The Argument against Using Quantitative Cultures in Clinical Trials and for the Management of Ventilator-Associated Pneumonia

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Quantitative cultures have been proposed as the most accurate way to both establish the presence of ventilator-associated pneumonia (VAP) and define the etiologic pathogen. Although the clinical diagnosis of VAP has been much maligned, it may be very accurate, particularly if it is objectively defined by calculating the Clinical Pulmonary Infection Score and if the score incorporates a Gram stain of a lower respiratory tract sample. After the clinical diagnosis of VAP is made, a culture is needed to identify the etiologic pathogen, but this culture does not need to be quantitative or bronchoscopic. Quantitative culture-based diagnosis may not be more accurate than clinical diagnosis, and quantitative cultures have a number of methodologic limitations that can cause both false-positive and false-negative results. Finally, a number of studies have suggested that clinical management without quantitative cultures may be accurate and that outcomes, such as mortality and change in antibiotics to a focused regimen, are not improved by the use of quantitative cultures. In clinical trials, management using nonquantitative cultures of a tracheal aspirate specimen may be preferable. Reliance on quantitative cultures can complicate enrollment and will ensure that only a subset of patients with VAP is studied because of the relatively high false-negative rate of quantitative culture results, particularly among patients treated with antibiotics before samples are obtained.

In the conduct of clinical trials of therapy for ventilator-associated pneumonia (VAP), it is vitally important to enroll only patients who have the disease and to identify, whenever possible, the etiologic pathogen. The clinical diagnosis of VAP is very sensitive but not often specific, and many patients with the clinical findings of VAP may have a noninfectious etiology for their new lung infiltrate and associated findings. Older studies have reported that as many as two-thirds of all patients who meet the clinical diagnosis of VAP may not meet microbiologic criteria for infection [1, 2]. The 2005 guidelines of the American Thoracic Society and the Infectious Diseases Society of America described this controversy, tried to combine features of both approaches to help guide VAP management, and suggested ways that either approach could be used [3].

Because of the well-known mortality associated with VAP among patients who receive delayed and inappropriate empirical antibiotic therapy, in clinical practice, there is often pressure to start antibiotics before the diagnosis is unequivocally confirmed. In the conduct of clinical trials, this issue must be considered, with the understanding that the pressure to treat potential VAP may mean that some patients will be treated with antibiotics when they are not needed and that many patients with VAP can have other simultaneous infections (eg, sinusitis and central venous catheter infection); if all episodes of fever and lung infiltrates are attributed to VAP, these infections may be overlooked [3]. For these reasons, some investigators have proposed that, when VAP is suspected, the patient should have a lower respiratory tract secretion sample obtained (by bronchoscopic protected brush, bronchoalveolar lavage, blind brush or lavage, or endotracheal aspiration) and cultured quantitatively; the results are then used to de-
fine both the presence of pneumonia and the etiologic pathogen [1]. However, quantitative cultures also have limitations, and it is uncertain whether decisions based on these data can lead to better enrollment in clinical trials or whether obtaining a quantitative culture could lead to a delay in the initiation of therapy. In addition, to the extent that quantitative methods lead to false-negative results, a finding that is common for patients receiving antibiotic therapy before secretion samples are obtained, the use of quantitative cultures for enrollment will ensure that only a subset of patients with VAP will be studied.

**CLINICAL DIAGNOSIS OF VAP**

The clinical diagnosis of VAP is made when the patient has a new or progressive lung infiltrate plus at least 2 of the following 3 criteria: fever, purulent sputum, or leukocytosis. As discussed, this definition is sensitive for the presence of pneumonia but not specific. However, most clinicians use multiple criteria to diagnose pneumonia, often emphasizing certain findings over others. A numerical score for the clinical definition of VAP, the Clinical Pulmonary Infection Score (CPIS), has been developed using a weighting of multiple criteria (Table 1) [4]. In the original description of the CPIS, points were assigned on the basis of the magnitude of abnormality in 6 clinical assessments, each worth 0–2 points: fever, leukocyte count, quantity and purulence of tracheal secretions, oxygenation, type of radiographic abnormality, and results of sputum culture and Gram stain. When applied prospectively, the last criterion cannot always be used, and if omitted, the score range is 0–10, instead of 0–12. Recently, several modifications of the CPIS have been proposed and may be quite accurate [5–10]. When first reported, the correlation between the CPIS and the bacterial infection was 0.8, showing that clinical diagnosis can be as accurate as a microbiologic approach [4]. In addition, if a CPIS >6 was used to define pneumonia, 93% of the BAL fluid samples from such patients were diagnostic of pneumonia by microbiologic criteria. In addition, if the CPIS was ≤6, no patient satisfied the microbiologic definition of pneumonia. Thus, use of a CPIS >6 as the clinical definition of pneumonia, had a sensitivity of 93% and a specificity and positive predictive value of 100%.

