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Diagnosis and Treatment of Ventilator-Associated Pneumonia*

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Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the ICU. Patients who acquire VAP have higher mortality rates and longer ICU and hospital stays. Because there are other potential causes of fever, leukocytosis, and pulmonary infiltrates, clinical diagnostic criteria are overly sensitive in the diagnosis of VAP. Employing quantitative cultures of bronchopulmonary secretions in the diagnostic algorithm leads to less antibiotic use and probably to lower mortality. With respect to microbiologic diagnosis, it is not clear that the use of a particular sampling method (bronchoscopic or nonbronchoscopic), when quantitatively cultured, is associated with better outcomes. Delayed administration of adequate antibiotic therapy is linked to an increased mortality rate. Hence, the focus of initial antibiotic therapy should be to rapidly provide antibiotic coverage for all likely pathogens and to then narrow or focus the antibiotic spectrum based on the results of quantitative cultures. Eight days of antibiotic therapy appears equivalent to 15 days of therapy except when treating nonlactose-fermenting Gram-negative organisms. In this latter situation, longer treatment durations appear to reduce the risk of recrudescence after discontinuation of antibiotic therapy. A guideline-based approach using the local hospital or ICU antibiogram can increase the likelihood that adequate initial antibiotic therapy is used and reduce the overall use of antibiotics and the associated selection pressure for multidrug-resistant organisms. (CHEST 2006; 130:597-604)

Key words: antibiotics; drug therapy; diagnosis; nosocomial pneumonia; review; treatment; ventilator-associated pneumonia

Abbreviations: CPIS = clinical pulmonary infection score; MRSA = methicillin-resistant *Staphylococcus aureus*; MDR = multidrug resistant; NNIS = National Nosocomial Infection Surveillance System; PSB = protected specimen brush; TA = tracheal aspirate; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) continues to be the most common nosocomial infection in the ICU, making up almost one third of the total nosocomial infections.¹⁻⁴ Patients who acquire VAP

have worse outcomes and have longer ICU and hospital stays.^{1-3,5-7} Ten to 20% of patients who require mechanical ventilation for > 48 h will acquire VAP, with mortality rates of 15 to 50%.^{5,8,9} VAP appears to be an independent risk factor for death, with a doubling of the mortality rate directly attributable to VAP.⁸ This is not uniform, however, and is dependent on the patient population and the infecting organisms.^{5,10-12} ICU length of stay in patients with VAP is increased by a mean of 6.1 days, and the excess costs can be as high as \$40,000 per patient.⁸

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DIAGNOSIS

The evaluation of patients with suspected VAP should begin with a comprehensive medical history and clinical examination^{2,13,14} and a chest radiograph

to determine the degree of lung parenchymal involvement and the presence of any complications such as a pleural effusion or cavitation.^{3,15} Often-applied clinical criteria for the diagnosis of VAP are the presence of a new lung infiltrate on chest radiography plus at least two of the following: fever > 38°C, leukocytosis or leukopenia, and purulent secretions.³ A standardized diagnostic algorithm employing clinical and microbiologic data are used in the National Nosocomial Infection Surveillance System (NNIS) to facilitate the application of consistent criteria in reporting nosocomial pneumonia. The clinical pulmonary infection score (CPIS) [which uses microbiologic data] or a modified CPIS (which does not use microbiologic data) have also been proposed to improve diagnostic consistency among clinicians and investigators. A CPIS > 6 is often regarded as consistent with a diagnosis of pneumonia.¹⁶ Tables 1, 2 detail both the NNIS and CPIS criteria for diagnosis of nosocomial pneumonia. Colonization of the airway in intubated patients is common, and the presence of potentially pathogenic organisms in tracheal secretions in the absence of clinical findings does not suggest VAP.¹⁷⁻¹⁹ Further, there are other common causes of fever and lung infiltrates in patients receiving mechanical ventilation, and the application of only these clinical criteria will result in the diagnosis of VAP in a large number of patients who likely do not have pneumonia. Recently, Miller and colleagues²⁰ compared the NNIS criteria with clinical suspicion confirmed by quantitative culture of BAL in 292 trauma patients. The NNIS criteria and clinical identification confirmed by BAL had a similar incidence of VAP, confirming the epidemiologic utility of the NNIS criteria. However, when applied to individual patients using BAL results as the criterion standard, the

