Use of different diagnostic methods for ventilator-associated pneumonia did not affect mortality or targeted antibiotic use

Heyland D, Cook D, Dodek P, Muscedere J, Day A. **A randomized trial of diagnostic techniques for ventilator-associated pneumonia.** N Engl J Med. 2006;355:2619-30.

Clinical impact ratings: Hospitalists ★★★★★☆☆ Critical Care ★★★★★★☆ Pulmonology ★★★★★☆☆

QUESTION

In critically ill patients suspected of having ventilator-associated pneumonia (VAP), does the diagnostic method used affect mortality and antibiotic use?

METHODS

Design: Randomized controlled trial.
Allocation: Concealed.*
Blinding: Unblinded.*
Follow-up period: 28 days or to hospital discharge.
Setting: 28 intensive care units (ICUs) in Canada and the United States.
Patients: 740 critically ill patients ≥ 18 years of age (mean age 59 y, 69% men) who had received mechanical ventilation in the ICU for ≥ 4 days and were suspected of having VAP. Patients were excluded if they were immunocompromised, unsuitable for bronchoscopy, or infected or colonized with *Pseudomonas* species or methicillin-resistant *Staphylococcus aureus*.
Intervention: Bronchoalveolar lavage (BAL) with quantitative culture of the bronchoalveolar-lavage fluid (n = 365) or endotracheal aspiration (ETA) with nonquantitative culture of the aspirate (n = 375). Empirical intravenous antibiotic therapy (meropenem, 1 g every 8 h, with or without ciprofloxacin, 400 mg every 12 h, randomly assigned) was initiated in all patients until culture results were available, at which time a protocol of targeted therapy was to be used.
Outcomes: 28-day mortality, ICU and hospital mortality and length of stay, duration of mechanical ventilation, and use of targeted therapy after culture results were known.
Patient follow-up: 99.9% (intention-to-treat analysis).

MAIN RESULTS

A positive culture was identified in 60% of patients in the BAL group and 52% in the ETA group (P = 0.03). Groups did not differ for 28-day, ICU, or hospital mortality; use of targeted therapy by day 6 (Table); or rates of clinical and microbial cure at 28 days. The BAL and ETA groups had similar median durations (after randomization) of mechanical ventilation (8.9 vs 8.8 d, P = 0.31), ICU stay (12 vs 12 d, P = 0.22), and hospital stay (40 vs 47 d, P = 0.13).

CONCLUSION

In critically ill patients suspected of having ventilator-associated pneumonia, a diagnostic strategy using bronchoalveolar lavage with quantitative culture was associated with mortality and overall antibiotic use similar to that of a strategy based on endotracheal aspiration with nonquantitative culture.

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*See Glossary.

Bronchoalveolar lavage vs endotracheal aspiration for diagnosis of ventilator-associated pneumonia in critically ill patients†

Outcomes	Bronchoalveolar lavage	Endotracheal aspiration	RRI (95% CI)	NNH
28-day mortality	19%	18%	1% (–25 to 37)‡	Not significant
			RRR (CI)	NNT
Intensive care unit mortality	16%	17%	10% (–25 to 35)‡	Not significant
Hospital mortality	23%	26%	13% (–12 to 33)‡	Not significant
			RBR (CI)	NNH
Targeted therapy at 6 d	74%	75%	0% (–8 to 9)	Not significant

†RBR = relative benefit reduction. Other abbreviations defined in Glossary; RRI, RRR, RBR, NNH, NNT, and CI calculated from data in article.
‡Adjusted for Acute Physiology and Chronic Health Evaluation (APACHE) II score and type of empirical antibiotic regimen.

COMMENTARY

The study by the Canadian Critical Care Trials Group (CCCTG) is the largest to date to compare "invasive" (i.e., bronchoscopic BAL and quantitative cultures) and "noninvasive" (i.e., ETA and nonquantitative cultures) sampling techniques to diagnose VAP. The study found no evidence of superiority of the invasive approach, contrary to the results of the second largest study done in France (1).

The CCCTG trial used a factorial design to evaluate both the diagnostic approach and antibiotic therapy (single vs combination), assuming that the 2 interventions would not interact. However, using a fixed empirical regimen is problematic because acting on early culture results is an integral part of the "invasive" strategy, which was used in the French study. Indeed, the 2 studies differed in several important respects. In the CCCTG trial, BAL fluid culture was considered positive if a potential pathogen was isolated, regardless of the colony count, which probably explains both the unexpected finding of a higher rate of positive BAL fluid cultures and the very high proportion of patients (85%) classified as having pneumonia. Furthermore, Gram stains were used in part to initiate therapy and early cultures were used to adapt therapy in both groups of the French trial, whereas all patients in the CCCTG trial received broad-spectrum therapy for a median of 3 days. Finally, the CCCTG trial excluded patients known to be colonized with "high-risk" organisms; however, it is in this more difficult-to-treat population that the invasive–quantitative techniques may be most useful.

While ample evidence exists that early appropriate treatment of patients with sepsis is important, broad-spectrum antibiotic coverage for all patients clinically suspected of pneumonia is questionable. As many as half such patients may not have overt sepsis or even pneumonia. When all patients with suspected VAP receive broad-spectrum antibiotic coverage for several days, the outcome is mainly driven by the adequacy of the empirical regimen and is unlikely to be affected by culture results. Although the CCCTG study adds to our knowledge, it does not provide a definitive answer to the respective value of alternative strategies for diagnosing VAP.

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Reference

1. **Fagon JY, Chastre J, Wolff M, et al.** Ann Intern Med. 2000;132:621-30.