Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia*

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Objective: **To compare a strategy of combination therapy with a strategy of monotherapy with broad-spectrum antibiotics for suspected late ventilator-associated pneumonia.**

Design: **Randomized trial.**

Setting: **Twenty-eight intensive care units in Canada and the United States.**

Patients: **The study included 740 mechanically ventilated patients who developed suspected ventilator-associated pneumonia after 96 hrs in the intensive care unit. Patients known to be colonized or infected with *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* or who were immunocompromised were excluded from the study.**

Interventions: **As initial unblinded therapy, patients were allocated to receive meropenem (1 g every 8 hrs) and ciprofloxacin (400 mg every 12 hrs) or meropenem alone. Before starting antibiotics, patients were also randomized to bronchoalveolar lavage with quantitative cultures or endotracheal aspirates. When culture results were available, physicians were encouraged to adjust antibiotics. Adequacy of antibiotics was defined as the organism present in the enrollment culture having *in vitro* susceptibility to one or more of the study antibiotics.**

Measurements and Main Results: **Baseline characteristics and etiologies of ventilator-associated pneumonia were similar in the two groups. There was no difference in 28-day mortality between the combination and monotherapy groups (relative risk = 1.05, 95% confidence interval 0.78–1.42, $p = .74$). Duration of intensive care unit and hospital stay, clinical and microbiological treatment response, emergence of antibiotic-resistant bacteria, isolation of *Clostridium difficile* in stool, and fungal colonization were also similar in the two groups. In a subgroup of patients who had infection due to *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacilli at enrollment (n = 56), the adequacy of initial antibiotics (84.2% vs. 18.8%, $p < .001$) and microbiological eradication of infecting organisms (64.1% vs. 29.4%, $p = .05$) was higher in the combination group compared with the monotherapy group, but there were no differences in clinical outcomes.**

Conclusions: **For critically ill patients who have suspected late ventilator-associated pneumonia and who are at low risk for difficult-to-treat Gram-negative bacteria, monotherapy is associated with similar outcomes compared with combination therapy. For those patients at high risk of difficult-to-treat Gram-negative bacteria, combination therapy is safe and may be associated with better microbiological and clinical outcomes. (Crit Care Med 2008; 36:●●●–●●●)**

KEY WORDS: ventilator-associated pneumonia; antibiotics; empirical therapy; combination therapy; randomized controlled trial; outcomes; broad spectrum antimicrobials

Ventilator-associated pneumonia (VAP) is associated with increased attributable mortality, length of stay in the intensive care unit (ICU), and consumption of health care resources (1, 2). Based on observations that delays in initiating adequate antibiotic therapy for VAP are associated with poor clinical outcomes (3–5), initial therapy should be started immediately after diagnostic specimens are obtained. However, empirical antibiotic therapy is often inadequate because cultures from initial specimens may grow organisms that are resistant to initial antibiotics resulting in increased complications (6), prolonged stay in ICU (7), and excess mortality (7–11). Therefore, to maximize the probability of adequate antibiotic coverage, combination therapy with two broad-spectrum antibiotics may be necessary (12).

However, there are no rigorous trials that support this recommendation, and use of broad-spectrum antibiotics is not without its own complications. For example, overuse of broad-spectrum antibiotics is implicated in the development of infections due to multiresistant bacteria and fungi (13). Therefore, the risks and benefits of using more than one broad-spectrum antibiotic need to be evaluated in a rigorous randomized clinical trial.

The primary purpose of this trial was to compare the effect of combination therapy with the effect of monotherapy with broad-spectrum antibiotics on 28-day mortality in the initial treatment of

***See also p. 00.**

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critically ill patients who had suspected late-onset VAP. We hypothesized that maximizing the adequacy of initial antibiotics by using two antibiotics would improve clinical outcomes compared with monotherapy.

METHODS

We conducted a multicenter, randomized trial of 740 critically ill patients from 28 ICUs in Canada and the United States who had suspected VAP. Using a factorial 2 × 2 design, we randomized patients to bronchoscopy with quantitative cultures from bronchoalveolar lavage or endotracheal aspirates and to receive either empirical combination antibiotics or monotherapy. The results of the diagnostic intervention were reported in a companion publication (14); herein, we focus on the antibiotic intervention.

Eligible patients were stratified according to site and illness severity (Acute Physiology and Chronic Health Evaluation [APACHE] II (15) score ≤24 or >24 in the 24-hr period before enrollment) and were randomized using a central telephone system with a variable undisclosed block size. Adult patients who were mechanically ventilated in ICU for ≥96 hrs were potentially eligible if they developed suspected pneumonia while they were intubated and ventilated. Suspected pneumonia was defined by the presence of new or persistent radiographic features suggestive of pneumonia without another obvious cause and any two of the following: fever >38°C, leukocytosis (>11.0 × 10^9/L) or neutropenia (<3.5 × 10^9/L), purulent endotracheal aspirate secretions, recent isolation of pathogenic bacteria from the endotracheal aspirates, and increasing oxygen requirements.

