The Invasive (Quantitative) Diagnosis of Ventilator-Associated Pneumonia

Jean Chastre MD, Alain Combes MD, and Charles-Edouard Luyt MD

Although appropriate antibiotics may improve survival in patients with bacterial pneumonia, use of empirical broad-spectrum antibiotics in patients without infection is potentially harmful, facilitating colonization and superinfection with multiresistant microorganisms. Invasive diagnostic methods, including bronchoalveolar lavage and/or protected-specimen bronchial brushing, could improve identification of patients with true bacterial pneumonia and facilitate decisions whether or not to treat, and thus clinical outcome. Bronchoalveolar lavage and/or protected-specimen bronchial brushing permit collecting distal pulmonary secretions with minimal or no upper-airway contamination, either through a fiberoptic bronchoscope or blindly using an endobronchial catheter that is wedged in the tracheobronchial tree. Due to the inevitable oropharyngeal bacterial contamination that occurs in the collection of all respiratory secretion samples, quantitative culture techniques are always needed to differentiate oropharyngeal contaminants present at low concentration from higher-concentration infecting organisms. Because even a few doses of a new antimicrobial agent can negate results of microbiologic cultures, pulmonary secretions in patients suspected of having developed pneumonia should always be obtained before new antibiotics are administered. Bronchoalveolar lavage may also provide useful clues for the diagnosis of other forms of respiratory failure, such as pulmonary hemorrhage or other types of infections, especially in immunocompromised patients. *Key words: ventilator-associated pneumonia, fiberoptic bronchoscopy, protected specimen brush, bronchoalveolar lavage, quantitative culture techniques, management.* [Respir Care 2005; 50(6):797–807.

Jean Chastre MD, Alain Combes MD, and Charles-Edouard Luyt MD are affiliated with the Service de Réanimation Médicale, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France.

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Correspondence: Jean Chastre MD, Service de Réanimation Médicale, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, 43-87 bd de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: jean.chastre@psl.ap-hop-paris.fr.

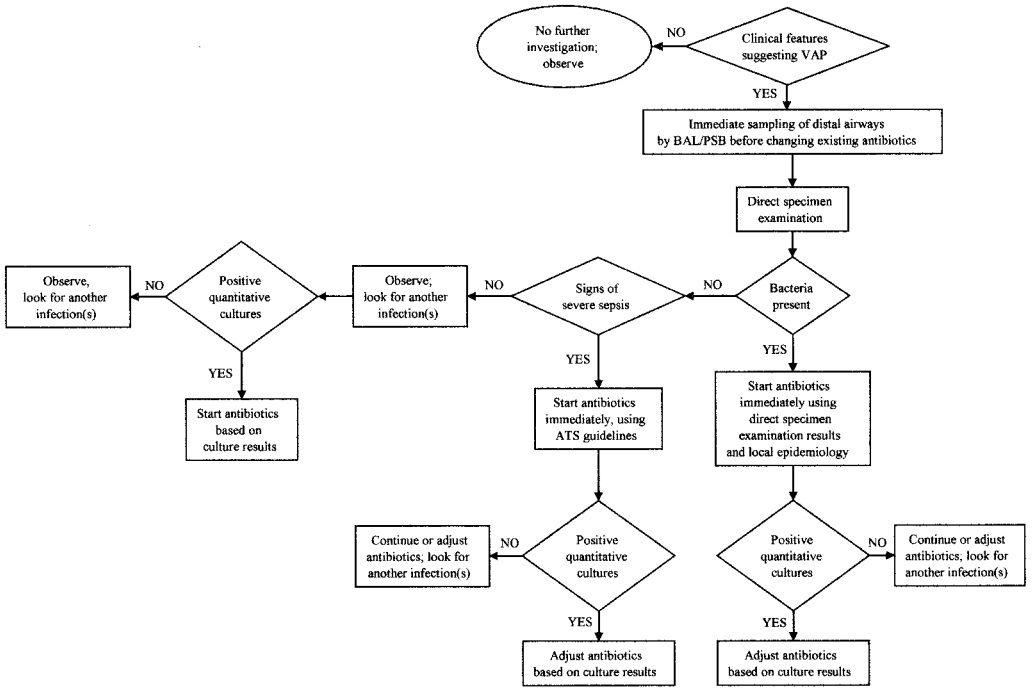

Fig. 1. Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of ventilator-associated pneumonia (VAP) managed according to the "invasive" strategy.

Introduction

Concern about the inaccuracy of clinical approaches to ventilator-associated pneumonia (VAP) recognition and the impossibility of using such a strategy to avoid overprescription of antibiotics in the intensive care unit (ICU) has led numerous investigators to postulate that "specialized" diagnostic methods, including quantitative cultures of specimens obtained with bronchoscopic or nonbronchoscopic techniques, such as bronchoalveolar lavage (BAL) and/or protected-specimen-brush (PSB), could improve identification of patients with true VAP and facilitate decisions whether or not to treat, and thus clinical outcome.[1–3] Using such a strategy, therapeutic decisions are tightly protocolized, based on results of direct examination of distal pulmonary samples and results of quantitative cultures (Fig. 1).

This report reviews the potential advantages and drawbacks of using these techniques, compared with using noninvasive modalities and/or clinical evaluation alone for the diagnosis of VAP, based on our personal experience and major additions to the literature that have appeared in recent years.

Bronchoscopic Versus Nonbronchoscopic Techniques

Bronchoscopy provides direct access to the lower airways for sampling bronchial and parenchymal tissues directly at the site of lung inflammation. One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. Almost all intubated patients have purulent-looking secretions, and the secretions first seen may represent those aspirated from another site into gravity-dependent airways or from upper-airway secretions aspirated around the endotracheal tube. Usually the sampling area is selected based on the location of infiltrate on chest radiograph or the segment visualized during bronchoscopy as having purulent secretions.[4] Collection of secretions in the lower trachea or mainstem bronchi, which may represent recently aspirated secretions around the endotracheal tube cuff, should be avoided. In patients with diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest radiograph, determining the correct airway to sample may be difficult. In these cases, sampling should be directed to the area where endobronchial abnormalities are maximal. In case of doubt, and because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be sampled preferentially.[5] While in the immunosuppressed host with diffuse infiltrates bilateral sampling has been advocated, there is no convincing evidence that multiple specimens are more accurate than single specimens for diagnosing nosocomial bacterial pneumonia in patients requiring mechanical ventilation.[6]

At least 15 studies have described a variety of nonbronchoscopic techniques for sampling lower-respiratory-tract

secretions; results have been similar to those obtained using fiberoptic bronchoscopy.[7] Compared to conventional PSB and/or BAL, nonbronchoscopic techniques are less invasive, can be performed by clinicians not qualified to perform bronchoscopy, have lower initial costs than fiberoptic bronchoscopy, avoid potential contamination by the bronchoscopic channel, are associated with less compromise of gas exchange during the procedure, and can be performed even in patients intubated with small endotracheal tubes.

