Role of Flexible Bronchoscopy in Immunocompromised Patients With Lung Infiltrates*

Prasoon Jain, MD, FCCP; Sunder Sandur, MD, FCCP; Yvonne Meli, RN; Alejandro C. Arroliga, MD, FCCP; James K. Stoller, MD, MS, FCCP; and Atul C. Mehta, MD, FCCP

Study objective: To study the diagnostic role of flexible bronchoscopy (FB) in immunocompromised patients with pulmonary infiltrates.

Design: Prospective, observational study.

Setting: Tertiary care hospital.

Patients: A total of 104 consecutive non-HIV-infected immunocompromised patients with lung infiltrates in whom FB was performed.

Methods: The primary outcome measure was the diagnostic yield of FB, which was derived as the number of the diagnoses made using FB results divided by all final diagnoses. Final diagnoses were established using data from FB, surgical lung biopsy (SLB), and microbiology and serology testing, and by the clinical response to empiric therapy. We also studied the diagnostic yields of individual sampling procedures such as BAL, transbronchial biopsy (TBB), and protected-specimen brush (PSB) sampling.

Results: Overall, 128 diagnoses were made in 104 patients. The overall diagnostic yield of FB was 56.2% (95% confidence interval [CI], 47 to 64%). FB provided at least one diagnosis in 53 of 104 patients (51%; 95% CI, 40 to 62%). FB was more likely to establish the diagnosis when the lung infiltrate was due to an infectious agent (81%; 95% CI, 67 to 90%) than to a noninfectious process (56%; 95% CI, 43 to 67%; p = 0.011). The diagnostic yields of BAL (38%; 95% CI, 30 to 47%) and TBB (38%; 95% CI, 27 to 51%) were similar (p = 0.94). The diagnostic yield of PSB sampling was lower (13%; 95% CI 6 to 24%; p = 0.001) than that of BAL. The combined diagnostic yield of BAL and TBB (70%; 95% CI, 57 to 80%) was higher than that of BAL alone (p < 0.001). Finally, the diagnostic yield of FB with PSB sampling, BAL, and TBB was similar to that of FB with BAL and TBB. The complication rate from FB was 21% (95% CI, 15 to 31%). Minor bleeding (13%) and pneumothorax (4%) were the most common complications.

Conclusions: FB has a high diagnostic yield in immunocompromised patients with pulmonary infiltrates. Based on our results, we recommend performing TBB in these patients, whenever possible.

(CHEST 2004; 125:712–722)

Key words: BAL; bronchoscopy; immunocompromised patients

Abbreviations: BW = bronchial washing; CI = confidence interval; CMV = cytomegalovirus; DAH = diffuse alveolar hemorrhage; FB = flexible bronchoscopy; FIO2 = fraction of inspired oxygen; PDP = Pneumocystis carinii pneumonia; PSB = protected-specimen brush; PT-INR = prothrombin time-international normalized ratio; SLB = surgical lung biopsy; TBB = transbronchial biopsy

Pulmonary complications account for significant morbidity and mortality in immunocompromised patients.1–6 The optimal outcome in these patients depends on identifying the cause of the lung infiltrate and instituting specific therapy as soon as possible. Because several infectious and noninfectious diseases can present with similar clinical and radiologic features in immunocompromised patients with lung infiltrates, establishing the cause of pulmonary infiltrates is challenging in this setting.7 The

*From the Department of Medicine (Dr. Jain), Louis A. Johnson Veterans Affairs Medical Center, Clarksburg, WV; the Department of Pulmonary and Critical Care Medicine (Dr. Sandur), St. Mary’s Hospital, Waterbury, CT; and the Department of Pulmonary and Critical Care Medicine (Drs. Arroliga, Stoller, and Mehta, and Ms. Meli), The Cleveland Clinic Foundation, Cleveland, OH. Received December 11, 2002; revision accepted August 12, 2003.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Atul C. Mehta, MD, FCCP, Head, Section of Bronchology, Department of Pulmonary and Critical Care Medicine/A-90, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195; e-mail: mehtaa1@ccf.org
The current study was performed to better understand the value of flexible bronchoscopy (FB) in assessing the cause of pulmonary infiltrates in non-HIV-infected immunocompromised patients. We report the diagnostic yields of different sampling techniques including BAL, protected-specimen brush (PSB) sampling, and transbronchial biopsy (TBB) in these patients. This study also examines the frequency of complications of FB in immunocompromised patients with lung infiltrates.

