

Commentary

Pro/con clinical debate: The use of a protected specimen brush in the diagnosis of ventilator associated pneumonia

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Abstract

Although mechanical ventilation is instituted as a life-saving technique, it may lead to complications that can negatively impact on patients' morbidity and/or mortality. Ventilator associated pneumonia (VAP) is one such complication that is a common challenge to intensivists. Although most experts would agree that early 'appropriate' antibiotic use is essential in patients who develop VAP, the best diagnostic test to guide decision-making is far from clear. One diagnostic test that is capable of providing microbiological samples from the lower respiratory tree is invasive bronchoscopy with a protected specimen brush. Such a procedure has long been available to intensivists and is frequently employed in many intensive care units. However, this procedure has associated costs and potential complications, and its utility in VAP has been challenged. In this issue of *Critical Care Forum*, the two sides of this debate are brought forward with compelling arguments. The authors' arguments should fuel future trials.

Keywords bronchoscopy, pneumonia, protected specimen brush, quantitative cultures

The scenario

A 50-year-old man has been in your intensive care unit (ICU) for 10 days. He was initially admitted with respiratory failure secondary to congestive heart failure. Since admission he has been intubated and mechanically ventilated. His progress in the ICU has been relatively slow as a result of a variety of minor setbacks. Finally, his condition seems to be improving and you

have started the weaning process. On your rounds, you identify a new temperature and purulent secretions that are being suctioned from his endotracheal tube. The chest X-ray also shows a new infiltrate. You suspect VAP and you need to decide whether to perform a bronchoscopy to assist you with making a diagnosis and guiding future antibiotic choice.

Pro: a protected specimen brush should be used in the diagnosis of VAP

Daren Heyland

Given the absence of a true 'gold standard', discussions about the sensitivity and specificity of various diagnostic techniques for VAP are not illuminating. However, a question still remains: Does a management strategy that incorporates the results from invasive diagnostic tests lead to important differences in patient management and improved outcomes

compared with results from endotracheal aspirates? This important question cannot be answered without examining issues related to antibiotic use.

For a patient with VAP, what is probably more important to the final outcome than the diagnostic test is the use of

appropriate broad spectrum empiric antibiotics. Several studies have documented that patients with a suspicion of VAP who receive inadequate empiric antibiotic therapy are more likely to die or experience complications [1,2]. The use of broad spectrum antibiotics as the initial management of suspected VAP is likely to result in less microbiologic failure and improved clinical outcomes. However, the overuse or indiscriminate use of broad spectrum antibiotics is implicated in the development of infections due to multiresistant bacteria and fungi [3,4]. The primary strategy for preventing antibiotic-resistant nosocomial infections is eliminating or reducing the unnecessary use of antibiotics [5]. Several studies have demonstrated that narrowing the spectrum of antibiotics and/or discontinuing antibiotics are more probable with the use of bronchoscopy with quantitative cultures [6–8]. The same cannot be said for quantitative cultures from endotracheal aspirates.

Do invasive diagnostic tests influence patient outcomes? A recent randomized trial suggested that patients managed according to results from invasive tests had a lower mortality at 14 days (16.2% versus 25.8%, $P=0.022$) compared with patients who underwent endotracheal aspiration [8]. Mortality rates were similar in both groups at 28 days. In this study [8],

the non-standardized antibiotic administration represents an important confounding variable. The choice of individual antibiotics was left to the attending physician, who was to follow the American Thoracic Society Consensus Conference guidelines on antibiotic therapy [9]. Using these guidelines can result in several different combinations of antibiotics. There was a much lower rate of inappropriate empiric antibiotics in the group that underwent invasive testing (0.5% versus 13%, $P<0.001$). Thirty-two percent of patients with inappropriate empiric antibiotics died compared with 20.4% of patients who received appropriate initial therapy ($P>0.02$). Of the cohort receiving inappropriate antibiotics, 33% died (all in the non-invasive group) before day 14. It is plausible that the mortality difference between the two groups had less to do with the diagnostic strategy and more to do with the antibiotic choices.

In conclusion, the potential advantage of using invasive techniques is that antibiotic therapy may be tailored to the results of diagnostic tests. This may reduce unnecessary broad spectrum antibiotics, which could have important clinical implications, such as minimizing the emergence of resistant microorganisms in the ICU and reducing antibiotic costs.

Con: a protected specimen brush should not be used in the diagnosis of VAP

Santiago Ewig and Antoni Torres

There is no doubt that clinical symptoms, laboratory results, and chest radiographs are only of limited value in establishing the diagnosis of VAP, thereby mounting a considerable risk of antimicrobial overtreatment [10]. The key question is whether independent microbiological criteria are able to correct for the bias arising from clinical judgment.

Of all diagnostic techniques, the bronchoscopic protected specimen brush (PSB) has been studied most extensively. Theoretically, the double catheter and the distal plug design should preserve a very high specificity. On the contrary, since the PSB samples a very small amount of respiratory secretions (about 0.01–0.001 ml), it is expected to yield a relatively limited sensitivity. The results of clinical studies evaluating the PSB technique have in fact been conflicting, with wide variations of operative indices being a striking feature. Overall, false-negative and false-positive results were reported in 10–40% of cases [11–15].

