

Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia

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Objective: To assess how data obtained by invasive diagnostic techniques may affect management and outcome of patients with suspected ventilator-associated pneumonia (VAP), in comparison with noninvasive qualitative techniques.

Design: Prospective study.

Setting: An 18-bed medical and surgical intensive care unit.

Patients: A total of 91 patients suspected of having VAP were randomized into two groups. In group A (n = 45), quantitative cultures obtained by either bronchoscopic or nonbronchoscopic techniques were performed, whereas in group B (n = 43), patients were treated based on clinical judgment and nonquantitative tracheal aspirates cultures. Three patients were excluded because of the absence of follow-up.

Results: In patients with positive cultures, therapeutic changes were made in 20 patients. In four patients (three from group A and one from group B, $p = \text{NS}$), initial empirical antibiotic treatment was modified because the isolated microorganisms were not susceptible (all of them had late-onset pneumonia). The isolated organisms responsible for antibiotic modifications were methicillin-resistant *Staphylococcus aureus* (three patients) and *Pseudo-*

monas aeruginosa (one patient). In three patients, the antimicrobial therapy was considered inappropriate because the isolated microorganisms were multiresistant and treated with only one effective antibiotic. In 13 patients (ten from group A and three from group B, $p < .05$), treatment was changed to select a narrower spectrum antibiotic. No therapeutic modifications were made in patients with negative cultures based on the results of quantitative cultures.

The overall mortality was 22.2% in group A and 20.9% in group B. There were no differences in intensive care unit stay or days of mechanical ventilation (23.67 ± 3.15 vs. 22.42 ± 3.01 and 19.99 ± 2.88 vs. 19.24 ± 3.04 , respectively).

Conclusions: In our study population, the routine use of quantitative invasive diagnostic tools is not justified in the setting of ventilated patients clinically suspected of having nosocomial pneumonia. (Crit Care Med 2000; 28:2737-2741)

KEY WORDS: ventilator-associated pneumonia; protected specimen brush; bronchoalveolar lavage; non-bronchoscopic-protected bronchoalveolar lavage; antibiotics; mortality

The accurate diagnosis of ventilator-associated pneumonia (VAP) is difficult to establish, and despite the huge literature published on this topic, the diagnostic strategy remains controversial (1, 2). Quantitative bacterial cultures of lower respiratory tract secretions collected with a protected specimen brush (PSB) or by bronchoalveolar lavage (BAL) may en-

hance the accuracy of diagnosis of VAP and may help justify the use of antibiotics, and hence these methods have been advocated for the routine care of patients with suspected pneumonia (1, 3). However, the impact of invasive diagnostic techniques in the outcome of ventilated patients suspected of having nosocomial pneumonia is unknown. Recently, a well-conducted study was published that compared the impact of invasive and noninvasive quantitative culture sampling on the outcome of VAP, and no differences were found in mortality and morbidity between both diagnostic methods (4). However, quantitative cultures are not readily accessible to the majority of physicians, and therefore therapy based on clinical judgment and nonquantitative cultures of tracheal aspirates remains the standard diagnostic strategy in the majority of patients (5).

The aim of this work was to prospectively evaluate whether quantitative culture of samples obtained by invasive techniques modifies empirical antibiotic treatment in patients suspected of having VAP or improves their outcome compared with clinical management based on nonquantitative cultures.

MATERIALS AND METHODS

Patients. Over a 26-month period, from January 1996 to March 1998, 91 consecutive immunocompetent patients who were intubated and mechanically ventilated for >48 hrs entered a prospective study. Patients were eligible if they fulfilled the following criteria: fever > 38.5°C, presence of purulent tracheobronchial secretions, leukocytosis (>12,000 cells/mm³) or leukopenia (<4,000/mm³), and new infiltrates on chest radiograph. When these patients showed at least three of these criteria, radiographic infiltrates being always present, they were randomly assigned to one

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of two groups, according to the method for establishing an etiological diagnosis of VAP. The first group (group A) underwent fiberoptic bronchoscopy with PSB and/or BAL, except when the clinical diagnosis of pneumonia arose between 12 pm and 8 am, in which case nonbronchoscopic BAL (PBAL) was performed. The second group (group B) was managed based on clinical suspicion and nonquantitative cultures of tracheal aspirates.

