OBJECTIVE: To evaluate the safety, diagnostic yield, and therapeutic implications of flexible bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy in patients with febrile neutropenia and pulmonary infiltrates.

PATIENTS AND METHODS: We retrospectively reviewed the medical records of all patients with neutropenic fever and pulmonary infiltrates evaluated by flexible bronchoscopy and BAL between January and December 2002 at the Mayo Clinic in Rochester, Minn. Appropriate demographic, clinical, microbiological, and histological data and procedure-related complications were summarized. Therapeutic decisions implemented based on information obtained by bronchoscopy, and 28-day mortality were determined.

RESULTS: Thirty-five patients with febrile neutropenia and associated pulmonary infiltrates were identified. Flexible bronchoscopy, including 35 BALs and 9 transbronchial biopsies, was performed safely (3 complications). The diagnostic yield of BAL was 49% Sputum analysis was underused (only 34%) but complementary to BAL. The combined diagnostic yield of BAL and sputum analysis was 63%. Transbronchial biopsy provided additional information to BAL and sputum analysis in only 1 patient and did not substantially increase the combined diagnostic yield. The 2-month mortality rate was 26% and was highest in patients who required mechanical ventilatory assistance before bronchoscopy.

CONCLUSION: The favorable safety record, good diagnostic yield, and frequent therapeutic implications support the routine use of BAL for the evaluation of pulmonary infiltrates in neutropenic patients. Bronchoalveolar lavage should be combined with the analysis of several sputum specimens. Transbronchial biopsy did only change the management of 1 patient.


ANC = absolute neutrophil count; BAL = bronchoalveolar lavage; CXR = chest x-ray; DAH = diffuse alveolar hemorrhage

Febrile neutropenia has emerged as a commonly encountered oncologic emergency due to the frequent use of highly potent chemotherapeutic regimens and hematopoietic stem cell transplantation. It is predominantly caused by infectious pathogens. The risk of sepsis and death is high, and prompt antimicrobial therapy is essential for a favorable outcome. Therefore, empirical therapy with broad-spectrum antibiotics is recommended. Several recently introduced new antimicrobial agents have simplified the administration and decreased the toxicity of these regimens.

Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy is frequently used during the diagnostic evaluation of patients with febrile neutropenia and pulmonary infiltrates. We retrospectively evaluated the diagnostic yield, safety, and therapeutic implications of flexible bronchoscopy with BAL and transbronchial biopsy in the setting of aggressive empirical antimicrobial therapy in this patient population.

PATIENTS AND METHODS

All patients with febrile neutropenia and pulmonary radiographic abnormalities who underwent bronchoscopic evaluation including BAL between January 1, 2002, and...
December 31, 2002, at the Mayo Clinic in Rochester, Minn, were included in the study. Febrile neutropenia was defined as an absolute neutrophil count (ANC) lower than $1 \times 10^9/L$ with a predicted nadir of less than $0.5 \times 10^9/L$ and a coexisting isolated increase of body temperature to $38.3^\circ C$ or a sustained temperature elevation to $38.0^\circ C$ for at least 1 hour\textsuperscript{11} (Figure 1).

We reviewed the electronic medical record database for all patients who underwent BAL at the Mayo Clinic during the study period. These data were subsequently cross-referenced with ANCs and clinical information, including body temperature and chest radiographic abnormalities. The following data were retrospectively collected from the patient’s medical record: age, sex, underlying diagnosis, ANC at the time of bronchoscopy, cause and duration of neutropenia, chest radiographic findings, other cultures before bronchoscopy (blood, sputum), serologic studies, empirical antibiotic regimen, requirement of mechanical ventilation at the time of bronchoscopy, bronchoscopic procedures performed and results, effect of bronchoscopy on patient management, other invasive diagnostic tests performed, final diagnosis, and 28-day mortality.

