Bronchoscopy in Nonresolving Nosocomial Pneumonia*

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Abbreviations: APACHE = acute physiology and chronic health evaluation; CPIS = clinical pulmonary infection score; PSB = protected-specimen brush; VAP = ventilator-associated pneumonia

Few investigators have studied the role of bronchoscopy in evaluating and managing patients with nosocomial pneumonia who are not responding to initial antibiotic therapy. This discussion examines whether the information provided by bronchoscopy has value in this setting, as well as whether the concept of using bronchoscopy for the nonresponding patient is a logical one.

Importantly, serial bronchoscopy is generally performed while the patient is receiving antibiotic therapy. Such therapy can reduce the yield and accuracy of quantitative cultures of respiratory secretions. The presumption for using serial cultures in the nonresponding patient is that bacteria are present that have not been eliminated by currently administered antibiotics. Moreover, these organisms can be identified early enough so that changes in therapy will improve the outcome in these patients.

CAN CLINICAL FEATURES BE USED TO PREDICT THE LIKELIHOOD OF A NONRESPONSE TO THERAPY?

A number of clinical findings have been identified as risk factors for mortality from nosocomial pneumonia. If a patient has a multitude of these features and is not responding to initial antibiotic therapy, the nonresponse may be the inevitable outcome of serious systemic illness and comorbidity. Serial bronchoscopic data are unlikely to reduce the expected high mortality rate in such a population. Such risk factors, identified in multivariate analysis, included the following: prolonged duration of ventilation, comatous admission, creatinine levels > 1.5 mg/dL, and transfer to the ICU from another ward67; the presence of certain high-risk pathogens, abnormal bilateral radiographic findings, inappropriate initial therapy, age > 60 years, and an ultimately terminal underlying radiologic condition62; shock, inappropriate initial therapy, and rapidly fatal underlying illness41; prior antibiotic therapy128; infection with a resistant organism, particularly Pseudomonas aeruginosa or Staphylococcus aureus120; multiple systems organ failure, nonsurgical primary diagnosis, late-onset infection with a high-risk pathogen, and prophylaxis for intestinal bleeding with a pH-elevating agent.127 More recently, Rello et al130 observed that if acute physiology and chronic health evaluation (APACHE) II scores are followed serially after the onset of P aeruginosa ventilator-associated pneumonia (VAP), the mortality rate in patients who had a rising score at 72 h, particularly if this score was ≥ 20, was nearly 100% (Table 22).

DEFINING PNEUMONIA RESOLUTION

The resolution of nosocomial pneumonia can be defined clinically or microbiologically, but presumably a clinical nonresponse will the prompt consideration of bronchoscopic evaluation. Definable clinical end points include the following: resolution of all signs and symptoms of infection; improvement in all signs and symptoms of infection; slow or delayed resolution of signs and symptoms; relapse after initial infection (presumably representing recurrent infection); progression of signs and symptoms (rapid or gradual); superinfection that clinically resembles delayed resolution, progression, or relapse, but is characterized by these clinical findings in conjunction with the microbiological finding of an organism not present at the onset of pneumonia; and, finally, death due to unresolved infection, the ultimate outcome of a lack of response to therapy. Measurements to define these clinical end points include assessment of the following: fever, sputum purulence, leukocytosis, oxygenation, radiographic improvement, duration of organ failure, duration of mechanical ventilation, and need for changes in antibiotic therapy.

One way to assess the clinical resolution of pneumonia is to combine a number of clinical findings into a scoring system, such as the clinical pulmonary infection score (CPIS) of Pugin et al30 Using a modification of this system, Garrard and A’Court131 measured the CPIS on a daily basis in 83 patients with nosocomial pneumonia. The CPIS was used to diagnose pneumonia if the score was ≥ 6 (highest possible score, 10), based on the assessment of five variables, each with a score range of 0 to 2. These variables were the following: temperature, WBC count, purulence of secretions, oxygenation, and extent of radiographic infiltrates. The CPIS was observed to increase progressively from a baseline value of < 6 to a value of > 6 over the 2 days preceding the day of diagnosis and initiation of antibiotic therapy.30 Once therapy was begun, the CPIS fell gradually over the next 9 days, generally dropping below 6 by the fifth day. When the CPIS did not fall, clinical deterioration was usually due to infection with P aeruginosa.

