The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 21, 2006 VOL. 355 NO. 25

A Randomized Trial of Diagnostic Techniques for Ventilator-Associated Pneumonia

The Canadian Critical Care Trials Group*

ABSTRACT

BACKGROUND

Critically ill patients who require mechanical ventilation are at risk for ventilator-associated pneumonia. Current data are conflicting as to the optimal diagnostic approach in patients who have suspected ventilator-associated pneumonia.

METHODS

In a multicenter trial, we randomly assigned immunocompetent adults who were receiving mechanical ventilation and who had suspected ventilator-associated pneumonia after 4 days in the intensive care unit (ICU) to undergo either bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid or endotracheal aspiration with nonquantitative culture of the aspirate. Patients known to be colonized or infected with pseudomonas species or methicillin-resistant *Staphylococcus aureus* were excluded. Empirical antibiotic therapy was initiated in all patients until culture results were available, at which point a protocol of targeted therapy was used for discontinuing or reducing the dose or number of antibiotics, or for resuming antibiotic therapy to treat a preenrollment condition if the culture was negative.

RESULTS

We enrolled 740 patients in 28 ICUs in Canada and the United States. There was no significant difference in the primary outcome (28-day mortality rate) between the bronchoalveolar-lavage group and the endotracheal-aspiration group (18.9% and 18.4%, respectively; P=0.94). The bronchoalveolar-lavage group and the endotracheal-aspiration group also had similar rates of targeted therapy (74.2% and 74.6%, respectively; P=0.90), days alive without antibiotics (10.4±7.5 and 10.6±7.9, P=0.86), and maximum organ-dysfunction scores (mean [±SD], 8.3±3.6 and 8.6±4.0; P=0.26). The two groups did not differ significantly in the length of stay in the ICU or hospital.

CONCLUSIONS

Two diagnostic strategies for ventilator-associated pneumonia — bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid and endotracheal aspiration with nonquantitative culture of the aspirate — are associated with similar clinical outcomes and similar overall use of antibiotics. (Current Controlled Trials number, ISRCTN51767272.)

The Steering Committee (study chair, Daren Heyland, M.D., Kingston General Hospital and Queens University, Kingston, ON; Deborah Cook, M.D., St. Joseph's Hospital and McMaster University, Hamilton, ON; Peter Dodek, M.D., St. Paul's Hospital and University of British Columbia, Vancouver, BC; and John Muscedere, M.D., and Andrew Day, M.Sc., Kingston General Hospital and Queens University, Kingston, ON — all in Canada) of the Canadian Critical Care Trials Group assumes responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Heyland at Angada 4, Kingston General Hospital, Kingston, ON K7L 2V7, Canada, or at dkh2@post.queensu.ca.

*The investigators and staff of the Canadian Critical Care Trials group who participated in this study are listed in the Appendix.

N Engl J Med 2006;355:2619-30.

Ventilator-associated pneumonia develops in approximately 20% of critically ill patients receiving mechanical ventilation.[1-3] Patients in whom ventilator-associated pneumonia develops have a higher mortality rate, stay longer in the intensive care unit (ICU), and require more resources than those without the disease.[3-7]

Previous studies have documented that reliance on the results of endotracheal aspiration frequently leads to misclassification of ventilator-associated pneumonia.[8,9] Bronchoscopy with quantitative culture of bronchoalveolar-lavage fluid or of specimens collected through a protected brush catheter may yield superior diagnostic information. However, in the absence of a reference standard for the diagnosis of ventilator-associated pneumonia, the true sensitivity and specificity of such methods are uncertain, as is their effect on patient care and outcomes.

In an observational study, we found that quantitative culture of bronchoalveolar-lavage fluid, as compared with culture of endotracheal aspirate, resulted in more confident decision making, less use of antibiotics, and lower mortality rates.[10] However, bronchoscopic techniques require special training, are not universally available, and may delay treatment of ventilator-associated pneumonia. Subsequently, two randomized trials compared the quantitative culture of bronchoalveolar-lavage fluid and the quantitative culture of endotracheal aspirate,[11,12] and two other randomized trials have compared the quantitative culture of bronchoalveolar-lavage fluid and nonquantitative culture of endotracheal aspirate.[13,14] The results of these studies are conflicting. More trials are needed to determine the overall clinical utility of these diagnostic approaches.[15] Therefore, we conducted a randomized trial to compare the quantitative culture of bronchoalveolar-lavage fluid and culture of endotracheal aspirate in critically ill patients with suspected ventilator-associated pneumonia. Our a priori hypothesis was that bronchoscopy with quantitative culture would be associated with lower mortality rates and less use of antibiotics.

METHODS

We studied 740 critically ill patients with suspected ventilator-associated pneumonia in 28 ICUs across Canada and the United States. Using a 2-by-2 factorial design, we randomly assigned patients to undergo bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid or standard endotracheal aspiration with culture of the aspirate and to receive empirical combination antibiotic therapy or monotherapy. This article focuses on the diagnostic methods of the study. Patients were stratified according to the center and to the severity of illness within 24 hours of enrollment (less severe illness was defined as an Acute Physiology and Chronic Health Evaluation [APACHE] II[16] score of 24 or less, and severe illness as an APACHE II score greater than 24).[17] Treatment was randomly assigned with the use of a central telephone system, with a variable, undisclosed block size.

Consecutive adults who had received mechanical ventilation in the ICU for at least 4 days were eligible if they had suspected pneumonia, defined by new or persistent radiographic features of pneumonia without another obvious cause and any two of the following clinical features: a temperature exceeding 38°C, leukocytosis (defined as a leukocyte count exceeding 11.0×10^3 per cubic millimeter) or neutropenia (defined as a neutrophil count of less than 3500 per cubic millimeter), purulent endotracheal secretions, potentially pathogenic bacteria isolated from the endotracheal aspirate, and increasing oxygen requirements.

We excluded patients who were immunocompromised; considered to be unsuitable for bronchoscopy by the attending physician; allergic to penicillins, cephalosporins, carbapenems, or ciprofloxacin; infected or colonized with pseudomonas species or methicillin-resistant *Staphylococcus aureus*; recent recipients of study drugs (ciprofloxacin within 24 hours and meropenem within 7 days before enrollment); expected to die or undergo withdrawal of treatment within 72 hours after enrollment; unlikely to leave the ICU within 3 weeks; pregnant or lactating; or previously enrolled in this or another interventional trial. We obtained written informed consent from family members of all patients.

We developed an implementation manual to standardize the procurement and laboratory processing of samples, according to conventional techniques[18] (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). This manual was sent to and agreed upon by all participating laboratories before initiation of the study. In patients in the bronchoal-

veolar-lavage group, the ICU physician or attending respirologist performed bronchoalveolar lavage in the affected region of the lung, identified from a chest radiograph. For all patients, immediately after the diagnostic tests, ICU physicians were asked to rate the pretest likelihood of ventilator-associated pneumonia as low, moderate, or high, on the basis of their clinical judgment; this estimate was not standardized.

Since previous studies of diagnostic techniques for ventilator-associated pneumonia have been confounded by a lack of standardization of empirical antibiotic therapy, we standardized antibiotic administration in all study patients in order to ensure that any differences observed were due to the diagnostic technique and not to differences in empirical antibiotic therapy between the two groups. To maximize the likelihood of achieving a high rate of adequacy of empirical antibiotic therapy (defined as the susceptibility of cultured organisms to the study antibiotics), we selected two broad-spectrum antibiotics that are active against pseudomonas species.

After the diagnostic tests had been completed, patients were randomly assigned to receive either meropenem (1 g every 8 hours) and ciprofloxacin (400 mg every 12 hours) or meropenem alone, all provided intravenously in an open-label fashion. According to the study protocol, after enrollment, antibiotics were not adjusted until culture results and culture sensitivities had been reported. In both groups, if a patient had a positive culture, physicians prescribed a single antibiotic with the narrowest spectrum, according to the usual practice at their institutions. If the culture showed no growth, study antibiotics were discontinued except, at the discretion of the physicians, in patients with a high pretest likelihood of ventilator-associated pneumonia. Cultures with normal flora, *S. epidermidis,* or candida species were considered to be nonpathogenic; these cultures and those that showed no growth were classified as negative cultures for purposes of analysis. The decision to treat other pathogens found in the cultures was left to the ICU physician. Given that previous exposure to antibiotics influences culture results, if potential pathogens grew on bronchoalveolar-lavage fluid in culture at levels below the diagnostic threshold (less than 10,000 colony-forming units [CFU] per milliliter), physicians could still treat these pathogens without violating the protocol. Semiquantitative information on the cultures of endotracheal aspirate was not considered in clinical decision making or in the adjudication of the final diagnosis of ventilator-associated pneumonia.

We recorded age, sex, chronic diseases that were present, the diagnosis on admission, and the APACHE II score for each patient.[16] Patients were monitored daily for signs and symptoms of infection and organ dysfunction; organ-dysfunction scores ranged from 0 to 24, with higher scores indicating greater dysfunction.[19] The duration of mechanical ventilation, length of stay in the ICU, and length of stay in the hospital were also documented. After discharge or death, site investigators reviewed hospital records, incorporating the culture results, response to antibiotics, and other features of the clinical course to adjudicate whether patients had had ventilator-associated pneumonia and to determine the final clinical and microbiologic outcomes according to standard definitions (see the Supplementary Appendix). Because these determinations of diagnosis and outcomes were made by physicians who were aware of the patients' treatment assignments, to standardize the determinations across sites, they were reviewed centrally by the study chair to ensure consistency and completeness. The study chair also reviewed all results of culture and susceptibility testing to determine the adequacy of empirical therapy.

The primary outcome was the 28-day mortality rate. Secondary outcomes included survival in the ICU and discharge from the hospital, duration of mechanical ventilation, length of stay in the ICU and the hospital, response to clinical and microbiologic treatment (see the Supplementary Appendix), organ-dysfunction score, and use or nonuse of antibiotics after culture results were known. Antibiotic use was further described for analysis as the proportion of patients for whom all antibiotics were discontinued within 5 days after randomization, the number of days patients were alive and were not receiving antibiotics within 28 days after randomization, and the proportion of patients who received targeted therapy (defined as the discontinuation or modification of study antibiotics on the basis of culture results or the readministration of antibiotics to treat a preenrollment condition if the culture was negative).

