Diagnosis of ventilator-associated pneumonia: Where do we go from here?

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Nosocomial (hospital-acquired) pneumonia is the second most common nosocomial infection, after urinary tract infections, but the leading cause of death related to a nosocomial infection (1). Patients at the greatest risk for acquiring nosocomial pneumonia are those receiving mechanical ventilation. Ventilator-associated pneumonia is reported to occur in 10% to 70% of patients undergoing invasive mechanical ventilation, the rate varying with the patient population studied and diagnostic criteria used (2-4). The crude mortality is as high as 70%, but debate over the attributable mortality and whether nosocomial pneumonia is an independent risk factor for death continues (3-5). At least part of the debate is fueled by a lack of confidence in the criteria used to define nosocomial pneumonia, particularly in critically ill patients who are ventilated. The difficulties in diagnosing nosocomial pneumonia can be summarized broadly by the recognition that many other noninfectious processes may mimic ventilator-associated pneumonia and that the airway of the intubated patient is frequently colonized by bacteria (6).

Historically, clinical criteria have been used by clinicians and researchers to define nosocomial pneumonia. Clinical criteria continue to form the backbone of definitions that also incorporate microbiology and/or histopathology findings. Subject to minor differences in the exact parameters used, the usual clinical criteria used to define the presence of nosocomial pneumonia have been a new or progressive infiltrate on chest radiograph with one to three of the following: leukocytosis (or leukopenia), fever (or temperature less than 35°C), or purulent tracheobronchial secretions (7-9). Using clinical criteria as well as the presence of pathogenic bacteria in pulmonary secretions or biopsies and response to antibiotics, Andrews et al (10) compared clinical prediction of the presence or absence of bacterial pneumonia at the time of death with autopsy findings in 24 patients with adult respiratory distress syndrome. They found that the presence or absence of pneumonia was successfully predicted in 71% of patients (statistically significantly better than chance), with prediction better for excluding (80%) pneumonia than diagnosing (64%) it. No single parameter was able to discriminate between the presence and absence of pneumonia in this small study (10). In another study (2), the diagnostic accuracy of portable chest radiographs was evaluated in 69 critically ill, ventilated patients who came to autopsy. The authors assessed a number of standard radiographic abnormalities including air bronchograms (single or multiple), silhouetting, alveolar infiltrates (unilateral or bilateral), fissure abutment and atelectasis, and found that none had a diagnostic efficiency over 68% (2). The most accurate sign was the presence of air bronchograms with a sensitivity of 83.3%, specificity of 57.8%, positive predictive value of 51.3% and negative predictive value of 86% (2). They found that clinical criteria were 72% sensitive, but were only 43% specific (2). However, in an elegant study by Fagon et al (11), combining clinical criteria in a logistic regression model failed to identify any combination of variables that were useful in distinguishing patients with and without ventilator-associated pneumonia.

Faced with clinical and radiographic signs that appear to perform poorly, researchers began to investigate diagnostic techniques that would offer better performance characteristics than clinical diagnosis. Over the past 25 years a variety of techniques have been developed and evaluated. The first of these was the protected specimen brush (PSB). This device consists of a telescoping double catheter housing a sterile brush that can be extended beyond the distal end (6). An occlusive plug is expelled by the brush as it is extended through the catheter (6). It is estimated that the PSB samples approximately 10^{-3} mL from a single area of the lung (12). Bronchoalveolar lavage (BAL) involves the sequential instillation and aspiration of a physiological solution (usually 100 to 200 mL) into a lung subsegment (13). The first few millilitres of instillation and aspirate are usually discarded in an attempt to minimize contamination from upper airway secretions. BAL samples a considerably larger volume of the distal airspace than does the PSB and, if the sample is examined directly by Gram and/or Giemsa stains, can provide an immediate result (6). Protected BAL (PBAL) involves a balloon-tipped catheter that occludes the airway, preventing contamination by upper airway secretions that the bronchoscope contacts (13). Specimens obtained by PSB, BAL and PBAL are cultured quantitatively as a further step to differentiate colonization and infection and results expressed as the number of colony forming units per millilitre (cfu/mL). Refinements of BAL include Gram and, preferrably, Giemsa staining to quantify the percentage of cells with intracellular bacteria and to identify elastin fibres (3,5,6,14). Originally, PSB and BAL were designed to be done through a fibreoptic bronchoscope. More recently investigators have compared blindly collected PSB and BAL specimens to those obtained through bronchoscopy in an attempt to find noninvasive diagnostic tests. Additionally, quantitative cultures of endotracheal aspirates

