Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

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H OSPITALS AND PARTICULARLY intensive care units (ICUs) are faced with the emergence and rapid dissemination of multiresistant bacteria.[1-4] In some cases, the choice of potential therapies is limited or even nonexistent.[5-8] The response to this challenge lies in a policy of prevention and better utilization of antimicrobial therapy, notably shortening the duration and decreasing the number of antibiotics given to ICU patients to contain the emergence and dissemination of such pathogens.[3,9-12] Because of its frequency and severity,[13,14] nosocomial pneumonia in patients requiring prolonged mechanical ventilation represents 1 of the principal reasons for the prescription of antibiotics in the ICU.[15] At present, most experts recommend that

Context The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU).

Objective To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

Design, Setting, and Participants Prospective, randomized, double-blind (until day 8) clinical trial conducted in 51 French ICUs. A total of 401 patients diagnosed as having developed VAP by quantitative culture results of bronchoscopic specimens and who had received initial appropriate empirical antimicrobial therapy were enrolled between May 1999 and June 2002.

Intervention A total of 197 patients were randomly assigned to receive 8 days and 204 to receive 15 days of therapy with an antibiotic regimen selected by the treating physician.

Main Outcome Measures Primary outcome measures—death from any cause, microbiologically documented pulmonary infection recurrence, and antibiotic-free days—were assessed 28 days after VAP onset and analyzed on an intent-to-treat basis.

Results Compared with patients treated for 15 days, those treated for 8 days had neither excess mortality (18.8% vs 17.2%; difference, 1.6%; 90% confidence interval [CI], −3.7% to 6.9%) nor more recurrent infections (28.9% vs 26.0%; difference, 2.9%; 90% CI, −3.2% to 9.1%), but they had more mean (SD) antibiotic-free days (13.1 [7.4] vs 8.7 [5.2] days, $P<.001$). The number of mechanical ventilation–free days, the number of organ failure–free days, the length of ICU stay, and mortality rates on day 60 for the 2 groups did not differ. Although patients with VAP caused by nonfermenting gram-negative bacilli, including *Pseudomonas aeruginosa*, did not have more unfavorable outcomes when antimicrobial therapy lasted only 8 days, they did have a higher pulmonary infection-recurrence rate compared with those receiving 15 days of treatment (40.6% vs 25.4%; difference, 15.2%, 90% CI, 3.9%-26.6%). Among patients who developed recurrent infections, multiresistant pathogens emerged less frequently in those who had received 8 days of antibiotics (42.1% vs 62.0% of pulmonary recurrences, $P=.04$).

Conclusions Among patients who had received appropriate initial empirical therapy, with the possible exception of those developing nonfermenting gram-negative bacillus infections, comparable clinical effectiveness against VAP was obtained with the 8- and 15-day treatment regimens. The 8-day group had less antibiotic use.

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treatment of ventilator-associated pneumonia (VAP) last 14 to 21 days in most cases, even though these recommendations remain largely empirical, primarily because of an absence of prospective randomized controlled studies specifically devoted to this issue.[16,17] This recommendation is justified, in theory, by the high risk of infection relapse after a shorter duration of antibiotic administration. The risk is probably low for bacteria considered highly susceptible to antimicrobial agents, such as methicillin-susceptible *Staphylococcus aureus* or *Haemophilus influenzae*, but might be high for certain species, especially *Pseudomonas aeruginosa*, which is particularly difficult to eradicate from the respiratory tract.[18,19] Thus, at present, a short-term regimen is rarely prescribed, despite the potential major advantages it could have in terms of bacterial ecology and prevention of the emergence of multiresistant strains in the ICU.

Results obtained with various antibiotic strategies investigated in patients with VAP are difficult to assess because the diagnosis of pulmonary infection in this setting is difficult; thus, the populations studied are often ill defined, including patients with various lower respiratory tract infections, ranging from tracheobronchitis to severe pneumonia.[16,17] The use of invasive diagnostic techniques, such as fiberoptic bronchoscopy, coupled with quantitative cultures of distal pulmonary secretions obtained with a protected specimen brush, bronchoalveolar lavage, or both, might more precisely identify patients with VAP and more accurately select patients for inclusion in clinical trials.[20-22] We therefore undertook a randomized trial to compare the outcomes of therapy with an 8-day or 15-day antibiotic regimen for a well-defined group of ICU patients who had developed VAP, as confirmed by quantitative culture results of bronchoscopic specimens.

METHODS
Study Design and Organization
This randomized, double-blind (until day 8) trial was performed on 2 paral-lel groups in 51 ICUs in France (FIGURE 1). The protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Hôpital Saint-Louis, Paris, France, in May 1999. All patients or their relatives gave written informed consent before enrollment.

Patients
The ICU patients who were intubated and had received mechanical ventilation for at least 48 hours were eligible for the study if they met all the following criteria: (1) older than 18 years; (2) clinical suspicion of VAP, defined by a new and persistent infiltrate on chest radiography associated with at least 1 of the following: purulent tracheal secretions, temperature of 38.3°C or higher, and a leukocyte count higher than 10 000/µL (for patients experiencing acute respiratory distress syndrome and for whom it was difficult to demonstrate deterioration of radiologic images, at least 1 of the 3 preceding criteria sufficed for inclusion); (3) positive quantitative cultures of distal pulmonary secretion samples, obtained by fiberoptic bronchoscopy, of bronchoalveolar lavage fluid (significant threshold ≥10^4 colony-forming units/mL), or with a protected specimen brush or catheter (significant threshold ≥10^3 colony-forming units/mL)[23]; and (4) instigation within the 24 hours following bronchoscopy of appropriate empirical antibiotic therapy directed against the microorganism(s) responsible for the pulmonary infection, as determined by their susceptibility patterns.[24]

Patients were excluded if they (1) were pregnant; (2) were enrolled in another trial; (3) had little chance of survival, as defined by a Simplified Acute Physiology Score (SAPS II) of more than 65 points; (4) had neutropenia (leukocyte counts <1000/µL or neutrophils <500/µL); (5) had concomitant acquired immunodeficiency syndrome (stage 3 according to the Centers for Disease Control and Prevention 1993 classification); (6) had received immunosuppressants or long-term corticosteroid therapy (≥0.5 mg/kg per day for

