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Quantitative Cultures of Bronchoscopically Obtained Specimens Should Be Performed for Optimal Management of Ventilator-Associated Pneumonia

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Ventilator-associated pneumonia (VAP) is a leading cause of health care-associated infection. It has a high rate of attributed mortality, and this mortality is increased in patients who do not receive appropriate empirical antimicrobial therapy. As a result of the overuse of broad-spectrum antimicrobials such as the carbapenems, strains of *Acinetobacter*, *Enterobacteriaceae*, and *Pseudomonas aeruginosa* susceptible only to polymyxins and tigecycline have emerged as important causes of VAP. The need to accurately diagnose VAP so that appropriate discontinuation or de-escalation of antimicrobial therapy can be initiated to reduce this antimicrobial pressure is essential. Practice guidelines for the diagnosis of VAP advocate the use of bronchoalveolar lavage (BAL) fluid obtained either bronchoscopically or by the use of a catheter passed through the endotracheal tube. The CDC recommends that quantitative cultures be performed on these specimens, using ≥10^4 CFU/ml to designate a positive culture (http://www.cdc.gov/nhsn/TOC_PSCManual.html, accessed 30 October 2012). However, there is no consensus in the clinical microbiology community as to whether these specimens should be cultured quantitatively, using the aforementioned designated bacterial cell count to designate infection, or by a semiquantitative approach. We have asked Vickie Baselski, University of Tennessee Health Science Center, who was the lead author on one of the seminal papers on quantitative BAL fluid culture, to explain why she believes that quantitative BAL fluid cultures are the optimal strategy for VAP diagnosis. We have Stacey Klutts, University of Iowa, to advocate the semiquantitative approach.

POINT

> **Keep an open mind toward pneumonia. Our grandchildren will be interested and are likely to have as many differences of opinion regarding the disease as we have.**
> —Sir William Osler (1)

The best approach in establishing a diagnosis of ventilator-associated pneumonia (VAP) is quite controversial (2, 3). VAP contributes to excess morbidity, mortality, and costs, and these consequences have led to the designation of VAP as a quality performance monitor by the National Healthcare Safety Network (NHSN), the Institute for Healthcare Improvement, and the Joint Commission (4). Despite the importance of VAP, there is no universally accepted diagnostic approach.

The controversies surrounding VAP diagnosis are directly related to its clinicopathologic complexity. VAP represents inflammation of lung parenchyma following microaspiration of secretions that have accumulated around the ventilatory device. These secretions harbor significant concentrations of mixed bacterial microflora that may include health care-associated, multiply antimicrobial-resistant strains (5). Histopathologically, there is an inflammatory continuum along the airway from tracheobronchitis, to peribronchial pneumonitis, and eventually to progressive bronchopneumonia (6). The pneumonia may be multifocal and heterogeneous, a feature that complicates diagnosis (5).

Clinical findings are the result of the inflammation and include fever, leukocytosis or leukopenia, purulent secretions, and development of a new or persistent radiographic infiltrate. Unfortunately, these symptoms are not specific for pneumonia and may result from either noninfectious pulmonary conditions or infections at other anatomic sites. As a result, it is well accepted that using clinical features alone results in overdiagnosis of VAP, and microbiologic information is desirable (2, 7).

The newly proposed NHSN definitions of ventilator-associated events, including infections, attempt to integrate the complex clinical, histopathologic, and microbiologic features. In this new definition, VAP occurs in persons who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal intubation within the 48-hour period before the onset of infection. VAP is deemed "possible" when microscopically purulent secretions are noted and "probable" when a quantitative culture of lower respiratory material is above a designated threshold as shown in Table 1 (8). However, the actual necessity and utility of such cultures, particularly on bronchoscopically obtained specimens, remain controversial.