At the time of entry, the following variables were recorded: age, gender, admitting service, smoking history, history of chronic obstructive pulmonary disease, indication for ventilatory support, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (6). Temperature, blood leukocytosis/mm³, and PaO₂/FIO₂ were recorded daily. Chest radiographs were obtained daily.

Specimen Collection. Endotracheal aspirates were obtained by sterile suction from group B by using a mucus collector (Mocstrap, Kendall Procline, Barcelona, Spain). Fiberoptic bronchoscopy was performed in the invasive group while patients were ventilated with 100% oxygen and without positive end-expiratory pressure. The fiberoptic bronchoscope (Olympus BF, P20D, Optical Corp. of America, New Hyde Park, NY) was introduced into the trachea through an 8.5-mm endotracheal tube through a special connector (Bodai Suction Safe Y, Sontek Medical, Lexington, MA) and advanced to the bronchial orifice of the radiographically abnormal pulmonary lobe. The PSB (MBB, 120388-5504, Mill-Rose Lab, Mentra, OH) was inserted through the inner suction channel and advanced under direct vision to a wedge peripheral position to obtain lower airway secretions. No suction was applied before taking the specimen, and no local anesthetic agents were used. Samples of bronchial secretions were obtained by PSB, according to the technique of Wimerley et al. (7). The brush was introduced in a vial containing 1 mL of saline 0.9% and vigorously vortexed for at least 60 secs to suspend all material from the brush. BAL was carried out with 150 mL of sterile saline solution in 50-mL aliquots, each of them hand-aspirated to permit sufficient suction without collapsing the airway. The first aliquot was discarded, and the subsequent ones were pooled and submitted for bacteriologic analysis. The sequence of sampling was always PSB followed by BAL. The PBAL was performed by means of a special catheter (Combicath, Plastimed, Saint Leu La Foret, Cedex, France).

Processing of Specimens. Specimens were processed as soon as they were obtained. Aliquots of 0.01 mL and 0.002 mL were taken from the original PSB and BAL unconcentrated suspensions, respectively, by means of calibrated loops; that is, a minimum concentration of 100 colony forming units (cfu)/mL could be detected in PSB specimens and 500 cfu/mL in BAL specimens. All the samples were inoculated onto blood agar, chocolate agar, and MacConkey agar and were incubated, at 35°C

during 48 hrs, in a CO₂-enriched atmosphere. Samples obtained by PSB, BAL, and PBAL also were inoculated into Brucella agar with vitamin K and hemin and were incubated under anaerobic conditions for 48 hrs.

Bacterial counts $\geq 10^3$ cfu/mL for PSB, 10^4 cfu/mL for BAL, and 10^3 cfu/mL for PBAL were used as the cutoff point to establish a positive result. Recovery of $>1\%$ of squamous epithelial cells in the BAL specimens was considered an accurate predictor of heavy oropharyngeal contamination (i.e., unsatisfactory specimen).

