Retrieval of microbiological specimens through the fiberoptic bronchoscope[1]

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Lower respiratory tract infections in the immunocompromised host and hospitalized patient are a leading cause of morbidity and mortality. The methods of determining the causative agent range from sputum Gram staining to open lung biopsy. Because of the inadequacy of the former and the invasiveness of the latter, the fiberoptic bronchoscope is being used more frequently as a diagnostic tool. This paper reviews its utility in diagnosing infectious pneumonias and concentrates on the use of the microbiology specimen brush and bronchoalveolar lavage.

Index terms: Bronchoscopy • Pneumonia

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Since its introduction the fiberoptic bronchoscope (FOB) has greatly facilitated the diagnosis of endobronchial abnormality and diffuse parenchymal diseases of the lung.[1] However, early evaluations of its usefulness in infections of bacterial origin were disappointing because of contamination by oropharyngeal flora.[2] The FOB did gain popularity in patients with sputum-negative tuberculosis and is favored for the initial procedure in immunocompromised patients with diffuse pulmonary infiltrates.[3,4] Recent development of two new methods of obtaining specimens has added greatly to the utility of the FOB in patients with pneumonia. The first of these is the use of the microbiology specimen brush (MSB), which allows protection of the specimens from oropharyngeal contamination. The second is bronchoalveolar lavage (BAL), which delivers, for microscopic examination, cells and organisms from the small

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airway and alveolar levels.[5,6] This article reviews the methods of and the indications for fiberoptic bronchoscopy in patients with suspected pneumonias.

Pyogenic bacterial pneumonia

Community-acquired pneumonias in a normal host have only a small number of causes, *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* being the most common agents involved. Good results can be obtained for the most part with Gram staining of a sputum specimen and empiric antibiotic treatment. Hospital-acquired pneumonias, however, are a much greater threat and have a larger number of causative agents. Hospital-acquired pneumonias rank as the third most common nosocomial infection, after urinary tract infections and wound infections. Pneumonia is involved in 5% of all hospital admissions.[7] In the intensive care unit, this is a serious problem, with an incidence of nearly 60% in all patients admitted to critical care areas and a mortality of 50%. This contrasts with the mortality of approximately 4% in intensive-care patients in whom pneumonia does not develop.[8] In patients who have the adult respiratory distress syndrome (ARDS), the mortality with associated pneumonia is nearly 70%.[9] The mortality of patients with hospital-acquired pneumonia is related, in part, to the causative agent; with *Pseudomonas aeruginosa* and other gram-negative bacteria mortality is 70% and 33%, respectively, and with gram-positive cocci only 5%.[8] Mortality is also related to age and underlying disease.

There may be numerous reasons for the ineffectiveness of antibiotics in the hospital setting.[10] These include a weakened host response due to the patient's underlying disease, inadequate tissue levels of the chosen antibiotics, or resistance of the organisms to these antibiotics. Complicating these issues is the fact that it is difficult to define the specific origin of hospital-acquired pneumonias in many cases; without this, antibiotics must be chosen empirically. This can lead to inadequate antimicrobial coverage for the invading organism and unnecessary toxicity secondary to the antibiotics used.

Difficulty in diagnosing a specific causative agent can be ascribed in part to the pathophysiologic mechanisms associated with nosocomial pneumonia. The most important of these is the fact that upon admission to the hospital, there is usually a change in the resident flora of the oropharynx.[11] This turnover occurs quickest in those patients with serious underlying illness.[12] The pathogenesis of hospital-acquired pneumonia has been clearly shown to be aspiration of oropharyngeal material, which in most cases has changed to gram-negative bacteria and *Staphylococcus aureus.*[11] Noninvasive methods of obtaining material from the lower respiratory tract for culture require the specimen to pass through the oropharyngeal secretions, which contain colonizing organisms. This leads to contamination of specimens with oropharyngeal flora, so that simple sputum samples are not reliable for the selection of the specific causative agent.[13] Another method of defining a specific cause is to use blood cultures; in cases of *Strep pneumoniae* these are positive approximately one third of the time, but they are positive less often in patients with pneumonia caused by gram-negative organisms.[10,13] Pleural fluid is also a potential source for defining a specific causative agent, but while fluid may be present in approximately 40% of patients with infectious pneumonia, it is only culture-positive in 8% of these.[14] Another invasive procedure, the percutaneous needle aspirate, has a high specificity, but because of sampling error it has relatively low sensitivity. This procedure also has a high rate of false-negative cultures and a high complication rate, including pneumothorax in 20–30% of patients. Therefore, it has not gained wide acceptance.[15] Transtracheal aspiration is useful, but this procedure also can be falsely positive (a reported false-positive rate up to 18% when compared with percutaneous transthoracic needle aspiration),[16] and it is not without associated morbidity or mortality.[17,18] Another drawback of transtracheal aspiration is that it cannot be performed in patients who have an endotracheal tube in place.