NNIS criteria had a sensitivity of 84% and a specificity of 69%. Similarly, the CPIS has not consistently demonstrated either an improvement in diagnostic accuracy when used as an adjunct in clinical decision making, or reproducibility of scoring when used as a research tool to classify patients.^{21,22}

Nonquantitative cultures of tracheal aspirates often contain bacterial isolates when there are neither clinical nor radiographic evidence of infection (false-positive findings) and isolates that cannot be confirmed by other methods (bronchoscopic or post-mortem sampling).²³ Forty to 60% of patients meeting clinical criteria for VAP will not have the diagnosis confirmed by an alternate objective method such as quantitative cultures of protected specimen brush (PSB) or BAL samples or pathologic examination of lung tissue.^{23,24} A metaanalysis²⁵ of 23 studies of the use of BAL in the diagnosis of VAP reported a sensitivity of 22 to 93% (mean ± SD, 73 ± 18%) and a specificity of 45 to 100% (mean, 82 ± 19%).

Often-used thresholds applied to quantitative cultures for the diagnosis of VAP are 10³ cfu/mL for PSB, 10⁴ cfu/mL for BAL, and 10⁵ cfu/mL or 10⁶ cfu/mL for tracheal aspirates. It is important to realize that any such thresholds are a compromise between sensitivity and specificity and that no arbitrary culture threshold should be used in isolation for diagnosis.^{26,27} However, the number of bacteria cultured is not the only analysis of respiratory secretions that can be utilized. An examination of the Gram-stained secretions can also be helpful, especially with regard to decreasing the likelihood of pneumonia. A Gram-stained smear of a tracheal aspirate without bacteria or inflammatory cells in a patient whose antibiotic therapy has not been changed in 3 days has a negative predictive value of 94% for VAP.²⁸ In

Table 1—NNIS Clinical Criteria for the Diagnosis of Pneumonia*

Radiographic

Two or more serial chest radiographs with new or progressive and persistent infiltrate or cavitation or consolidation (one radiograph is sufficient in patients without underlying cardiopulmonary disease)

Clinical

One of the following:

Fever > 38°C (> 100.4°F) with no other recognized cause

WBC count < 4,000/μL or ≥ 12,000 μL

For adults ≥ 70 yr old, altered mental status with no other recognized cause

And at least two of the following:

New-onset purulent sputum or change in character of sputum, or increase in respiratory secretions or suctioning requirements

New-onset or worsening cough, dyspnea, or tachypnea

Rales or bronchial breath sounds

Worsening gas exchange, increased oxygen requirements, increased ventilatory support

Microbiology (optional)

Positive culture result (one): blood (unrelated to other source), pleural fluid, quantitative culture by BAL or PSB, ≥ 5% BAL-obtained cells contain intracellular bacteria

*From Miller et al.²⁰

Table 2—CPIS Clinical Criteria for the Diagnosis of Pneumonia*

| Variables | Points | | |
|---|---------------------|---|----------------------|
| | 0 | 1 | 2 |
| Temperature, °C | ≥ 36.1 to ≤ 38.4 | ≥ 38.5 to ≤ 38.9 | ≥ 39 to ≤ 36 |
| WBC count, /μ L | ≥ 4,000 to ≤ 11,000 | <4,000 to > 11,000 | |
| Secretions: | Absent | Present, nonpurulent | Present, purulent |
| Pao ₂ /fraction of inspired oxygen | > 240 or ARDS | | ≤ 240 and no ARDS |
| Chest radiography | No infiltrate | Diffuse or patchy infiltrate | Localized infiltrate |
| Microbiology | No or light growth | Moderate or heavy growth; add 1 point for same organism on Gram stain | |

