapy including narrowing the spectrum of activity, as well as complete discontinuation of therapy, but patients in the E-DC group were more likely to have their first change in antibiotic therapy involve complete discontinuation. An empiric antibiotic regimen that included double antipseudomonal and antistaphylococcal coverage per institutional protocol recommendation was more common in E-DC patients compared with L-DC patients (22 [55.0%] vs. 15 [30.6%], respectively, $p = 0.035$).

Mortality

Mortality was unchanged with early discontinuation of antibiotics (25.0% vs. 30.6%, $p = 0.642$), and duration of antibiotics postculture finalization was not different for those who survived (median [interquartile range], 3 days [1–7.5]) vs. those who died (3 days [1.75–6.25], $p = 0.873$; **Table 3**). Patients who died had a statistically higher mean APACHE II score (28.8 ± 5.7 vs. 24.9 ± 5.7, $p = 0.004$) and median SOFA score (median [interquartile range], 10 [8–13] vs. 8 [7.5–10], $p = 0.021$). There was no difference in the rate of mini-BALs in the group who died (42.2%) compared with those who survived (44.0%, $p = 0.934$). Of the 25 patients who died during hospitalization, 19 patients (76%) died within 2 weeks of bronchoscopy. There was no difference in time to mortality in E-DC patients (median [interquartile range], 8 days [4–12]) compared with L-DC patients (11 days [6.5–19.25],

TABLE 1. Baseline Characteristics of Patients With Negative (<10^4 Colony-Forming Units/mL) Quantitative BAL Cultures Categorized by Patients Who Had Antibiotics Discontinued Within 1 Day of Culture Finalization Versus Later

	Early Discontinuation ($n = 40$)	Late Discontinuation ($n = 49$)	p
Age (years), mean ± SD	61.7 ± 17.9	60.4 ± 14.7	0.714
Sex, female	19 (47.5)	17 (34.7)	0.279
Race, White	28 (70.0)	35 (71.4)	1.00
Comorbidities			
Cardiovascular Disease	25 (62.5)	40 (86.1)	0.056
Diabetes/ Endocrine	13 (32.5)	22 (44.9)	0.279
Respiratory Disease	10 (25.0)	7 (14.3)	0.279
Liver Disease	4 (10.0)	4 (8.2)	1.00
Renal Disease	3 (7.5)	7 (14.3)	0.502
Immunosuppression	3 (7.5)	18 (36.7)	0.001
Sepsis-Related Organ Failure Assessment, median (interquartile range)	8 (7.5, 10.0)	9 (8, 10.3)	0.227
Acute Physiology and Chronic Health Evaluation II, mean ± SD	24.8 ± 4.6	27.0 ± 6.8	0.291
CPIS on day of BAL, mean ± SD	5.8 ± 1.8	6.2 ± 1.7	0.223
Patient numbers by CPIS			
CPIS > 6	14 (35.0)	22 (44.9)	0.390
CPIS = 6	8 (20.0)	13 (26.5)	0.617
CPIS = 5	8 (20.0)	4 (8.2)	0.127
CPIS < 5	10 (25.0)	10 (20.4)	0.620
Type of bronchoscopy			
Mini-BAL	21 (52.5)	17 (34.7)	0.014
Full BAL	19 (47.5)	32 (65.3)	
Reason for hospital admission			
Neurologic condition	17 (42.5)	7 (14.3)	0.004
Motor vehicle accident	5 (12.5)	8 (16.3)	0.765
Elective surgery	4 (10.0)	7 (14.3)	0.748
Gastrointestinal condition	3 (7.5)	7 (14.3)	0.502
Respiratory condition	2 (5.0)	11 (22.5)	0.044
Cardiovascular condition	6 (15.0)	6 (12.2)	0.762
Other condition	3 (7.5)	3 (6.1)	1.00

CPIS = Clinical Pulmonary Infection Score; BAL = bronchoalveolar lavage.
All data presented as number (percentage), unless otherwise specified.

p = 0.405). After attempting to adjust for several variables including differences in group baseline characteristics using multivariate logistic regression analyses, only severity of illness was identified as a confounding suppressor variable. Early discontinuation of antibiotics was not associated with hospital mortality when controlling for APACHE II or SOFA scores in separate multivariate analyses (**Table 4**).