Microbiology specimen brush

When first evaluated, it was clear that aspirates obtained via the fiberoptic bronchoscope were significantly contaminated by upper airway organisms; on the average there were five such organisms per culture in individuals who had no proved pneumonia.[2] To overcome this drawback, Wimberley et al[5] introduced a protected telescoping brush-in-catheter system for the purpose of obtaining uncontaminated specimens from the lower respiratory tract. This system, which has a brush protected by two catheters and a polyethylene glycol plug, surpassed other types of

brushes tested in an in vitro study.[5] Since then, at least 12 studies have been published evaluating the specificity (lack of contamination) and the sensitivity of this method. Overall, there appears to be a low rate of contamination in obtaining culture material from the lower respiratory tract.

The best animal study to date is that of Higuchi et al,[19] done in an ARDS model in primates that were intubated and mechanically ventilated. Only one of 18 specimens was contaminated (specificity 95%) despite typical gram-negative bacterial colonization of secretions suctioned from the endotracheal tube. In 10 animals with proved pneumonias, the MSB specimen was positive for the appropriate organism in seven, a sensitivity of 70%. These may well be the maximum obtainable results by this method. This is the only study we have found reporting complications from this technique that included one pneumothorax and one case of significant bleeding. In this study cultures were taken as a blind procedure, with the brush inserted into a lobe as far as possible. This method may explain the complications seen.

In the two largest clinical studies, a total of 124 cases of pneumonia (46 and 78 respectively) was defined by clinical criteria[20,21] and studied using the MSB. One hundred twenty potential pathogens were cultured, an estimated sensitivity of 97%. Within these two studies, there were 23 patients with positive blood cultures, all of whom had the same organism in the MSB specimen culture. The most common organisms in both studies were *Strep pneumoniae* and *Hemophilus influenzae*. The presence of these organisms suggests that the majority of patients had a community-acquired pneumonia. Neither study had significant isolation of gram-negative bacteria.

Despite use of the MSB, both studies showed a significant rate of contamination; the study of Wimberly et al[20] showed an average of three isolates per patient. Both studies found that a cutoff concentration of 10^3 colony-forming units (CFU) per milliliter could be used to distinguish true pathogens from contaminants. This cutoff concentration is in agreement with theory. If it is assumed that in a true lower respiratory tract infection organisms are present at a greater concentration than 10^6 CFU/ml, then placing 0.001 ml of lower respiratory tract secretions (the volume estimated to be present on an MSB) into 1 ml of lactated Ringer's or normal saline solution will yield a concentration of greater than 10^3 CFU/ml. Organisms isolated at lower concentrations then would be considered contaminants. A possible explanation for this low-grade contamination is that the procedure was performed in the manner described by Zavala, with the patient in the sitting position.[22] This may allow greater contamination of the lower airways during the procedure simply because of gravity.

Another significant finding in the study of Pollock et al[21] was that when an anatomic abnormality of the airway was present, specimens frequently were cultured at concentrations greater than 10^3 CFU/ml when there was no evidence for the presence of pneumonia.

The study of Wimberly et al[20] included seven patients who were being treated with antibiotics; all of these cultures grew organisms, but at a concentration of less than 10^3 CFU/ml. Pollock et al[21] eliminated from their study all of the patients already receiving antibiotics at the time of culture.