*From Luyt et al.²¹

addition, the clinician must be mindful of the impact of specimen adequacy on any test. Several variables, including the volume of lavage fluid used to obtain the BAL and prior antibiotic use, have been demonstrated to affect the accuracy and especially the sensitivity of quantitative culture techniques.²⁹ False-negative culture results can be the result of poor sampling technique or antibiotic administration in the preceding 24 to 72 h.^{26,30,31} Therefore, all biological samples should ideally be obtained prior to the initiation of antimicrobial treatment. In patients with a very high clinical likelihood of pneumonia, or in whom the risk of not adequately treating infection is high (eg, septic shock), consideration should be given to employing a culture threshold 10-fold lower than usual.^{26,31}

While blood cultures have a low yield in patients suspected of having VAP, and most patients will not have pleural effusions, culture of these normally sterile sites can provide confirmation of the presence or absence of pneumonia or extrapulmonary infection.³² Therefore, patients should have blood samples drawn and diagnostic thoracentesis considered prior to the initiation of antibiotics whenever possible.

Regardless of the methodologies used, agreement among diagnostic approaches or techniques is imperfect at best.^{33–35} Because there is no “gold standard” for the diagnosis of VAP, deriving an evidenced-based, universally applicable diagnostic algorithm is not possible at this time.²⁹ A more relevant discussion than which diagnostic approach is most accurate, is which diagnostic approach is associated with the best clinical outcomes. Fagon and colleagues³⁶ compared a noninvasive strategy using qualitative cultures of tracheal aspirates with an invasive management strategy employing quantitative BAL or PSB samples obtained bronchoscopically in a randomized prospective trial enrolling > 200 patients in each group. In the invasive management strategy group, there were significantly fewer deaths at 14 days (16% vs 25%, $p = 0.02$) and less antibiotic use

(11.9 antibiotic-free days vs 7.7 antibiotic-free days, $p = 0.001$). Furthermore, when corrected for severity of illness, the 28-day mortality was also lower in the invasive strategy group. Importantly, these investigators³⁶ compared invasively obtained quantitative culture results against a strategy using qualitative culture results of tracheal aspirates (TAs). However, bronchoscopy is not readily available in many institutions, and even when it is it may not be rapidly available at all times. Bronchoscopic sampling also entails costs and risks that are greater than those associated with TA or nonbronchoscopic BAL. Quantitatively cultured nonbronchoscopic BAL and TA samples have demonstrated performance characteristics (sensitivity, specificity, predictive value) similar to bronchoscopically collected specimens in several studies.^{37–40} There have been no adequately powered prospective controlled trials comparing outcomes using invasive and noninvasive samples when both were cultured quantitatively. However, small prospective trials and trials using case matching suggest that using quantitatively cultured tracheal aspirates or quantitatively cultured PSB or BAL provide similar patient outcomes.^{41–43} The ultimate choice of strategy used to diagnose VAP will be dependent on consideration of local expertise and availability of personnel to perform the procedure, perceived risk to the patient, experience, and cost.^{36,44} In many institutions, realizing that antibiotic administration can alter the results of bronchoscopic cultures, and recognizing that even relatively short delays in the initiation of adequate antibiotic therapy are associated with increased mortality,⁴⁵ the immediate availability of quantitative tracheal aspirate cultures or nonbronchoscopic BAL is a powerful argument for their use.

TREATMENT

Prompt initiation of antibiotic therapy is a cornerstone of treatment of VAP. Even relatively short

delays in administering adequate antibiotic therapy are associated with an increased mortality rate.^{36,45–47} While various authors have used the terms *adequate* and *appropriate*, and *inadequate* and *inappropriate* interchangeably, in this article adequate and inadequate will be used. Adequate antibiotic therapy is defined as the administration of at least one antibiotic at an appropriate dose to which the isolated organisms are sensitive. Iregui and colleagues⁴⁵ found a higher mortality rate in patients in whom administration of adequate antibiotic therapy was delayed (69.7% vs 28.4% mortality, $p = 0.001$). In this study, the delayed group received antibiotics approximately 16 h later than the group that was not delayed (28.6 ± 5.8 h vs 12.5 ± 4.2 h after meeting criteria for the diagnosis of VAP, respectively). This relatively narrow time frame in which adequate therapy must be begun may account for the finding that changing antimicrobial therapy once culture results are available does not appreciably reduce the excess mortality associated with inadequate initial therapy.^{47–50}