Figure 1. Patient Flow Diagram
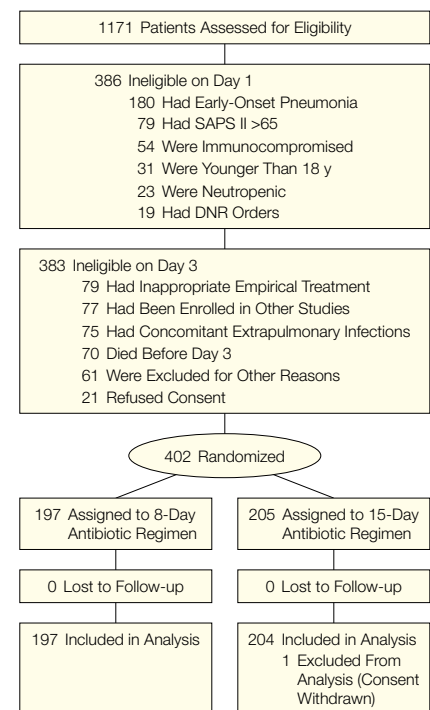
DNR indicates do not resuscitate; SAPS II, Simplified Acute Physiologic Score II.

>1 month); (7) had a concomitant extrapulmonary infection diagnosed between days 1 and 3 that required prolonged (>8 days) antimicrobial treatment; or (8) their attending physician declined to use full life support. Patients who had early onset pneumonia (within the first 5 days of mechanical ventilation) and no antimicrobial therapy during the 15 days preceding infection were also excluded because the causative pathogens in such a setting are usually highly sensitive to antibiotics.[16,25]

Randomization
Patients were randomly assigned to receive antibiotics for 8 or 15 days 3 days after the bronchoscopy, as soon as it was possible to verify that the inclusion or exclusion criteria had been met and that the pathogens isolated at significant concentrations by quantitative cultures of bronchoscopic specimens were appropriately covered by the initial empirical antibiotic regimen selected

on day 1 (defined as the day of bronchoscopy), based on the results of antibiograms. Randomization was performed centrally, using an interactive voice system, and stratified by center in blocks of 4 according to a computer-generated random-number table. In order not to influence antibiotic prescriptions, the randomization assignment was not communicated to the investigators until day 8; thus, all patients, medical and nursing staffs, and pharmacists remained blinded until then. On that day, investigators had to telephone the randomization center to receive the treatment assignment by fax. If this call was not made before 3 PM, a fax was automatically sent by the randomization center to remind the investigator to call.

Antibiotic Treatments

Drug selection was left to the discretion of the treating physicians, including any adaptation considered necessary as a function of the definitive microbiologic results identifying the pathogen(s) and its susceptibility patterns. Nevertheless, it was specified in the protocol that the initial empirical antibiotic regimen (ie, before the susceptibility patterns of the responsible microorganisms were known) should preferably combine at least an aminoglycoside or a fluoroquinolone and a broad-spectrum betalactam antimicrobial agent, unless the microorganism(s) was not considered to be sensitive to these classes or a contraindication to their use was present, as recommended by the American Thoracic Society.[16] Investigators were strongly encouraged to convert this initial regimen into a narrow-spectrum therapy, based on culture results, which in all cases were obtained within 48 to 72 hours after bronchoscopy. All antibiotics were withdrawn, either at the end of day 8 or day 15, according to the randomization assignment, except those prescribed for a documented pulmonary infection recurrence before that day or for an infection predating VAP, when its total duration of treatment was considered insufficient, for example, endocarditis.

In that situation, only the antibiotics prescribed before inclusion were continued and those prescribed for the VAP episode were stopped.

Baseline Assessment and Data Collection

At admission to the ICU, we recorded each patient's age, sex, preexisting comorbidities, severity of underlying medical condition(s) stratified according to the criteria of McCabe and Jackson,[26] admission categories, SAPS II,[27] Sepsis-related Organ Failure Assessment (SOFA) score,[28] the organ dysfunction and/or infection (ODIN) score (range, 0-7, according to the presence or absence of cardiovascular, respiratory, renal, hepatic, hematologic and/or neurologic dysfunctions and/or infection)[29]; and the primary reason for initiating mechanical ventilation (**TABLE 1**).

The following baseline variables were recorded before randomization (**TABLE 2**): numbers and types of microorganisms responsible for pneumonia (only those recovered at significant concentrations from bronchoscopic specimens were considered to be responsible for pulmonary infection); duration of prior mechanical ventilation; use of any antibiotics before VAP onset; SAPS II; ODIN score; SOFA score; temperature; leukocyte count; ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FIO_2); radiologic score (range, 0-12 according to the density of pulmonary infiltrate[s])[13]; bacteremia; presence of shock, defined as systolic arterial pressure lower than 90 mm Hg with signs of peripheral hypoperfusion or need for continuous infusion of vasopressor or inotropic agents[30]; and presence of the acute respiratory distress syndrome, defined as a generalized pulmonary infiltrate, PaO_2/FIO_2 less than 200, and the absence of clinical evidence of left atrial hypertension.[31]

Follow-up and Definitions

The following data were recorded daily during the 28-day period after the initial bronchoscopy: temperature; leukocyte counts; PaO_2/FIO_2; presence or

absence of purulent tracheal secretions; patient's mechanical ventilation status; vital signs; and ODIN score. The SOFA and radiologic scores were determined again on days 3, 7, 14, 21, and 28. Extreme vigilance for pneumonia recurrence was maintained throughout the study to detect any possible relapse or new episode of pulmonary infection, and fiberoptic bronchoscopy was performed before the introduction of any new antibiotics as soon as a patient became febrile, had purulent tracheal secretions, a new pulmonary infiltrate developed, or an existing infiltrate progressed. Distal pulmonary secretions were also collected bronchoscopically when unexplained hemodynamic instability required higher vasopressor doses ($>$30%) or their introduction; in the case of unexplained deterioration of blood gases, with a PaO_2/FIO_2 decrease of more than 30%; or when an intercurrent event imposed an urgent change of antibiotic therapy, regardless of the reason. Any antibiotic use was recorded daily until day 28. In addition, the patient's status at discharge from the hospital and 60 days after bronchoscopy was recorded.

