# An Evidence-Based Approach to the Diagnosis of Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined as a pneumonia that develops after 48 hours of mechanical ventilation. VAP is the most common nosocomial infection in the intensive care unit (ICU) and an important cause of morbidity in the ICU. While the incidence varies according to the diagnostic criteria used and the patient population, it complicates the hospital course of approximately 20% of patients receiving mechanical ventilation, or about 5 episodes per 1,000 ventilator days.[1] VAP increases the number of days requiring mechanical ventilation as well as ICU and hospital length of stay; however, it is unclear if VAP independently increases mortality.[1]

SEE THE ORIGINAL STUDY ON PAGE 1453

Aspiration of colonized oropharyngeal secretions is believed to be the major pathogenic mechanism causing VAP.[2] In mechanically ventilated patients, colonization of the oropharynx with potentially pathogenic organisms occurs within 36 hours of intubation, with colonization of the endotracheal biofilm within 96 hours.[3] Using molecular bio-typing Bahrani-Mougeot and colleagues demonstrated that 88% of patients with VAP had the same bacteria isolated from the lungs (via bronchoalveolar lavage [BAL]) as from their oral cavity.[4] The common pathogens causing VAP include *Pseudomonas aeruginosa* and methicillin resistant *Staphylococcus aureus* (MRSA), followed by *Klebsiella pneumoniae*, *Acinetobacter* species, *Stenotrophomonas maltophilia, Streptococcus pneumoniae*, and *Haemophilus influenzae*.[2] Less common pathogens include *Escherichia coli* as well as *Enterobacter*, *Citrobacter*, *Serratia*, and *Legionella* species. Polymicrobial infection is common. Importantly, the incidence of VAP caused by multiple-drug-resistant (MDR) organisms is increasing.[5] VAP caused by an MDR organism(s) is associated with increased mortality.[2,6,7] Risk factors for infection by MDR organisms include intubation for longer than 7 days, previous broad-spectrum antibiotics, hemodialysis, hospitalization for 2 days or more (in the last 90 d) prior to admission to the ICU, nursing home residence, immunosuppression, and chronic wound care.[5,8,9]

The clinical criteria that have "traditionally" been used to diagnose VAP include a new or progressive pulmonary infiltrate, together with fever, leukocytosis, and purulent tracheobronchial secretions. These criteria are, however, non-specific and of little clinical utility in the diagnosis of VAP.[10,11] An autopsy investigation demonstrated that only 52% of patients with pneumonia at autopsy had a localized infiltrate on their chest radiograph, and that 40% did not have a leukocytosis close to their death.[12] The Clinical Pulmonary Infection Score (CPIS) was developed as a "noninvasive" method to diagnose VAP, and uses a combination of clinical features, together with the culture of a tracheal aspirate to diagnose pneumonia.[13] The CPIS assigns 0–12 points based on 6 clinical criteria: fever, leukocyte count, oxygenation, quantity and purulence of secretions, type of radiographic abnormality, and results of sputum (tracheal aspirate) Gram stain and culture. Both the original CPIS and the modified CPIS have, however, proven unreliable for the diagnosis of VAP, with a low sensitivity and specificity, with considerable inter-observer variability in the calculation of the score.[11,14-16] It should be emphasized that the upper respiratory tracts of intubated patients are rapidly colonized with potentially pathogenic organisms and that Gram stain and culture of tracheal aspirates are unable to distinguish between upper-airway colonization and lower-respiratory-tract infection (pneumonia).

As the clinical criteria of VAP lack specificity, a number of diagnostic techniques have been reported that attempt to distinguish between patients with lung infection from those colonized with potentially pathogenic organisms or those with a tracheobronchitis. Lower-respiratory-tract sampling is based on the premise that the lower respiratory tract is normally sterile, that there is a good correlation between the concentration of bacteria in the lung and the severity of the pulmonary inflammatory process, and that BAL quantitative culture closely correlates with the concentration of bacteria in the lung.[17] Chastre and colleagues documented the similarity between BAL quantitative cultures obtained from patients who were dying with VAP and quantitative cultures obtained soon after their death.[18] Fagon and colleagues compared a diagnostic approach based on lower-respiratory-tract sampling and quantitative culture with that of the "standard approach" using clinical criteria and tracheal aspirates.[19] Compared with the noninvasive strategy, the invasive strategy was associated with fewer deaths at 14 days, earlier resolution

of organ dysfunction, and less antibiotic use in patients suspected of having VAP. A meta-analysis of randomized controlled trials of invasive diagnostic strategies demonstrated that this technique led to a change in antibiotics in over 50% of patients.[20]