Subsequent changes in clinical outcome and radiographic findings were recorded, and alternative explanations for the findings, such as atelectasis or pulmonary edema, were always excluded. When pneumonia was present at or before the fourth day of intubation, it was considered an early-onset pneumonia. Pneumonia that developed >4 days after intubation was considered late pneumonia (8). The time without antibiotics and the type of treatment received before and after diagnostic procedures were recorded. When patients of both groups were receiving antibiotics before pneumonia episode suspicion, these were withheld ≥ 12 hrs before the sampling techniques. Antibiotic therapy specifically for pneumonia was started immediately after protocol sampling was done, according to the following therapeutic plans: a) early-onset pneumonia in patients without risk factors: cefotaxime or ceftriaxone; b) late-onset pneumonia or pneumonia that developed after the use of antibiotics: aminoglycoside plus ceftazidime, piperacillin, or imipenem. Vancomycin was added to the previous groups if risk factors for *Staphylococcus aureus* were present (patients with head trauma, coma, or renal failure). The same antibiotic regimen was used for both groups of patients. Antibiotic modifications were performed on the basis of culture and sensitivity results of PSB and/or BAL in group A and nonquantitative endotracheal aspirates in group B.

The study protocol was approved by the hospital Ethics Committee, and informed consent was obtained from family members.

Statistical Analysis. Patients were randomly assigned by using a computer-generated randomization table. Data were expressed as mean \pm SD. We tested proportions for statistical significance by using the chi-square test for categorical variables, Student's *t*-test for normally distributed variables, and Mann-Whitney U test for nonnormally distributed variables. We considered $p < .05$ to be significant. Predicted hospital mortality rates were calculated from APACHE II and the diagnostic categories scores (6). Attributable mortality was defined as the difference between crude mortality and predicted mortality.

RESULTS

A total of 91 mechanically ventilated patients suspected of having VAP were

included in the study. Of these patients, three were excluded because of transfer to another institution and loss of follow-up. Of the remaining 88 patients, 45 were randomly assigned to group A and 43 to group B. Patients were admitted to the intensive care unit and required ventilatory assistance because of head injury ($n = 17$), multiple trauma ($n = 16$), heart failure ($n = 15$), postoperative respiratory insufficiency ($n = 13$), cerebrovascular disease ($n = 12$), respiratory failure ($n = 5$), drug overdose ($n = 2$), and miscellaneous conditions ($n = 8$). There were no differences between groups A and B regarding intensive care unit stay or days of mechanical ventilation (23.6 ± 3.1 vs. 22.4 ± 3.1 and 19.9 ± 2.8 vs. 19.2 ± 3 , respectively). Sixteen patients in group A (35.6%) and 19 in group B (44.2%) had received antibiotics before inclusion in the study, but no new antibiotics were administered in the previous 72 hrs. Clinical characteristics of the patients are shown in Table 1.

In group A, bronchoscopic procedures were performed in 31 patients (31 PSB and 28 BAL) and PBAL in the remaining 14 patients of the group. PSB yielded significant bacterial growth in 13 patients and nonsignificant growth in four and was sterile in 14. BAL yielded significant bacteria growth in 19 and nonsignificant growth in five and was sterile in four. PBAL yielded significant bacteria growth in 12 and was sterile in two. In group B, nonquantitative cultures of tracheal aspirates were positive in 32 patients and sterile in 11.

The etiological agents of pneumonia are shown in Table 2. Overall, *S. aureus* and *Haemophilus influenzae* were the organisms most often isolated in both groups of patients. The incidence of infection with *Pseudomonas aeruginosa* was significantly higher in the patients from group A ($p < .05$). Pneumonia was polymicrobial in 15 patients from group A and 11 from group B ($p = \text{NS}$).

Thirty-two patients developed early-onset pneumonia (16 patients in each group), and 56 had late nosocomial pneumonia (29 from group A and 27 from group B). *S. aureus* (16 patients, one of them methicillin-resistant) and *H. influenzae* (12 patients) were the organisms most often isolated in patients with early-onset pneumonia, accounting for 63.6% of the total causative organisms. *S. aureus* (14 patients, two of them methicillin-resistant) and *P. aeruginosa* (13 patients) were the most frequently isolated