Patients were considered to have microbiologically documented recurrent pulmonary infection when at least 1 bacterial species grew at a significant concentration from samples collected during a second bronchoscopy. Recurrence was considered a relapse if at least 1 of the initial causative bacterial strains (ie, same genus, species, and serotype when available) grew at a significant concentration from a second distal sample; otherwise, it was considered to be a superinfection. Multiresistant bacteria were defined as 1 of the following: ticarcillin-resistant *P aeruginosa*, *Acinetobacter baumannii*, or *Stenotrophomonas maltophilia*; extended-spectrum betalactamase-producing Enterobacteriaceae; and methicillin-resistant *S aureus*. We calculated the number of antibiotic-free days as the number of days during the 28 days after living patients had been randomized and had not received any antibi-

otic.[32] Using the same method, we determined the number of mechanical ventilation–free days and the number of organ failure–free days, as defined by the ODIN score.

Outcome Measures

The primary outcome measures were death from any cause; microbiologically documented pulmonary infection recurrence, defined using the same microbiologic criteria as those that led to patient inclusion in the trial; and antibiotic-free days, all of which were assessed 28 days after the first bronchoscopy for suspected VAP onset.

Secondary outcome measures were the number of mechanical ventilation–free days; the number of organ failure–free days; the evolution of the 6 parameters comprising the SOFA and the ODIN scores from day 1 to day 28; the evolution of signs and symptoms potentially linked to pulmonary infection, including fever, leukocyte counts, PaO_2/FIO_2, and radiologic score; the length of stay in the ICU; the rate of unfavorable outcomes, defined as death, infection recurrence, or prescription of a new antibiotic for any reason provided that this new treatment lasted longer than 48 hours; mortality at day 60; in-hospital mortality; and the percentage of emerging multiresistant bacteria during the ICU stay, as assessed by microbiologic examination of all bronchoscopic samples collected for pulmonary infection recurrence.

Statistical Analyses

The trial was designed to demonstrate the noninferiority of the 8-day vs the 15-day regimen in terms of death and pulmonary infection recurrence rates, and its superiority in terms of antibiotic use, as assessed by the number of days alive and antibiotic-free. Owing to the objective of noninferiority for the first 2 end points and to potentially include fewer patients and shorten the duration of the trial, a repeated 1-sided, $100 \times (1 - \alpha)$–percent confidence interval (CI) approach was used for planning and monitoring the study, with the α risk being set at 10%.[33] To test for

Table 1. Admission Characteristics of the Study Patients as a Function of the Duration of Antibiotic Administration*

Characteristic	8-Day Regimen (n = 197)	15-Day Regimen (n = 204)
Age, mean (SD), y	60 (17)	61 (17)
Men, No. (%)†	151 (76.6)	138 (67.6)
McCabe and Jackson[26] classification, No. (%)		
Nonfatal underlying disease	117 (59.4)	132 (64.7)
Ultimately fatal underlying disease	63 (32)	61 (29.9)
Rapidly fatal underlying disease	17 (8.6)	11 (5.4)
Admission category, No. (%)		
Medical	137 (69.5)	128 (62.7)
Emergency surgery	41 (20.8)	53 (26.0)
Elective surgery	19 (9.6)	23 (11.3)
Origin, No. (%)		
Home	75 (38.1)	76 (37.3)
Medical or surgical department	49 (24.9)	56 (27.5)
Other ICU	73 (37.1)	72 (35.3)
Diagnostic score, mean (SD)‡		
SAPS II	45 (15)	45 (15)
SOFA	7.3 (4.0)	7.4 (4.0)
ODIN	2.3 (1.2)	2.3 (1.1)
Reason for mechanical ventilation, No. (%)		
Cardiovascular failure	24 (12.2)	20 (9.8)
Acute respiratory failure	94 (47.7)	101 (49.5)
Trauma	11 (5.6)	15 (7.4)
Neurologic failure	39 (19.8)	39 (19.1)
Sepsis	15 (7.6)	16 (7.8)
Miscellaneous	14 (7.1)	13 (6.4)

Abbreviations: ICU, intensive care unit; ODIN, organ dysfunction and/or infection, SAPS II, Simplified Acute Physiologic Score II; SOFA, Sepsis-related Organ Failure Assessment.
*Percentages may not sum to 100 because of rounding.
†P = .046. There were no significant differences between the groups with respect to any other characteristic.
‡Higher values indicate greater severity for all scores.

Table 2. Baseline Characteristics of the Study Patients as a Function of the Duration of Antibiotic Administration*

Characteristic	8-Day Regimen (n = 197)	15-Day Regimen (n = 204)
MV duration before VAP onset, mean (SD), d	13.4 (11.2)	13.8 (14.9)
Antimicrobial therapy 15 days before VAP	167 (84.8)	170 (83.3)
Diagnostic score, mean (SD)		
SAPS II	40 (11)	39 (11)
ODIN	1.7 (0.9)	1.7 (0.8)
SOFA	6.4 (3.6)	6.2 (3.5)
Organ/system failure†		
Respiratory	111 (56.3)	111 (54.4)
Cardiovascular	49 (24.9)	49 (24.0)
Renal	23 (11.7)	28 (13.7)
Central nervous	47 (23.9)	35 (17.2)
Hepatic	10 (5.1)	7 (3.4)
Coagulation	7 (3.6)	7 (3.4)
Temperature, °C, mean (SD)	38.6 (1.1)	38.6 (0.9)
Leukocyte count, mean (SD), µL	15 460 (7150)	15 509 (6760)
PaO2/FIO2, mean (SD), mm Hg	196 (82)	201 (85)
Radiologic score, mean (SD)	5.4 (2.5)	5.5 (2.4)
Bacteremia	14 (7.1)	14 (6.9)
Shock	66 (33.5)	73 (35.8)
Acute respiratory distress syndrome	51 (25.9)	42 (20.6)

Abbreviations: MV, mechanical ventilation; ODIN, organ dysfunction and/or infection; PaO2/FIO2, the ratio of arterial oxygen partial pressure to the fraction of inspired oxygen; SAPS II, Simplified Acute Physiologic Score; SOFA, Sepsis-related Organ Failure Assessment; VAP, ventilator-associated pneumonia.
*Data are presented as No. (%) unless otherwise indicated, and percentages may not sum to 100 because of rounding.
†Organ/system failure was deemed present when the corresponding SOFA score was >2.

noninferiority with an α risk of 10%, 200 patients were required for each group to achieve a power of 90% to exclude a 10% difference between the 2 groups, assuming respective death and recurrent pulmonary infection rates of 40% and 25% for the 15-day regimen. This sample was also sufficiently large to ensure the detection of a 20% lower mean number of antibiotic-free days for patients assigned to the 8-day regimen, assuming a mean (SD) of 10 (5) antibiotic-free days for the group treated for 15 days (α = .05, β = .02). Thus, in this noninferiority trial, using 90% CIs around the estimate of effect, criteria are met for noninferiority if the upper limit of the CI is less than 10% (the prespecified clinically acceptable difference, δ) for mortality and pulmonary infection recurrence.