The most common reason that initial antibiotic therapy is inadequate is that the responsible pathogens are resistant to the initially prescribed antibiotics.^{48,49} Antibiotic-resistant pathogens are an increasingly common cause of all pneumonia, but especially VAP. The most commonly reported drug-resistant pathogens in most series are *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), but resistant *Acinetobacter* species and *Klebsiella* species are also common in many hospitals. Hence, once the decision is made to treat a patient for VAP, antibiotic selection should be based on the risk factors for multidrug-resistant (MDR) pathogens and the local hospital antibiogram.^{3,51} Risk factors for MDR organisms are detailed in Table 3, but duration of mechanical ventilation (and hospitalization) and prior antibiotic exposure appear especially important.⁵² As the duration of hospitalization or mechanical ventilation increase, so does the likelihood of infection with resistant organisms. Hence, it is common to categorize VAP into “early onset” and “late onset.” Early onset pneumonia is

often defined as that occurring on or before day 5 with late onset pneumonia occurring thereafter. While the reported risk of *Pseudomonas* and MRSA is consistently associated with duration of hospitalization, it is important to note that $\geq 40\%$ of early onset VAP may be due to MRSA or *Pseudomonas*, and that this may rise to $\geq 60\%$ in late onset VAP.^{53,54} Hence, MRSA and *Pseudomonas* must be considered in any patient with one or more of the risk factors in Table 3, regardless of the duration of their hospitalization.

Because initially adequate antibiotic therapy is so important in reducing the mortality from VAP, when patients are at risk for MDR organisms, initial therapy should be broad and known to be effective against MDR pathogens, especially *P aeruginosa* and MRSA, and tailored to the local antibiogram. Current guidelines³ suggest that this will usually require three antibiotics: two drugs of different classes active against *Pseudomonas*, and a third for MRSA. A recommended empiric regimen for these patients is: an antipseudomonal cephalosporin (cefepime, ceftazidime), or an antipseudomonal carbapenem (imipenem, meropenem), or a β -lactam/ β -lactamase inhibitor (piperacillin/tazobactam) plus an antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin), or an aminoglycoside (amikacin, gentamicin, tobramycin) plus either linezolid or vancomycin.³ The initial choice of agents should also take into account any antibiotics the patient has received in the past 2 weeks, striving not to repeat the same antimicrobial class if possible, as recent exposure to one antibiotic can provoke resistance to the entire class.^{55,56} In patients with suspected VAP who do not have risk factors for MDR pathogens (Table 3), limited-spectrum antibiotic therapy is appropriate. Recommended antibiotics are as follows: ceftriaxone or a fluoroquinolone, or ampicillin/sulbactam or ertapenem.³ The selection of antibiotic therapy is based on patient risk factors, recent exposure to specific antibiotic classes, and the local antibiogram. Because microbiologic culture data will not be immediately available, the initial antibiotic selection will be the same regardless of the diagnostic methodology employed (BAL, PSB, TA).

Combination therapy for Gram-negative and particularly *P aeruginosa* treatment is common practice. Cited reasons for this are to achieve synergy and to prevent the emergence of resistance during therapy. However, antibiotic synergy against pseudomonal infections is an *in vitro* phenomenon and appears associated with improved outcomes only in neutropenic patients and bacteremic infections.^{3,57,58} A recent metaanalysis⁵⁹ of prospective, randomized trials of combination β -lactam/aminoglycoside vs β -lactam monotherapy for septic patients (of which

Table 3—Risk Factors for MDR Pathogens*

| |
|---|
| Antibiotics in the preceding 90 d |
| Hospitalization in preceding 90 d |
| Current hospitalization ≥ 5 d |
| Duration of mechanical ventilation ≥ 7 d |
| History of regular visits to an infusion or dialysis center |
| Residence in a nursing home or extended-care facility |
| Immunosuppressive disease or therapy |
| High frequency of antibiotic resistance in the community or ICU |

