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Evidence-Based Assessment of Diagnostic Tests for Ventilator-Associated Pneumonia*

Executive Summary

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Abbreviations: BBS = blinded bronchial sampling; BPSB = blinded sampling with the protected-specimen brush; PSB = protected-specimen brush; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is difficult to diagnose, and the precise role of invasive testing is controversial. Confronted with a changing clinical or radiographic setting demanding specific therapy, clinicians increasingly use invasive testing to supplement their clinical judgment. Invasive techniques include the protected-specimen brush (PSB) technique and BAL.

The PSB technique was developed in 1987 by Wimberly et al[1] and has since been improved. Because it was found that samples may become contaminated by organisms of the upper airway, methods have been advanced to protect the sampling fluid. In addition, quantitative culture methods have been developed to permit distinguishing infection from colonization. However, because of concerns about diagnostic accuracy, reproducibility of results, diagnostic thresholds, nonstandardized methodology, and lack of data on clinical outcome, few definitive recommendations have been reached.[2,3]

The Health and Science Policy Committee of the American College of Chest Physicians assembled a panel of scientific experts to develop diagnostic recommendations based on a rigorous review of the literature. The panel included experienced methodologists to ensure that the review process was justifiable and unbiased. Recommendations were developed through group discussion and were based on direct evidence, when it was available, and expert consensus opinion, when direct evidence was not available.

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To implement the evidence-based assessment, the panel adopted the following grading system for most recommendations:

- Grade A: Recommendation based on direct scientific evidence;
- Grade B: Recommendation based on scientific evidence, supplemented by expert opinion;
- Grade C: Recommendation based on expert opinion alone; and
- Grade D: There is no definitive evidence or consensus opinion.

This manuscript covers the following topic areas:

- Panel methodology;
- Epidemiology of VAP;
- Radiologic diagnosis of VAP;
- Clinical criteria in the diagnosis of VAP;
- Endotracheal aspiration sampling;
- BAL sampling;
- The PSB technique;
- Blinded, invasive diagnostic procedures; and
- Invasive procedures in nonresolving pneumonia.

This executive summary reports the panelists' major conclusions and final recommendations. The reader may assess the thoroughness of the evaluation process and the validity of the conclusions by reviewing each section.

Epidemiology

VAP is a common disorder, with a prevalence of 6 to 52 cases per 100 patients, depending on the population studied.[4] VAP must be distinguished from other forms of hospital-acquired pneumonia, because treatment, prognosis, and outcome may differ significantly.

Nosocomial pneumonia is an intrahospital infection that develops ≥ 48 h after admission; VAP is a complication of intubation and mechanical ventilator support. Early-onset VAP occurs during the first 4 days of mechanical ventilation and often is caused by *Streptococcus pneumoniae*, *Haemophilus influenzae,* or *Moraxella catarrhalis*. Uncommonly, anaerobes are the causative agents. Late-onset VAP develops ≥5 days after the initiation of mechanical ventilation, and is commonly caused by *Pseudomonas aeruginosa,* Acinetobacter or Enterobacter spp, or methicillin-resistant *Staphylococcus aureus*.[5]

Each day the patient receives endotracheal intubation and mechanical ventilation, the crude rate of VAP in-

creases by 1 to 3% and the risk of death increases twofold to 10-fold. When the causative pathogen is *P aeruginosa*, disease-specific (attributable) mortality may be as high as 43%.[6] In addition, VAP is often associated with a dramatic increase in length of hospital stay and total hospital costs.[7]

Radiologic Diagnosis

The initial diagnosis of VAP is based on clinical suspicion and the presence of new or progressive radiographic infiltrates. Unfortunately, the accuracy of interpretation of chest radiographs has not been extensively evaluated. Moreover, the incidence of pneumonia in immunocompetent patients with normal findings on chest radiograph and a compatible clinical presentation is unknown. Such findings are common among immunocompromised patients with *Pneumocystis carinii* pneumonia.

