Bronchoscopic BAL in the Diagnosis of Ventilator-Associated Pneumonia*

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**Studies**

We reviewed 23 studies published since 1988 regarding the use of bronchoscopic BAL for the diagnosis of VAP. All studies employed quantitative cultures on the BAL samples, and four studies used protected BAL methods with balloon occlusion.23 41 97 98 The remaining studies used the conventional BAL method. In five studies,18 19 41 97 99 the procedure was performed immediately after death in patients receiving mechanical ventilation.

**How Were Patients Enrolled?**

The study population was recruited prospectively in all 23 studies. In 4 studies, enrollment was consecutive; in the remaining 19, patients were selected by the investigators. Some data in these studies were collected retrospectively.

**Description of the Population**

The main descriptive parameter of the study populations was the duration of mechanical ventilation, which varied from 24 h93 100 to 90 days.101 The average period was 10 days. One study102 did not mention the duration. Another parameter was classification of the diagnosis as suspected, unsuspected, or postmortem. In 16 studies, the pneumonia episode was suspected on the patient's inclusion into the study. In two of the five postmortem studies, pneumonia was not suspected before the patient’s death. In one study, the study population included suspected and nonsuspected pneumonia cases (Table 12).

**Were the Test Results and the Reference Standard Assessed by Investigators Who Were Unaware of the Results of the Other Investigators?**

The reference test used in most of the studies was not standardized, varying markedly among studies. It appears from the reports that in seven studies (29%) the test results and the reference standard were assessed blindly by investigators who were unaware of the results of the other investigations.15 18 20 41 97 102 In the remaining 13 studies, it appears that the investigators may have been aware of test results, reference standards, and the results of other investigations. In three studies, this could not be deduced.24 100 101

**Were the Methods of Performing the Tests Described Adequately?**

Overall, the test methods were well described. Usually, they were of two types: bronchoscopic methods and...
microbiological methods. Five studies did not adequately describe the methodology, three of those referenced microbiological methods to prior publications, and two referenced the BAL method to prior publications (Table 12).

**Criteria Used to Assess the Quality of the Sample**

The best way to assess the quality of a BAL sample is to examine the cells of the fluid retrieved from preparations that had undergone centrifugation. The presence of >1% squamous epithelial cells is evidence of oropharyngeal contamination. Ten studies did not mention the use of any criteria to assess sample quality. The remaining studies used cellular assessment, but only two looked for squamous epithelial cells. To our knowledge, none of the studies looked for ciliated bronchial cells as a marker of contamination.

**Intracellular Organism Detection**

Twelve studies looked for intracellular organisms (ICOs) as a possible marker for VAP. Ten of these reported ICO thresholds ranging from 2 to 25% to distinguish colonization from true infection. Of the 12 studies, eleven (92%) mentioned sensitivities and specificities. Sensitivities ranged from 37\% to 100\%, and specificities ranged from 89\% to 100\%. These studies suggest that ICO detection is a very specific marker for VAP.

**Number of Patients and Episodes**

A total of 957 patients receiving mechanical ventilation were studied in the 23 series reported. The most patients in a single study was 102, and the fewest was 9.

As shown in parentheses in Table 13, 431 episodes of VAP were studied. The criterion used for determining the number of episodes was the confirmation of VAP by clinical, microbiological, or histologic parameters. These parameters represent the reference standards. Many studies included control patients (ie, patients in whom pneumonia was not suspected). The selection of control patients was based on the absence of pulmonary infection or on the presence of a confirmed alternative diagnosis. Two studies prospectively included only control subjects. Some studies included patients who were suspected of having pneumonia but lacked definite criteria. These patients were not included in the 431 episodes we computed.

**Study Design**

The most common design was a case series of patients with suspected VAP, selected by the investigators. Some studies evaluated control patients, as defined above. Two studies investigated only control subjects. Five studies were performed immediately after death and included data from histologic examination or microbiological studies of lung tissue. The diagnostic values of BAL and other sampling methods were compared in histologic and non-histologic studies. Comparisons included endotracheal
Aspiration, PSB, balloon-tipped BAL, and mini-BAL. Only 3 studies investigated conventional BAL alone, and the remaining 20 studies compared one or more of the techniques mentioned above. The most common technique was PSB, which was compared in 15 studies.

### Antibiotics

Sixteen studies included patients with and without prior antibiotic treatment, four studies included only patients not receiving antibiotic therapy, and one study...
included only patients receiving antibiotic treatment. In three studies, the presence or absence of antibiotic therapy is unknown.

More patients (544) received antibiotics than did not (375). Most studies stated the presence of antibiotics as a dichotomous variable.

### Reference Standard

Several reference standards have been used to differentiate between the presence and absence of pneumonia. Seventeen studies used histology studies as the reference standard. The histologic criterion was the presence of neutrophil infiltration in the alveoli. Five of the 17 studies used immediate postmortem histology. Eleven studies combined histologic and clinical or microbiological data. Only one study used postmortem lung cultures as the reference test. Seven additional studies used clinical data with or without microbiological reference tests (Table 13).

Clinical reference standards varied among studies and included the following: the presence of radiographic cavitiation; classical signs of pulmonary infection (chest radiographic infiltrates, fever, leukocytosis, and purulent secretions); and good response to antibiotics. All reference standards included ruling out alternative diagnoses that could explain the presence of fever and pulmonary infiltrates. In one study, the authors developed a clinical pulmonary infection score that included the following six points: body temperature, leukocyte count, characteristics of tracheal secretions, oxygenation, chest radiographic findings, and a semiquantitative score for cultures of tracheal aspiration. The threshold to distinguish infection from noninfection was six points. Other studies used microbiological standards as reference tests. Most studies included the results of blood and pleural fluid cultures, the isolation of definite pathogens, and the isolation of pathogens above threshold levels from respiratory sample cultures.