Exclusion criteria are described in detail elsewhere (14). In brief, we excluded patients who were immunocompromised; could not tolerate bronchoscopy; had known or suspected anaphylaxis to penicillins, cephalosporins, carbapenems, or ciprofloxacin; were expected to die or undergo withdrawal of life support within 24 hrs; and, in the judgment of the site investigator, were unlikely to be discharged from ICU within 3 wks from admission to the ICU. In addition, we excluded patients who were known to be previously infected or colonized with *Pseudomonas* species (physicians may not be comfortable randomizing to monotherapy) or methicillin-resistant *Staphylococcus aureus* (MRSA) (not susceptible to study antibiotics). At the time this trial was designed, the overall prevalence of MRSA was low enough that empirical use of vancomycin was not considered justifiable. Patients who had received carbapenems or ciprofloxacin within 7 days of enrollment and patients who had received any antibiotic for the current suspicion of VAP were also excluded. We obtained informed, written consent from family members.

We developed an implementation manual to standardize procurement of diagnostic specimens and associated laboratory processing (14). Immediately after these specimens were obtained, the attending ICU physicians used their clinical judgment to qualitatively estimate the pretest likelihood that the patient had VAP. No formal decision rules were applied to this prediction. Patients were then randomly allocated to receive either meropenem (AstraZeneca) 1 g every 8 hrs and ciprofloxacin (Bayer) 400 mg every 12 hrs, or meropenem alone, all provided intravenously in an unblinded fashion. We protocolized the mandatory review of culture results and adjustment of antibiotics; physicians were requested to adjust antibiotic therapy according to these results (targeted therapy) as soon as possible. In both groups, if patients had a positive culture result, physicians were recommended to prescribe a single antibiotic with the narrowest spectrum that had activity against the infecting organism. As this was a trial of empirical therapy, we did not specify the choice, dose, or duration of subsequent antibiotics. If *Pseudomonas* species were cultured, we recommended two antibiotics with activity against PSEUDOMONAS. If the culture result was "no growth" or in the bronchoalveolar lavage group nonsignificant growth (<10^4 colony-forming units/mL), study antibiotics were discontinued in both groups except in patients who had a high pretest likelihood of VAP. In this scenario, at the physicians' discretion, antibiotics could continue. "Mixed or common flora," *Staphylococcus epidermidis*, or *Candida* species were considered to be nonpathogenic.

Patients were monitored daily for signs and symptoms of infection and organ dysfunction (16). Culture results, antibiotic administration, duration of mechanical ventilation, ICU stay, and hospital stay were also documented. We used a standardized protocol to wean patients from mechanical ventilation in all sites (17). Site investigators used standard definitions (found here in the Appendix) to determine whether the patient had VAP and to determine the final clinical and microbiological outcomes.

The primary outcome for this study was 28-day all-cause mortality. Secondary outcomes included duration of mechanical venti-

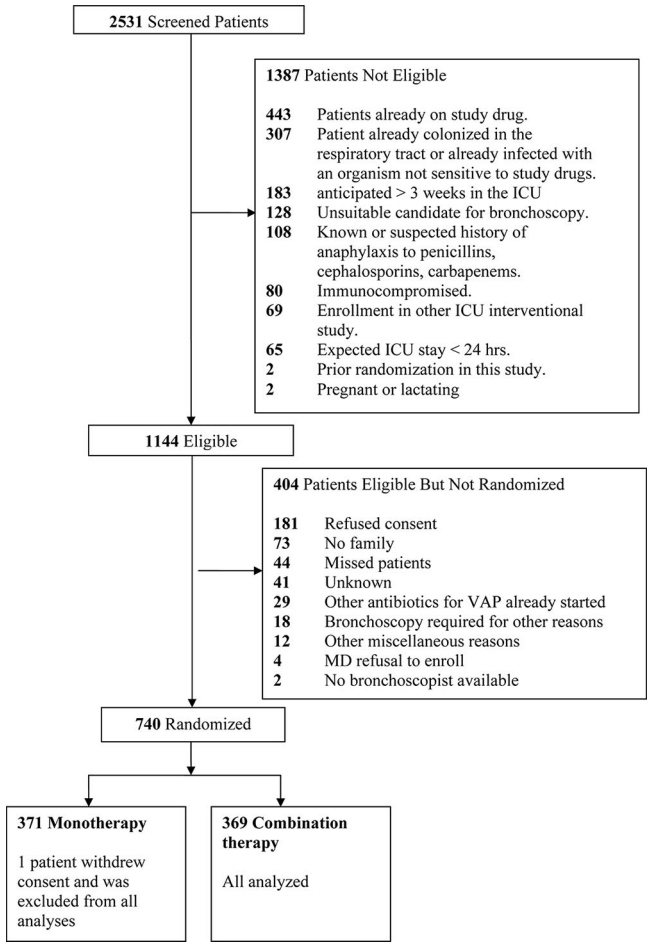

Figure 1. Flow of study participants. *ICU*, intensive care unit; *VAP*, ventilator-associated pneumonia.