Other studies have corroborated the value of the CPIS to diagnose VAP (Table 2). A study based on postmortem lung biopsy found that the CPIS had a sensitivity of 77% and a specificity of 42% [11], whereas another study revealed a higher diagnostic accuracy, with a sensitivity of 77% and a specificity of 85% [12]. Although many physicians do not routinely calculate the CPIS, the aggregate score is very similar to a clinician using all available data to decide how strongly the diagnosis of pneumonia is suspected. The aforementioned data suggest that the clinical diagnosis of VAP may not be inaccurate.

Not all recent studies have corroborated such a high accuracy for the CPIS, and its value may be more limited in trauma patients. Most recent studies have used a modified clinical scoring system, because the method of Pugin et al [4] could not be routinely applied owing to the unavailability of tracheal aspirate culture at the time of initial clinical evaluation, the intensive care unit nurses not recording sputum volume, or to the laboratory not measuring band forms of white blood cells. In addition, some studies calculated the CPIS retrospectively, which may be less accurate than when the data are collected prospectively. The reproducibility of the score has also been questioned. In a study, 2 observers calculated the score, but some of the calculations were done retrospectively [9]. The investigators found that interobserver variability was large (κ score for level of agreement, 0.16) and that variability was often the result of ambiguities in the scoring system or missing data. It is difficult to understand such variability, because most of the data points are objective, and the one subjective variable (quantity of secretions) was omitted from the analysis.

The accuracy of the CPIS is not high without microbiologic data but can be improved if a reliable lower respiratory tract sample is obtained and studied carefully using Gram staining. In a study involving 99 patients, 69 of whom had VAP diagnosed by quantitative BAL criteria, the investigators used a modified CPIS that did not include any microbiologic data; although the sensitivity was 83%, the specificity was only 17% [9]. Flanagan et al [8] compared the CPIS with nonbronchoscopic lung lavage data in a population of 145 patients; with use of a score of 7 to diagnose pneumonia, the sensitivity was 85%, the specificity was 91%, the positive predictive value was 61%, and the negative predictive value was 96%. Why the CPIS performed so well in that study is unclear, because the modified

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**Table 1. Components of the Clinical Pulmonary Infection Score**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score (0–2)</th>
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<tbody>
<tr>
<td>Time of diagnosis</td>
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<tr>
<td>Temperature: &lt;38 or &gt;38.4°C</td>
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<tr>
<td>Oxygenation: PaO₂/FiO₂ &lt; 240</td>
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<tr>
<td>Leukocytosis: &lt;4000 or &gt;11,000 leukocytes/mm³ (extra points for &gt;500 band forms)</td>
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<tr>
<td>Chest radiograph: infiltrate (yes or no), diffuse, patchy or localized infiltrate</td>
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<tr>
<td>Tracheal secretions: present and purulent or not</td>
<td></td>
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<tr>
<td>Day 3</td>
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<tr>
<td>Radiographic progression</td>
<td></td>
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<tr>
<td>Lower respiratory tract culture results: negative, positive, and magnitude of growth</td>
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</table>

**NOTE.** The extent of abnormality is used to derive a point value for each category (0–2). PaO₂/FiO₂, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.
Table 2. Comparison of the Accuracy of the Clinical Pulmonary Infection Score (CPIS) in Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of CPIS criteria used</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pugin et al [6]</td>
<td>6</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Fabregas et al [11]</td>
<td>6</td>
<td>77</td>
<td>42</td>
<td>...</td>
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<tr>
<td>Papazian et al [12]</td>
<td>6</td>
<td>77</td>
<td>85</td>
<td>...</td>
</tr>
<tr>
<td>Schurink et al [9]</td>
<td>5</td>
<td>83</td>
<td>17</td>
<td>...</td>
</tr>
<tr>
<td>Flanagan et al [8]</td>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>85</td>
<td>91</td>
<td>61</td>
</tr>
<tr>
<td>Luyt et al [10]</td>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

<sup>a</sup> With use of a score ≥7 as positive.
<sup>b</sup> Including microbiologic data on day 3.

