Commentary

Is bronchoalveolar lavage with quantitative cultures a useful tool for diagnosing ventilator-associated pneumonia?

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Abstract

The results of a recently published Canadian study suggest that bronchoalveolar lavage and endotracheal aspiration are associated with similar clinical outcomes and similar overall use of antibiotics in critically ill patients with suspected ventilator-associated pneumonia (VAP). The study, however, does not provide convincing information on the best strategy to diagnose VAP, to accurately choose initial treatment and to exclude VAP in order to avoid administering antibiotics to patients without bacterial infection. In fact, this trial has several limitations or drawbacks: patients at risk for developing VAP due to *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* were excluded, far from the real-life scenario; a significant number of patients were receiving recent antimicrobial therapy at the time of sampling, with, consequently, difficult-to-interpret culture results; randomization of included patients for initial treatment – meropenem plus ciprofloxacin or meropenem alone – resulted in a high rate of inappropriate initial empirical therapy due to the absence of customization to local epidemiology; and the initial decision to treat and the re-evaluation at day 3 were, in fact, based on clinical judgment and not on direct examination and quantitative culture results. In summary, because antimicrobial treatment was initiated in all suspected patients and was rarely withheld in patients with negative cultures, the study does not suggest an appropriate strategy for improving the use of antibiotics in intensive care unit patients. Such a strategy has two requirements: immediate administration of adequate therapy in patients with true VAP, and avoidance of administering antibiotics in patients without bacterial infection.

A new trial conducted by the Canadian Critical Care Trials Group investigated the impact of different diagnostic approaches on outcomes of patients suspected of having ventilator-associated pneumonia (VAP) [1]. The diagnosis of VAP has been a controversial subject for more than 15 years [2,3]. Immediate administration of adequate antibiotic therapy is critical to improving survival in patients with VAP. At the same time, appropriate antimicrobial stewardship includes not only limiting the use of inappropriate agents in patients with VAP, but also improving our ability to diagnose and exclude infection in the intensive care unit (ICU) setting in order to avoid administering antibiotics to patients without bacterial infection [4].

This recent published randomized trial [1] comparing the quantitative culture of bronchoalveolar lavage (BAL) fluid and the culture of endotracheal aspirate in critically ill patients with suspected VAP adds to the information presented by four previous trials [5-8]. The Canadian Critical Care Trials Group found that the two diagnostic techniques were associated with similar clinical outcomes and similar overall use of antibiotics (Table 1). Several considerations should be taken into account, however, to appropriately evaluate the possible impact of diagnostic techniques on the individual (patient morbidity and mortality) and on the collective (emergence and dissemination of antibiotic-resistant strains) outcomes.

First, as clearly underlined by Kollef in his related editorial [9], the exclusion of patients previously colonized or infected with methicillin-resistant *Staphylococcus aureus* or *Pseudomonas* species and the exclusion of those patients having previously received the 'study drugs' (that is, meropenem and/or ciprofloxacin) resulted in a low rate of studied patients with 'high-risk' pathogens responsible for VAP. A proportion of less than 12% of difficult-to-treat pathogens, such as *P. aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and/or methicillin-resistant *S. aureus*, as compared with more than 30% in the French study [8], diminishes the usefulness of the results of this study in real life.

Second, 29% of patients managed using BAL had new antibiotics initiated within 3 days before randomization, probably after the onset of the first signs in relation to VAP,

BAL = bronchoalveolar lavage; ICU = intensive care unit; VAP = ventilator-associated pneumonia.

Table 1

Outcomes and antibiotics in the Canadian Critical Care Trials Group study [1]

	Endotracheal aspiration ($n = 374$)	Bronchoalveolar lavage ($n = 365$)
Outcomes		
Mortality at day 28 (%)	18.4	18.9
Duration of mechanical ventilation (days)	8.8 (7.0–10.7)	8.9 (7.4–10.7)
Duration of intensive care unit stay (days)	12.2 (10.9–14.2)	12.3 (10.9–13.8)
Final diagnosis of ventilator-associated pneumonia (%)	82.9	86.3
Antibiotics		
Adequacy of empirical treatment among patients with positive cultures (%)	89.5	89.0
Targeted therapy by day 6 (%)	74.6	74.2
Number of days alive without antibiotics	10.4 ± 7.5	10.6 ± 7.9

No differences were statistically significant.

which is problematic when using quantitative culture techniques. In this case, a negative finding or a result below the usual threshold of 10^4 colony-forming units/ml could indicate either that the patient has been successfully treated for pneumonia and the bacteria are eradicated, or that there was no lung infection to begin with [10]. These authors did not give any information on how decisions regarding antibiotic treatment were taken in this group of patients.