Table 1. Clinical characteristics of study patients

	Total Patients (n = 88)	Group A (n = 45)	Group B (n = 43)
Age (yrs)	52.9 ± 2.1	50.4 ± 3.0	55.6 ± 2.9
Male (%)	64 (72.7)	34 (75.5)	30 (69.7)
Female (%)	24 (27.3)	11 (24.5)	13 (30.3)
APACHE II on inclusion	15.4 ± 0.7	15.8 ± 0.9	15.0 ± 0.9
Predicted mortality at admission ^a	21.7 ± 2.1	23.4 ± 2.9	19.8 ± 3.1
Observed mortality rate	21.5 ± 2.0	22.2 ± 2.7	20.9 ± 2.8
PaO ₂ /FIO ₂	181.5 ± 7.5	171.8 ± 8.6	191.7 ± 12.2
Temperature	38.6 ± 0.1	38.8 ± 0.1	38.5 ± 0.1
Leukocytes	15,137 ± 668	15,460 ± 955	14,798 ± 942
Unilateral radiographic infiltrate (%)	36 (40.9)	16 (35.5)	20 (46.5)
Bilateral radiographic infiltrate (%)	52 (59.1)	29 (64.5)	23 (53.5)
Days of MV before inclusion	7.6 ± 0.7	7.8 ± 1.1	7.3 ± 0.9
Previous antibiotic treatment (%)	35 (39.7)	16 (35.5)	19 (44.1)
Early-onset pneumonia (%)	32 (36.3)	16 (35.5)	16 (37.2)
Late-onset pneumonia (%)	56 (63.7)	29 (64.5)	27 (62.8)
Medical admissions (%)	42 (47.7)	20 (44.4)	22 (51.1)
Trauma admissions (%)	33 (37.5)	18 (40)	15 (34.8)
Surgical admissions (%)	13 (14.7)	6 (13.3)	7 (16.2)

APACHE, Acute Physiology and Chronic Health Evaluation; MV, mechanical ventilation.

^aCalculated from APACHE II scores and the diagnostic category scores according to Knaus et al. (6). *p* values are not significant.

Table 2. Microorganisms isolated from the different techniques in patients with suspected pneumonia

Microorganisms	Group A				Group B
	PSB ^a	BAL ^a	PBAL ^a	Total ^b	TA
<i>Staphylococcus aureus</i> ^c	6 (2)	9 (1)	1	13 (2)	17 (2)
<i>Haemophilus influenzae</i>	6	6	3	12	10
<i>Pseudomonas aeruginosa</i>	3	4	5	10 ^d	3
<i>Streptococcus pneumoniae</i>	3	4	2	6	2
<i>Streptococcus</i> species	1	3	1	4	1
<i>Acinetobacter</i> species	—	1	—	1	4
<i>Klebsiella</i> species	1	1	1	3	1
<i>Escherichia coli</i>	1	1	1	2	1
<i>Enterobacter cloacae</i>	2	1	—	2	1
<i>Proteus</i> species	—	—	—	0	2
<i>Serratia</i> species	1	2	—	2	0
<i>Neisseria</i> species	1	—	—	1	1
<i>Corynebacterium</i> species	2	1	—	2	0
<i>Stenotrophomonas maltophilia</i>	—	—	—	0	1
<i>Moraxella catarrhalis</i>	—	1	—	1	0

PSB, protected specimen brush; BAL, bronchoalveolar lavage; PBAL, nonbronchoscopic bronchoalveolar lavage; TA, tracheal aspirates; —, data not available.

^aMicroorganisms isolated in significant growth; ^bepisodes of pneumonia produced by the different microorganisms in group A; ^cnumber of methicillin-resistant *S. aureus* is shown in parenthesis; ^dbetween groups A and B (*p* < .005).

organisms in patients with late-onset pneumonia.