Although all patients had at least one clinical finding suggestive of pneumonia and all had suspected VAP, an additional analysis was performed including only patients who

TABLE 2. Antibiotic Utilization Categorized by Antibiotic Discontinuation Within 1 Calendar Day of Negative Culture Finalization

	Early Discontinuation ($n = 40$)	Late Discontinuation ($n = 49$)	p
Duration of antibiotics	4 (3, 4)	9 (6, 14)	<0.001
Duration of antibiotics postculture finalization	1 (1, 2)	6 (4, 12)	<0.001
Duration of antibiotics prior to therapy modification	3 (2, 3)	4 (3, 6.25)	<0.001
De-escalation with first change (*n*, %)	16 (40.0)	32 (65.3)	0.03
Discontinuation with first change (*n*, %)	24 (60.0)	12 (24.5)	0.001

All duration data presented in days as median (interquartile range), unless otherwise specified.

met the ATS/IDSA clinical definition for VAP ($n = 80$). These patients, like the general cohort, had similar APACHE II scores (24.8 ± 4.7 vs. 26.8 ± 6.8, $p = 0.141$) and SOFA scores (median [interquartile range], 8 [7–10] vs. 9 [8–11], $p = 0.267$] for the E-DC and L-DC groups, respectively. There was no difference in mortality noted between E-DC patients (9/34 [27.3%]) and L-DC patients (14/46 [30.4%], $p = 0.957$) in this subgroup.

Clinical Sign and Symptom Resolution

Clinical resolution occurred in the majority of patients, suggested by a CPIS score of 4.10 ± 1.9 on the day of culture finalization. Furthermore, CPIS was not significantly different in E-DC (median [interquartile range], 4 [2–5.5]) compared with L-DC patients (4 [3–5.25], $p = 0.523$) on the day of final culture report. There were 11 patients overall (12.4%) who had a CPIS greater than 6 at the time of culture finalization; they were also equally distributed between the two groups ($p = 1.00$). Persistence of individual signs and symptoms such as temperature, WBC count, Pao_2:FIO_2 ratio, and sputum purulence were common but not significantly different between the E-DC and L-DC groups (Table 3). Persistence of individual signs and symptoms on the day of final culture report was not predictive of mortality in univariate or multivariate analyses, with the exception of sputum purulence, which displayed an opposite effect; mortality was 45% in patients with normal sputum vs. 20.7% of patients with purulent sputum ($p = 0.044$). Mortality was 28.6% in patients whose fever resolved compared with that of 33.3% in patients whose temperature persisted ($p = 0.788$), 45% in patients with WBC normalization vs. 27.9% with persistence ($p = 0.252$), and 35.7% in patients with a normal Pao_2:FIO_2 ratio vs. 22.9% with an abnormal value ($p = 0.488$).

TABLE 3. Clinical Outcomes in Patients With Negative Bronchoalveolar Lavage Cultures Partitioned by Antibiotic Discontinuation Within 1 Day of Negative Culture Finalization

	Early Discontinuation ($n = 40$)	Late Discontinuation ($n = 49$)	p
Hospital mortality	10 (25)	15 (30.6)	0.642
Clinical Pulmonary Infection Score on day of culture finalization (median, 25% to 75%)	4 (2, 5.5)	4 (3, 5.25)	0.523
Signs/symptoms			
Abnormal temperature persisted	15 (48.4)	21 (61.8)	0.324
Abnormal WBC persisted	20 (69.0)	23 (65.7)	1.00
Abnormal Pao_2:FIO_2 ratio persisted	21 (75)	27 (77.1)	1.00
Sputum purulence persisted	24 (66.7)	34 (80.9)	0.196
Superinfection[a]	9 (22.5)	18 (42.9)	0.008
Bacteremia	1 (2.5)	3 (7.1)	0.616
Respiratory infection	4 (10.0)	12 (28.6)	0.036
Bacteriuria	3 (7.5)	3 (7.1)	1.00
Multidrug resistant superinfection	3 (7.5)	15 (35.7)	0.003

All data presented as number (percentage), unless otherwise specified.

[a]The denominator for the late discontinuation (L-DC) group was 42 patients for this analysis, as seven L-DC patients had a secondary positive culture within 1 day of the final culture report and were excluded from this analysis.