Disadvantages include the potential sampling errors inherent in a blind technique and the lack of airway visualization. Although autopsy studies indicate that pneumonia in ventilator-dependent patients has often spread into every pulmonary lobe and predominantly involves the posterior portion of the lower lobes, several clinical studies on ventilated patients with pneumonia contradict those findings, as some patients had sterile cultures of PSB specimens from the noninvolved lung.[6,8] Furthermore, although the authors of most studies concluded that the sensitivities of nonbronchoscopic and bronchoscopic techniques were comparable, the overall concordance was only approximately 80%, emphasizing that, in some patients, the diagnosis could be missed by a blind technique, especially in the case of pneumonia involving the left lung, as demonstrated by Meduri et al.[6]

Complications

The risk inherent in bronchoscopy appears slight, even in critically-ill patients requiring mechanical ventilation, although the associated occurrence of cardiac arrhythmias, hypoxemia, or bronchospasm is not unusual. A study conducted by Trouillet et al in 107 ventilated patients has shown that fiberoptic bronchoscopy under midazolam sedation is practicable in this setting.[9] No death or cardiac arrest occurred during or within the 2 hours immediately following the procedure. However, patients in the ICU are at risk of relative hypoxemia during fiberoptic bronchoscopy, even when high levels of oxygen are provided to the ventilator and gas leaks around the endoscope are minimized by a special adaptor. An average decline in mean P_{aO_2} of 26% was observed at the end of the procedure, compared to the baseline value, and this was associated with a mild increase in P_{aCO_2}. The degree of hypoxemia induced by fiberoptic bronchoscopy in this study was linked to the severity of pulmonary dysfunction and the decrease in alveolar ventilation. Clinical hypoxemia, as defined by P_{aO_2} lower that 60 mm Hg, was more frequent in patients with ARDS and in those who "fought" the ventilator during the procedure, as shown by multivariate analysis. Careful methodical attention to the anesthetic protocol, with addition of a short-acting neuromuscular blocking agent, and monitoring of patients during bronchoscopy should probably permit rapid correction and more frequent prevention of hypoxemia in this setting, and therefore should further decrease the morbidity of this procedure. In another study that was conducted in a large series of patients with ARDS, only 5% of patients had arterial oxygen desaturation to $< 90\%$ during bronchoscopy, despite severe hypoxemia in many patients before bronchoscopy.[10]

Certain procedures, however, increase the risk of complications, particularly in some subsets of patients. The bleeding risk observed with the PSB technique is thus particularly important in patients with thrombocytopenia or a coagulopathy. Pneumothorax is also principally a complication of PSB, although it can occur after BAL alone in mechanically ventilated patients. In fact, the risk of fiberoptic bronchoscopy is, paradoxically, more important in nonventilated patients than in patients receiving mechanical ventilation, since performance of bronchoscopy in a critically ill patient with impending respiratory failure may lead to profound hypoxemia and rapid decompensation. While bacteremia does not appear to occur after PSB, release of the cytokine TNF (tumor necrosis factor), has been documented in patients undergoing BAL.[11] Transbronchial spread of infection is also an extremely remote possibility.[4]

Specimens Types and Laboratory Methods

The methodology for PSB sampling was originally described by Wimberley et al.[12] This method is in fact based on the combination of 4 different techniques: (1) the use of fiberoptic bronchoscopy to directly sample the site of inflammation in the lung, (2) the use of a double-lumen catheter brush system with a distal occluding plug to prevent secretions from entering the catheter during passage through the bronchoscope channel, (3) the use of a brush to calibrate the volume of secretions retrieved, and (4) the use of quantitative culture techniques to aid in distinguishing between airway colonization and serious underlying infection, with a cutoff point of 10^3 colony-forming units (CFU)/mL for making this distinction. In an in vitro study, this system proved to be the most effective among 7 different types, tested as follows. Catheters containing a protected brush were passed through a fiberoptic bronchoscope heavily contaminated with saliva to reach the distal sample (ie, a Petri dish containing a known number of organisms).[12] Single-sheathed catheter brushes and telescoping plugged catheter tips with or without distal plugs are, however, also available and have been used for the diagnosis of pneumonia, even though neither has been subjected to the rigorous evaluation reported for the PSB.

BAL requires careful wedging of the tip of the bronchoscope into an airway lumen, isolating that airway from the rest of the central airways. Infusion of at least 120 mL of saline in several (3–6) aliquots is needed to sample

fluids and secretions in the distal respiratory bronchioles and alveoli.[1,4,13] It is estimated that the alveolar surface area distal to the wedged bronchoscope is 100 times greater than that of the peripheral airway and that approximately 1 million alveoli (1% of the lung surface) are sampled, with approximately 1 mL of actual lung secretions retrieved in the total lavage fluid. The fluid return on BAL varies greatly and may affect the validity of results. In patients with emphysema, collapse of airways with the negative pressure needed to aspirate fluid may limit the amount of fluid retrieved. A very small return may contain only diluted material from the bronchial rather than alveolar level and results in false-negative results.

Regardless of the technique used, rapid processing of specimens for culture is desirable to prevent loss of viability of pathogens or overgrowth of contaminants. For PSB it is recommended that the brush be aseptically cut into a measured volume (1 mL) of sterile diluent, most commonly, nonbacteriostatic saline or lactated Ringer's solution.[13] For BAL, transport in a sterile, leak-proof, nonadherent glass container is recommended to avoid loss of cells for cytologic assessment. The initial aliquot, which is usually considered as essentially representative of distal bronchi, should be either discarded or transported separately from the remaining pooled fractions.[4,13] Excessive delays in transport to the laboratory should be avoided. Quantitative cultures of freshly collected sputa versus samples transported at room temperature over an approximately 4-hour period showed selective decreases in *Staphylococcus pneumoniae* and *Haemophilus influenzae* isolation rates, and fewer bacterial species overall in delayed specimens but higher counts of some other organisms, particularly Gram-negative bacilli.[14] Although no absolute guideline exists, it is generally accepted that no more than 30 min should elapse before specimens are processed for microbiologic analysis. According to some investigators, refrigeration to prolong transport time may be used, but this technique remains controversial.[15,16]

Once specimens are received in the laboratory, they should be processed according to clearly defined procedures (see References 13 and 14 for complete description). Because of the inevitable oropharyngeal bacterial contamination that occurs in the collection of all respiratory secretion samples, quantitative culture techniques are always needed to differentiate infecting organisms from oropharyngeal contaminants present at low concentrations. Pathogens are present in lower-respiratory-tract inflammatory secretions at concentrations of at least 10^5 to 10^6 CFU/mL, whereas contaminants are generally present at less than 10^4 CFU/mL.[17] The diagnostic thresholds proposed for PSB and BAL are based on this concept. Since PSB collects between 0.001 and 0.01 mL of secretions, the presence of greater than 10^3 bacteria in the originally diluted sample (1 mL) actually represents 10^5 to 10^6 CFU/mL of pulmonary secretions. Similarly, 10^4 CFU/mL for BAL, which collects 1 mL of secretions in 10–100 mL of effluent, represents 10^5 to 10^6 CFU/mL.[14]