In patients with positive cultures, therapeutic changes were made in 20 patients. In four patients (three patients from group A and one from group B, *p* = NS), initial empirical antibiotic treatment was modified because the isolated microorganisms were not susceptible (all patients had late-onset pneumonia). The isolated organisms responsible for these antibiotic modifications were methicillin-resistant *S. aureus* (three patients) and *P. aeruginosa* (one patient). In three pa-

tients (two from group A and one from group B), the antimicrobial therapy was considered inappropriate because the isolated microorganisms (one patient with *Acinetobacter baumannii* and two with *P. aeruginosa*) were treated with only one effective antibiotic. In 13 patients (ten from group A and three from group B, *p* < .05), treatment was changed to select a narrower spectrum antibiotic.

Among patients with negative results (sterile or nonsignificant growth), we did not change empirical antibiotic therapy in any case. The antimicrobial treatment

was discontinued only much later, when clinical status was considered as having improved enough to justify stopping antibiotics.

The overall mortality was 22.2% (10/45) in group A and 20.9% (9/43) in group B. (Table 1). The 15-day mortality rate was 15.6% (7/45) in group A and 11.6% (5/43) in group B. The predicted mortality rates according to APACHE II score for groups A and B on admission were 23.4% and 19.8%, respectively (*p* = NS).

Among nontrauma patients, there was no difference in the mortality rate be-

tween group A and B (23.1% vs. 27.6%) Neither were there differences with regard to mortality among patients from groups A and B in relation to the positivity or negativity of the diagnostic techniques used: Group A, 10 of 39 (25.6%) vs. 0 of 6, $p = \text{NS}$; Group B, 7 of 32 (21.9%) vs. 2 of 11 (18.2%), $p = \text{NS}$. When analyzing mortality according to the adequacy of antibiotic treatment, we observed that in 84 patients in whom antibiotic treatment was adequate, 17 (20%) died (nine from group A and eight from group B). On the other hand, in patients in whom isolated microorganisms were not susceptible to the initial antibiotic therapy ($n = 4$), two (50%) died (one in each group). If these patients were grouped with the three additional patients who were initially receiving antibiotic therapy that was not sufficient, the mortality rate would be 28.5% (two of seven patients) (NS).

There was no difference in the mortality rate between patients with VAP associated with *P. aeruginosa*/*Acinetobacter* species and those with VAP produced by other microorganisms (Group A: 2 of 11 [18.2%] vs. 8 of 34 [23.5%], $p = \text{NS}$; Group B: 1 of 7 [14.2%] vs. 8 of 36 [22.2%], $p = \text{NS}$).

No complications related to PSB, BAL, or PBAL were encountered during this study.

DISCUSSION

In the present work, we evaluated the outcome of patients suspected of having VAP in a prospective randomized study. In this work, we compared management based on quantitative cultures obtained by means of bronchoscopy (PSB and BAL) or PBAL to management based on clinical judgment and nonquantitative cultures of tracheal aspirates, and we found no differences in terms of mortality or morbidity between the two strategies.

The outcome of an episode of pneumonia is likely to reflect the virulence and antibiotic resistance of infecting organisms, the efficacy and adverse consequences of the host response, and the severity of the underlying disease (9). To change morbidity and mortality, a diagnostic test must provide information to prescribe more appropriate antibiotics in patients who have pneumonia or to withhold antibiotic treatment in those patients who do not have pneumonia.

Interestingly, therapeutic changes based on the results of quantitative cul-

ture results were made in 15 (33.3%) of the 45 patients judged to have pneumonia, either because appropriate antibiotics were not given ($n = 5$) or because the therapeutic regimen was reduced to select a narrower and more rational therapy ($n = 10$). On the other hand, therapeutic changes based on clinical judgment and endotracheal aspirates were made in five (11.6%) of the 43 patients. Methicillin-resistant *S. aureus* was the microorganism that most frequently motivated these changes, because therapy against this microorganism is not usually included in the initial empirical regimens. In general, invasive diagnostic techniques led to more antibiotic changes without a clear influence on outcome. Similar data have been reported by others (4, 10) as well as ourselves (11).