In contrast, Fartoukh et al [6] found that the modified CPIS correlated poorly with a diagnosis of VAP based on culture of BAL fluid samples unless Gram staining of respiratory secretions was included in the score. In that study, 40 of 79 patients had pneumonia confirmed by culture of BAL fluid samples, and the mean CPIS without use of bacteriologic information for those with confirmed VAP was 6.5, compared with 5.9 for those without VAP (P = .07). However, when Gram staining of a BAL fluid sample was added to the mean CPIS, the score for confirmed VAP was 8.2, compared with 6.4 for patients without VAP (P < .001). A group of French investigators confirmed the value of microbiologic information to improve the accuracy of the CPIS. When the score was calculated without microbiologic data on day 1 in 201 patients who had a bronchoscopic evaluation at the time of pneumonia suspicion, the result was similar in patients with and without pneumonia (6.4 vs 6.2) [10]. However, the values were significantly different on day 3 when microbiologic data were added (8.7 vs 7.0; P < .001), and these findings had a sensitivity of 89% and a negative predictive value of 84%. It remains to be determined whether a similar degree of accuracy could be obtained using Gram staining of a tracheal aspirate specimen, thus allowing an accurate diagnosis without either quantitative cultures or invasive methods for obtaining samples.

In addition to its value in the diagnosis of VAP, the CPIS may help the clinician to evaluate the clinical response to therapy and determine the appropriate duration of therapy. In a study, investigators found that the duration of therapy was directly correlated (P < .001) with the CPIS at the time of pneumonia diagnosis [13]. In a study by Luna et al [7], the CPIS, when calculated prospectively and used serially throughout the course of VAP management, decreased in patients who survived but not in those who did not, thus reflecting the clinical evolution of pneumonia. Thus, initial values of the CPIS may help guide the duration of therapy, and serial measurements of the CPIS could be used to define the need for a modification of antibiotics during the course of therapy.

**QUANTITATIVE DIAGNOSIS OF VAP VERSUS CLINICAL DIAGNOSIS COMBINED WITH A TRACHEAL ASPIRATE CULTURE**

Determination of the accuracy of any diagnostic approach is difficult without the establishment of a clearly accepted gold standard to define the presence of pneumonia. For this purpose, some investigators have used postmortem lung biopsy and culture. Marquette et al [14] performed prospective quantitative cultures for 28 patients who subsequently died and had the diagnosis of VAP determined histologically at autopsy. The authors correlated results of testing of protected specimen brush (PSB), BAL, and quantitative endotracheal aspirate samples obtained within 3 days before death to autopsy findings from both central and peripheral lung samples and reported that no quantitative method had a sensitivity >60%, whereas specificity was 75%–100%. Similarly, Kirtland et al [15] performed autopsy studies with peripheral lung biopsy samples from 39 patients and found that no quantitative diagnostic method had a high positive predictive value for VAP but that tracheal aspirate samples were 87% sensitive for defining the organisms present in lung tissue. In addition, the finding of a sterile BAL fluid specimen had >90% positive predictive value for a sterile lung culture. Thus, a sterile BAL fluid sample can rule out pneumonia, whereas a positive tracheal aspirate culture result can identify the likely etiologic pathogen.

Other studies have confirmed the value of tracheal aspirate samples to identify the etiologic pathogen in patients with VAP [16–18]. In general, tracheal aspirate samples, studied qualitatively, will rarely fail to grow an organism that can be found in lung tissue or using bronchoscopy. However, the use of quantitative tracheal aspirate samples may improve the specificity of tracheal aspirate culture by defining the organisms that are likely to be the cause of pneumonia. In several studies, the...
sensitivity of quantitative tracheal aspirate samples, with use of a cutoff of $1 \times 10^3$ organisms/mL, has been >80% for identifying an etiologic pathogen—results that were often comparable to bronchoscopic findings in the same patients [19–21]. In a study of VAP in 60 surgical patients, quantitative cultures of both tracheal aspirate specimens ($1 \times 10^3$ colony-forming units [cfu]/mL) and BAL fluid specimens ($1 \times 10^4$ cfu/mL) were comparably sensitive for identifying the etiologic agents, and both were more sensitive than PSB ($1 \times 10^4$ cfu/mL) [19]. In another study involving 15 surgical patients, tracheal aspirate specimens had a sensitivity of 82% and a specificity of 79% with use of a threshold of $1 \times 10^4$ cfu/mL; however, frequently, culture of tracheal aspirate samples recovered organisms at threshold concentrations when culture of PSB samples did not [21]. In nonresponding patients with VAP who were receiving antibiotic therapy for at least 72 h, the result of culture of a tracheal aspirate sample was positive for several patients but the result of bronchoscopic examination was not, and the authors suggested that some of the bronchoscopic findings may have been falsely negative [20]. Although studies have shown a high sensitivity of quantitative tracheal aspirate samples, the specificity was as low as <50% at a threshold of $1 \times 10^3$ cfu/mL but increased at the expense of sensitivity if a threshold of $1 \times 10^4$ cfu/mL was used.

