Invasive and Noninvasive Strategies for Management of Suspected Ventilator-Associated Pneumonia

A Randomized Trial

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Background: Optimal management of patients who are clinically suspected of having ventilator-associated pneumonia remains open to debate.

Objective: To evaluate the effect on clinical outcome and antibiotic use of two strategies to diagnose ventilator-associated pneumonia and select initial treatment for this condition.

Design: Multicenter, randomized, uncontrolled trial.

Setting: 31 intensive care units in France.

Patients: 413 patients suspected of having ventilator-associated pneumonia.

Intervention: The invasive management strategy was based on direct examination of bronchoscopic protected specimen brush samples or bronchoalveolar lavage samples and their quantitative cultures. The noninvasive ("clinical") management strategy was based on clinical criteria, isolation of microorganisms by nonquantitative analysis of endotracheal aspirates, and clinical practice guidelines.

Measurements: Death from any cause, quantification of organ failure, and antibiotic use at 14 and 28 days.

Results: Compared with patients who received clinical management, patients who received invasive management had reduced mortality at day 14 (16.2% and 25.8%; difference, −9.6 percentage points [95% CI, −17.4 to −1.8 percentage points]; $P = 0.022$), decreased mean Sepsis-related Organ Failure Assessment scores at day 3 (6.1 ± 4.0 and 7.0 ± 4.3; $P = 0.033$) and day 7 (4.9 ± 4.0 and 5.8 ± 4.4; $P = 0.043$), and decreased antibiotic use (mean number of antibiotic-free days, 5.0 ± 5.1 and 2.2 ± 3.5; $P < 0.001$). At 28 days, the invasive management group had significantly more antibiotic-free days (11.5 ± 9.0 compared with 7.5 ± 7.6; $P < 0.001$), and only multivariate analysis showed a significant difference in mortality (hazard ratio, 1.54 [CI, 1.10 to 2.16]; $P = 0.01$).

Conclusions: Compared with a noninvasive management strategy, an invasive management strategy was significantly associated with fewer deaths at 14 days, earlier attenuation of organ dysfunction, and less antibiotic use in patients suspected of having ventilator-associated pneumonia.

Ann Intern Med. 2000;132:621-630.

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The diagnosis and treatment of ventilator-associated pneumonia, a nosocomial infection that develops in mechanically ventilated patients and causes considerable morbidity and mortality, remain a challenge (1–3). A presumptive clinical diagnosis of pneumonia is often made when a patient develops a new radiographic infiltrate associated with fever, leukocytosis, and purulent tracheal secretions and when microorganisms are isolated by nonquantitative analysis of endotracheal aspirates (4). This "clinical" approach leads to overestimation of the incidence of ventilator-associated pneumonia because cases of tracheobronchial colonization and noninfectious processes mimicking it are included (5–7). The nonspecificity of a strategy based on clinical evaluation has potentially deleterious consequences: Many patients may receive unneeded antibiotics; this exposes them to unnecessary toxicity, increases hospital costs, and favors the emergence of resistant microorganisms. In addition, antibiotic overuse in such patients delays diagnosis of the true cause of fever and pulmonary infiltrate.

Concern about the inaccuracy of clinical approaches to diagnosis of ventilator-associated pneumonia led numerous investigators to postulate that "invasive" diagnostic methods, including quantitative cultures of specimens obtained by using bronchoscopic bronchoalveolar lavage or protected specimen brush, could improve identification of patients with true ventilator-associated pneumonia and selection of appropriate antibiotics (8–10). However, these procedures require rigorous adherence to bronchoscopic and microbiological techniques and are not universally available; moreover, in the absence of a definite gold standard for the diagnosis of ventilator-associated pneumonia, the value of such tests is uncertain, and their use in everyday practice remains controversial (4, 11, 12).

To test the hypothesis that an invasive management strategy is superior to a clinical, noninvasive one in terms of improving clinical outcomes and minimizing antibiotic use, we initiated a multicenter, randomized, uncontrolled trial to compare these strategies in patients suspected of having ventilator-associated pneumonia. The primary end points were

death from any cause, antibiotic use for any reason, and quantification of organ failure during the first 14 days of follow-up.

Methods

Patient Selection and Study Design

After obtaining approval of the institutional review boards at each participating institution and informed consent from patients or their proxies, we enrolled patients at 31 intensive care units. Inclusion criteria were age older than 18 years; at least 48 hours of mechanical ventilation; and clinical suspicion of ventilator-associated pneumonia, defined by new and persistent infiltrate on chest radiography associated with at least one of the following: purulent tracheal secretions, body temperature of at least 38.3 °C, and leukocytosis. Exclusion criteria were pregnancy; enrollment in another interventional study; little chance of survival, defined by a Simplified Acute Physiologic Score II (SAPS II) of more than 65 points (corresponding to a probability of death exceeding 77%) (13); and introduction or modification of antibiotic therapy, instigated by new clinical symptoms, during the 3 days before collection of respiratory samples.

For patients in the clinical management group, the decision on whether to treat was based on clinical evaluation and results of immediate microscopic examination of Gram-stained endotracheal aspirates. The results of the Gram stain and recommendations of the American Thoracic Society on hospital-acquired pneumonia were used to guide the initial choice of antibiotics (3). Results of qualitative aspirate cultures were used to adjust the initial antibiotic regimen; when cultures were negative, no treatment was given (**Figure 1A**).