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lation, ICU length of stay, hospital length of stay, clinical and microbiological treatment response, antibiotic use, adequacy of initial treatment, emergence of resistant organisms, rates of infection due to *Clostridium difficile*, and fungal colonization (defined in the Appendix). Adequate initial treatment meant that the organisms that grew in the enrollment specimen were susceptible to meropenem or ciprofloxacin *in vitro*. Cultures that did not grow any pathogens were not considered in the calculation of adequacy. If *Pseudomonas* species were isolated, two antibiotics were necessary for empirical therapy to be considered adequate (12). We evaluated outcomes for all patients based on an intention-to-treat analysis and in a prespecified subgroup of patients whose enrollment cultures grew difficult-to-treat Gram-negative bacteria (*Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacteria).

This study was approved by the research ethics boards of participating institutions and was conducted in collaboration with the Canadian Critical Care Trials Group.

Statistical Analysis. We used a previously published study of VAP to estimate the control group mortality at 40% (18). We enrolled 740 patients to achieve 80% power to detect a 10% absolute risk reduction in 28-day mortality using the Mantel-Haenszel test at a two-sided $\alpha = .049$. This final significance level accounts for one negative interim analysis done after the first 370 patients were enrolled and tested at $\alpha = .003$, according to the method of Lan and DeMets (19) using O'Brien Fleming-type boundaries. The design of this factorial study assumed that the two study interventions (diagnostic and antibiotic strategies) do not interact. This assumption was confirmed by demonstrating the similarity of the antibiotic treatment effect in the two diagnostic intervention groups and by testing for a treatment interaction using logistic regression that adjusted for APACHE II stratum. Due to small numbers, the frequency of organisms and their susceptibility were compared between the combination therapy and the monotherapy group by Fisher's exact test. All other statistical tests and relative risk estimates were adjusted for diagnostic intervention (endotracheal aspirate and bronchoalveolar lavage) and APACHE II stratum; binary variables were compared by the stratified Mantel-Haenszel test and time to event variables by the stratified log-rank test with Kaplan-Meier median estimates. Patients who died before or within 24 hrs after discontinuation of mechanical ventilation (n = 114), died before or within 24 hrs after ICU discharge (n = 128), or died in hospital (n = 182) were considered to never have achieved these end points and were censored after the end of follow-up. As specified *a priori*, a subgroup analysis was performed on patients with at least one *Pseudomonas*, *Acinetobacter*, or another multidrug-resistant Gram-negative organism present in their enrollment culture. All tests were two-sided without adjustment for multiplicity of the secondary outcomes. This intent-to-treat analysis was done according to a prespecified analysis plan using SAS version 9.1 (SAS Institute, Cary, NC).

Table 1. Enrollment characteristics of study patients

	Combination Therapy (n = 369)	Monotherapy (n = 370)	All (n = 739)
Age-years	59.1 ± 17.9	58.9 ± 17.7	59.0 ± 17.8
Female sex-no. of patients (%)	108 (29.3)	119 (32.2)	227 (30.7)
APACHE II Score	19.9 ± 6.4	20.0 ± 6.2	20.0 ± 6.3
APACHE II Score >24	86 (23.3%)	84 (22.7%)	170 (23.0%)
Admission Category-no. of patients (%)			
Medical	231 (62.6)	219 (59.2)	450 (60.9)
Surgical	138 (37.4)	151 (40.8)	289 (39.1)
Primary Diagnosis on Admission-no. of patients (%)			
Cardiovascular disorder	86 (23.3)	95 (25.7)	181 (24.5)
Trauma	95 (25.7)	92 (24.9)	187 (25.3)
Respiratory disorder	67 (18.2)	61 (16.5)	128 (17.3)
Neurologic disorder	46 (12.5)	52 (14.1)	98 (13.3)
Gastrointestinal disorder	29 (7.9)	31 (8.4)	60 (8.1)
Other condition	26 (7.0)	22 (5.9)	48 (6.5)
Sepsis	16 (4.3)	13 (3.5)	29 (3.9)
Renal disorder	4 (1.1)	4 (1.1)	8 (1.1)
Number of Comorbidities-no. of patients (%)			
0	105 (28.5)	114 (30.8)	219 (29.6)
1	100 (27.1)	86 (23.2)	186 (25.2)
2	73 (19.8)	72 (19.5)	145 (19.6)
3	91 (24.7)	98 (26.5)	189 (25.6)
Baseline PaO_2/FiO_2 at enrollment	223 ± 87.5	210 ± 77.1	217 ± 82.7
Multi organ dysfunction score at Day 1	5.4 ± 2.9	5.8 ± 3.0	5.6 ± 3.0
Pretest Likelihood of ventilator associated pneumonia-no. of patients (%)			
High	180 (48.8)	159 (43.0)	339 (45.9)
Moderate	139 (37.7)	154 (41.6)	293 (39.6)
Low	50 (13.6)	57 (15.4)	107 (14.5)
No. of days in ICU before enrollment	8.0 ± 4.9	7.8 ± 5.5	7.9 ± 5.2
Time from start of mechanical ventilation to enrollment	7.8 ± 4.9	7.7 ± 5.7	7.7 ± 5.3
Use of antibiotics within 3 days prior to randomization			
None	131 (35.5)	140 (37.8)	271 (36.7)
Antibiotics in use but initiated beforehand	136 (36.9)	116 (31.4)	252 (34.1)
New antibiotics initiated	102 (27.6)	114 (30.8)	216 (29.2)

