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.)

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VENTILATOR-ASSOCIATED PNEUMONIA DE-velops 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 fac-torial 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 group (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 broncho-alveolar-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 endotrache-al-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.

A Effect on 28-Day Mortality Rate

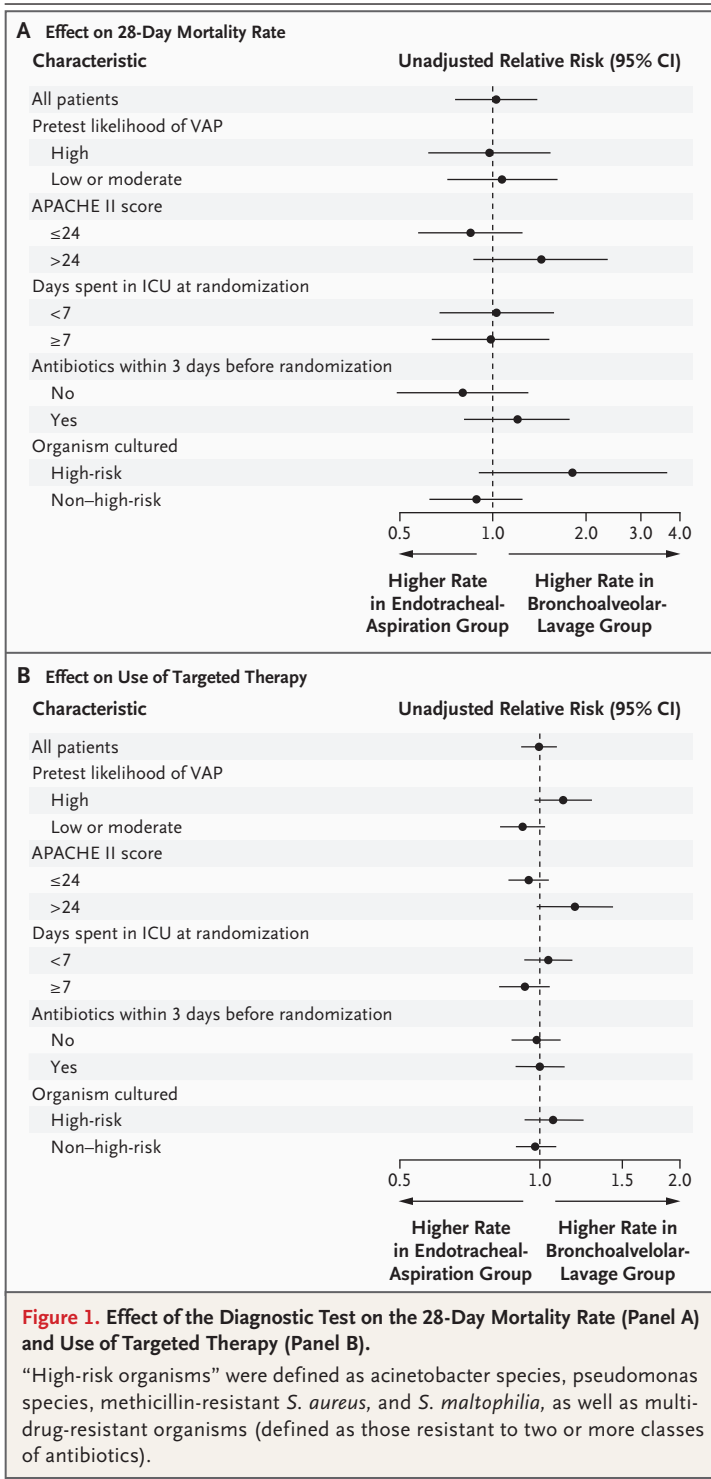## B Effect on Use of Targeted Therapy

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 ap-

propriate 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.

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.

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