The invasive strategy used fiberoptic bronchoscopy to obtain protected specimen brush samples or bronchoalveolar lavage samples for direct microscopic examination. Results of these examinations were used to diagnose ventilator-associated pneumonia, to decide to treat, and to guide the initial choice of antibiotics when specimens were positive. Results of quantitative cultures were used to adjust therapy; treatment was discontinued when results were negative, and use of antibiotics with narrower spectra of activity was based on identification of and susceptibility-test results for pathogens cultured at significant concentrations (protected specimen brush sample that yielded $\geq 10^3$ colony-forming units [CFU]/mL or bronchoalveolar lavage fluid sample that yielded $\geq 10^4$ CFU/mL [4, 8–10]) (**Figure 1B**). For both groups, the recommended duration of therapy for ventilator-associated pneumonia was 14 days.

Randomization and Data Collection

Patients were randomly assigned to receive the clinical or the invasive management strategy. Computer-generated random-number tables were used to assign patients in blocks of 8, with stratification according to treatment center.

At admission to the intensive care unit, we recorded each patient's age; sex; severity of underlying medical condition, stratified as rapidly fatal, ultimately fatal, or not fatal according to the criteria of McCabe and Jackson (14); SAPS II score (range, 0 to 174; higher scores indicate more severe illness) (13); Sepsis-related Organ Failure Assessment (SOFA) score (range, 0 to 24, with scores for each organ system [respiration, coagulation, liver, cardiovascular, central nervous system, and kidney] ranging from 0 [normal] to 4 [most abnormal]) (15); the Organ Dysfunction and Infection (ODIN) score (range, 0 to 7, according to the presence or absence of cardiovascular, respiratory, renal, hepatic, hematologic, and neurologic dysfunctions or infection) (16); classification as medical patient, surgical patient with trauma, or surgical patient without trauma according to the admitting diagnosis; and reason for initiating mechanical ventilation (17).

The following baseline variables were recorded before randomization: SAPS II score; SOFA score; ODIN score; body temperature; leukocyte count; radiologic score (range, 0 to 12 according to the density of radiologic infiltration) (18); ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FIO_2); presence of shock, defined as systolic arterial pressure less than 90 mm Hg with signs of peripheral hypoperfusion or need for continuous infusion of vasopressor or inotropic agents (19); and presence of the acute respiratory distress syndrome, defined as the presence of a generalized pulmonary infiltrate and a lung injury score more than 2.5 (20); duration of previous mechanical ventilation; and use or no use of antibiotics. These baseline variables (except SAPS II score) were measured again 3, 7, 14, 21, and 28 days after the day of inclusion. All infections requiring specific therapeutic measures during the first 3 days after inclusion were recorded. Antibiotic use was recorded daily until day 28.

Specimen Collection and Microbiological Processing

Patients who received invasive management underwent fiberoptic bronchoscopy according to each center's protocol. Premedication, use of a short-acting neuromuscular blocking agent, and adjustment of FIO_2 to 95% or more were recommended; protected specimen brush, bronchoalveolar lavage, or both were performed at the investigator's discre-