Statistical analysis was based on the intention-to-treat principle. SAS 8.2 software (SAS Inc, Cary, NC) was used for statistical analyses. Each of the 4 planned interim analyses was conducted after the inclusion of 100 consecutive patients. At each analysis, repeated 1-sided 90% CIs were calculated for the percentage point differences between death and pulmonary infection-recurrence rates for patients treated with 8 or 15 days of antibiotics, according to the method described by Jennison and Turnbull[34] and Fleming et al.[35] Conversely, the difference in the numbers of antibiotic-free days between the 2 randomized groups was analyzed using the nonparametric Wilcoxon test and calculation of 95% CIs for the mean difference between the groups. The independent Main End Point and Safety

Monitoring Committee met after each of the planned 4 interim analyses to decide whether the study should be continued or stopped. A decision to stop the trial could be made if and only if (1) the upper limit of the CI was less than 10% for the 2 primary end points used to evaluate noninferiority—ie, mortality and pulmonary infection recurrence and (2) the superiority of the 8-day vs 15-day regimen on the number of antibiotic-free days was demonstrated, on the basis of a significance level defined as α risk/4 or less, using a conventional α risk for comparative studies of 5%.

To define further the prognostic importance of duration of antimicrobial therapy and other baseline variables, logistic regression analysis was applied to the outcomes of death and pulmonary infection recurrence. The consistency of treatment effects within each center or key baseline characteristics, such as the type of responsible microorganism (segregating between nonfermenting gram-negative bacilli [ie, *P aeruginosa*, *A baumannii*, and *S maltophilia*]), methicillin-resistant *S aureus*, and other pathogens), was evaluated using the Gail and Simon test.[36] Cumulative-event curves were estimated with the Kaplan-Meier method. Statistical analyses of secondary end points were based on the use of conventional 1-sided 90% CIs.

Baseline characteristics of patients were compared with the unpaired *t* test or the Wilcoxon rank sum test for continuous variables, depending on their distributions. Percentage differences were compared with the Fisher exact test (or the χ² test, when appropriate).

RESULTS
Characteristics of the Patients

A total of 402 patients were enrolled in the study between May 1999 and June 2002; one subsequently withdrew his consent to receive a randomly assigned treatment and for use of his data, leaving 401 patients: 197 in the 8-day group and 204 in the 15-day group (Figure 1). The clinical characteristics of these 401 patients at

Table 3. Etiology of Ventilator-Associated Pneumonia Documented Microbiologically on Bronchoscopic Specimens From Patients as a Function of Duration of Antibiotic Administration*

Organisms	No. (%) of Pathogens	
	8-Day Regimen (n = 316)	15-Day Regimen (n = 317)
Bacilli	169 (53.5)	189 (59.6)
Pseudomonas aeruginosa	58 (18.4)	62 (19.6)
Acinetobacter baumannii	8 (2.5)	3 (0.9)
Stenotrophomonas maltophilia	2 (0.6)	3 (0.9)
Escherichia coli	24 (7.6)	34 (10.7)
Enterobacter	13 (4.1)	11 (3.5)
Proteus	10 (3.2)	14 (4.4)
Serratia	11 (3.5)	5 (1.6)
Klebsiella	7 (2.2)	13 (4.1)
Citrobacter	2 (0.6)	10 (3.2)
Morganella morganii	1 (0.3)	4 (1.3)
Moraxella	1 (0.3)	1 (0.3)
Haemophilus	24 (7.6)	21 (6.6)
Hafnia	2 (0.6)	2 (0.6)
Others	6 (1.9)	6 (1.9)
Cocci	141 (44.6)	126 (39.7)
MSSA	43 (13.6)	37 (11.7)
MRSA	22 (7)	23 (7.3)
Coagulase-negative staphylococci	12 (3.8)	10 (3.2)
Streptococcus	44 (13.9)	40 (12.6)
Neisseria	13 (4.1)	14 (4.4)
Enterococcus	7 (2.2)	2 (0.6)
Fungi	6 (1.9)	2 (0.6)

Abbreviations: MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.
*Organisms shown are those isolated at significant concentrations from quantitative cultures of protected specimen brush (≥103 colony-forming units/mL), protected telescoping catheter (≥103 colony-forming units/mL), and/or bronchoalveolar lavage (≥104 colony-forming units/mL) 23 samples. Not all percentages sum to 100 because of rounding.

admission (Table 1) and at baseline (Table 2) were similar, except that the percentage of female patients was slightly but significantly higher (P=.046) for the group receiving 15 days of antibiotics (Table 1).

Microorganisms considered responsible for VAP are listed in **TABLE 3**. Nonfermenting Gram-negative bacilli and methicillin-resistant *S aureus* were isolated, respectively, from 64 (32.5%) and 22 (11.2%) potentially polymicrobial episodes that were treated with 8 days of antibiotics compared with 63 (30.9%) and 23 (11.3%) infections that were treated with a 15-day regimen (P=.67 and P=.99, respectively).

No statistically significant between-group differences were found among the agents used during the first 8 days of the study. A regimen combining an aminoglycoside or a fluoroquinolone plus a betalactam was prescribed on day 1 to 179 (90.9%) of 197 patients in the 8-day group compared with 187 (91.7%) of 204 patients in the 15-day group (P=.86); on day 8, those values were 63 (32.8%) of 192 in the 8-day group and 63 (39.2%) of 199 in the 15-day group (P=.21). Thirty-nine percent of patients in the 8-day group and 37% in the 15-day group received vancomycin on the first day of the study (P=.61).

