A consensus approach to diagnosis and management of ventilator-associated pneumonia has been clouded by uncertainty because a gold standard for ventilator-associated pneumonia has never been clearly established. Application of invasive procedures to obtain respiratory tract cultures has been the most common approach applied by research investigators. The most studied invasive procedures in large-scale investigations are protected specimen brush (PSB) and bronchoalveolar lavage (BAL). Despite the fact that variabilities exist for the methodology, researchers have been successful in using these invasive approaches as a working model for studies of ventilator-associated pneumonia.

The most prominent study was performed by Fagon and colleagues [1] and remains a benchmark in the field of ventilator-associated pneumonia. Those authors enrolled 413 patients in a labor-intensive, multicenter, randomized trial. A noninvasive management strategy (clinical criteria, isolation of organisms by nonquantitative analysis of endotracheal aspirate) was compared with an invasive management strategy of direct examination of bronchoscopic BAL or PSB specimens with quantitative cultures. Patients randomized to the invasive strategy group experienced significantly fewer deaths at 14 days, earlier attenuation of organ dysfunction, and decreased antibiotic use compared with patients randomized to the noninvasive strategy group.

However, despite the results from this oft-cited study, the use of invasive procedures for the diag-
nosis of ventilator-associated pneumonia has not enjoyed widespread use in clinical practice. The necessity for an invasive procedure with timely performance has been an obstacle for clinicians. Moreover, in controlled studies [2] as well as clinical practice, results of the procedure sometimes failed to alter antibiotic administration [3] and did not necessarily improve outcome [4]. As a result, other less invasive approaches, including nonbronchoscopic BAL including the mini-BAL, blinded PSB, and blinded bronchial sampling (BBS), were developed to obtain lower respiratory tract specimens.

The obvious gold standard of isolation by culture from biopsy or autopsy lung specimens is difficult to obtain. Isolation of the pneumonic pathogens at other nonsterile sites such as blood or pleural fluid is infrequent. Even these standards are not wholly satisfactory because autopsy, histology, and culture of lung aspirates can also give inaccurate results [5-7]. As Chinsky [8] editorialized, “Is there any gold in these standards”? This issue has been reviewed elsewhere, and methods of fluid retention, specimen handling, thresholds for interpretation, and methodology were problematic [9-12]. A meta-analysis of studies of PSB, BAL, and endotracheal aspirates found design-related bias for patient selection, BAL volume, and use of prior antibiotics in evaluations of these procedures [6].

The foundation for these less invasive diagnostic procedures is not as well established. We conducted a review similar to that of Campbell [10] focusing on the factor of quantitation; we excluded 1 study that used qualitative culture [13] and added 2 studies published after the year 2000 [14, 15]. The inclusion criteria for our review were that all studies had to be prospective with explicit data on inclusion criteria for our review were that all studies had to be prospective with explicit data on infection may lead to a false-negative result [26]. As a result, the sensitivity and the specificity were highly variable as documented by Campbell [10]. Only 1 study out of a total of 16 studies [7, 14-25, 27-29] excluded patients who had received or were receiving antibiotics at the time of the procedure [21]. Not surprisingly, receipt of antibiotics within 24 hours of sample collection markedly decreases the sensitivity of the procedure [26, 30]. Souweine et al [30] suggested that if antibiotics were administered before the procedure, the threshold of PSB and BAL should be decreased to $10^2$ colony-forming units (CFU)/mL and $10^3$ CFU/mL, respectively.

Because of more difficult access, higher cost, and absence of compelling evidence for these newer procedures, the use of endotracheal aspirates as a means to diagnose ventilator-associated pneumonia remains common. Cook and Mandell [31] reviewed 9 published studies in which cultures were obtained by endotracheal aspirates [5, 26, 32-38]. Unfortunately, in all 9 studies, patients who were receiving antibiotics when endotracheal aspiration was performed were not excluded. Three studies used qualitative cultures as diagnosis of ventilator-associated pneumonia [34, 37, 38]; the remaining 6 studies used quantitative cultures [5, 26, 32, 33, 35, 36]. The threshold varied from $>10^6$ CFU/mL (2 studies) [32, 35] to $>10^6$ CFU/mL (4 studies) [5, 26, 33, 36]. In 1 study, several thresholds were evaluated; $10^6$ CFU/mL was considered the optimal cutoff for endotracheal aspirate [36]. The gold standards for ventilator-associated pneumonia were variable: 4 studies used clinical diagnosis [26, 32, 35, 36]; 1 study used PSB or blood/pleural fluid culture, serology, or open lung biopsy [38]; 1 study used clinical diagnosis and PSB or BAL; and the remaining 3 studies used autopsy with or without clinical diagnosis [5, 34, 37]. Cook and Mandell [31] concluded that the data compiled in fewer than 600 patients were so diverse that studies on use of endotracheal aspiration were insufficient to generate policy recommendations. Wu et al found that results from endotracheal cultures correlated well with PSB and BAL in 48 patients suspected of having ventilator-associated pneumonia [39]. This study had weaknesses similar to other studies, but the authors’ review of the literature and
Table 1. Differences in Methodology in Comparative Evaluation of Nonbronchoscopic Bronchoalveolar Lavage (BAL) (Including Mini-BAL)

