Protected-Specimen Brush Technique in the Diagnosis of Ventilator-Associated Pneumonia*

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Abbreviations: LR = likelihood ratio; PSB = protected-specimen brush; VAP = ventilator-associated pneumonia

The protected-specimen brush (PSB) technique has been used for almost 20 years in diagnosing pneumonia, and the technique has been refined for VAP. Of the many studies, those included in our analysis met certain criteria.

The 42 studies reviewed were identified through a MEDLINE search and presented primary data of bronchoscopy samples from patients receiving mechanical ventilation. All studies had rigorous clinical criteria for the diagnosis of pneumonia, including response to antibiotics, that were independent of the results of PSB or BAL procedures. The review methodology for this section is described in Dr. Steven H. Woolf’s section on the search of the literature.

Independent nonbronchoscopic diagnostic criteria were required to ensure that there were no derivative data. Five studies compared PSB sampling to the use of specimens obtained immediately after autopsy as the final criteria for diagnosis. The remaining 13 studies used clinical assessment, response to antibiotics, and histologic data, including eventual autopsy information, when available. Of the 846 patients evaluated, pneumonia was diagnosed in 287.

The quality of the PSB technique used in making the diagnosis was not described in detail for most of the studies in Tables 14 and 15.

A few studies have examined assessing the quality of bronchial brushings. The issue of reproducibility was addressed by Marquette et al., who obtained five specimens from one area of the lung. In 25% of the patients, the variability in one or more of the bronchial specimens was > 10³ cfu/mL, and in the remainder it was < 10³ cfu/mL, which was the cutoff point. This suggests that 25% of the time a single PSB determination would have the possibility of being a false positive or a false negative. Another study, in patients who had localized pneumonia and were not receiving antibiotics, compared brush samples from the affected lobe and an unaffected lobe. The bacterial concentration in specimens from the affected area was at least 100-fold higher than in the unaffected lobe.

Assessing the quality of the PSB sample involves examining a cell sample and looking directly at a brush sample. The problem is that two brush samples have to be obtained, since the slide could contaminate the culture results. Using the PSB technique allows for assessment of the quality of the sample, because the presence of squamous epithelial cells indicates that the sample is unacceptable. In one study, this was looked for and was found in some cases, but the number of unacceptable specimens was not given. In two studies, Gram’s stain was found to be sensitive and fairly specific in the identification of bacteria. It provides information within the first 24 h of the procedure, which is useful. As noted above, 5 of the 18 studies used autopsy data from VAP patients as a “gold standard.” Obviously, this does not provide information about patients who did not die. The other studies did not have histologic confirmation of the final diagnosis in all patients.

None of the studies included a PSB procedure on every patient in the ICU. Entry criteria for all patients required either a clinical suspicion of pneumonia or availability of autopsy studies. One study had autopsy confirmation of the diagnosis, but the bronchoscopy had been performed up to 3 days before death.

Among other factors contributing to variability are the skill of the health-care worker performing the procedure. It is not clear how much skill is required, but suctioning through the catheter before brushing may interfere with the results. Few studies specify that the secretions were cleared out with a separate bronchoscope before the PSB sample was taken. Also, where and what to brush is poorly defined. Other problems include the selection of patients to undergo the procedure and the lack of standard protocols for therapy, such as the selection of prior antibiotics and the use of empirical therapy pending the results of the cultures. Because clinical outcome is often used in assessing the PSB technique, the use of antibiotics pending the culture result can influence the study outcome.

Qualifications for Inclusion in the Tables

The 18 studies covered were published from 1984 to 1995 and used semiquantitative culture results for the PSB sample. All studies used the technique described for patients not receiving ventilator support. A standard method of bronchoscopy and handling of specimens was published in 1992, but was not significantly different from the methodology used in the studies.

How Were Patients Enrolled?

All studies apparently enrolled patients prospectively, although two studies do not make this clear. Although the studies were prospective, none included all ICU patients. Most studies also were limited by the ability to perform the procedure. Some studies stated that patients were enrolled only during daytime. Most others probably followed this practice.

Description of the Population

The studies can be divided into two groups. The first includes patients who died while receiving mechanical ventilation. Bronchoscopy and autopsy were performed on these patients in the immediate postmortem period. There were no other selection criteria, so pneumonia was not necessarily suspected prior to autopsy. One study

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compared the results in ventilator-assisted patients with and without clinically suspected pneumonia. The rest of the studies report results in patients studied because of the clinical suspicion of pneumonia. One study analyzed findings in patients who had bronchoscopy for possible pneumonia then underwent autopsy within 72 h.

