Pneumonia represents an infectious process of the gas exchanging units of the lung parenchyma. Despite previous and ongoing research in the field, the diagnosis of pneumonia remains problematic.\textsuperscript{1,2} However, there are areas in which a great deal of information has been learned and an apparent diagnosis can be readily made. This is usually by the identification of what are always considered pathogens. This would include organisms such as \textit{Pneumocystis carinii}, \textit{Mycobacterium tuberculosis}, and \textit{Legionella pneumophila}.\textsuperscript{3-5} Any of those organisms, regardless of method for identification, will always be considered pathogenic. However, other organisms, such as most bacteria and viruses, are known to colonize the upper respiratory tract in selected instances, making the diagnosis more difficult. However, even for these pathogens, we have been able to make the diagnosis of pneumonia with some confidence in selected cases.\textsuperscript{2,6,7}

Lower respiratory tract infections occur in both immunocompromised and nonimmunocompromised patients. The first group comprises patients affected by AIDS and those who have undergone organ transplantation or antineoplastic chemotherapy. In this group, the use of invasive diagnostic techniques has proved quite useful. It is based on these experiences that invasive procedures have been exported to the nonimmunocompromised area.

In AIDS patients, diagnostic procedures have proved to be extremely useful in evaluating lung infections, especially \textit{P carinii}.\textsuperscript{3,8-9} BAL has been shown to be a cost-effective technique. Although it has been argued that empiric therapy may be used in the initial approach to these patients, the risk of multiple infections has made others advocate bronchoscopy with BAL.\textsuperscript{10} Whenever the procedure is done with two or more areas of sampling, it appears that BAL has >90\% sensitivity and a near perfect specificity for the diagnosis of \textit{P carinii}.\textsuperscript{11,12} The overall diagnostic yield of bronchoscopy in evaluating an AIDS patient is >50\%.\textsuperscript{3}

In transplant recipients, bronchoscopy is most useful in high-risk situations such as the sixth through 26th weeks posttransplant.\textsuperscript{13,14} This is especially true in the patient who is not receiving \textit{P carinii} prophylaxis and/or has been exposed to cytomegalovirus. Diagnostic procedures are less useful early or late in the posttransplant course but are still useful in refractory pneumonias. In this case, biopsy may have a more important role. In other immunocompromised situations, the diagnostic yield may be less; however, it can still be a useful procedure.

As mentioned above, the recovery of certain organisms is believed to be almost always pathologic. For example, the recovery of \textit{P carinii} and \textit{M tuberculosis} is always believed to be an indication of disease. However, the relative yield is different for these two. \textit{P carinii} is much more frequently recovered by BAL than by bronchial wash.\textsuperscript{15} \textit{M tuberculosis} is more frequently found in the wash than in...
However, the patient with acid-fast smear-negative sputum will have only a smear-positive bronchial wash sample in half the cases. The culture technique is more sensitive, with a >90% diagnostic yield; however, there is a significant delay waiting for culture results. Transbronchial biopsy appears to have a higher sensitivity for acid-fast smear than bronchial wash. For other pathogens, the sensitivity of bronchoscopy samples is less clear. For certain fungi such as histoplasmosis and coccidioidomycosis, the sensitivity is probably about 50%, although large studies are still lacking. L pneumophila can be cultured in the BAL sample; however, the sensitivity of this technique vs others is unclear. It appears that L pneumophila can be cultured in >80% of patients who are subsequently determined to have Legionella pneumonia. The recovery of any of these organisms would be considered diagnostic for that pathogen.

For most pneumonias, especially in the normal host, one has to consider the fact that recovery of a bacterial pathogen does not necessarily mean infection. This is because the upper respiratory tract is normally loaded with bacteria. Normal pharyngeal flora are usually not considered the cause of pneumonia unless the patient has received a large bolus of organisms (eg, aspiration pneumonia). Some presumed pathogens, such as pneumococcus, are known to colonize the upper respiratory tract. The patient in the ICU may soon be colonized with Gram-negative bacilli without ever developing a lower respiratory tract infection. We also have come to accept that in a significant percent of cases, we never are able to identify the causative agent for pneumonia. In the setting of ventilator-associated pneumonia, this is even more common. In this group, the widespread use of antibiotics confounds the ability to identify a pathogen. This inability to diagnose the underlying pathogen is not limited to ventilator-associated pneumonia. Intense studies of community-acquired pneumonia and those in immunocompromised patients failed to make a diagnosis in nearly half of the cases. In autopsy studies in the ICU, histopathologic studies will demonstrate pneumonia when cultures remain negative.