All patients underwent flexible bronchoscopy. After local anesthesia of the larynx with lidocaine, the bronchoscopist performed the BAL of the most prominently affected pulmonary segment. Considering its potential bacteriostatic effects, endotrachial or endobronchial lidocaine is avoided before BAL at our institution.\textsuperscript{12} The BAL was performed by wedging the bronchoscope followed by installation of at least 100 mL of sterile saline and recovery of the BAL fluid in a suction trap. A return of at least 40 mL was considered an adequate sample. The BAL fluid was subsequently analyzed according to the immunocompromised host protocol, which includes microbial stains (Gram stain, potassium hydroxide preparation, acid-fast stain, special stains for \textit{Nocardia} and \textit{Pneumocystis}, and direct fluorescent antibody staining for \textit{Legionella}), microbial cultures (bacterial, mycobacterial, fungal, viral, and special cultures for \textit{Legionella} and the shell vial assay for cytomegalovirus detection), cytology, cell count and differential, and Prussian blue staining for hemosiderin-laden macrophages. In the absence of thrombocytopenia (platelet count, $<50 \times 10^9/L$), systemic anticoagulation, antiplatelet agents, coagulopathy, and a serum creatinine level greater than 3 mg/dL, transbronchial biopsies (4-6 tissue samples) were performed as requested by the treating pulmonary specialist. Specimens were analyzed by cultures, stains, and histologic testing.

A final diagnosis was assigned to each patient based on the information available at hospital discharge and the discharge diagnosis of the treating physicians. In the absence of an established diagnostic gold standard test for this patient population, this retrospectively determined diagnosis was considered the gold standard.

\textbf{Bacterial pneumonia} was defined as characteristic radiographic abnormalities associated with the identification of bacterial organisms by either stain or culture from BAL fluid, transbronchial biopsy specimens, surgical lung biopsy specimens, or pleural fluid. \textit{Cytomegalovirus pneumonia} was defined as characteristic radiographic findings in the setting of identification of cytomegalovirus by culture or shell vial assay from BAL fluid and associated cytomegalovirus viremia or histologic identification of typical cytomegalovirus inclusions on transbronchial or surgical lung biopsy specimens.\textsuperscript{13-17} \textit{Definite fungal pneumonias} were defined as the presence of hyphae or yeast by stain or culture in lung tissue or pleural fluid obtained by a sterile technique (surgical lung biopsy). Probable fungal infections were diagnosed if molds or cryptococcal organisms were identified in lung tissue obtained by transbronchial biopsy, BAL, or not orally contaminated sputum samples.\textsuperscript{18} A \textbf{DAH} was diagnosed if the BAL fluid revealed increasingly hemorrhagic returns and/or there were more than 20% hemosiderin-laden macrophages present on Prussian blue staining of BAL fluid. \textbf{Change in management} was considered present when the clinicians caring for the patient chose to appropriately add or withdraw use of an antimicrobial drug, add or withdraw use of an anti-inflammatory medication, or alter the course of antimicrobial therapy in response to the results of bronchoscopy.

\textbf{FIGURE 1.} Case identification flow diagram. ANC = absolute neutrophil count.
TABLE 1. Demographic and Clinical Characteristics Before Bronchoscopic Evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of patients (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Male</td>
<td>20 (57)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>25 (72)</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (17)</td>
</tr>
<tr>
<td><strong>Cause of neutropenia</strong></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Underlying disease process</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Drug induced (not chemotherapy)</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Severity of neutropenia</strong></td>
<td></td>
</tr>
<tr>
<td>Moderate (ANC &lt;1 × 10^9/L but ≥0.5 × 10^9/L)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Severe (ANC &lt;0.5 × 10^9/L)</td>
<td>23 (66)</td>
</tr>
<tr>
<td><strong>Duration of neutropenia</strong></td>
<td></td>
</tr>
<tr>
<td>Short (&lt;10 d)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Prolonged (&gt;10 d)</td>
<td>29 (83)</td>
</tr>
<tr>
<td><strong>Radiographic findings</strong></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>25 (71)</td>
</tr>
<tr>
<td>Empirical antimicrobial therapy (before bronchoscopy)†</td>
<td></td>
</tr>
<tr>
<td>Antibacterial</td>
<td>35 (100)</td>
</tr>
<tr>
<td>Antifungal</td>
<td>26 (74)</td>
</tr>
<tr>
<td>Antiviral</td>
<td>6 (17)</td>
</tr>
</tbody>
</table>

*Patient mean (SD) age was 55 (17) years. ANC = absolute neutrophil count.
†Fifteen patients received liposomal amphotericin B, 8 received amphotericin B, 1 received itraconazole, and 1 received fluconazole.