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(EAs) are being compared with PSB and BAL as a diagnostic tool.

Chastre et al (15) were the first to study the use of PSB in ventilated patients. Their study population was 26 intensive care unit (ICU) patients who had postmortem lung biopsies. Immediately after death and while still ventilated, each patient had a PSB sample taken through the anterobasal bronchus of the left lower lobe, followed by lung biopsy in the same area with six segments (measuring approximately 5 mm^3 each) taken. Six patients had histological evidence of pneumonia and all had positive lung and PSB cultures. All patients with pneumonia had positive PSB cultures at a level of 10^3 cfu/mL or greater (15). It was therefore suggested that a threshhold of 10^3 cfu/mL be used to exclude the presence of pneumonia and as a guide for initiating antimicrobial therapy (15). Based on 26 patients, the performance characteristics of this new technique were as follows: sensitivity 100%, specificity 60%, positive predictive value 43% and negative predictive value 100% (15). PSB became the new standard against which other techniques were compared. Incidentally, the authors observed that specificity and positive predictive value were lower in patients taking antibiotics at the time of bronchoscopy (15).

Fagon et al (11) validated the PSB test in 147 ICU patients, comparing it with clinical definitions for pneumonia or autopsy findings. Similar to the study by Chastre et al (15), they found that no patient with a PSB growth less than 10^3 cfu/mL proved to have pneumonia. In their hands, PSB had 100% sensitivity and 91% specificity (11).

Not all studies have confirmed these initial findings. In an animal model (ventilated baboons) using autopsy findings as the reference, Johanson et al (16) found that PSB detected only 41% of bacterial species present in lung tissue compared with BAL (74%) and needle aspirates (56%). EA, while detecting 78% of species, found an additional 40% of organisms not cultured in lung tissue, supporting previous concerns of poor specificity of endotracheal specimens, even when cultured quantitatively (16). Other observations in this study were the polymicrobial nature of the pneumonias and the reduction in colony counts in animals given antimicrobials (16).

Several human studies have had similar findings. Based on postmortem findings as the comparator, not only have they provided more information on the performance characteristics of invasive (and noninvasive) tests, but they have provided insight into the nature of ventilator-associated pneumonia. Fàbregas et al (8) correlated noninvasive and invasive specimens with postmortem lung cultures and histopathology in 25 intensive care unit (ICU) patients. After death, but while still ventilated, each patient had the following specimens collected: EA, PSB, PBAL, BAL and lung biopsy (16 biopsy segments/patient). The associated sensitivities and specificities were as follows: EA 69% and 92%, PBAL 39% and 100%, BAL 77% and 58%, and PSB 62% and 75%, with only 52% of histological pneumonias having positive lung cultures (8). Similar to other studies, performance characteristics of the tests differed between those taking and not taking antibiotics, although whether these differences were statistically different was not noted (8). These results were very similar to an earlier study by these investigators (17) that found sensitivities and specificities of invasive tests ranging from 36% to 50% and 45% to 50%, respectively. Investigators in France had similar results using postmortem findings as the reference (18,19). They found that PBAL had a sensitivity of 80% and specificity of 66% in the diagnosis of ventilator-associated pneumonia, suggesting again that invasive tests perform similarly to noninvasive tests (18). In a later and larger study, they confirmed a sensitivity of 70% and specificity of 69% for PBAL (19). Two other groups also found that blind bronchial or endotracheal sampling performed similarly to PSB (20,21).