In diagnosing VAP, the presence of alveolar infiltrates, determined by invasive techniques or by histologic studies, has a sensitivity of 58 to 83% for air bronchogram signs, and 50 to 78% for new or worsening infiltrates.[8,9] Specificity is unknown, because reports do not state the appropriate denominator (*ie*, the number of patients receiving ventilator assistance who do not have pneumonia and who have normal findings on a chest radiograph).

The presence of any one radiographic sign does not significantly increase the likelihood of VAP, because other potential causes of radiographic abnormalities occur in ventilator-assisted patients.[9] Chest radiographs are not a reliable diagnostic tool, as there is only marginal reproducibility of the findings obtained from two readers.[10] Finally, the negative clinical and economic impacts of misinterpreting chest radiographs have not been evaluated.

Clinical Criteria

The standard diagnostic criteria in VAP include at least two of the following three findings: fever, leukocytosis, and purulent tracheal secretions, usually with abnormal findings from chest radiographic studies. When these conditions occur, the likelihood of VAP is high.[11] The presence of a radiographic infiltrate in a patient with fever, leukocytosis, or purulent tracheobronchial secretions has high diagnostic sensitivity but low specificity. When all four criteria are present, specificity improves but sensitivity drops to $< 50\%$, which is clinically unacceptable.[12] The only study examining interobserver diagnostic reliability found no major differences between individual physicians or those physicians grouped by level or training.[11]

These findings suggest that the presence of abnormal clinical manifestations, combined with abnormal radiographic findings, can be used for the initial screening for VAP. However, the lack of specificity with this method suggests that additional procedures are needed, such as cultures of lower respiratory tract secretions (grade B recommendation).

Role of Endotracheal Aspiration

Qualitative cultures of endotracheal secretions are often used in lieu of invasive diagnostic testing, because healthcare workers with minimal training can perform the aspiration procedure at the bedside. Qualitative cultures usually identify pathogenic organisms found by invasive tests, suggesting high sensitivity, but, frequently, they also identify nonpathogenic organisms, reducing the positive predictive value of the procedure. If the culture results are negative for pathogens, VAP is very unlikely to be present, unless the patient has been treated with antibiotics.[13]

The results of quantitative cultures on specimens obtained by aspiration vary with the bacterial load, the duration of mechanical ventilation, and prior use of antimicrobial therapy. Sensitivity ranges from 38 to 100%, and specificity ranges from 14 to 100%.[14,15] Antibody coating and the presence of elastin fibers are not diagnostically sensitive or specific for VAP.[16–18] A Gram's stain and culture of endotracheal secretions obtained by aspiration may be useful in diagnosing VAP (grade D recommendation). The presence of antibody coating or elastin fibers is an unreliable indicator and is not recommended for clinical diagnostic use (grade C recommendation).

Role of BAL

Bronchoscopic BAL has been used in the diagnosis of VAP since 1988, but bronchoscopic and bacteriologic methods have not been standardized. Only 2 of 23 published studies on this topic have investigated the quality of BAL specimens.[18,19]

The sensitivity of quantitative BAL fluid cultures ranges from 42 to 93%, with a mean of 73%. The variability reflects the characteristics of the study population, the prior administration of antibiotics (which reduces sensitivity), and the reference test used.[20,21]

For quantitative cultures, a finding of 10^3 to 10^5 cfu/mL is considered a positive result. Most studies cite 10^4cfu/mL as a positive result. Sensitivity varies inversely with the cutoff point. Similar problems exist in calculating specificity. When specificity could be accurately determined, it ranged from 45 to 100%, with a mean of 82%.[22,23,] The detection of intracellular organisms by BAL is highly specific (89 to 100%) and has a high positive predictive value, but is not highly sensitive (37 to 100%).[18, 24]

BAL is generally a safe procedure in patients with acute lung injury, some of whom have pneumonia. The major risk is the reduction of arterial oxygenation, as oxygenation may not be fully reestablished for several hours after injury.[25]

Role of PSB Sampling

PSB sampling has been used for almost 20 years, but the technique has not been standardized. Most studies do not report the quality of the samples, or state whether secretions were cleared out by using a separate bronchoscope before the test.[26]

One study has examined the reproducibility of PSB sampling.[27] In 25% of cases, a single bronchial-brush determination led to a false positive or a false negative.