A prospective evaluation of the MSB method was performed by Chastre et al[23] in a human population of intubated patients in whom bronchoscopy was performed within one hour after death, while mechanical ventilation was still being performed through an endotracheal tube. Immediately thereafter, a thoracotomy was done to obtain specimens for cultures and histologic evaluation. This allowed a standard against which to evaluate sensitivity and specificity. A nondependent lobar segment (left lower lobe anterior basal segment) was chosen. The study included 26 patients, 20 of whom did not have histologic evidence of pneumonia and 15 of whom had negative cultures of lung tissue. None of the MSB cultures had greater than 10^3 CFU/ml in these patients. In the six patients who had histologically proved pneumonia, the MSB specimens yielded 15 of the 19 organisms found by direct culture of lung tissue. Overall correlation between the MSB specimen culture and direct culture of lung tissue was better in patients not already receiving antibiotics.

Methods

Before the bronchoscopy is performed, a specific area should be selected radiographically that will be used for obtaining culture specimens if no visible secretions are found in the airways. Atropine is used to reduce secretions if there are no contraindications. A number of studies have used an aerosol preparation of lidocaine at 4% concen-

Table 1. Culture media for plating

Medium	Organism
Sheep blood agar	
Charcoal yeast extract agar	*Legionella* sp
Chocolate agar	*Haemophilus* sp
MacConkey's agar	Gram-negative bacilli
Modified Caseman agar	anaerobic bacteria

tration for anesthesia. The best delivery system is by ultrasound nebulizer.[20,21] It is important to remember that the lidocaine used should not contain methyl paraben, as this is an antibacterial preservative that may suppress bacterial growth. Lidocaine itself has been shown to have some suppressive activity for mycobacterial and pyogenic bacterial cultures, and this inhibition is time-dependent. Therefore, the specimen should be cultured as soon as possible after it has been obtained.[24–26] As the bronchoscope is passed, the suction should be completely turned off.

The patient's position has not been stressed sufficiently in the past. It was suggested by Halperin et al[27] that the Trendelenburg position is better than the supine, which is better than the sitting position, in reducing the number of contaminants. A reduction of contamination may allow direct application via the bronchoscope of lidocaine on the vocal cords and trachea, replacing the use of the aerosol form of lidocaine, which is time-consuming and at times inadequate for proper local anesthesia of the vocal cords. Once the lobe has been approached, the brush is placed through the channel. The plug is best pushed out using visual guidance. The plug is made of polyethylene glycol and is easily absorbed by the bronchial mucosa. Visible secretions may be obtained or the brush may be placed into a subsegmental bronchus and the specimen obtained blindly. However, this procedure may increase the risk of pneumothorax, as reported by Higuchi et al.[19] As the catheter and brush are so thin, fluoroscopic guidance is difficult at this time. Once the specimen is obtained, the brush should be pulled back into the inner catheter. The entire catheter system is then pulled out, the inner catheter is wiped off with 70% alcohol and cut with sterile scissors. The brush is then advanced and cut with sterile wire cutters and placed into 1 ml of sterile saline or lactated Ringer's solution. Quantitative cultures of this material are indicated, unless the operator's technique has been shown to involve few instances of contamination. The brush should be transported to the microbiology laboratory as quickly as possible and the specimen plated on a variety of culture media; some examples are listed in *Table 1.* The utility of Gram staining for this specimen has not been evaluated. Before diluting the specimen, the brush may be smeared on a sterile slide for Gram staining, taking care not to contaminate the brush; this has the drawback of reducing the volume of secretions for culture, which is already small (approximately 0.001 ml). Gram staining may also be done on the diluted specimen, but organisms may not be present in adequate concentrations to be seen.

Table 2. Bronchoalveolar studies

Cell count and differential
Stains
Gram stain
Partial acid-fast stain for acid-fast bacilli and *Nocardia*
KOH stain
India ink
Silver methenamine stain
Immunologic studies
Aspergillus RIA
Legionella direct fluorescent antibody
Cultures
Mycobacterial
Fungal
Cytologic examination

Bronchial aspirates

Simple bronchial aspirates via the FOB have been shown to be inadequate for culture because of contamination.[2] This does not apply, however, to isolation of fungal and mycobacterial organisms. For every patient in whom infectious pneumonia is considered to be a possibility, bronchial aspirates should be obtained for acid-fast stains and culture, as well as fungal culture and potassium hydroxide preparation. As already noted this material is often contaminated with oropharyngeal flora so that it is inappropriate to perform usual bacterial cultures of it. Interpretation of positive fungal cultures may not be straightforward. Cultures positive for *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis* indicate an infectious process. Cultures positive for *Candida* species and *Torulopsis* species usually indicate contamination. A culture positive for *Aspergillus* species indicates that the clinical picture must be taken into account in order to determine significance. Biopsy material showing invasion is the standard for diagnosing

invasive *Aspergillus* organisms, but in the severely immunocompromised host isolation of this organism in bronchial washings is probably highly significant.[28] A newer technique has been added by Winterbauer et al,[29] in which immunofluorescent antibody is used to detect bacteria that are already coated by antibody, indicating lower respiratory tract infection. This may be more definitive for infectious pneumonia, but it does not identify a specific causative agent.