**Materials and Methods**

**Patients**

One hundred four consecutive immunocompromised patients with lung infiltrates seen on chest roentgenograms who were referred to the inpatient Pulmonary Consult Service of the Cleveland Clinic Foundation over a 2-year period comprised the patient population. Eligibility criteria included the following: (1) immunocompromised state; (2) the presence of either a focal or diffuse pulmonary infiltrate; (3) a decision by pulmonary consultant to perform FB; and (4) informed consent to undergo FB given by the patient.

The following conditions defined the immunocompromised state: hematologic malignancy (eg, leukemia, lymphoma, myelodysplastic syndrome, and multiple myeloma); chemotherapy in the last 6 months; long-term corticosteroid therapy (ie, ≥ 20 mg/d prednisone or its equivalent for ≥ 2 months) or high-dose corticosteroid therapy (≥ 60 mg/d prednisone or its equivalent for ≥ 2 weeks within 3 months); bone marrow or solid organ transplantation; and the current use of immunosuppressive and cytotoxic medications. Patients were excluded from the study if: (1) they were HIV positive or (2) they had received a lung transplantation; and the current use of immunosuppressive and cytotoxic medications.

Patients were included if they were receiving antimicrobial therapy at the time of FB.

**Data Collection**

Demographic features and details of underlying causes of the immunocompromised state, current medications including antimicrobial therapy, and relevant clinical, laboratory, and radiologic findings were recorded at the time of FB using a standard data collection form. The pulmonary consultant, who was aware of the ongoing study, directed the patient management (eg, antibiotics, or the need for FB or surgical lung biopsy [SLB]). Cultures of sputum and blood, serology tests, and other laboratory tests were performed at the discretion of the managing physicians. The final diagnosis was determined using data from clinical presentation, serology, and microbiological tests, the results of FB and SLB, response to therapy, and postmortem examination.

**FB**

All FBs were performed in an inpatient bronchoscopy suite or in the ICU with extensive cardiopulmonary monitoring. The choice of sedating medications was at the discretion of the pulmonary physician. Neuromuscular blocking agents were not routinely employed in intubated patients undergoing FB. Local anesthesia was provided with sterile methylparaben-free 2% lidocaine. Prophylactic antibiotics were used in intubated patients undergoing FB. In patients with diffuse pulmonary infiltrates, BAL was performed either in the right middle lobe or lingula. For patients with focal lung infiltrates, BAL was performed from the pulmonary segment corresponding to the radiologic abnormality.

**Definitions and Diagnostic Criteria**

Infiltrates were defined as focal if they involved one lobe or less, and diffuse (ie, either unilateral or bilateral) if they were otherwise. Pulmonary lesions were classified as lung nodules (solitary or multiple, depending on the number) when the diameter was ≤ 3 cm, and were defined as pulmonary masses if the diameter was > 3 cm. Hypoxemia was considered to be mild when the PaO₂/fraction of inspired oxygen (FiO₂) ratio exceeded 301, to be moderate when the PaO₂/FiO₂ ratio was 201 to 300, and to be severe when the PaO₂/FiO₂ ratio was < 200.

Information obtained from BAL was considered to be diagnostic when any of the following organisms were identified: *Pneumocystis carinii*; *Mycobacterium tuberculosis*; Histoplasma capsulatum; Legionella species; influenza and parainfluenza viruses; herpes simplex virus; variella-zoster virus; respiratory syncytial virus; and mycoplasma species.9,10 Sarcoïdosis,11 hypersensitivity pneumonitis,12 bronchiolitis obliterans organizing pneumonia13 were diagnosed according to previously described criteria. The diagnostic criteria for other processes are presented in Table 1.9,13-15

**Outcome Measures**

The primary outcome measure was the yield of FB for the diagnosis of the lung infiltrate. As several patients had more than one cause of lung infiltrates, the diagnostic yield of FB was calculated as the number of diagnoses provided by FB divided by all final diagnoses. Secondary outcome measures were the diagnostic yields of the individual sampling procedures, such as BAL, PSB sampling, and TBB, and of combinations of these techniques.