Our study was approved by the research ethics board of each participating institution and was

conducted under the auspices of the Canadian Critical Care Trials Group. The sponsors had no role in the conception or design of the study, data collection, data analysis, interpretation of the results, or preparation of the manuscript. The steering committee designed and executed the study, analyzed the data, interpreted the findings, wrote the manuscript, and holds the data. The authors vouch for the accuracy and completeness of the reported data.

STATISTICAL ANALYSIS

Assuming a 28-day mortality rate of 40%,[11,12,14] we calculated that we needed to enroll 740 patients for the study to have a statistical power of 80% to detect an absolute risk reduction in the 28-day mortality rate of 10%[14] with the use of the Mantel–Haenszel test and a two-sided significance level of 0.049. This significance level allowed for one interim analysis, which was performed after 370 patients were enrolled. The interim analysis did not show a difference that met the early-stopping criterion ($P<0.003$), according to the method of Lan and DeMets[20] with O'Brien–Fleming–type boundaries. The design of our factorial study involved an assumption that the two types of study intervention (diagnostic and antibiotic) would not interact. We confirmed this assumption by demonstrating the similarity of the treatment effect of bronchoalveolar lavage and of endotracheal aspirates within each antibiotic group and by testing for a treatment interaction using logistic regression and controlling for the APACHE II score (24 or less or greater than 24).

In all comparisons of bronchoalveolar lavage and endotracheal aspiration, we controlled for the antibiotic group and APACHE II score (24 or less or greater than 24). We compared nominal variables by using the stratified Mantel–Haenszel test, the number of species in positive culture and the number of antibiotics administered within 24 hours before randomization by using the stratified Mantel–Haenszel mean score test for trend,[21] the time-to-event variables by using the stratified log-rank test (with Kaplan–Meier median estimates), and continuous variables by using analysis of variance with blocking factors for the antibiotic group and APACHE II score (24 or less or greater than 24). A culture of bronchoalveolar-lavage fluid was considered positive if a potential pathogen was isolated, regardless of the number of CFU per milliliter. Subgroup analyses were performed with the use of the pretest likelihood of ventilator-associated pneumonia, severity of illness, length of stay in the ICU before randomization, prior use or nonuse of antibiotics, and the presence or absence of high-risk organisms in the culture (defined as pseudomonas species, methicillin-resistant *S. aureus*, *Stenotrophomonas maltophilia*, acinetobacter species, and multidrug-resistant bacteria). This intention-to-treat analysis was performed according to a prespecified plan of analysis with the use of SAS software, version 8.2. All tests were two-sided without adjustment for multiplicity of the secondary outcomes.

RESULTS

Between May 2000 and February 2005, we screened 2531 patients; 1144 were eligible and 740 were enrolled (Fig. E1 in the Supplementary Appendix). One patient withdrew consent 2 days after randomization and data for that patient were not analyzed further. There were no clinically significant differences in baseline characteristics between the endotracheal-aspiration group and the bronchoalveolar-lavage group (Table 1), including in the antibiotics prescribed within 24 hours before enrollment (Table E1 in the Supplementary Appendix). The total number of antibiotics used per patient before enrollment was not significantly different between groups ($P=0.83$).

The mean (±SD) time between admission to the ICU and enrollment was 7.9±5.2 days. The most common pathogens in the specimens collected at enrollment are listed in Table 2. More patients in the bronchoalveolar-lavage group had a positive culture than did those in the endotracheal-aspiration group (59.7% vs. 51.9%, $P=0.03$). Among patients who had a positive culture, there was a significant but not clinically important difference in the number of types of organisms cultured (1.6 per culture in the bronchoalveolar-lavage group vs. 1.4 in the endotracheal-aspiration group, $P=0.009$).

The time from clinical suspicion of ventilator-associated pneumonia to initiation of study antibiotics was slightly longer in the bronchoalveolar-lavage group than in the endotracheal-aspiration group (median, 8.0 hours [interquartile range, 6.0 to 12.4] vs. 6.8 hours [4.0 to 10.5], $P<0.001$). Use of meropenem continued for a median of 3 days (interquartile range, 2 to 5) in all study patients. In the group receiving meropenem plus

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Endotracheal Aspiration (N=374)	Bronchoalveolar Lavage (N=365)	All (N=739)
Age — yr	58.7±18.0	59.3±17.6	59.0±17.8
Female sex — no. of patients (%)	118 (31.6)	109 (29.9)	227 (30.7)
APACHE II score	19.8±6.2	20.1±6.4	20.0±6.3
Admission category — no. of patients (%)			
Medical	224 (59.9)	226 (61.9)	450 (60.9)
Surgical	150 (40.1)	139 (38.1)	289 (39.1)
Primary diagnosis on admission — no. of patients (%)			
Cardiovascular disorder	89 (23.8)	92 (25.2)	181 (24.5)
Trauma	90 (24.1)	97 (26.6)	187 (25.3)
Respiratory disorder	73 (19.5)	55 (15.1)	128 (17.3)
Neurologic disorder	51 (13.6)	47 (12.9)	98 (13.3)
Gastrointestinal disorder	24 (6.4)	36 (9.9)	60 (8.1)
Other condition	25 (6.7)	23 (6.3)	48 (6.5)
Sepsis	18 (4.8)	11 (3.0)	29 (3.9)
Renal disorder	4 (1.1)	4 (1.1)	8 (1.1)
No. of chronic diseases — no. of patients (%)			
0	112 (29.9)	107 (29.3)	219 (29.6)
1	101 (27.0)	85 (23.3)	186 (25.2)
2	67 (17.9)	78 (21.4)	145 (19.6)
3	94 (25.1)	95 (26.0)	189 (25.6)
PaO_2:FIO_2 at enrollment	223.0±86.2	210.9±78.6	217.1±82.7
Organ-dysfunction score at day 1	5.6±3.1	5.6±2.9	5.6±3.0
Receipt of vasopressors — no. of patients (%)	86 (23.0)	78 (21.4)	164 (22.2)
Result on chest radiograph at enrollment — no. of patients (%)			
New infiltrate	101 (27.0)	114 (31.2)	215 (29.1)
Worsening or persistent infiltrate	273 (73.0)	251 (68.8)	524 (70.9)
Pretest likelihood of ventilator-associated pneumonia — no. of patients (%)			
High	162 (43.3)	177 (48.5)	339 (45.9)
Moderate	163 (43.6)	130 (35.6)	293 (39.6)
Low	49 (13.1)	58 (15.9)	107 (14.5)
No. of days in ICU before enrollment	7.6±5.4	8.2±5.0	7.9±5.2
Total length of stay in ICU — no. of patients (%)			
<7 days	235 (62.8)	200 (54.8)	435 (58.9)
≥7 days	139 (37.2)	165 (45.2)	304 (41.1)
Use of antibiotics within 3 days before randomization — no. of patients (%)			
None	133 (35.6)	138 (37.8)	271 (36.7)
Antibiotics in use but initiated beforehand	130 (34.8)	122 (33.4)	252 (34.1)
New antibiotics initiated	111 (29.7)	105 (28.8)	216 (29.2)
High-risk organism cultured — no. of patients (%)†	49 (13.1)	56 (15.3)	105 (14.2)

* Plus–minus values are means ±SD. PaO_2 denotes the partial pressure of arterial oxygen, and FIO_2 the fraction of inspired oxygen.
† High-risk organisms included acinetobacter species, pseudomonas species, methicillin-resistant *Staphylococcus aureus, Stenotrophomonas maltophilia,* and multidrug-resistant organisms (defined as those resistant to two or more classes of antibiotics).

ciprofloxacin, ciprofloxacin was administered for a median of 3 days (interquartile range, 2 to 6). The median duration of antibiotic treatment for ventilator-associated pneumonia was 10 days (interquartile range, 5 to 15). The adequacy of empirical treatment did not differ significantly between the two groups (among patients who had positive cultures, 89.0% of those undergoing bronchoalveolar lavage had adequate empirical antibiotic therapy, as did 89.5% of those undergoing endotracheal aspiration; P=0.85). The percentage of patients who were found not to have ventilator-associated pneumonia was similar in the bronchoalveolar-lavage group and the endotracheal-aspiration group (13.7% and 17.1%, respectively; P=0.19) (Table 3).

PRIMARY END POINT

Overall, the 28-day mortality rate was 18.7% (95% confidence interval [CI], 15.9 to 21.7). The adjust-

Table 2. Findings on Culture of Specimens at Enrollment.

Organism or Finding	Endotracheal Aspiration (N=374)	Bronchoalveolar Lavage*		All (N=739)
		≥10^4 CFU (N=185)	<10^4 CFU (N=180)	
		number of patients (percent)		
None	67 (17.9)	0	67 (37.2)	134 (18.1)
Staphylococcus aureus	61 (16.3)	50 (27.0)	16 (8.9)	127 (17.2)
Candida spp.	51 (13.6)	41 (22.2)	26 (14.4)	118 (16.0)
Normal flora	74 (19.8)	0	38 (21.1)	112 (15.2)
Haemophilus influenzae	46 (12.3)	46 (24.9)	7 (3.9)	99 (13.4)
Enterobacter spp.	33 (8.8)	30 (16.2)	6 (3.3)	69 (9.3)
Klebsiella spp.	29 (7.8)	22 (11.9)	10 (5.6)	61 (8.3)
Other†	12 (3.2)	25 (13.5)	12 (6.7)	49 (6.6)
Pseudomonas spp.	21 (5.6)	20 (10.8)	6 (3.3)	47 (6.4)
Escherichia coli	20 (5.3)	15 (8.1)	7 (3.9)	42 (5.7)
Streptococcus spp.	5 (1.3)	26 (14.1)	3 (1.7)	34 (4.6)
Serratia spp.	11 (2.9)	8 (4.3)	3 (1.7)	22 (3.0)
Acinetobacter spp.	8 (2.1)	4 (2.2)	3 (1.7)	15 (2.0)
Coagulase-negative staphylococcus	4 (1.1)	10 (5.4)	1 (0.6)	15 (2.0)
Enterococcus spp.	5 (1.3)	7 (3.8)	2 (1.1)	14 (1.9)
Proteus spp.	6 (1.6)	8 (4.3)	0	14 (1.9)
Moraxella catarrhalis	4 (1.1)	8 (4.3)	1 (0.6)	13 (1.8)
Methicillin-resistant *S. aureus*	7 (1.9)	3 (1.6)	2 (1.1)	12 (1.6)
Stenotrophomonas maltophilia	6 (1.6)	5 (2.7)	1 (0.6)	12 (1.6)
Aspergillus spp.	5 (1.3)	1 (0.5)	2 (1.1)	8 (1.1)
Total‡				
Multidrug-resistant organisms	15 (4.0)	17 (9.2)	6 (3.3)	38 (5.1)
High-risk organisms	49 (13.1)	42 (22.7)	14 (7.8)	105 (14.2)

* CFU denotes colony-forming unit per milliliter.

