

The Clinical Diagnosis of Ventilator-Associated Pneumonia

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Summary

There has long been a controversy about whether to use a clinical or microbiologic approach to diagnose ventilator-associated pneumonia (VAP) and about which approach to use in managing patients. Although the clinical approach has often been criticized, a number of recent studies have shown that it is possible to use such an approach to effectively manage patients. This approach involves using all available clinical data to define the presence of pneumonia and then to initiate empiric therapy in a timely fashion, based on therapy guidelines, modified by local microbiologic data. Often the clinical diagnosis is made using the clinical pulmonary infection score, and this tool can be very accurate, especially if it incorporates a Gram stain of a lower-respiratory-tract sample. Once the clinical diagnosis of VAP is made, all patients should have a tracheal aspirate collected for culture, followed by prompt initiation of therapy. Using a clinical approach to management, the key decision point is not whether to start antibiotics, but whether to continue them at day 2–3. This requires serial clinical evaluation to define whether a response to empiric therapy has occurred. Based on this assessment, in conjunction with the results of tracheal aspirate cultures, therapy can be either modified or continued. A number of studies have shown that the clinical approach leads to a large number of patients receiving adequate empiric therapy, while still permitting de-escalation of antibiotic regimens, along with short durations of therapy. Thus a clinical approach to management can be successful in allowing for effective management of VAP, without promoting the unnecessary use of broad-spectrum antimicrobial therapy. *Key words: ventilator-associated pneumonia, diagnosis, clinical pulmonary infection score, antibiotic, antibiotic resistance, de-escalation.* [Respir Care 2005;50(6):788–796. © 2005 Daedalus Enterprises]

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Introduction

The diagnosis of ventilator-associated pneumonia (VAP) has long been a subject of controversy, with no agreement about whether the decision to start antibiotic therapy, in the setting of suspected infection, should be guided by clinical criteria (the "clinical approach") or by microbiologic data from quantitative (often invasive) samples of lower-airway secretions (the "bacteriologic approach").^{1,2} This controversy exists because the clinical definition of pneumonia, although sensitive, is not very specific, and many patients with the clinical findings of VAP may have noninfectious etiologies for their findings of a new lung infiltrate accompanied by fever, purulent sputum, and leukocytosis. In fact, some studies have reported that as many as two thirds of all patients with the clinical diagnosis of VAP may not meet microbiologic criteria for infection.³ The recently published guidelines of the American Thoracic Society and the Infectious Disease Society of America have discussed this controversy, and have tried to combine features of both approaches to help guide VAP management.⁴ This article focuses on the advantages of management guided by a clinical approach, pointing out potential problems of using the bacteriologic approach.

Even though the use of a clinical definition of pneumonia may be overly inclusive, a large body of data has demonstrated that mortality (including death directly attributable to the presence of pneumonia) in VAP is reduced when patients receive prompt and adequate empiric therapy.^{5,6} Thus, when faced with a patient who on clinical grounds may have pneumonia, the clinician must often initiate broad-spectrum empiric therapy, accounting for all pathogens that are likely to be causing infection (based on a knowledge of local patterns of predominant pathogens and their antibiotic susceptibilities), in an effort to "protect" the at-risk patient. Unfortunately, this approach has a number of adverse consequences. First, some patients will be treated with antibiotics when they are not needed, and antibiotic use has been identified as a risk factor for subsequent nosocomial pneumonia, particularly with resistant pathogens.⁷ Second, many patients with VAP can have other infections at the same time (sinusitis, central line infection), and if all episodes of fever and lung infiltrate are attributed to VAP, these infections may be overlooked.^{8,9}