The quantitative approach. It must be admitted that the basis for a quantitative approach is largely theoretical. Pneumonia is believed to occur when there is an overwhelmed host response to microbial intrusion into a sterile environment. Concentrations of bacteria in lung tissue reach levels of ≥10^4 CFU/g, while levels in secretions are ≥10^5 CFU/ml (5). Accounting for dilutional effects,

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corresponding thresholds can be set for tracheal aspirates (TA), protected specimen brushings (PSB), or bronchoalveolar lavage (BAL) fluid (2). In contrast, organism levels in samples from individuals without pneumonia are generally below the established thresholds (7). By convention, even semiquantitative cultures attach greater significance to abundant or predominant growth of potential pathogens in a sample containing indigenous microbial flora. What may not be appreciated is the fact that there is an easily demonstrated relationship between semiquantitative and quantitative results, a finding that has been verified for BAL fluid samples (9).

Regarding microbiologic results obtained from different sample types, the data have been deemed "reasonably similar" (10) and "rather equivalent" (7). However, advocates of bronchoscopy cite many studies showing that directed lower airway sampling is an excellent proxy for lung tissue (5) and better captures the incidence of VAP (11). Qualitatively, there is relatively good agreement among sample types, particularly when samples are collected prior to initiating therapy for a new-onset infection (5), which agrees "with the common sense notion that specimens obtained from locations only 5-15 cm apart along a widely patent airway in continuous motion are unlikely to have substantially different bacterial populations" (6). However, the finding that a greater proportion of patients have positive results when less invasive specimens are used also implies that organism diversity may decrease moving toward the lung parenchyma (11). In all studies, antibiotic therapy has been shown to confound interpretation of data (2, 5, 7).

Practical considerations. If a noninvasive strategy is used, TA are easily obtained and microscopy may provide useful initial information (12). However, when an invasive strategy is used, BAL is often preferred due to the increased volume available for analysis (7). BAL also appears to offer improved microscopic data, as the probability of VAP with a positive Gram stain on BAL fluid is greatly increased (12). In addition, a positive Gram stain correlates reasonably well with quantitative cultures (7).

Methodologically, a quantitative culture can be performed similarly to a urine culture, with calibrated loops performing acceptably and easily incorporated into the workflow (13). However, as has been previously shown for other fluid samples, accuracy may exceed ±10% and intra-assay variability for colony counts is high. Therefore, it is recommended that BAL fluid quantitative culture results near an established threshold should not be strictly or solely used to characterize a patient as VAP positive or negative (14). The question then becomes whether this method offers any advantages over a semiquantitative approach. One recent study suggests that a semiquantitative method may overestimate potential pathogens (9), but the choice to use a calibrated loop method is actually rooted in historical observations that quantitative methods may improve recognition of more slowly growing organisms (15) and the observation that the "superiority over other methods can only be judged by experience and depends to some extent on ease in recognition and comfort in counting which cannot be readily communicated in a paper" (16).

Another factor that must be considered but is only rarely specifically addressed in studies is specimen quality. It stands to reason that any sample with excessive contamination may yield noninterpretable quantitative or semiquantitative culture results, but a standard approach to assessing quality has not been established. A related issue is that few studies specifically differentiate organ-

TABLE 1 Comparison of various sampling methods used for NHSN microbiologic thresholds

Specimen	Collectors	Site(s) sampled	Sample amt	Diluent vol	Dilution factor	Quantitative threshold[a]	Semiquantitative equivalent[b]	Comment(s)
Lung tissue	Trained physicians	Lung parenchyma	~1.0 g	~1.0 ml	1	$\geq 10^4$ g	Few-moderate or 2-3+	Often obtained postmortem, is not representative of all patients
Bronchoscopic[c] protected specimen brushing	Trained physicians	Bronchioles	0.001–0.01 ml	1.0 ml	1/100–1/1,000	$\geq 10^3$ ml	Rare-few or 1-2+	Low-volume sampling restricts utility
Bronchoscopic bronchoalveolar lavage fluid	Trained physicians	Bronchioles and alveoli	~1 ml	10–100 ml	1/10–1/100	$\geq 10^4$ ml	Few-moderate or 2-3+	Adequate volume for multiple analyses, including microscopy
Nonbronchoscopic protected specimen brushing	Respiratory therapists or trained personnel	Bronchioles	0.001–0.01 ml	1.0 ml	1/100–1/1,000	$\geq 10^3$ ml	Rare-few or 1-2+	Low-volume sampling restricts utility
Nonbronchoscopic bronchoalveolar lavage fluid	Respiratory therapists or trained personnel	Bronchioles and alveoli	~1 ml	10–100 ml	1/10–1/100	$\geq 10^4$ ml	Few-moderate or 2-3+	Comparable to bronchoscopic alveolar lavage but often lower in lavaged volume
Endotracheal aspirate	Respiratory therapists or nurses	Tracheal secretions	1–10 ml	1–10 ml	1–1/10	$\geq 10^5$ ml	Moderate-numerous or 3-4+	Easily obtained; primarily reported semiquantitatively with microscopy