Specimens taken from an affected lobe have a much higher concentration of organisms than those taken from an unaffected lobe.

Sensitivity for PSB tests ranges from 33 to 100%,[28,29] with a median of 67%. Specificity ranges from 50 to 100%, with a median of 95%. PSB sampling appears to be somewhat more specific than sensitive in diagnosing VAP. In all but one of the 18 studies reviewed, the diagnostic likelihood ratio in VAP was significantly > 1.

The complications of this procedure have not been determined. As noted above, bronchoscopy alone in a patient receiving ventilation may lead to transient alterations in oxygenation; it is not clear whether the PSB technique adds to the risk.

Role of Blinded Invasive Procedures

Because of the inconvenience, expense, need for operator expertise, and potential risks of diagnostic fiberoptic bronchoscopy, other diagnostic tests have been developed. These include three blinded, nonbronchoscopic techniques: blinded bronchial sampling (BBS), mini-BAL, and blinded sampling with PSB (BPSB).

In BBS, a catheter is blindly wedged into a distal bronchus, and secretions are aspirated without the instillation of fluid. In mini-BAL, a sterile, single-sheathed, 50-cm, plugging, telescoping catheter usually is used, and 20 to 150 mL of BAL fluid is instilled. Sometimes an unprotected catheter is used instead. In BPSB, a sterile brush, protected from contamination, is used. None of these techniques have been standardized.

The sensitivity of these tests is as follows: BBS, 74 to 97%; mini-BAL, 63 to 100%[28–30]; and BPSB, 58 to 86%.[28–31] Specificity of these tests is as follows: BBS, 74 to 100%; mini-BAL, 66 to 96%; and BPSB, 71 to 100%. These specificity ranges are similar to those reported for BAL and PSB. Unlike established invasive procedures, these newer techniques have not been validated in postmortem studies.

The risks from blinded techniques appear to be minimal and are no greater than those with fiberoptic bronchoscopy.

Invasive Procedures in Nonresolving Pneumonia

When antimicrobial therapy reduces the yield and accuracy of quantitative cultures of respiratory secretions, serial bronchoscopy is usually performed. The prognostic usefulness of repeated quantitative cultures in patients with VAP has not been fully studied. If serial studies show consistently high concentrations of potential pathogens, the mortality risk is high.[32] In two studies, the basing of frequent changes in antibiotic therapy on the results of bronchoscopic cultures had no impact on mortality rate when compared with empirical therapy or with therapy based on the results of single or multiple quantitative endotracheal cultures obtained by aspiration.[33,34] Thus, the data are insufficient to clarify the impact of repeated bronchoscopy on survival in patients who do not respond to initial therapy.

Conclusion

The following diagnostic algorithm may be helpful when VAP is suspected (Fig 1).

An associated pneumonia should be suspected in patients receiving mechanically ventilated if two or more of the following clinical features are present: temperature of $> 38°C$ or $< 36°C$; leukopenia or leukocytosis; purulent tracheal secretions; and decreased Pa_{O_2}. In the absence of such findings, no further investigations are required, and observation will suffice (grade B recommendation).

If two or more of these abnormalities are present, however, a chest radiograph should be evaluated. If the findings are normal, other causes of the abnormal clinical features should be investigated (grade C recommendation). If the radiograph shows alveolar infiltrates or an air bronchogram sign, or if the findings have worsened, the panel recommends one of two management options. The first option involves quantitative testing; and the second involves empirical treatment and nonquantitative (qualitative) testing.