The study was approved by the Mayo Foundation Institutional Review Board. The reported data are presented as mean ± SD for continuous variables and percentages for categorical variables. The Fisher exact test was used for statistical analysis. P<.05 was considered statistically significant.

**RESULTS**

During the study period, 416 patients underwent BAL. Thirty-five patients met the inclusion criteria. Three patients had 2 distinct episodes of febrile neutropenia during the study period. For these individuals, only the first event was included. Demographics and clinical characteristics are outlined in Table 1.

Computed tomography of the chest was the most commonly used radiographic study (n=31). It was frequently performed to further characterize an abnormal chest x-ray (CXR) result. The results of all 20 CXRs obtained were abnormal. In 4 patients, a CXR represented the only radiograph obtained before bronchoscopy. Twenty-five patients had diffuse (bilateral) radiographic changes, whereas the abnormalities were focal in 10 cases. There was a wide variety of radiographic findings, ranging from single nodular opacities, lobar consolidations, and bilateral nodular infiltrates to diffuse bilateral alveolar or interstitial infiltrates. Radiographic abnormalities strongly suggestive of pulmonary aspergillosis (crescent sign, halo sign) were not reported in any patient.

All patients had several blood cultures performed before bronchoscopy, but organisms responsible for febrile neutropenia and associated chest radiographic abnormalities were isolated in only 2 cases (5.7%). These organisms were *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*.

Sputum samples were analyzed by microbial stains (Gram stain, acid-fast stain, and potassium hydroxide preparation) in only 12 patients (34%). Ten samples represented spontaneously expectorated specimens, whereas 2 were induced sputa. Five samples correlated with the final clinical diagnosis (5/12), resulting in a diagnostic yield of 42%. All these patients had probable fungal infections. In 2 cases, the sputum specimen was the only test that confirmed the diagnosis. Furthermore, in 2 additional cases the diagnosis suggested by sputum analysis was confirmed by transbronchial biopsy but not BAL. In 3 sputum samples, bacterial organisms were identified, all of which were not considered pathogenic based on the findings during BAL. One case of aspergillosis subsequently identified by surgical lung biopsy was missed by sputum analysis.

Serologic tests were performed in 7 patients before bronchoscopy, and all were nondiagnostic.

Bronchoalveolar lavage was safe in patients with febrile neutropenia. The only documented complications involved the requirement of invasive mechanical ventilation (2 patients) and the need for observation in the intensive care unit (1 patient). The diagnostic yield was 49% (17/35 patients), and the most frequent diagnoses established by BAL were probable fungal pneumonia (n=7) and DAH (n=5). No statistically significant difference occurred in diagnostic yield of BAL between patients with focal (4 [40%] of 10 patients) or diffuse (13 [52%] of 25 patients) radiographic changes (P=.71). Of the 15 cases of definite and probable fungal infections identified at hospital discharge, only 7 (47%) were identified by BAL. The additional diagnoses were established by sputum analysis in 4 patients (2 confirmed by transbronchial biopsy), 1 by transbronchial biopsy alone, 1 by repeat BAL and transbronchial biopsy, and 2 by surgical lung biopsy. Four organisms identified by BAL were not believed to be pathogens (*Mycobacterium avium-intracellulare*, *Haemophilus influenzae*, cytomegalovirus, and herpes simplex virus).