### Sensitivity

Sensitivity values are reported in all but two studies, which included control patients (ie, patients without pneumonia). The BAL method to detect VAP had a variable sensitivity (22% in the study by Torres et al to 100% in the study by Meduri et al). The calculated mean (± SD) sensitivity in the 23 studies was 73 ± 18%. The variability depends on prior antibiotic treatment, type of study population, and the reference test used. In six studies, the calculated sensitivity differed from that reported by the authors. In three studies, sensitivity could not be calculated. In some studies, sensitivity was calculated for patients with and without prior antibiotic treatment. Obviously, such treatment decreased sensitivity.

The method of calculating sensitivity was not standardized among studies, although formulas were applied uniformly. Sensitivity can be calculated by taking into account the number of patients or the number of microorganisms, and only one study made this distinction in computing the diagnostic yield parameters, although it did not do so specifically for sensitivity. The remaining articles do not describe how sensitivity was calculated in relation to this issue. Importantly, the calculation of sensitivity depends on the cutoff points of quantitative cultures. Most manuscripts used 10^4 cfu/mL, one study used 10^5 cfu/mL, and another study used 10^7 cfu/mL. One study calculated sensitivity by using the bacterial index instead of a definite threshold of quantitative cultures. The bacterial index is the sum of the logarithms base 10 (log_{10}) of the different isolated microorganisms. The cutoff point used was 5. Another study used a similar index (simplified bacterial index) with a cutoff point of 4. Several articles calculated sensitivity using different cutoff points.

### Specificity

The situation regarding the specificity of BAL is similar to that of sensitivity. Three studies included only patients with VAP, so they did not report specificity values. The mean (± SD) calculated for specificity in the 23 studies considered was 82 ± 19%. The two studies that investigated only specificity for BAL reported values of 65% and 82%, respectively. In eight studies, specificity was reported by the authors but could not be calculated. Another study reported values of 85% and 82%, respectively. In the remaining studies, the calculated and reported specificities were the same.

Variability in specificity and in sensitivity is explained by differences in prior antibiotic treatment, the type of study population, and the manner in which pneumonia was confirmed (the reference test). The way specificity was calculated was not standardized among the studies, although formulas apparently were applied uniformly. Specificity can be calculated on the basis of the number of patients or the number of microorganisms, and we found only one article that specifically addressed this concern. Several articles calculate sensitivity using different cutoff points. Receiver operating characteristic curves were reported in only four studies.

### Risks

BAL is not without risk. The risks are of the following two types: those inherent to the use of the fiberoptic bronchoscope (which this report does not address); and those inherent to the instillation of fluid during bronchoscopy. The most important and most common consequences involve blood-gas exchange and include important decreases in oxygenation and slight increases in CO2 values. In addition, hemodynamic parameters can be altered after the BAL procedure. Alterations in blood-gas exchange depend on the type of lavage used (conventional BAL or protected BAL) and the amount of liquid instilled, which ranges from 50 mL in mini-BAL to 150 mL in conventional BAL.

Recent articles have examined the effects of BAL on gas exchange. Steinberg and coworkers did not find significant changes in oxygenation, mean arterial pressure, heart rate, peak inspiratory pressure, or static thoracic compliance after BAL in 110 patients with ARDS. Papazian and colleagues found a significant decrease in PaO2 after BAL and a moderate drop in PaCO2. Guerra and Baugh-
man\textsuperscript{102} observed a median decrease in \( \text{PaO}_2 \) of 8 mm Hg (range, 63 to 29 mm Hg), which could be treated by increasing the fraction of inspired oxygen. However, the authors concluded that BAL using fiberoptic bronchoscopy is well tolerated in critically ill patients who are receiving mechanical ventilation.

Our group examined the effects on oxygenation of protected BAL and mini-BAL in patients with VAP and in control subjects. We found important reductions in the \( \text{PaO}_2/\text{fraction of inspired oxygen} \) ratio 5 and 24 h after the procedure (a 20% drop from baseline to postbronchoscopy values). The decrease was independent of the type of BAL used. \( \text{PaCO}_2 \) values showed a minor, transient increase (average, 7 mm Hg).\textsuperscript{106}

Montravers et al\textsuperscript{25} observed similar effects on arterial oxygenation 3 and 5 h after BAL. These authors did not find important alterations in hemodynamic parameters (arterial pressure, heart rate, and cardiac index) after BAL. From these studies, it seems that the major side effect of BAL is the postprocedural reduction in arterial oxygenation in VAP patients. The patient may recover from the oxygenation impairment after several hours or may not recover completely. The variables involved in this response need detailed study. They include type of lavage, amount of liquid instilled, prior alteration in blood-gas exchange, and severity of the VAP.

One study described sepsis-like effects after BAL in VAP patients.\textsuperscript{107} This response is characterized by fever and by a decrease in mean arterial pressure and arterial oxygenation, and it seems related to the level of endotoxins in the BAL fluid. The reaction may be a \textit{bacterial migration-like effect} from the alveoli to the systemic circulation during BAL. Further investigation is warranted.

**Conclusions**

- The sensitivity of quantitative BAL fluid cultures ranges from 42 to 93%, with a mean of 73%. The clinical implication is that BAL cultures are not diagnostic for pneumonia in almost one fourth of cases.
- The specificity of quantitative BAL fluid cultures ranges from 45 to 100%, with a mean of 82%. This means that the diagnosis is incorrect (ie, false-positive result) in about 20% of cases.
- Detecting intracellular organisms in BAL cultures is a quick, specific test and has a high positive predictive value.
- Only two studies assessed the quality of BAL samples as measured by the presence of squamous epithelial cells.