[a] Number of colonies meeting threshold value varies with calibrated loop volume.
[b] Assuming an ~0.01-ml inoculum and a quadrant streak method with the following observations: rare or 1+ is growth in first quadrant, few or 2+ is growth in second quadrant, moderate or 3+ is growth in third quadrant, and numerous or 4+ is growth in fourth quadrant.
[c] Bronchoscopic sampling is performed via fiber optic bronchoscopy and incurs greater costs but allows targeted sampling.

isms considered potential pathogens from those considered primarily nonpathogens. It is of note that the proposed NHSN criteria attempt to address both specimen quality, using microscopic criteria similar to those accepted for sputa, and organism significance, through exclusion of organisms considered to be of low pathogenic potential (8).

The value of quantitative cultures. A determination of the value of quantitative cultures is difficult to make given the lack of a universally accepted definition. However, several recent summary analyses have provided some insights. In terms of clinical outcome, a comprehensive Cochrane review of the impact of qualitative culture of noninvasive samples and quantitative culture of invasive samples revealed no significant differences with respect to number of days on mechanical ventilation, length of intensive care unit (ICU) stay, or antibiotic change (17). In contrast, a meta-analysis of invasive approaches to the diagnosis of VAP concluded that invasive sampling led to significantly more antibiotic modifications (11), and in a separate study, de-escalation therapy rates were significantly higher when guided by results of quantitative BAL fluid cultures than when guided by quantitative TA cultures (18). Since de-escalation therapy by definition requires that a pathogen has been identified, the greater impact using invasive approaches supports the general concept of equivalent sensitivity but greater specificity of diagnosis using invasive strategies (2, 7). The lack of impact on other outcome monitors likely reflects the empirical use of effective broad-spectrum agents (11).

Should quantitative cultures of BAL fluid be performed? The opinion of this author is that quantitative culture of BAL fluid should be performed for optimal management in patients with VAP. Practically speaking, the method is comparable to that typically used for urine cultures, and there are potential benefits in recognizing more slowly growing organisms, including multiply resistant pathogens. In addition, there are substantial data that specificity of diagnosis and therefore appropriate antimicrobial therapy are improved using this approach. At the same time, one should recognize that quantitative culture results are "inherently unstable" (3). As for urine cultures, procrustean adherence to a quantitative threshold in interpreting results for an individual patient is overly simplistic (19). This is particularly true when using results to define VAP rates for public reporting, as rates may be manipulated simply by adjusting thresholds (4). In fact, the revised draft NHSN guidelines for public reporting of ventilator-associated complications (VAC) and infection-related VAC (IVAC) do not rely upon use of quantitative culture results. Rather, results based on "positive" cultures are used primarily for internal monitoring and quality improvement (8). One should also remain aware of the overall complexity of diagnosis of VAP. Rarely is a single result the basis for diagnosis, and algorithms that integrate clinical and microbiologic findings are recommended (12). The evidence suggests that clinical findings can alert the physician to the possibility of VAP, and examination of noninvasive secretions can refine the clinical suspicions. When suspicion leads to a decision to initiate treatment, then bronchoscopy with BAL fluid collection prior to initiating or changing therapy can reliably rule out VAP and perhaps direct efforts toward other sources of infection or confirm an etiology so that the therapeutic approach can be reassessed. Finally, cumulative antibiogram data on significant isolates can be developed to determine appropriate empirical therapy in subsequent cases (7, 11, 12). However, it is clear that the diagnosis of VAP will remain a controversial, even contentious topic (2, 3). Recent molecular findings that traditional methods may have underestimated the microbial complexity of infected lungs (20) will only add to the controversy.