Primary Outcomes

Twenty-eight days after VAP onset, 37 (18.8%) of 197 patients in the 8-day group and 35 (17.2%) of 204 patients in the 15-day group had died (**TABLE 4**). The absolute difference was 1.6%, with the 90% CI for the between-group difference ranging from –3.7% to 6.9%. Repeated bronchoscopic specimens for clinically suspected recurrence or other reasons were obtained from 120 patients (60.9%) in the 8-day group (for a total of 188 bronchoscopies) and 93 patients (45.6%) in the 15-day group (for a total of 158 bronchoscopies; P=.003).

Based on quantitative culture results, the microbiologically documented pulmonary infection-recurrence rate was 28.9% of patients

receiving the 8-day regimen and 26% of those taking antibiotics for 15 days, with an absolute difference of 2.9% (90% CI, –3.2% to 9.1%; Table 4). Thus, the noninferiority of the 8-day regimen was retained. The percentages of pulmonary infection recurrences considered to be relapses were similar for the 2 groups (16.8% among the 8-day vs 11.3% among the 15-day regimen groups [absolute difference, 5.5%; 90% CI, 0.7%-10.3%]), as were the percentages of those considered to be superinfections (19.8% among the 8-day vs 18.6% in the 15-day groups [absolute difference, 1.2%; 90% CI, –4.3% to 6.6%]; Table 4).

As estimated with the Kaplan-Meier method using a log-rank test, survival rates were similar (**FIGURE 2**). Also similar were the mean (SD) times to pulmonary infection recurrence: 21.6 (0.5) days for the 8-day and 22.5 (0.5) days for the 15-day treatment groups (P=.38); times to relapse: 23.8 (0.5) days and 24.1 (0.4) days (P=.12); and times to the development of superinfections: 22.8 (0.5) and 23.8 (0.5) days (P=.65).

In contrast, the patients who received antibiotics for 8 days had significantly more mean (SD) antibiotic-free days (13.1 [7.4] vs 8.7 [5.2] days, P<.001), and significantly more broad-

Table 4. Primary Study Outcomes 28 Days After Bronchoscopy as a Function of Duration of Antibiotic Administration

Event	No./Total (%)		Between-Group Risk Difference (90% CI), %
	8-Day Regimen (n = 197)	15-Day Regimen (n = 204)	
Death from all causes*			
All patients	37/197 (18.8)	35/204 (17.2)	1.6 (–3.7 to 6.9)
Nonfermenting GNB†	15/64 (23.4)	19/63 (30.2)	–6.7 (–17.5 to 4.1)
MRSA	6/21 (28.6)	5/21 (23.8)	4.8 (–13.9 to 23.4)
Other bacteria	16/112 (14.3)	11/120 (9.2)	5.1 (–0.7 to 10.9)
Pulmonary infection recurrence*			
All patients	57/197 (28.9)	53/204 (26.0)	2.9 (–3.2 to 9.1)
Superinfection‡	39/197 (19.8)	38/204 (18.6)	1.2 (–4.3 to 6.6)
Relapse‡	33/197 (16.8)	23/204 (11.3)	5.5 (0.7 to 10.3)
Nonfermenting GNB†	26/64 (40.6)	16/63 (25.4)	15.2 (3.9 to 26.6)
Superinfection‡	13/64 (20.3)	8/63 (12.7)	7.6 (1.1 to 14.2)
Relapse‡	21/64 (32.8)	12/63 (19.0)	13.8 (7.8 to 19.7)
MRSA	7/21 (33.3)	9/21 (42.9)	–9.5 (–30.1 to 11.1)
Superinfection‡	6/21 (28.6)	5/21 (23.8)	4.8 (–8.8 to 18.3)
Relapse‡	3/21 (14.3)	4/21 (19.0)	–4.8 (–9.9 to 0.4)
Other bacteria	24/112 (21.4)	28/120 (23.3)	–1.9 (–9.5 to 5.6)
Superinfection‡	20/112 (17.9)	25/120 (20.8)	–3.0 (–8.2 to 2.2)
Relapse‡	9/112 (8.0)	7/120 (5.8)	2.2 (–1.3 to 5.7)

	Mean (SD)		Mean Difference (95% CI), %
No. of antibiotic-free days*			
All patients	13.1 (7.4)	8.7 (5.2)	4.4 (3.1 to 5.6)
Nonfermenting GNB†	12.0 (7.4)	7.5 (5.4)	4.5 (2.2 to 6.7)
MRSA	12.9 (7.0)	4.9 (5.7)	8.0 (4.6 to 12.1)
Other bacteria	13.7 (7.5)	10.0 (4.6)	3.7 (2.1 to 5.3)

Abbreviations: CI, confidence interval; GNB, gram-negative bacilli; MRSA, methicillin-resistant *Staphylococcus aureus*.
*The interaction between the duration of antibiotic administration and stratification for the responsible microorganism at baseline was not significant with respect to the risk of death (P = .41), pulmonary infection recurrence (P = .16), or the number of antibiotic-free days (P = .25).
†One episode in the 8-day group and 2 in the 15-day group were polymicrobial infections with MRSA and nonfermenting GNB classified as nonfermenting GNB.
‡Patients with polymicrobial pulmonary infection recurrence were classified as having developed both superinfection and relapse when 1 of the initial causative bacterial strains (ie, same genus, species, and serotype when available) grew at a significant concentration from a second bronchoscopic sample in addition to a microorganism that was never isolated previously.
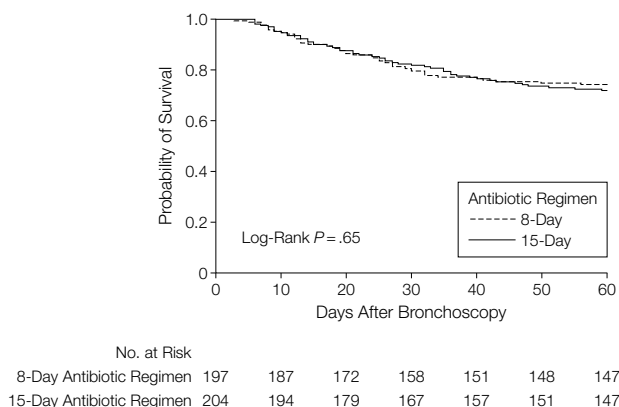
spectrum (imipenem, piperacillin-tazobactam, ticarcillin-clavulanic acid, cefepime, cefpirome, ceftazidime, or ciprofloxacin) antibiotic-free days (18.4 [8.0] vs 15.3 [8.4] days; P = .01). As shown in **TABLE 5**, there were no significant differences between the 2 groups in the numbers of patients for whom antibiotics were continued after the end of the randomly assigned regimen or the numbers of patients who received an additional course of antibiotics.