Thus, if clinical criteria, such as those in the CPIS, are used in clinical trials to define the presence of pneumonia and when to start therapy, microbiologic data can be obtained from examination of tracheal aspirate specimens. These samples do not need to be cultured quantitatively if the goal is to achieve maximum sensitivity, but quantitation may improve their specificity, depending on the threshold selected. Tracheal aspirate samples are certainly sufficient for defining the etiologic pathogen, and invasive bronchoscopic samples are not necessary. Although it is likely that not all organisms present on a tracheal aspirate culture are necessarily etiologic pathogens because some may represent colonizing organisms, it is also unlikely that an organism causing pneumonia will be absent from a tracheal aspirate culture. Therefore, tracheal aspirate samples can be used in a clinical trial to guide deescalation therapy, ruling out the presence of multidrug-resistant pathogens if the cultures do not show such organisms.

### METHODOLOGIC LIMITATIONS OF QUANTITATIVE CULTURES

The value of quantitative cultures in clinical trials would be negated if there was a high rate of false-positive or false-negative findings (Table 3). False-positive results could mean that patients without VAP were erroneously enrolled in a clinical trial, which could be harmful in evaluating the true efficacy of a new agent. False-positive results have been reported for patients receiving prolonged mechanical ventilation, who are often colonized at high bacterial concentrations. In a study involving 14 patients receiving long-term mechanical ventilation who were not suspected of having pneumonia, 29 of the 32 lobes from which BAL sample fluid samples were obtained and tested had an organism concentration of $>1 \times 10^4$ colony-forming units/mL [22].

In a clinical trial, a false-negative quantitative culture result could mean that some patients with VAP, who should be studied, will not qualify for inclusion. This is certainly possible, because many patients with suspected VAP are receiving antibiotic therapy, which can cause false-negative results. Although this is a common concern, it may be less of a consideration if the patient has been receiving the same therapy for at least 72 h before diagnostic samples are obtained [23]. In this context, quantitative culture results may be positive and may show a drug-resistant organism, although it seems likely that the same data could be obtained from a nonquantitative endotracheal aspirate culture. If, however, the patient has had an antibiotic change within 24 h before having samples obtained for quantitative analysis, the sensitivity of invasive methods may be as low as 40%, making these methods unreliable, whereas a nonquantitative sample might still identify the etiologic pathogen [23].

In addition to antibiotics, there are other factors that could cause a quantitative sample result to be falsely negative. For example, quantitative methods are based on the idea that there is a bacteriologic threshold, or a bacterial concentration below which infection is absent. However, this concept may be biologically implausible because infection is on a microbiologic continuum; thus, a sample taken from an area of early infection may have organisms present below the threshold, whereas a sample taken from a more advanced area of infection may have more organisms present. Several studies have suggested that VAP is on a histologic and bacteriologic continuum and that low pathogen counts may not necessarily mean no pneumonia.

**Table 3. Potential Limitations of Quantitative Culture Methods**

<table>
<thead>
<tr>
<th>Limitation</th>
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<tr>
<td>False-positive results: if prolonged mechanical ventilation</td>
<td></td>
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<tr>
<td>False-negative results: if patient is receiving antibiotic therapy that was recently started before samples were obtained</td>
<td></td>
</tr>
<tr>
<td>Obtain sample from nonpneumonic area: pneumonia is patchy and in various stages of evolution</td>
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<tr>
<td>The idea of a diagnostic threshold may not be accurate</td>
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<tr>
<td>Results may not be reproducible</td>
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<tr>
<td>Qualitative evaluation of tracheal aspirate specimens is more sensitive to identify the pathogens present than are quantitative methods</td>
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<tr>
<td>No evidence that management guided by these methods can improve patient outcomes</td>
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but rather, early (and potentially treatable) pneumonia [24, 25]. In an animal model of VAP in piglets, Wermert et al [25] found that there was no exact bacteriologic threshold to define the presence of histologic pneumonia. In addition, in that study, the histologic lesions of pneumonia were unevenly distributed throughout the lung. Thus, obtaining a sample from some areas could lead to negative findings and noninclusion of the patient in a clinical trial, whereas obtaining a sample from another area could allow inclusion of the same patient. In clinical practice, VAP may be present in patients who have quantitative results at subthreshold concentrations. In a study involving 246 trauma or surgical patients who had analysis of BAL fluid samples performed, nearly 75% of all samples had bacteria at subthreshold concentrations [26]. However, 11% of the patients with BAL fluid findings below the threshold concentration had bacteremia, compared with 16% who had bacteremia when BAL fluid findings were above threshold concentrations.