. . . a man misses a good part of his education who does not get knocked about a bit by his colleagues in discussions and criticisms.

—Sir William Osler (1)

Vickie Baselski

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COUNTERPOINT

From the start, it must be made clear that this is an issue with no clear answer. The literature is not definitive on whether quantitative results of bronchoalveolar lavage (BAL) fluid cultures are clinically reliable in the diagnosis of ventilator-associated pneumonia (VAP), and there are widely varying opinions on what truly represents best practice. Indeed, if there was a clear best practice, this discussion would be unnecessary. In this context, what this whole issue boils down to is whether we trust the quantitative values on BAL fluid cultures.

There is no gold standard for the diagnosis of VAP, and the diagnosis of VAP is often a difficult one to make. Clinicians must rely on a combination of clinical, radiologic, and laboratory data on severely ill patients. The diagnostic difficulties are highlighted by guidelines for management of VAP from the American Thoracic Society in which the recommendations for the diagnosis of VAP were left as an open choice between a clinical strategy, a microbiological strategy, or combinations of the two (1). Further, even if the more conservative microbiological strategy was chosen, no recommendation was made as to whether the culture should be quantitative or semiquantitative (SQ) (1). This issue was also discussed in a 2010 position paper jointly published by the Infectious Diseases Society of America, the American College of Chest Physicians, the American Thoracic Society, and the Society for Critical Care Medicine that recommended design features for future clinical trials on VAP (2). While there were strong stances on most of the recommendations in this position paper, there was considerable disagreement on the role of microbiology. Indeed, the recommendations state only that microbiologic confirmation should be used in conjunction with clinical criteria to determine enrollment status for patients into trials without any recommendations on what microbiologic criteria to use (2).

The complicated nature of making a VAP diagnosis, the lack of a gold standard, and the comorbid nature of the patients susceptible to VAP make interpretation of the literature evaluating the roles of microbiology difficult, at best. For example, Riaz and colleagues recently compared quantitative and semiquantitative (SQ) culture for the diagnosis of VAP (3). They concluded that SQ culture had poor specificity and poor positive predictive value (PPV) and led to overuse of antibiotics. However, they used the quantitative culture result (VAP if $>1 \times 10^5$ CFU/ml) as the gold standard for VAP diagnosis and then determined the diagnostic accuracy of SQ culture compared to that as the standard (3). This is a self-fulfilling approach if the goal is to argue against use of SQ culture, as it assumes 100% diagnostic accuracy of the quantitative approach. To extend this, would antibiotics be improperly withheld in some patients with below-threshold quantitative results? In contrast, a multicenter study published in the *New England Journal of Medicine* randomized patients with suspected VAP based on clinical and laboratory criteria into a quantitative culture arm and an SQ culture arm (4). The investigators observed no differences in clinical outcomes or antibiotic usage between the two arms (4). The bottom line is that the literature just does not support the conclusion that quantitative cultures of BAL fluid are clinically useful. This lack of evidence prompted the British Society for Antimicrobial Chemotherapy in 2008 to recommend the following: "Although they may provide an indication to the causal pathogen, we recommend that quantitative cultures of respiratory specimens such as PSB and BAL should not be relied on for the diagnosis of HAP/VAP. Recommendation Grade A" (5) So, while the CDC has included quantitative culture of a "minimally contaminated" respiratory specimen as one criterion in a complex VAP diagnostic algorithm (http://www.cdc.gov/nhsn/PDFs/pscManual/6pscVAPcurrent.pdf), this suggestion is not evidence based, and indeed, it is not annotated with references. Further, this algorithm highlights the point that microbiology represents only a fraction of the information needed to make a diagnosis of VAP, and often it is not needed to make the diagnosis.