For all of these reasons, some investigators have proposed that whenever VAP is suspected, the patient should have a sampling of lower-respiratory-tract secretions (by bronchoscopic protected brush, bronchoalveolar lavage [BAL], blind brush or lavage, or endotracheal aspirate) which is then cultured quantitatively and the results used for several purposes.^{10,11} The results can be used to decide whether to start therapy and, at a later time point, whether to continue it. In addition, the information can be used to

guide specific antibiotic choices, which are initially empiric and later organism-directed. Although the logic for such an approach is appealing, the use of quantitative cultures also has limitations, and it is uncertain whether decisions based on these data can lead to improved pneumonia management, or if this approach will simply mean that some patients with VAP will have either a delay in the initiation of therapy or even a lack of therapy in the setting of a progressive and potentially lethal infection. The potential impact of relying on quantitative cultures will depend on whether this approach is used to determine not only which antibiotics to use, but whether to withhold therapy in selected patients, even in the face of a potentially serious infection.

If quantitative methods are to be used in clinical practice, they must lead to better outcomes than can be achieved by other approaches. These improved end points may be reduced mortality or less use of unnecessary antibiotics. Recent data have shown that although the use of quantitative cultures can reduce the use of antibiotics in the intensive care unit (ICU), a similar benefit can occur if clinical methods are used to guide therapy.^{9,12-14} There is less convincing evidence that quantitative culture data can help reduce pneumonia mortality. However, for such a claim to be credible, it must be accompanied by a mechanism explaining how such a result is possible. Based on many studies, the only unequivocal way to reduce VAP mortality is to improve the accuracy of initial empiric therapy, and it is unlikely that quantitative culture methods could accomplish this end.

There are many common goals that all clinicians accept, and they can be achieved using either a clinical or a bacteriologic approach to management. These goals include: avoiding untreated patients, delayed therapy, or inadequate therapy (wrong dose, wrong agent), all in an effort to reduce the mortality of VAP; and avoiding the overusage of antibiotics in an effort to control the problem of antimicrobial resistance. In order to prevent the overuse of antibiotics, 3 approaches are available: (1) restricting the use of broad-spectrum agents, (2) limiting the use of antibiotics until the diagnosis of pneumonia is certain, or (3) de-escalating therapy, from broad to narrow, once clinical and culture data are available. In addition, as the patient's clinical response to therapy is observed, it may be possible to avoid overuse of antibiotics by reducing the duration of therapy to the shortest effective period.^{15,16} There may be no single best way to diagnose and manage VAP, and each hospital is likely to have different capabilities for applying the various diagnostic techniques. The key issue is to be sure that, whatever management strategy is used, the clinician is able to achieve the goals stated above.

Defining the “Clinical Approach” to Empiric Therapy of VAP, and Its Accuracy

Methods for Clinical Diagnosis, Including the Clinical Pulmonary Infection Score

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. Although this definition is sensitive, it is not specific, and some investigators have reported that as few as one third of all patients who meet these criteria have microbiologic confirmation of pneumonia using quantitative cultures.^{2,3} However, most clinicians use multiple criteria to diagnose pneumonia, often emphasizing certain findings over others. In fact, such a “weighted” approach to clinical diagnosis has been developed, in the form of a clinical pulmonary infection score (CPIS), and this diagnostic tool was quite accurate when it was first described.¹⁷ The original description of the scoring system assigned points to patients, based on 6 clinical assessments, each worth 0–2 points, including: 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 criteria cannot always be used, and if omitted, the score varies from 0–10, instead of 0–12, but recently several modifications of the CPIS have been proposed and applied, as discussed below.^{12,18–22}

Using all 6 criteria, Pugin et al compared the CPIS to the quantitative diagnosis of pneumonia using bronchoscopic BAL (and calculating a bacterial index).¹⁷ The bacterial index is the numeric sum of the logarithmic concentrations of each of the organisms present in the BAL sample. The correlation between the CPIS and the bronchoscopic BAL bacterial index was 0.8, showing that clinical diagnosis can be as accurate as a microbiologic approach. In addition, if a CPIS > 6 was used as a clinical definition of pneumonia, then 93% of the BAL 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, using a CPIS > 6 as the clinical definition of pneumonia had a sensitivity of 93% and a specificity and positive predictive value of 100%. In another study, using post-mortem lung biopsy to define the presence of pneumonia, the CPIS had a sensitivity of 77% and a specificity of 42%.²³ A study of 38 patients revealed a higher diagnostic accuracy, with a sensitivity of 77% and a specificity of 85%.²⁴ 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, and the findings from studies of

the CPIS suggest that the clinical diagnosis of VAP may not be so inaccurate.