One other foundation to the validity of using quantitative methods to guide enrollment in clinical trials is the reproducibility of the process used to obtain samples. If either BAL or PSB are not inherently reproducible, the methods may not be useful for defining the presence of pneumonia. Either because of sample obtainment or technical issues (such as laboratory error), studies have shown limited reproducibility of quantitative methods. When multiple repeat samples were taken from the same patient at the same time with use of either PSB or BAL, the results varied between positive and negative [27, 28]. In a study, investigators placed a PSB in the same site 5 times in each of 22 patients, and in 59% of the patients, the sample findings showed >1 log difference; in 3 of the 22 patients, the results were on opposite sides of the diagnostic threshold [27]. Thus, in these patients, depending on which of the 5 samples was examined, the patient could either be included or excluded from enrollment in a VAP study. Similarly, in a study involving 44 patients who had 2 BAL samples taken from the same site within 30 min, 2 patients had mixed results of testing of the samples, but only 5 of 16 patients with positive results had the same logarithmic concentration of bacteria in both samples [28].

The lack of reproducibility of quantitative results may be an inherent methodologic limitation of bronchoscopy, or as suggested by the histologic data, samples may have been taken from areas in different stages of pneumonia evolution. Variability can also occur from operator to operator and from center to center. This could explain why there is such a wide range of reported sensitivities and specificities of invasive methods. For example, the sensitivity of PSB has varied from 38% to 100%, and some centers that have had poor results with PSB have had excellent results with BAL and vice versa [29–31].

**Efficacy and outcomes of managing suspected VAP without using quantitative cultures**

Several studies have shown that it is possible to use a clinical approach to successfully treat patients with suspected VAP, and the body of available data does not show improved outcomes in patients for whom quantitative cultures are performed [32]. Singh et al [5] evaluated patients with suspected VAP with use of a modified CPIS that included 5 criteria to assess the likelihood of pneumonia. If the score was >6 on a scale with a maximum of 10, patients received a diagnosis of pneumonia and were treated for 10–21 days. However, patients with a score =6 were randomized to receive standard care or 3 days of ciprofloxacin (400 mg every 8 h). The CPIS was repeated on day 3, adding the criteria of radiographic progression and the results of respiratory cultures (for a maximum score of 14, based on 7 clinical criteria), and if the score remained =6, antibiotic therapy was stopped in the intervention arm. With use of this approach, the 42 patients with a score =6 who received standard therapy had more total exposure to antibiotics and more frequent development of antibiotic resistance than did the 39 patients randomized to receive 3 days of ciprofloxacin; mortality was similar in both groups.

Another study used the CPIS with tracheal aspirate surveillance cultures to drive a successful clinical approach to treatment of patients with VAP [33]. In this study, 299 patients receiving mechanical ventilation were followed up daily and underwent diagnostic bronchoscopy when there was a clinical suspicion of pneumonia. Among the 75 patients who had a diagnostic BAL sample obtained, the 41 with confirmed VAP had a higher CPIS than did those without confirmed VAP (6.6 vs 5.0; P = .001). Initial empirical therapy was chosen for these patients by using the results of twice-weekly surveillance cultures of endotracheal aspirate specimens, and this led to 95% of the patients with VAP receiving adequate therapy. In addition, with use of this approach, only 35% of patients who had negative BAL fluid samples received initial antibiotic therapy at a time when it was not needed. When surveillance culture data were used to guide empirical therapy choices, only 45% of patients with VAP received broad-spectrum β-lactam antibiotics; however, even with this relatively low rate, there was a high frequency of appropriate therapy. Thus, a clinical approach, combined with tracheal aspirate surveillance cultures, led to appropriate therapy without excessive use of antibiotics in general and without overuse of broad-spectrum agents in particular.