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) is a recognized research tool in the evaluation of diffuse, inflammatory lung conditions. It is a relatively noninvasive method of assessing the alveolar milieu. In immunocompromised hosts it is gaining popularity as an adjunct to diagnosing infectious pulmonary infiltrates. The procedure consists of wedging the tip of the bronchoscope into a subsegmental bronchus selected by the location of radiographic abnormality. Aliquots of 20–60 ml of normal saline are instilled and then aspirated, up to total instilled volumes of 200–300 ml. The fluid is then centrifuged and studied with various stains for organisms, cell counts, and culture (*Table 2*). By this method, Stover et al[6] had a diagnostic yield of 66%. It is especially useful for the diagnosis of opportunistic infections and can be helpful in diagnosing pulmonary hemorrhage. Its most notable feature is that the procedure is relatively noninvasive, with little to no risk for inducing hemorrhage or pneumothorax. This is particularly important for patients requiring ventilator support, in whom a transbronchial biopsy has 100-fold greater risks. The complications associated with bronchoalveolar lavage include fever, myalgias, chills, and a lowering of the partial pressure of oxygen in arterial blood. BAL may be the best means of diagnosing lower respiratory tract infection with *Legionella pneumophilia* when direct fluorescent antibody staining is added. This may allow for a more rapid diagnosis and has been shown to have a greater sensitivity than direct fluorescent antibody staining of expectorated sputum.[30] BAL has also been shown to be helpful in diagnosing invasive aspergillomas by testing the fluid with a radioimmunoassay for aspergillus antigen.[31]

Diagnosis of pulmonary tuberculosis

The bronchoscope has been shown to be a valuable tool in the diagnosis of pulmonary tuberculosis. The specimens obtained should include bronchial aspirates for acid-fast stains and mycobacterial culture, as well as transbronchial biopsy specimens for histologic examination with special stains, including culture of a biopsy specimen. The latter increases the overall sensitivity.[30,32] The most sensitive specimen is the first postbronchoscopy expectorated sputum, as shown by Laforet and Strieder[33] using the rigid bronchoscope. This was verified with flexible fiberoptic bronchoscopy by Danek and Bower.[32] The theoretical reason for this phenomenon is that these secretions have lower concentrations of lidocaine. The fiberoptic bronschoscope should only be used in those patients who have negative acid-fast sputum studies, or who are unable to raise sputum and where tuberculosis has not been ruled out. FOB has a 48% sensitivity for making an immediate diagnosis in this group of patients.[3]

Table 3. Order of obtaining specimens

Microbiology specimen brush
Bronchoalveolar lavage from a different segmental bronchial site
Bronchial aspirates
Cytological brushing
Transbronchial biopsy

Order of procedures

When performing bronchoscopy in patients with pulmonary infiltrates and where a wide differential diagnosis is being considered, the bronchoscopist needs to decide a number of things ahead of time. The first is where to obtain the samples. This can be done adequately with posteroanterior and lateral chest radiographs. The possibilities considered in the differential diagnosis determine what specimens should be obtained and what studies should be done on them.

Table 4. Complications

Hypotension
Respiratory center depression
Airway problems (bronchospasm, laryngospasm)
Cardiac arrhythmias
Hypoxemia
Pneumothorax
Hemorrhage
Iatrogenic pneumonia
Fever

Common sense determines the order in which specimens are collected (*Table 3*). The MSB procedure should be done first to reduce the possibility of contamination. BAL is performed next. The FOB should be wedged in a subsegment different from the one from which the MSB specimen is taken, because the distal brushing may cause some bleeding and can make the BAL cell count suggestive of pulmonary hemorrhage. Bronchial aspirates are next, followed by brushings for cytologic studies, and transbronchial biopsy is last. Because of the expense and risk involved, it is the bronchoscopist's responsibility to see to it that all specimens are taken to their respective laboratories as soon as possible. In the case of MSB specimens, the presence of lidocaine can suppress bacterial growth; the quicker the dilution and plating are done the more this suppression may be reduced.[24,25]