Continued interest in the CPIS as a diagnostic tool has led to several recent studies that suggest some utility for the tool, but the studies are all somewhat different from each other and from earlier studies because of methodologic variations.^{18–22} Most of the studies have used a “modified” clinical scoring system, finding that they could not routinely apply Pugin’s method because of the unavailability of tracheal-aspirate cultures at the time of initial clinical evaluation, or because the ICU nurses did not record sputum volume or the laboratory did not measure band forms of white blood cells. In addition, some of the recent studies actually calculated the CPIS retrospectively, and it remains uncertain if this leads to the same results as when collected prospectively. In a 2004 study, one group looked at the reproducibility of the score itself by having 2 observers calculate the score, although some of these calculations were done retrospectively.²¹ The investigators found that interobserver variability was large and that it was often the result of ambiguities in the scoring system or missing data that were required to calculate the score. When all the data were available, the kappa score for level of agreement was only 0.16. In spite of these data, it is difficult to understand such variability, since most of the data points are objective, and the one subjective variable, quantity of secretions, was omitted from this analysis.

Studies comparing the accuracy of CPIS to a bacteriologic diagnosis of VAP using quantitative cultures have shown a wide range of sensitivity and specificity, but it does appear that the accuracy of the CPIS can be improved if a reliable lower-respiratory-tract sample is obtained and studied carefully with a Gram stain.¹⁸ In a study of 99 patients, of whom 69 had VAP using quantitative BAL criteria, the investigators used a modified CPIS that did not include any microbiologic study of lower-respiratory-tract secretions, and this led to a sensitivity of 83% but a specificity of only 17%.²¹ Flanagan et al compared the CPIS to nonbronchoscopic lung lavage data in a population of 145 patients.²⁰ The CPIS for all 34 patients with VAP was significantly higher than the score of the non-pneumonia patients (7.6 vs 4.1, $p < 0.0001$), and using a score of 7 to diagnose pneumonia, the sensitivity was 85%, the specificity 91%, the positive predictive value 61%, and the negative predictive value 96%. It is interesting that the CPIS performed so well, since these authors used a modified score that did not include culture data or Gram stain of lower-respiratory-tract secretions. In another study, using microbiologic confirmation of pneumonia as the accepted standard, the prospective finding of a CPIS score > 6, using the Pugin scoring system, was associated with an odds ratio of pneumonia of 3.0, and this score, and no other clinical finding, predicted the presence of pneumonia.²⁵ A score > 6 was present in 61% with VAP and 34%

without this diagnosis. In contrast, Fartoukh et al found that the CPIS correlated poorly with a BAL diagnosis of VAP, unless a Gram stain of respiratory secretions was included in the score.¹⁸ In this study, 40 of 79 patients had BAL-confirmed pneumonia, and the CPIS for those with confirmed VAP was 6.5 versus 5.9 in those without ($p = 0.07$), but this involved a scoring system without a Gram stain of respiratory secretions. When a Gram stain of a BAL sample was added to the CPIS scoring system (similar to Pugin's original description), then the score for confirmed VAP was 8.2, compared to 6.4 in those without VAP ($p < 0.001$). It remains to be determined if a similar degree of accuracy could be obtained with a Gram stain of a tracheal aspirate, thus allowing an accurate diagnosis without either quantitative cultures or invasive sampling.