The largest study to compare quantitative and nonquantitative culture methods for the management of VAP was the Canadian Clinical Trials study. The study included 740 patients with suspected VAP that developed after 4 days of mechanical
ventilation [34]. Patients were randomized to treatment guided by quantitative cultures of BAL fluid specimens or by culture of endotracheal aspirate specimens without quantitation, and no difference in mortality was seen between the 2 groups. The result differed from that in a French randomized study that compared an invasive management approach with a clinical approach and found a significantly lower 14-day mortality with the invasive approach but no differences in 28-day mortality, duration of intensive care unit stay, or emergence of antibiotic resistance [35]. One criticism of the Canadian study was that an effort was made to exclude patients who were known to be infected with multidrug-resistant pathogens, because the study also randomized patients to receive monotherapy or combination therapy, which included a broad-spectrum carbapenem for all patients. However, 14.2% of patients in the study were infected with high-risk pathogens. In addition to finding no benefit of quantitative methods for mortality, the Canadian study found that the frequency of deescalation was comparable for both diagnostic approaches. Recently, a systematic review was performed that evaluated all prospective randomized trials comparing invasive with noninvasive management of VAP, including both the Canadian and French studies [32]. Of the 5 studies included, 3 compared invasive quantitative methods with noninvasive, nonquantitative methods, whereas 2 studies used quantitative methods in both the invasive and noninvasive arms of the study. The evaluation revealed no difference in mortality, duration of intensive care unit stay, duration of mechanical ventilation, or rate of antibiotic change, with use of quantitative methods for VAP management.

CONCLUSIONS

There are multiple approaches to managing VAP, and management without quantitative cultures can be successful for assuring timely and adequate antibiotic therapy and avoiding the overuse of antibiotics. Clinical trials of VAP require culture data to define the etiology of infection, but quantitative cultures are not necessary for this purpose, nor are they needed for effective clinical management. For enrollment in a clinical trial, only patients with a CPIS ≥6 should be included, with the score based on an assessment of 5 criteria: fever, leukocytosis, purulence of secretions, radiographic pattern, and oxygenation. All patients should have a lower respiratory tract culture performed before initiation of antibiotic therapy, but a nonquantitative tracheal aspirate culture is sufficient and will accurately identify the etiologic pathogen. Enrollment might be enhanced and accuracy of initial empirical therapy may be improved if surveillance cultures of lower respiratory tract secretions are collected prospectively from at-risk patients. After antibiotic therapy is started, treatment can be modified on the basis of data from nonquantitative culture of tracheal aspirate specimens combined with serial assessment of clinical response, usually by the third day. If culture results are positive and the patient’s condition is improving, it may be possible to narrow (to monotherapy) and focus (to a less broad-spectrum agent) therapy, unless a highly drug-resistant pathogen is present. If, at the same time, the patient is not improving, cultures should be performed to ensure that all pathogens present are being treated. In addition, when the patient is not improving, diagnostic studies should be done to search for other sites of infection that could coexist with VAP (eg, central venous catheter infection, intra-abdominal abscess, and sinusitis), noninfectious processes (eg, acute lung injury and inflammatory lung disease), unusual organisms (eg, viruses and fungi), or complications of VAP or therapy for VAP (eg, empyema, antibiotic-induced colitis, and pulmonary embolism).

Quantitative cultures are not necessary for enrollment in a clinical trial and for modification of initial antibiotic therapy, and both false-negative and false-positive results will interfere with trial results. False-positive results are common for patients receiving long-term mechanical ventilation and could lead to enrollment of patients without infection, whereas false-negative results are common for patients who have received prior antibiotic therapy. Reliance on such data could lead to inclusion of only a subset of patients with VAP. In addition, the concept of defining a bacteriologic threshold to distinguish colonization from infection may not be biologically plausible, because VAP is on a bacteriologic spectrum, and stages of early and late infection may exist at different sites at the time that it is clinically recognized.

Acknowledgments

Potential conflicts of interest. M.S.N. has received honorarium and/or consulting income from Bayer, Ceragenix, Merck, Ortho-McNiel, Pfizer, and Theravance.

Supplement sponsorship. This article was published as part of a supplement entitled “Workshop on Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia,” sponsored by the US Food and Drug Administration, Infectious Diseases Society of America, American College of Chest Physicians, American Thoracic Society, and the Society of Critical Care Medicine, with financial support from the Pharmaceutical Research and Manufacturers of America, AstraZeneca Pharmaceuticals, and Forest Pharmaceuticals.

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