Are Quantitative Cultures Useful in the Diagnosis of Hospital-Acquired Pneumonia?*

Gerry San Pedro, MD

Noninvasive and invasive tests have been developed and studied for their utility in diagnosing and guiding the treatment of hospital-acquired pneumonia, a condition with an inherently high mortality. Early empiric antibiotic treatment has been shown to reduce mortality, so delaying this treatment until test results are available is not justifiable. Furthermore, tailoring therapy based on results of either noninvasive or invasive tests has not been clearly shown to affect morbidity and mortality. This may be related to quantitative limitations of these tests or possibly to a high false-negative rate in patients who receive early antibiotic treatment and may therefore have suppressed bacterial counts. Results of these tests, however, do influence treatment. It is therefore hoped that they may ultimately provide a rational basis for making therapeutic decisions. In the future, outcomes research should be a part of large-scale clinical trials, and noninvasive and invasive tests should be incorporated into the design in an attempt to provide a better understanding of the value of such tests.

(CHEST 2001; 119:385S–390S)

Key words: bacteriology; BAL; bronchoscopy; diagnosis; endotracheal aspiration; hospital-acquired pneumonia

Abbreviations: APACHE = acute physiology and chronic health evaluation; HAP = hospital-acquired pneumonia; PSB = protected specimen brushing; QEA = quantitative endotracheal aspiration

This article examines the utility of quantitative and qualitative (nonquantitative) cultures and of invasive and noninvasive techniques in the diagnosis of hospital-acquired pneumonia (HAP). I shall seek to address whether quantitative cultures are truly necessary and how important it is to identify a specific agent as a cause of the pneumonia. Ventilator-associated pneumonia as well as hospital-acquired infections, in general, are considered.

How good are we at making a diagnosis of HAP? Our clinical skills at making this diagnosis seem to be suboptimal at times. Consider the patient who is in the hospital and receiving mechanical ventilation and develops fever, leukocytosis, pulmonary infiltration on chest radiography, and purulent tracheobronchial secretions. In this clinical setting, we can certainly entertain a diagnosis of HAP. Andrews and colleagues¹ discussed this issue in patients with preexisting abnormal chest radiographic findings and symptomatology compatible with pneumonia. Their study¹ utilized necropsy material to validate the presence or absence of pneumonia. It was demonstrated, however, that 29% of these cases were misdiagnosed clinically.¹ Other conditions, such as “pulmonary fibroproliferation,” sinusitis, cholecystitis, and various noninfectious conditions, can also produce findings that might suggest the presence of pneumonia.² Similarly, the chest radiograph may be misleading at times.³ In the report by Andrews and colleagues,¹ 36% of patients had pneumonia at necropsy, even though their chest radiographs may not have changed. Work from our own group⁴ has also clearly shown that there are many other potentially lethal conditions that can create a picture resembling pneumonia. Access to pulmonary tissue for making a histologic diagnosis would clearly be a desirable objective. The histopathologic findings that characterize nosocomial pneumonia have been described in detail.⁵

Diagnosis of HAP

Clinical findings and chest radiography alone may not always suffice for making a definitive diagnosis of pneumonia. However, we can attempt to make a diagnosis by examining respiratory secretions. The number of organisms present in an infection, which may in turn be dependent on the virulence of the

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organism and the host’s response, is of prime importance. How many organisms must be detected to assume the presence of infection vs mere colonization? Johanson and colleagues have suggested that about $10^3$ cfu/g of tissue indicate the presence of bacteria present. Tissue is often not available, however, and counts may have to be obtained in secretions. In this case, about $10^5$ bacteria per milliliter of exudate may have similar import. Sources of sampling for making a diagnosis include blood and other body fluids as well as several techniques available for obtaining samples. These techniques include needle aspiration, endotracheal aspiration, and both blind and invasive procedures to obtain bronchial secretions (Table 1).