Results of postmortem studies have revealed that pneumonia involved predominantly lower lobes compared with upper and middle lobes (57% versus 30% versus 13%, $P<0.001$) with different histological phases coexistent (4). Additional biopsy findings were bronchiolitis (52%) and diffuse alveolar damage (32%) (4). Lung cultures were frequently polymicrobial (80% of pneumonias) and did not always yield the same pathogen from one lung culture to the other (4). Finally, lung culture counts of 10^3 cfu/mL or greater did not distinguish those with and without histological pneumonia (4). Others have noted that 25% of patients had evidence of pneumonia only on total lung biopsy, suggesting limited value of small biopsy specimens as the gold standard for diagnosing pneumonia (18). On histopathological examination, Rouby et al (19) found pneumonia was preferential in dependent segments, and in one-third of patients the abnormalities were limited to small areas of pneumonia within different lung segments and coexisting with nonspecific alveolar damage. In the majority of patients, different sections within each lung segment had differing histologies (19). They also found that 17 of 83 patients had bronchiolotis in the absence of pneumonia, 69% of whom had positive lung cultures in concentrations less than 10^3 cfu/mL (19). Kirtland et al (22) found that not only was there generally poor correlation between histology and premortem culture results, but that there was considerable variation between pathologists in the identification of patients with pneumonia. While these postmortem studies raise questions about the accuracy of diagnostic tests, it should be noted that the findings may not be reflective of all patients with ventilator-associated pneumonia or with the early presentation of ventilator-associated pneumonia. These studies should be recognized as offering insights into the limitations of invasive tests and cautioning us to consider them in the light of clinical findings.

To date, a number of investigators have compared the performance characteristics of the various noninvasive and invasive diagnostic tests with the finding that they perform similarly in the research setting (14,23-30). This observation has been confirmed by a meta-analysis of 40 studies examining the accuracy of PSB and BAL (31). Both performed similarly, although it was noted that BAL was more resistant to the effects of antibiotics (31), a key factor identified to affect results in many other studies (4,8,15,16,30,32,33). This is of practical importance because many, if not most, ICU patients will have received antibiotics within 24 h of bronchoscopy.

Two studies examining clinical outcomes in patients who underwent bronchoscopy with BAL and PSB or noninvasive testing with quantitative culture of EAs found no difference in mortality, suggesting similar performance of these two diagnostic methods (3,34).

More recent studies have suggested that respiratory therapists can be trained to perform blind PSB and mini-BAL safely with similar diagnostic accuracy to invasive testing (33,35). One major advantage of noninvasive tests is lower cost (28,35) and availability. Noninvasive tests are also presumed to be

safer, although complications of invasive tests have generally not been commented on or are reported as not serious in the various studies (3,11,13,14,23-25,28,29). The most commonly reported complications have been pulmonary hemorrhage (0% to 14.3%) and pneumothorax (0% to 8.9%).

While a number of studies have suggested that these diagnostic tests may be valid tests to use in the diagnosis of ventilator-associated pneumonia, the question still remains as to how useful they are. Several criteria by which diagnostic technologies can be evaluated have been suggested, including not only diagnostic accuracy but also impact on health care providers, therapeutic decisions and patient outcome (36). Heyland et al (37) examined the effect of PSB or BAL on physician perception of the probability of ventilator-associated pneumonia as well as their confidence in that diagnosis and on changes to antibiotic management. After bronchoscopy, physicians were less likely to believe a patient had ventilator-associated pneumonia and were more confident of their decision (37). Compared with a control group of patients who did not undergo bronchoscopy, those in the bronchoscopy group received fewer antibiotics and were more likely to have antibiotics stopped. Of interest, however, was that in the subgroup of patients with negative cultures, physicians were not more confident in their abilities to rule out pneumonia and stopped antibiotics in only 26.5% (37).

