Transbronchial Biopsy in the Diagnosis of Pulmonary Infiltrates in Immunocompromised Patients

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Bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) frequently are performed in the investigation of immunocompromised patients with lung disorders. The risk-benefit ratio of TBB currently is debated, since several authors have found that the less invasive BAL may provide as much information as TBB, with the avoidance of some biopsy-related side effects. We retrospectively evaluated 157 instances of bronchoscopy carried out on 142 immunocompromised patients, with both BAL and TBB performed in every case. Immunosuppressant conditions were HIV infection (79), hematologic malignancies (36), and antirejection therapy in renal transplant recipients (27). Transbronchial biopsy provided a diagnostic yield significantly higher than that obtained by BAL in all categories investigated; diagnostic rates were 77.3% for TBB and 47.6% for BAL (p <0.001) in patients with HIV infection, 55 and 20% (p <0.001) in patients with hematologic malignancies, and 57.5 and 27.2% (p <0.001) in renal transplant recipients. Looking at the whole series, the diagnostic rates of TBB and BAL were 67.5 and 36.3%, respectively (p <0.001), with a total additional yield of 33% provided by TBB, while in only 2% of cases BAL gave rise to diagnostic information not achieved by TBB. Considering that side effects followed TBB at a negligible rate (2.5%), we believe that TBB should be routinely carried out in these patients once the diagnostic strategy has been oriented to bronchoscopy. (Chest 1995; 107:101-06)

Many are the disorders developing or secondarily affecting the lungs of immunocompromised patients. In a limited number of circumstances, diagnostic attempts like sputum examination and culture or, more rarely, serologic assays, may provide enough information for starting the appropriate chemotherapy. When these simple noninvasive investigations fail to disclose the etiology, the choice of the diagnostic procedure that will quickly achieve reliable diagnostic findings depends on several factors. Rates of occurrence of specific opportunistic disease vary according to the underlying immuno-suppressive condition, so that the knowledge of what is more likely to develop in some defined risk groups may greatly influence the choice of a specific diagnostic process. Fiberoptic bronchoscopy has greatly improved the diagnosis of pulmonary disorders, since different procedures like bronchial washing, bronchoalveolar lavage (BAL), bronchial brushing, and transbronchial biopsy (TBB) have been made possible by this maneuver. Such diagnostic procedures are of varying degrees of invasiveness and, in terms of diagnostic yield, it is not established yet when the most invasive should be adopted, since several authors support the notion that in some clinical circumstances BAL has the same diagnostic value as TBB, with a lesser invasive impact.

We retrospectively evaluated the diagnostic usefulness of TBB in 157 procedures carried out on 142 immunocompromised patients investigated over the years, 1987 to 1992. This group consisted of subjects with HIV infection, renal transplant recipients, and patients with hematologic malignancies. The diagnostic yield and safety of TBB and BAL were compared in the same patients to see in which circumstances the former procedure provided otherwise inaccessible diagnostic information.

**Study Population**

At the General Hospital of Verona, 142 immunocompromised patients underwent bronchoscopy for the investigation of 157 episodes of pulmonary infiltration from 1987 to 1992. Further, 18 patients with similar conditions underwent bronchoscopy in the same study period but were not considered in the comparative evaluation here concerned, because BAL only was performed in these patients.

**Materials and Methods**

**Key words:** bronchoalveolar lavage; bronchoscopy; immunocompromised patients; transbronchial biopsy

**Table:**

| BAL=bronchoalveolar lavage; CMV=cytomegalovirus; KS=Kaposi’s sarcoma; PCC=Pneumocystis carinii pneumonia; TBB=transbronchial biopsy |**Study** Population **Material and Methods**

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The study population described here is limited to patients who had an established diagnosis of an immunosuppressant condition, with three distinct groups of subjects identified as having, respectively, HIV infection or hematologic malignancies or being renal transplant recipients. In all cases, sputum-based analyses (direct detection and culture of microbiological agents, cytologic examination) were negative and an empiric wide-spectrum antibiotic therapy did not lead to clearance of pulmonary infiltrates nor to any sort of clinical improvement.

**Group A (HIV-Infected Patients):** This group consisted of 79 subjects with HIV infection, as determined with a licensed enzyme-linked immunosorbent assay method and subsequently confirmed by Western blot analysis. Sixty-one patients were men and 18 were women, with a mean age of 31 years (range, 21 to 57 years). They all presented with acute diffuse or localized pulmonary infiltration, with a cumulative number of 84 episodes. According to the Centers for Disease Control criteria for staging of HIV infection,11 25 subjects were classified as A2, 24 as B3, and 30 as C3. The HIV-related risk factors were intravenous drug use in 64 subjects (81%), homosexuality in 10 (12.7%), and promiscuous heterosexuality in 5 (6.3%).