† "Other" included citrobacter species, morganella species, *Neisseria meningitidis,* aeromonas species, *Burkholderia (Pseudomonas) cepacia,* pasteurella species, *Torulopsis (Candida) glabrata,* sphingomonas species, bacteroides species, prevotella species, *Haemophilus parainfluenzae,* eikenella species, and neisseria species.

‡ The incidences of multidrug-resistant organisms (defined as those resistant to two or more classes of antibiotics) and high-risk organisms (defined as pseudomonas species, methicillin-resistant *S. aureus, S. maltophilia,* acinetobacter species, and multidrug-resistant bacteria) differed significantly between the endotracheal-aspiration group and the two subgroups of bronchoalveolar lavage (P=0.02 and P<0.001, respectively). The incidence of high-risk organisms did not differ significantly between the endotracheal-aspiration group and the entire bronchoalveolar-lavage group. Among patients infected or colonized with multidrug-resistant bacteria, 16 had enterobacter species, 9 had pseudomonas species, 7 had *E. coli,* 5 had klebsiella species, and 1 had acinetobacter species.

ed relative risk of death by day 28 in the bronchoalveolar-lavage group as compared with the endotracheal-aspiration group was 1.01 (95% CI, 0.75 to 1.37; P=0.94). There were no significant differences in the 28-day mortality rate in any of our subgroup analyses (Fig. 1). In addition, the mortality rate did not differ significantly between the group receiving combination antibiotic therapy and the group receiving monotherapy (relative risk, 1.05; 95% CI, 0.78 to 1.42; P=0.74). The treatment effect of the two diagnostic tests was the same regardless of the antibiotic therapy used, and the treatment effect of the two antibiotic therapies was the same regardless of the diagnostic test used (P=0.37 for the interaction).

SECONDARY END POINTS

There were no significant differences between the bronchoalveolar-lavage group and the endotracheal-aspiration group in the time from randomization to the discontinuation of mechanical ventilation (median, 8.9 days [95% CI, 7.4 to 10.7] and 8.8 days [7.0 to 10.7], respectively; P=0.31), to discharge from the ICU (12.3 days [10.9 to 13.8] and 12.2 days [10.9 to 14.2], respectively; P=0.22), or to discharge from the hospital (40.2 days [36.0 to 45.7] and 47.0 days [38.1 to 55.0], respectively; P=0.13). Patients who died before or within 24 hours after the discontinuation of mechanical ventilation (114 patients), died before or within 24 hours after discharge from the ICU (128 patients), or died in the hospital (182 patients) were considered to never have had any of these events, and data for these patients were censored after the end of follow-up. The number of deaths within 14 days, in the ICU, and in the hospital were similar between the two groups (Table E2 in the Supplementary Appendix), as were the incidences

Table 3. Classification of Ventilator-Associated Pneumonia (VAP).*

Classification	Endotracheal Aspiration	Bronchoalveolar Lavage	All
		number of patients (percent)	
All patients			
No. of patients	374	365	739
Definite VAP	0	1 (0.3)	1 (0.1)
Probable VAP	0	180 (49.3)	180 (24.4)
Possible VAP	310 (82.9)	134 (36.7)	444 (60.1)
No VAP	64 (17.1)	50 (13.7)	114 (15.4)
Pretest likelihood of VAP			
High			
No. of patients	162	177	339
Probable VAP	0	100 (56.5)	100 (29.5)
Possible VAP	145 (89.5)	59 (33.3)	204 (60.2)
No VAP	17 (10.5)	18 (10.2)	35 (10.3)
Moderate			
No. of patients	163	130	293
Definite VAP	0	1 (0.8)	1 (0.3)
Probable VAP	0	57 (43.8)	57 (19.5)
Possible VAP	132 (81.0)	55 (42.3)	187 (63.8)
No VAP	31 (19.0)	17 (13.1)	48 (16.4)
Low			
No. of patients	49	58	107
Probable VAP	0	23 (39.7)	23 (21.5)
Possible VAP	33 (67.3)	20 (34.5)	53 (49.5)
No VAP	16 (32.7)	15 (25.9)	31 (29.0)

* Classifications are defined in the Supplementary Appendix.

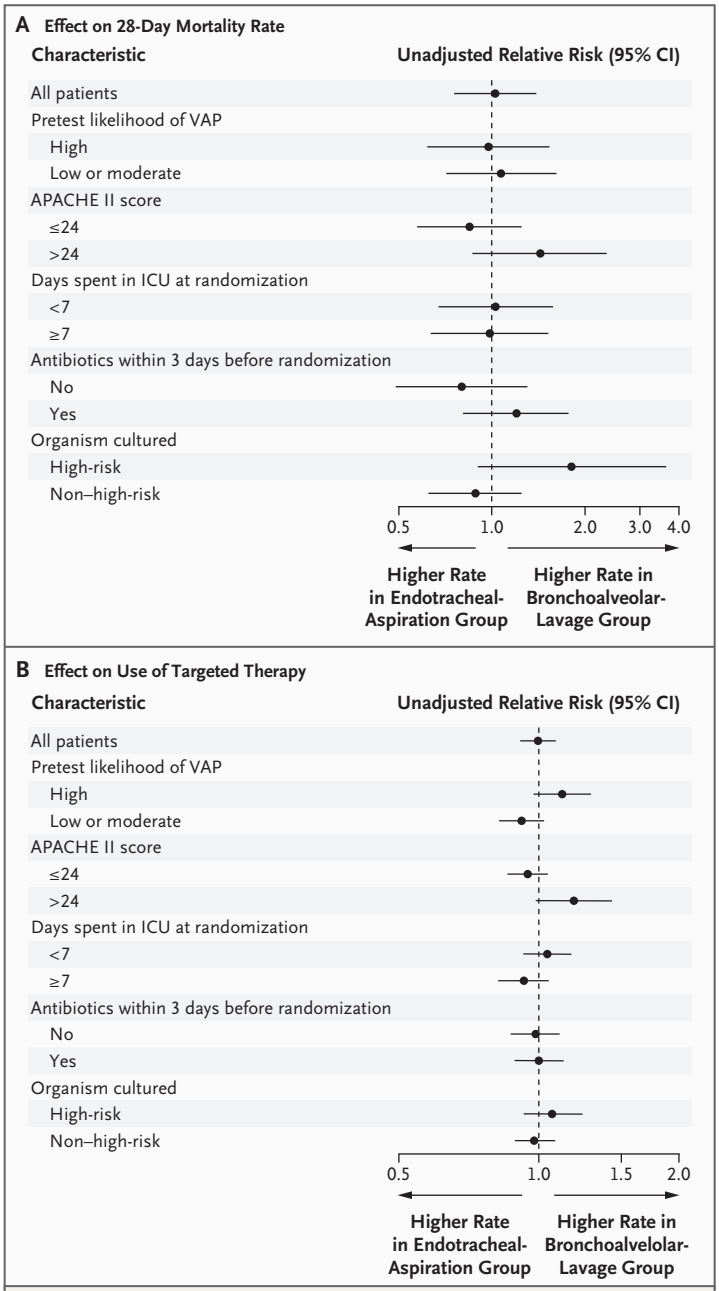

Figure 1. Effect of the Diagnostic Test on the 28-Day Mortality Rate (Panel A) and Use of Targeted Therapy (Panel B).

"High-risk organisms" were defined as acinetobacter species, pseudomonas species, methicillin-resistant *S. aureus,* and *S. maltophilia,* as well as multidrug-resistant organisms (defined as those resistant to two or more classes of antibiotics).

of clinical and microbiologic outcomes at day 28 (Table 4).

By day 6, all antibiotics had been discontinued in 21.1% of patients and study antibiotics had been discontinued in 59.9% of patients; the percentages did not differ significantly between the bronchoalveolar-lavage group and the endotracheal-aspiration group. The rates of targeted therapy were similar in the two groups, regardless of whether all patients were analyzed or only patients with negative or positive cultures were analyzed (Table 5). In the subgroup of patients whose pretest likelihood of ventilator-associated pneumonia was low or moderate and who had a negative culture, physicians were more likely to use targeted therapy in the endotracheal-aspiration group than in the bronchoalveolar-lavage group (85.0% vs. 70.0%, P=0.009). Patients in the bronchoalveolar-lavage group and the endotracheal-aspiration group had similar numbers of days alive without antibiotics (10.4±7.5 and 10.6±7.9, respectively; P=0.86) and similar maximum organ-dysfunction scores (8.3±3.6 and 8.6±4.0, respectively; P=0.26).

DISCUSSION

In this randomized trial of diagnostic strategies for patients with suspected ventilator-associated pneumonia, we enrolled 740 patients from 28 hospitals in both community and academic settings. A priori, we expected that the use of quantitative culture of bronchoalveolar-lavage fluid would be associated with an increased use of targeted therapy and improved clinical outcomes. Early empirical therapy with broad-spectrum antibiotics was initiated in all patients after the diagnostic test had been completed. We detected no important differences in clinical outcomes or in the use of antibiotics between the groups undergoing either diagnostic test in the main analysis or in any prespecified subgroup analysis. There was a very low prevalence of pseudomonas and methicillin-resistant *S. aureus*; our findings may not be generalizable to settings in which these high-risk organisms are more prevalent.