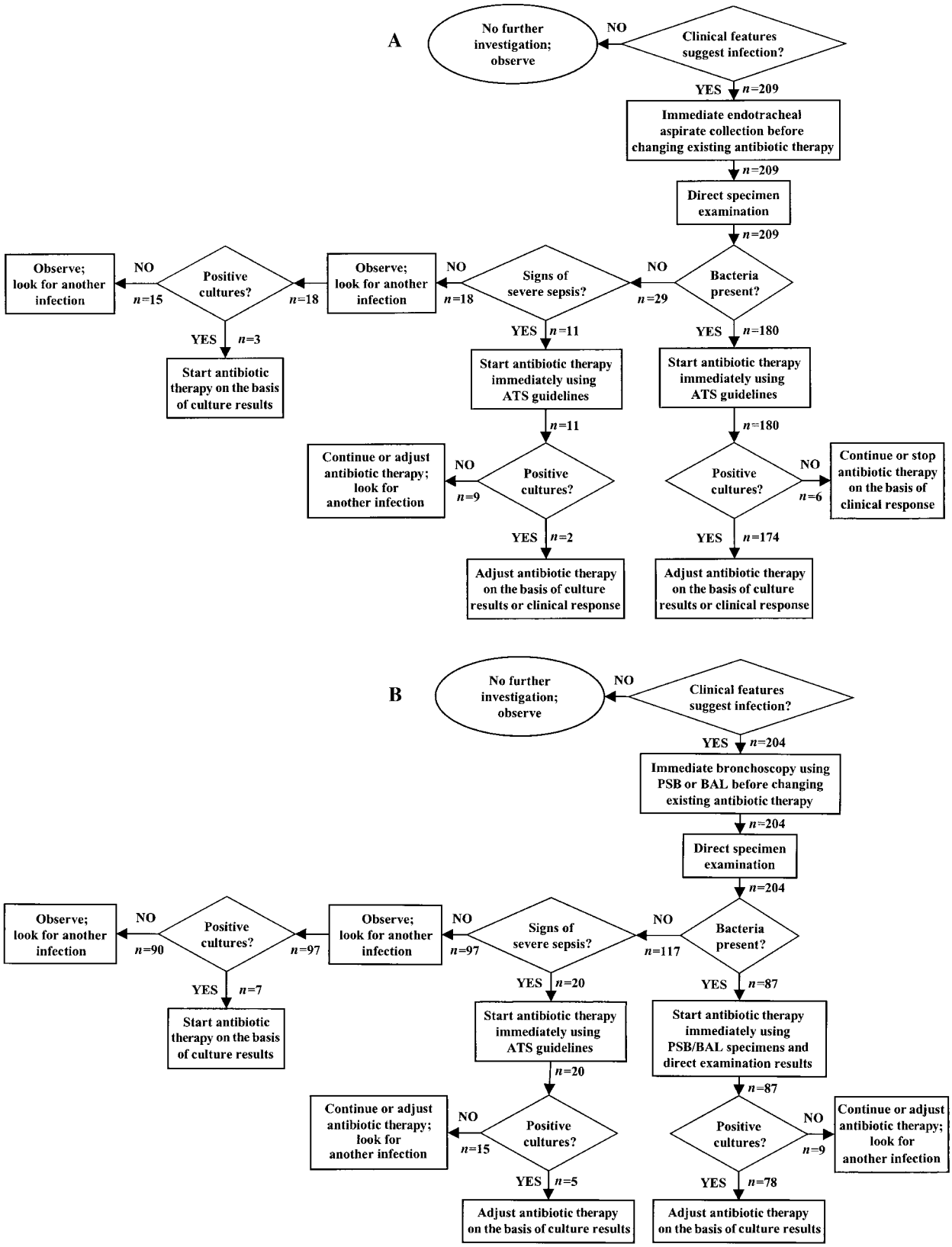

Figure 1. Diagnostic and therapeutic strategy applied to patients managed with the clinical strategy (A) or invasive strategy (B). ATS = American Thoracic Society; BAL = bronchoalveolar lavage; PSB = protected specimen brush.

tion. Processing of microbiological specimens has been described in detail elsewhere (10, 21). Briefly, recovered bronchoalveolar lavage fluid was divided into two samples: one for direct microscopic examination of cytocentrifuge preparations after Gram or modified Wright–Giemsa staining to determine the

Table 1. Admission and Baseline Characteristics of the Study Patients*

Characteristic	Patients Who Received Invasive Management (n = 204)	Patients Who Received Clinical Management (n = 209)
Admission		
Age, *y*	63 ± 16	63 ± 15
Sex, *n* (%)		
Male	141 (69.1)	148 (70.8)
Female	63 (30.9)	61 (29.2)
McCabe–Jackson classification, *n (%)*		
Nonfatal underlying disease	133 (65.2)	141 (67.5)
Ultimately fatal underlying disease	61 (29.9)	63 (30.1)
Rapidly fatal underlying disease	10 (4.9)	5 (2.4)
SAPS II score†‡	44 ± 15	42 ± 14
SOFA score†‡	7.8 ± 4.1	7.1 ± 3.9
ODIN score†‡	2.1 ± 1.1	1.9 ± 1.0§
Classification of patients, *n (%)*		
Medical	142 (69.6)	139 (66.5)
Surgical, no trauma	48 (23.5)	59 (28.2)
Surgical, trauma	14 (6.9)	11 (5.3)
Reason for mechanical ventilation, *n (%)*		
Acute exacerbation of COPD	26 (12.7)	27 (12.9)
Acute respiratory failure	69 (33.8)	63 (30.1)
Postoperative respiratory failure	61 (29.9)	58 (27.8)
Drug overdose	3 (1.5)	1 (0.5)
Neurologic	37 (18.1)	46 (22.0)
Miscellaneous	8 (3.9)	14 (6.7)
Baseline		
Duration of mechanical ventilation before study entry, *d*	10.4 ± 10.2	10.7 ± 10.0
Previous antimicrobial therapy, *n (%)*	105 (51.5)	103 (49.3)
SAPS II score†‡	41 ± 12	41 ± 12
SOFA score†‡	7.3 ± 3.7	7.0 ± 4.0
ODIN score†‡	2.0 ± 1.0	1.9 ± 0.9
Site of organ failure, *n (%)*†		
Cardiovascular system	84 (41.2)	83 (39.7)
Renal system	38 (18.6)	46 (22.0)
Central nervous system	65 (31.9)	40 (19.1)
Hepatic system	18 (8.8)	16 (7.7)
Hematologic system	11 (5.4)	5 (2.4)
Body temperature, *°C*	38.7 ± 0.9	38.7 ± 0.9
Leukocyte count, *cells/mm³*	15 190 ± 7150	15 670 ± 6800
Radiologic score†	5.2 ± 2.7	5.0 ± 2.6
Pao_2/Fio_2, *mm Hg*	221 ± 86	215 ± 93
Shock, *n* (%)†	74 (36.3)	81 (38.8)
Acute respiratory distress syndrome, *n (%)*†	26 (12.7)	22 (10.5)

