CORRESPONDENCE

Diagnosis of Ventilator-Associated Pneumonia

TO THE EDITOR: Heyland and colleagues, on behalf of the Canadian Critical Care Trials Group (Dec. 21 issue),[1] report on the comparison between bronchoalveolar lavage and endotracheal aspiration for the diagnosis of ventilator-associated pneumonia. The two techniques were associated with similar clinical outcomes and similar overall antibiotic use. However, 105 (28.8%) of the 365 patients in the bronchoalveolar-lavage group had received new antibiotics within 3 days before randomization, probably after the onset of the first symptoms related to ventilator-associated pneumonia. Since these patients were different from the rest of the patients,[2,3] we wonder how decisions concerning their antimicrobial treatment were made. Furthermore, we would like to emphasize that on day 6, the rate of targeted therapy was only 74.2% in the bronchoalveolar-lavage group; thus, many patients in this group did not undergo early treatment de-escalation, even though it was indicated on the basis of the microbiologic results. More information on the application of decision algorithms in the bronchoalveolar-lavage group and the endotracheal-aspiration group after culture results were available (as early as day 3) would be informative. Obviously, the potential benefit of using a diagnostic tool, such as bronchoalveolar lavage, to restrict unnecessary use of antibiotics safely in this setting can be achieved only when decisions regarding antimicrobial therapy reflect the culture results.[4]

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1. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 2006;355:2619-30.
2. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867-903.
3. Souweine B, Veber B, Bedos JP, et al. Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: impact of previous antimicrobial treatments. Crit Care Med 1998;26:236-44.
4. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: a randomized trial. Ann Intern Med 2000;132:621-30.

TO THE EDITOR: The Canadian Critical Care Trials Group compared quantitative culture of bronchoalveolar-lavage fluid with nonquantitative culture of endotracheal aspirate for the diagnosis of ventilator-associated pneumonia. The diagnostic confirmation was considered to be acceptable if the pretest probability of ventilator-associated pneumonia was high, even if the culture of bronchoalveolar-lavage fluid had a level of less than 10^4 colony-forming units per milliliter, the level used

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as a nonquantitative test. This approach contributed to the finding of a higher proportion of confirmed cases of ventilator-associated pneumonia in the bronchoalveolar-lavage group than in the endotracheal-aspiration group (86.3% and 82.9%, respectively). The pretest opinion obviously played an important role and contributed to the clinicians' providing antibiotic treatment for all the bacteria identified, including bacteria detected in nonsignificant quantities.

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TO THE EDITOR: The exclusion of patients known to be colonized with methicillin-resistant *Staphylococcus aureus* or pseudomonas species severely limits the usefulness of the data reported by the Canadian Critical Care Trials Group, since these are the pathogens most commonly reported to cause ventilator-associated pneumonia. It is disappointing that the study investigators did not follow current guidelines for ventilator-associated pneumonia, according to which empirical treatment is based on the risk of infection with multidrug-resistant pathogens.[1] Patients at risk for infection with such pathogens are most likely to benefit from the bronchoalveolar lavage.[2,3] If all patients with suspected ventilator-associated pneumonia are treated with broad-spectrum antibiotics, difference between the groups will of course be minimal, regardless of the diagnostic technique. We hope that readers will not embrace treatment with meropenem with or without ciprofloxacin for all patients with suspected ventilator-associated pneumonia.

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1. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.
2. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 2000;31:Suppl 4:S131-S138.
3. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998;157:531-9.

THE AUTHORS REPLY: In response to Chastre and Fagon: patients partially treated for ventilator-associated pneumonia were excluded from the study. However, excluding patients with recent changes in antibiotics would have seriously limited the generalizability of our findings. We conducted a subgroup analysis based on the presence or absence of prior antibiotic exposure but did not observe any suggestion of a benefit from bronchoscopy in the patients with prior exposure.