Our results differ from those in a French trial of 413 patients who had clinically suspected ventilator-associated pneumonia and who were randomly assigned to undergo quantitative culture of specimens collected by means of bronchoalveolar lavage, protected brush catheters, or both or to nonquantitative culture of specimens collected by means of endotracheal aspiration; antibiotics were initiated in both groups on the basis of findings on Gram's staining and the clinical condition of the patient.[14] In the intention-to-treat analysis in that study, as compared with patients who underwent endotracheal aspiration, those who under-

Table 4. Clinical and Microbial Outcomes at Day 28.*

Outcome	Endotracheal Aspiration (N=374)	Bronchoalveolar Lavage (N=365)	All (N=739)
		number of patients (percent)	
Detailed clinical assessment			
Clinical resolution	214 (57.2)	209 (57.3)	423 (57.2)
Delayed resolution	12 (3.2)	9 (2.5)	21 (2.8)
Relapse or recurrent infection	8 (2.1)	8 (2.2)	16 (2.2)
Superinfection	22 (5.9)	30 (8.2)	52 (7.0)
Clinical failure	8 (2.1)	3 (0.8)	11 (1.5)
Indeterminate outcome	41 (11.0)	37 (10.1)	78 (10.6)
Death	69 (18.4)	69 (18.9)	138 (18.7)
Overall clinical assessment			
Cure	226 (60.4)	218 (59.7)	444 (60.1)
Clinical failure	107 (28.6)	110 (30.1)	217 (29.4)
Indeterminate outcome	41 (11.0)	37 (10.1)	78 (10.6)
Detailed microbial assessment			
Resolution	133 (35.6)	149 (40.8)	282 (38.2)
Relapse or recurrent infection	6 (1.6)	10 (2.7)	16 (2.2)
Superinfection	28 (7.5)	47 (12.9)	75 (10.1)
Clinical failure	17 (4.5)	15 (4.1)	32 (4.3)
Colonization	39 (10.4)	28 (7.7)	67 (9.1)
No positive culture	136 (36.4)	100 (27.4)	236 (31.9)
Indeterminate outcome	15 (4.0)	16 (4.4)	31 (4.2)
Overall microbial assessment†			
Cure	172 (77.1)	177 (71.1)	349 (73.9)
Failure	51 (22.9)	72 (28.9)	123 (26.1)

* The P value for the overall clinical assessment was 0.90 and for the overall microbial assessment was 0.14. "Cure" was defined as either clinical or delayed resolution and "failure" as relapse or recurrent infection, superinfection, or failure (see the Supplementary Appendix for definitions of individual outcomes).

† The overall microbial assessment did not include results of "no positive culture" and "indeterminate." Thus, the percentages were calculated for 223 patients in the endotracheal-aspiration group, 249 patients in the bronchoalveolar-lavage group, and 472 patients in total.

went bronchoscopy had more antibiotic-free days by day 28 (7.5 days vs. 11.5 days, P<0.001) and a lower mortality rate at day 14 (25.8% vs. 16.2%, P=0.02) but a similar 28-day mortality rate (38.8% vs. 30.9%, P=0.10). It is plausible that the difference in mortality rate between the two groups at day 14 in the French study had less to do with the diagnostic strategy and more to do with the choice of antibiotics. In the group that underwent bronchoalveolar lavage, fewer patients received inappropriate empirical antibiotics (1 patient [0.5%], vs. 24 patients [13%] in the endotracheal-aspiration group; P<0.001). Of the patients who received inappropriate antibiotics, 32.0% died, as compared with 20.4% of the 388 patients who received appropriate therapy (P=0.02). Of those who received inappropriate antibiotics, 33% died (all in the endotracheal-aspiration group) before day 14.

Our trial was designed to detect a 10% absolute risk reduction or a 25% relative risk reduction from a 28-day mortality rate of 40%. Given that the actual mortality rate was lower than expected, our study achieved a statistical power of 98% to detect an absolute risk reduction of 10% but a statistical power of only 41% to detect a relative risk reduction of 40%. Our findings are consistent with those of three Spanish trials, which did not show any advantage of bronchoalveolar lavage with quantitative cultures with respect to the mortality rate or any other clinical outcome.[11-13] When

Table 5. Incidence of Targeted Therapy by Day 6.*

Patients	Endotracheal Aspiration	Bronchoalveolar Lavage	All	P Value
		no. of patients/total no. (%)		
All	279/374 (74.6)	271/365 (74.2)	550/739 (74.4)	0.90
Pretest likelihood of pneumonia				
High	108/162 (66.7)	132/177 (74.6)	240/339 (70.8)	0.11
Low or moderate	171/212 (80.7)	139/188 (73.9)	310/400 (77.5)	0.11
Positive culture				
All	148/194 (76.3)	172/218 (78.9)	320/412 (77.7)	0.63
Pretest likelihood of pneumonia				
High	68/89 (76.4)	96/120 (80.0)	164/209 (78.5)	0.71
Low or moderate	80/105 (76.2)	76/98 (77.6)	156/203 (76.8)	0.73
Negative culture				
All	131/180 (72.8)	99/147 (67.3)	230/327 (70.3)	0.28
Pretest likelihood of pneumonia				
High	40/73 (54.8)	36/57 (63.2)	76/130 (58.5)	0.28
Low or moderate	91/107 (85.0)	63/90 (70.0)	154/197 (78.2)	0.009

* Targeted therapy was defined as the discontinuation or modification of study antibiotics on the basis of the organisms cultured or the resumption of antibiotics to treat a preenrollment condition if the culture was negative.

the results of our trial are combined with those of the Spanish and French trials, bronchoalveolar lavage with quantitative cultures is not associated with a significant beneficial effect on the mortality rate (relative risk, 0.93; 95% CI, 0.76 to 1.15). To confirm or refute the small risk reduction suggested by this pooled estimate, a randomized trial would need to include more than 10,000 patients per treatment group in order to achieve a statistical power of 80% to detect a relative risk reduction of 7% from a 28-day mortality rate of 20%. Furthermore, in the setting of adequate initial empirical treatment with antibiotics, as in our trial, it is difficult to postulate the mechanism by which bronchoalveolar lavage with quantitative culture would increase survival.

In a recent meta-analysis[22] of the four randomized trials of bronchoalveolar lavage as compared with endotracheal aspiration,[11-14] quantitative culture of bronchoalveolar-lavage fluid was associated with an increased likelihood of adjustment of antibiotic therapy (odds ratio, 2.85; 95% CI, 1.45 to 5.59). However, the meaning of "adjustment" differed among the four primary studies and sometimes included the addition or modification of empirical antibiotics. In our trial, we did not find that tailoring or de-escalating antibiotic therapy was more frequent among patients who underwent quantitative bronchoalveolar-lavage cultures than among those who underwent endotracheal aspiration. An important distinction between the French study and our trial is that the French study incorporated findings on Gram's staining into treatment algorithms for ventilator-associated pneumonia. For example, for a patient who had no organisms on Gram's staining and no signs of severe sepsis, antibiotics were withheld, pending culture results. If the patient did have signs of severe sepsis, empirical antibiotic therapy was initiated. Thus, only 52.5% of patients in the bronchoalveolar-lavage group received empirical therapy, as compared with 91.4% of patients in the endotracheal-aspiration group, explaining the observed difference in the use of antibiotics between the two groups in the French study.

We took a different approach to antibiotic therapy in our trial. The use of inadequate empirical antibiotics and delays in the initiation of appropriate antibiotic therapy are associated with worse clinical outcomes than is the timely use of adequate antibiotics.[23-27] Even if cultures of bronchoalveolar-lavage fluid can be used to identify infective organisms more accurately than cultures

of endotracheal aspirate, the information may come too late to influence survival.[27] Finally, reliance on Gram's staining of pulmonary secretions may result in erroneous decisions about antibiotic therapy up to one third of the time.[28-30] Therefore, to maximize the adequacy of empirical therapy and improve clinical outcomes, we designed our trial so that all patients received empirical, broad-spectrum antibiotics.

The absence of a significant difference in the use of antibiotics between the two groups in our study may also be explained by the fact that research personnel monitored all patients and reminded the clinical team to review culture results and adjust antibiotic therapy as soon as they were available. A single-center, randomized trial suggested that a consistent policy of antibiotic discontinuation is associated with less frequent use of antibiotics than with standard care.[31] In our trial, the research protocol and the research nurses may have facilitated appropriate discontinuation of antibiotics or of targeted therapy in both groups, minimizing any difference between them. This feature of our study should be considered in applying our findings in practice.

Limitations of our study include the fact that investigators were aware of the study interventions and that clinical judgment was involved in determining the pretest likelihood and final classification of ventilator-associated pneumonia. These issues are inherent in all trials enrolling patients with suspected ventilator-associated pneumonia and testing these diagnostic techniques. Strengths of our study include concealed randomization, 100% follow-up, the use of intention-to-treat analysis, and efforts to standardize key aspects of the protocol (adjustment of antibiotic therapy and discontinuation of mechanical ventilation). In addition, the large sample and multicenter nature of the study enhance the generalizability of our findings.

In conclusion, we found that endotracheal aspiration with nonquantitative culture of the aspirate to diagnose ventilator-associated pneumonia is associated with clinical outcomes and antibiotic use similar to those that are associated with bronchoalveolar lavage and quantitative culture of the bronchoalveolar-lavage fluid.

Supported by grants from the Canadian Institutes of Health Research and Physicians' Services Incorporated of Ontario, and by unrestricted grants from AstraZeneca and Bayer.

Dr. Heyland reports receiving lecture fees from AstraZeneca; Dr. Muscedere, lecture fees from Bayer; and Drs. Heyland and Muscedere, research grants from AstraZeneca and Bayer. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The investigators, staff, and members of the steering committee of the Canadian Critical Care Trials Group who participated in this study were as follows: **Investigators** — *Kingston General Hospital* — C. D'Arsigny, M. Myers, S. Hammond; *St. Joseph's Hospital* — D. Cook, E. McDonald, F. Clarke; *Ottawa Hospital General Campus* — A. Baxter, I. Watpool, T. McCardle; *Ottawa Hospital Civic Campus* — J. Pagliarello, R. Hodder, J. Foxall, M.J. Lewis; *Oregon Health and Science University* — M. Haupt, I. DeSouza-Cedillo; *Walter C. Mackenzie Health Sciences Centre* — I. Mayers, M. Miller; *Hôpital Maisonneuve–Rosemount* — M. Legare, J. Harvey; *St. Paul's Hospital* — P. Dodek, K. Foley, L. Lazosky, I. Jessup, S. Helderweirt; *London Health Science Centre* — D. Leasa, V. Binns, J. Kehoe; *Hôpital Charles-Lemoyne* — G. Poirier, H. Skidmore, L. Provost; *Royal Columbian Hospital* — S. Keenan, J. Murray, M. Van Osch, K. Haveman; *Royal University Hospital* — J. Pinilla, S. Hattori, L. Lapointe; *Hospital Saint-Luc* — P. Aslanian, P. Deroy, N. Morin; *Hôtel-Dieu Hospital* — R. Bouali, M. Vallieres; *Hamilton Health Sciences* — M. Meade, C. Hamielec, L. Hand; *Mount Sinai Hospital* — S. Mehta, A. Suri; *Sunnybrook & Women's College* — A. Cooper, C. Dale, M. Keogh; *Sudbury Regional Hospital* — J. Theriault, L. Innes, L. Legrand; *Grey Nun's Community Hospital* — D. Stollery, J. Barchard, M. Krause; *Foothills Medical Centre* — P. Boiteau, L. Knox; *Peter Lougheed Hospital* — D. Zuege, C. Dielissen; *Rockyview Hospital* — A. Kirby, P. Bishop; *Vancouver Hospital* — D. Chittock, D. Foster, S. Gabriel, T. Massier, L. Bennett-Scott; *Hôpital du Sacre-Coeur* — M. Albert, C. Sirois; *Royal Alexandra Hospital* — J. Kutsogiannis, N. Whalen, P. Thompson; *Queen Elizabeth Health Sciences* — W. Patrick, G. Rocker, G. Sloan; *St. Joseph's Health Care* — J. Fuller, T. Hurlock-Chorostecki, C. McCallum; *Hôtel-Dieu Hospital* — J. Muscedere, C. Diemer; *Health Science Centre St. John's* — S. Peters, E. Condon; **Methods Center Staff** — D. Campbell, J. Korol, V. Cao, Y. Su; **Statisticians** — A. Day, M. Lam.