To diagnose lower respiratory tract infection, several techniques have been proposed. These include clinical diagnosis, analysis of tracheal secretions, and lower respiratory tract sampling. Clinical diagnosis is based on the presence of the classic signs and symptoms of pneumonia, including fever, rigors, chest pain, and cough productive of purulent secretions in association with physical findings and radiographic manifestations of lung consolidation. Because of its safety and simplicity, clinical diagnosis has been used as part of the initial evaluation in almost all studies. Therefore, its sensitivity is reported as >95%. Unfortunately, its specificity is reported to be only 30 to 50% in most studies using other diagnostic criteria for infection. In particular, autopsy studies suggest only a 30% specificity. Even the high sensitivity of clinical diagnosis is in question, since at least one report found that up to a third of elderly patients with pneumococcal pneumonia and bacteremia did not have fever. Analysis of tracheal secretions includes collection and analysis of sputum, transtracheal aspirates, and suctioned endotracheal secretions. Although the presence of purulent tracheobronchial secretions is necessary to satisfy most definitions of pneumonia, the specificity of tracheal secretion analysis remains low, probably <50%. This specificity may be improved by requiring the presence of neutrophils and elasin fibers as evidence of lung destruction. However, this technique is still probably overly sensitive. Overdiagnosis may lead to increased treatment with antibiotics and missed opportunities to identify other treatable problems (eg, congestive heart failure and pulmonary embolism).

Lower respiratory sampling includes protected brush sampling and BAL performed either under bronchoscopic guidance or blindly. The technique of protected brush specimen (PBS) was introduced in 1979 by Wimberley et al. A plugged catheter is placed through the bronchoscope, an inner cannula is used to remove the plug, and a sterile brush is used to obtain the sample. The brush is placed into the area of interest. If purulent secretions are seen, the brush is directly applied there. This technique has been investigated extensively in both mechanically ventilated and nonmechanically ventilated patients. Multiple studies have suggested excellent sensitivity and specificity for diagnosing bacterial infection. The average sensitivity is 80%, with specificity of 90%. The utility of the technique is limited to bacterial infection only. This technique is most useful in patients who are not receiving antibiotics or whose antibiotics therapy has been discontinued for at least 48 h. Semiquantitative cultures remain the key to understanding the significance of the pathogen. A growth of 1,000 cfu/mL is considered significant and corresponds to an initial concentration of $10^3$ to $10^6$ bacteria per milliliter of the retrieved secretions. Figure 1 summarizes the sensitivity and specificity of eight studies using the 1,000 cfu/mL cutoff for diagnosing pneumonia. However, repeated brushings of the same area of pneumonia demonstrate a 10% variance at the 1,000 cfu/mL cutoff, suggesting that a lower cutoff, such as 100 cfu/mL, may be appropriate in certain settings.

BAL has been utilized for nearly two decades. The procedure is performed by advancing and wedging the bronchoscope into a subsegmental bronchus in the area of interest. Sterile saline solution is then
instilled and aspirated by hand-held syringe. There is no consensus concerning the optimal volume to be instilled, but it is believed that a volume of at least 100 mL is required to retrieve secretions from the periphery of the subsegment.\textsuperscript{26} This technique has been shown to be particularly useful for identifying certain pathogens such as \textit{P carinii}, \textit{M tuberculosis}, and deep-seated fungal infections.\textsuperscript{5,4} The technique is relatively simple and most pulmonary physicians have acquired the technical skills to perform it. The returned volume may range from 5 to 70\% of the total volume instilled, but it is usually low in dependent lobes and is further reduced by airway edema from pneumonia. Some procedures yield <10\% of the instilled volume. In this case, the procedure is probably not an adequate BAL. The lavage process itself is more likely to induce hypoxemia than a bronchoscopy or brush procedure is.

Semi-quantitative results are necessary to interpret bacterial cultures of BAL lavage. A growth of at least 10,000 cfu/mL is considered significant, although certain authors prefer a 100,000 cfu/mL cutoff, which provides higher specificity.\textsuperscript{27,28} The report by Cantrel et al\textsuperscript{38} further refines these observations. In that study, some normal control subjects had >10,000 cfu/mL of bacteria. However, the normal subjects all grew non-pathogenic mouth flora, suggesting oral contamination as a problem with the BAL procedure.\textsuperscript{29} A summary of seven studies examining the semi-quantitative results of BAL from nonintubated patients is shown in Figure 2, top. Overall, the prescribed cutoff of >100,000 cfu/mL was almost always bacterial pneumonia. Likewise, those with <10,000 cfu/mL rarely were believed to have pneumonia. The patients with between 10 and 100,000 cfu/mL were diagnosed either way. Although the data appear consistent and acceptable for nonintubated patients, the results are less clear cut for patients receiving mechanical ventilation. Figure 2, bottom summarizes three studies that show that although those patients with >100,000 cfu of organism were believed to have pneumonia, many patients confirmed to have bacterial pneumonia had <10,000 cfu/mL BAL fluid. Studies comparing BAL with PBS have yielded conflicting results. Initial observations suggested a higher specificity for PBS over BAL samples. However, subsequent studies have shown a higher sensitivity for BAL samples. The presence of intracellular bacteria or a positive Gram’s stain increased the specificity of BAL samples.\textsuperscript{19} However, a major limitation of PBS is that it will only diagnose bacterial infections, making it less useful in the clinical setting of obscure pneumonias, where nonbacterial pathogens such as \textit{P carinii} may be found.