**Group B (Hematologic Malignancies):** This group consisted of 36 patients who underwent bronchoscopy for the investigation of 40 episodes of acute diffuse or localized pulmonary infiltration. Twenty-six were men and 10 were women, with a mean age of 40 years (range, 15 to 70 years). Included in this group were 16 patients with Hodgkin’s disease, 11 with acute lymphoblastic or myeloid leukemia, 4 with non-Hodgkin’s lymphoma, and 5 with chronic lymphoproliferative disease.

**Group C (Renal-Transplant Recipients):** This group consisted of 27 subjects who underwent bronchoscopy for the investigation of 93 episodes of acute diffuse or localized pulmonary infiltration. Nineteen were men and 8 were women, with a mean age of 37 years (range, 17 to 59 years). All patients were receiving immunosuppressive treatment (cyclosporine, azathioprine, and steroids); pulsed doses of steroids and OKT3 antibody also were administered in case of rejection episodes.

**Bronchoscopy**

Before bronchoscopy, routine laboratory tests including platelet counts and blood gas level measurements were performed. Bronchoscopy was carried out with various Olympus bronchoscopes accompanied by continuous electrocardiographic and oxygen saturation monitoring. The bronchoscope was passed transnasally into the trachea after application of local anesthesia (1% lidocaine [Xylocaine]). In three patients receiving mechanical ventilation, the bronchoscope was passed directly into the trachea through an endotracheal tube by using a connector providing an airtight seal.

After routine examination of the tracheobronchial tree, the bronchoscope was wedged into a segmental bronchus supplying an area of radiographic abnormalities or into the middle lobe or lingula in case of diffuse infiltration of the lung. Bronchoalveolar lavage was then performed by segmental instillation and suctioning of 50-mL volumes of physiologic saline solution. The procedure was repeated thrice and the fluids were then pooled.

Transbronchial biopsies were performed by using single-plane fluoroscopic control from the right middle lobe or lingula in case of diffuse infiltrate and from the appropriate segment in case of a localized lesion. Three to six biopsy specimens were obtained from each patient (with a mean of four). All nonintubated patients had a PaO2 of at least 50 mm Hg while breathing room air. Transbronchial biopsies were not done (only BAL was performed) in 11 patients with severe thrombocytopenia (<50,000 platelets/ mm3) and in 7 nonintubated patients with severe hypoxemia (PaO2 <50 mm Hg while the patient was breathing room air). These patients were excluded from the study. Chest radiographs were obtained 4 to 6 h after TBB.

**Processing of Specimens**

Samples taken by BAL were immediately submitted for bacterial, mycobacterial, fungal, and viral cultures. A portion of each of these samples was centrifuged and was subsequently fixed and stained on glass slides. Staining included Comori’s methamine-silver, Ziehl-Neelsen, Gram, and Giemsa.

Biopsy specimens were fixed in a 37% aqueous solution of formaldehyde (Formalin) and embedded in paraffin. Routine hematoxylin and eosin stain and all the staining described for BAL samples were performed.

**Diagnostic Criteria**

Pulmonary disease was evaluated on the basis of results from analyses of the specimens obtained by bronchoscopy. Transbronchial biopsy with only histologic abnormalities with specific changes was considered diagnostic, while in the case of nonspecific pathologic findings (alveolar damage, organizing pneumonia, chronic interstitial pneumonitis, or alveolar hemorrhage), a normal lung; in the case of inadequate material, it was considered nondiagnostic. Bronchoalveolar lavage was considered diagnostic when the specific stains showed an opportunistic pathogen or abnormalities consistent with a malignant disorder on cytologic examination.

In most cases, cultures made on BAL specimens gave evidence of a mixed flora with some candidate pathogen but no conclusive diagnostic findings were drawn from them. As usual, growth of mycobacteria became detectable after a minimum of 22 days following bronchoscopy. For these reasons, since the results obtained from BAL cultures did not satisfy firm diagnostic criteria, they were not considered in the comparative evaluation between TBB and BAL.

**Statistical Analysis**

The significance of the results was tested by McNemar’s test12 for paired alternatives. A significance level of 0.05 was always adopted.

**Results**

The results are summarized in Table 1, and the specific pulmonary disorders diagnosed in each group of patients are listed in Table 2 together with the diagnostic yields, respectively, obtained by TBB and BAL in each disorder here encountered.

**Group A (HIV-Infected Patients)**

Eighty-four bronchoscopic examinations (all including BAL and TBB) were performed on 79 patients, with an overall diagnostic yield of 79.7% (67 cases). Transbronchial biopsy was found to be of diagnostic value in 65 cases (77.3%) with an additional contribution of 27 cases (32.1%) to the yield gathered by BAL (40 cases, 47.6%; p<0.001). The findings obtained by BAL served to increase the diagnostic yield of TBB from 65 to 67 cases (2.4%).