Although PSB samples can be subjected to direct microscopy, the optimal method for smear preparation has not yet been established. For BAL it is recommended that a total cell count be performed to assess adequacy and a differential count be performed to assess cellularity. For quality assessment, the percentages of squamous and bronchial epithelial cells may be used to predict heavy upper-respiratory contamination. Although only a few studies have directly assessed this point, it is proposed that the sample be rejected if more than 1% of the total cells are squamous or bronchial epithelial cells.[18] Modified Giemsa staining (eg, Diff-Quik) is recommended, as it offers a number of advantages over Gram staining, including better visualization of host-cell morphology, improved detection of bacteria, particularly intracellular bacteria, and detection of some protozoan and fungal pathogens (eg, *Histoplasma, Pneumocystis, Toxoplasma*, and *Candida* species).[14]

Because BAL harvests of cells and secretions from a large area of the lung and specimens can be microscopically examined immediately after the procedure to detect the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, it is particularly well suited to provide rapid identification of patients with pneumonia (Figs. 2–4). In one study in which the diagnostic accuracy of direct microscopic examination of BAL cells could be directly assessed with both histologic and microbiologic postmortem lung features in the same segment, Chastre et al could demonstrate a very high correlation between the percentage of BAL cells containing intracellular bacteria and the total number of bacteria recovered from the corresponding lung samples and with the histologic grades of pneumonia.[19] In 10 of 11 lung segments with $\geq 10^4$ bacteria/g lung tissue cultured, $\geq 5\%$ of the cells recovered by lavage contained intracellular organisms. In contrast, $< 1\%$ of cells recovered by lavage contained intracellular bacteria in 8 of 9 noninfected lung segments, and $> 5\%$ of the cells contained intracellular organisms in only one lung segment, in which the diagnosis of infection in the same lung segment was excluded. In this study the morphology of intracellular and extracellular bacteria observed in BAL fluid preparations obtained from infected lung segments was consistent with the types of organisms ultimately cultured at high concentrations from lung tissue samples, confirming the potential usefulness of this technique for selecting an effective antimicrobial treatment before culture results are available (see Figs. 2 and 3). Several other studies have confirmed the diagnostic value of this approach.[19–25] However, assessment of the degree of qualitative agreement between Gram stains of BAL fluid and PSB quantitative cultures for a series of

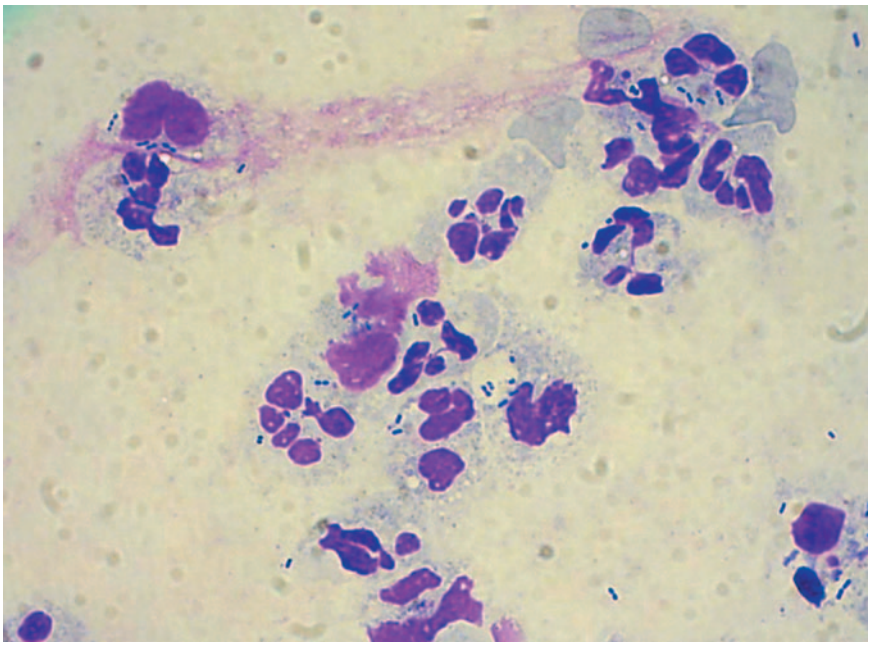

Fig. 2. Light micrograph (magnification ×1000) of cells (Diff-Quick stain) recovered by bronchoalveolar lavage from a patient with *Klebsiella pneumoniae* pneumonia. Many neutrophils contain multiple intracellular bacilli, and some extracellular organisms are also present.

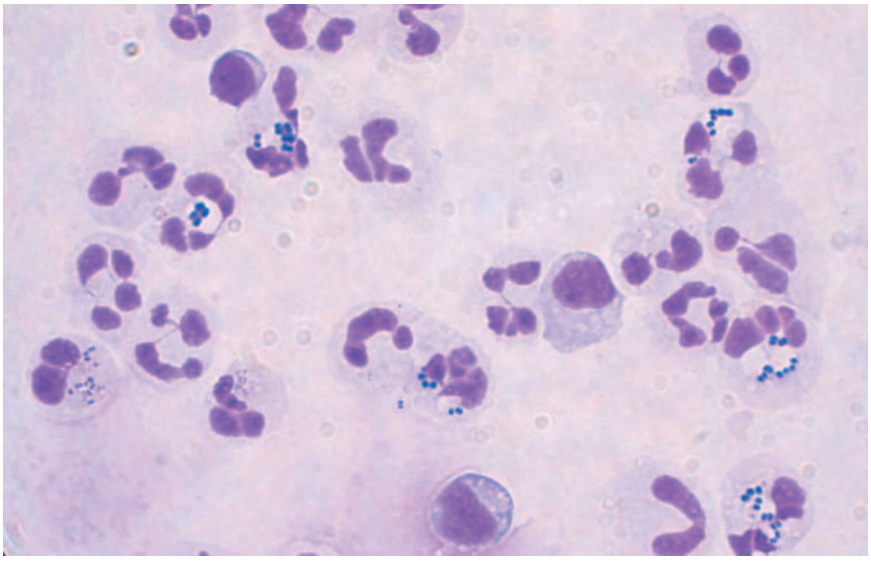

Fig. 3. Light micrograph (magnification ×1000) of cells (Diff-Quick stain) recovered by bronchoalveolar lavage from a patient with *Staphylococcus aureus* pneumonia. Many neutrophils contain multiple intracellular cocci, and some extracellular organisms are also present.

51 patients with VAP showed the correspondence to be complete for 51%, partial for 39%, and nonexistent for 10% of the cases.[22]

Diagnostic Accuracy of PSB and BAL Techniques

The potential contribution of the PSB technique to evaluate ICU patients suspected of having developed VAP has been extensively investigated in both human and animal studies, including 8 investigations in which the accuracy of this culture technique was determined by comparison of both histologic features and quantitative cultures from the same area of the lung.[19,26–32] Despite the need for cautious interpretation, the results of those studies indicate that the PSB technique offers a sensitive and specific approach to identifying the microorganisms involved in pneumonia in critically ill patients, and to differentiating between colonization of the