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

In all patients studied during life, the results from the PSB procedure affected long-term treatment. The four studies in which postmortem bronchoscopy and autopsy were performed did not have that bias. The fact that the results from the autopsy studies were similar to those from the clinical studies supports the results of the latter.

Were Methods of Performing the Tests Described Adequately?

Overall, the authors provided sufficient details on methodology. As noted, the PSB technique has remained virtually unchanged for years.

### Table 14—Studies of Protected Specimen Brush*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Enrollment</th>
<th>Description of Population</th>
<th>Reason for Enrollment</th>
<th>Investigators Blinded to Reference Standard</th>
<th>Adequate Methods of PSB</th>
<th>Criteria for Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagon et al40/1988</td>
<td>Prospectively</td>
<td>All patients in surgical ICU who developed clinical criteria, were on vent &gt; 72 h</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Marquette et al20/1993</td>
<td>Prospectively</td>
<td>3-mo period, 3 ICUs, vent time unknown</td>
<td>Suspected VAP</td>
<td>Appears so</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>El-Ebiary et al21/1993</td>
<td>Not stated</td>
<td>Patients in respiratory ICU, on vent &gt; 72 h, who either had suspicion for pneumonia (74) or bronchoscopy (28)</td>
<td>Suspected, 78; not suspected, 28</td>
<td>Yes</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Chastre et al20/1984</td>
<td>Prospectively</td>
<td>Patients on vent &gt; 1 h, not prolonged, brain-dead</td>
<td>Postmortem</td>
<td>Yes</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Papazian et al20/1995</td>
<td>Prospectively</td>
<td>Vent &gt; 72 h, nonimmunocompromised</td>
<td>Postmortem</td>
<td>Yes</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Marquette et al20/1995</td>
<td>Prospectively</td>
<td>Vent &gt; 1 h, suspected of pneumonia, had bronch, died within 3 d</td>
<td>Postmortem on suspected VAP</td>
<td>Yes</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Torres et al18/1994</td>
<td>Prospectively</td>
<td>Vent &gt; 72 h, died</td>
<td>Postmortem</td>
<td>Yes</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Chastre et al20/1995</td>
<td>Prospectively</td>
<td>Patients died in daytime, Vent &gt; 72 h, no change in ATBS for 72 h</td>
<td>Postmortem</td>
<td>Yes</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Lambert et al10/1989</td>
<td>Prospectively</td>
<td>Vent &gt; 72 h, ATBS &lt; 24 h, nosocomial (17) and CAP (8)</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Torres et al20/1988</td>
<td>Prospectively</td>
<td>Vent &gt; 24 h, nosocomial (17) and CAP (8)</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Meduri et al10/1992</td>
<td>Prospectively</td>
<td>One yr study, vent &gt; 24 h, no ATBs for 48 h</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Timsit et al13/1993</td>
<td>Prospectively</td>
<td>Vent &gt; 24 h, could tolerate bronch</td>
<td>Suspected VAP</td>
<td>Yes</td>
<td>Yes</td>
<td>Compared 2 brushes, 17–24% discordance</td>
</tr>
<tr>
<td>Timsit et al28/1995</td>
<td>Prospectively</td>
<td>Vent &gt; 48 h, no change in ATB</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Solé-Violán et al30/1994</td>
<td>Prospectively</td>
<td>15 mo study, vent &gt; 72 h</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Compared 2 brushes</td>
</tr>
<tr>
<td>Richard et al11/1998</td>
<td>Prospectively</td>
<td>10 mo, vent unknown time</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Baughman et al10/1987</td>
<td>Prospectively</td>
<td>Vent &gt; 48 h, not ATBS 48 h, localized infiltrate</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Compared PSB in affected and nonaffected</td>
</tr>
<tr>
<td>Solé-Violán et al10/1993</td>
<td>Prospectively</td>
<td>Vent &gt; 48 h, 14 mo study</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
<tr>
<td>Chastre et al20/1998</td>
<td>Unclear</td>
<td>Vent &gt; 48 h, no antibiotics &gt; 10 d</td>
<td>Suspected VAP</td>
<td>No</td>
<td>Yes</td>
<td>Not described</td>
</tr>
</tbody>
</table>

*Bronch = bronchoscopy; vent = ventilation; ATB = antibiotic; CAP = community-acquired pneumonia. Values in parentheses are No. of patients.
bronchoscopes (the first used to suction the airways, and the second used without suction) on all patients, the results were not significantly different from those of other studies. One study found that it did not matter which segment of the lung was brushed. Criteria Used to Assess the Quality of the Sample