REFERENCES

1. Cook DJ, Walter SD, Cook RJ, et al. Incidence and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 1998;129:433-40.
2. Vincent JL, Bihari D, 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. JAMA 1995;274:639-44.
3. Safdar N, Dexfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 2005;33:2184-93.
4. Heyland DK, Cook DJ, Griffith L, Keenan S, Brun-Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. Am J Respir Crit Care Med 1999;159:1249-56.
5. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002;122:2115-21.
6. Girou E, Stephan F, Novara A, Safar M, Fagon JY. Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. Am J Respir Crit Care Med 1998;157:1151-8.
7. Bueno-Cavanillas A, Delgado-Rodriguez M, Lopez-Luque A, Schaffino-Cano S, Galvez-Vargas R. Influence of nosocomial infection on mortality rate in an intensive care unit. Crit Care Med 1994;22:55-60.

8. Andrews CP, Coalson JJ, Smith JD, Johanson WG Jr. Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest 1981;80:254-8.
9. Fagon JY, Chastre J, Hance AJ, et al. Detection of nosocomial lung infection in ventilated patients: use of a protected specimen brush and quantitative culture techniques in 147 patients. Am Rev Respir Dis 1988;138:110-6.
10. Heyland DK, Cook DJ, Marshall J, et al. The clinical utility of invasive diagnostic techniques in the setting of ventilator associated pneumonia. Chest 1999;115:1076-84.
11. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. Am J Respir Crit Care Med 1998;157:371-6. [Erratum, Am J Respir Crit Care Med 1998;157:1005.]
12. Ruiz M, Torres A, Ewig S, et al. Noninvasive versus invasive microbiological investigation in ventilator associated pneumonia: evaluation of outcome. Am J Respir Crit Care Med 2000;162:119-25.
13. Sole Violan J, Fernandez JA, Benitez AB, Cardenosa Cendrero JA, Rodriguez de Castro F. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. Crit Care Med 2000;28:2737-41.
14. 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.
15. Pittet D, Bonten MJ. Towards invasive diagnostic techniques as standard management of ventilator-associated pneumonia. Lancet 2000;356:874.
16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
17. Rello J, Rue M, Jupert P, et al. Survival in patients with nosocomial pneumonia: impact of the severity of illness and the etiologic agent. Crit Care Med 1997;25:1862-7.
18. Meduri GU, Chastre J. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. Chest 1992;Suppl 1:102:557S-564S.
19. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638-52.
20. 20 Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
21. Stokes ME, Davis CS, Koch GG. Categorical data analysis using the SAS system. 2nd ed. Cary, NC: SAS Institute, 2000.
22. Shorr AF, Sherner JH, Jackson WL, Kollef MH. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. Crit Care Med 2005;33:46-53.
23. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. Intensive Care Med 1996;22:387-94.
24. Dupont H, Mentec H, Sollet JP, Bleichner G. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. Intensive Care Med 2001;27:355-62.
25. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 1997;111:676-85.
26. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.
27. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002;122:262-8.
28. Duflo F, Allaouchiche B, Debon R, Bordet F, Chassard D. An evaluation of the Gram stain in protected bronchoalveolar lavage fluid for the early diagnosis of ventilator-associated pneumonia. Anesth Analg 2001;92:442-7.
29. Blot F, Raynard B, Chachaty E, Tancrede C, Antoun S, Nitenberg G. Value of Gram stain examination of lower respiratory tract secretions for early diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 2000;162:1731-7.
30. Namias N, Harvill S, Ball S, et al. A reappraisal of the role of Gram's stains of tracheal aspirates in guiding antibiotic selection in the surgical intensive care unit. J Trauma 1998;44:102-6.
31. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 2004;125:1791-9.

Appendix: Definitions of Clinical and Microbiological Outcomes

Clinical Outcomes:

Clinical resolution: the elimination of fever, purulence of secretions, and leukocytosis, improved oxygenation and radiographic improvement within 14 days of enrollment.

Delayed resolution: the patient improved but persisted on mechanical ventilation more than 14 days after enrollment.

Relapse or Recurrent infection: after initial improvement, the patient suffered a clinical and radiographic deterioration with the same organism that was responsible for the initial infection.

Superinfection: similar to relapse or recurrent infection but involves a different or new organism.

Clinical failure: death or persistence of clinical and radiographic features of infection throughout the study period requiring additional antibiotics.

Indeterminate: If while on treatment for respiratory symptoms the patient developed a requirement for additional antibiotics for non-respiratory tract infections (e.g., line sepsis requiring vancomycin).

Microbiological Outcomes:

Microbiological resolution: the elimination of the putative pathogen from repeated culture of lower respiratory tract.

Relapse or Recurrent infection: after initial eradication, the patient suffered a clinical and radiographic deterioration with the same organism that was responsible for the initial infection.

Superinfection: similar to relapse or recurrent infection but involved a different or new organism.

Failure: Persistence of the enrollment microorganism from secretions of the lower respiratory tract throughout the study period.

Colonization: the acquisition (after enrollment) of yeast or bacteria not associated with features of infection.

Indeterminate: If a patient died early and no subsequent cultures were available they were considered indeterminate.

Adequacy of Empiric Therapy: The organism(s) that grow in the enrollment specimen show in vitro susceptibility to meropenem or ciprofloxacin. If Pseudomonas species were isolated, 2 drugs were necessary for empiric therapy to be considered adequate.

Classification of VAP:

1) Definite bacterial pneumonia- if at least one of the following three criteria was fulfilled:

-positive result of pleural fluid culture

-rapid cavitation of the lung infiltrate as determined by computed tomography or

-histopathologic demonstration of pneumonia (presence of consolidation with intense polymorphonuclear leukocyte accumulation in bronchioles and adjacent alveoli involving several adjacent low-power microscopic fields, with or without tissue necrosis) during biopsy or autopsy.

2) Probable bacterial pneumonia- if none of the above criteria were met yet patient had cultures of specimens obtained using a bronchoalveolar lavage which grew at least one organism in significant concentration ($>10^4$ cfu/ml).

3) Possible pneumonia- if none of the above criteria were met yet patient's chest radiograph, sputum culture, temperature, white blood cell count and clinical course were consistent with pneumonia.

4) No pneumonia- if in the opinion of the study investigator, the patient’s course was not compatible with pneumonia.

Protocol for Bronchoscopy and BAL

Patient prepared for bronchoscopy with 100% FiO2, adequate sedation with or without paralysis. Patient on assist mode on the ventilator (RR 16-20) with continuous monitoring and oximetry. Suction through the endotracheal tube prior to starting bronchoscopy.

Sampling area is selected on the basis of the location of the new or progressive infiltrate seen on CXR. When passing the bronchoscope down into the lung, avoid suctioning secretions in the ETT, trachea or large airways to minimize contamination of the working channel.

Do not use lidocaine spray.

Tip of the bronchoscope is wedged into the subsegment of the lung and 20 ml sterile saline solution are injected, aspirated, and discarded. A new trap is positioned and additional 20-60 ml aliquots are injected slowly and aspirated. The total amount of fluid injected should be around 140 ml.

Note in chart percent retrieved fluid, presence or degree of haemorrhage or purulent secretions and location of sampling.

Send labelled specimens to lab immediately for Gram stain on cytospun fluid and quantitative culture.

Protocol for Endotracheal Suctioning

Patient prepared for suctioning with 100% FiO2, bagging (if necessary), adequate sedation.

A sterile suction catheter (not a closed, inline system) and suction trap will be used.

3-5 ml of sterile saline will be instilled if an adequate specimen not obtained.

Note in chart quantity and nature of the specimen.

Send labelled specimens to lab immediately for Gram stain and culture.

Protocol for BAL Sample Processing

POTENTIAL PATHOGENS

Any of the following may be pathogenic if greater than 1 X 10^6 CFU/L:
Haemophilus influenzae, S. pneumoniae, S. aureus, M. catarrhalis, Gram negative bacilli, anaerobes, *N. meningitidis*

NORMAL FLORA

Coagulase negative Staphylococci, Corynebacterium species, Viridans streptococcus group, Neisseria species (not *N. meningitidis*)

INTERPRETATION OF CULTURES

Quantitative cultures are used to assess the concentration of organisms present in the lower respiratory tract and to help distinguish between low level contamination and a significant concentration of bacteria. (These numbers are for use in patients not on antibiotic therapy).

A significant colony count in BAL specimens is $\exists 10^4$ CFU/mL ($\exists 10X10^6$ CFU/L). However, because many of our patients may have been on antibiotic therapy at the time of sampling (not always known to the laboratory), and because our technique allows us to isolate organisms at a one log lower level, our threshold for work up of potential pathogens in a BAL is $\exists 10^3$ CFU/ml ($\exists 1X10^6$ CFU/L).

Day 1:

1. If less than 1 X 10^6 CFU/L of an organism per plate, no work-up. Reincubate plates.
2. If greater than or equal to 1 X 10^6 CFU/L of any potential pathogen per plate perform full ID and susceptibilities. See "Interpretation of Count".

