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Shigeki Fujitani and Victor L. Yu  
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# Diagnosis of Ventilator-Associated Pneumonia: Focus on Nonbronchoscopic Techniques (Nonbronchoscopic Bronchoalveolar Lavage, Including Mini-BAL, Blinded Protected Specimen Brush, and Blinded Bronchial Sampling) and Endotracheal Aspirates

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Shigeki Fujitani, MD\*  
Victor L. Yu, MD†

**The ideal diagnostic approach for ventilator-associated pneumonia currently is based on invasive procedures to obtain respiratory tract cultures. Given the lack of consensus and relatively poor acceptance of full bronchoscopic bronchoalveolar lavage (BAL) and protected specimen brush (PSB), less invasive procedures have been developed. We review the nonbronchoscopic procedures (nonbronchoscopic bronchoalveolar lavage, including mini-BAL, blinded protected specimen, and blinded bronchial sampling) and endotracheal aspiration. We provide a critique of the methods used, the types of catheters inserted, and the sample collection methods. Most studies were flawed in that antibiotic use before initiation of the procedure was not controlled. The variability of both the methods and the criteria for the gold standard in the numerous investigations show that these procedures are neither standardized nor proven to be accurate and often did not improve management. Pending future studies, use of endotracheal aspirates without the use of quantitation seems to be a reasonable approach for clinicians who are not committed to an invasive procedure.**

From \*the Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, and the †Division of Infectious Diseases, VA Medical Center and University of Pittsburgh, Pittsburgh, PA.

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Address correspondence to Victor L. Yu, MD, Division of Infectious Diseases, VA Medical Center and University of Pittsburgh, University Drive C, Pittsburgh, PA 15240, or e-mail: vly+@pitt.edu

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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 quantitation given in the article. Even within the same procedure of nonbronchoscopic BAL, blinded PSB, and BBS, the catheters used were different: 4 different catheters in 6 studies of nonbronchoscopic BAL including mini-BAL [16-19] (Table 1), 5 instruments for 6 studies of blinded PSB [15, 20-23], and 3 instruments for 5 studies of BBS [14, 24, 25]. Sample collection was variable, including blind versus directed and protected versus nonprotected (Table 1). Concern has been expressed that blindly wedging the catheter into a lung area not involved in infection may lead to a false-negative result [26]. For purposes of this discussion, mini-BAL was defined as a nonbronchoscopic BAL in which the volume of aspiration was 25 mL or less. For mini-BAL, the volumes of fluid for instillation and retrieval by aspiration were highly variable. Five studies instilled 25 mL or less [7,16,17,19,27], but

the volume retrieval by aspiration ranged from at least 1 mL to 4-8 mL [7,16,17,19,27] (Table 1). Pugin et al [18] used instillation volumes of 100 mL; the retrieval volumes were not given. Differing gold standards were used: clinical diagnosis, results from BAL and PSB, and autopsy. The quantitative cultures used for the reference standards of bronchoscopic BAL and bronchoscopic PSB were also variable (Table 1). 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  $>10^5$  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)

Author	Number of Patients	Population	Instrument	Previous Antibiotic	Blind/Directed	Protected Catheter	Lavage	Aspiration	Quantitation Threshold	Reference Standard
Rouby et al [19] (1989)	59 (29 controls, 30 VAP)	MV >48 h (11 ± 8 d)	Combicath (a single-sheathed, 50-cm, sterile, plugged, telescoping catheter)	NA	Blind	Yes	20 mL	At least 1 cc	≥10 <sup>3</sup> BI≥5 equivalent	Postmortem histology
Pugin et al [18] (1991)	28	MV > 72 h (11 ± 7 d)	A flexible 14F catheter with guidewire	28.6% (8/28)	Blind	No	100 mL	Not described	to ≥10 <sup>5</sup> of quantitation	CPIS >6
Rouby et al [7] (1992)	69	MV > 489 h (17 ± 13 d)	Combicath (a single-sheathed, 50-cm, sterile, plugged, telescoping catheter)	90.7% (39/43)	Blind	Yes	20 mL	At least 1 cc	≥10 <sup>3</sup>	Autopsy and histology
A'Court et al [16] (1993)	150 (including CAP & VAP)		A standard 50-cm, 14-gauge tracheal catheter (Argyle Sherwood Medical)	NA	Blind	No	20 mL	4-8 cc	≥10 <sup>4</sup>	Clinical
Kollef et al [17] (1995)	42	MV > 24 h	BALcath <sup>®</sup> telescoping catheter	59.5% (25/42)	Directed	Yes	25 mL	Not described	≥10 <sup>3</sup>	Clinical and PSB culture
Papazian et al [27] (1995)	38	MV > 72 h (23 ± 27 d)	Combicath (a single-sheathed, 50-cm, sterile, plugged, telescoping catheter)	55.3% (5(21/38)	Blind	Yes	20 mL	2 cc	≥10 <sup>4</sup>	Autopsy, histology, and lung culture

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  $\geq 10^3$  CFU/mL to  $>10^5$  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 [1]. (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.

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