* Data presented with a plus/minus sign are the mean ± SD. COPD = chronic obstructive pulmonary disease; ODIN = Organ Dysfunction and Infection; Pao_2/Fio_2 = ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen; SAPS = Simplified Acute Physiology Score; SOFA = Sepsis-related Organ Failure Assessment.
† Described more fully in the Methods section.
‡ Higher values indicate greater severity.
§ P = 0.031 compared with the invasive therapy group. The groups did not significantly differ for any other characteristic.

percentages of cells containing intracellular bacteria, and the other for quantitative cultures. The tip of the protected specimen brush was cut, dropped into 1 mL of sterile water, and vortexed for 1 minute; samples were examined directly and serially diluted for culture. The number of bacteria in the original specimens was estimated by colony counts and is expressed as CFU/mL. Patients in the invasive treatment group were considered to have ventilator-associated pneumonia if more than 5% of the cells in cytocentrifuge preparations of bronchoalveolar lavage fluid contained intracellular bacteria or at least one bacterial species grew at a significant concentration from the protected specimen brush sample ($\geq 10^3$ CFU/mL) or from bronchoalveolar lavage fluid ($\geq 10^4$ CFU/mL) (10, 22).

In patients who received clinical treatment, endotracheal aspirates were collected sterilely by using a suction catheter in a mucus collector; secretions were aspirated without instilling saline. Aspirates were vortexed for 1 minute; Gram staining and qualitative aerobic cultures were performed for all patients.

Definitions

Inappropriate treatment, evaluated initially and at 3 days, was defined as the use of antibiotics to which at least one cultured isolate was resistant in vitro. For patients in the clinical management group, all pathogens grown in qualitative endotracheal aspirate cultures were considered for this analysis; for patients in the invasive management group, only pathogens cultured at significant concentrations were taken into account.

Resistant bacteria were defined as ticarcillin-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and *Stenotrophomonas maltophilia*; extended-spectrum β-lactamase–producing Enterobacteriaceae; and methicillin-resistant *Staphylococcus aureus.*

We calculated the number of antibiotic-free days

(days without antibiotic therapy) at 14 and 28 days after inclusion. For example, a patient who survived 28 days and received no antibiotics was assigned a value of 28. If antibiotics had been given for 10 days and the patient died on day 14, a value of 4 was assigned. Using the same method, we calculated the number of mechanical ventilation–free days. We also calculated the number of antibiotics per day by dividing the sum of number of days of administration of each antibiotic by the duration of survival at 14 and 28 days.

Outcome Measures

During their stay in the intensive care unit, many patients experience an adverse event that can influence their outcome. Because these complications are potential confounding factors in a study whose principal judgment criterion is outcome, we decided to evaluate mortality during the first 14 days because this period corresponds to that during which ventilator-associated pneumonia has its maximal impact on patient survival (2, 4, 21). In addition, numerous factors come into play during the subsequent 14 to 28 days. Thus, the primary end points of the study were mortality at 14 days; antibiotic-free days at 14 days; and quantification of organ failure at 3, 7, and 14 days according to the SOFA and ODIN scores. Secondary end points were mortality at 28 days, antibiotic-free days at 28 days, quantification of organ failure at 28 days (assessed by using the SOFA and ODIN scores), mechanical ventilation–free days at 28 days, duration of stay in the intensive care unit, duration of hospital stay, emergence of resistant bacteria, and emergence of *Candida* species during 28 days.

Statistical Analysis

Data are presented as the mean (±SD). Survival between groups was compared by using Kaplan–Meier curves and the log-rank test. Measurements expressed as means or percentages were compared by using the *t*-test for continuous data and the chi-square statistic with Yates correction for proportions. All tests of statistical significance were two-sided. We did not correct for multiple testing. An intention-to-treat analysis was performed. To analyze the effect of management strategies on mortality at day 28, we used a Cox multivariate proportional hazards model that included age, SAPS II score, and McCabe–Jackson score at admission (variables strongly associated with outcome of patients in the intensive care unit), and duration of mechanical ventilation before inclusion, ODIN score, PaO_2/FIO_2 ratio, and radiologic score measured at inclusion (variables strongly associated with outcome of nosocomial pneumonia) as covariates with the randomization group. SAS software (SAS Institute, Inc., Cary, North Carolina) was used for statistical analyses. A target sample size of 400 patients was chosen to ensure, with a probability of 80%, the detection of a 10% difference between the mortality rates of the two groups; a mortality rate of 30% was assumed for the clinical treatment group.