Five patients satisfied the diagnostic criteria for DAH. Two patients had increasingly hemorrhagic returns during BAL and more than 20% hemosiderin-laden macrophages on Prussian blue staining, whereas 3 additional patients fulfilled 1 of the 2 criteria. Two patients developed DAH.
after bone marrow transplantation, 2 patients developed DAH after chemotherapy, and 1 patient had underlying myelodysplastic syndrome. After the diagnosis of DAH, all patients were treated with high-dose glucocorticoids. There was a statistically nonsignificant trend toward a higher 28-day mortality rate in patients with DAH (40% compared with 23%; \( P= .56 \)). Surprisingly, the treating physicians made a clinical diagnosis of DAH in 3 additional patients despite coexisting infections. The microorganisms isolated from these patients included *Fusarium*, *Aspergillus fumigatus*, and methicillin-susceptible *Staphylococcus aureus*. All these patients were also treated with high-dose corticosteroids. Two of these 3 patients died during hospitalization.

In 9 patients, BAL was supplemented by transbronchial biopsy. The procedure provided diagnostic information in 3 (33%) of 9 patients, adding 1 additional diagnosis and change in management compared with the combination of BAL and sputum analysis (*Candida glabrata* infection). One episode of self-limited hemorrhage was the only complication attributable to the addition of transbronchial biopsy to BAL during the study period. Transbronchial biopsies only identified the diagnosis in 3 (50%) of 6 patients with fungal pneumonias. These patients’ conditions were diagnosed by surgical lung biopsy and pleural fluid (n=2) or sputum (n=1) analysis. The small number of transbronchial biopsies performed in our series does not allow conclusions regarding the diagnostic yield of this procedure in patients with focal compared with diffuse radiographic abnormalities. The clinically relevant diagnoses obtained by sputum analysis, BAL, and transbronchial biopsy are summarized in Table 2.

The diagnostic yield of sputum analysis, BAL, and transbronchial biopsy is summarized in Figure 2. The combination of sputum and BAL (63% diagnostic yield) appears to be most valuable because little additional information is obtained by transbronchial biopsy. After an initially nondiagnostic bronchoscopy, 3 patients subsequently underwent surgical lung biopsy, and 1 patient had repeat bronchoscopy with transbronchial biopsy for further diagnostic work-up. The retrospectively assigned final diagnoses are summarized in Figure 3.

On the basis of the results of bronchoscopy, patient management was changed appropriately in 18 patients (51%). Most of these changes (17 patients [49%]) were made based on BAL findings. Management alterations included the addition of antimicrobial (5 patients) or glucocorticoid (6 patients) therapy, the withdrawal of antimicrobial therapy (6 patients), and alteration in duration of therapy (6 patients). However, bronchoscopic evidence of DAH resulted in the potentially harmful treatment of 3 patients with high doses of glucocorticoids despite existing evidence of fungal or bacterial infections by sputum analysis and BAL.

The 28-day mortality rate was 26%. There was no statistically significant association between ANC (\( P>.99 \),...
FLEXIBLE BRONCHOSCOPY IN FEBRILE NEUTROPENIC PATIENTS

Figure 3. Final retrospective diagnoses for patients (n=35) with febrile neutropenia and pulmonary infiltrates. DAH = diffuse alveolar hemorrhage.

Duration of neutropenia ($P=0.16$), and the extent of chest radiographic involvement ($P=0.69$) with 28-day mortality. Patients who required invasive mechanical ventilatory assistance before bronchoscopy had an extremely high mortality rate compared with the remaining patients (83% vs 17%; $P<0.005$). A trend toward a higher hospital mortality was observed among patients in whom a specific diagnosis was established (33%) compared with patients with no diagnosis (0%; $P=0.08$).

DISCUSSION

Flexible bronchoscopy is a valuable tool during the evaluation of pulmonary infiltrates in immunocompromised patients, however, only a few studies have focused on patients with febrile neutropenia. In this patient population, more than 75% of all pulmonary infiltrates are attributable to infectious pathogens. The pathogens include a broad variety of bacteria, viruses, and fungi. Aspergillus species and other molds, such as Fusarium and Zygomycetes, represent an increasing problem in neutropenic patients. These organisms are notoriously difficult to diagnose, and the average diagnostic yield of bronchoscopic specimens for histologically proven invasive pulmonary aspergillosis is only 43% (range, 0%-67%).