*From American Thoracic Society³ and Trouillet et al.⁵²

1,200 of the reported 7,586 patients had VAP) showed that there was no advantage to combination therapy in the treatment of *P aeruginosa* infections compared with monotherapy, but there was a higher rate of nephrotoxicity in the combination group. Further, a separate metaanalysis⁶⁰ of monotherapy vs combination therapy found that combination therapy did not reduce the rate of emergence of resistant organisms during treatment. Therefore, the role for combination therapy is to increase the likelihood that potential MDR pathogens will be adequately treated by the initial empiric antibiotics.

Three antibiotics may not always be needed in all patients with MDR pathogen risk factors. Beardsley and colleagues⁵³ recently described a process to analyze local antibiogram data and use these results to develop an institutional guideline for the treatment of hospital-acquired pneumonia. In this analysis⁵³ of 111 consecutive patients with culture-positive VAP in a mixed medical and surgical population, the most common organism (38% of patients) was *S aureus*, with 50% of these being MRSA. Resistance of Gram-negative pathogens to piperacillin-tazobactam, cefepime, or meropenem was uncommon before hospital day 10. Hence, in this institution, for VAP occurring before day 10, the combination of either vancomycin and piperacillin-tazobactam, or vancomycin and cefepime would have provided adequate therapy in 93% of patients, and thus became the recommended regimens in patients with pneumonia occurring before day 10. After 10 days, organisms resistant to piperacillin-tazobactam, cefepime, and meropenem were encountered much more frequently, and neither ciprofloxacin nor gentamicin added significant coverage for these resistant organisms; only amikacin provided additive coverage. Hence, in patients hospitalized for ≥ 10 days, the suggested regimen of vancomycin, cefepime or piperacillin-tazobactam, and amikacin would have provided adequate coverage in 96% of patients.

A retrospective analysis⁶¹ of two prospective, randomized, double-blind studies comparing linezolid and vancomycin for Gram-positive VAP showed that initial linezolid therapy was an independent predictor of clinical cure in patients with VAP caused by MRSA, and that these patients had a significantly higher survival rate than those treated with vancomycin. It is not certain what role the relatively low, fixed dose of vancomycin may have had on these results.

In the management of any infection and particularly VAP, it is not only important that the appropriate antibiotics be chosen but that they are administered in adequate amounts and at the appropriate intervals. The risk of selection of resistant bacteria appears related both to excessive duration of antibi-

otic therapy and to doses that are too low.^{62,63} Naturally, antibiotic dosing may need to be adjusted in patients with impaired renal or hepatic function. The dose may have to be adjusted daily and, in some instances, redosed after procedures such as dialysis. In the treatment of VAP, initial antibiotic doses should be IV administered with conversion to enteral therapy in patients who are responding to therapy, have intact GI function, and whose causative organism is sensitive to an orally administrable agent. Fluoroquinolones and linezolid are equally bioavailable in either IV or oral preparations. Early transition from IV to oral fluoroquinolone therapy has been shown to be safe and effective.⁶⁴ There are not enough data available to determine the role of either aerosolized or locally instilled antibiotics in the treatment of VAP.³

With regard to duration of treatment, Chastre et al,⁶⁵ in their prospective, randomized trial, demonstrated that among patients who had received appropriate initial empirical therapy, with the exception of patients with VAP due to nonfermenting Gram-negative bacilli, comparable clinical effectiveness against VAP was obtained with 8-day or 15-day treatment regimens without significant differences in mortality, ventilator-free days, and length of ICU stay. However, patients in whom VAP was due to *P aeruginosa* or *Acinetobacter* species had a greater risk of recurrence following discontinuation of antibiotics when treated for 8 days. As the 8-day treatment group had more antibiotic-free days, unless *P aeruginosa* or *Acinetobacter* species are isolated, antibiotic treatment should usually be discontinued after day 8. Several studies^{36,66} have suggested that patients in whom there is a clinical suspicion of VAP, but whose PSB or BAL culture results are negative at 3 days and who are clinically improving, can safely have their antibiotic therapy discontinued. Similar data do not exist for negative quantitative culture of TA, although it is the authors' opinion that the generally high sensitivity of this method in comparison to PSB and BAL would permit similar conclusions. Appropriately shortening the treatment duration and removing unnecessary antibiotics is an important aspect of decreasing unnecessary exposure to antibiotics in our ICUs. In addition to reducing antibiotic-associated costs, it may help to reduce selection pressures for resistant organisms in our ICUs.