Day 2:

1. Re-examine all aerobic plates
2. Examine anaerobic culture if requested, determine count and workup as per Day 1 protocol.
3. Correlate aerobic to anaerobic growth if anaerobic culture was requested.

INTERPRETATION OF COUNT (BAL)

Volume Plated	Colony Count	Report
0.01 ml (10 μl)	1 - 9	<1 X 10^6 CFU/L -----no further work-up (Report: <10 x 10^6 CFU/L; No significant growth)
	10 - 100 (confirm count from 0.001 ml volume)	<10 X 10^6 CFU/L(normal flora)---no further work up <10 x 10^6 CFU/L(potential pathogen)---ID & STF
0.001 ml (1 μl)	1 - 9	<10 x 10^6 CFU/L(normal flora)---no further work up <10 x 10^6 CFU/L(potential pathogen)---ID & STF
	∃10	∃10 x 10^6 (normal flora)---no further work up ∃10 x 10^6 (potential pathogen)---ID & STF

REPORTING GUIDELINES

Note: ! significant aerobic counts should be reported within 24 hours.
! non-significant aerobic counts should not be reported until anaerobic counts are available if anaerobic culture was requested

1. No growth observed.
2. Less than 10 x 10^6 CFU/L; No significant growth (LIS=L10106 NG)
3. Less than 10 x 10^6 CFU/L of _____ (Organisms consistent with normal respiratory flora) (LIS=NRF: L10106)
4. Less than 10 x 10^6 CFU/L of _____ (Potential Pathogen) ⌋ ID and STF {record as 10^3CFU/ml in the case report form

5. Greater than 10 x 10^6 CFU/L of _____ ⌋ ID and STF {record as 10^4 CFU/ml in the case report form

EDITORIALS

Diagnosis of Ventilator-Associated Pneumonia

Marin H. Kollef, M.D.

In this issue of the *Journal*, Heyland et al., writing for the Canadian Critical Care Trials Group, report the results of a multicenter, randomized trial comparing the use of bronchoalveolar lavage and endotracheal aspiration for the diagnosis of ventilator-associated pneumonia.[1] This study was part of a larger 2-by-2 factorial design also comparing empirical antimicrobial monotherapy (a carbapenem) and combination therapy (a carbapenem plus a fluoroquinolone). The authors conclude that bronchoalveolar lavage and endotracheal aspiration are associated with similar clinical outcomes and similar overall use of antibiotics. However, several important limitations of the study must be appreciated in order to place it into proper context.

Heyland et al. restricted the patient population and the pathogens evaluated in their study. Of the 2531 screened patients, 307 (12.1%) were excluded because they were already colonized or had a respiratory tract infection with an organism not sensitive to one of the study drugs, and 706 (27.9%) were excluded because they were immunocompromised, had already received one of the study drugs, or had a chronic disease. Therefore, at least 40% of the screened patients who were excluded had risk factors for colonization or infection with potentially antimicrobial-resistant bacteria. Unfortunately, these exclusions probably represent the majority of patients undergoing real-time evaluation for suspected ventilator-associated pneumonia.[2-5]

Initial administration of an appropriate antimicrobial regimen (i.e., one to which the pathogens are sensitive, on the basis of in vitro susceptibility testing) in patients with suspected ventilator-associated pneumonia should be regarded as one of the primary determinants of in-hospital outcome. Use of an initial antimicrobial regimen that is inappropriate for the microorganisms causing ventilator-associated pneumonia has been associated with a significantly greater risk of death than use of an appropriate initial regimen.[6,7] These findings strongly suggest that initial antimicrobial therapy for ventilator-associated pneumonia and other serious infections should be selected according to the presence or absence of risk factors for infection associated with health care (e.g., recent hospitalization, admission from a chronic care environment, current hemodialysis, immunocompromised state, late-onset infection, or prior use of antimicrobial agents during the current period of hospitalization).[5,8] Initial antimicrobial regimens in patients with suspected ventilator-associated pneumonia who have these risk factors should appropriately treat potentially resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.[8]

The guidelines for the management of nosocomial pneumonia, recently published by the American Thoracic Society and the Infectious Diseases Society of America, propose a de-escalation approach to treatment that attempts to address the need for balancing appropriate initial antimicrobial therapy and emerging antibiotic resistance.[8] In patients with clinically suspected ventilator-associated pneumonia, specimens should be obtained from the respiratory tract for microbiologic processing, followed by the timely administration of an empirical antimicrobial regimen selected according to the presence or absence of risk factors for infection with antimicrobial-resistant bacteria. Microorganism identification and antibiotic susceptibility testing should also be conducted so that the use of antimicrobial agents can be deescalated when appropriate. An important caveat in applying this guideline is that

hospitals should use their own local microbiologic data to formulate appropriate initial treatment regimens.[9]

In addition to administering an initial antimicrobial regimen that is likely to be active against the pathogens causing infection, the clinician has the obligation to minimize future emergence of antimicrobial resistance. De-escalation promotes both the narrowing of the initial antimicrobial regimen once the microbiologic data become available and the use of antimicrobial therapy for the shortest duration that is clinically effective. Bronchoalveolar lavage is a tool used to facilitate modification of initial antimicrobial treatment regimens for ventilator-associated pneumonia. The airway of a patient receiving mechanical ventilation is commonly colonized with potentially pathogenic bacteria. Consequently, the testing of secretions obtained from an endotracheal tube or tracheostomy tube cannot consistently differentiate between upper airway colonization and lower respiratory tract infection.[10] Sampling methods that minimize contamination from the upper airway (e.g., bronchoalveolar lavage or protected brush catheter sampling) offer the advantage of establishing a more precise microbiologic diagnosis of ventilator-associated pneumonia to guide subsequent changes in antimicrobial therapy.[11]

Heyland et al. found that the use of bronchoalveolar lavage did not influence in-hospital mortality or length of stay as compared with endotracheal aspiration. However, the main potential effect of bronchoalveolar lavage is to permit the de-escalation or cessation of unnecessary antimicrobial therapy on the basis of microbiologic findings, especially when initial broad-spectrum antimicrobial agents are prescribed for patients at risk for infection with resistant bacteria.[8,10] The exclusion of patients colonized or infected with MRSA, *P. aeruginosa*, and other multidrug-resistant pathogens diminishes the usefulness of the results of Heyland et al. for clinical decision making. There is less concern about administering inappropriate initial antimicrobial therapy when the risk of infection with resistant pathogens is low, thus allowing for the initial use of more narrow-spectrum antimicrobial agents. The culture of bronchoalveolar-lavage fluid is more likely to result in modification of prescribed broad-spectrum regimens than is the culture of an endotracheal aspirate.

Clinicians appear to be confident that the culture of bronchoalveolar-lavage fluid, as compared with endotracheal aspirate, for the microbiologic diagnosis of ventilator-associated pneumonia actually reflects the presence or absence of ventilator-associated pneumonia and the etiologic agents of the infection.[10] A meta-analysis was recently conducted of four randomized trials comparing lower respiratory tract sampling and quantitative culture with clinical criteria for the diagnosis of ventilator-associated pneumonia; the likelihood of modifying initial antimicrobial therapy in the sampling group was almost three times that in the clinical-criteria group.[12] However, in patient populations with a low prevalence of infection or colonization with antibiotic-resistant bacteria, the use of endotracheal aspiration should suffice, since initial empirical treatment with broad-spectrum antimicrobial agents is not required.

In addition to the narrowing of initially prescribed broad-spectrum antimicrobial regimens on the basis of microbiologic data, the shortening of the duration of antibiotic treatment is an important component of de-escalation. Patterns of excess administration of antibiotics, especially beyond 7 or 8 days in patients receiving mechanical ventilation, have been linked with subsequent infection with potentially resistant bacteria.[8] These findings suggest that clinicians caring for patients with suspected ventilator-associated pneumonia should use antimicrobial treatment strategies that minimize the prolonged and potentially unnecessary administration of antibiotics, in order to curtail resistance.[8,10,11]

In summary, given the rapid emergence of antimicrobial resistance and the limited number of new antimicrobial agents, clinicians treating patients with suspected ventilator-associated pneumonia not only must prescribe appropriate initial antimicrobial regimens to optimize outcomes but also must minimize the development of resistance by rigorously using a de-escalation strategy. When applied properly, bronchoalveolar lavage and endotracheal aspiration are tools that can facilitate de-escalation.

Dr. Kollef reports receiving consulting fees or honoraria from Pfizer, Merck, Kimberly Clark, and Elan, and grant support from Pfizer, Merck, Elan, and Bard Medical. No other potential conflict of interest relevant to this article was reported.

From the Pulmonary and Critical Care Division, Washington University School of Medicine; and Medical Critical Care and Respiratory Care Services, Barnes–Jewish Hospital — both in St. Louis.

1. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 2006;355:2619-30.

2. Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005;41:848-54.
3. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 2005;128:3854-62. [Erratum, Chest 2006;129:831.]
4. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004;32:470-85.
5. Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). Diagn Microbiol Infect Dis 2004;50:59-69.
6. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest 1998;113:412-20.
7. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000;118:146-55.
8. American Thoracic Society, 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.
9. Beardsley JR, Williamson JC, Johnson JW, Ohl CA, Karchmer TB, Bowton DL. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. Chest 2006;130:787-93.
10. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867-903.
11. Ibrahim EH, Ward S, Sherman G, Schaiff R, Fraser VJ, Kollef MH. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med 2001;29:1109-15.
12. Shorr AF, Sherner JH, Jackson WL, Kollef MH. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. Crit Care Med 2005;33:46-53.

Carbapenems for Surgical Prophylaxis?

Daniel J. Sexton, M.D.

