hosts other than children, and about its spread in the community and in hospitals; and as soon as possible, develop the means to prevent and treat human metapneumovirus infection.

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# Diagnosing Ventilator-Associated Pneumonia

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The establishment of an appropriate diagnosis of ventilator-associated pneumonia is one of the most crucial and difficult issues in the care of critically ill patients. Established clinical criteria alone, such as new or progressive infiltrates on chest radiography, together with fever, leukocytosis or leukopenia, and purulent tracheobronchial secretions, have been shown to be of limited diagnostic value. When the findings on histologic analysis and cultures of lung samples obtained immediately after death were used as references, the presence of chest infiltrates plus two of the three criteria mentioned above had a sensitivity of 69 percent and a specificity of 75 percent for the diagnosis of ventilator-associated pneumonia.[1] Alternative sets of criteria such as the "clinical pulmonary infection score" (a composite of clinical, microbiologic, and oxygenation-related criteria) have not been consistently superior, either in their original form or in modified forms. The addition of qualitative analysis of cultures of tracheobronchial secretions, although possibly helpful in the identification of a potential underlying pathogen, results in a lack of specificity for the diagnosis of ventilator-associated pneumonia.

On the other hand, empirical strategies also have important limitations. Several studies have shown that when the initiation of appropriate antimicrobial treatment is delayed, patients have adverse outcomes and that the adverse prognostic implications of delayed or inappropriate antimicrobial treatment cannot be overcome by the correction of the initial management strategy. Conversely, overtreatment with antimicrobial drugs can have a substantial adverse effect on the prognosis because of the selection of multidrug-resistant pathogens. Thus, both restricted and unrestricted empirical antimicrobial treatment strategies may be hazardous. The obvious need for better criteria for the diagnosis of ventilator-associated pneumonia has stimulated extensive investigational efforts in the past two decades.

A major effort was made to study the role of quantitative analysis of cultures of respiratory secretions, retrieved by means of simple tracheobronchial aspiration or with the use of bronchoscopic techniques and devices such as the protected specimen brush and several bronchoscopic and nonbronchoscopic variations of bronchoalveolar lavage. However, the results reported were highly variable, in terms of both the value of the culture technique and the roles of bronchoscopic and nonbronchoscopic approaches to the retrieval of respiratory secretions. In fact, postmortem studies in animals and humans demonstrated poor performance of quantitative cultures, regardless of the method of sampling used. Although there was an evident association between an increasing bacterial load in cultures of lung tissue and a greater degree of histologic damage, no quantitative threshold could be determined that would permit the separation of normal lung tissue from that showing bronchitis or pneumonia. Thus, individual predictions will always be subject to considerable error.

It has become clear that there is no irrefutable reference on which to rely in the calculation of the sensitivity and specificity of diagnostic tests for ventilator-associated pneumonia; there are simply too many confounders. As a result, attention has shifted from such indexes to an evaluation of the effects on important outcome variables. Noninvasive approaches (blind sampling of tracheobronchial aspirates) and invasive approaches (bronchoscopically retrieved samples of respiratory secretions) have been compared in four highly ambitious prospective studies evaluating the effects of their use on morbidity, the use of antimicrobial drugs, and mortality. Unfortunately, the four studies had different designs, as well as important methodologic limita-

tions, including an inappropriate selection of diagnostic techniques for comparison, insufficient control for previous antimicrobial treatment, inconsistent ways of managing antibiotic treatment in patients who had negative microbiologic assays, and insufficient power to detect clinically important differences among alternative strategies. Not surprisingly, the results were again controversial. One study comparing noninvasively retrieved qualitative cultures of tracheobronchial secretions with an invasive bronchoscopic approach involving quantitative cultures showed a significant advantage of the latter in terms of all outcome measures. However, the three other studies, which used quantitative cultures with both invasive and noninvasive approaches, showed no difference between the two strategies.

Since alternative techniques such as counts of intracellular organisms, the detection of elastin fibers, cell counts and Gram's staining, and measurements of interleukin-6 and procalcitonin in bronchoalveolar-lavage fluid have all failed to resolve the diagnostic dilemmas, interest has turned from the evaluation of diagnostic techniques to approaches that obviate the need to make a specific diagnosis of ventilator-associated pneumonia. Strategies have been proposed for the identification of low-risk patients who can receive short-term monotherapy, thereby minimizing the risk of delayed antimicrobial treatment as well as the risks associated with overtreatment. Such strategies, though worthy of consideration, have not been validated to date.