Clinical improvement usually takes 48 to 72 h; therefore, unless the patient is declining clinically, antibiotics should not be modified during this time unless dictated by the results of microbiologic sensitivity data. In patients without ARDS, improved oxygenation and normalization of temperature usually occur within 3 days.⁶⁷⁻⁶⁹ If there is no clinical

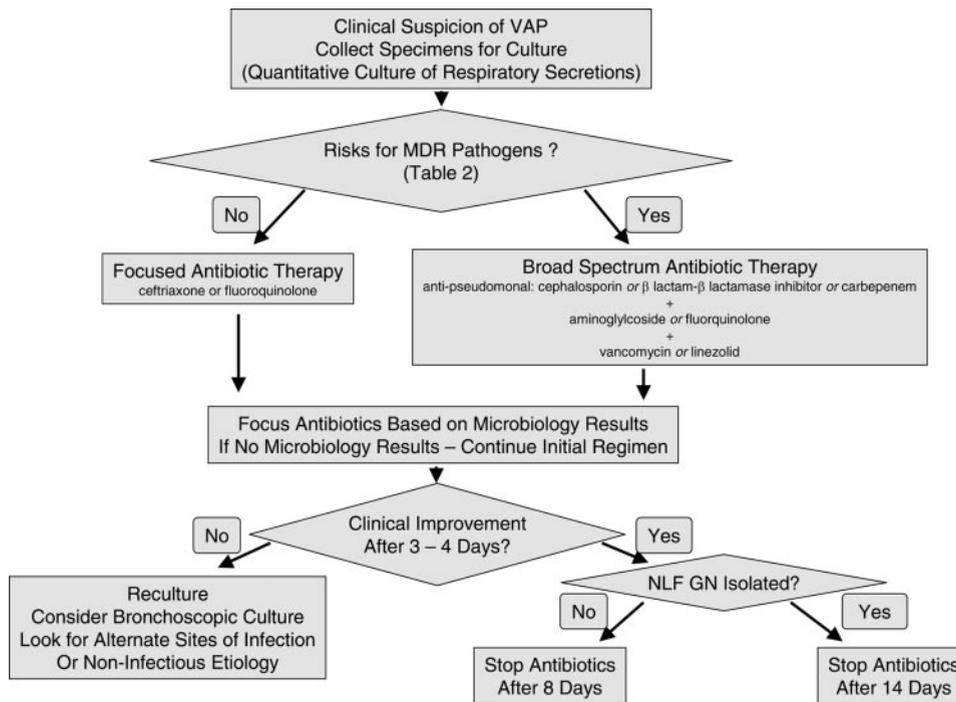


FIGURE 1. VAP treatment algorithm. NLF-GN = non-lactose-fermenting Gram-negative rods.

response by day 3, the patient should be evaluated for noninfectious mimics of pneumonia, MDR organisms, extrapulmonary infection, and the complications of pneumonia.⁷⁰ A summary of this discussion is provided in Figure 1.

SUMMARY

There are many aspects of the diagnosis and treatment of VAP that remain to be clarified. However, a systematically applied strategy that addresses early intervention with broad-spectrum antibiotics based on the risks for MDR organisms, and which is appropriate to the local antibiogram, can improve outcomes. This strategy also includes quantitative culture of respiratory secretions, de-escalation of antibiotic therapy once culture results are available, and discontinuation of antibiotics after 8 days of treatment in patients without *Pseudomonas* or *Acinetobacter* as the causative agent.

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