TABLE 4. Adjusted Odds of Mortality in Patients With Negative Bronchoalveolar Lavage Cultures Partitioned by Antibiotic Discontinuation Within 1 Day of Negative Culture Finalization

Variable	Model 1	Model 2
Constant	0.02 (0.00–0.38), 0.010	0.04 (0.00–0.34), 0.004
Acute Physiology and Chronic Health Evaluation II score	1.12 (1.01–1.24), 0.038	
Sepsis-Related Organ Failure Assessment score		1.26 (1.03–1.54), 0.024
Early discontinuation	0.88 (0.27–2.82), 0.83	0.96 (0.29–3.16), 0.95

Numbers represent an adjusted odds ratio with corresponding 95% confidence interval, *p* value.

Additional variables assessed for confounding included Hispanic race, diabetes, liver, or endocrine disease, human immundeficiency virus, hematologic disease, immunosuppression, Acute Physiology and Chronic Health Evaluation II score, Sepsis-Related Organ Failure Assessment score, hospital length of stay, and sputum persistence.

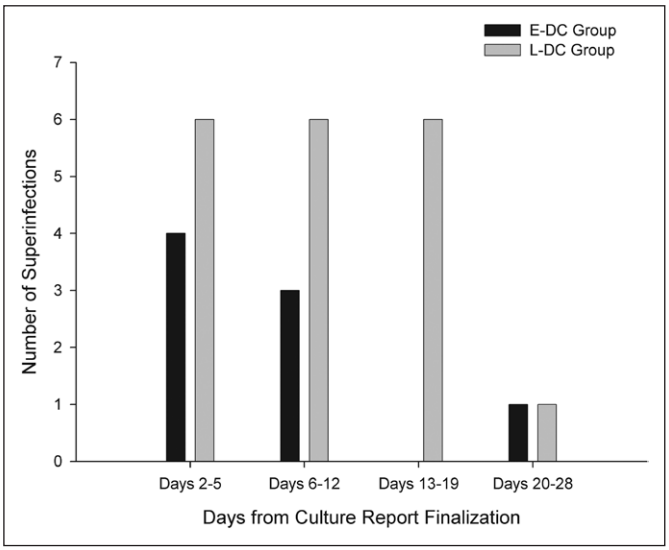

Figure 1. Time to superinfection from the day of the final negative bronchoalveolar lavage culture for early discontinuation (E-DC) vs. late discontinuation (L-DC) groups.

Superinfections

A superinfection occurred in 27 patients (30.3%) at least one day after BAL culture finalization. The frequency of superinfections by E-DC vs. L-DC group is presented in Table 3. Of the late superinfections (occurring 2 wk after the report of the negative culture), all but one occurred in the L-DC cohort (**Fig. 1**). Superinfections were more common between patients who survived to discharge vs. those who died (37.5% vs. 12.0%, $p = 0.036$).

Seven patients had a positive culture within 1 day of BAL-negative culture finalization deemed as concomitant infections. All of these patients were in the L-DC cohort; excluding these seven patients revealed a similar mortality rate between the two groups (25.0% in E-DC vs. 26.2% in L-DC, $p = 0.844$).

DISCUSSION

This study assessed the impact of early antibiotic discontinuation on mortality in a cohort of critically ill patients with suspicion of VAP and negative bronchoscopic cultures as defined by a quantitative threshold of less than 10^4 CFU/mL organisms. Our findings suggest that antibiotics can be safely discontinued in patients with a negative quantitative bronchoscopic culture with no significant impact on mortality, despite persistence of signs and symptoms of pneumonia in many patients. Baseline severity of illness scores (i.e., APACHE II or SOFA) were the only factors predictive of mortality in these patients. Furthermore, patients whose antibiotics were discontinued early had fewer superinfections, including those caused by MDR bacteria.