In the first option, quantitative procedures include nonbronchoscopic techniques (quantitative endotracheal aspiration, BBS, mini-BAL, or BPSB) and bronchoscopic techniques (BAL, PSB, or protected BAL). Because these tests have similar sensitivities, specificities, positive predictive values, and likelihood ratios, the choice depends on local expertise, experience, availability, and cost factors (grade D recommendation). Treatment should be based on the results of diagnostic testing. Decisions about empirical therapy should be determined by the patient's clinical stability, the degree of clinical suspicion, and the results of preliminary tests.

In the second option, the selection of appropriate empirical therapy is based on risk factors, local epidemiology, and resistance patterns, and involves qualitative testing to identify possible pathogens. Some clinicians include quantitative testing. Therapy is adjusted according to culture results or clinical response.

These two options are offered (grade D recommendation) because of insufficient high-level evidence to indicate that quantitative testing produces better clinical outcomes than empirical treatment. While invasive tests may avoid the use of antibiotics for clinically insignificant organisms, no direct evidence or consensus indicates the superiority of one invasive test over another (grade B recommendation). In a recent study, the withholding of antibiotic therapy when invasive tests did not confirm a clinical suspicion of VAP was not associated with the recurrence of VAP or with increased mortality rates.[35] Factors to consider in choosing a test include sensitivity and specificity, ability to improve patient outcome, potential adverse effects, availability of the test, and cost. The panel did not determine whether the potential benefits of diagnostic testing outweigh the potential risks.