A group of French investigators calculated the CPIS retrospectively in 201 patients who had a bronchoscopic evaluation at the time of pneumonia suspicion, and measured the score on days 1 and 3.²² The score on day 1 did not include any respiratory-tract culture data, while this information, as well as data about radiographic progression, was incorporated into the score at day 3. The authors found that the initial CPIS score, calculated without bacteriologic information, was similar in both groups (6.4 vs 6.2), but the values were significantly different on day 3 (8.7 vs 7.0, $p < 0.0001$). In fact the data on day 3 were associated with a sensitivity of 89% and a negative predictive value of 84%. Thus, using a clinical approach, patients could be started on empiric therapy when there was any clinical suspicion of VAP, but therapy continued beyond day 3 only if the CPIS remains elevated. The French investigators acknowledged that using the CPIS in this fashion might allow for a clinical strategy that permitted the use of less antibiotics than with a traditional clinical strategy, but they argued that a bacteriologic approach was even better and led to a more selective application of antimicrobial therapy.

In addition to its value in diagnosing VAP, the CPIS has other uses. In one study, investigators found that the duration of therapy was directly correlated ($r = 0.419$, $p < 0.001$) with the CPIS score at the time of pneumonia diagnosis.¹⁴ In this study, the CPIS was calculated prospectively, and the mean score for patients with VAP was 7.2, using microbiologic data in the calculation. Another study used the CPIS to define if a patient was responding to therapy. In this study, Luna et al found that the CPIS, when calculated prospectively and followed serially throughout the course of VAP management, fell in patients who survived, but not in those who did not.¹⁹ The most accurate indicator of adequate therapy was a rapid improvement in the ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2} ratio), and this improvement was evident in responding patients by day 3. Thus, initial values of the CPIS may help guide the duration of therapy, while serial

measurements of the CPIS could be used to guide the modification of antibiotics during the course of therapy (discussed below). In applying a clinical approach to management, available data suggest that an assessment of patient response should be done at day 3 of therapy. For patients who do not have a fall in score at this time point, careful reassessment is necessary, while for those with a good response it may be possible to design an abbreviated course of therapy.

Comparison of Clinical and Bacteriologic Diagnosis

While many investigators have argued that invasive methods are more accurate than the clinical diagnosis of VAP, not all studies support that contention. For example, Marquette et al did prospective quantitative cultures in 28 patients who subsequently died and had the diagnosis of VAP defined histologically at autopsy, and they reported that no quantitative method had a sensitivity $> 60\%$.²⁶ Similarly, Kirtland et al performed autopsy studies on 39 patients and found that no quantitative diagnostic method had a high positive predictive value for VAP, but that tracheal aspirates were 87% sensitive for defining the organisms that were present in lung tissue.²⁷ This finding has generally been corroborated by other investigators, and based on these studies it seems safe to conclude that tracheal aspirates, studied qualitatively, will rarely fail to grow an organism that can be found in lung tissue or with bronchoscopy.²⁸⁻³⁰

There have, however, been a number of studies of quantitative cultures of tracheal aspirates to both diagnose the presence of pneumonia and also to define the etiologic pathogens. In several studies the sensitivity of tracheal aspirates, using a cutoff of 10^5 CFU/mL, has been $> 80\%$ for identifying an etiologic pathogen: results that were often comparable to bronchoscopic findings in the same patients being more sensitive than protected-specimen-brush and similar to BAL.³¹⁻³³ In one study of nonresponding patients with VAP, the tracheal aspirate was positive in several patients when the bronchoscopy was not, and the authors suggested that, based on the clinical findings of the patients, the bronchoscopic findings were falsely negative.³² Compared to protected-specimen-brush results, tracheal aspirates had a sensitivity of 82% and a specificity of 79% in a small study of 15 surgical patients, using a threshold of 10^4 colony-forming units (CFU)/mL.³³ Another study used the CPIS to define the presence of VAP in 60 surgical patients, and quantitative cultures of both tracheal aspirates (at 10^5 CFU/mL) and BAL (at 10^4 CFU/mL) were comparably sensitive for identifying the etiologic agents.³¹ In the studies showing high sensitivity of quantitative tracheal aspirates, the specificity was as low as $< 50\%$ at a threshold of 10^5 CFU/mL, but rose,

at the expense of sensitivity, if a threshold of 10^6 CFU/mL was used.