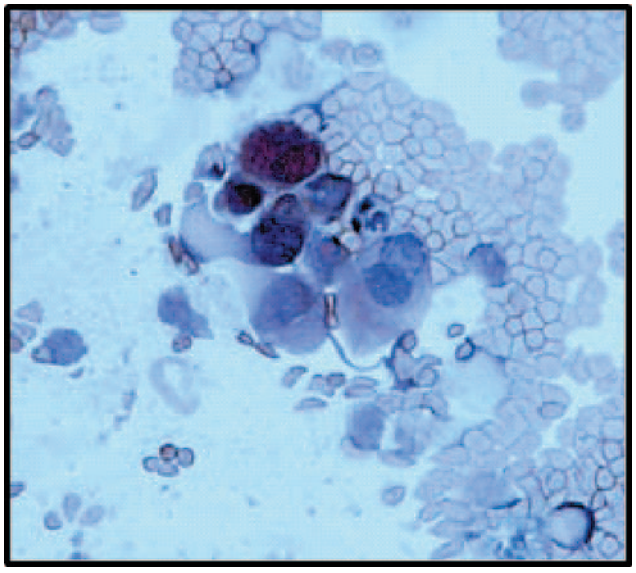

Fig. 4. Light micrograph (magnification ×1000) of cells (Papanicolaou stain) recovered by bronchoalveolar lavage from a patient with herpes simplex virus tracheobronchitis. Many epithelial cells demonstrate characteristic intranuclear inclusions.

upper respiratory tract and distal lung infection. Pooling the results of the 18 studies evaluating the PSB technique in a total of 795 critically ill patients shows that the overall accuracy of this technique for diagnosing pneumonia is high: sensitivity is 89% (95% confidence interval 87 to 93%) and specificity is 94% (95% confidence interval 92 to 97%).[33,34]

Although providing a broader image of lung content than PSB, BAL is subject to the same risk of contamination as protected bronchial brushings. Many groups have now investigated the value of quantitative BAL culture for the diagnosis of pneumonia in ICU patients.[19,33,35] Although some investigators have concluded that BAL provides the best reflection of the lung's bacterial burden, both quantitatively and qualitatively, others have reported mixed results, with poor specificity of BAL fluid cultures for patients with high tracheobronchial colonization. When the results of the 11 studies evaluating BAL fluids from a total of 435 ICU patients suspected of having developed nosocomial pneumonia were pooled, the overall accuracy of this technique was found to be very close to that of PSB; the Q value was 0.84 (Q represents the intersection between the summary receiver operating characteristics curve and a diagonal from the upper left corner to the lower right corner of the receiver-operating-characteristics space).[33] Similar conclusions were drawn in another meta-analysis when the results of 23 studies were pooled. These data indicate that the sensitivity and specificity of BAL are 73 ± 18% and 82 ± 19%, respectively.[35]

Patients Already Receiving Antimicrobial Therapy

Performing microbiologic cultures of pulmonary secretions for diagnostic purposes after initiation of new antibiotic therapy in patients suspected of having developed nosocomial pneumonia can clearly lead to a high number of false-negative results, regardless of the way in which these secretions are obtained. In fact, all microbiological techniques are probably of little value in patients with recent pulmonary infiltrates who have received new antibiotics for that reason, even for less than 24 hours. In this case, a negative finding could indicate either that the patient has been successfully treated for pneumonia and the bacteria are eradicated, or that he had no lung infection to begin with. In one study, in which follow-up cultures of protected bronchoscopic specimens were obtained in 43 cases of proven nosocomial pneumonia, 24 hours and 48 hours after the onset of antimicrobial treatment, nearly 40% of cultures were negative after only 24 hours of treatment and 65% after 48 hours.[36] Similar results were obtained by Montravers et al in a series of 76 consecutive patients with VAP evaluated by fiberoptic bronchoscopy after 3 days of treatment.[37] In this study, using follow-up PSB sample cultures to directly assess the infection site in the lung, 88% of patients had negative cultures after the onset of treatment. Using both PSB and BAL, Souweine et al prospectively investigated 63 episodes of suspected VAP.[38] Based on prior antibiotic treatment, 3 groups were defined: no previous antibiotic treatments ($n = 12$), antibiotic treatment initiated > 72 hours earlier ($n = 31$), and new antibiotic treatment class started within the last 24 hours ($n = 20$). Results were entirely consistent with the studies referenced above. If patients had been treated with antibiotics but did not have a recent change in antibiotic class, then the sensitivity of PSB and BAL culture (83% and 77%, respectively) were similar to the sensitivity of these methods when applied to patients not being treated with antibiotics. In other words, prior therapy did not reduce the yield of diagnostic testing among those receiving current antibiotics given to treat a prior infection. On the other hand, if therapy was recent, the sensitivity of invasive diagnostic methods, using traditional thresholds, was only 38% with BAL and 40% with PSB. These 2 clinical situations should be clearly distinguished before interpreting pulmonary secretion culture results, however they were obtained. In the second situation, when the patient had received new antibiotics after the appearance of the signs suggesting the presence of pulmonary infection, no conclusion concerning the presence or absence of pneumonia can be drawn if culture results are negative. Pulmonary secretions therefore need to be obtained before new antibiotics are administered, as is the case for all types of microbiologic samples.

Potential Limitations of Bronchoscopic Techniques

Four recent studies using a protocol based on postmortem lung biopsies have suggested that, in the presence of prior antibiotic treatment, many patients with histopathologic signs of pneumonia have no or only minimal growth from lung and bronchoscopic specimens cultures.[5,32,39,40] In one study, lesions of bronchopneumonia were characterized by bacterial concentrations $> 10^3$ CFU/mL of lung tissue in only 55% of lobes, and one third of lung segments with histologic bronchopneumonia even remained negative when cultured. Similarly, in a study of 30 patients who died under mechanical ventilation after having received prior antibiotic treatment, Torres et al found that quantitative bacterial cultures of lung biopsies using 10^3 CFU/g of tissue as a cutoff point had low sensitivity (40%) and low specificity (45%) and could not differentiate the histologic absence or presence of pneumonia.[41] Interestingly, in this study the operating characteristics of the PSB technique were very similar to those obtained with lung cultures.

It should be remembered, however, that several constraints specific to the evaluation of any procedure used in the diagnosis of bacterial pneumonia must be respected, even when using a model in which the accepted standard includes both histologic features and quantitative cultures of lung tissue. First, diagnostic methods based on microbiologic techniques can only document, both qualitatively and quantitatively, the bacterial burden present in lung tissue. In no cases can these techniques retrospectively identify a resolving pneumonia, at a time when antimicrobial treatment and lung antibacterial defenses might have been successful in suppressing microbial growth in lung tissue. Therefore, to evaluate the accuracy of any technique that uses lung cultures as the accepted standard, it is imperative that no new antibiotics were introduced during this time interval. Second, using histologic criteria as a reference implies that the patient had not developed a lung infection before the episode under evaluation; otherwise, it would be difficult (if not impossible) to distinguish a recent infection from the sequelae of a previous infection, and thus correctly interpret the results of the diagnostic tool(s) under evaluation. Finally, lesions of bronchopneumonia in patients with VAP may be confined to certain locations of the lungs.[5,39] Therefore, if postmortem tissue samples are too small, the histologic diagnosis of pneumonia can be underestimated.

Conversely, a technique based on peripheral samplings can provide information only on the lung segment from which specimens had been taken; so-called "false-negative" results of PSB or BAL, as defined by the entire examination of the lung, can be explained by the absence of pneumonia at the very location of sampling.