Plus-minus values are mean ± SD.
PaO_2 denotes the partial pressure of arterial oxygen and FiO_2 the fraction of inspired oxygen.
Apache II Score-Acute Physiology and Chronic Health Evaluation.
ICU-Intensive Care Unit.

RESULTS

Between May 2000 and February 2005, 2,531 patients were screened in 28 ICUs; 1,144 were truly eligible and 740 patients were randomized (Fig. 1). One patient withdrew consent 2 days after randomization and was excluded from all analyses. There were no clinically important differences in enrollment characteristics between groups (Table 1). There was no difference in the time from suspicion of VAP to initiation of study antibiotics between the two groups (median 4 hrs in each group). The most common pathogens grown from enrollment specimens are shown in Table 2. The susceptibility profiles of Gram-negative bacteria grown in enrollment specimens to common antibiotic regimens are shown in Table 3. Of all patients whose specimens were tested for susceptibility to meropenem, 136 of 144 (94.4%) were susceptible in the combination group compared with 130 of 147 (88.4%) patients in the monotherapy group ($p = .09$). These rates did not differ based on prior antibiotic administration (data not shown).

While all patients initially had suspected VAP, upon final adjudication, one (0.1%) patient had definite pneumonia, 180 (24.4%) had probable pneumonia, 444 (60.1%) had possible pneumonia, and 114 (15.4%) did not have VAP. Initial use of meropenem was given for a median of 3 days (interquartile range [IQR] 2–5) in all study patients. In the combination

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group, ciprofloxacin was given for a median of 3 days (IQR 2–5). The median duration of VAP treatment was 10 days (IQR 5–15). Rates of targeting therapy once culture results were back were not different between the two groups (monotherapy vs. combination therapy, 75.1% vs. 73.7%, $p = .63$). Antibiotic-free days in the first 28 days were also similar between groups (monotherapy vs. combination therapy 10.7 ± 7.6 vs. 10.2 ± 7.8, $p = .35$).

Primary End Point. Overall mortality at 28 days was 18.7% (95% confidence intervals 15.9% to 21.7%). The relative risk of 28-day mortality in the combination group vs. monotherapy group was 1.05 (0.78–1.42, $p = .74$; Table 4) after stratification for APACHE II and diagnostic technique. There was no evidence that the effect of the treatment was different between the two diagnostic groups (test of interaction $p = .37$), and there was no effect of bronchoscopy or endotracheal aspirates on mortality (Table 4).

Secondary End Points. There were no differences between the combination and monotherapy groups in the median (IQR) time from randomization to discontinuation of mechanical ventilation alive (8.7 [3.8–24.8] vs. 9.3 [3.8–21.6] days, $p = .79$), discharge from ICU alive (12.1 [6.4–35.2] vs. 12.8 [6.1–27.0] days, $p = .84$), or discharge from hospital alive (45.8 [24.0–316.8] vs. 39.1 [19.7 to undefined] days, $p = .49$). Mortality rates at 14 days, ICU discharge, and hospital discharge were similar between groups (data not shown). There were no differences in clinical response or microbiological outcomes between groups (data not shown).

The proportion of patients who received adequate initial antibiotics was significantly greater in the combination group than in the monotherapy group (93.1% vs. 85.1%, $p = .01$). Reasons for inadequate initial therapy were related to the presence of *Pseudomonas* species, *Acinetobacter* species, *Stenotrophomonas maltophilia*, other multidrug-resistant Gram-negative bacteria, and MRSA in the enrollment cultures. Of the 412 patients who had positive enrollment cultures, 38 (9.2%) acquired resistance to a single antibiotic class during the study (9.1% of patients in combination group and 9.3% in the monotherapy group, $p = .99$). Rates of colonization of sputum with *Pseudomonas* species, MRSA, *Acinetobacter* species, vancomycin-resistant enterococci, or any multidrug-resistant organisms (resistant to two or more drug classes) and yeast were not significantly different between groups (Table 5). *C. difficile* toxin was isolated from stool in 5.4% of patients receiving combination therapy and 7.6% of patients in the monotherapy group during the study period ($p = .46$).