In this issue of the *Journal*, Itani and colleagues[1] describe a study in which 1002 patients were randomly assigned to receive either ertapenem or cefotetan in a single dose before elective colorectal surgery. Many experienced surgeons and hospital epidemiologists will probably be surprised that the overall rate of failure in the modified intention-to-treat analysis was approximately 40% for patients receiving ertapenem and 50% for those receiving cefotetan. A possible explanation for these high failure rates is that the authors of the study, unlike those of most previous trials, included unexplained use of postoperative antibiotics and anastomotic leaks in their definition of prophylaxis failure. However, this fact does not explain why nearly one in six patients receiving ertapenem and approximately one in four patients receiving cefotetan had a surgical-site infection. These rates are substantially higher than those reported by the National Nosocomial Infections Surveillance System and our infection-control network of 36 community hospitals.[2] Although the authors cite previous reports with similarly high rates of surgical-site infection with cefotetan, most studies examining outcomes of colorectal surgery have reported lower rates of infection.[3]

The high rates of surgical-site infection reported by Itani et al. may relate to a combination of factors. For example, more than a quarter of the patients were obese, and as in other studies,[4,5] obesity was identified as an independent risk factor for surgical-site infection. Failure of antibiotic therapy in many obese patients may be related both to technical factors, such as inadequate obliteration of nonvascularized "dead space" during wound closure, and to inadequate administration of antibiotics and subsequent low drug levels in serum and tissue at the end of long procedures.[6] Other surgery-related factors that could have contributed to the high rates of postoperative infection were inappropriate (or inappropriately early) removal of hair, technical errors (such as bowel perforation or spillage of fecal material), the failure to maintain normothermia, and uncontrolled hyperglycemia during the perioperative period. The Surgical Infection Prevention and Surgical Care Improvement Projects have emphasized the need for careful management of these factors in preventing infections after colorectal surgery.[7] Thus, it is important to remember that the selection of an antimicrobial agent as prophylaxis is only one of many considerations in reducing rates of postoperative infection.

Even though the authors demonstrated that ertapenem was superior to cefotetan in this trial, is it reasonable to conclude that ertapenem should be a preferred agent for prophylaxis before colorectal surgery? Only one third of Medicare patients undergoing colorectal surgery currently receive cefotetan as prophylaxis,[7] and there are numerous

CORRECTION

Diagnosis of Ventilator-Associated Pneumonia

Diagnosis of Ventilator-Associated Pneumonia . Dr. Kollef's disclosure statement should have read ``Dr. Kollef reports receiving consulting fees or honoraria from Pfizer, Merck, Kimberly Clark, and Elan, and grant support from Pfizer, Merck, Elan, and Bard Medical. No other potential conflict of interest relevant to this article was reported.´´ The text has been corrected on the *Journal*'s Web site at www.nejm.org.

N Engl J Med 2007;356:1283-a

University of Pittsburgh
Department of Critical Care Medicine

Evidence-Based Medicine Journal Club
EBM Journal Club Section Editor: Eric B. Milbrandt, MD, MPH

Journal club critique

Diagnostic techniques for ventilator-associated pneumonia: Conflicting results from two trials

Younghoon Kwon [1], Eric B. Milbrandt[2], and Sachin Yende[2]

[1] Clinical Fellow, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[2] Assistant Professor, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Published online: 14th May 2009
This article is online at http://ccforum.com/content/13/3/303

Critical Care 2009, 13:303 (DOI: 10.1186/cc7797)

Expanded Abstract

Citation

A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med* 2006, 355:2619-2630 [1].

Background

Critically ill patients who require mechanical ventilation are at risk for ventilator-associated pneumonia. Current data are conflicting as to the optimal diagnostic approach in patients who have suspected ventilator-associated pneumonia.

Methods

Objective: To compare the quantitative culture of bronchoalveolar-lavage fluid and nonquantitative culture of endotracheal aspirate in critically ill patients with suspected ventilator-associated pneumonia, testing the hypothesis that bronchoscopy with quantitative culture would be associated with lower mortality rates and less use of antibiotics.

Design: Multi-center non-blinded randomized controlled trial.

Setting: 28 intensive care units (ICUs) across Canada and the United States.

Subjects: 740 immunocompetent critically ill adult patients with suspected ventilator-associated pneumonia after 4 days in the ICU. Patients known to be colonized or infected with *Pseudomonas* species or methicillin-resistant *Staphylococcus aureus* were excluded.

Intervention: Using a 2-by-2 factorial design, subjects were randomly assigned to a) undergo bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid or endotracheal aspiration with nonquantitative culture of the aspirate, and to b) receive empirical combination antibiotic therapy or monotherapy. Empirical antibiotic therapy was initiated in all patients until culture results were available, at which point a protocol of targeted therapy was used for discontinuing or reducing the dose or number of antibiotics, or for resuming antibiotic therapy to treat a pre-enrollment condition if the culture was negative.

Outcome: The primary outcome was 28-day mortality. Secondary outcomes included ICU and hospital survival, duration of mechanical ventilation, response to clinical and microbiologic treatment, discontinuation of antibiotics after culture results known, and other measures of antibiotic use.

Results

There was no significant difference in 28-day mortality rate between the bronchoalveolar-lavage group and the endotracheal-aspiration group (18.9% and 18.4%, respectively; P=0.94). The bronchoalveolar-lavage group and the endotracheal-aspiration group also had similar rates of targeted therapy (74.2% and 74.6%, respectively; P=0.90), days alive without antibiotics (10.4+/-7.5 and 10.6+/-7.9, P=0.86), and maximum organ-dysfunction scores (mean [+/-SD], 8.3+/-3.6 and 8.6+/-4.0; P=0.26). The two groups did not differ significantly in the length of stay in the ICU or hospital.

Conclusions

Two diagnostic strategies for ventilator-associated pneumonia--bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid and endotracheal aspiration with nonquantitative culture of the aspirate--are associated with similar clinical outcomes and similar overall use of antibiotics. (Current Controlled Trials number, ISRCTN51767272.)

Commentary

Ventilator-associated pneumonia (VAP) is common, costly, and associated with increased morbidity and mortality. Diagnosis of VAP is based on clinical suspicion and microbiologic confirmation of a sample obtained from the lower respiratory tract. Several methods are available to sample lower respiratory tract secretions, including "non-invasive" sampling via endotracheal aspirate (ETA) and "invasive" sampling via bronchoscopy using either a protected specimen brush or bronchoalveolar alveolar lavage (BAL). Debate exists regarding the best sampling approach. However, in the absence of a gold standard to diagnose VAP, a rigorous comparison of different diagnostic techniques is challenging [2]. Therefore, focus has shifted to evaluating the effects of different diagnostic strategies on clinical outcomes, such as use of antibiotics, length of stay, and mortality.

Randomized trials comparing invasive versus non-invasive approaches have produced conflicting results. Three small (n<100) single center trials suggest no difference in mortality for patients managed using invasive versus non-invasive approaches [3-5]. Yet, these studies were underpowered to detect differences in mortality. In contrast, a large multi-center French study of 413 patients with suspected VAP showed that an invasive approach reduced 14-day mortality, organ dysfunction, and antibiotic use [6].

In the current study, the Canadian Critical Care Trials Group conducted the largest randomized trial to date comparing invasive and noninvasive VAP diagnostic techniques [1]. This is a multi-center trial in 740 patients with suspected VAP in which they tested the hypothesis that quantitative culture of BAL fluid would be associated with lower mortality rates and increased use of targeted antibiotic therapy compared to non-quantitative cultures using ETA. Importantly, patients known to be colonized or infected with pseudomonas species or methicillin-resistant *Staphalococus. aureus* (MRSA) were excluded. Once diagnostic sampling was performed, subjects were randomly assigned to one of two empiric antibiotic regimens, meropenem and ciprofloxacin vs. meropenem alone, in a two-by-two factorial design. Antibiotics were then adjusted by the clinical team once culture results were known. There were no differences between diagnostic strategy groups for either clinical outcomes (28-day mortality, organ dysfunction scores, or length of say) or measures of antibiotic use. The initial empiric antibiotic(s) subjects were randomized to did not alter these findings.

Why did these two large seemingly similar multi-center studies yield different results [1,6]? It is important to recognize differences in the study design between the French and Canadian studies. The criteria to initiate and de-escalate antibiotic therapy differed. In the French study, initial antibiotic therapy, including the decision to withhold all antibiotics, was guided by the results of the Gram-stained respiratory specimen. If no organisms were present and there were no signs of severe sepsis, antibiotics could be withheld. The Canadian study used broad spectrum initial antibiotic therapy in all subjects. This practice to administer prompt antibiotics in patients suspected to have VAP is consistent with current guidelines, though the use of broad spectrum antibiotics in patients at low risk of Pseudomonas or MRSA infections is not recommended [7]. It is therefore not surprising that the initial antibiotic strategy was judged as adequate (based on organism cultured) in nearly 90% of subjects in the Canadian study, irrespective of diagnostic strategy. This is in contrast to the French study, where the cultured organism(s) was not susceptible to initial antibiotic therapy in 1% of the invasive group, but 13% of the non-invasive group (p<0.001). Furthermore, because antibiotics could be withheld in the French study, it is also not surprising that this study showed reduced antibiotic use with an invasive approach, while the Canadian study did not.

Another key difference between the two studies is the eligibility criteria. In the Canadian study, excluded were patients known to be colonized or infected with pseudomonas species or MRSA, pathogens which were likely not susceptible to their initial empiric antibiotic regimens. The authors note this was to permit standardization of empirical antibiotic treatment such that any differences in observed outcomes could be better attributed to the diagnostic strategy. As pointed out by others, patients at risk for infection with these pathogens may be the ones most likely to benefit from an invasive diagnostic approach [8]. Though there is some face-validity to this argument, it remains unproven. Interestingly, in a pre-specific subgroup analysis, the authors of the Canadian study found a non-significant tendency toward increased mortality in the invasive group when these high-risk pathogens were present.

These studies yet again emphasize that no diagnostic test, whether it be a thermometer, pulmonary artery catheter, bronchoscope, or biomarker, will improve outcomes unless its provides data that drives management decisions that in turn improve outcomes.

Recommendation

Current evidence does not support use of invasive techniques over non-invasive approaches to diagnose VAP in most patients [9,10], with the possible exception of those at high risk of multi-drug resistant infections. It is important to remember that the most important strategy is to initiate prompt, appropriate antimicrobial therapy when VAP is suspected and to de-escalate or adjust the therapy as soon as culture results become available [7].

Competing interests

The authors declare no competing interests.

References

1. **A randomized trial of diagnostic techniques for ventilator-associated pneumonia**. *N Engl J Med* 2006, **355**:2619-2630.