Interestingly, when analysis in these studies was limited to patients with no prior antibiotics or when only lung tissue cultures were used as the accepted standard, results obtained using bronchoscopic techniques for diagnosing nosocomial pneumonia were much better, with a sensitivity always greater than 80%.

Other studies have confirmed the accuracy of bronchoscopic techniques for diagnosing nosocomial pneumonia. In a study evaluating spontaneous lung infections occurring in baboons with permeability pulmonary edema and undergoing mechanical ventilation, Johanson et al found an excellent correlation between the bacterial content of lung tissue and results of quantitative culture of lavage fluid and PSB specimens.[26] BAL recovered 74% of all species present in lung tissue, including 100% of those present at a concentration $\geq 10^4$ CFU/g of tissue. In this study, PSB specimens identified only 41% of all species recovered from lung tissue, but it must be noted that only microorganisms present at low concentrations in the lung were missed, since 78% of species present at concentrations $> 10^4$ CFU/g of tissue were correctly isolated. Similarly, in a study of 20 ventilated patients who had not developed pneumonia before the terminal phase of their disease and who had no recent changes in antimicrobial therapy, Chastre et al found that bronchoscopic PSB specimens obtained just after death were able to identify 80% of all species present in the lung, with a strong correlation between the results of quantitative cultures of both specimens.[19] Using a discriminative value of $\geq 10^3$ CFU/mL to define positive PSB cultures, this technique identified lung segments yielding $\geq 10^4$ bacteria/g of tissue, with a sensitivity of 82% and a specificity of 89%. These findings confirm that bronchoscopic PSB and/or BAL samples very reliably identify, both qualitatively and quantitatively, microorganisms present in lung segments with bacterial pneumonia, even when the infection develops as a superinfection in a patient already receiving antimicrobial treatment for several days.

Values within 1 $\log_{10}$ of the cutoff must, however, be interpreted cautiously, and fiberoptic bronchoscopy should be repeated in symptomatic patients with a negative ($< 10^3$ CFU/mL) result.[42] Many technical factors, including medium and adequacy of incubation and antibiotic or other toxic components may influence results. The reproducibility of PSB sampling has been recently evaluated. Three groups have concluded that, although in vitro repeatability is excellent and in vivo qualitative recovery is 100%, quantitative results are more variable. In 14–17% of patients, results of replicate samples fell on both sites of the 10^3 CFU/mL threshold, and results varied by more than 1 $\log_{10}$ in 59–67% of samples.[43–45] This variability is presumably related to both irregular distribution of organisms in secretions and the very small volume actually sampled by PSB. The conclusion is that, as with all diagnostic tests,

borderline PSB and/or BAL quantitative culture results should be interpreted cautiously and the clinical circumstances considered before drawing any therapeutic conclusion.

The Argument for Quantitative Technique in the Diagnosis of VAP

The use of invasive techniques such as fiberoptic bronchoscopy coupled with quantitative cultures of PSB or BAL specimens helps direct the initial antibiotic therapy, in addition to confirming the actual diagnosis of nosocomial pneumonia. When culture results are available, they allow for the precise identification of the offending organisms and their susceptibility patterns. Such data are invaluable for optimal antibiotic selection. They also increase the confidence and comfort level of health care workers in managing patients with suspected nosocomial pneumonia.[46] Rello et al found that 43% of patients required a change in their initial antibiotic regimen, based on the results of bronchoscopic evaluation: 27% of patients were receiving ineffective antibiotic therapy, 9% of patients were receiving less than optimal antibiotic therapy, and 7% of patients were receiving unnecessary antibiotic therapy.[47] Similar results were found by Alvarez-Lerma, in a large series of 499 patients with proven VAP.[48] Therefore, antibiotic therapy that is directed by quantitative culture results may be more effective than empiric treatment. It is clear that the inadequate initial management of VAP is associated with increased mortality, and there is evidence that the clinical recognition of treatment failure may be delayed.

The second most compelling argument for invasive bronchoscopic techniques is that they can reduce excessive antibiotic use. There is little disagreement that the clinical diagnosis of nosocomial pneumonia is overly sensitive and leads to the unnecessary use of broad-spectrum antibiotics. Because bronchoscopic techniques may be more specific, their use would reduce antibiotic pressure in the ICU, thereby limiting the emergence of drug-resistant strains and the attendant increased risks of superinfection.[49,50] Most epidemiologic investigations have clearly demonstrated that the indiscriminate use of antimicrobial agents in ICU patients may have immediate as well as long-term consequences, which contribute to the emergence of multiresistant pathogens and increase the risk of serious superinfections.[51] This increased risk is not limited to one patient but may increase the risk of colonization or infection by multiple-drug-resistant bacterial strains in patients throughout the ICU and even the entire hospital. Virtually all reports emphasize that better antibiotic control programs to limit bacterial resistance are urgently needed in ICUs and that patients without true infection should not receive antimicrobial treatment.[51]

The more targeted use of antibiotics also could reduce overall costs, despite the expense of bronchoscopy and quantitative cultures, and minimize antibiotic-related toxicity. This is particularly true in the case of patients who have late-onset VAP, in whom expensive combination therapy is recommended by most authorities in the field. A conservative cost analysis performed in a trauma ICU suggested that the discontinuation of antibiotics upon the return of negative bronchoscopic quantitative culture results could lead to a savings of more than $1,700 per patient suspected of VAP.[52]

Finally, probably the most important risk of not performing bronchoscopy for the patient is that another site of infection may be missed. The major benefit of a negative bronchoscopy may in fact be to direct attention away from the lungs as the source of fever. Many hospitalized patients with negative bronchoscopic cultures have other potential sites of infection that can be identified via a simple diagnostic protocol. In a study of 50 patients with suspected VAP who underwent a systematic diagnostic protocol designed to identify all potential causes of fever and pulmonary densities, Meduri et al confirmed that lung infection was present in only 42% of cases and that the frequent occurrence of multiple infectious and noninfectious processes justifies a systematic search for the source of fever in this setting.[53] Delay in the diagnosis or definitive treatment of the true site of infection may lead to prolonged antibiotic therapy, more antibiotic-associated complications, and induction of further organ dysfunction.

Other than decision-analysis studies[54–56] and one retrospective study,[46] only 4 trials have so far assessed the impact of a diagnostic strategy on antibiotic use and outcome of patients suspected of having hospital-associated pneumonia using a randomized scheme.[3,57–59]

One of the first studies to clearly demonstrate a benefit in favor of the bacteriological strategy was a prospective cohort study conducted in 10 Canadian ICUs.[46] The authors compared 92 patients suspected of having developed pneumonia who underwent fiberoptic bronchoscopy and 49 patients who did not. Mortality among bronchoscopy patients was 19% versus 35% for controls ($p = 0.03$). Furthermore, patients managed with a bacteriological strategy received fewer antibiotics, and more patients had all their antibiotics discontinued compared to the clinical strategy group, thereby confirming that the 2 strategies actually differed.

No differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP in 3 Spanish randomized studies.[57–59] However, those studies were based on relatively few patients (51, 76, and 88, respectively) and antibiotics were continued in all patients despite negative cultures, thereby neutralizing one of the potential advantages of any

diagnostic test in patients clinically suspected of having VAP. Concerning the latter, several prospective studies have concluded that antibiotics can indeed be stopped in patients with negative quantitative cultures, with no adverse effects on the recurrence of hospital-associated pneumonia and mortality.[2,20]

A large, prospective randomized trial compared clinical versus bacteriological strategy for the management of 413 patients suspected of having VAP.[3] The clinical strategy included empirical antimicrobial therapy, based on clinical evaluation and the presence of bacteria on direct examination of tracheal aspirates, and possible subsequent adjustment or discontinuation according to the results of qualitative cultures of endotracheal aspirates. The bacteriological strategy consisted of fiberoptic bronchoscopy with direct examination of BAL and/or PSB samples and empirical therapy initiated only when results were positive; a definitive diagnosis based on quantitative culture results of samples obtained with PSB or BAL was awaited before adjusting, discontinuing, or, for some patients with negative direct examination (no bacteria identified on cytocentrifuge preparation of BAL fluid, or PSB samples) and positive quantitative cultures ($> 10^3$ CFU/mL for the PSB and $> 10^4$ CFU/mL for BAL), starting therapy (Fig. 1). Empirical antimicrobial therapy was initiated in 91% of the patients in the clinical strategy group and in only 52% of those in the bacteriological strategy group. Compared with patients managed clinically, those receiving bacteriological management had a lower mortality rate on day 14 (25% and 16%, $p = 0.02$), lower sepsis-related organ failure assessment scores on days 3 and 7 ($p = 0.04$), and less antibiotic use (mean number of antibiotic-free days 2 ± 3 and 5 ± 5, $p < 0.001$). Multivariate analysis showed a significant difference in mortality on day 28, in favor of bacteriological management, associated with a significant reduction of antibiotic consumption. Pertinently, 22 nonpulmonary infections were diagnosed in the bacteriological strategy group and only 5 in the clinical strategy group, suggesting that overestimation of VAP may lead to missed nonpulmonary infections. The possible consequences of delayed treatment or definite diagnosis due to antibiotic interference are prolonged antibiotic therapy, more antibiotic-associated complications, and induction of additional organ dysfunctions.

Therefore, our personal bias is that the use of bronchoscopic techniques to obtain PSB and BAL specimens from the affected area in the lung in ventilated patients with signs suggestive of pneumonia allows definition of a therapeutic strategy superior to that based exclusively on clinical evaluation. These bronchoscopic techniques, when they are performed before introduction of new antibiotics, enable physicians to identify most patients who need immediate treatment and help to select optimal therapy, in a manner that is safe and well tolerated by patients. On the other hand, these techniques prevent resorting to broad-spectrum drug coverage in all patients who develop a clinical suspicion of infection.[60] Although the true impact of this decision tree on patient outcome remains controversial, being able to withhold antimicrobial treatment from some patients without infection may constitute a distinct advantage in the long term, by minimizing the emergence of resistant microorganisms in the ICU and redirecting the search for another (the true) infection site.

In patients with clinical evidence of severe sepsis with rapidly worsening organ dysfunction, hypoperfusion or hypotension, or patients with a very high pretest probability of the disease, the initiation of antibiotic therapy should not, however, be delayed with awaiting bronchoscopy, and patients should be given immediate treatment with antibiotics. It is probably in this latter situation that simplified nonbronchoscopic diagnostic procedures could find their best justification, allowing distal pulmonary secretions to be obtained on a 24-hours basis, just before starting new antimicrobial therapy.

Despite broad clinical experience with the PSB and BAL techniques, it remains, nonetheless, unclear which one should be used in clinical practice. Most investigators prefer to use BAL rather than PSB to diagnose bacterial pneumonia, because BAL (1) has a slightly higher sensitivity to identify VAP-causative microorganisms, (2) enables better selection of an empiric antimicrobial treatment before culture results are available, (3) is less dangerous for many critically ill patients, (4) is less costly, and (5) may provide useful clues for the diagnosis of other types of infections. However, it must be acknowledged that a very small return on BAL may contain only diluted material from the bronchial rather than alveolar level and thus give rise to false-negative results, particularly for patients with very severe chronic obstructive pulmonary disease. In these patients, the diagnostic value of BAL techniques is greatly diminished and the PSB technique should be preferred.[13]

Summary

The rapid emergence and dissemination of antimicrobial-resistant microorganisms in hospitals worldwide is a problem of crisis dimensions. The root causes of this problem are multifactorial, but the core issues are clear. The emergence of antimicrobial resistance is highly correlated with selective pressure that results from inappropriate use of antimicrobial agents. 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 ICU setting, in order to avoid administering unnecessary antibiotics in patients without infection.

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Discussion

Kollef: Jean, you showed one of your animal studies[1] in which, if you gave a mouse with pneumococcus one dose of antibiotic, you essentially killed the majority of the organisms by 2–3 log order. That's been shown in other studies as well with animal models,[2,3] One of the problems that I have seen with doing the invasive approach is that if it comes up at an odd hour of the day, let's say after hours or on the weekend, sometimes there are delays because clinicians can't get there in time. I'm just going to throw this out. If someone were to do this—because anecdotally I think I've seen this happen, where the patient gets an antibiotic started in the middle of the night, they're lavaged the next morning after the one dose—if you find an organism, it's helpful if you find pseudomonas or MRSA [methicillin-resistant *Staphylococcus aureus*], but if you *don't* find an organism, is that information helpful as well? Can you use that information to say that if the patient did have an infection, the antibiotics are eliminating the organism and you can get by with a shorter course of therapy?

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Chastre: My own bias is that it's too late. You have to follow the clinical approach and base your antimicrobial treatment on clinical data, and, therefore, I will probably continue antibiotics for 3–5 days, and, considering the patient's clinical course, maybe discontinue antibiotics after 3–5 days; but it's only a clinical approach. But I agree with you: in some cases we have no choice, and if you miss the window to sample the lung just before the introduction of new antibiotics, it's too late. There is—to the best of my knowledge—no possibility to do otherwise.

Niederman: Well, no. I agree that it's hard to know. I mean, I agree that if the lung is getting sterilized quickly, you probably can go for a short duration of therapy. How short, I guess, is what's debated. If you had the quantitative culture results, you might go 7 or 8 days; it's difficult to know. If you follow what Jean's saying—if you have a positive quantitative culture, you'd probably go 7 or 8 days. If you had a negative quantitative culture prior to starting antibiotics, you might not treat at all. If you get a good clinical response with a negative culture when you collected it after starting antibiotics, he's saying go 3–5 days.

So I think a lot of this is empiric. I don't think there's any problem getting a tracheal aspirate culture, so I think in that situation, even if you're a believer in quantitative techniques, get a tracheal aspirate culture, and you can compare that to your quantitative culture that you get in a delayed fashion. I wouldn't agree to collecting nothing.

Chastre: I agree, but my problem is not only to diagnose lung infection, but to implement a policy concerning antibiotics in the ICU, and this is a key issue.

Niederman: I was just going to say exactly that. I think what we're comparing is a lot of studies that were done in different time periods, and I think our thinking has evolved. I think what we really need is a study that compared the best invasive approach to the best de-escalation clinical approach. My guess is it would be hard to show a difference.

Chastre: We need to study it.