One article discussed the examination of the bush sample for the presence of cells. Technically, this may not be feasible, because dilution of the sample relies on
the vigorous agitation of the brush in a solution immediately after sampling.\textsuperscript{1,85} The Gram’s stain may provide an early guide to therapy.\textsuperscript{25,109}

**Study Design**

The most common study design selected patients suspected of having VAP who could undergo bronchoscopy. One study was limited to patients with localized infiltrates, so that an unaffected lobe could be analyzed.\textsuperscript{26} One study included patients who had no clinical suspicion of pneumonia.\textsuperscript{13} One postmortem study examined bronchoscopy results obtained within 3 days before death.\textsuperscript{18} The remaining postmortem studies compared only the specimens obtained after death.

**Antibiotics**

Antibiotic therapy is a significant variable in the assessment of a diagnostic technique. In three studies, patients were not receiving any antibiotics.\textsuperscript{24,26,100} Others studies attempted to study only patients who had not undergone a recent change in antibiotic therapy.\textsuperscript{41,99} In the rest of the studies, patients took antibiotics for varying periods. Since most patients with VAP are already taking antibiotics at the time of bronchoscopy, this remains an unresolved dilemma.

**Reference Standard**

Table 14 discusses the reference standards for each study. The postmortem studies used histology reports and culture results.\textsuperscript{18,20,29,41,99} In the clinical studies, the most common criteria were response to therapy or the identification of an alternative diagnosis. In many studies, some patients died and underwent postmortem examination. The autopsy results did not change the clinical impression to any degree.

**Sensitivity**

The sensitivity of the studies varied from about 33 to 36\textsuperscript{20,41} to > 95\%\textsuperscript{29,40}. This wide range cannot be explained by diagnostic criteria alone. The lowest\textsuperscript{29} and highest\textsuperscript{29} sensitivities were in autopsy studies. As noted above, the recommended cutoff of 10\textsuperscript{3} cfu/mL\textsuperscript{85} is arbitrary. In one series looking at the reproducibility of results for the brush technique, 25\% of the results were discordant.\textsuperscript{57} The median sensitivity of brush sampling for all studies was 67\%.

**Specificity**

The calculated specificity, shown in Table 14, ranged from 50\%\textsuperscript{41} to 100\%.\textsuperscript{16,24,26,45,100,103,116,117} with a median specificity of 95\%. The PSB may be more specific than sensitive.

**Likelihood Ratio**

Table 14 also includes the calculated likelihood ratios (LRs), based on sensitivity and specificity. Since several studies reported the PSB procedure to be highly specific, the likelihood that a positive finding would mean pneumonia was quite high. The median LR was 16. Only one study reported an LR of < 1,\textsuperscript{41} and several studies reported ratios of > 50 based on a 100\% specificity.\textsuperscript{16,24,26,100,103,116,117} In the one study reporting an LR of < 1, all patients were receiving antibiotics and only three patients had recently changed antibiotics.\textsuperscript{41} Since histology studies were the criteria for diagnosis, it is not clear whether a negative result for a PSB culture and a positive result of a histologic examination may indicate a treated, but not resolved, case of pneumonia.

**Comparison to Other Techniques**

Fourteen studies were direct comparisons between PSB and other invasive diagnostic techniques, usually BAL.\textsuperscript{13,18,20,24,28,41,93,99,100,103,116} None of the studies comparing the PSB and BAL techniques convincingly showed a benefit for one over the other, although BAL was generally more sensitive and PSB more specific. It is not clear that these tests are complimentary.

The other studies compared PSB with relatively less invasive techniques, such as aspiration samples,\textsuperscript{13,20,118} blind BAL,\textsuperscript{20,45} and nonprotected brush.\textsuperscript{117} The comparisons showed little difference between the techniques.

**Risks**

The reports are strangely silent regarding complications from the PSB procedure. Bronchoscopy in the patient receiving mechanical ventilation is associated with significant risks, but it is not clear that the brush technique adds to the risk.

**Conclusion**

Despite the wide array of studies and the use of high-quality diagnostic techniques in several studies to determine the cause of pneumonia, sensitivity ranged from 33 to 100\% and specificity ranged from 50 to 100\%. Overall, PSB appears more specific than sensitive in diagnosing VAP. In a patient with suspected VAP and a positive result of testing a PSB sample, the LR of VAP appears to be much > 1.