**Complications**

All complications of FB were recorded during and immediately after the FB. Potential complications of FB include bleeding, pneumothorax, bronchospasm, fever, cardiac arrhythmia, hypoxemia, and death. Bleeding, which was classified as minor (ie, < 100 mL or clinically insignificant) or major (ie, > 100 mL or clinically significant [eg, required an RBC transfusion, caused hemodynamic instability, or led to intubation to protect the airway]), was considered to be related to FB if it occurred within 24 h after the procedure. Pneumothorax was classified as major...
Bacterial pneumonia\textsuperscript{15–17} Using either Z-statistics with continuity correction or the proportions in two independent groups were compared with the \textit{ware} package (Sigmastat, version 2.0; SPSS Inc; Chicago, IL).

**Statistical Analysis**

All statistical analyses were performed using a statistical software package (Sigmastat, version 2.0; SPSS Inc; Chicago, IL). The proportions in two independent groups were compared using either Z-statistics with continuity correction or $\chi^2$ test with continuity correction. The confidence intervals (CIs) for the difference in the percentage yields of individual sampling procedures and the combinations of procedures were calculated using standard statistical techniques. Univariate analysis was used to identify the association between the complications during FB and clinically relevant parameters such as TBB, PT-INR $> 1.5$, a serum creatinine level of $> 1.5$ mg/dL, a respiratory rate of $> 20$ breaths/min, supplemental oxygen therapy with an FIO\(_2\) of $> 40\%$ prior to bronchoscopy, a platelet count $< 50 \times 10^9$ cells/L, and mechanical ventilation received prior to bronchoscopy. A two-sided p value of $\leq 0.05$ was considered to be significant.

**RESULTS**

**Patients**

Table 2 presents the demographic features of the study group. Forty-eight patients (46.2\%) had hematologic malignancy. Of these, 15 and 6 patients, respectively, had received allogenic and autologous...
bone marrow transplantation. Fifteen patients (14.4%) had received solid organ transplantation, 9 heart transplantation, 4 renal transplantation, and 2 liver transplants. The remaining patients had collagen vascular disorders, systemic vasculitis, nontuberculosis granulomatous diseases such as sarcoidosis and Crohn disease, and other conditions requiring long-term use of immunosuppressive agents. More than 75% of patients were receiving long-term therapy with systemic corticosteroids. Nearly 60% of patients were receiving or had recently completed cancer chemotherapy. Thirty percent of patients were receiving or had recently completed cancer chemotherapy. Thirty percent of patients

were receiving immunosuppressive medications for nonmalignant medical illnesses.

Two thirds of patients were febrile at the time of FB. Ten patients were receiving oxygen therapy at 100% FiO\textsubscript{2} before FB. Arterial blood gas results were available in 58 patients, of whom 25 (43.1%) had severe hypoxemia (PaO\textsubscript{2}/FiO\textsubscript{2} ratio, < 200), 23 (39.7%) had moderate hypoxemia (PaO\textsubscript{2}/FiO\textsubscript{2} ratio, 200 to 300), and 10 (17.2%) had mild hypoxemia (PaO\textsubscript{2}/FiO\textsubscript{2} ratio, > 300).

FB was performed for the evaluation of diffuse lung infiltrates in 52 patients (50%), for focal lung infiltrates in 34 patients (32.6%), for multiple lung nodules in 14 patients (13.5%), and for the evaluation of a solitary lung nodule in 1 patient (1%). Three patients had normal chest roentgenogram findings, and FB was performed to evaluate unexplained fever and hypoxemia. The median duration of lung infiltrates was 5 days (range, 1 to 365 days). Most patients were receiving therapy with antimicrobial agents prior to undergoing FB, with 83 (80%) receiving IV antibiotic therapy, 39 (37.5%) receiving antifungal medications, and 28 (27%) receiving antiviral agents.