Third, the authors report a relatively high rate (14%) of inappropriate initial empirical therapy in the BAL group. As indicated above, the low frequency of high-risk, difficult-to-treat pathogens responsible for pneumonia cannot explain such a disappointing result, when compared with the 0.5% rate of inappropriate initial therapy reported by Fagon and coworkers in the invasive strategy group [8]. The most probable explanation is that all patients included in this study were also randomized to receive a fixed combination therapy or monotherapy as initial treatment: meropenem plus ciprofloxacin or meropenem alone. Several studies have clearly established that initial antimicrobial therapy in patients with VAP should be customized to local epidemiology at the ICU level [11].

Fourth, even on day 6 the rate of targeted therapy was only 74.2% in the BAL arm, underlining the fact that, in many patients managed using this diagnostic technique, early de-escalation was not performed although clearly indicated. Unfortunately, information on how decision algorithms were followed in the two study arms once cultures were available (as soon as day 2 or day 3) was not given. Obviously, the potential benefit of using a diagnostic tool such as BAL for safely restricting unnecessary antimicrobial therapy in such a setting can only be obtained when decisions regarding antibiotics are closely linked to bacteriological – both direct examination and cultures – results [12]. In the current study, BAL was not used for identifying patients with VAP who needed antimicrobial therapy; this decision was essentially left to the ICU physicians in charge of the included patients on the basis of their clinical judgment, even when BAL culture results were $<10^4$ colony-forming units/ml. Interestingly, the proportion of 'confirmed pneumonia' was 86% in the BAL group and 83% in the endotracheal aspirate group. In contrast to previous recommendations concerning the use of quantitative BAL, therefore, many patients with quantitative culture results below the cut-off point of 10^4 colony-forming units/ml continued to receive antibiotics, even after day 3. This could entirely explain why there was a similar use of antibiotics in the two study arms.

Finally, a major benefit of a negative BAL specimen may be to direct attention away from the lungs as the source of fever and, in the absence of antibiotic interference, to more readily diagnose other potential sites of infection. Delaying diagnosis or definitive treatment of the true site of infection may lead to prolonged antibiotic therapy and to induction of additional dysfunction [13,14]. In the current trial, we are left with uncertainties regarding the numbers of extrapulmonary infection in the two arms of the trial, as well as how long the recommended duration of therapy in patients with VAP should be and the how patients were managed in case of a second episode.

In summary, even if the results of the Canadian study are consistent with those of the three Spanish trials (Table 2) in which antimicrobial treatment was also initiated in all suspected patients and rarely withheld in patients with negative cultures, our own bias is that additional studies will be needed before one can conclude that a strategy based on the systematic collection of distal pulmonary secretions prior to the introduction of new antibiotics and quantitative culture techniques is useless. In real life, the key issue is to be able to

Table 2

Results of the randomized studies of diagnostic techniques

		28-day mortality (%)		Antibiotic usage	
Study	Sample size	Invasive arm	Clinical arm	Invasive arm	Clinical arm
Sanchez-Nieto *et al.* [5]	51	45.8	26.7	ND	ND
Ruiz *et al.* [6]	76	37.8	46.1	13 ± 4[a]	12 ± 4
Sole Violan *et al.* [7]	88	22.2	20.9	ND	ND
Fagon *et al.* [8]	413	30.9	38.8	11.5 ± 9.0[b]	7.5 ± 7.6
Canadian Critical Care Trials Group [1]	739	18.9	18.4	10.4 ± 7.5[c]	10.6 ± 7.9

ND, not determined. [a]Ruiz *et al.* [6] reported the total duration of antibiotic treatment; $p = 0.48$. [b]Fagon *et al.* [8] reported antibiotic-free days; $p < 0.002$. [c]The Canadian Critical Care Trials Group [1] reported antibiotic-free days; $p = 0.86$.

adhere to a de-escalation strategy, which is the only way to curb the unnecessary use of antibiotics in the ICU. The predominant impact of pretest opinion and the absence of clear bacteriological-based decision algorithms in the current study may unfortunately encourage physicians to pursue antibiotics in most patients after 2 days, even once results of bacterial cultures are available.

Competing interests

The authors declare that they have no competing interests.

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