Our study supports the findings described by Kollef et al (21), as their study also evaluated safe discontinuation of antibiotics in patients with negative BAL cultures. However, unlike Barnes-Jewish, our hospital does not have a protocol requiring clinical resolution of pneumonia signs and symptoms. The majority of patients in our study still displayed at least one clinical sign or symptom of VAP at the time of culture finalization (Table 3). Furthermore, we were unable to identify an independent relationship with persistence of any sign or symptom and increased mortality. Although Dennesen et al (30) have previously demonstrated improvement in signs and symptoms of VAP by day 7 with appropriate antibiotic therapy, our observations are not unexpected as our population all had negative ($<10^4$ CFU/mL) bronchoscopies and thus are unlikely to have VAP. We can only speculate that persistence of nonspecific pneumonia signs or symptoms in these patients is due to their underlying acute comorbidities. Other nonspecific biomarkers of pneumonia, such as procalcitonin or C-reactive protein, were not assessed because these are not routinely measured in our ICU patients. Importantly, our data suggest that the provider need not wait until clinical resolution of pneumonia signs and symptoms in the face of a negative bronchoscopy, as this practice only appears to lead to prolonged antibiotic therapy in the absence of VAP.

These findings are also in congruence with the de-escalation strategy proposed by Singh et al (22), who used the CPIS score to identify patients with low suspicion for VAP and in whom a short course (i.e., 3 days) of antibiotics did not affect mortality. At the time of BAL, 60% of the patients included had a CPIS less than or equal to 6, warranting assessment for short-course

antibiotics per Singh et al. Within 1 day of culture finalization (typically 3 days from initial BAL), the median CPIS was 4, with 78 patients (88%) having CPIS less than or equal to 6. According to the CPIS algorithm, these patients could safely have discontinued antibiotics, which was echoed by our findings of unchanged mortality in patients with antibiotics discontinued early. Notably, CPIS is currently used as a common research study tool but has not been implemented as a tool for clinical assessment of patients at our institution.

Additionally, we observed a relationship between extended courses of antibiotics and the development of superinfections. Patients who had antibiotics discontinued within 1 day of the final BAL report had fewer superinfections (22.5% vs. 42.9%, $p = 0.008$); the majority of this difference was among respiratory superinfections (10% vs. 28.5%, $p = 0.036$); however, bacteremia was also numerically lower in E-DC patients (Table 3). Importantly, the E-DC cohort developed fewer MDR superinfections (7.5% vs. 35.7%, $p = 0.003$) compared with the L-DC patients. This observation is consistent with the landmark study by Chastre et al (31), who also observed increasing resistant superinfections with prolonged antibiotic therapy. Although the population described by Chastre had culture-positive VAP and our patient population only had suspected VAP, both studies reflect the potential negative effects of excessive antibiotic use. Notably, almost all of the superinfections occurring greater than 2 wk after antibiotic initiation were in the L-DC group, re-enforcing the correlation between longer durations of antibiotics and subsequent infections (32). Using antibiotics when clinically not indicated for active treatment for an infection may predispose patients to subsequent infections, thus further emphasizing the role of early discontinuation in the setting of negative cultures.

The population assessed in this study was unique in that patients had a high severity of illness, with a mean APACHE II score of 26.0 ± 6.0 and mean SOFA score of 9.2 ± 2.7. Hospital mortality (28.4%), however, was significantly lower than predicted mortality (40% to 55%) (27). All patients had suspicion of pneumonia, as indicated by receipt of a quantitative bronchoscopy, antibiotic therapy, and at least one sign of pulmonary infection. The majority of the patients (89.9%) also met the predefined criteria for VAP based on common signs and symptoms. Post hoc analyses in this subset of patients meeting the a priori definition for VAP resulted in no change in mortality rates between the E-DC and L-DC groups.

There were some limitations to this study. This was a retrospective cohort study conducted at a single institution but in multiple ICUs. We did not have sufficient numbers in any single ICU to conduct an analysis by type of unit, and future work in this area is required to determine if early antibiotic discontinuation is equally safe in all ICU populations. There was some heterogeneity between the E-DC and L-DC cohorts, and given the observational nature of the study, it is impossible to rule out the possibility that there were patients in the L-DC cohort who did require the additional days of antibiotics; however, a logistic regression was performed to control for these variables. All indices of clinical severity (APACHE II, SOFA, CPIS) were calculated retrospectively and therefore may have been limited by sporadic missing information. Finally, the relatively small sample size may raise questions related to the finding of no difference in mortality; however, a post hoc power analysis using the data obtained in this study suggests that more than 800 records would be needed in each group (i.e., more than 20 times the actual number of records available); thus, our findings are consistent with our single-center design.