2. Corley DE, Kirtland SH, Winterbauer RH, Hammar SP, Dail DH, Bauermeister DE, Bolen JW: **Reproducibility of the histologic diagnosis of pneumonia among a panel of four pathologists: analysis of a gold standard**. *Chest* 1997, **112**:458-465.
3. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, el Ebiary M, Carrillo A, Ruiz J, Nunez ML, Niederman M: **Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study**. *Am J Respir Crit Care Med* 1998, **157**:371-376.
4. Ruiz M, Torres A, Ewig S, Marcos MA, Alcon A, Lledo R, Asenjo MA, Maldonaldo A: **Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome**. *Am J Respir Crit Care Med* 2000, **162**:119-125.
5. Sole VJ, Fernandez JA, Benitez AB, Cardenosa Cendrero JA, Rodriguez dC: **Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia**. *Crit Care Med* 2000, **28**:2737-2741.
6. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A: **Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial**. *Ann Intern Med* 2000, **132**:621-630.
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. Marik PE, Baram M: **Diagnosis of ventilator-associated pneumonia**. *N Engl J Med* 2007, **356**:1470-1471.
9. Berton DC, Kalil AC, Cavalcanti M, Teixeira PJ: **Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia**. *Cochrane Database Syst Rev* 2008, CD006482.
10. Rea-Neto A, Youssef NC, Tuche F, Brunkhorst F, Ranieri VM, Reinhart K, Sakr Y: **Diagnosis of ventilator-associated pneumonia: a systematic review of the literature**. *Crit Care* 2008, **12**:R56.

CORRESPONDENCE

Diagnosis of Ventilator-Associated Pneumonia

TO THE EDITOR: Heyland and colleagues, on behalf of the Canadian Critical Care Trials Group (Dec. 21 issue),[1] report on the comparison between bronchoalveolar lavage and endotracheal aspiration for the diagnosis of ventilator-associated pneumonia. The two techniques were associated with similar clinical outcomes and similar overall antibiotic use. However, 105 (28.8%) of the 365 patients in the bronchoalveolar-lavage group had received new antibiotics within 3 days before randomization, probably after the onset of the first symptoms related to ventilator-associated pneumonia. Since these patients were different from the rest of the patients,[2,3] we wonder how decisions concerning their antimicrobial treatment were made. Furthermore, we would like to emphasize that on day 6, the rate of targeted therapy was only 74.2% in the bronchoalveolar-lavage group; thus, many patients in this group did not undergo early treatment de-escalation, even though it was indicated on the basis of the microbiologic results. More information on the application of decision algorithms in the bronchoalveolar-lavage group and the endotracheal-aspiration group after culture results were available (as early as day 3) would be informative. Obviously, the potential benefit of using a diagnostic tool, such as bronchoalveolar lavage, to restrict unnecessary use of antibiotics safely in this setting can be achieved only when decisions regarding antimicrobial therapy reflect the culture results.[4]

Jean Chastre, M.D.
Groupe Hospitalier Pitié–Salpêtrière
75651 Paris, France
jean.chastre@psl.aphp.fr

Jean-Yves Fagon, M.D.
Hôpital Européen Georges Pompidou
75908 Paris, France

1. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 2006;355:2619-30.
2. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867-903.
3. Souweine B, Veber B, Bedos JP, et al. Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: impact of previous antimicrobial treatments. Crit Care Med 1998;26:236-44.
4. 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.

TO THE EDITOR: The Canadian Critical Care Trials Group compared quantitative culture of bronchoalveolar-lavage fluid with nonquantitative culture of endotracheal aspirate for the diagnosis of ventilator-associated pneumonia. The diagnostic confirmation was considered to be acceptable if the pretest probability of ventilator-associated pneumonia was high, even if the culture of bronchoalveolar-lavage fluid had a level of less than 10^4 colony-forming units per milliliter, the level used

THIS WEEK'S LETTERS

1469 Diagnosis of Ventilator-Associated Pneumonia
1471 Lapatinib plus Capecitabine in Breast Cancer
1472 Biomarkers for Prediction of Cardiovascular Events
1475 Door-to-Balloon Time in Acute Myocardial Infarction
1479 Whipple's Disease
1481 Retraction of Letter
1481 Multiple-Triazole–Resistant Aspergillosis

as a nonquantitative test. This approach contributed to the finding of a higher proportion of confirmed cases of ventilator-associated pneumonia in the bronchoalveolar-lavage group than in the endotracheal-aspiration group (86.3% and 82.9%, respectively). The pretest opinion obviously played an important role and contributed to the clinicians' providing antibiotic treatment for all the bacteria identified, including bacteria detected in nonsignificant quantities.

Benoît Misset, M.D.
Maïté Garrouste-Orgeas, M.D.
Jean Carlet, M.D.
Groupe Hospitalier Paris Saint-Joseph
75014 Paris, France

TO THE EDITOR: The exclusion of patients known to be colonized with methicillin-resistant *Staphylococcus aureus* or pseudomonas species severely limits the usefulness of the data reported by the Canadian Critical Care Trials Group, since these are the pathogens most commonly reported to cause ventilator-associated pneumonia. It is disappointing that the study investigators did not follow current guidelines for ventilator-associated pneumonia, according to which empirical treatment is based on the risk of infection with multidrug-resistant pathogens.[1] Patients at risk for infection with such pathogens are most likely to benefit from the bronchoalveolar lavage.[2,3] If all patients with suspected ventilator-associated pneumonia are treated with broad-spectrum antibiotics, difference between the groups will of course be minimal, regardless of the diagnostic technique. We hope that readers will not embrace treatment with meropenem with or without ciprofloxacin for all patients with suspected ventilator-associated pneumonia.

Paul E. Marik, M.D.
Michael Baram, M.D.
Thomas Jefferson University
Philadelphia, PA 19107
paul.marik@jefferson.edu

1. 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. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 2000;31:Suppl 4:S131-S138.
3. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998;157:531-9.

THE AUTHORS REPLY: In response to Chastre and Fagon: patients partially treated for ventilator-associated pneumonia were excluded from the study. However, excluding patients with recent changes in antibiotics would have seriously limited the generalizability of our findings. We conducted a subgroup analysis based on the presence or absence of prior antibiotic exposure but did not observe any suggestion of a benefit from bronchoscopy in the patients with prior exposure.

An antibiotic-management algorithm delineating de-escalation therapy was provided to all clinicians. In both study groups, the median duration of study antibiotic use was 3 days (interquartile range, 2 to 5), indicating that the algorithm was applied early after enrollment. Since for some intensive care units, there were delays in reporting culture results, we allowed up to 5 days after randomization before determining whether the targeted therapy had been administered. On day 6, the rates of targeted therapy were similar in the bronchoalveolar-lavage group and the endotracheal-aspiration group. Recalculating rates of targeted therapy on the basis of the first 3 days showed no significant difference between bronchoalveolar lavage with quantitative cultures (45.2%) and endotracheal aspiration (51.1%) ($P=0.10$).

We agree with Misset et al. that pretest probability estimates of ventilator-associated pneumonia influence management decisions, since culture results are not a reference standard for infection and are influenced by prior antibiotic use. In this trial, as in practice, many clinicians interpreted the quantitative results of the analysis of bronchoalveolar-lavage fluid conservatively; for patients with a high pretest probability of ventilator-associated pneumonia, a pathogen yielding less than 10^4 colony-forming units per milliliter was still treated. But clinicians did not provide antibiotic treatment for all bacteria identified in this trial. Among the patients in the two study groups who had positive cultures, all antibiotics were discontinued by day 6 in 8.7% of the patients in the bronchoalveolar-lavage group and 11.3% of those in the endotracheal-aspiration group, and the study antibiotics were discontinued by day 6 in 56.9 and 56.2%, respectively.

Marik and Baram refer to our exclusion of patients known to be colonized or infected with methicillin-resistant *S. aureus* or pseudomonas spe-

cies. Nonstandardized empirical antibiotic therapy has confounded the interpretation of findings in some previous trials of the diagnosis of ventilator-associated pneumonia. Therefore, the initial antibiotic therapy in our trial, consisting of meropenem with or without ciprofloxacin, served to standardize empirical treatment until culture results became available. Patients with known pathogens not susceptible to these drugs were excluded; thus, differences observed in outcomes could be better attributed to the diagnostic strategy. It is important not to interpret the use of these antibiotics as clinical recommendations for the treatment of ventilator-associated pneumonia. The treatment guidelines of the American Thoracic Society were published after our trial had been completed.[1]

Daren Heyland, M.D.
Queen's University
Kingston, ON K7L 2V7, Canada
dkh2@post.queensu.ca

Deborah Cook, M.D.
McMaster University
Hamilton, ON L8N 3Z5, Canada

John Muscedere, M.D.
Queen's University
Kingston, ON K7L 2V7, Canada

for the Canadian Critical Care Trials Group

1. 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.

Lapatinib plus Capecitabine in Breast Cancer

TO THE EDITOR: In the trial reported by Geyer et al. (Dec. 28 issue),[1] which compared capecitabine alone with a combination of lapatinib and capecitabine in women with HER2-positive advanced breast cancer, approximately 60% of patients had received trastuzumab within the previous 8 weeks. It is possible that the activity of lapatinib was enhanced by the persistence of trastuzumab levels in blood. Earlier studies of the pharmacokinetics of trastuzumab administered weekly or every 3 weeks indicate that the drug's half-life is 3 to 4 weeks, although this may be an underestimate. Therefore, synergism between lapatinib and trastuzumab, leading to a more complete blockade of the HER2 pathway, cannot be excluded and may partly account for the impressive improvement in outcomes with the combined regimen.

Guru Sonpavde, M.D.
U.S. Oncology Research
Houston, TX 77598
guru.sonpavde@usoncology.com

1. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-43.

THE AUTHORS REPLY: We agree that many of the patients entering our trial probably had persistent levels of trastuzumab, which could have enhanced the activity of lapatinib. An exploratory analysis to determine whether the interval from the last dose of trastuzumab to randomization affected the activity of lapatinib was planned as a component of a subsequent updated analysis of the overall trial data. However, to provide a response to Sonpavde's question, we proceeded with an analysis of data

Table 1. Effect of the Interval between the Administration of Trastuzumab and Randomization on Time to Disease Progression.*

Interval between Last Trastuzumab Dose and Randomization	Lapatinib plus Capecitabine		Capecitabine Alone		Hazard Ratio (95% CI)	P Value
	No. of Patients	Median Time to Progression	No. of Patients	Median Time to Progression		
		wk		*wk*		
≤8 Wk	98	36.7	94	19.7	0.54 (0.34–0.86)	0.007
>8 Wk	59	39.3	60	14.6	0.48 (0.26–0.88)	0.01

* P values were calculated by the log-rank test. CI denotes confidence interval.