Thus, if clinical diagnosis is used to decide when to start therapy, and microbiologic data from tracheal aspirates are used to define the organisms present in the lung and their antibiotic susceptibilities, it is possible to treat pneumonia at its earliest time point and to target therapy to the pathogens that are present. One limitation of this approach is that not all organisms present on a tracheal-aspirate culture are necessarily pathogens, as some may represent colonizing organisms, but conversely, it is unlikely that an organism causing pneumonia will not be present in a tracheal-aspirate culture. Therefore, tracheal aspirates can be used, in a clinical approach to management, to guide de-escalation therapy, ruling out the presence of a highly resistant pathogen if the cultures do not show such organisms.

Studies Showing the Efficacy of a Clinical Approach

Several studies have now shown that it is possible to use a clinical management approach to limit the use of antibiotics and thereby control resistance but still treat patients with suspected VAP in an aggressive fashion.¹²⁻¹⁴ In a study by Singh et al, patients with suspected VAP were clinically evaluated with the CPIS, which included measurements of fever, leukocytosis, appearance of tracheal secretions, radiographic patterns, and oxygenation to assess the likelihood of pneumonia.¹² If the score was > 6 (each of the 5 features was scored 0-2, for a maximum of 10 points), patients were diagnosed as having pneumonia and treated for 10-21 days. However, for those with a score of ≤ 6 , there was a randomization to "standard care" or 3 days of ciprofloxacin at 400 mg every 8 hours. After 3 days, for the patients treated with ciprofloxacin, the CPIS was measured again, adding the criteria of radiographic progression and the results of respiratory cultures (now giving a maximum score of 14, based on 7 clinical criteria), and if the score remained ≤ 6 , antibiotics were stopped. Using this approach, 42 patients with a score of ≤ 6 received standard therapy, and 39 were randomized to 3 days of ciprofloxacin therapy. Only 11 of the 39 patients needed antibiotics for > 3 days (because the CPIS had increased to > 6), and the rest of the group had therapy stopped after 3 days. The entire short-course therapy group had the same clinical course (CPIS at day 3) and the same mortality as the 42 patients randomized to standard therapy. However, antibiotic resistance was less frequent and the withholding of therapy was more frequent in the short-course therapy group. Thus, the authors demonstrated the safety and feasibility of using a clinical assessment as a method to limit the use of prolonged antibiotic therapy in patients with suspected VAP.

Ibrahim et al compared the management of 50 patients with VAP in a time period without an antibiotic protocol

to 52 patients with VAP who were managed by an ICU-specific protocol.¹³ The protocol-directed therapy was based on information about ICU-specific pathogens and their susceptibilities and required initial intravenous combination antimicrobial treatment with vancomycin, imipenem, and ciprofloxacin. The guideline also required that antibiotic treatment be modified after 48 hours, based on the results of cultures, and de-escalation was commonly achieved. In fact, only 2% remained on all 3 drugs for a complete course of therapy, 36.5% of patients had one drug discontinued, and 61.5% had 2 antibiotics stopped within 48 hours of treatment. This high rate of de-escalation was achieved even though 25% of the pathogens were *Pseudomonas aeruginosa* and 15.4% were methicillin-resistant *Staphylococcus aureus*, and other multiple-drug-resistant pathogens were also present. In addition to using less antibiotics, an additional feature of the protocol was an attempt to limit therapy to a 7-day course of appropriate antibiotic(s) for patients with VAP. Administration of antimicrobials beyond day 7 was recommended only for patients with persistent signs and symptoms consistent with active infection (eg, fever $> 38.3^\circ\text{C}$, circulating leukocyte count $> 10,000/\text{mL}$, lack of improvement on the chest radiograph, continued purulent sputum). Use of the guideline was associated with a statistically significant increase in the administration of appropriate antimicrobial treatment (94% of the protocol patients got accurate therapy, compared to $< 50\%$ in the absence of a protocol) and a decrease in the development of secondary episodes of antibiotic-resistant VAP. A significant reduction in the total duration of antimicrobial treatment, to 8.1 ± 5.1 days from 14.8 ± 8.1 days, ($p < 0.001$) was also achieved.