Table 2. Features and Organisms Associated with Ventilator-Associated Pneumonia*

Feature or Organism	Patients Who Received Invasive Management (n = 204)	Patients Who Received Clinical Management (n = 209)
Negative culture, *n (%)*	114 (55.9)	30 (14.4)
Monomicrobial pneumonia, *n (%)*	65 (31.9)	84 (40.2)
Polymicrobial pneumonia, *n (%)*	25 (12.3)	95 (45.5)
Total number of pathogens, *n*	121	312
Bacilli, *n (%)*		
Pseudomonas aeruginosa	27 (22.3)	57 (18.3)
Haemophilus influenzae	9 (7.4)	12 (3.8)
Escherichia coli	6 (5.0)	23 (7.4)
Acinetobacter baumannii	6 (5.0)	11 (3.5)
Enterobacter species	4 (3.3)	12 (3.8)
Proteus species	3 (2.5)	14 (4.5)
Serratia marcescens	3 (2.5)	7 (2.2)
Klebsiella species	2 (1.7)	11 (3.5)
Citrobacter species	1 (0.8)	7 (2.2)
Morganella morganii	1 (0.8)	3 (1.0)
Moraxella species	1 (0.8)	1 (0.3)
Stenotrophomonas maltophilia	0	4 (1.3)
Corynebacterium	0	4 (1.3)
Alcaligenes xylosoxidans	0	1 (0.3)
Cocci, *n (%)*		
Staphylococcus aureus	20 (16.5)	40 (12.8)
Streptococcus species	19 (15.7)	28 (9.0)
Neisseria species	7 (5.8)	6 (1.9)
Streptococcus pneumoniae	3 (2.5)	10 (3.2)
Coagulase-negative staphylococci	3 (2.5)	17 (5.4)
Enterococcus species	1 (0.8)	6 (1.9)
Fungi, *n (%)*	5 (4.1)	38 (12.2)

* Organisms shown are those that were isolated at significant concentrations from quantitative cultures of protected specimen brush samples ($\geq 10^3$ colony-forming units/mL) or bronchoalveolar lavage samples ($\geq 10^4$ colony-forming units/mL) in the invasive management group and from qualitative cultures of endotracheal aspirates from the clinical management group. Because of rounding, percentages do not always add up to 100.

Role of the Funding Sources

The funding agencies played no role in the design of the study; collection, analysis, and interpretation of data; or the decision to submit the paper for publication.

Results

Comparison of Study Groups

From September 1996 to January 1998, 418 patients were enrolled; 5 subsequently withdrew their consent to receive a randomly assigned strategy and for use of their data, leaving 413 patients (204 in the invasive management group and 209 in the clinical management group). All variables correlated with mortality and morbidity, except ODIN score at admission, were similar in the two groups (**Table 1**). Antibiotic management adhered to a prespecified protocol (**Figure 1**).

Table 3. Study Outcomes according to the Intention-to-Treat Analysis*

End Point	Patients Who Received Invasive Management (n = 204)	Patients Who Received Clinical Management (n = 209)	Difference (95% CI)	P Value
Primary				
Mortality at 14 days, *n (%)*	33 (16.2)	54 (25.8)	−9.6 (−17.4 to −1.8)†	0.022
Multiple organ dysfunction‡§				
At 3 days				
SOFA score	6.1 ± 4.0	7.0 ± 4.3	−0.9 (−1.7 to −0.1)	0.033
ODIN score	1.7 ± 0.9	1.9 ± 1.1	−0.2 (−0.4 to −0.05)	0.014
At 7 days				
SOFA score	4.9 ± 4.0	5.8 ± 4.4	−0.9 (−1.8 to −0.03)	0.043
ODIN score	1.4 ± 1.0	1.6 ± 1.1	−0.2 (−0.4 to 0.02)	0.082
At 14 days				
SOFA score	3.9 ± 4.1	4.3 ± 4.3	−0.4 (−1.3 to 0.6)	>0.2
ODIN score	1.2 ± 1.2	1.2 ± 1.2	−0.03 (−0.3 to 0.2)	>0.2
Antibiotic-free days at 14 days, *d*‡	5.0 ± 5.1	2.2 ± 3.5	2.8 (1.9 to 3.6)	<0.001
Antibiotics per day at 14 days, *n*	1.2 ± 0.8	1.5 ± 0.7	−0.3 (−0.5 to −0.2)	<0.001
Antibiotic-treatment days at 14 days, *d*	8.7 ± 5.4	10.9 ± 4.5	−2.2 (−3.2 to −1.2)	<0.001
Secondary				
Mortality at 28 days, *n (%)*	63 (30.9)	81 (38.8)	−7.9 (−17.0 to 1.2)	0.099
Multiple organ dysfunction at 28 days‡§				
SOFA score	3.1 ± 3.4	3.1 ± 3.8	−0.02 (−1.2 to 1.1)	>0.2
ODIN score	1.0 ± 1.0	1.0 ± 1.0	−0.06 (−0.4 to 0.3)	>0.2
Antibiotic-free days at 28 days, *d*‡	11.5 ± 9.0	7.5 ± 7.6	−3.9 (−5.5 to −2.3)	<0.001
Antibiotics per day at 28 days, *n*	1.0 ± 1.8	1.3 ± 0.7	−0.3 (−0.45 to −0.16)	<0.001
Antibiotic-treatment days at 28 days, *d*	12.8 ± 8.5	14.9 ± 7.9	−2.1 (−3.7 to −0.5)	0.009
Duration of intensive care unit stay, *d*	19.3 ± 9.0	17.6 ± 9.4	1.5 (−0.3 to 3.2)	0.11
Duration of hospital stay, *d*	26.7 ± 23.9	25.1 ± 28.5	1.6 (−0.3 to 3.4)	>0.2
Mechanical ventilation–free days, *d*‡	7.8 ± 9.8	7.0 ± 9.4	0.8 (−1.0 to 2.9)	>0.2
Emergence of resistant bacteria, *n (%)*	125 (61.3)	125 (59.8)	1.5 (−7.9 to 10.9)	>0.2
Emergence of *Candida* species, *n (%)*	23 (11.3)	47 (22.5)	−11.2 (−18.3 to −4.1)	0.0025

* Unless otherwise indicated, data are presented as the mean ± SD. ODIN = Organ Dysfunction and Infection; SOFA = Sepsis-related Organ Failure Assessment.
† Expressed as percentage points.
‡ Described more fully in the Methods section.
§ Higher values indicate greater severity.