Logistic regression-based adjustment of the baseline variables listed in Tables 1 and 2 did not substantially modify these findings. The adjusted risk ratio for death of patients in the 8-day regimen vs those in the 15-day regimen was 1.2 (95% CI, 0.6-2.1) after adjustment for age, sex, McCabe and Jackson classification, admission category, duration of mechanical ventilation before VAP onset, site and severity of organ/system failure based on the SOFA score at baseline, bacteremia, and type(s) of pathogens responsible for VAP. The adjusted risk ratio for recurrent pulmonary infection was 1.2 (95% CI, 0.8-2.1). No significant interactions could be established between treatment assignment and any covariate, particularly between the types of pathogens responsible for VAP and the treatment group with respect to the 3 primary outcome measures (Table 4). However, for primary infections caused by nonfermenting Gram-negative bacilli, a higher percentage of patients developed documented pulmonary infection recurrence in the 8-day group than in the 15-day group (40.6% vs 25.4%; risk difference, 15.2%; 90% CI, 3.9%-26.6%, respectively); 21 of 26 and 12 of 16 in the respective groups experienced relapse (Table 4).

Secondary Outcomes

None of the secondary outcome measures listed in **TABLE 6** or the observed changes of fever, leukocyte count, PaO_2/FIO_2, or organ dysfunction and radiologic scores from day 1 through day 28 (**FIGURE 3**) differed significantly between patients in the 8-day or 15-day groups. The 2 groups also had similar mean (SD) number of days without cardiovascular failure (21.4 [9.3] vs 21.0 [9.3] days), hematologic failure (25.4 [6.3] vs 25.5 [6.0] days), hepatic failure (25.0 [6.8] vs 24.9 [6.8] days), neurologic failure (24.1 [7.5] vs 24.6 [6.9] days), and renal failure (23.8 [8.0] vs 22.6 [9.2] days). Ninety-one patients (46.2%) in the 8-day group and 89 patients (43.6%) in 15-day group had unfavorable outcomes. As reported in Table 6, none of the secondary outcome events—mortality at days 28 and 60, number of organ failure–free days, number of mechanical ventilation–free days, length of ICU stay, and unfavorable outcome rate—was higher for patients with VAP caused by nonfermenting gram-negative bacilli and

Figure 2. Kaplan-Meier Estimates of the Probability of Survival

No. at Risk							
8-Day Antibiotic Regimen	197	187	172	158	151	148	147
15-Day Antibiotic Regimen	204	194	179	167	157	151	147

Probability of survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration of antibiotic administration.

Table 5. Antibiotic Use as a Function of the Duration of Antibiotic Administration

	No./Total (%)		
Event	8-Day Regimen (n = 197)	15-Day Regimen (n = 204)	Mean Between-Group Difference (90% CI), %
Antibiotics continued after the end of treatment*	33/188 (17.6)	43/183 (23.5)	−6.0 (−12.8 to 0.9)
Pulmonary infection recurrence before the end of treatment	13 (6.9)	21 (11.5)	−4.6 (−9.5 to 0.4)
Continuation of antibiotics predating inclusion	4 (2.1)	5 (2.7)	−0.6 (−3.2 to 2.0)
Extrapulmonary infection	16 (8.5)	17 (9.3)	−0.8 (−5.6 to 4.1)
Antibiotic courses introduced after the end of the assigned regimen*	87/188 (46.3)	81/183 (44.3)	2.0 (−6.5 to 10.5)
Pulmonary infection recurrence after the end of treatment	57 (30.3)	50 (27.3)	3.0 (−4.7 to 10.7)
Extrapulmonary infection proven, pulmonary infection FOB excluded	17 (9.0)	17 (9.3)	−0.3 (−5.2 to 4.7)
Extrapulmonary infection proven, pulmonary infection not FOB excluded	13 (6.9)	14 (7.6)	−0.7 (−5.2 to 3.7)

	Mean (SD)		Mean Difference (90% CI), %
Antibiotic-treatment days at 28 days	12.6 (6.2)	17.1 (4.9)	−4.5 (−5.4 to −3.6)
1 to 8	7.9 (0.4)	7.9 (0.3)	0.0 (−0.1 to 0.1)
9 to 15	1.3 (2.3)	6.6 (1.4)	−5.3 (−5.6 to −5.0)
16 to 21	1.6 (2.4)	1.2 (2.1)	0.4 (0.0 to 0.8)
22 to 28	1.8 (2.7)	1.3 (2.6)	0.5 (0.0 to 1.0)

Abbreviations: CI, confidence interval; FOB, fiberoptic bronchoscopy.
*Nine and 21 patients in the 8-day and 15-day regimens, respectively, died before the end of the assigned treatment.

treated for 8 days although they did have a slightly higher rate of recurrence (Table 4). Notably, among patients who developed recurrent pulmonary infections, multiresistant pathogens emerged significantly less frequently in those who had received 8 days of antibiotics (42.1% vs 62.3% of recurrent infections; P=.04).

COMMENT

In this large, multicenter, randomized, double-blind (until day 8) clinical trial, we observed no benefit to prolonging antibiotics to 15 days from an 8-day regimen, for patients with VAP for whom strict bronchoscopic criteria had been applied to diagnose pulmonary infection and who received appropriate initial empiric antimicrobial treatment. The CIs for the between-group differences in mortality and pulmonary infection-recurrence rates exclude an absolute difference exceeding 10% in favor of the 15-day regimen. No differences in other outcome parameters could be established, including the duration of mechanical ventilation, the number of organ failure–free days, the evolution of signs and symptoms potentially linked to pulmonary infection, the duration of ICU stay, and mortality rates on day 60 or status at hospital discharge. The rates of unfavorable outcomes, defined as death, infection recurrence or prescription of a new antimicrobial treatment during the study period, were also similar for the 2 groups.