In a more recent study, Micek et al developed a policy to discontinue antibiotics when patients with suspected VAP were found to have a noninfectious cause of lung infiltrates or to have resolution of clinical signs of pneumonia.¹⁴ Essential to effectively implementing this policy was a plan to diagnose pneumonia clinically and then use broad-spectrum empiric therapy for all patients, which included cefepime, ciprofloxacin or gentamicin, and vancomycin or linezolid. This therapy led to 93.5% of patients getting initially effective therapy. Using this approach, compared to a group randomized not to receive this intervention, 94.7% of the discontinuation group ($n = 142$) had a recommendation to stop therapy, and this recommendation was followed in 88.7% of all patients ($n = 126$) within 48 hours of the recommendation. The duration of therapy was related to the magnitude of clinical findings initially present, as reflected by the CPIS. Duration of therapy was reduced to as low as 5.8 days in those with Gram-negative bacteria, even though resistant organisms were commonly present.

A 2005 study has shown the utility of the CPIS, along with tracheal aspirate surveillance cultures, to drive

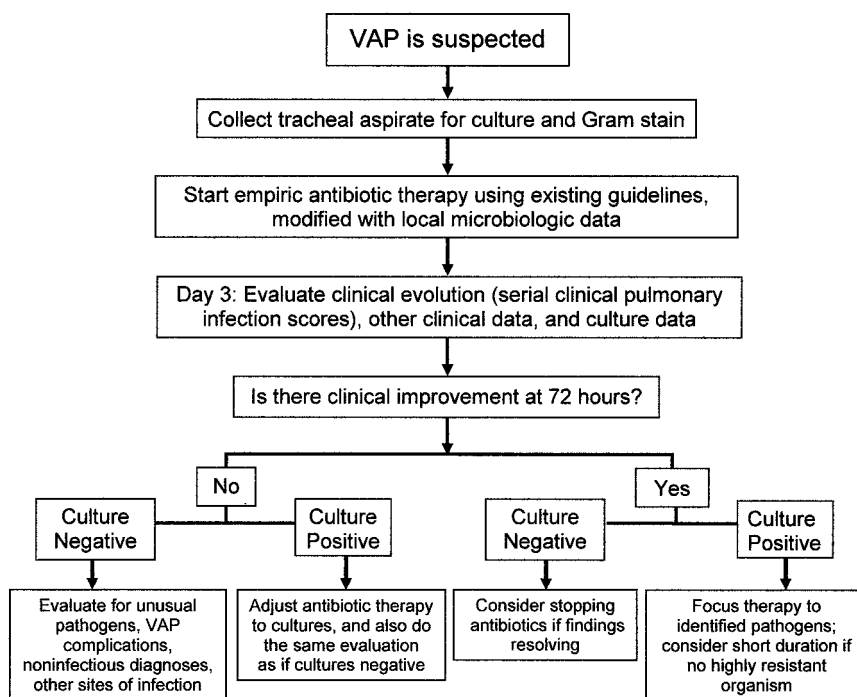


Fig. 1. Summary of the clinical approach to managing suspected ventilator-associated pneumonia (VAP). The key features of this approach are to start empiric therapy as soon as there is a clinical suspicion of pneumonia, but to make an effort to collect a tracheal aspirate sample for culture from all patients and then start therapy based on existing guidelines, modified by a knowledge of local microbiology. A key feature of this approach is to reevaluate the patient at day 2–3, using serial clinical assessments and the results of tracheal-aspirate cultures. Based on this assessment, a decision should be made about whether to focus therapy, using de-escalation when possible. If the patient is not responding at day 3, a careful evaluation for unusual pathogens, VAP complications, noninfectious diagnoses, and a search for other sites of infection is essential. (Adapted from Reference 4.)