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Population</th>
<th>Instrument</th>
<th>Previous Antibiotic</th>
<th>Blind/Protected Catheter</th>
<th>Lavage</th>
<th>Aspiration</th>
<th>Quantitation Threshold</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rouby et al [19] (1989)</td>
<td>59</td>
<td>MV &gt;48 h (11 ± 8 d)</td>
<td>Combicath (a single-sheathed, 50-cm, sterile, plugged, telescoping catheter)</td>
<td>NA</td>
<td>Blind</td>
<td>Yes</td>
<td>20 mL</td>
<td>≥10⁴</td>
<td>Postmortem histology</td>
</tr>
<tr>
<td>Pugin et al [18] (1991)</td>
<td>28</td>
<td>MV &gt; 72 h (11 ± 7 d)</td>
<td>A flexible 14F catheter with guidewire</td>
<td>28.6% (8/28)</td>
<td>Blind</td>
<td>No</td>
<td>100 mL</td>
<td>Not described</td>
<td>CPIS &gt;6</td>
</tr>
<tr>
<td>Rouby et al [7] (1992)</td>
<td>69</td>
<td>MV &gt; 489 h (17 ± 13 d)</td>
<td>Combicath (a single-sheathed, 50-cm, sterile, plugged, telescoping catheter)</td>
<td>90.7% (39/43)</td>
<td>Blind</td>
<td>Yes</td>
<td>20 mL</td>
<td>≥10⁴</td>
<td>Autopsy and histology</td>
</tr>
<tr>
<td>A’Court et al [16] (1993)</td>
<td>150</td>
<td>(including CAP &amp; VAP)</td>
<td>A standard 50-cm, 14-gauge tracheal catheter (Argyle Sherwood Medical)</td>
<td>NA</td>
<td>Blind</td>
<td>No</td>
<td>20 mL</td>
<td>4-8 cc</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kollef et al [17] (1995)</td>
<td>42</td>
<td>MV &gt; 24 h</td>
<td>BALcath® telescoping catheter</td>
<td>59.5% (25/42)</td>
<td>Directed</td>
<td>Yes</td>
<td>25 mL</td>
<td>≥10⁴</td>
<td>Clinical and PSB culture</td>
</tr>
<tr>
<td>Papazian et al [27] (1995)</td>
<td>38</td>
<td>MV &gt; 72 h (23 ± 27 d)</td>
<td>Combicath (a single-sheathed, 50-cm, sterile, plugged, telescoping catheter)</td>
<td>55.3% (21/38)</td>
<td>Blind</td>
<td>Yes</td>
<td>20 mL</td>
<td>2 cc</td>
<td>Autopsy, histology, and lung culture</td>
</tr>
</tbody>
</table>

VAP = ventilator-associated pneumonia; MV = mechanical ventilation; NA = not applicable; BI = bacterial index; CPIS = clinical pulmonary infection score; CAP = community-acquired pneumonia; PSB = protected specimen brush. Mini-BAL is defined as lavage volume ≤25 mL.
a well-reasoned analysis noted the major advantage of practicality while reserving PBS and BAL for selected patients.

Given the presence of an endotracheal tube for patients who are being mechanically ventilated, colonization of the trachea by oropharyngeal bacterial flora is expected. Various cut-points of quantitation to distinguish colonization from infection have been proposed [31, 40]. The threshold for quantitation in invasive procedures ranged from $\geq 10^5$ CFU/mL to $>10^3$ CFU/mL (Table 1). The variability in the amount of lavage fluid instilled and the amount aspirated can lead to tremendous variation in quantitation as measured by CFU/mL. In 1 study of PSB, about 40% of respiratory specimens increased from below the threshold for diagnosis of pneumonia to above threshold a few days later [41].

Moreover, many studies of validation of ventilator-associated pneumonias are inherently flawed because many of the gold standards also used quantitative cultures as a criterion for infection [5]; this is circular reasoning. Wunderink [12] concluded that because a gold standard is not available, the “truth” simply cannot be determined.

So, what is the clinical solution of this difficult issue? Two conclusions warrant thoughtful consideration by clinicians: (1) Ideally, commitment to an invasive procedure should be evidence based. PBS and BAL have been evaluated as a management strategy for patients suspected of having ventilator-associated pneumonia. The concept is biologically plausible, and studies have suggested that PBS and BAL might have a positive impact on management [42]. Validation in a large-scale study was performed by Fagon et al [11]. (2) However, our overview of the invasive procedures of nonbronchoscopic BAL including mini-BAL, blinded PBS, and BBS shows that these newer procedures should be considered as investigational procedures until clinical validation has been performed. Thus, we agree with Wood et al [15] and Wu et al [39] that it is rational to use the least invasive procedure. Two limited studies of endotracheal aspirate culture versus cultures obtained by invasive methods found no differences in mortality rate or clinical response [15, 43]. A meta-analysis of 4 studies totaling 628 patients also showed that there was no difference in mortality rate of ventilation-associated pneumonia using an invasive diagnostic method versus a noninvasive method, although significance was seen in prescription and use of antibiotics [4]. It is appropriate that these innovative, less invasive procedures continue to be evaluated. Our review shows that these procedures need to be standardized and validated in clinical trials. Until then, using endotracheal aspirate cultures without the necessity for quantitation is certainly a reasonable and legitimate approach for clinicians who are not committed to an invasive procedure.

References

Diagnosis of Ventilator-Associated Pneumonia