In the invasive management group, protected specimen brush (n = 67) or bronchoalveolar lavage (n = 31) was used, alone or together (n = 106). Microbial cultures were positive in 64 of 173 (37.0%) protected specimen brush samples and 46 of 137 (33.6%) bronchoalveolar lavage samples, for a total of 90 cases of bacteriologically confirmed ventilator-associated pneumonia in 204 patients (44.1%). In the clinical management group, endotracheal aspirate cultures were positive in 179 of 209 patients (85.6%). All identified microorganisms are reported (**Table 2**).

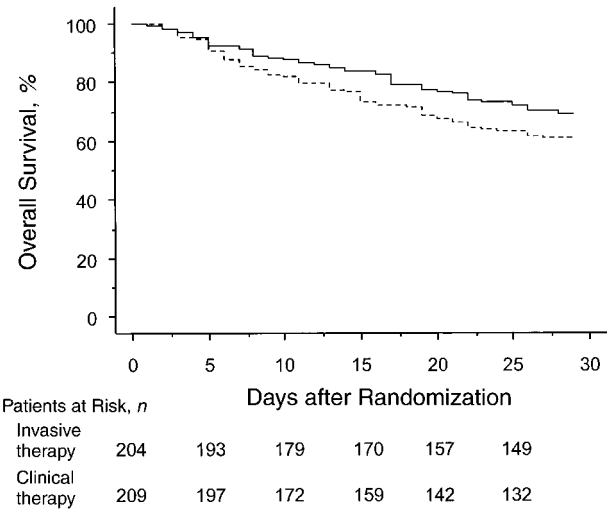

Figure 2. Actuarial 28-day survival among 413 patients assigned to the invasive (*solid line*) or clinical (*dashed line*) management strategy. P = 0.07 for difference between groups (log-rank test).

End Point Analyses

At 14 days, 33 of 204 patients in the invasive management group and 54 of 209 patients in the clinical management group had died (16.2% and 25.8%, respectively; difference, −9.6 percentage points [95% CI, −17.4 to −1.8 percentage points]; P = 0.022) (**Table 3**). As seen in **Figure 2**, survival curves remained parallel once this difference between groups was established. The mean SOFA score was significantly lower in the invasive management group than the clinical management group at 3 and 7 days but not at 14 days. The invasive management group had significantly more antibiotic-free days and received significantly fewer antibiotics per day (**Table 3**).

At 28 days, no significant differences in survival, number of organ failures, duration of ICU stay, mechanical ventilation–free days, or emergence of resistant bacteria were seen between groups (**Table 3**). However, multivariate proportional hazards regression analysis of the prognostic role of age, SAPS II score, and McCabe–Jackson classification at admission; duration of mechanical ventilation before inclusion; and ODIN score, PaO_2/FIO_2 ratio,

and radiologic score at baseline showed that mortality at 28 days was significantly higher in the clinical management group (hazard ratio, 1.54 [CI, 1.10 to 2.16]; $P = 0.01$) (**Table 4**).

The invasive management group had significantly more antibiotic-free days and fewer antibiotics per day at 28 days (**Table 3**). Twenty-nine patients (14%) in this group received no antibiotics up to day 28 compared with only 4 (2%) in the clinical management group ($P < 0.001$). **Figure 3** shows the use of the 14 most commonly prescribed antibiotics in patients of both groups. Colonization or infection with *Candida* species was documented in 23 patients in the invasive management group and 47 patients in the clinical management group (11.3% and 22.6%, respectively; $P = 0.0025$).

Significant differences between the primary and secondary end points in the entire study sample were also observed for the subgroup of 318 patients with suspected late-onset pneumonia, defined as a period between intubation and inclusion that exceeded 4 days. In contrast, for patients with early-onset pneumonia, only the number of antibiotic-free days at 14 days was significantly higher in the invasive management group than in the clinical management group (3.63 and 1.86 days, respectively; $P = 0.024$). In the subgroup of 208 patients who had received previous antibiotic therapy, the only significant differences were lower rates of antibiotic use and mortality in the invasive management group (hazard ratio, 1.7 [95% CI, 1.03 to 2.71]; $P = 0.039$). The effects of the invasive strategy on outcome were not modified after stratification by intensive care unit.