a successful clinical approach to management of VAP patients.³⁴ In this study, 299 ventilated patients were followed daily and had diagnostic bronchoscopy when they had a clinical suspicion of pneumonia. Of the 75 who had a diagnostic BAL, 41 had positive results. In those with a BAL confirmation of the clinical suspicion of pneumonia, the CPIS was 6.6, compared to 5.0 in those without confirmation ($p = 0.001$). Initial empiric therapy was chosen for these patients, based on a strategy of using the results of twice-weekly surveillance cultures of endotracheal aspirates, and this led to 95% of the VAP patients receiving adequate therapy. In addition, this approach led to only 35% of those who were BAL-negative receiving initial antibiotic therapy at a time when it was not needed. In addition, when surveillance culture data were used to guide empiric therapy choices, only 45% of the patients with VAP received broad-spectrum β -lactam antibiotics, yet even with this relatively low rate, there was still a high frequency of adequate therapy. Thus a clinical approach combined with tracheal-aspirate surveillance cultures led to adequate therapy, without excessive use of antibiotics in general, and without overuse of broad-spectrum agents in particular.

Summary of the Clinical Approach

The clinical approach to VAP management is based on the following management strategy (Fig. 1). Use all the available clinical data (including CPIS) to decide *if* pneumonia is present, and make the decision *whether* to use antibiotics based on this assessment. Prior to starting therapy, collect a tracheal aspirate from an intubated patient, and start antibiotics based on existing treatment algorithms, supplemented by a knowledge of local microbiologic data. Continue antibiotics, pending tracheal-aspirate cultures and serial assessment of clinical response, but once this information is available, make a decision about whether to discontinue, modify, or simplify antibiotic choices. This decision can usually be made by the third day. At this time, if the patient's clinical findings have completely resolved and the cultures are negative (in the absence of changing antibiotics within 72 h of collecting the culture), then it may be possible to conclude that pneumonia was not present, and if the likely diagnosis is another process (atelectasis, heart failure), then therapy can be stopped. If cultures are positive and the patient is improving, then it may be possible to narrow (to monotherapy) and to focus

(to a less broad-spectrum agent) therapy, unless a highly-resistant pathogen is present. If at the same time point the patient is not improving, then cultures should be used to assure that all pathogens present are being treated. Regardless of whether cultures are positive or negative, if the patient is not improving, then diagnostic studies should be done to search for other sites of infection that could co-exist with VAP (central line infection, intra-abdominal abscess, sinusitis), noninfectious processes (acute lung injury, inflammatory lung disease), unusual organisms (viruses, fungi), or complications of VAP or its therapy (empyema, antibiotic-induced colitis, pulmonary embolism).

Problems With Quantitative Cultures and Their Use for the Management of Suspected VAP

The reliance on quantitative cultures to guide management decisions in VAP has a number of practical limitations, including: (1) some patients will have false-positive results, as a consequence of prolonged mechanical ventilation and subsequent airway colonization, thereby negating some of the putative value of quantitative cultures; (2) some patients may have false-negative results, and depending on the management strategy, this could result in a delay in the initiation of therapy; (3) a number of technical considerations affect the results of quantitative cultures, and these may explain why the reported accuracy of invasive methods (from one method to another and from one investigator to another) vary so widely; (4) quantitative methods rely on the idea that there is a bacteriologic "threshold," or a bacterial concentration below which infection is absent (and not treated), and this concept may be biologically implausible, since infection is on a microbiologic continuum; and (5) the accuracy of quantitative sampling is greatly influenced by antibiotic therapy, and many patients with suspected VAP are already on antibiotics.^{1,35}