Immunocompromised host

Bronchoscopy has found favor as the first-line invasive approach to the diagnosis of diffuse pulmonary infiltrates in immunocompromised hosts after basic sputum and blood studies are found to be unrevealing and/or there is a failure of the empiric antibiotics. In this group of patients, differential diagnosis includes, in addition to the usual bacterial pathogens, opportunistic organisms, underlying neoplastic disease, pulmonary hemorrhage, and injury due to cytotoxic agents and radiation. The overall sensitivity for a specific diagnosis using the bronchoscope and all of the specimens obtained by it is unknown. For transbronchial biopsy alone, it is 40%.[34–37] This value can vary according to selection of patients; for example, a high prevalence of *Pneumocystis carinii* pneumonia would increase the yield. Overall yield in research studies can also be affected by placement of specimens without alveolar tissue in a nonspecific group or a separate "inadequate" group.[4] Bronchoalveolar lavage alone has been reported to have a yield of 66% in immunocompromised hosts.[6]

The question of whether one proceeds directly to an open-lung biopsy or first does fiberoptic bronchoscopy should be decided on a individual basis. An absolute contraindication to FOB with transbronchial biopsy is any severe bleeding abnormality. An open-lung biopsy in patients with a bleeding diathesis may be a safer procedure. Another consideration is whether the patient's clinical condition allows enough time to be wrong, weighing the time to process the specimens against the rate of clinical deterioration of the patient.

Complications

Overall, bronchoscopy is considered to be a relatively safe procedure. The general complications are listed in *Table 4*. The most comon set of complications, hypotension and hypoventilation, is due to use of premedication and local anesthesia.[38] Airway complications include laryngospasm and bronchospasm. The three complications of particular concern in patients with pneumonia are hypoxemia, pneumothorax, and serious hemorrhage. It has been shown that there is an average fall in arterial oxygen tension of 20 mmHg with FOB.[38] In patients with consolidating pneumonias, shunt-related hypoxemia may be present or low partial pressures of arterial oxygen may be due to ventilation-perfusion abnormalities.[39] If hypoxemia is present, a method of continuous monitoring, such as a pulse oximeter, should be available. All patients undergoing bronchoscopy should receive some form of supplemental oxygen. Pneumothorax may occur as a complication of transbronchial biopsies, and can be devastating in this population because of concurrent respiratory compromise. The reported incidence of pneumothorax when fluoroscopy is used is less than 5%,[40] however, in an immunocompromised host, it averages 7%.[37] The incidence of serious bleeding with transbronchial biopsy is 4% in normal hosts,[40] and may be as high as 7% in immunocompromised individuals.[37] This necessitates selecting a segmental or subsegmental bronchus that can be totally occluded by wedging the tip of the scope into the bronchus, which will effect a tamponade in the case of serious bleeding.[22]

Summary

Fiberoptic bronchoscopy has gained utility in the diagnosis of infectious pulmonary problems. Besides bronchial aspirates and transbronchial biopsy, the two newer techniques of bronchoalveolar lavage and use of the microbiology specimen brush have made this procedure the next logical step after sputum and blood studies in many patients with pneumonias. In the immunocompromised host, it may allow a specific diagnosis without the need for open-lung biopsy.

In hospital-acquired pneumonias, it may allow a more specific antibiotic regimen, saving the patient unneeded broad-spectrum coverage and thereby reducing toxicity, expense, and the incidence of superinfections. It may also be a better standard by which to judge the efficacy of antibiotics in the treatment of nosocomial pneumonias. Fiberoptic bronchoscopy is a safe procedure, but is not recommended for every pneumonia; community-acquired pneumonia and anaerobic infections of the lung can be evaluated by history, clinical findings, and sputum Gram staining, and treated empirically. The bronchoscope should be reserved for patients who are unable to raise sputum, have a relevant underlying disease, have a hospital-acquired pneumonia, or may have fungal or parasitic infections. For suspected cases of tuberculosis, if tests of morning sputum are negative, bronchoscopy should be performed and the first postbronchoscopy sputum obtained for further testing.

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