Resolution also can be defined by bacteriologic end points that are based on the assessment of serial qualitative cultures of respiratory secretions. Microbiological eradication is defined by the elimination of the original pathogen from the culture of the secretion, usually sputum. Persistence is defined by a failure to eliminate the organism. Reinfection refers to elimination of the organism, followed by its return, and superinfection refers to the appearance of a new organism in the culture. Quantitative microbiology cultures of respiratory secretions obtained bronchoscopically or nonbronchoscopically also can be used to define the resolution of nosocomial pneumonia.

Garrard and A’Court131 used serial quantitative cultures of nondirected, nonbronchoscopic lung specimens ob-
tained by lavage from patients receiving ventilation who have nosocomial pneumonia and correlated the findings with serial measurement using the CPIS. Using a 14-gauge tracheal suction catheter with 20 mL normal saline solution, the authors evaluated 89 episodes of nosocomial in 83 patients by using alternate-day sampling and quantitative cultures of respiratory secretions. Culture counts rose during the 2 days preceding the clinical onset of pneumonia and fell rapidly with the initiation of therapy. Patients showing a clinical response to therapy had a rapid fall in colony counts by 24 h, in most instances, and usually no later than 48 to 72 h, unless there was a lack of response to treatment. The patients who had no response to treatment usually had *P. aeruginosa* pneumonia; these patients had a persistence of colony counts of $10^3$ cfu/mL and a high mortality rate. Serial quantitative cultures correlated well with clinical response and mortality, with the counts of those patients responding falling rapidly. This microbiological pattern was analogous to the clinical findings, as reflected by the CPIS. Nonresponse to therapy was not predicted more accurately by microbiological findings than by clinical findings. While a microbiological nonresponse could be defined at 24 to 72 h, recognizing a clinical nonresponse generally took longer.

Serial bronchoscopy also has been used to determine whether a patient is not responding to initial therapy, and if so, why. Dreyfuss et al. collected data using a serial protected-specimen brush (PSB) technique for 34 episodes in 30 patients in whom there was clinical suspicion of pneumonia and found borderline results ($10^2$ to $10^3$ cfu/mL) with the initial cultures. Patients had repeat bronchoscopy within 72 h if the suspicion of pneumonia persisted and if patients were not given antibiotics. In 12 episodes, the same organism was isolated on the repeat bronchoscopy, but the concentration was then $>10^3$ cfu/mL and antibiotics were given. In 22 episodes, pneumonia was excluded as a diagnosis. The mortality rate in the eight patients having a positive culture finding on repeat bronchoscopy was 75% (6 patients), which was significantly higher than the mortality rate in the 18 patients with a negative culture finding on repeat bronchoscopy (22%; 4 patients; $p < 0.04$). Serial bronchoscopy can identify pneumonia patients who cannot contain a bacterial challenge or who had a prior false-negative culture finding. The high mortality rate may be related to the delayed initiation of antibiotic therapy after an initial false-negative culture result.

Montravers et al. studied the results of cultures with specimens gathered using the serial PSB method in 76 patients with VAP. A clinical suspicion of pneumonia in the enrolled patients was confirmed by a bacteria count of $\geq 10^5$ cfu/mL in a sample. The clinicians' initial antibiotic choice was modified on the basis of bronchoscopy results. All patients had a second bronchoscopy 3 days after entry into the study. The clinical outcome and serial microbiological data were compared, with clinical outcomes classi-
fied as improved, relapse, or failure. Bacteriologic outcomes were grouped by the eradication of the pathogen, the continued isolation of the pathogen, or the emergence of a new pathogen. Any pathogens present on the repeat bronchoscopy were noted as being at low (ie, $<10^3$ cfu/mL) or high (ie, $\geq10^3$ cfu/mL) concentrations.

In the study by Montravers et al,$^{32}$ 51 patients had sterile pulmonary secretions by day 3, 16 patients had persistent low-level infection, and 9 patients had persistent high-level infection (Table 23). Clinical improvement was seen in 96% of those with microbiological eradication, in 81% of those with persistent low-level infection, and in 44% of those with persistent high-level infection ($p < 0.01$).