An antibiotic-management algorithm delineating de-escalation therapy was provided to all clinicians. In both study groups, the median duration of study antibiotic use was 3 days (interquartile range, 2 to 5), indicating that the algorithm was applied early after enrollment. Since for some intensive care units, there were delays in reporting culture results, we allowed up to 5 days after randomization before determining whether the targeted therapy had been administered. On day 6, the rates of targeted therapy were similar in the bronchoalveolar-lavage group and the endotracheal-aspiration group. Recalculating rates of targeted therapy on the basis of the first 3 days showed no significant difference between bronchoalveolar lavage with quantitative cultures (45.2%) and endotracheal aspiration (51.1%) ($P=0.10$).

We agree with Misset et al. that pretest probability estimates of ventilator-associated pneumonia influence management decisions, since culture results are not a reference standard for infection and are influenced by prior antibiotic use. In this trial, as in practice, many clinicians interpreted the quantitative results of the analysis of bronchoalveolar-lavage fluid conservatively; for patients with a high pretest probability of ventilator-associated pneumonia, a pathogen yielding less than 10^4 colony-forming units per milliliter was still treated. But clinicians did not provide antibiotic treatment for all bacteria identified in this trial. Among the patients in the two study groups who had positive cultures, all antibiotics were discontinued by day 6 in 8.7% of the patients in the bronchoalveolar-lavage group and 11.3% of those in the endotracheal-aspiration group, and the study antibiotics were discontinued by day 6 in 56.9 and 56.2%, respectively.

Marik and Baram refer to our exclusion of patients known to be colonized or infected with methicillin-resistant *S. aureus* or pseudomonas spe-

cies. Nonstandardized empirical antibiotic therapy has confounded the interpretation of findings in some previous trials of the diagnosis of ventilator-associated pneumonia. Therefore, the initial antibiotic therapy in our trial, consisting of meropenem with or without ciprofloxacin, served to standardize empirical treatment until culture results became available. Patients with known pathogens not susceptible to these drugs were excluded; thus, differences observed in outcomes could be better attributed to the diagnostic strategy. It is important not to interpret the use of these antibiotics as clinical recommendations for the treatment of ventilator-associated pneumonia. The treatment guidelines of the American Thoracic Society were published after our trial had been completed.[1]

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1. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

Lapatinib plus Capecitabine in Breast Cancer

TO THE EDITOR: In the trial reported by Geyer et al. (Dec. 28 issue),[1] which compared capecitabine alone with a combination of lapatinib and capecitabine in women with HER2-positive advanced breast cancer, approximately 60% of patients had received trastuzumab within the previous 8 weeks. It is possible that the activity of lapatinib was enhanced by the persistence of trastuzumab levels in blood. Earlier studies of the pharmacokinetics of trastuzumab administered weekly or every 3 weeks indicate that the drug's half-life is 3 to 4 weeks, although this may be an underestimate. Therefore, synergism between lapatinib and trastuzumab, leading to a more complete blockade of the HER2 pathway, cannot be excluded and may partly account for the impressive improvement in outcomes with the combined regimen.

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1. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-43.

THE AUTHORS REPLY: We agree that many of the patients entering our trial probably had persistent levels of trastuzumab, which could have enhanced the activity of lapatinib. An exploratory analysis to determine whether the interval from the last dose of trastuzumab to randomization affected the activity of lapatinib was planned as a component of a subsequent updated analysis of the overall trial data. However, to provide a response to Sonpavde's question, we proceeded with an analysis of data

Table 1. Effect of the Interval between the Administration of Trastuzumab and Randomization on Time to Disease Progression.*

Interval between Last Trastuzumab Dose and Randomization	Lapatinib plus Capecitabine		Capecitabine Alone		Hazard Ratio (95% CI)	P Value
	No. of Patients	Median Time to Progression	No. of Patients	Median Time to Progression		
		wk		*wk*		
≤8 Wk	98	36.7	94	19.7	0.54 (0.34–0.86)	0.007
>8 Wk	59	39.3	60	14.6	0.48 (0.26–0.88)	0.01

* P values were calculated by the log-rank test. CI denotes confidence interval.