Recently, nonbronchoscopic PBS and BAL have been introduced as simple methods to sample lower respiratory tract secretions.\textsuperscript{29,30} Both techniques have compared favorably with the results of immediate autopsy studies.\textsuperscript{30} A recent report of an adap-

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{The sensitivity and specificity of eight studies using protected brush samples. Specimens with >1,000 cfu/mL of bacteria were considered positive.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Pooled results of seven studies in nonventilated patients (top) and three studies of ventilated patients (bottom) undergoing BAL to diagnose pneumonia. The patients were classified as having either pneumonia or no pneumonia. The results of the BAL cultures in cfu/mL are shown. Almost all patients with >100,000 cfu/mL were believed to have pneumonia.}
\end{figure}
tation of this procedure, using a 60-mL aliquot of instilled fluid, found this technique useful in the ICU setting.31 The major advantage of this procedure is the fact that nonphysicians can perform it, and thus it can be readily performed at night or on weekends and may prove a useful way to bypass the excuse that the physician does not want to wait until the diagnostic procedure could be performed.

As attractive as these procedures are, there are several issues that have to be further evaluated. The first is that the results of the specimen have to be critically examined. Although this is standard for the pulmonologist in doing a bronchoscopy, this will not be as easy for the blind procedures. The blind catheter will follow gravity and so will almost always sample the right lower lobe. A study comparing the yield for right vs left localized pneumonias demonstrated that the yield for blind brushing was 85% for right lower lobe pneumonia, but 28% for left lower lobe pneumonia.32 The catheters may be kinked during placement, something which may be difficult to appreciate at the time of the procedure. There is some risk from these procedures, including bleeding for the brush procedure and hypoxemia for the BAL procedure. The hypoxemia can be significant, similar to that observed for routine BAL. In patients requiring high inspired oxygen, one should take care to adequately oxygenate after the procedure and monitor for evidence of increased airway pressure.33,34 Analysis should be made of the Gram stain to look for appropriate inflammatory cells. For the blind BAL procedure, the return should be at least 10%. From experience with BAL in other diseases, we know that returns of less than that probably are not representative of the lower respiratory tract. Analysis of the cellular product of the aspirate should not show >5% epithelial cells and in the case of pneumonia, <10% neutrophils. Samples should still be handled in semiquantitative manner. Gram stain probably enhances the specificity of the technique.

The volume of instilled fluid has been important in obtaining an adequate BAL using the bronchoscopic technique. Studies have shown that 20 mL is merely sampling the bronchial tree and poorly reflects the alveolar space.35 In comparisons of the fluid after the first 60 mL have been instilled compared with the next 60 to 180 mL, it is clear that even 60 mL is not an adequate volume to achieve alveolar sampling. This has been documented for normal subjects as well as patients with interstitial lung diseases.26 For the diagnosis of infection, alveolar sampling may not be necessary.31 It has been shown that there was no difference between 60 and 240 mL lavage to diagnose P carinii pneumonia.36

The current techniques have not been well correlated to clinical outcome. The best studies determining sensitivity and specificity for the various diagnostic techniques have been autopsy studies.19,30 However, these studies are on patients in whom a poor clinical outcome has already been achieved and may not be a good reflection of what is occurring in the alive patient. Unfortunately, outcome measures for pneumonia are still poorly defined, and therefore we are left with the difficult task of assessing the utility of these procedures as carefully as we look at other interventions, such as antibiotics. It has proved difficult to demonstrate any advantage to the patient in diagnosing pneumonia with any of these techniques. This may be due in part to the fact that nosocomial pneumonia in the patient receiving mechanical ventilatory assistance may not lead to increased mortality.37,38

In assessing the role of the various methods used to diagnose lower respiratory tract infections, it is important to keep several factors in mind. The ideal test should be easy enough that it does not require highly skilled personnel to perform, otherwise it will be done only during certain parts of the day. It must be viewed as cost efficient, or else this will be a barrier to its application. This would be demonstrated if we could reduce the overall cost of care for the patient with pneumonia. Finally, the sample must be understandable.

The lower respiratory tract specimens are somewhat analogous to those obtained to diagnose a urinary tract infection. The midstream urine is similar to the expectorated sputum. The straight catheter specimen is the same as the respiratory therapist obtaining a blind BAL or PBS. The more invasive suprapubic sample is similar to the bronchoscopic BAL or PBS. In evaluating urine samples, we have all learned how to handle the results of a urine culture. We look at the urine analysis and Gram’s stain to better understand the quality of the sample provided. We look at the semiquantitative culture results, since this tells us the relative burden of organism. For the patient receiving antibiotics, we realize that urine cultures are less reliable, but probably a value of >100,000 cfu/mL reveals a true pathogen.

In conclusion, we have learned a great deal about diagnosing certain lower respiratory tract infections. Bronchoscopy has been shown to be quite useful in diagnosing certain pathogens, such as P carinii and M tuberculosis. For organisms that may colonize or invade, the simple recovery of the pathogen is not sufficient. Its recovery at a high enough concentration, with an appropriate inflammatory response, and in the correct clinical setting remains useful information.
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