If a bacteriologic management approach is used, then a quantitative cutoff is chosen to decide whether pneumonia is present. This approach could be problematic if antibiotics are withheld *until* quantitative data show a threshold concentration of organisms. Several studies have suggested that VAP is on a histologic and bacteriologic continuum, and that low counts may not necessarily mean no pneumonia but, rather, early (and potentially treatable) pneumonia.^{36,37} In an animal model of VAP in piglets, Wermert et al found that there was no exact bacteriologic threshold to define the presence of histologic pneumonia.³⁷ This may be related to the finding in this study that the histologic lesions of pneumonia were unevenly distributed throughout the lung, and thus no sampling method could reliably sample well enough to find all patients with pneumonia.

If a bacteriologic threshold is to be used to define the need for antibiotic therapy, then certainly the result obtained should be reliable and reproducible. However, for

both protected-specimen-brush and BAL, studies have shown that when multiple repeat samples are taken from the same patient, at the same time, the results may vary between positive and negative.^{38,39} The lack of reproducibility may be an inherent methodologic limitation of bronchoscopy, or as suggested by the histologic data, since VAP is a patchy process, not all samples will be taken from an area involved with pneumonia. Variability can also occur from operator to operator and from center to center. This explains why there is a wide reported range of sensitivity and specificity of invasive methods in the literature. For example, protected-specimen-brush has a reported sensitivity varying from 38% to 100%, and some centers that have had poor results with protected-specimen-brush have had excellent results with BAL, and vice versa.^{1,10,11,40} With this type of experience reported in the literature, how can one decide which method to use and which to rely upon? One possible answer is to use multiple types of samples in any one patient, but the accuracy of this effort, compared to clinical management, remains uncertain.

Many patients with suspected VAP are on antibiotics, which can cause false-negative results, but one recent study has shown that this is less likely if the patient has been on therapy, without change, for at least 72 hours before diagnostic sampling.³⁵ In this setting, quantitative cultures may be positive and may show a resistant organism, although it seems likely that the same data could be obtained from an endotracheal-aspirate culture. If, however, the patient has had an antibiotic change within 24 hours of undergoing a quantitative sampling, then the sensitivity of invasive methods may be as low as 40%, making these methods unreliable.³⁵ A meta-analysis of bacteriologic sampling methods has concluded that very few studies have been well-conducted. The suggestions from this analysis were that future studies be conducted only on populations with a high clinical suspicion of pneumonia, that a clear and independent gold standard be selected for defining the sensitivity and specificity of the test being evaluated, that BAL involve at least a 140-mL sample, and that samples be collected prior to change or initiation of antibiotic therapy.⁴¹

Summary

There are multiple approaches to managing VAP, and a clinical approach can be successful for assuring timely and adequate antibiotic therapy, while at the same time avoiding the overuse of antibiotics. In order to be successful, a clinical approach should: (1) include use of all available clinical data to define the suspicion of pneumonia and guide the decision about when to treat, (2) collect lower-respiratory-tract samples for culture before the initiation of therapy, and (3) reevaluate the clinical response and cul-

ture data at day 2–3 of therapy, with an aim to focus therapy to the most narrow-spectrum regimen that is effective. When a clinical approach has been applied, it has often involved the use of the CPIS to define both the presence of pneumonia and the response to therapy. Several large studies have shown that even without the use of quantitative microbiology, effective management of VAP can be achieved without promoting the unnecessary use of broad-spectrum antimicrobial therapy.

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Discussion

The discussion pertaining to Dr Niederman's presentation took place together with the discussion that followed Dr Chastre's presentation, which appears following that paper (Chastre J. The Invasive [Quantitative] Diagnosis of Ventilator-Associated Pneumonia. *Respir Care* 2005;50[6]:797-807).