Niederman: Well, I'm not so sure we need to study it. I think the question remains: do you think, when you read these studies of clinical approaches with de-escalation, that another approach is going to lead to as good or better outcomes with less antibiotic use? Because if you don't think you can do better than them, I'm not so sure. Look at the latest study from Marin Kollef's group,[1] in which 93% got adequate therapy, and the duration of therapy was reduced with an intervention to 6 days. Boy, it's hard for me to imagine you're going to do better than that with any other protocol.

And I think what's important to point out is that you're right. The Spanish study[2] and your study[3] point out all of the issues that you discussed. But the important thing is that in your study you said—but I think it often gets lost by people who read it—that you are a good clinician, you're a good doctor, you're smart enough to know that if a patient looks terrible, regardless of what the bronchoscopy shows, you're going to use antibiotics. And at least 10% of your invasive group got antibiotics, despite negative bronchoscopy. And that's an important point for everybody to understand. In addition, the clinical strategy that you compared to was a legitimate clinical strategy at the time you did the study.[3] Probably the clinical strategy has evolved since then.

All I'm saying is that what I was hoping we got to in the new guidelines was at least an understanding that the goal is to use less antibiotics. And there are many different ways to do that. And your approach is to focus on the front end, but maybe an equally valid approach is to focus later on down the line as well.

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Chastre: I completely agree, Michael. Patients need doctors, and good doctors are probably better. But the problem is that the doctors need protocols. It was perfectly demonstrated by, for example, the ARDS Network. Maybe using 6 mL/kg is too low in some patients, but still I think that using a protocol is better.

Niederman: I think you've said it very well, and I think that an invasive strategy in the hands of a good doctor is a good tool, and maybe a clinical strategy in the hands of a good doctor is also a good tool. But I think an invasive strategy in the hands of a bad doctor is not a good tool. The problem is that many doctors will use the invasive strategy, do it wrong, technically, do it wrong with regard to timing and with regard to antibiotics, and interpret it badly and not use good

clinical judgment, and that's, I think, the real danger.

Solomkin: That's really an education issue, not a clinical research issue, and I think the importance for this kind of work at this level is to define "optimum practice." How that gets translated into therapeutics at a local level is a separate issue.

Dr Chastre, I want to ask you a question that Marin Kollef alluded to. We're debating the interval between when one suspects a pulmonary infection and when one should have accomplished diagnostics. The debate really comes down to what does one do with an invasive strategy during a certain period of off-hours. What's the evidence that waiting 6 hours to do the test harms the patient? That would be a good role for mini-BAL, for example, if you had that concern.

Chastre: As you know, if you make 2 rounds that day, I am pretty confident that you will diagnose most of the cases of pulmonary infection. It's very unusual, at least in my ICU, to see a patient perfectly well at 6:00, and 3 hours later, in septic shock. It's possible, of course, but it's very unusual for pulmonary infection. But, OK, it's a difficult protocol, and I'll agree that at Christmas Eve, for example, even in my ICU it could be difficult to follow the protocol. In that case, I prefer either to obtain a nonbronchoscopic specimen or to follow a clinical approach, such as Victor Yu's strategy, using the clinical pulmonary infection score to decide whether to treat the patient,[1] or to follow the new American Thoracic Society guidelines,[2] but using explicit, not implicit, guidelines to withdraw antibiotics. I think it's probably the only caveat of the new guidelines. There are no explicit guidelines for stopping antibiotics. But I participated in creating those guidelines, so it's partly my fault too.

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Niederman: No, I think it's not a matter of fault. It's a matter of there not being enough data to give very firm recommendations about exactly when to stop antibiotics.

Kallet: I want to ask this of either Dr Chastre or Dr Niederman. At the University of California, San Francisco there's a big move toward using mini-BAL and getting rid of tracheal aspirates, and I want your opinions about the role of mini-BAL. In the United States we have respiratory therapists around the clock, so we could do these procedures if someone does get septic in the middle of the night. There wouldn't be a delay. Is there an advantage to doing mini-BAL over tracheal aspirate, in your opinion?

Chastre: I don't know, in fact.

Solomkin: We're really having a problem with it, because our initial data were obtained by one individual, Robert Campbell RRT, and it was clean data. When the test then became a clinical service item, done by a variety of respiratory therapists, the data quality really degraded. One approach is simply to move away from the immediate diagnosis/therapy approach and wait 6 or 10 hours to get these tests done by a small group of practitioners. I believe this will greatly improve the quality of the data and, in turn, greatly improve patient care.

Kallet: I'm curious whether it was opened up so that all staff were trained to do it, or just a select number, because I have the same concern. If everyone can do it, the quality may go right down the tubes.

Branson: We limit it to a core staff in the ICUs. Probably in a given month there might be 20 different people doing mini-BAL, and we really think that that's a problem. If you watch it with the mini-BAL, there are problems, one of the biggest being convincing respiratory therapists that we don't want sputum samples. Therapists are trained in school to get sputum samples. In the nonintubated patient you want this brought-deep-from-the-lung mucus, and that's not what we want for a mini-BAL. So I think it's partially training, and I think it's going to be very important to limit the number of people who are involved.

Maki: Have you looked at Gram stains in your quantitative studies? There's a good correlation between a Gram stain and quantitative numbers of organisms. I've always been distressed that we pull the trigger with 3 barrels right off the bat, send some cultures, and then 3 or 4 days later we'll decide to step down, whereas with a lot of patients, a good Gram stain of a BAL, or even a tracheal aspirate, shows absolutely no bacteria whatsoever, and, because of a high negative predictive value, you don't need to treat the patient. And I've been doing this for 25 years. We had a Gram stain lab until the federal government didn't let us have a lab in the ICU any more, and we did Gram stain of the tracheal aspirate on all our intubated patients every day. We did a study 20 years ago [unpublished] that showed that this cut our antibiotic use in half, eliminating treating just cultures. With the average person who is intubated and has pseudomonas and moderate enterobacter after 5 or 6 days, it's a mid-brain reflex to start antimicrobial therapy, but we need more than that,

and I think a Gram stain is something simple; it's reproducible, and technicians can do it reliably.

Chastre: I completely agree, but the problem is that nobody wants to do the Gram stain. Everybody would prefer to use a fancy biologic marker, such as the soluble TREM-1 in the BAL fluid, as done by Sebastien Gibot in his *New England Journal of Medicine* paper.[1] But remember; we have no proof that such a marker would give better results than a good Gram stain.

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Maki: We have a policy in our hospital that if the Gram stain shows no bacteria whatsoever, the lab doesn't even culture the specimen and you specifically have to request it. I don't think that's a bad policy.

Niederman: Again, in one of the papers I cited,[1] I pointed out that use of the Gram stain, or the use of some microbiologic assessment as part of the clinical pulmonary infection score calculation, improves its diagnostic accuracy. Ultimately, I'm a little confused by this discussion, because if we have people from academic medical centers saying that in those centers, with protocols, under close observation, they don't trust all of their staff to be doing these techniques, then I guess I wonder who you're recommending this to as the accepted standard? Because if what you're saying is that you believe in these techniques, but not if Joe does them, only if Bill does them, why would anyone accept the message that this technique ought to be used in day-to-day clinical practice?

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Chastre: But, Michael, it's the same for a weaning protocol: exactly the same.