Observational studies have looked at outcomes in patients who have had invasive diagnostic tests and compared those with microbiologically confirmed pneumonia to those in whom pneumonia could not be confirmed by culture. Timsit et al (38) performed bronchoscopy with PSB or BAL on 112 patients suspected of having ventilator-associated pneumonia. Pneumonia was confirmed microbiologically in 50%. Mortality was the same in the two groups, even after multivariate analysis (38). In a similarly designed study, the outcomes of patients suspected to have ventilator-associated pneumonia who had positive BAL results were compared with those who had a negative BAL (7). Mortality was the same for BAL-positive (71%) and negative (64%) patients, but significantly higher for those BAL-positive patients on inadequate antibiotic therapy for pathogens isolated at the time of BAL (91% versus 38%) (7). Among those patients who died, half died within 48 h of bronchoscopy, before susceptibility results would generally be available. Mortality was improved by adequate antimicrobial therapy only for patients where the appropriate treatment was started before bronchoscopy (7). Thus, while BAL results gave information regarding the pathogens involved, there was no impact on outcome.

The above nonrandomized studies suggest that invasive diagnostic tests may not improve the outcome of patients with suspect ventilator-associated pneumonia. This question was more directly examined by Fagon et al (39) in a noncontrolled study where patients were randomly assigned to undergo bronchoscopy with PSB or BAL or qualitative culture of EAs (clinical management). In multivariate analysis, the clinical management group had a higher 14-day mortality than the invasive group (25.8% versus 16.2%) and fewer (2.2±3.5 versus 5.0±5.1) antibiotic-free days (39). While this suggests benefit to invasive testing, there are some limitations to the study. Given that it was nonblinded, it is possible that patients were managed differently in ways that could affect outcome. The invasive group was less likely to have received inadequate therapy than the clinical group (1.1% versus 13.4%, P<0.001), a variable not examined in multivariate analysis (39). Finally, there was no cost analysis. Thus, the question remains whether invasive diagnostic testing is a cost effective strategy to improve survival in patients with ventilator-associated pneumonia.

The literature indicates that the sensitivity (39% to 85%) and specificity (50% to 100%) of invasive diagnostic tests vary considerably. In retrospect, clinical diagnosis may offer comparability that is not essentially different from the invasive-based diagnosis. The early study by Andrews et al (10) found that clinical prediction by one person was 64% sensitive and 80% specific. Fagon et al (40) had remarkably similar findings in a study where the clinical predictions of senior consultants, staff physicians and residents were compared with a clinically and microbiologically defined pneumonia diagnosis. Of the 408 predictions made, the diagnosis was accurate in 77%, with physicians more correct in excluding pneumonia than diagnosing it (84% versus 62% correct predictions, P<0.001) (40). There were no differences between consultants, staff and residents and predictions were more accurate in the subset of patients where there was complete agreement (40). Unfortunately, therapeutic plans were poor. Plans were appropriate for only 33% of patients with pneumonia, improving to only 46.9% even when the diagnosis was accurately predicted (40).

Pugin et al (24) developed a clinical pulmonary infection score (CPIS) and assessed it in correlation with BAL findings. They found that a CPIS score of greater than six correlated well with BAL, allowing differentiation of infected and noninfected patients (24). A different group of investigators using postmortem pneumonectomy as the comparison found that a CPIS greater than six had a sensitivity of 72% and specificity of 85%, comparing favourably with BAL and PSB in diagnostic accuracy (21). More recently, the original criteria by Johanson et al (8) and the CPIS score have been evaluated against the postmortem findings. The sensitivities and specificities of these two clinical definitions were 69% and 77%, and 75% and 42%, respectively (8). While the value of invasive and noninvasive tests (including qualitative culture of EAs) need further exploration directed at outcomes, we need to re-evaluate and explore how to better apply clinical criteria and link making a clinical diagnosis to appropriate therapeutic decisions.

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