**Percutaneous Needle Aspiration**

How useful in general is percutaneous needle aspiration? As noted above, much depends on the bacterial counts in the area being aspirated. The sensitivity of the technique for patients who are not receiving mechanical ventilation is about 60%, with the figure somewhat lower (approximately 40%) for patients receiving mechanical ventilation. Thus, the procedure may prove to be less useful in the population of patients in which it is most needed. From the standpoint of predictive value, a positive test result is helpful, but a negative test result may not be helpful since about a third of patients with a negative test result may actually have the disease. The main objection to percutaneous needle aspiration is the high incidence of complications, including hemorrhage, hemoptysis, and pneumothorax. This is true even though the procedure itself may be fairly easy to carry out. The incidence of pneumothorax is about 20%, but may be up to 60% in patients receiving mechanical ventilation. About half of these patients will require a chest tube.

**Endotracheal Aspiration**

Results of endotracheal aspiration may be compared with those of other invasive and noninvasive techniques (Table 2), including open-lung biopsy, postmortem lung cultures, blood and pleural fluid analysis, and protected specimen brushing (PSB) and BAL. Sensitivity and specificity of routine endotracheal aspiration have a broad scatter in relation to these other measurements, with sensitivity ranging from 57 to 88%, but with specificity in a relatively low range, from 0 to 33%. Thus, nonquantitative endotracheal cultures may have limited utility. One of the chief values of endotracheal cultures is that they exclude certain types of infection when the organism is absent. For example, absence of Pseudomonas in an endotracheal aspirate makes it unlikely that this organism is the cause of an infection. Attempts have also been made to perform quantitative endotracheal aspiration (QEA). Jourdain and colleagues have attempted to establish a cutoff for assigning significance to colony counts in endotracheal aspirates by examining sensitivity, specificity, and overall accuracy (Table 3). They concluded that a level of $10^{3}$ to $10^6$ bacteria per milliliter of exudate was optimal for diagnostic purposes. Although counts higher than this figure improved specificity, there was an unacceptable decline in sensitivity.

**Noninvasive Techniques**

Can noninvasive techniques that can be conducted at the bedside be used to obtain bronchial samples? We can employ blind bronchial sampling, blind BAL fluid sampling, or blind performance of PSB. We know somewhat more about the sensitivity and specificity of these techniques. For blind bronchial sampling, the sensitivity is about 50%; for blind BAL, the sensitivity is about 73% with a specificity of 96%. The figures are also good for blind PSB, at 66% and 91%, respectively, and with a high diagnostic yield (66%) and good concordance with bronchofibroscopic PSB (85%). Then why not use these techniques routinely? Unfortunately, they are relatively new, and experience with their use is limited. These procedures, however, may have considerable utility in the future since they are easy to perform; in some centers, the specimens are even obtained by respiratory technicians.

**Table 1—Diagnostic Techniques**

<table>
<thead>
<tr>
<th>Blood, Pleural Fluid Analysis, and Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonbronchoscopic evaluations</td>
</tr>
<tr>
<td>• Percutaneous needle aspiration</td>
</tr>
<tr>
<td>• Endotracheal aspiration</td>
</tr>
<tr>
<td>• Blind bronchial sampling</td>
</tr>
<tr>
<td>Bronchoscopic techniques</td>
</tr>
<tr>
<td>• PSB</td>
</tr>
<tr>
<td>• BAL</td>
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<tr>
<td>Tissue diagnosis</td>
</tr>
</tbody>
</table>

**PSB**

PSB is a standard invasive method for diagnosing HAP. The brush is small and obtains a sample in the range of 0.001 mL. After the sample is obtained, it is diluted in about 1 mL of transport medium, an approximately 1,000-fold dilution. Consequently,
the standards for colony counts must be appropriately adjusted, and counts of $10^3 \text{ cfu/mL}$ of transport medium would be considered diagnostic. Overall, this technique has about 82% sensitivity and 89% specificity.\textsuperscript{19} However, the repeatability of this procedure in the same patient is not perfect, and quantitative discordance may be considerable.\textsuperscript{20,21} Another problem with this technique and others already discussed is that colony counts fall in patients previously treated with antibiotics.\textsuperscript{22,23} The incidence of such treatment is high, and most patients entering the intensive-care environment are already being treated with one or more antibiotics. However, PSB could play a role in identifying patients with recurrent or resistant infection. In a study by Montravers and colleagues,\textsuperscript{24} 76 patients with positive specimen findings who were treated with antibiotics were restudied 3 days later. Of 173 organisms originally identified, 11 organisms (6%) were shown to be still present, 3 of which were in significant numbers. However, 32 new organisms were also identified, 9 of which were in significant numbers. Resistance was observed in 26 of these 32 organisms (81%). Thus, a total of 12 old or new organisms were noted to be present in significant numbers, and resistance did appear to represent a problem. Of the 9 patients with significant numbers of new organisms, only 44% subsequently responded to treatment; however, in the other 67 patients, the response was 93%, a highly significant difference. Thus, perhaps there may be a role for repeating PSB in the setting of poorly responding patients. However, further studies need to document that repeating PSB in these patients results in changes in management that lead to improved outcomes.