Several factors limit the routine use of bronchoscopic-directed BAL in the clinical setting; bronchoscopy is expensive, time-consuming, and not readily available in many ICUs. A number of investigators have demonstrated a high concordance between the results of quantitative culture of BAL fluid performed via bronchoscopy with that performed "blindly" (*m*-BAL).[13,21] The advantages of *m*-BAL are that bronchoscopy is not required and that sampling can readily and safely be performed by trained respiratory therapists.[22,23] This is a very practical and cost-effective alternative to invasive diagnostic testing. In this issue of RESPIRATORY CARE, Fujitani and colleagues compared the results of *m*-BAL and quantitative culture with those of qualitative culture of tracheal aspirates in 256 patients with suspected VAP.[24] Concordance between the 2 techniques was only 58%. Most importantly, the diagnosis of VAP based on endotracheal aspirate was associated with a high rate of both false positive and false negative results, many of these misclassifications involving MRSA and *P aeruginosa*. These results have important clinical ramifications; if endotracheal aspirates are used to diagnose VAP, many patients with VAP caused by MRSA and *P. aeruginosa* would receive inadequate or no antibiotic treatment, while many patients without VAP would unnecessarily receive broad-spectrum antibiotics.

The Canadian Critical Care Trials Group randomized patients with suspected VAP to undergo either BAL and quantitative culture, or endotracheal aspiration with non-quantitative culture of the aspirate.[25,26] Patients were further randomized to therapy with meropenem or meropenem and ciprofloxacin. There was no difference in any of the outcome measures between the invasive and noninvasive groups, nor between antibiotic treatment with combination or monotherapy. This study is often cited to support the use of a noninvasive approach to diagnose VAP, as well as to support monotherapy in the treatment of suspected VAP.[27] It should, however, be noted that patients suspected of being infected with MRSA, *P. aeruginosa*, or other MDR organisms were excluded from this study. This is a critical issue in interpreting the results of this study, as *S. aureus* and *P. aeruginosa* are the 2 most common pathogens causing VAP, and infection with an MDR organism is an independent predictor of mortality. Furthermore, all patients received a broad-spectrum carbapenem (meropenem), making it unlikely to detect any difference in outcome between any of the groups of patients infected with highly susceptible pathogens.

Multiple studies have demonstrated that the most important factor determining the outcome of VAP is the early initiation of appropriate antibiotic therapy.[8,28-30] Due to the spectrum of potential pathogens and the increasing prevalence of MDR organisms, a broad-spectrum, multi-drug, empirical antibiotic protocol is required in most patients with suspected VAP (except those at low risk of infection with an MDR organism). BAL and quantitative culture allows for the de-escalation of antibiotics once a pathogen(s) is identified. Furthermore, negative lower-respiratory-tract cultures can be used to stop antibiotic therapy in a patient who had cultures obtained in the absence of an antibiotic change in the past 72 hours.[9] The results of the study by Fujitani and colleagues demonstrate that such an approach is not feasible using qualitative culture of endotracheal aspirates.

It should be acknowledged that *m*-BAL and quantitative culture have a number of limitations, most notably a false-negative rate of between 3–10% and a delay of up to 48 hours before the results are available.[31-33] With the expanding use of biomarkers and rapid assays for bacterial products it is likely that in the future these techniques will be combined with the results of *m*-BAL to more accurately diagnose VAP and identify the implicated pathogens.[34]

**Paul E Marik MD**
Division of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School
Norfolk, Virginia

## REFERENCES

1. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 2005;33(10):2184-2193.
2. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165(7):867-903.
3. Feldman C, Kassel M, Cantrell J, Kaka S, Morar R, Goolam Mahomed A, Philips JI. The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. Eur Respir J 1999;13(3):546-551.
4. Bahrani-Mougeot FK, Paster BJ, Coleman, Barbuto S, Brennan MT, Noll J, et al. Molecular analysis of oral and respiratory bacterial species associated with ventilator-associated pneumonia. J Clin Microbiol 2007;45(5):1588-1593.
5. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, Gilbert C. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998; 157(2):531-539.
6. Rello J, Jubert P, Vallés J, Artigas A, Rué M, Niederman MS. Evaluation of outcome for intubated patients with pneumonia due to *Pseudomonas aeruginosa*. Clin Infect Dis 1996;23(5):973-978.
7. Rello J, Torres A, Ricart M, Vallés J, Gonzalez J, Artigas A, Rodriguez-Roisin R. Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes Am J Respir Crit Care Med 1994;150(6 Pt 1):1545-1549.
8. Garnacho-Montero J, Ortiz-Leyba C, Fernández-Hinojosa E, Aldabó-Pallás T, Cayuela A, Marquez-Vácaro JA, et al. *Acinetobacter bau-*