Differing references and thresholds for the calculation of diagnostic indices account for a large part of these variations [15]. Moreover, the PSB technique exhibits a considerable variability. One study could demonstrate that the qualitative repeatability was 100%, whereas in 59% of the patients the quantitative results varied by more than 1 \log_{10} , with 14% spreading out on each side of the chosen threshold [16]. In addition, several problems inherent to the evaluation of acutely ill patients do have a significant bearing on the

interpretation of PSB results. Reasons for false-negative results include sampling errors owing to the multifocal evolution of VAP, prior antimicrobial treatment, and borderline results in an early stage of infection. Reasons for false-positive results include contamination of the sample during bronchoscopy or in the processing laboratory, colonization rather than infection, and bronchiolitis [15].

Several investigations have been performed using postmortem histology or lung culture as an independent reference [17–21]. The postmortem model added significantly to our understanding of the relationships of histology and microbiology, and to the diagnosis of VAP. Nevertheless, as regards operative indices, roughly the same results were obtained as in studies without strictly independent references. Of concern, it became evident that whereas the reported results strongly depend on the reference used, no reference is irrefutable. An important clinical implication was a comparable yield of bronchoscopic diagnostic tools, such as PSB and broncho-alveolar lavage (BAL), as well as of invasive and non-invasive techniques in most studies.

In view of these findings, it seems unlikely that PSB (and/or BAL) could have an advantage over non-invasive tools in terms of clinical outcomes. Overall, four corresponding randomized studies have so far been published evaluating non-invasive and invasive diagnostic tools [7,8,22,23].

Whereas all Spanish studies [7,22,23] could not find any difference with regard to outcome measures (such as length of hospitalization, length of ICU stay, length of intubation, mortality, and costs), the multicenter French study [8] found a bronchoscopic strategy including quantitative cultures of PSB and/or BAL to be superior compared with a clinical strategy using qualitative tracheobronchial aspirates in terms of 14-day mortality, morbidity, and use of antimicrobial treatment.

Differences in study design may again have accounted for most of the differences. In our view, however, it is unclear from the French study data how the invasive strategy accounted for the better outcome. Moreover, the clinical group had a significantly higher rate of patients with inadequate antimicrobial treatment [8]. Finally, since the French study compared inhomogeneous strategies (a bronchoscopic approach with quantitative cultures versus a clinical approach with qualitative cultures), it does not allow us to make any conclusions about the value of invasive bronchoscopic tools as compared with the quantitative tracheobronchial aspirate [24]. In our recent randomized study evaluating the impact of diagnostic techniques on the outcome, we could not find any difference in outcome when quantitative tracheobronchial aspirates were compared with a bronchoscopic strategy [23].

What therefore is the role of PSB in clinical practice? We argue that currently available data do not support a regular bronchoscopic approach to the diagnosis of suspected VAP. Relying on microbiological data as an independent reference

would clearly introduce a new bias; we could show that the microbiological correction of false-positive clinical judgments is countered by the misclassification of correctly positive judgments [25].

Instead, we support an approach that is based on extended clinical criteria (including not only the classical four criteria as defined by Johanson [26], but also the Clinical Pulmonary Infection Score [27]) and quantitative cultures of tracheobronchial aspirates. In this approach, microbiological data do not form independent criteria for the diagnosis of VAP, but support a clinical decision that inevitably is not fully standardized and is open to bias. The selection of an antimicrobial regimen should be based on local microbial and resistance patterns.

New investigational concepts that define subgroups of low-risk patients in whom antimicrobials may be stopped after 3 days, and that hint at reducing the antimicrobial selection pressure by reducing the time of exposure to and by introducing crop rotation of antimicrobials, are in line with our approach [28–30]. The bronchoscopic investigation would then be regarded as a second-line target in case of a failure to respond to empiric antimicrobial treatment. In these patients, several conditions favor the use of bronchoscopic techniques: PSB in combination with BAL; a higher pretest probability of VAP; a higher probability of drug-resistant pathogens; and the possible presence of opportunistic pathogens, non-infectious mimics, and specific tracheobronchial conditions that require a visualization of the tracheobronchial tree [15].

Pro's response

Daren Heyland

I have not suggested that we 'rely on microbiological data [from bronchoscopic specimens] as an independent reference standard'. Microbiological data, from whatever source, need to be incorporated as a variable in a complex equation that considers other patient characteristics to determine the likelihood of pneumonia. 'Pulmonary infection scores' have not been properly validated, and suggesting the use of them is not

consistent with current evidence. I posit that sufficient evidence exists to conclude that bronchoscopy can help clinicians manage the use of broad spectrum antibiotics more appropriately. Whether bronchoscopy influences patient outcomes remains to be determined. When completed, a multicenter randomized trial being conducted by the Canadian Critical Care Trials Group will provide the definitive answer.

Con's response

Santiago Ewig and Antoni Torres

We respond with two points. First, given the failure of any diagnostic tool to independently establish the presence of VAP, no tool is helpful in reducing 'unnecessary' broad spectrum antimicrobial treatment. Treatment decisions must still be based on both clinical and microbiological data. Second, given the comparable yield of quantitative PSB/BAL

and tracheobronchial aspirates in the detection of potentially pathogenic microorganisms, antimicrobial treatment may be satisfactorily tailored according to general microbial and susceptibility patterns prevalent in a given institution and to the results of quantitative tracheobronchial aspirates in the individual patient.

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