### BAL

How effective is BAL as a diagnostic tool? This technique samples a large number (approximately $10^6$) of alveoli and can recover a larger number of organisms. The threshold is in the range of $10^4$ organisms per milliliter of lavage fluid, which is equivalent to $10^6$ organisms per milliliter of alveolar fluid from the periphery.\textsuperscript{25} Sensitivity and specificity are high, in the range of 72 to 100% for sensitivity and 69 to 100% for specificity.\textsuperscript{13} Qualitatively, the same organisms are recovered repeatedly in the range of 95%, but as in the case with PSB, there is considerable quantitative discordance.\textsuperscript{26} Sensitivity and specificity of BAL have also been compared with those of PSB (Table 4), and the results are comparable. The question also arises about the comparability of results of PSB vs BAL in patients already receiving antibiotics. As can be seen in Table 5, the range was broad, but the two studies\textsuperscript{27,28} in patients receiving antibiotics showed values similar to the two studies\textsuperscript{29,30} in patients not receiving antibiotics. In general, however, the yield of organisms is believed to be lower in patients receiving antibiotics than in those not receiving antibiotics.

### OUTCOMES RESEARCH

Treatment outcome is an important consideration in determining whether invasive or noninvasive

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### Table 2—Value of Endotracheal Aspirates With Routine Cultures*

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill et al\textsuperscript{24}</td>
<td>48</td>
<td>82</td>
<td></td>
<td>Open-lung biopsy, blood, pleural fluid</td>
</tr>
<tr>
<td>Berger and Arango\textsuperscript{25}</td>
<td>19</td>
<td>74</td>
<td></td>
<td>Postmortem lung</td>
</tr>
<tr>
<td>Villers et al\textsuperscript{26}</td>
<td>17</td>
<td>88</td>
<td></td>
<td>Blood, pleural fluid, open-lung biopsy, serology</td>
</tr>
<tr>
<td>Torres et al\textsuperscript{27}</td>
<td>41</td>
<td>57</td>
<td></td>
<td>PSB, BAL</td>
</tr>
<tr>
<td>Lambert et al\textsuperscript{28}</td>
<td>22</td>
<td>88</td>
<td></td>
<td>PSB</td>
</tr>
</tbody>
</table>

*Adapted from Meduri.\textsuperscript{13}

### Table 3—Value of Endotracheal Aspirates With Quantitative Cultures*

<table>
<thead>
<tr>
<th>Threshold, cfu/mL</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Overall Accuracy, %</th>
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</thead>
<tbody>
<tr>
<td>$\geq 10^3$</td>
<td>86</td>
<td>52</td>
<td>61</td>
</tr>
<tr>
<td>$\geq 10^4$</td>
<td>71</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>$\geq 10^5$</td>
<td>71</td>
<td>88</td>
<td>75</td>
</tr>
<tr>
<td>$\geq 10^6$</td>
<td>71</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>$\geq 10^7$</td>
<td>43</td>
<td>95</td>
<td>82</td>
</tr>
</tbody>
</table>

*Adapted from Jourdain et al.\textsuperscript{14}

### Table 4—Comparison of PSB and BAL*

<table>
<thead>
<tr>
<th>Source</th>
<th>PSB Sensitivity, %</th>
<th>PSB Specificity, %</th>
<th>BAL Sensitivity, %</th>
<th>BAL Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chastre et al\textsuperscript{28}</td>
<td>100</td>
<td>60</td>
<td>67</td>
<td>96</td>
</tr>
<tr>
<td>Vallés et al\textsuperscript{29}</td>
<td>82</td>
<td>89</td>
<td>91</td>
<td>78</td>
</tr>
<tr>
<td>Marquette et al\textsuperscript{25}</td>
<td>58</td>
<td>89</td>
<td>47</td>
<td>100</td>
</tr>
</tbody>
</table>