Noninfectious causes encountered in these patients included diffuse alveolar hemorrhage, drug or radiation toxicity, recurrent malignancies, and idiopathic pneumonitis syndrome in patients who underwent bone marrow transplantation.

The first retrospective series that evaluated bronchoscopy in patients with febrile neutropenia was published in 1994 by Cordonnier et al. They compared the results of BALs in 57 episodes of pulmonary infiltrates in neutropenic patients to 58 episodes in nonneutropenic immunocompromised patients. Their analysis confirmed that BAL can be performed safely in these patients. They identified only 2 complications (1.7%) in 113 procedures. The overall diagnostic yield of BAL was 53%. It was higher for the first episode (77%) of neutropenia than for subsequent events (45%) and with multifocal (69%) rather than focal (47%) chest radiographic abnormalities. Bronchoscopic findings changed patient management in 46% of episodes. Infectious causes were most commonly identified (70%), and invasive aspergillosis represented the most frequent infectious pathogen (20%). The most common noninfectious cause was DAH. The sensitivity of BAL was poor for fungal infections. In 9 patients, fungal infections, most commonly aspergillosis (7 cases), were missed by BAL.

Ramila et al found a similar diagnostic yield of BAL in 22 patients who underwent high-resolution computed tomography–guided BAL. In contrast to Cordonnier et al, they identified fewer management changes (27%) based on BAL results.

Most recently, Gruson et al prospectively evaluated the utility of fiberoptic bronchoscopy in 93 critically ill patients with respiratory failure and neutropenic fever. The diagnostic yield of BAL was 49% and resulted in management changes in 28% of patients. Not surprisingly, they observed a higher frequency of procedure-related complications (16.7%) even though most had only minor consequences. Similar to Cordonnier et al, Gruson et al observed a significant false-negative rate of 34%, but in this series the most commonly missed diagnosis was DAH. Our findings confirm the high diagnostic yield (49%) of BAL in patients with febrile neutropenia and pulmonary infiltrates shown in previous series.

If BAL is combined with the results of sputum stains and cultures obtained before bronchoscopy, the overall diagnostic yield increases to 63%. Interestingly, a retrospective analysis conducted by Horvath and Dummer, reviewing all respiratory secretions analyzed at Vanderbilt University during a 14-year period, showed an estimated 72% positive predictive value for invasive aspergillosis if
fungal organisms consistent with *Aspergillus* were identified by sputum stain or cultures. The sensitivities were similar for invasively and noninvasively collected respiratory tract specimens. Furthermore, patients with invasive aspergillosis were more likely to have multiple positive sputum tract specimens. Furthermore, patients with invasive aspergillosis were more likely to have multiple positive sputum specimens. These findings by Horvath and Dummer confirmed prior data from Yu et al. who concluded that the isolation of *Aspergillus fumigatus* and *Aspergillus flavus* from respiratory specimens is highly predictive of invasive aspergillosis in patients with leukemia and/or neutropenia. Unfortunately, sputum specimens were analyzed before bronchoscopy only in a few of our patients (34%), and no patient had multiple samples. This lack of sputum analysis may be attributable to the absence of respiratory secretions in these patients. Our data and the findings by Yu et al and Horvath and Dummer suggest that, to optimize the diagnostic yield for invasive fungal infections, several sputum samples should be obtained in addition to invasively obtained respiratory specimens. If the patient is unable to produce a specimen, sputum induction may be an alternative approach.

In most patients, infectious pathogens were identified (60%), and fungal organisms represented the most frequent isolates. Despite recent advances in empirical antimicrobial therapy, information obtained by bronchoscopy resulted in management changes in 51% of episodes. The changes involved the addition or withdrawal of antimicrobial drugs, changes in duration of therapy, or the initiation of glucocorticoid therapy. This number is higher than previously reported in other recent series. As described by previous investigators, BAL had a limited sensitivity for fungal infections and missed 8 (53%) of 15 cases identified by alternative techniques.