**FB**

Bronchoscope insertion was through an endotracheal tube in 18 patients (17.3%), nasally in 49 patients (47.1%), and orally in the remainder (in whom uncorrected coagulopathy was present). The median duration of FB was 15 min (range, 3 to 60 min).

As indicated in Table 3, most subjects underwent more than one sampling procedure during FB. BAL was the single most common sampling procedure (performed in 95.2%; 99 patients), followed by TBB in 43.2% (45 patients) and PSB sampling in 40.4% (42 patients). No patient who underwent TBB was receiving mechanical ventilation at the time of FB, and 13 of 45 patients (28.8%) undergoing TBB had a platelet count of < 150 × 10\textsuperscript{9} cells/L.

**Final Diagnoses**

Table 4 shows the 128 final diagnoses in 104 patients. FB provided 72 of 128 diagnoses (56.2%;
95% CI, 47 to 64%), with at least one diagnosis made by FB in 53 of 104 patients (51%; 95% CI, 42 to 60%), and more than one diagnosis made by FB in 19 patients (18.3%; 95% CI, 12 to 26%). As shown in Table 4, the most common final diagnosis was lung infection (36.7%), most frequently bacterial (49% of infections), followed by viral causes (26%), fungal causes (21% of infections), and \( \text{P carinii} \) (4%). The bacterial infections included \( \text{Pseudomonas aeruginosa} \) (six patients), \( \text{Staphylococcus aureus} \) (four patients), \( \text{M tuberculosis} \) (two patients), atypical mycobacterial infection (three patients), \( \text{Escherichia coli} \) (two patients), \( \text{Xanthomonas maltophilia} \) (two patients), Legionella species (two patients), \( \text{Enterococcus faecium} \) (one patient), and Mycoplasma species (one patient). Fungal infections included invasive pulmonary aspergillosis (five patients), semi-invasive pulmonary aspergillosis (three patients), Candida (one patient), and histoplasmosis (one patient). Viral infections were due to cytomegalovirus (CMV) [nine patients] and herpes simplex virus (three patients).

Of noninfectious causes of final diagnoses, diffuse alveolar hemorrhage (DAH) accounted for 14.8%, ARDS or acute lung injury for 8.6%, and radiation or chemotherapy-induced pneumonitis for 3.9%. Miscellaneous etiologies comprised 18%. The basis for final diagnoses was FB in 56.2% (72 patients), SLB in 13.3% (17 patients), and clinical course, culture (other than bronchoscopy specimens), and serology in 30.5% (39 patients). Included in the last category were 23 patients (18%) in whom the etiology of lung infiltrates was inconclusive, and the clinicians treated these patients on the basis of overall clinical evaluation.

FB was more likely to establish the diagnosis when the infiltrate was due to infection (81%; 95% CI, 67 to 90%) than to a noninfectious etiology (55.7%, 95% CI, 43 to 67%; \( p = 0.011 \)). Overall, FB was the primary source of diagnosis in 78% of bacterial infections (including three cases of mycobacterial infections), 80% of fungal infections, 83% of viral infections, and 100% of \( \text{P carinii} \) pneumonia (PCP) infection in our patients. All except one patient with bacterial infections were receiving antibiotics at the time of bronchoscopy, and the median duration of lung infiltrate prior to FB was 5 days. Blood culture results (two patients), Legionella serology (two patients), and positive sputum cultures for the same organism (three patients) supported the diagnosis provided by FB in seven patients with bacterial infections. CMV antigenemia was present in six of eight patients (75%) with CMV pneumonitis. In patients with proven bacterial infection, FB results led to the addition of a new antibiotic agent in eight patients, to the withdrawal of antibiotic therapy in three patients, and to the addition of antituberculous treatment in three patients.
Candida species were isolated from bronchoscopy specimens in five patients, but only one of them had a lung biopsy, and it showed evidence of invasive Candida infection. In the remaining patients, Candida was thought to be due to contamination or colonization according to the study criteria. In addition, coagulase-negative Staphylococcus (three patients) and CMV (one patient) found on BAL specimens were judged to be due to airway colonization. Overall, 8 of 99 BAL procedures (8%) yielded potentially false-positive results.