*Adapted from Meduri.\textsuperscript{15}
methods are best for obtaining specimens for bacterial culture. Does making a specific etiologic diagnosis make a difference in outcome? Do results of culture techniques influence antibiotic choices and, ultimately, outcome? Does the use of a quantitative technique result in improved outcomes compared with nonquantitative techniques?31

Many efforts have been made to compare the bacteriology of quantitative vs nonquantitative techniques; some research is beginning to address patient outcomes as well. Luna and colleagues32 from Argentina investigated outcomes in 132 patients with ventilator-associated pneumonia who underwent BAL within 24 h of clinical diagnosis. Of this number, 107 patients (81%) were previously receiving antibiotics. Using the criterion of \(10^4\) cfu/mL as a cutoff, 65 of the 132 patients (49%) had positive findings; of this number, 46 patients (71%) died. However, mortality did not differ significantly in patients who either had or had not previously received antibiotics, in those with positive vs negative findings by BAL, or in those whose antibiotic regimen was changed after the lavage procedure. A significantly lower mortality was found in patients who were deemed to have received adequate vs inadequate therapy before their procedure (38% vs 91%). In patients receiving no antibiotic therapy before the procedure, mortality was 60%. It is also noteworthy that half of the mortality in this study in patients with positive BAL findings was experienced within 48 h of the procedure, before culture results were available, so that this information could not always be used to direct therapy. In this study, early initiation of adequate therapy for ventilator-associated pneumonia reduced mortality, although overall mortality was high and not influenced by culture results or by switching antibiotics based on these results. Also, if therapy is delayed until bronchoscopy is performed or while awaiting BAL results, mortality is higher.32

In a second study from Spain, Sanchez-Nieto and colleagues33 studied 51 patients who were randomly classified into two groups. One group received extensive investigation, including QEA, BAL, and PSB; the other group received only QEA. Of the 24 patients in the first group, 16 patients (67%) had positive findings by both QEA and BAL and 14 patients by PSB (58%), although there were substantial within-patient inconsistencies. In this group, 10 of the patients (42%) had their regimens modified as the result of testing, and overall mortality was 11 of 24 patients (46%). In the second group of 27 patients, QEA findings were positive in 20 patients (74%), 4 of 27 patients had their regimens modified, and the mortality was 7 of 27 patients (26%). Although more patients in the extensively tested group had their regimens modified after testing, the difference in mortality between the two groups was not significant. A potentially confounding factor in this study, however, was that a much higher percentage of the first group had culture findings that were positive for Pseudomonas, an organism known to be associated with a high mortality. Despite the more frequent change in antibiotic regimen in the former group, the authors concluded that there was no substantial difference in mortality between patients undergoing intensive, compared with less intensive, investigation, although the numbers in the study were too small to warrant drawing strong conclusions.

Despite the fact that neither of these two studies provides strong evidence favoring an aggressive diagnostic approach in HAP, they are indicative of the type of investigations needed to improve our understanding and treatment of this condition. The database regarding sensitivity and specificity of invasive and noninvasive tests is now well characterized. We should begin to direct our energies toward determining the outcomes of applying these therapies.

Appendix

Dr. George Eliopoulos: You have convinced me of the difficulty of using this kind of information to make clinical decisions. However, let me ask this question: If you were to design a study to show superiority of one regimen over another for the treatment of pneumonia, what would you demand of