Follow-up bronchoscopy can be used to identify patients with a clinical nonresponse to therapy. The highest rates of clinical nonresponse occurred in the patient whose follow-up bronchoscopy showed a high concentration of bacteria. The finding of persistent bacterial infection can be used to predict a poor outcome, but there are no data to suggest that interventions based on these results will improve patient outcome.

**ARE SERIAL BRONCHOSCOPY DATA LIKELY TO HELP THE NONRESPONDING PATIENT?**

The results of the study by Montravers et al$^{32}$ suggest that data taken from serial PSB sampling provide a microbiological explanation for clinical nonresponse. However, it is uncertain whether this information leads to improved outcome. The outcome in patients with nosocomial pneumonia may be dictated by the efficacy of initial antibiotic therapy, prior to the bronchoscopy, which was performed within 24 h after the clinical diagnosis of pneumonia. For 16 of 65 patients (25%) whose initial therapy was adequate (as defined by BAL bacteriology study), the mortality rate was 38%; for those with inadequate therapy, the mortality rate was 91%.

After bronchoscopy was completed, 42 of the 65 patients (65%) received adequate therapy and the other 23 received inadequate therapy, but the mortality rate in the two groups was comparable. Similarly, outcomes did not improve after bronchoscopic data were known, although almost all patients received adequate therapy at that time. The generalizability of these findings is limited by the very high mortality rates reported by Luna et al$^{30}$ in all patient groups. Bronchoscopy may identify organisms that are not responding to the initial antibiotic regimen. Whether this information will improve the outcome is uncertain but needs to be formally investigated.

Recently Rello et al$^{132}$ studied 113 patients with VAP, 100 of whom (88%) had an organism identified by bronchoscopy. Based on these data, 27 patients had initial inadequate antibiotic therapy. This group had a significantly higher mortality rate than those receiving adequate therapy (37% vs 15.4%, respectively). However, when antibiotic therapy was changed, based on bronchoscopic data, 17 of the 27 patients (63%) had clinical resolution, and 10 of those 17 patients (59%) survived and were discharged. Thus, bronchoscopically directed changes in therapy may have been beneficial, although aspiration cultures may have provided similar data.

The potential limitations of serial bronchoscopy include the following: (1) information may become available too late; (2) the bacteriologic information could be provided by simpler, more readily available methods, such as tracheal aspiration culture; and (3) repeat testing usually isolates highly resistant organisms that would not be eliminated by changes in antibiotic therapy. The last limitation was suggested by Garrard and A'Court,$^{131}$ who found that nonresponding patients had persistent high-level infections with organisms that are difficult to eradicate, such as *P aeruginosa*. Similarly, Silver et al$^{133}$ described the phenomenon of recurrent infection with *P aeruginosa* in critically ill patients. Silver et al$^{133}$ documented that recurrent infection with this organism is common (ie, found in 10 of 20 patients [50%] who survived a first episode of *P aeruginosa* pneumonia) and often fatal (mortality rate, 60% for those patients with recurrent *P aeruginosa* pneumonia vs 10% for those without).

Souweine and colleagues$^{36}$ confirmed that bronchos-
copy can identify the bacteria responsible for nonresponse to therapy in patients with VAP. When bronchoscopy was performed in 31 patients who had received antibiotic therapy for > 72 h, diagnostic sensitivity was 83% for BAL and 77% for PSB. Of the 15 organisms isolated, 11 were resistant to the current antibiotic, suggesting that bronchoscopy can document the presence of persistent and resistant pathogens in patients not responding to therapy.

CONCLUSIONS

- The impact of repeated quantitative cultures (bronchoscopic or nonbronchoscopic) on the outcomes of patients with VAP has been incompletely studied.
- Serial microbiological diagnostic studies in VAP patients may identify those at increased risk for mortality.
- With invasive techniques, the persistent recovery of high concentrations of potential pathogens identifies patients at high risk for mortality.
- There are insufficient data to show that repeated bronchoscopy affects the survival rate of patients who did not respond to initial therapy.

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