The diagnostic yield of FB did not differ between focal lung infiltrates (56%; 95% CI, 40 to 72%) and diffuse lung infiltrates (59%; 95% CI, 48 to 70%; p = 0.91). Similarly, there was no difference in the diagnostic yield of FB for solid-organ transplantation patients (50%; 95% CI, 28 to 72%) vs patients with either hematologic malignancy or bone-marrow transplantation (50%; 95% CI, 37 to 63%; p = 0.77).

Table 5 summarizes the yields of individual sampling procedures performed during FB. Considered individually, BAL provided 38.4% of final diagnoses, TBB provided 37.7% of final diagnoses, and PSB sampling provided 12.7% of final diagnoses. The combination of BAL, PSB sampling, and TBB rendered a diagnosis in 86.4% of instances. BAL established a diagnosis in 65% of bacterial infections (95% CI, 43 to 84%), in 75% of viral infections (95% CI, 43 to 95%), and in 40% of fungal infections (95% CI, 17 to 69%). PSB sampling provided exclusive evidence of bacterial infection in three cases in which BAL cultures were negative. The diagnosis of DAH was made by BAL in all 17 patients in whom FB had established this diagnosis. Although TBB confirmed three cases of DAH, all such diagnoses already had been established with BAL. In the remaining two patients, SLB established the diagnosis of DAH. Six patients with DAH had a concomitant disease process, including bacterial infection (three patients), CMV pneumonia (one patient), lupus pneumonitis (one patient), and Wegener granulomatosis (one patient). Table 6 shows that BAL had a higher diagnostic yield than PSB sampling and that the addition of TBB to BAL enhanced the diagnostic yield (p < 0.001).

TBB provided 27 diagnoses and was the only source of diagnosis in 17 cases (63%) [Table 7]. All the exclusive diagnoses by TBB except two (Candida pneumonia, one patient; CMV infection, one patient) were noninfectious in origin.

SLB was performed in 14 patients and established 17 diagnoses (Table 4). Although 2 of the 17 diagnoses were suggested by FB, SLB provided the diagnosis exclusively in all instances. No instance of prolonged air leak or death was attributed to SLB in this series.

Complications of FB

Procedure-related complications (Table 8) occurred in 22 patients (21.2%; 95% CI, 15 to 31%). Bleeding was the most common complication (13.5%; 95% CI, 8 to 21%) but was minor in all except one patient who required transfusion with packed RBCs. A worsening of hypoxemia was observed in 9.6% of patients (95% CI, 6 to 17%). Two patients required short-term ventilatory support after FB due to respiratory failure. There were no deaths due to FB.

The complications after FB were encountered in 14 of 45 patients (31%; 95% CI, 20 to 46%) in whom transbronchial biopsies were performed compared with 8 of 59 patients (13.6%; 95% CI, 7 to 25%) in whom TBB was not performed. This difference was statistically significant (p = 0.036). Univariate analysis showed no association between the bronchoscopy-related complications and a PT-INR of < 1.5, a platelet count of < 50 × 10³ cells/L, and a serum creatinine level of > 1.5 mg/dL, a baseline respiratory rate of > 20 breaths/min, a need for an FiO₂ of > 0.40 prior to FB, age > 70 years, and mechanical ventilation prior to bronchoscopy. Similarly, compli-