In our view, treatment decisions must therefore be based on principal considerations such as those summarized in the Table. In short, the decision to

**Table. Proposed Strategy for Management of Suspected Ventilator-Associated Pneumonia.**

| Clinical Condition | Management Strategy | Rationale |
|---|---|---|
| **Step 1: initial evaluation** | | |
| Clinical suspicion of ventilator-associated pneumonia (based on classic criteria or a clinical pulmonary infection score > 6)* | Retrieval of respiratory secretions for quantitative cultures (of tracheobronchial aspirate or bronchoscopic samples); immediate initiation of antimicrobial treatment | Risk of delayed or inappropriate antimicrobial treatment outweighs risks associated with antimicrobial overuse |
| **Step 2: reevaluation at 48–72 hr** | | |
| Clinical suspicion of ventilator-associated pneumonia confirmed (clinically, microbiologically, or both) | Continuation of antimicrobial treatment (with adjustment according to culture results) | Therapeutic benefit in terms of outcome evident |
| Clinical diagnosis likely, culture results nonsignificant, and no severe sepsis or shock† | No firm general recommendation; individual decision (usually to continue antimicrobial treatment)‡ | Risks of both selection pressure and lack of treatment should be considered; culture results must not be only criterion for decision, given 10–40% false negative rate |
| Nonpulmonary site of infection identified (or unexplained severe sepsis or shock) | Adjustment of antimicrobial treatment according to the site of infection and culture results | Therapeutic benefit in terms of outcome evident |
| Clinical diagnosis of ventilator-associated pneumonia unlikely and culture results nonsignificant (low risk of ventilator-associated pneumonia) or alternative (noninfectious) diagnosis confirmed; no severe sepsis or shock§ | Discontinuation of antimicrobial treatment | No harm to patient; reduces antimicrobial selection pressure |

* The clinical criteria are the presence of new and persistent infiltrates plus two of the following (or one in patients with the acute respiratory distress syndrome): a body temperature of more than 38.3°C, leukocytosis or leukopenia, and purulent tracheobronchial secretions. Scores for clinical pulmonary infection range from 0 to 12, with higher scores indicating a greater probability of pneumonia.

† Nonsignificant culture results are defined as colony counts below the predefined thresholds for microbiologic diagnosis of ventilator-associated pneumonia.

‡ Antimicrobial treatment can be stopped if there has been no previous antimicrobial treatment and if the cultures are negative. One study suggests that it is reasonable to use monotherapy in low-risk patients (clinical pulmonary infection score ≤6), with discontinuation if the score remains below 6 after 72 hours.[2] Another approach is to limit the duration of treatment: a recent study suggests that 7 days of antimicrobial treatment are as effective as 14 days.[3]

§ Low risk of ventilator-associated pneumonia: there are no definite infiltrates found on chest radiography at follow-up and two of the three clinical criteria are absent.

treat should be based on simple clinical criteria or the clinical pulmonary infection score, along with consideration of the short-term evolution of the clinical condition of the patient, after a vigorous search for noninfectious conditions that may mimic ventilator-associated pneumonia and for alternative nonpulmonary sites of infection. When nonpulmonary sites of infection have been ruled out, antimicrobial treatment may be stopped in patients who are in otherwise stable condition and have a low risk of ventilator-associated pneumonia. However, there remains a considerable proportion of patients for whom there is a discordance between the clinical diagnosis and the microbiologic results; in such patients, the risk of overtreatment has to be weighed against the risk of insufficient antimicrobial treatment.

In this context, the study reported by Gibot and colleagues in this issue of the *Journal* (pages 451–458) offers a new perspective on the diagnostic dilemmas associated with ventilator-associated pneumonia. The authors used the triggering receptor expressed on myeloid cells (TREM-1) in samples of bronchoalveolar-lavage fluid as a marker of pneumonia in patients receiving mechanical ventilation. Soluble TREM-1 (sTREM-1) is a member of the immunoglobulin superfamily, and its expression on phagocytes is specifically up-regulated by microbial products. Human tissues infected with bacteria that are infiltrated by neutrophils and monocytes express high levels of TREM-1. In mechanically ventilated patients with ventilator-associated pneumonia, the detection of sTREM 1 in mini–bronchoalveolar lavage was a much more accurate diagnostic tool than any clinical finding, was the strongest independent factor predicting pneumonia (odds ratio, 41.5) according to a logistic-regression analysis, and had a sensitivity of 98 percent and a specificity of 90 percent for the diagnosis of ventilator-associated pneumonia. Thus, the measurement of sTREM-1 could be a useful marker as an addition to the classic clinical criteria and the results on microbiologic culture, particularly in patients with negative cultures and positive clinical findings and vice versa.

However, many aspects have to be studied before such a measurement can be incorporated into diagnostic approaches. We need to understand the influence of bacterial colonization, the effects of previous antimicrobial treatment, and the usefulness of this test in patients with the acute respiratory distress syndrome. Moreover, it is important to confirm that the test is valid particularly in the group of patients with diagnoses that cannot be determined by means of the current approaches. Finally, it seems important to determine whether this indicator could be measured with the same accuracy in a way that would not require the use of fiberoptic bronchoscopy to obtain samples (e.g., tracheobronchial aspirates). In the meantime, we advocate pragmatic approaches based on current evidence, such as those outlined in the Table.

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# A Clearer View of Effusive–Constrictive Pericarditis

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In the 1920s and 1930s, when pericardiectomy first became an established therapy for constrictive pericarditis, surgeons recognized the condition in which pericardial effusion coexists with a visceral constrictive pericarditis (or constrictive epicarditis) (see Figure). In 1971, clinical and hemodynamic features were described that allowed the diagnosis to be made before an operation or autopsy had been performed. Since that time, individual cases have been reported nearly every year. Many of these cases, including at least one reported in the Case Records of the Massachusetts General Hospital,[1] occurred in