Table 4. Cox Regression Analysis Hazard Ratios for Death at 14 and 28 Days*

Covariate	Hazard Ratio (95% CI)	
	14 Days	28 Days
Age, per 10-year increase	1.17 (0.98–1.40)	1.23 (1.06–1.42)
McCabe–Jackson classification		
Nonfatal underlying disease	0.44 (0.13–1.46)	0.56 (0.22–1.44)
Ultimately fatal underlying disease	0.64 (0.22–1.83)	0.73 (0.31–1.70)
Rapidly fatal underlying disease	0.83 (0.29–2.37)	0.94 (0.40–2.23)
SAPS II score at admission, per 10-point increase	0.91 (0.77–1.07)	0.94 (0.83–1.07)
Duration of mechanical ventilation before entry, per 5-day increase	0.97 (0.87–1.08)	1.01 (0.94–1.10)
Radiologic score at baseline, per 1-point increase	1.03 (0.94–1.12)	1.02 (0.95–1.09)
Pao_2/Fio_2 ratio at baseline, per 50–mm Hg decrease	1.06 (0.93–1.20)	1.04 (0.94–1.15)
ODIN score at baseline, per 1-point increase	2.10 (1.69–2.61)	1.77 (1.48–2.12)
Clinical strategy	1.96 (1.26–3.05)	1.54 (1.10–2.16)

* ODIN = Organ Dysfunction and Infection; Pao_2/Fio_2 = ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen; SAPS = Simplified Acute Physiology Score.

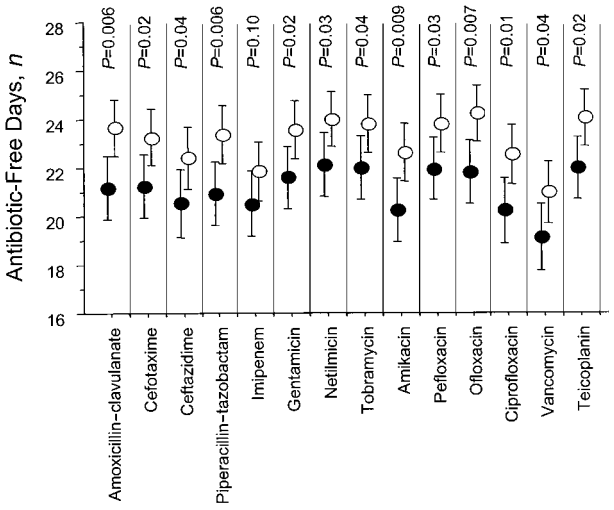

Figure 3. Comparison of clinical (*black circles*) and invasive (*white circles*) management strategies for the number of days of survival without use of 1 of the 14 most commonly prescribed antibiotics. For every antibiotic except imipenem, patients in the invasive management group had significantly more antibiotic-free days. Error bars represent 95% CIs.

Antibiotic Treatment

Of the 114 patients in the invasive management group who had negative quantitative cultures, 97 did not receive antibiotics immediately, compared with 18 of 30 patients in the clinical management group who had negative endotracheal aspirate cultures (85.1% and 60.0%, respectively; $P = 0.0017$) (**Figure 1**). Respective mortality rates at 14 days for these groups of initially untreated patients were similar (15 of 97 patients [15.5%] and 3 of 18 [16.7%]).

For patients whose quantitative bronchoscopic specimen cultures (invasive management group) or qualitative endotracheal aspirate cultures (clinical management group) grew pathogens, analysis of adequacy of prescribed antibiotics and susceptibility-test results showed that 1 patient in the former group and 24 patients in the latter group had at least one pathogen that was resistant to the antibiotic initially prescribed ($P < 0.001$). Thirty-two percent of these 25 patients died compared with 20.4% of the 388 patients who received appropriate initial therapy ($P > 0.2$).

Of the 24 patients in the clinical management group who initially received inappropriate antibiotics, 22 (92%) had been treated according to the American Thoracic Society guidelines; 10 received imipenem and an aminoglycoside and 6 received an antipseudomonal β-lactam, aminoglycoside, and vancomycin. These 24 instances of inappropriate use of antibiotics were attributed to methicillin-resistant *S. aureus* ($n = 10$), multiresistant *P. aeruginosa* ($n = 8$), *A. baumannii* ($n = 4$), and class 1 cephalosporinase-producing Enterobacteriaceae ($n = 2$). At 3 days, after culture results had been obtained, no patient in the invasive management group and 2

patients in the clinical management group were still receiving inappropriate therapy. At 14 days, no patient in the invasive management group and 8 patients (33.3%) in the clinical management group who initially received inappropriate antibiotics had died ($P > 0.2$).

Between days 1 and 3, 22 infections requiring specific therapeutic measures occurred in the invasive management group; these included 10 operation-site infections, 7 catheter-related infections, 3 cases of nosocomial pneumonia, and 2 cases of maxillary sinusitis. In contrast, only 5 such infections occurred in the clinical management group (2 operation-site infections, 2 catheter-related infections, and 1 case of sinusitis) ($P < 0.001$).

Discussion

We found that in patients suspected of having ventilator-associated pneumonia, an invasive strategy based on use of fiberoptic bronchoscopy to directly sample a suspected area and quantitative cultures to distinguish infecting pathogens from colonizing microorganisms improved the survival rate, decreased antibiotic use, and was associated with fewer organ failures 3 and 7 days after inclusion.