---

**Table 5—Diagnostic Yield of Sampling Procedures Performed During FB**

<table>
<thead>
<tr>
<th>Sampling Procedure</th>
<th>Final Diagnoses</th>
<th>Diagnostic Yield of Sampling Procedure*</th>
<th>95% CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL (n = 99)</td>
<td>125</td>
<td>48 (38.4)</td>
<td>30–47</td>
</tr>
<tr>
<td>BW (n = 44)</td>
<td>57</td>
<td>4 (7)</td>
<td>3–16</td>
</tr>
<tr>
<td>TBB (n = 45)</td>
<td>61</td>
<td>27 (44.2)</td>
<td>27–51</td>
</tr>
<tr>
<td>PSB (n = 42)</td>
<td>55</td>
<td>7 (12.7)</td>
<td>6–24</td>
</tr>
<tr>
<td>BAL + PSB (n = 40)</td>
<td>51</td>
<td>23 (45.1)</td>
<td>32–58</td>
</tr>
<tr>
<td>BAL + TBB (n = 40)</td>
<td>57</td>
<td>40 (70.1)</td>
<td>57–80</td>
</tr>
<tr>
<td>BAL + PSB + TBB (n = 25)</td>
<td>37</td>
<td>32 (86.4)</td>
<td>71–94</td>
</tr>
</tbody>
</table>

*Diagnostic yield for a sampling procedure is the ratio of diagnoses provided by a sampling procedure or combination of sampling procedures (numerator) and all final diagnoses in patients undergoing those sampling procedures (denominator). Values given as No. (%).
The diagnostic yield of FB in immunocompromised patients with lung infiltrates has varied from 15 to 93% in prior studies.8,35 In this context, the diagnostic yield of FB in our study (56%) is similar to that reported by some investigators41–43,48 but lower than that reported by others.37–40,49 Heterogeneity in patient populations in different studies appears to be the most likely explanation for the wide variation in the reported yield of FB. For example, because FB has a higher diagnostic yield for infectious causes of lung infiltrates, studies that enroll a greater proportion of patients with lung infections38–40,50 report a higher diagnostic yield of FB than studies with a higher proportion of patients with noninfectious causes of lung infiltrates.35,36 Indeed, the 56% diagnostic yield of FB in our study appears high in the context that a large proportion of our study patients had noninfectious causes of lung infiltrates. Furthermore, the inclusion of a greater proportion of patients with PCP infection37,47,51 and the inclusion of HIV-infected patients52,53 also may have contributed to higher diagnostic yields of FB in some studies. We excluded HIV-infected patients from our study, and only two of our patients had PCP infection.

Another important explanation for the variation in the reported diagnostic yield of FB diagnosis is the manner in which diagnostic yield is calculated in different studies. For instance, in one study, patients in whom the specific etiology of lung infiltrate could not be identified were excluded from the denominator.37 Consequently, the reported diagnostic yield of FB in that study (83%) was higher than the actual diagnostic yield of FB. Other studies have used the number of FB procedures in the denominator to calculate the diagnostic yield. However, several immunocompromised patients with lung infiltrates had more than one cause of lung infiltrates. Therefore, it appears more appropriate to use all final diagnoses rather than the number of procedures in the denominator to calculate the diagnostic yield of FB. In calculating the diagnostic yield of FB, we used all final diagnoses, including 39 clinical diagnoses in the denominator. We therefore believe that our results more accurately reflect the diagnostic yield of FB in these patients than do some of the prior studies.

FB was the single most useful procedure for identifying an infectious cause of lung infiltrates in our study. FB identified the bacterial pathogens in 78% of patients in whom an underlying infectious agent was identified, fungal agents in 80%, and viral agents in 83%. However, we believe that its actual sensitivity for the diagnosis of infectious causes of lung infiltrates was lower, because FB might have failed to identify a causative organism in many cases that were subsequently included under “pulmonary infiltrates of unclear etiology.” Still, our ability to identify and isolate bacterial pathogens was quite impressive considering that the majority of our patients were receiving antimicrobial therapy prior to undergoing FB. In this regard, our findings concur with those of prior studies in which FB had similar

### Table 6—Comparison of Diagnostic Yields of Individual and Combinations of Sampling Procedures

<table>
<thead>
<tr>
<th>Sampling Procedure</th>
<th>95% CI for Difference of Proportion</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL vs PSB</td>
<td>0.11–0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>BAL vs TBB</td>
<td>−0.14–0.16</td>
<td>0.945</td>
</tr>
<tr>
<td>BAL + PSB vs BAL</td>
<td>−0.09–0.22</td>
<td>0.514</td>
</tr>
<tr>
<td>BAL + TBB vs BAL</td>
<td>0.16–0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BAL + TBB + PSB vs BAL + TBB</td>
<td>−0.02–0.33</td>
<td>0.125</td>
</tr>
</tbody>
</table>