Table 2. Organisms grown in enrollment specimens in study patients

	Combination Therapy (n = 369)	Monotherapy (n = 370)	All (n = 739)
Organism			
None	60 (16.3)	74 (20.0)	134 (18.1)
Staphylococcus *aureus*	65 (17.6)	62 (16.8)	127 (17.2)
Candida sp.	66 (17.9)	52 (14.1)	118 (16.0)
Normal flora	58 (15.7)	54 (14.6)	112 (15.2)
Haemophilus *influenzae*	47 (12.7)	52 (14.1)	99 (13.4)
Enterobacter sp.	30 (8.1)	39 (10.5)	69 (9.3)
Klebsiella sp.	30 (8.1)	31 (8.4)	61 (8.3)
Pseudomonas sp.	31 (8.4)	16 (4.3)	47 (6.4)
Escherichia *coli*	19 (5.1)	23 (6.2)	42 (5.7)
Streptococcus *pneumoniae*	9 (2.4)	5 (1.4)	14 (1.9)
Other Streptococcus sp.	10 (2.7)	10 (2.7)	20 (2.7)
Serratia sp.	16 (4.3)	6 (1.6)	22 (3.0)
Acinetobacter sp.	11 (3.0)	4 (1.1)	15 (2.0)
Staphylococcus coagulase negative	5 (1.4)	10 (2.7)	15 (2.0)
Enterococcus sp.	9 (2.4)	5 (1.4)	14 (1.9)
Proteus sp.	6 (1.6)	8 (2.2)	14 (1.9)
Moraxella *catarrhalis*	5 (1.4)	8 (2.2)	13 (1.8)
Methicillin-resistant Staphylococcus *aureus*	5 (1.4)	7 (1.9)	12 (1.6)
Stenotrophomonas *maltophilia*	3 (0.8)	9 (2.4)	12 (1.6)
Aspergillus sp.	5 (1.4)	3 (0.8)	8 (1.1)
Other[b]	25 (6.8)	24 (6.5)	49 (6.6)
Polymicrobial	79 (21.4)	90 (24.3)	169 (22.9)
Total			
Multi-drug resistant organisms[a]	20 (5.4)	18 (4.9)	38 (5.1)
High Risk organisms[a]	59 (16.0)	46 (12.4)	105 (14.2)

[a]The incidence of multi drug resistant organisms (defined as those resistant to 2 or more classes of antibiotics) and high-risk organisms (defined as Pseudomonas species, Methicillin Resistant Staphylococcus *aureus,* Stenotrophomonas *maltophilia,* Acinetobacter species, and Multi drug resistant bacteria): [b]Other included: Citrobacter species, Morganella species, Neisseria *meningitidis,* Aeromonas species, Pasteurella species, Torulopsis (Candida) *glabrata,* Sphingmononas species, Bacteroides species, Prevotella species, Haemphilus *parainfluenza,* Eikenella species, Neisseria species.

Table 3. Susceptibility patterns of enrollment organisms

Enrollment Organsim	Meropenem	Imipenem/ Cilastatin	Pip/Taz Ticar/Clav	Ciprofloxacin	Piperacillin Ticarcillin	Ceftazidime Cefepime	Ceftriaxone Cefotaxime	Cefazolin Cefuroxime	Tobramycin Amikacin Gentamicin
Acinetobacter sp.	14/14 (100%)	5/5 (100%)	8/8 (100%)	15/15 (100%)	4/7 (57%)	12/14 (86%)	1/3 (33%)	0/2 (0%)	12/15 (80%)
Citrobacter sp.	7/7 (100%)	0/0	2/2 (100%)	8/8 (100%)	4/4 (100%)	0/0	2/3 (67%)	3/8 (38%)	8/8 (100%)
Enterobacter sp.	60/60 (100%)	6/6 (100%)	18/28 (64%)	67/67 (100%)	23/27 (85%)	6/15 (40%)	25/38 (66%)	1/60 (2%)	66/66 (100%)
Escherichia coli	36/36 (100%)	4/4 (100%)	12/13 (92%)	39/42 (93%)	11/17 (65%)	8/8 (100%)	13/14 (93%)	36/39 (92%)	41/42 (98%)
Klebsiella sp.	52/52 (100%)	4/4 (100%)	17/18 (94%)	59/61 (97%)	28/31 (90%)	12/12 (100%)	12/13 (92%)	53/59 (90%)	61/61 (100%)
Proteus sp.	10/10 (100%)	1/1 (100%)	1/1 (100%)	12/12 (100%)	5/5 (100%)	3/3 (100%)	6/6 (100%)	10/12 (83%)	12/12 (100%)
Pseudomonas sp.	36/40 (90%)	8/10 (80%)	18/19 (95%)	33/44 (75%)	28/33 (85%)	37/42 (88%)	1/4 (25%)	1/5 (20%)	36/41 (88%)

Sp., species; Pip/Taz, Piperacillin/Tazobactam; Ticar/Clav, Ticarcillin/Clavulanate. The denominator is the subset of enrollment organisms tested for susceptibility against the named antibiotic.

