



Evidence-Based Medicine Journal Club

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Journal club critique

Diagnostic techniques for ventilator-associated pneumonia: Conflicting results from two trials

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Expanded Abstract

Citation

A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med* 2006, 355:2619-2630 [1].

Background

Critically ill patients who require mechanical ventilation are at risk for ventilator-associated pneumonia. Current data are conflicting as to the optimal diagnostic approach in patients who have suspected ventilator-associated pneumonia.

Methods

Objective: To compare the quantitative culture of bronchoalveolar-lavage fluid and nonquantitative culture of endotracheal aspirate in critically ill patients with suspected ventilator-associated pneumonia, testing the hypothesis that bronchoscopy with quantitative culture would be associated with lower mortality rates and less use of antibiotics.

Design: Multi-center non-blinded randomized controlled trial.

Setting: 28 intensive care units (ICUs) across Canada and the United States.

Subjects: 740 immunocompetent critically ill adult patients with suspected ventilator-associated pneumonia after 4 days in the ICU. Patients known to be colonized or infected with *Pseudomonas* species or methicillin-resistant *Staphylococcus aureus* were excluded.

Intervention: Using a 2-by-2 factorial design, subjects were randomly assigned to a) undergo bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid or endotracheal aspiration with nonquantitative culture of the aspirate, and to b) receive empirical combination

antibiotic therapy or monotherapy. Empirical antibiotic therapy was initiated in all patients until culture results were available, at which point a protocol of targeted therapy was used for discontinuing or reducing the dose or number of antibiotics, or for resuming antibiotic therapy to treat a pre-enrollment condition if the culture was negative.

Outcome: The primary outcome was 28-day mortality. Secondary outcomes included ICU and hospital survival, duration of mechanical ventilation, response to clinical and microbiologic treatment, discontinuation of antibiotics after culture results known, and other measures of antibiotic use.

Results

There was no significant difference in 28-day mortality rate between the bronchoalveolar-lavage group and the endotracheal-aspiration group (18.9% and 18.4%, respectively; $P=0.94$). The bronchoalveolar-lavage group and the endotracheal-aspiration group also had similar rates of targeted therapy (74.2% and 74.6%, respectively; $P=0.90$), days alive without antibiotics (10.4+/-7.5 and 10.6+/-7.9, $P=0.86$), and maximum organ-dysfunction scores (mean [+/-SD], 8.3+/-3.6 and 8.6+/-4.0; $P=0.26$). The two groups did not differ significantly in the length of stay in the ICU or hospital.

Conclusions

Two diagnostic strategies for ventilator-associated pneumonia--bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid and endotracheal aspiration with nonquantitative culture of the aspirate--are associated with similar clinical outcomes and similar overall use of antibiotics. (Current Controlled Trials number, ISRCTN51767272.)

Commentary

Ventilator-associated pneumonia (VAP) is common, costly, and associated with increased morbidity and mortality. Diagnosis of VAP is based on clinical suspicion and microbiologic confirmation of a sample obtained from the lower respiratory tract. Several methods are available to sample lower respiratory tract secretions, including “non-invasive” sampling via endotracheal aspirate (ETA) and “invasive” sampling via bronchoscopy using either a protected specimen brush or bronchoalveolar lavage (BAL). Debate exists regarding the best sampling approach. However, in the absence of a gold standard to diagnose VAP, a rigorous comparison of different diagnostic techniques is challenging [2]. Therefore, focus has shifted to evaluating the effects of different diagnostic strategies on clinical outcomes, such as use of antibiotics, length of stay, and mortality.

Randomized trials comparing invasive versus non-invasive approaches have produced conflicting results. Three small (n<100) single center trials suggest no difference in mortality for patients managed using invasive versus non-invasive approaches [3-5]. Yet, these studies were underpowered to detect differences in mortality. In contrast, a large multi-center French study of 413 patients with suspected VAP showed that an invasive approach reduced 14-day mortality, organ dysfunction, and antibiotic use [6].

In the current study, the Canadian Critical Care Trials Group conducted the largest randomized trial to date comparing invasive and noninvasive VAP diagnostic techniques [1]. This is a multi-center trial in 740 patients with suspected VAP in which they tested the hypothesis that quantitative culture of BAL fluid would be associated with lower mortality rates and increased use of targeted antibiotic therapy compared to non-quantitative cultures using ETA. Importantly, patients known to be colonized or infected with pseudomonas species or methicillin-resistant *Staphylococcus aureus* (MRSA) were excluded. Once diagnostic sampling was performed, subjects were randomly assigned to one of two empiric antibiotic regimens, meropenem and ciprofloxacin vs. meropenem alone, in a two-by-two factorial design. Antibiotics were then adjusted by the clinical team once culture results were known. There were no differences between diagnostic strategy groups for either clinical outcomes (28-day mortality, organ dysfunction scores, or length of stay) or measures of antibiotic use. The initial empiric antibiotic(s) subjects were randomized to did not alter these findings.

Why did these two large seemingly similar multi-center studies yield different results [1,6]? It is important to recognize differences in the study design between the French and Canadian studies. The criteria to initiate and de-escalate antibiotic therapy differed. In the French study, initial antibiotic therapy, including the decision to withhold all antibiotics, was guided by the results of the Gram-stained respiratory specimen. If no organisms were present and there were no signs of severe sepsis, antibiotics could be

withheld. The Canadian study used broad spectrum initial antibiotic therapy in all subjects. This practice to administer prompt antibiotics in patients suspected to have VAP is consistent with current guidelines, though the use of broad spectrum antibiotics in patients at low risk of Pseudomonas or MRSA infections is not recommended [7]. It is therefore not surprising that the initial antibiotic strategy was judged as adequate (based on organism cultured) in nearly 90% of subjects in the Canadian study, irrespective of diagnostic strategy. This is in contrast to the French study, where the cultured organism(s) was not susceptible to initial antibiotic therapy in 1% of the invasive group, but 13% of the non-invasive group (p<0.001). Furthermore, because antibiotics could be withheld in the French study, it is also not surprising that this study showed reduced antibiotic use with an invasive approach, while the Canadian study did not.

Another key difference between the two studies is the eligibility criteria. In the Canadian study, excluded were patients known to be colonized or infected with pseudomonas species or MRSA, pathogens which were likely not susceptible to their initial empiric antibiotic regimens. The authors note this was to permit standardization of empirical antibiotic treatment such that any differences in observed outcomes could be better attributed to the diagnostic strategy. As pointed out by others, patients at risk for infection with these pathogens may be the ones most likely to benefit from an invasive diagnostic approach [8]. Though there is some face-validity to this argument, it remains unproven. Interestingly, in a pre-specific subgroup analysis, the authors of the Canadian study found a non-significant tendency toward increased mortality in the invasive group when these high-risk pathogens were present.

These studies yet again emphasize that no diagnostic test, whether it be a thermometer, pulmonary artery catheter, bronchoscope, or biomarker, will improve outcomes unless it provides data that drives management decisions that in turn improve outcomes.

Recommendation

Current evidence does not support use of invasive techniques over non-invasive approaches to diagnose VAP in most patients [9,10], with the possible exception of those at high risk of multi-drug resistant infections. It is important to remember that the most important strategy is to initiate prompt, appropriate antimicrobial therapy when VAP is suspected and to de-escalate or adjust the therapy as soon as culture results become available [7].

Competing interests

The authors declare no competing interests.

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