<table>
<thead>
<tr>
<th>Source</th>
<th>No. With Pneumonia/Total</th>
<th>Undergoing Antibiotic Therapy, %</th>
<th>Qualitative Concordance, %</th>
<th>Quantitative Concordance, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chastre et al29</td>
<td>5/21</td>
<td>0</td>
<td>50</td>
<td>38</td>
<td>Blood cultures, clinical response, histology</td>
</tr>
<tr>
<td>Torres et al27</td>
<td>25/34</td>
<td>100</td>
<td>78</td>
<td>57</td>
<td>Blood cultures, clinical response, histology</td>
</tr>
<tr>
<td>Violán et al33</td>
<td>25/45</td>
<td>52</td>
<td>57</td>
<td>54</td>
<td>Blood cultures, clinical response, histology</td>
</tr>
<tr>
<td>Jiménez et al30</td>
<td>28/40</td>
<td>0</td>
<td>97</td>
<td>93</td>
<td>Blood cultures, clinical response, histology</td>
</tr>
</tbody>
</table>

*Adapted from Meduri.13
the investigators for making as ironclad as possible a
definition of nosocomial pneumonia or ventilator-
associated pneumonia?

**Dr. Gerry San Pedro:** You can define nosocomial pneumonia in various ways, but what most investigators are seeking is to know that they are studying comparable groups of patients in the different arms of their studies.

**Dr. Eliopoulos:** Not entirely true. For example, if you have 1,000 patients in both arms, and 999 of them have viral pneumonia, the groups are comparable. But what I want to know is how many patients have Pseudomonas infection and how many have pneumococcal infection, etc. These definitions, from my point of view, are crucial.

**Dr. David Bowton:** The key question is how to deal with the disquieting information concerning histology, BAL, PSB, correlates, and reclassification. There is no correlation between any of our diagnostic studies whether you use pathology or quantitative culture, and if you use different criteria for histologic analysis, you reclassify 30% of the patients. Coming up with a clinically relevant diagnostic schema at the moment seems almost impossible, and we must accept that we often simply cannot make the diagnosis. One approach is to simply pick criteria that are reproducible, obtain whatever microbiological information is available, accept that the method might be flawed, and then consistently apply it to all patients. There must also be a large enough patient population to achieve adequate power for subgroup analysis to detect outcome differences. This will, to some extent, avoid the question of whether the microbiology is sufficiently accurate. The microbiological classification can initially be considered a matter that is primarily of academic interest but may, in addition, provide some scientific underpinning if patients have comparable microbiology. The key feature is a large sample size. Patients can also be matched in other ways, such as having comparable APACHE (acute physiology and chronic health evaluation) scores. However, the mortality level in a large group is the key.

**Dr. Eliopoulos:** What criteria would you use?

**Dr. San Pedro:** I would employ a mix. There would have to be both clinical criteria and invasive techniques. Personally, I would use BAL.

**Dr. David Weber:** One must be careful about taking risk profiles that have been developed in one group of patients and assuming they will work in another group. We evaluated the risk factors for ventilator-associated pneumonia in elderly patients admitted to either a medical ICU or surgical ICU. APACHE II scores, which were developed and validated in surgical patients, were predictive for the development of pneumonia in elderly persons in our surgical ICU but were not predictive for elderly persons in our medical ICU. Another point regarding resistance, which will have a major impact on the development of resistance, is knowing which antibiotic a patient might have been taking before pneumonia developed.

**Dr. Louis Rice:** I have a question about the adjustments that were made in the antibiotic regimen. Was the therapy narrowed to target specific organisms or was it expanded to deal with resistant organisms?

**Dr. San Pedro:** That was not dealt with in the article by Sanchez-Nieto et al.33

**Dr. Bowton:** In a study40,41 that was similar to the study by Luna et al,32 when antibiotic therapy was discontinued based on BAL, there was a low mortality, only 14%.

**Dr. San Pedro:** The goal there was to narrow down antibiotic coverage, but in most hospitals, I suspect the practice would be to expand coverage by adding an antibiotic.

**Dr. Rice:** None of these would be techniques that would prevent physicians from narrowing down therapy.

**Dr. Steve Nelson:** In a patient doing poorly in the ICU receiving broad-spectrum therapy, I will often send an endotracheal aspirate, and if it returns in 2 to 3 days without showing a suspected pathogen, I will often trim back my therapy. This has not been studied very carefully, however.

**Dr. Bowton:** That should be a part of the study design. A study should have a standardized initial empiric approach and then perhaps be modified subsequently based on findings from testing such as QEA. Although some have argued that this may not lead to a difference in outcome, if you employ an empiric approach and narrow it back, there may be new information.

**REFERENCES**

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