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Table 4. 28-day mortality

	Combination Therapy	Monotherapy	RR Combination Therapy vs Monotherapy Conditional on Diagnostic Approach	Overall RR Combination Therapy vs Monotherapy
Bronchoscopy with BAL	38/182 (20.9%)	31/183 (16.9%)	1.23 (0.80–1.89)	1.05 (0.78–1.42)[a]
Endotracheal aspirates	33/187 (17.6%)	36/187 (19.3%)	0.92 (0.60–1.40)	
RR BAL vs. ETA conditional on antibiotics given	1.18 (0.78–1.80)	0.88 (0.57–1.36)		
Overall RR BAL vs. ETA	1.01 (0.75–1.37)[b]			

[a]Stratified by enrollment APACHE II score diagnostic strategy (ETA or BAL); [b]Stratified by enrollment APACHE II score and antibiotic therapy (Monotherapy or Combination).

Interaction Ratio between interventions: 1.34 (p = 0.37).

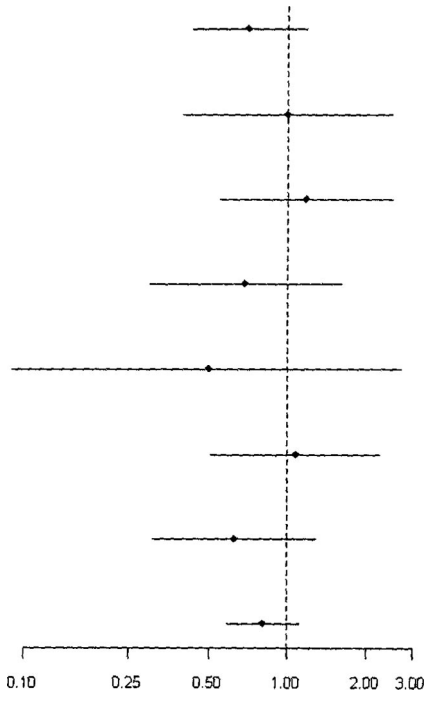
RR-Relative Risk.

ETA-endotracheal aspirates.

BAL-bronchoalveolar lavage.

Table 5. Frequency of organisms acquired after randomization

Organism	Combination Therapy (n = 369)	Monotherapy (n = 370)	All (n = 739)	Combo/Mono RR (95% CI)[b]
Pseudomonas sp.	24 (6.5%)	34 (9.2%)	58 (7.8%)	
Acinetobacter sp.	9 (2.4%)	9 (2.4%)	18 (2.4%)	
Methicillin resistant Staphylococcus *aureus*	14 (3.8%)	12 (3.2%)	26 (3.5%)	
Stenotrophomonas *maltophilia*	9 (2.4%)	13 (3.5%)	22 (3.0%)	
Vancomycin resistant Enterococcus	2 (0.5%)	4 (1.1%)	6 (0.8%)	
Yeast sp.	14 (3.8%)	13 (3.5%)	27 (3.7%)	
Multi-drug resistant Gram negative bacteria	12 (3.3%)	19 (5.1%)	31 (4.2%)	
Total high risk[a]	57 (15.4%)	71 (19.2%)	128 (17.3%)	



Sp., species.

[a]Includes Acinetobacter sp., Pseudomonas sp., Methicillin resistant Staphylococcus *aureus,* Stenotrophomonas *maltophilia* and multi-resistant organisms. They do not add up to the individual row totals as some of the Pseudomonas sp. and Acinetobacter sp. are multi-drug resistant pathogens as well; [b]relative risks and 95% confidence intervals estimated by the Mantel-Haenszel method stratified by APACHE II score (<= 24 vs. >24) and diagnostic technique (ETA vs. BAL).

Subgroup Analysis. Fifty-six patients who had at least one *Pseudomonas*, *Acinetobacter*, or another multidrug-resistant Gram-negative organism present in the enrollment cultures. In this subgroup, we observed a significant difference in the rate of adequacy of empirical antibiotic therapy favoring combination therapy over monotherapy (84.2% vs. 18.8%, $p < .001$). Among the 56 patients in the group who grew multidrug-resistant Gram-negative bacilli at enrollment, cultures from 30 of 33 (90.1%) patients, whose specimens were tested for susceptibility to meropenem, were susceptible in the combination group compared with 13 of 15 (87.7%) patients in the monotherapy group ($p = .64$). In this subgroup of 56 patients with multidrug-resistant Gram-negative bacilli at enrollment, we also observed trends toward greater rate of eradication of infecting microorganisms, a shorter duration of mechanical ventilation and ICU stay, and lower ICU and hospital mortality in the combination therapy group (Table 6). In the patients in this subgroup who received combina-