We found flexible bronchoscopy with BAL and selected transbronchial biopsies to be a safe procedure in patients with febrile neutropenia. In nonneutropenic patients, flexible bronchoscopy is considered a safe intervention, with a procedure-related mortality rate of 0.04% and a complication rate of 0.12%. If transbronchial biopsies are performed, the mortality rate increases to 0.12% and complications occur in 2% to 10% of patients. This increased risk is mainly attributed to higher rates of hemorrhage and pneumothorax. In the presence of thrombocytopenia, the risk of bleeding increases further (12%), and fatal outcomes due to massive hemorrhage after transbronchial biopsy have been reported. We generally try to limit transbronchial biopsy to patients with a platelet count greater than 50 × 10^9/L or alternatively use platelet transfusions to achieve this level. Even if these guidelines are followed, substantial bleeding can occur in these patients. Therefore, it is surprising that the 9 transbronchial biopsies performed in our series did not add significantly to the procedure-related complications. A potential explanation for this observation is the careful selection of the patients subjected to transbronchial biopsy. Furthermore, during our data collection, we did not capture potential adverse effects of platelet transfusions administered before bronchoscopy. Even though transbronchial biopsy appeared to be safe, it added little diagnostic yield to the combination of sputum and BAL staining and cultures. The use of transbronchial biopsy identified 1 additional diagnosis that resulted in a management adjustment in that patient. Its sensitivity for fungal infections was low, and the final diagnosis was missed in 50% of cases. White et al. reported a similarly low diagnostic yield of transbronchial biopsy when added to BAL in a series of patients who underwent bone marrow transplantation.

The most common noninfectious cause of pulmonary infiltrates identified in our series was DAH (14%). This diagnosis was established using bronchoscopic criteria. It represented the most frequent indication for the addition of glucocorticoids. In patients with DAH, the trend was toward a higher mortality rate.

In 3 additional patients, the treating physicians decided to add high-dose glucocorticoids to the antimicrobial regimen based on bronchoscopic evidence of DAH. Invasive fungal infections were subsequently identified in 2 of these patients, and 1 of these patients died during hospitalization. Corticosteroid therapy and neutropenia represent poor prognostic indicators in patients with invasive fungal infections. Bronchoscopic criteria for DAH are nonspecific and merely indicate bleeding into the alveolar space but do not imply corticosteroid responsiveness. Therefore, especially in light of the poor sensitivity of even the most invasive diagnostic tests for invasive fungal infections in this patient population, the risk and benefits of initiating high-dose glucocorticoid therapy should be evaluated carefully.

In support of previously reported data, the overall 28-day mortality rate was 26% in our series, and patients who required mechanical ventilatory assistance at the time of bronchoscopy had a significantly worse outcome. Patients in whom a specific diagnosis was established during the diagnostic work-up were also more likely to die. This difference may in fact be due to more severe disease, a higher burden of pathogenic organisms, or a decreased response to antimicrobial therapy in these patients.

We recognize that our findings may be limited by the relatively small sample size, but despite this, we believe that our observations are clinically valid. The major advantage of our series is that it reflects the clinical practice regarding the evaluation of pulmonary infiltrates in patients with febrile neutropenia during a confined and
recent period. Therefore, data should be less biased by the rapidly changing approach to the clinical care of these patients.

CONCLUSION

To assess patients with febrile neutropenia and pulmonary infiltrates for invasive fungal disease, several sputum samples for stains and cultures should be obtained. Bronchoscopy with BAL can be performed safely in neutropenic patients and represents an integral part of the evaluation of pulmonary infiltrates in this patient population. The BAL specimens should be analyzed for microorganisms and is a useful tool for the management of pulmonary infiltrates for invasive fungal disease, several sputum and cellular pattern.

REFERENCES