CONCLUSIONS

In patients who have clinical suspicion of pneumonia at our medical center, antibiotic discontinuation in the setting of negative quantitative bronchoscopic cultures has no impact on mortality and is associated with a lower incidence of MDR superinfections.

REFERENCES

1. American Thoracic Society and Infectious Diseases Society of America: 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
2. Cardo D, Horan T, Andrus M, et al: National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004; 32:470–485
3. Vincent JL, Bihari DJ, Suter PM, et al: The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA* 1995; 274:639–644
4. Rello J, Ollendorf DA, Oster G, et al; VAP Outcomes Scientific Advisory Group: Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002; 122:2115–2121
5. Chastre J, Fagon JY: Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165:867–903
6. Rello J, Ausina V, Ricart M, et al: Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. *Chest* 1993; 104:1230–1235
7. 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(4 Pt 1):1249–1256
8. Dellit TH, Owens RC, McGowan JE, et al: Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Inf Dis* 2007; 44:159–177
9. Eagye KJ, Nicolau DP, Kuti JL: Impact of superinfection on hospital length of stay and costs in patients with ventilator-associated pneumonia. *Semin Respir Crit Care Med* 2009; 30:116–123
10. Bonten MJ, Bergmans DC, Stobberingh EE, et al: Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use. *Am J Respir Crit Care Med* 1997; 156:1820–1824
11. 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; 132:621–630
12. 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
13. de Jaeger A, Litalien C, Lacroix J, et al: Protected specimen brush or bronchoalveolar lavage to diagnose bacterial nosocomial pneumonia in ventilated adults: A meta-analysis. *Crit Care Med* 1999; 27:2548–2560
14. Heyland D, Dodek P, Muscedere J, et al: Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *NEJM* 2006; 355:2619–2630

15. Baker AM, Bowton DL, Haponik EF: Decision making in nosocomial pneumonia. An analytic approach to the interpretation of quantitative bronchoscopic cultures. *Chest* 1995; 107:85–95
16. Brun-Buisson C, Fartoukh M, Lechapt E, et al: Contribution of blinded, protected quantitative specimens to the diagnostic and therapeutic management of ventilator-associated pneumonia. *Chest* 2005; 128:533–544
17. Chastre J, Combes A, Luyt CE: The invasive (quantitative) diagnosis of ventilator-associated pneumonia. *Respir Care* 2005; 50:797–807
18. Croce MA, Fabian TC, Mueller EW, et al: The appropriate diagnostic threshold for ventilator-associated pneumonia using quantitative cultures. *J Trauma* 2004; 56:931–936
19. Labelle AJ, Arnold H, Reichley RM, et al: A comparison of culture-positive and culture-negative health-care-associated pneumonia. *Chest* 2010; 137:1130–1137
20. El Solh AA, Akinnusi ME, Alfarah Z, et al: Effect of antibiotic guidelines on outcomes of hospitalized patients with nursing home-acquired pneumonia. *J Am Geriatr Soc* 2009; 57:1030–1035
21. Kollef MH, Kollef KE: Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. *Chest* 2005; 128:2706–2713
22. Singh N, Rogers P, Atwood CW, et al: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. *Am J Respir Crit Care Med* 2000; 162:505–511
23. 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
24. Niederman MS: The argument against using quantitative cultures in clinical trials and for the management of ventilator-associated pneumonia. *Clin Infect Dis* 2010; 51 Suppl 1:S93–S99
25. Fujitani S, Yu VL: Quantitative cultures for diagnosing ventilator-associated pneumonia: A critique. *Clin Infect Dis* 2006; 43:S106–S113
26. Luna CM, Chirino A: Qualitative cultures in ventilator-associated pneumonia–Can they be used with confidence? *Crit Care* 2004; 8:425–426
27. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
28. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996; 22:707–710
29. Pugin J, Auckenthaler R, Mili N, et al: Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991; 143(5 Pt 1):1121–1129
30. Dennesen PJ, van der Ven AJ, Kessels AG, et al: Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2001; 163:1371–1375
31. Chastre J, Wolff M, Fagon JY, et al; PneumA Trial Group: Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003; 290:2588–2598
32. 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