Niederman: It's *not* exactly the same. As you said, we can write a protocol for ventilators that everybody can use. We can write a protocol for weaning that everybody can use. But what 2 independent groups have just said is that they've tried to use these diagnostic techniques in their hospital and they don't work when everybody uses them. So that's an inherent problem in these techniques to begin with.

Solomkin: That's a problem in diffusion of technology.

Niederman: Clearly, it's a problem in diffusion of technology, if in the institution where you believe in this you don't even believe in half your staff to do it right. The other thing is, again, the gut-check issue of what are you going to do with the data? And how often, in a place that does it routinely, do you have doctors stopping antibiotics when they get results below a diagnostic threshold? Because, as Jean said, that is the one area where he disagrees with the algorithm as it exists, which is the stopping of antibiotics. In other words, if you're going to do this technique, and you're not going to stop antibiotics when cultures fall below the diagnostic threshold, then it sounds to me as if Jean would agree that it's not worth doing.

Rello: In my opinion, the issue of diagnosis is like a landscape with different pictures taken by different artists. But even with the same landscape it's not the same picture if you use different cameras; it's not the same picture if you use a different filter; and probably the same landscape would be different at sunset and sunrise. But this is very interesting and helps to understand the differences. Perhaps, if Michael was working in Jean's hospital, he would accept a different approach. And perhaps if Jean worked in Michael's hospital, he would follow a different approach. I change from one hospital to another, and I should customize my strategy to the patients and to the institution. And I also think this applies to microbiologic support, because not all hospitals have a microbiologist on call over 24 hours. And the skill of different professionals is different.

I want to emphasize some aspects that were not well understood about our study on de-escalation.[1] For example, it is not the same to prescribe one broad-spectrum drug, or two, or even three. For example, all patients in the study by Ibrahim et al[2] received an initially broad-spectrum regimen of 3 antibiotics, including an anti-MRSA antibiotic, in all empiric therapies. Obviously, when they isolated *Pseudomonas aeruginosa*, 100% of the episodes had de-escalation of the anti-MRSA agent. Our group does not use anti-MRSA agents in the empiric therapy because we are not working in an endemic area. MRSA is isolated in outbreaks in our ICU and consequently the rate of de-escalation is lower.

Second, different studies do not have the same case mix. Probably, in medical patients it is easier to de-escalate, but in trauma or surgical patients who have other causes of fever and other potential infection sites, the decision-making process is more complex. In my opinion, it would be a risk to stop antibiotics in a patient only because the Gram stain from the BAL is negative. You don't consider that the patient might have a subphrenic abscess, for example. But my point is that it is not the same to perform a PSB, a tracheal aspirate, or a BAL; sensitivities are different, and proba-

bly different conclusions can be taken with different techniques.

I want to emphasize 2 aspects. First, what I learned from the study is that in the absence of microbiologic information, de-escalation, in our cohort of patients, was extremely difficult. When we designed the protocol, it was expected to shorten therapy to 5 days if patients presented negative cultures and > 48 hours of defervescence. Unfortunately, when considering variables of resolution, 3 patients were getting worse, and the antibiotics were changed in them, but on the other side, the other 7 patients maintained fever (mean resolution of fever was 5.6 days and hypoxemia 7.9 days), and therefore it was not possible to stop antibiotics at day 3, despite our protocol. Half of these patients died. One patient was transferred to the ward with imipenem and low-degree fever, but he was re-admitted with a subphrenic abscess one month after ICU discharge. We learned that this patient probably did not have pneumonia, and he had a pleural effusion in relation to the subphrenic abscess.

The second thing that we learned was that, despite microbiologic confirmation in 111 episodes, de-escalation was not done in 46 episodes. It is very interesting to look at the causes of no de-escalation, because in the ideal life things would be different than in the real world. Nine patients had MRSA or *Acinetobacter baumannii* and did not have other alternative sensitive agents. Similarly, 13 patients with *Pseudomonas aeruginosa* did not have narrower-spectrum alternatives. Eight additional episodes were caused by patients with *Enterobacteriacea*e (eg, *Klebsiella* species) producing extended-spectrum beta-lactamase, in whom carbapenem was maintained as a first-line option. Five patients received a non-anti-pseudomonal agent, because of a combination of early-onset episodes, comorbidities, and Gram-negative stains. Finally, 11 episodes might have received de-escalation therapy from broader- to narrower-spectrum antibiotics. In these 11 cases, empirical therapy was maintained unchanged, because defervescence and other signs of clinical resolution were delayed or the microbiologic information was arriving with a considerable delay with respect to the 2 or 3 days that was expected. This is the real world, and I think it is possible to have different answers to the same question.

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Pierson:* I believe I've heard a consensus here, that de-escalation of antibiotics is a desirable goal. I have not heard a consensus on the best way to make the diagnosis of VAP—specifically, whether clinical or invasive methods should be used—and I want to introduce a subject we haven't talked about, which is money.

Dave Park presented data from Harborview Medical Center, such that in determining the current bacteriology of VAP in that institution, 560 bronchoscopies were done for VAP-diagnostic purposes in an 18-month period. That's 372 per year, or a bit more than 1 per day. Several years ago we made a determination of the charges generated for that procedure, and it was something over $1,600, counting the hospital fees for the procedure, the professional fees for the physicians, the quantitative cultures, and so forth. That is well in excess of half a million dollars a year in charges generated by bronchoscopy for BAL or PSB for the evaluation of suspected VAP in that one institution. These, of course, are charges and not costs, and they also don't necessarily reflect what is actually paid.

But in the United States, health care costs are really important, and if I were the third-party payer being presented the bill for that half-million dollars per year, in a context of a lack of consensus whether the procedure is necessary, or even best practice, even though it is within the standard of care, I wonder what my response would be.

Chastre: But David, there are at least 1 or 2 studies[1,2] demonstrating that with quantitative techniques it's possible to decrease the cost, because you reduce the quantities of antibiotics.

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Pierson: But there we're talking about de-escalation, which I believe Michael has shown us can be done with a noninvasive diagnostic approach, or at least we *think* could be done.

Niederman: But in defense of Jean, the fact that I don't want to use invasive techniques has nothing to do with money. It's got to do with the fact that I believe that I can manage patients effectively as well—maybe in some ways better—not using those techniques. There are probably places that feel the opposite about the invasive techniques. I think they ought to be given the freedom to do

* David J Pierson MD FAARC, Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.

that if they have a protocol and a belief that they're helping the patients. I think it would be a huge mistake to go to a place like Jean's, if it were in the United States, and say, "You can't do this because of cost considerations, because you haven't proven that you can do better cost-wise and efficacy-wise than clinically-guided de-escalation."

I think one of the things that we tried to emphasize in these new guidelines is that as long as you agree with what the goals are, which is to effectively treat patients and use as little antibiotics as possible, there are many ways to get there. And the way in which you choose to do it ought to be based on your expertise and on the way in which you feel you can achieve those goals best. Cost shouldn't be an issue, and I wouldn't seize on that as a way of attacking invasive methods. I believe that there are people who, whether it's true or not, believe they can take better care of patients with those techniques. They ought to be allowed to do that if they feel that's how they take best care of their patients.

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