Only a few studies have assessed the impact of diagnostic strategy on antibiotic use and outcome in patients suspected of having nosocomial pneumonia (23–27). On the basis of a randomized study evaluating 51 patients, Sanchez-Nieto and colleagues (24) reported significantly more modifications of the initial antimicrobial therapy for patients managed with an invasive strategy than in those managed with a clinical strategy, but they found no significant influence on mortality. Unfortunately, that study had several limitations related to the small sample size, the unbalanced distribution of factors pertinent to ventilator-associated pneumonia mortality despite randomization (higher frequencies of *P. aeruginosa* infections and inappropriate initial treatments in the invasive group), and lack of a coherent management protocol in the invasive management group (initiation of treatment based on clinical evaluation and continuation of antibiotic therapy in all patients despite negative cultures) (24). Concerning use of antibiotics, in a study of 138 patients evaluated by collection of bronchoscopic specimens, Bonten and coworkers (25) showed that antibiotic therapy can be stopped in patients with negative quantitative cultures with no adverse effect on recurrence of ventilator-associated pneumonia or mortality (25). Other researchers have also concluded that antibiotic therapy can be safely stopped in patients with negative quantitative cultures (7, 27). In our study, among patients in the invasive management group who had negative quantitative bronchoscopic specimen cultures and did not receive antibiotics immediately, the mortality rate was low (15.5%) and was similar to that in patients who received clinical management and had negative qualitative endotracheal aspirate cultures (16.7%). Results of studies by Sterling and associates (26), who conducted a decision analysis comparing clinical and invasive strategies, and Heyland and colleagues (27), who conducted a prospective, nonrandomized trial comparing clinical and invasive strategies, support our observations of improved management and less antibiotic use in the invasive management group.

Our study was limited by uncertainty about the potential effect of its unblinded design. Theoretically, comparison of two strategies precludes the use of a protocol in which the investigators are unaware of the strategy assignments. Nevertheless, our concerted efforts to standardize intensive care and use of rigorous criteria to evaluate patient outcome probably minimized additional bias due to differences in the management of severely ill patients (**Figure 1**). The second limitation was use of two different diagnostic techniques to obtain secretions for quantitative cultures from patients assigned to the invasive strategy (11). Protected specimen brush and bronchoalveolar lavage have been extensively evaluated, and the ranges of specificities and sensitivities found for these techniques have suggested similar overall accuracy (12). The rates of positivity observed in our study, which were similar for both techniques, suggest that the choice of one technique or the other probably did not significantly influence the results. Third, in the clinical group, qualitative rather than quantitative cultures of endotracheal aspirates were chosen because therapy based on clinical evaluation, nonquantitative cultures of endotracheal aspirates, and knowledge of epidemiologic data remains the working strategy of the overwhelming majority of physicians (4).

Finally, crude mortality rates differed significantly between the two groups at 14 days, when the death rate in the clinical management group significantly exceeded that in the invasive management group by about 9%; this difference persisted over the following 2 weeks but was no longer significant at 28 days. Nonetheless, the strategy applied continued to affect the outcome: Eighteen more deaths occurred in the clinical management group, and the Cox proportional hazards model identified a higher mortality rate in this group.

The lower mortality rate seen in the invasive management group might be explained by at least three different factors. First, the antibiotics initially prescribed were more often appropriate in this group; there were significantly fewer inappropriate treatments, a factor known to be associated with lower mortality (1, 2, 23, 28, 29). However, inappro-

priate use of antibiotics was particularly low in our clinical management group (13%) compared with previous studies (30, 31), probably because investigators were required to carefully follow the recommendations of the American Thoracic Society. Only one patient in the invasive management group with a positive bronchoscopic specimen was initially treated incorrectly, probably because of the additional information obtained by examination of specimens obtained directly (32).

Second, patients who underwent bronchoscopy ended up receiving fewer antibiotics, and antibiotic therapy was discontinued in more of them. This lowering of the risk for inadequate or unnecessarily administered empirical therapy has major advantages, namely avoidance of potentially harmful side effects and reduction of selection pressure, thereby limiting the emergence of resistant microorganisms and the corresponding heightened risk for superinfection known to adversely affect patient outcomes (33, 34). Almost all reports emphasize that better antibiotic control programs to limit bacterial resistance are urgently needed in this setting and that patients without true infections should not receive antibiotics.

Finally, probably the most important risk of not performing bronchoscopy is that another site of simultaneous or subsequent infection may be missed. The major benefit of a negative bronchoscopy specimen may be to direct attention away from the lungs as the source of fever, as demonstrated by the 22 infections at other sites documented between days 1 and 3 in patients in the invasive management group (compared with 5 patients in the clinical management group). Many hospitalized patients with negative bronchoscopic specimen cultures have other potential sites of infection that can more readily be identified in the absence of antibiotic interference (2, 12, 35, 36). Delaying diagnosis or definitive treatment of the true site of infection may lead to prolonged antibiotic therapy, more antibiotic-associated complications, and induction of additional organ dysfunction (2, 7, 37).

From this randomized study of two strategies to manage patients in whom ventilator-associated pneumonia was suspected, we conclude that a strategy based on quantitative bronchoscopic specimen cultures has beneficial effects: improved early survival, fewer early organ failures, and less antibiotic use. It provides arguments to stop giving antibiotics to patients without adequately identified microorganisms. Because the invasive treatment strategy prescribes fewer antibiotics, it limits their overuse and provides clearer guidelines for the management of ventilated patients suspected of having nosocomial pneumonia.

Appendix

The following persons and institutions participated in the VAP Trial.

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Grant Support: In part by the Société de Réanimation de Langue Française and the Délégation à la Recherche Clinique, Assistance Publique–Hôpitaux de Paris.

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