We also found that the average number of antibiotic-free days from day 1 to day 28 was 50% higher for patients who had been randomized to the 8-day regimen than for patients assigned to the 15-day regimen, thereby emphasizing that such a strategy could effectively lower the exposure of ICU patients with VAP to any unnecessary antimicrobial therapy after randomization. Pertinently, multiresistant pathogens emerged more frequently for patients with pulmonary infection recurrence who had received 15 days of antibiotics. These results are consistent with those of other observational studies conducted on ICU

patients that clearly demonstrated a direct relationship between the use of antimicrobial agents and increased resistance of Enterobacteriaceae and other pathogens.[2-4,6,37,38] Although appropriate antibiotics may improve the survival rate of patients with VAP, their indiscriminate use in treating ICU patients without infection should probably be discouraged.[5,10,32]

It is widely accepted that nonfermenting gram-negative bacilli, especially *P aeruginosa*, are difficult to eradicate from the respiratory tract and that the risk of therapeutic failure or re-

lapse, defined as the reappearance of signs of pneumonia and isolation of the same pathogen(s) that have acquired resistance or not, is high in such a setting.[18,19,39] In our study, slightly more patients with nonfermenting gram-negative bacilli assigned to the 8-day regimen had pulmonary infection recurrences and we were unable to demonstrate the noninferiority of this regimen for this end point compared with the 15-day course, either because of the relatively small number of studied patients or because the shorter duration of treatment leaves patients vulner-

Table 6. Secondary Study Outcomes as a Function of the Duration of Antibiotic Administration

Event	Mean (SD)		Mean Between-Group Difference (90% CI), %
	8-Day Regimen (n = 197)	15-Day Regimen (n = 204)	
No. of MV-free days, days 1 to 28			
All patients	8.7 (9.1)	9.1 (9.4)	−0.4 (−1.9 to 1.1)
Nonfermenting GNB*	8.1 (9.5)	6.6 (9.3)	1.4 (−1.3 to 4.2)
MRSA	6.1 (7.7)	7.4 (9.0)	−1.3 (−5.6 to 3.0)
Other bacteria	9.5 (9.0)	10.7 (9.2)	−1.2 (−3.2 to 0.8)
No. of organ failure-free days, days 1 to 28			
All patients	7.5 (8.7)	8.0 (8.9)	−0.5 (−1.9 to 1.0)
Nonfermenting GNB	7.0 (9.4)	5.8 (8.8)	1.2 (−1.5 to 3.9)
MRSA	6.0 (7.6)	4.7 (6.6)	1.3 (−2.3 to 4.9)
Other bacteria	8.1 (8.6)	9.7 (9.0)	−1.5 (−3.5 to 0.4)
Length of ICU stay, d			
All patients	30.0 (20.0)	27.5 (17.5)	2.5 (−0.7 to 5.2)
Nonfermenting GNB	28.4 (18.4)	27.5 (17.8)	0.9 (−4.4 to 6.2)
MRSA	35.8 (19.4)	32.9 (17.9)	2.9 (−6.6 to 12.4)
Other bacteria	29.2 (18.3)	26.5 (17.2)	2.7 (−1.1 to 6.6)

	No. (%) of Patients		Risk Difference (90% CI), %
Unfavorable outcome*			
All patients	91 (46.2)	89 (43.6)	2.6 (−5.6 to 10.7)
Nonfermenting GNB	37/64 (57.8)	31/63 (49.2)	8.6 (−5.9 to 23.1)
MRSA	12/21 (57.1)	16/21 (76.2)	−19.0 (−42.5 to 4.4)
Other bacteria	42/112 (37.5)	42/120 (35)	2.5 (−7.9 to 12.9)
Death, day 60			
All patients	50 (25.4)	57 (27.9)	−2.6 (−9.8 to 4.7)
Nonfermenting GNB	20/64 (31.3)	24/63 (38.1)	−6.8 (−20.7 to 7.0)
MRSA	8/21 (38.1)	8/21 (38.1)	0 (−24.6 to 24.6)
Other bacteria	22/112 (19.6)	25/120 (20.8)	−1.2 (−9.9 to 7.5)
In-hospital mortality			
All patients	63 (32)	61 (29.9)	2.1 (−5.5 to 9.7)
Nonfermenting GNB	22/64 (34.4)	26/63 (41.3)	−6.9 (−21.0 to 7.2)
MRSA	11/21 (52.4)	9/21 (42.8)	9.5 (−15.7 to 34.8)
Other bacteria	30/112 (26.8)	26/120 (21.7)	5.1 (−4.1 to 14.4)

Abbreviations: CI, confidence interval; GNB, gram-negative bacilli; ICU, intensive care unit; MV, mechanical ventilation; MRSA, methicillin-resistant *Staphylococcus aureus*.
*An unfavorable outcome was defined as death, pulmonary infection recurrence, or prescription of a new antibiotic for any reason provided that this new treatment exceeded 48 hours before day 28.

able to more pulmonary infection recurrences. However, despite this higher recurrence rate, neither the mortality nor unfavorable outcome rate was higher for patients with VAP caused by those pathogens when their antimicrobial therapy lasted only 8 days. Therefore, pending the results of studies directly evaluating this point, we believe