### Table 7—Exclusive Diagnosis by TBB (n = 17)*

- Infections: 2
- Radiation/chemotherapy-induced pneumonitis: 3
- Wegener granulomatosis: 2
- Diffuse alveolar damage: 4
- BOOP: 2
- Miscellaneous: 4
- Nonspecific pneumonia: 1
- Bronchopneumonia: 1
- Sarcoidosis: 1
- Lymphoma: 1

*See Table 4 for abbreviations not used in the text.
success with the isolation of bacterial pathogens in patients receiving antibiotic therapy.\textsuperscript{40–43} It is possible that the high success rate of FB in identifying bacterial pathogens despite antibiotic therapy may be related to the high bacterial load in the lower respiratory tract secretions or to the higher incidence of infection with virulent organisms that respond slowly to antimicrobial therapy in immunocompromised hosts.\textsuperscript{16} We believe that the optimal yield for bacterial pathogens also requires careful attention to technical details to prevent the contamination of BAL specimens from upper airway secretions, prompt transport of specimen to the laboratory, and the support of an advanced microbiology laboratory with experience in processing and interpreting semiquantitative cultures. Among the noninfectious causes of lung infiltrates, FB had a high yield for the diagnosis of DAH (89%), as reported in previous studies.\textsuperscript{37,38,44}

In contrast to the findings of Lanino et al.\textsuperscript{54} but in keeping with the results from White et al.\textsuperscript{36} the diagnostic yield of FB was similar for patients with focal and diffuse lung infiltrates in our study. We also failed to confirm the results of a prior study\textsuperscript{42} that reported a higher diagnostic yield of FB for solid organ transplant recipients compared with patients with hematologic malignancy.

Our data provide useful information on the diagnostic yields of individual sampling procedures during FB in immunocompromised patients with lung infiltrates. BAL had a good diagnostic yield for bacterial and viral infections, but BAL results identified only 4 of 10 fungal infections. Also, semiquantitative BAL cultures identified Candida species in four additional patients, but these patients did not meet the criterion of Candida pneumonia because lung biopsy was not performed. Unfortunately, the clinical significance of the isolation of Candida species from BAL remains controversial, as contamination from upper airways or colonization of lower airway is difficult to distinguish from invasive Candida pneumonia.\textsuperscript{39} Further work is needed in this regard.

In keeping with the results of Rano and coworkers\textsuperscript{41} (who reported only one diagnosis obtained by PSB sampling in addition to the diagnosis provided by BAL in 125 patients), our results suggest that PSB sampling adds little to the diagnostic yield of BAL and TBB. Based on these data, we question the value of routine PSB sampling in addition to BAL in immunocompromised patients with lung infiltrates. Still, PSB sampling may be considered when the clinical features strongly suggest bacterial pneumonia as the cause of lung infiltrates. Similarly, our results do not support routine BWs in this setting, provided that a BAL sample is obtained and tested comprehensively.

The diagnostic yield of TBB has varied from 26 to 68% in prior studies.\textsuperscript{23,37,53–61} However, routine TBB is not performed in immunocompromised patients due to safety issues.\textsuperscript{49} Furthermore, the clinical value of information obtained by TBB in these patients is not well-established.\textsuperscript{36} In our study, TBB was performed in 43% of patients, and its diagnostic yield was 38%. TBB provided 17 exclusive diagnoses, most of which were noninfectious. The addition of TBB to BAL in our study significantly improved the diagnostic yield of FB, confirming the complementary role of BAL and TBB in this setting.\textsuperscript{37,42,52} Based on these results, we favor performing TBB when it is deemed safe in this setting.

The diagnostic yield of SLB has been estimated to be 46 to 85% in immunocompromised patients with lung infiltrates.\textsuperscript{62–68} However, because of a higher potential for complications and higher cost, SLB is typically performed after BAL and/or TBB have failed to provide the diagnosis. Our study confirms that SLB provides specific diagnoses in most patients in whom FB is nondiagnostic.\textsuperscript{69,70} We encountered no major procedure-related complications in any patient who underwent SLB. Based on our results, we recommend early SLB when the initial FB is nondiagnostic and when there is no response to empiric treatment.