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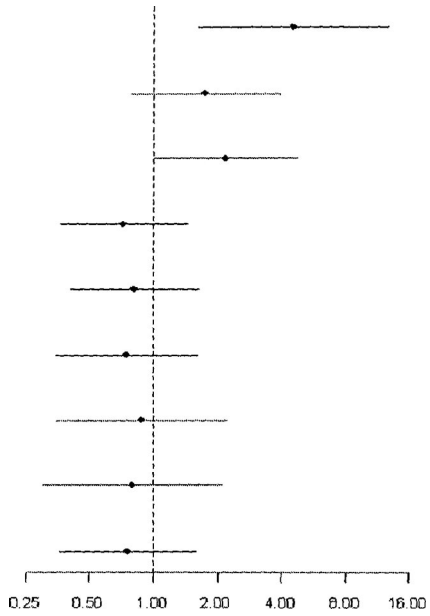
Table 6. Subgroup analysis of patients with difficult to treat gram negative bacilli on enrollment

	Combination Therapy (n = 39)	Monotherapy (n = 17)	Combo/Mono RR (95% CI)[d]
Adequacy of empiric therapy[a]	32 (84.2%)	3 (18.8%)	
Clinical resolution at 28 days	20 (51.3%)	5 (29.4%)	
Microbiological resolution at 28 days[b]	25 (64.1%)	5 (29.4%)	
Duration of mechanical ventilation[c]	10.7 [3.3, .]	15.0 [9.3, .]	
Duration of ICU Stay[c]	14.2 [8.1, .]	21.2 [14.1, .]	
Duration of Hospital Stay[c]	55.0 [33.0, .]	111.4 [27.8, .]	
28 Day Mortality	10 (25.6%)	5 (29.4%)	
ICU Mortality	9 (23.1%)	5 (29.4%)	
Hospital Mortality	13 (33.3%)	7 (41.2%)	



We present the a priori subgroup analysis for patients with difficult to treat Gram negative bacilli present on enrollement (Pseudomonas sp., Acinetobacter sp., and other multidrug resistant Gram negative bacilli).

[a]Adequacy of therapy not available for one patient in each group, n = 38 for Combination Group; n = 16 for Monotherapy Group ($p < 0.001$); [b]$p = 0.014$; [c]Median [IQR]. The upper quartile range of the time to discharge is undefined for the monotherapy group because more than 25% of patients died and were not discharged from the hospital; [d]Relative risks and 95% confidence intervals are adjusted for APACHE II score and diagnostic technique by the stratified Mantel-Haenszel method for binary outcomes and the proportional hazards model for duration outcomes.

tion therapy, 28 of 39 patients (71.8%) compared with 11 of 17 patents in the monotherapy group (64.7%) were treated with two or more antipseudomonal agents after the first 5 days ($p = .75$).

DISCUSSION

In this multicenter trial of 739 critically ill patients who developed a clinical suspicion of VAP after 4 days in the ICU, we found similar all-cause 28-day mortality whether patients were treated with empirical broad-spectrum combination antibiotic therapy or monotherapy. Duration of stay in hospital and ICU, clinical and microbiological response to treatment, and organ function were similar in both groups.

Was the lack of treatment effect we observed in this trial related to our choice of agents used for combination therapy? Although ciprofloxacin achieves higher concentrations in epithelial lining fluid and alveolar macrophages than aminoglycosides, resistance to ciprofloxacin has been reported (20). Furthermore, there is a theoretical rationale that fluoroquinolones may increase resistance to carbapenems by inducing efflux pump systems (21). However, to our knowledge, there are no reports of the short-term use of this combination causing increased resistance, and we did not observe this in our trial. We did not use aminoglycosides in this trial because of the high prevalence of renal dysfunction in ICU patients and the potential for nephrotoxicity and ototoxicity.

While our trial is the first study of the empirical use of combination compared with monotherapy, several randomized trials of treatment with combination vs. monotherapy in serious infections have recently been summarized. Compared with combination therapy, monotherapy is associated with less clinical failure (relative risk 0.87, 0.78–0.97), lower rates of nephrotoxicity (relative risk 0.36, 0.28–0.47), fewer superinfections (odds ratio 0.62, 0.42–0.93), a trend toward fewer treatment failures (odds ratio 0.62, 0.38–1.01), and a similar rate of emergence of antibiotic resistance (odds ratio 0.90, 0.56–1.47) (22, 23). Hence, our trial results, related to short-course empirical treatment only, are consistent with a larger body of literature related to longer term treatment of serious infections that fails to demonstrate a significant clinical advantage associated with combination therapy. Although we found no clinical advantages of combination therapy in our overall analysis, neither did we observe any differences in rates of superinfection, development of resistance, fungal overgrowth, and infection due to *C. difficile* associated with the addition of a short empirical course (median treatment of 3 days) of a second agent.