Figure 3. Physiological and Functional Score Changes From Day 1 to Day 28
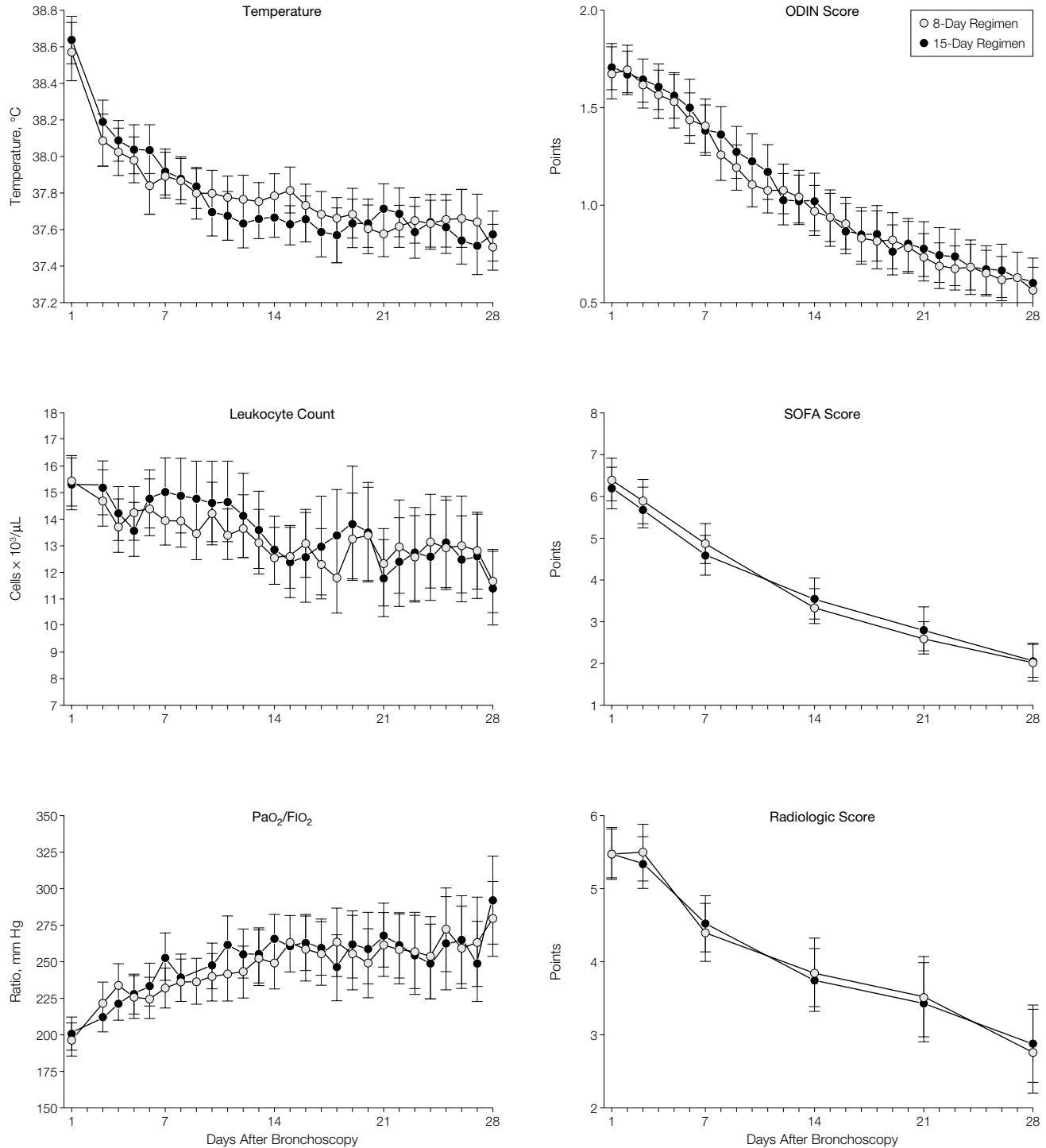
Data are expressed as mean (90% confidence interval). SOFA indicates Sepsis-related Organ Failure Assessment; ODIN, organ dysfunction and/or infection.

that 8 days of antibiotics could be safely implemented for all patients with VAP, including those with infections caused by nonfermenting gram-negative bacilli, provided that extreme vigilance be maintained after cessation of antimicrobial therapy and fiberoptic bronchoscopy be performed as soon as possible when relapse is suspected, as was the case in this study.

To the best of our knowledge, only a few studies have assessed the optimal duration of antimicrobial therapy in patients with VAP.[24,40,41] In a recent cohort study of 102 consecutive patients with VAP prospectively evaluated before and after the application of a clinical guideline restricting the total duration of antibiotics to 7 days for selected patients (those who were neither bacteremic nor neutropenic and who became afebrile under therapy), no statistically significant differences in hospital mortality rates and durations of hospitalizations were found between the 2 study groups; however, in contrast to our results, after-group patients whose mean duration of treatment was 7 days, were less likely to develop a second episode of VAP compared with those in the before group.[24] That study evaluated not only the implementation of a new therapeutic protocol but also new measures for VAP prevention, which could explain why a lower rate of VAP recurrences was documented during its second part.

This trial is limited by uncertainty about the potential effect of its unblinded design. A more rigorous design would have been to use a double-blind scheme throughout the entire study—ie, from day 1 to day 28. However, insofar as the choice of antibiotics was left to the treating physician, the use of a placebo for each of the drugs that was prescribed would have posed insurmountable and logistical problems. Furthermore, because of the necessity to be able to adapt the dosages of certain antibiotics as a function of their plasma concentrations, the "blind" aspect of the study would obviously have no longer existed for certain patients. However, investigators were not aware of the dura-

tion of antibiotics until day 8 and every effort was made to standardize patient follow-up, using rigorous criteria to evaluate their outcome.

The second limitation is that a relatively large subset of ICU patients, as indicated on the flow-chart (Figure 1), was excluded from our study, especially those with early-onset pneumonia who had not received previous antibiotics, those who were severely immunocompromised, those who had little chance of survival (as defined by a SAPS II >65) and, most importantly, those for whom the initial empirical antimicrobial therapy was not appropriate, as determined by the susceptibility patterns of the causative microorganisms. In addition, the diagnosis of pulmonary infection had to be confirmed by significant ($>10^3$ or $>10^4$ colony-forming units/mL) quantitative culture results of bronchoscopic specimens to avoid the inclusion of patients with less severe forms of respiratory-tract infection, such as tracheobronchitis. Thus, the results of this study cannot necessarily be extended to other ICU populations, which we did not evaluate.

Finally, it is important to acknowledge that our trial was not designed to directly test the hypothesis that 8 days of antibiotics for patients with VAP is superior to a 15-day regimen, in terms of minimizing adverse drug effects, or in documenting its cost effectiveness. We did not conduct a formal cost-benefit study.

In summary, for ICU patients who develop microbiologically proven VAP, we found no clinical advantage of prolonging antimicrobial therapy to 15 days compared with 8 days. The diverse clinical characteristics and reasons for mechanical ventilation among patients enrolled in this trial and the consistency of the results suggest that our conclusions may be applicable to many critically ill patients who develop VAP, with the possible exception of immunocompromised patients, those whose initial empiric antimicrobial treatment was not appropriate for the causative microorganisms, and those whose infections were caused by a nonfer-

menting gram-negative bacillus, including *P aeruginosa*. Such an approach could help control health care costs and contain the emergence of bacterial resistance in the ICU.

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