Most immunocompromised patients who require FB are critically ill and have several comorbid conditions that place them at a high risk for procedure-related complications. Complications during FB in our study were more likely to occur in patients who underwent TBB, which is expected in view of the more invasive nature of TBB compared with BAL or PSB sampling. However, none of our patients died due to bronchoscopy-related complications. In contrast to the results of Cunningham et al.,\textsuperscript{58} renal insufficiency was not associated with more frequent procedure-related complications in our patients. Also, we did not confirm independent association between elevated PT-INR and bronchoscopy-related complications, as was previously reported.\textsuperscript{43} However, our results in this regard need to be interpreted with caution due to the limited number of patients with elevated PT-INRs (i.e., > 1.5) who underwent FB.

Several limitations of our study should be noted. First, our conclusions about the safety of TBB may not generalize because TBB was not performed on every patient in this series. Although it is difficult to identify all factors that may have influenced the decision not to perform TBB, it is reasonable to presume that the assessment of procedure safety in
the individual patient must have played an important role. Such bias would cause these results to underestimate the complication rate in an unselected series.

A second limitation of this study is that most patients were receiving antimicrobial agents when bronchoscopy was performed. Although direct evidence is not available in non-HIV immunocompromised patients, empiric antimicrobial therapy impairs the diagnostic yield of FB in HIV-infected patients and in immunocompetent individuals with nosocomial infection. While the use of antimicrobial agents prior to FB could have reduced its diagnostic yield in our patients, we recognize the important role of administering antimicrobial agents promptly in these patients.

A third limitation is that 30% of all final diagnoses in this series were based on clinical course or outcome. Furthermore, in 23 patients (18%), no firm diagnosis was established. Nevertheless, all except one patient in this group survived and showed an adequate response to empiric treatment. It is important to note that prior investigators have also reported a failure to establish a final diagnosis in 14 to 31% of immunocompromised patients with lung infiltrates.

Fourth, even though our study deals with a diagnostic test (FB), we are unable to determine the true sensitivity or specificity of FB due to the lack of a “gold standard” test in this setting. Even SLB cannot identify the etiology of lung infiltrates in every immunocompromised patient. For this reason, neither our results nor the results from prior studies can accurately establish the sensitivity, specificity, and predictive value of FB in these patients. Nevertheless, we believe that our study provides useful information to treating clinicians regarding the value of FB in this difficult clinical setting.

Finally, our patients had varying causes of immunosuppression (other than HIV infection) and a wide variety of lung processes. Patients with solid tumors receiving chemotherapy were underrepresented in our patient population. Furthermore, because the number of patients in each diagnostic category in our study was small, our data regarding the yield of FB for the individual diagnostic categories (eg, bacterial infections or DAH) must be interpreted with caution.

CONCLUSION

In conclusion, our study supports the role of FB as the initial procedure of choice for identifying the cause of lung infiltrates in non-HIV immunocompromised patients. In this series, the rate of serious complications of FB was low, and FB accurately established the etiology of the lung infiltrate in 56% of cases. Because our results suggest that BAL and TBB are complementary, we recommend performing TBB whenever it is deemed safe. In contrast, PSB sampling and BW add little to BAL and TBB. SLB should be performed when the FB is nondiagnostic, especially when the patient is not responding to empiric treatment.

REFERENCES

17 Baselski VS, El-Torkey M, Coalsen JJ, et al. The standardization of criteria for processing and interpreting laboratory specimens in patients with suspected ventilator associated
51 Kahn FW, Jones JM. Analysis of bronchoalveolar lavage specimens from immunocompromised patients with a protocol applicable in the microbiology laboratory. J Clin Microbiol 1986; 26:1150–1155
59 Feldman NT, Pennington JE, Ehrie MG. Transbronchial lung biopsy in the compromised host. JAMA 1977; 238:1377–1379