If treatment decisions are going to be made based on a value reported from a quantitative assay, then it is imperative that we as laboratorians are confident in the accuracy of that reported value. We meticulously validate quantitative assays in virology, chemistry, hematology, and other areas of the clinical laboratory to ensure that the values being reported are accurately reflecting the patient's condition. However, we often fall short of this for quantitative bacteriology. The main argument against reporting quantitative values for BAL fluid cultures is based on preanalytical factors and basic principles of good laboratory medicine. In order for a quantitative result to be reliable, sampling has to be consistent and able to provide a sample that quantitatively represents the disease. This is not much of an issue when sampling blood or other body fluids that are in open compartments. In those situations, any sample from that compartment has an average consistency that reflects that of the entire compartment. This is not the case in the lung. Microenvironments can vary widely from one location to another, especially elements of an infectious process. Postmortem studies have shown that in VAP there are widely varying levels of disease in different parts of the lung (6). While BAL does sample a larger area of the lung than does a protected brush, there is still going to be natural variation depending on which area is sampled. In addition to this issue with disease being unevenly multifocal, there are also issues with standardization of BAL fluid acquisition. Fujitani and Yu argue that because of variability in the volume of fluid both instilled and retrieved, the mathematical relationship between bacterial load detected in culture and that truly found in the lung breaks down (7). If a smaller amount of fluid is instilled and retrieved, this would overestimate bacterial burden, and the converse is true if a larger amount of fluid is used. Thus, quantitation of the bacterial burden in this sample is not necessarily indicative of the true, average bacterial burden in the lung. By reporting a specific, quantitative value, one is implying to the treating physician that the value is universally interpretable. I submit here that we lend too much credence to this value by reporting it.

As mentioned above, VAP is a difficult diagnosis to make and clinicians must rely on a number of pieces of data along with their clinical acumen. One of the main arguments used in support of reporting quantitative values for BAL fluid in this situation is to reduce antibiotic use. This is a noble goal, assuming that undertreatment of disease is not the result. In the case of a suspected VAP, many clinicians are reluctant to withhold or withdraw antibiotics based on culture results alone, and indeed, it has been proposed that it is unsafe to do so (1). Treatment decisions for VAP should be based on the level of clinical suspicion of VAP in

conjunction with laboratory results, including culture results. In that case, a semiquantitative result that does not understate the inherent variability in sampling is sufficient for management of patients suspected to have VAP.

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SUMMARY

Points of agreement:

1. There is no clear standard for definitively establishing the etiology of ventilator-associated pneumonia (VAP), due in part to the complexity of this disease process.
2. Bronchoalveolar lavage (BAL) fluid acquisition is poorly standardized, making comparison between multiple samples from the same patient difficult and even more challenging among a population of patients.
3. Quantitative cultures add complexity to the processing and interpretation of bronchoscopically obtained specimens.
4. Quantitative cultures of BAL fluid near the $\geq 10^4$-CFU/ml threshold for positivity are more specific but less sensitive for the diagnosis of VAP. Semiquantitative results, on the other hand, lack specificity and likely contribute to overuse of antimicrobials in intensive care units (ICUs).
5. Quantitative culture supports the de-escalation of antimicrobial therapy, an important aspect of an antimicrobial stewardship program.

Issues to be resolved:

1. New molecularly based techniques have revealed that the microbiome of VAP is much more complex than is currently recognized using conventional techniques. We need to better understand how the interactions of organisms within this ecosystem impact disease pathology.
2. As these molecular methods migrate to the clinical laboratories, our understanding of and ability to distinguish infectious causes of lung pathology (pneumonia) from immunologically based ones (acute respiratory distress syndrome) should be enhanced.
3. Standard, easily performed approaches to measure the relative concentrations of lung secretions and diluent in bronchoalveolar lavage fluids are needed. This will allow more accurate quantitation of organisms present in the lung, whether it be based on CFU per milliliter or taxa per milliliter.
4. Outcome studies to establish the benefit of quantitative cultures of bronchoscopically obtained specimens are needed.

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