We recruited patients who developed late VAP (>4 days in ICU) who would potentially require treatment with broad-spectrum agents. Furthermore, in our trial, about two thirds of patients had previous antibiotic exposure. Notwithstanding, the overall prevalence of *Pseudomonas*, MRSA, and other difficult-to-treat organisms was low compared with other reports in the literature and may explain why the overall study results showed no difference in clinical outcomes. We excluded patients known to be colonized or previously infected with

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Pseudomonas and MRSA because of concerns of treating patients with meropenem alone. This exclusion criterion may be a useful strategy to define a patient at low risk of *Pseudomonas* and MRSA in ICUs similar to participating ICUs. In a prespecified subgroup analysis, we compared the efficacy of combination therapy with that of monotherapy in patients whose specimens grew *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacteria. We observed a greater eradication of the infecting organisms, shorter duration of ventilation and ICU stay, and lower ICU and hospital mortality in the combination therapy group. However, this subgroup analysis was underpowered to demonstrate statistical significance, and therefore these findings are hypothesis-generating only. If these differences are real, they may not be explained by differences in subsequent treatment because equal numbers of patients in each group received combination therapy after the initial treatment period. Equal numbers of these patients had effective monotherapy, as meropenem had activity against these pathogens in almost 90% of cases in both groups. This would suggest that differences in outcomes may be due to the empirical use of two antipseudomonal agents compared with monotherapy.

The strengths of our trial include the use of concealed randomization, complete follow-up, a protocolized approach to the diagnosis and treatment of patients with suspected VAP, and use of explicitly defined study outcomes in the largest multicenter trial to date addressing this question. One important limitation is that the trial was necessarily unblinded; however, we minimized bias by protocolizing patient management and outcome ascertainment using standardized definitions. In addition, we did not conduct molecular or genetic typing of the bacterial isolates to determine whether organisms isolated during the study were identical to organisms present at enrollment. Despite the large, multicenter design, the low prevalence of high-risk organisms we documented may limit the generalizability of our study findings to other centers where the prevalence of such resistant organisms is very high. Finally, while specified *a priori*, the small number of patients with resistant isolates limits the inferences that can be made from the subgroup analyses.

CONCLUSIONS

In immunocompetent critically ill patients, we observed that when broad-spectrum antibiotics are used for initial empirical therapy for clinically suspected late VAP in the setting of a low prevalence of high-risk organisms, outcomes appear similar whether combination therapy or monotherapy is used. Cost considerations and the desire to minimize unnecessary antibiotic exposure in critical care settings would favor the utilization of monotherapy. On the other hand, if local resistance patterns or individual patient risk factors suggest the possibility of multidrug-resistant organisms or other difficult-to-treat organisms, it is relevant that this trial did not identify increased complications associated with an empirical, short course of an antipseudomonal fluoroquinolone in combination with an antipseudomonal carbapenem, and this strategy may be associated with better microbiological and clinical outcomes.

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APPENDIX: DEFINITIONS OF CLINICAL AND MICROBIOLOGICAL OUTCOMES

Clinical Outcomes

Clinical resolution: Fever, purulence of secretions, and leukocytosis are eliminated, and oxygenation and radiographic findings improve within 28 days of enrollment.

Delayed resolution: The patient improves but remains on mechanical ventilation >28 days after enrollment.

Relapse or recurrent infection: After initial improvement, the patient suffers a clinical and radiographic deterioration with the same organism that was responsible for the initial infection.

Superinfection: The patient has an infection that is similar to relapse or recurrent infection but involves a different or new organism.

Clinical failure: The patient dies or has persistence of clinical and radiographic features of infection throughout the study period requiring additional antibiotics.

Indeterminate: While being treated for respiratory symptoms, the patient requires additional antibiotics for nonrespiratory tract infections (e.g., catheter-related sepsis requiring vancomycin).

Microbiological Outcomes

Microbiological resolution: The putative pathogen is eliminated from repeated culture of lower respiratory tract.

Relapse or recurrent infection: After initial eradication, the patient suffers a clinical and radiographic deterioration with the same organism that was responsible for the initial infection.

Superinfection: The patient has an infection that is similar to relapse or recurrent infection but involves a different or new organism.

Failure: The enrollment microorganism continues to appear in secretions of the lower respiratory tract throughout the study period.

Colonization: The patient acquires (after enrollment) yeast or bacteria not associated with features of infection.

Indeterminate: If a patient dies early and no subsequent cultures are available, outcomes are considered indeterminate.

Adequacy of empirical therapy: The organisms that grow in the enrollment specimen show *in vitro* susceptibility to meropenem or ciprofloxacin. If *Pseudomonas* species are isolated, two drugs are necessary for empirical therapy to be considered adequate.

Classification of VAP

Definite bacterial pneumonia: At least one of the following three criteria is fulfilled:

Positive result of pleural fluid culture.

Rapid cavitation of the lung infiltrate as determined by computed tomography.

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

Probable bacterial pneumonia: None of the preceding criteria are met, yet cultures of specimens are obtained (using bronchoalveolar lavage) that grow at least one organism in significant concentration ($>10^4$ colony-forming units/mL).

Possible pneumonia: None of the preceding criteria are met, yet patient's chest radiograph, sputum culture, temperature, white blood cell count, and clinical course are consistent with pneumonia.

No pneumonia: The study investigators believe that the patient's course is not compatible with pneumonia.

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