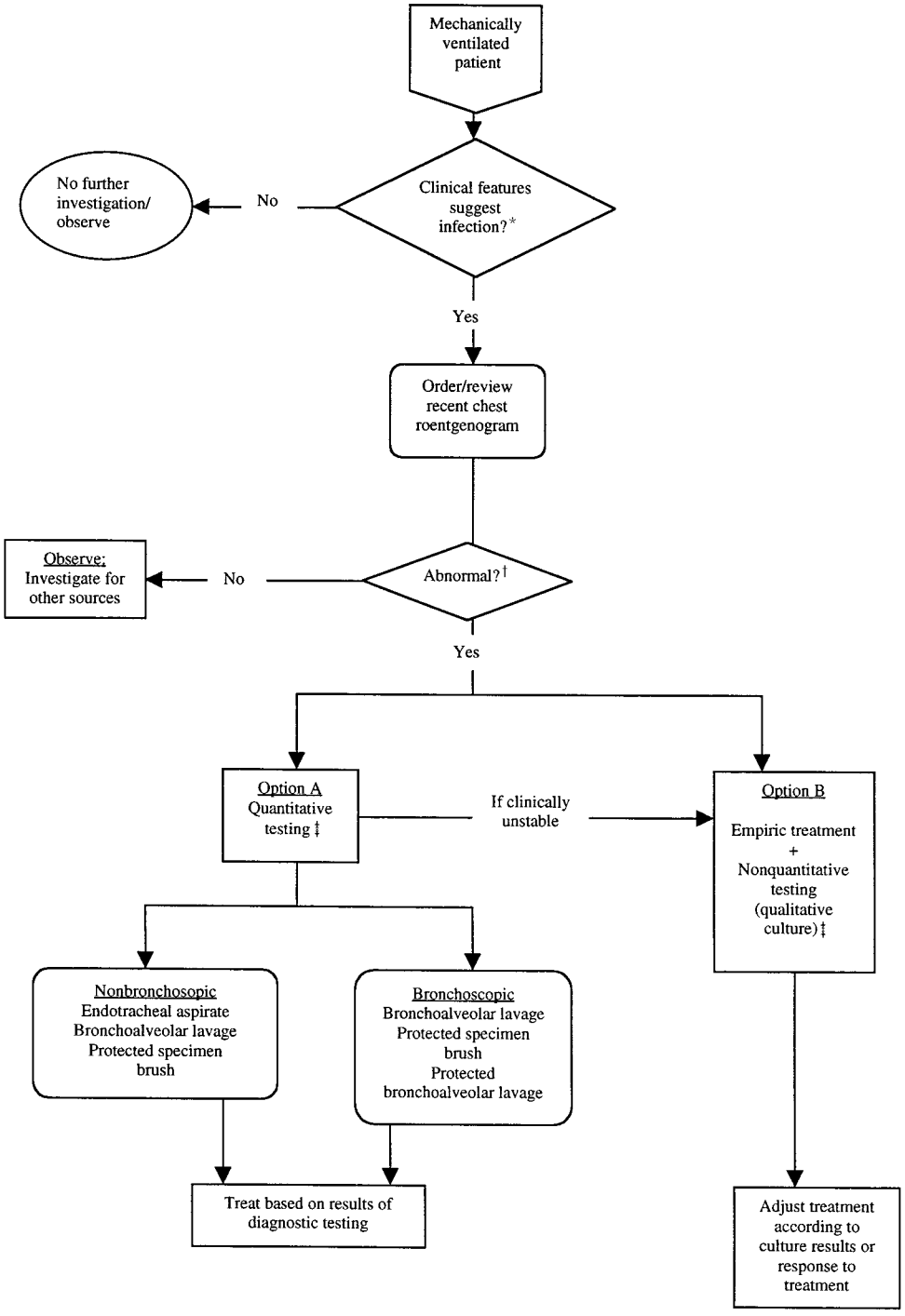

FIGURE 1. VAP diagnostic algorithm. * = Criteria consist of two or more of the following: temperature > 38°C or < 36°C, leukopenia/leukocytosis, purulent tracheal secretions, and decreased PaO_2. † = Criteria consist of radiographic evidence of alveolar infiltrates, air bronchograms, and new or worsened infiltrates. ‡ = There is no definitive scientific evidence or expert consensus that quantitative testing produces better clinical outcomes than empirical treatment. Scientific evidence of improved specificity, supplemented by expert opinion, supports the performance of invasive tests to avoid the use of antibiotics for clinically insignificant organisms, but there is no direct evidence or consensus regarding the superiority of one invasive test over another. Factors to consider in choosing an appropriate test include sensitivity and specificity, ability to improve patient outcome, potential adverse effects, test availability, and cost.

Substantial gaps exist in the scientific knowledge of all of these techniques. The best example is the lack of data on the specificity and reproducibility of findings from chest radiographs. Because many diagnostic techniques have not been standardized, reported data on sensitivity and specificity vary, and it is difficult to compare results between medical centers. Another problem is that the populations that have been studied have been very heterogeneous, and some studies have used only subsets of patients in order to make a specific point.

Many patients receive antimicrobial agents before testing is performed, making it difficult or impossible to interpret test results. Evidence suggests that after recent antibiotic treatment for suspected VAP, the diagnostic thresholds for numbers of organisms in the culture must be decreased to maintain accuracy.[36] In contrast, ongoing antibiotic therapy for a preexisting infectious disease does not affect the diagnostic accuracy of PSB or BAL. Future studies should define patient populations more carefully, particularly with respect to the onset of antimicrobial therapy. It is possible that the variability of invasive testing would diminish and the test characteristics would improve if this analysis were standardized. A "gold standard" should be defined, since autopsy studies and studies of lung tissue obtained by biopsy are obviously impractical. The only randomized, prospective clinical trial comparing invasive techniques and noninvasive quantitative techniques in patients with VAP found that invasive techniques led to more frequent changes in antibiotic therapy but that they did not change the mortality rate.[34]

We recommend formal outcome research with randomized, controlled trials to assess various diagnostic and management strategies. This approach would provide the opportunity to evaluate economic outcomes using cost-benefit, cost-effectiveness, and cost-utility analyses.