*mannii* ventilator-associated pneumonia: epidemiological and clinical findings. Intensive Care Med 2005;31(5):649-655.
9. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171(4):388-416.
10. Mabie M, Wunderink RG. Use and limitations of clinical and radiologic diagnosis of pneumonia. Semin Respir Infect 2003;18(2):72-79.
11. Lauzier F, Ruest A, Cook D, Dodek P, Albert M, Shorr AF, et al. The value of pretest probability and modified clinical pulmonary infection score to diagnose ventilator-associated pneumonia. J Crit Care 2008;23(1):50-57.
12. Fábregas N, Ewig S, Torres A, El-Ebiary M, Ramirez J, de La Bellacasa JP, et al. Clinical diagnosis of ventilator-associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax 1999;54(10):867-873.
13. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 1991;143(5 Pt 1):1121-1129.
14. Schurink CA, Van Nieuwenhoven CA, Jacobs JA, Rozenberg-Arska M, Joore HC, Buskens E, et al. Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. Intensive Care Med 2004;30(2):217-224.
15. Croce MA, Swanson JM, Magnotti LJ, Claridge JA, Weinberg JA, Wood GC, et al. The futility of the clinical pulmonary infection score in trauma patients. J Trauma 2006;60(3):523-527.
16. Pham TN, Neff MJ, Simmons JM, Gibran NS, Heimbach DM, Dlein MB. The clinical pulmonary infection score poorly predicts pneumonia in patients with burns. J Burn Care Res 2007;28(1):76-79.
17. Johanson WG Jr, Seidenfeld JJ, Gomez P de los Santos R, Coalson JJ. Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. Am Rev Respir Dis 1988;137(2):259-264.
18. Chastre J, Fagon JY, Bornet-Lecso M, Calvat S, Dombret MC, al Khani R, et al. Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 1995;152(1):231-240.
19. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stéphan F, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. Ann Intern Med 2000;132(8):621-630.
20. Shorr AF, Sherner JH, Jackson WL, Kollef MH. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. Crit Care Med 2005;33(1):46-53.
21. Kollef MH, Bock KR, Richards RD, Hearns ML. The safety and diagnostic accuracy of minibronchoalveolar lavage in patients with suspected ventilator-associated pneumonia. Ann Intern Med 1995;122(10):743-748.
22. Marik PE, Brown WJ. A comparison of bronchoscopic vs blind protected specimen brush sampling in patients with suspected ventilator-associated pneumonia. Chest 1995;108(1):203-207.
23. Marik PE, Careau P. A comparison of mini-bronchoalveolar lavage and blind -protected specimen brush sampling in ventilated patients with suspected pneumonia. J Crit Care 1998;13(2):67-72.
24. Fujitani S, Cohen-Melamed MH, Tuttle RP, Delgado E, Taira Y, Darby JM. Comparison of semi-quantitative endotracheal aspirates to quantitative non-bronchoscopic bronchoalveolar lavage in diagnosing ventilator-associated pneumonia. Respir Care 2009;54(11):1453-1461.
25. Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 2006;355(25):2619-2630.
26. Heyland DK, Dodek P, Muscedere J, Day A, Cook D; Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med 2008;36(3):737-744.
27. Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D; VAP Guidelines Committee; Canadian Critical Care Trials Group. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: diagnosis and treatment. J Crit Care 2008;23(1):138-147.
28. Kollef KE, Schramm GE, Wills AR, Reichley RM, Micek ST, Kollef MH. Predictors of 30-day mortality and hospital costs in patients with ventilator-associated pneumonia attributed to potentially antibiotic-resistant gram-negative bacteria. Chest 2008;134(2):281-287.
29. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002;122(1):262-268.
30. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003;31(12):2742-2751.
31. Nseir S, Marquette CH. Diagnosis of hospital-acquired pneumonia: postmortem studies. Infect Dis Clin North Am 2003;17(4):707-716.
32. Malhotra AK, Riaz OJ, Duane TM, Aboutanos MB, Goldberg AE, Smalara KM,et al. Subthreshold quantitative bronchoalveolar lavage: clinical and therapeutic implications. J Trauma 2008;65(3):580-588.
33. Miller PR, Meredith JW, Chang MC. Optimal threshold for diagnosis of ventilator-associated pneumonia using bronchoalveolar lavage. J Trauma 2003;55(2):263-267.
34. Gibot S, Cravoisy A, Levy B Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 2004;350(5):451-458.

---

The author has disclosed no conflicts of interest.

Correspondence: Paul E Marik MD, Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, HH Suite 410, 825 Fairfax Avenue, Norfolk VA 23507. E-mail: marikpe@evms.edu.