The antimicrobial agents used to treat VAP may affect outcome, and an association between mortality and inappropriate initial empirical antibiotics has been suggested (12, 13). The impact of further modifications on outcome is unclear (14). Other studies have suggested that mortality is reduced when antibiotics are initiated very early (10, 14, 15). Our data are consistent with the opinion that patients with nosocomial pneumonia benefit from prompt and effective antibiotic therapy. In our study, only 4.5% ($n = 4$) of patients were not adequately covered by the initial empirical antibiotic treatment, which might explain why the mortality rate we observed was lower than the one observed by Sánchez-Nieto et al. (4) and the similar mortality between early-onset and late-onset pneumonia in our population. We reported similar data in a recent study (11).

It is interesting to speculate that the lower rate of mortality of VAP in our study might also be caused, at least in part, by differences in the patient population. Severe underlying illness undoubtedly makes one susceptible to pneumonia, and the need to discriminate between associated and attributable mortality is well recognized. Moreover, outcome is also influenced by emerging conditions (9). It is important to measure the severity of illness or physiologic derangement at the time the pneumonia is diagnosed, to distinguish between VAP complicating a terminal condition and VAP causing death. In other words, it is not possible to demonstrate differences in mortality based on the diagnostic approach of VAP unless pneumonia itself affects mortality. We were not able to

Our results suggest that although invasive diagnostic techniques lead to more antibiotic changes, when empirical treatment is appropriately standardized by local flora, hospital stay, and risk factors, the use of protected specimen brush, bronchoalveolar lavage, and nonbronchoscopic bronchoalveolar lavage techniques does not seem to improve the outcome of mechanically ventilated patients suspected of having nosocomial pneumonia.

demonstrate a significant attributable mortality to pneumonia in comparison with predicted hospital mortality rates calculated from APACHE II. This finding could be partly explained by the fact that 33 patients in our series (37.5%) had undergone trauma, and some authors have suggested that VAP in trauma patients has no attributable mortality (16).

Some etiological agents appear to imply a worse prognosis, and several studies suggest that patients infected with multiresistant Gram-negative bacilli, particularly *P. aeruginosa* and *Acinetobacter* species, have higher mortality rates than other causes of VAP (17, 18). In our study, the small number of pneumonias caused by *P. aeruginosa* or *Acinetobacter* species in both groups limits our ability to conclude that such higher risk does indeed exist.

As in the study by Sánchez-Nieto et al. (4), we found that the incidence of *P. aeruginosa* was higher in patients managed with invasive techniques. This finding may reflect either a randomizing aberration, possibly as a consequence of a

limited sample size, or a higher sensitivity of invasive procedures.

A major limitation in our study was the continuation of antibiotics in all patients despite negative cultures. The antimicrobial treatment was discontinued only much later, when clinical status had improved enough. Moreover, this management neutralizes any cost analysis because the main cost benefit of any type of quantitative culture technique is avoidance or discontinuation of antibiotics in culture-negative cases. Another limitation in our study is the small sample size that hinders the demonstration of mortality differences based on diagnostic strategy.

Although the outcome of patients without pneumonia may not improve if antibiotics are withheld, treatment with unnecessary antibiotics or broadening initial regimen coverage could significantly affect the appearance of resistant microorganisms and drug toxicity (12, 19). In our study, invasive diagnostic techniques showed a greater ability to narrow the initial empirical antibiotic regimen compared with a less invasive approach. This may be significant, because probably no other factor is more important in the development of antimicrobial resistance than antibiotic use. Hence, diagnostic techniques that exclude VAP could facilitate a more rational strategy. Another additional benefit might be a more extensive evaluation of alternative diagnosis in patients with negative cultures.

CONCLUSIONS

Our results suggest that although invasive diagnostic techniques lead to more

antibiotic changes, when empirical treatment is appropriately standardized by local flora, hospital stay, and risk factors, the use of PSB, BAL, and PBAL techniques does not seem to improve the outcome of mechanically ventilated patients suspected of having nosocomial pneumonia.

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