**Group B (Patients With Hematologic Malignancies)**

Forty bronchoscopic examinations were carried out on 36 patients, with a cumulative diagnostic yield of 55% (22 cases). Transbronchial biopsy provided
Hematologic malignancies
Total transplant diagnosis
Effects of diagnostic yield and contribution to the diagnosis in 22 cases (55%), with an incremental yield of 14 cases (35%) as compared with BAL (p<0.001). Bronchoalveolar lavage gave rise to diagnostic information in 8 cases (20%) and added no contribution to the diagnostic yield of TBB.

**Group C (Renal Transplant Recipients)**

Thirty-three bronchoscopic examinations were performed on 27 patients, with a total diagnostic yield of 60.6% (20 cases). Transbronchial biopsy was diagnostic in 19 cases (57.5%) and gave an additional diagnostic contribution of 11 cases (33.3%) as compared with BAL (p<0.01). Bronchoalveolar lavage provided the diagnosis in 9 cases (27.2%) and increased from 19 to 20 (3%) the diagnostic yield of TBB.

**Side Effects**

In 4 cases (2.5%), untoward effects occurred as the result of TBB. Pneumothorax took place in three HIV-infected subjects (who were not receiving mechanical ventilation) who promptly recovered after conventional intervention (insertion of a chest tube for 36 to 48 h). In a patient with acute leukemia, a hemorrhage (with more than 100 mL of blood loss) followed TBB, which was subsequently controlled by wedging the fibroscope into the injured bronchus with local release of adrenalin.

**Discussion**

Pulmonary infiltrates are frequently a diagnostic challenge in immunocompromised patients and invasive techniques often are used in the diagnostic process. In the present study, we evaluated the diagnostic usefulness and safety of TBB in three groups of patients with different underlying immunodeficiencies, whose pulmonary infiltrates were not etiologically recognized by simple sputum-based investigations and failed to clear with an empiric wide-spectrum antibiotic therapy. All the patients underwent bronchoscopy followed by BAL and TBB, so that a comparative evaluation of the diagnostic yield and safety of these two techniques also was performed. Transbronchial biopsy provided conclusive diagnostic indications in 77% of patients with HIV infection, in 55% of patients with hematologic malignancies, and in 57% of renal transplant recipients. In the same patients, BAL was diagnostic in 48, 20, and 27% of cases, respectively. Overall diagnostic rates were 67.5 and 36.3% for TBB and BAL, respectively, with a total additional diagnostic yield of 35% (52 cases) provided by TBB (p<0.001). In only 3 cases (2%), BAL provided diagnostic information not achieved by TBB.

Untoward effects followed TBB at a negligible rate (2.5%); all were of mild intensity and promptly resolved. These figures suggest a favorable risk-

**Table 1—Patients and Diagnostic Yields Obtained With Procedures Adopted Represented as Single Groups and as Cumulative (Total) Findings**

<table>
<thead>
<tr>
<th>Category</th>
<th>No.</th>
<th>TBB, No. (%)</th>
<th>BAL, No. (%)</th>
<th>TBB &amp; BAL, No. (%)</th>
<th>Probability Value Less Than*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>84</td>
<td>65 (77.3)</td>
<td>40 (47.6)</td>
<td>67 (79.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>40</td>
<td>22 (55)</td>
<td>8 (20)</td>
<td>22 (55)</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal transplant recipients</td>
<td>33</td>
<td>19 (57.5)</td>
<td>9 (27.2)</td>
<td>20 (60.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>106 (67.5)</td>
<td>57 (36.3)</td>
<td>109 (64.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*The statistical significance of differences was measured with McNemar’s test.

**Table 2—Specific Lung Disorders Diagnosed in the Three Groups of Patients Investigated and Diagnostic Yields Obtained With Transbronchial Biopsy and Bronchoalveolar Lavage in Each Disorder**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Total</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>TBB</th>
<th>BAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td>44</td>
<td>39</td>
<td>1</td>
<td>4</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>16</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>KS</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Pyogenic infections</td>
<td>11</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>17</td>
<td>4</td>
<td>8</td>
<td>5</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>CMV infections</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>8</td>
<td>...</td>
<td>8</td>
<td>...</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Total diagnosed</td>
<td>109 (69.4%)</td>
<td>67</td>
<td>22</td>
<td>20</td>
<td>106 (67.5%)</td>
<td>57 (36.3%)</td>
</tr>
<tr>
<td>Total undiagnosed</td>
<td>48 (30.6%)</td>
<td>17</td>
<td>18</td>
<td>13</td>
<td>51 (32.5%)</td>
<td>100 (63.7%)</td>
</tr>
</tbody>
</table>

*Group A=patients with HIV infection; group B=patients with hematologic malignancies; group C=renal transplant recipients.
effectiveness ratio for TBB in these categories of patients, also considering that even with the most invasive procedures, namely, open lung biopsy (and autopsy), at least 20% of cases remain undisclosed. A debate currently is in progress about the diagnostic usefulness of TBB in immunocompromised subjects, since good diagnostic yields have been reported with the less invasive technique of BAL. Several authors have found that BAL may provide a diagnostic rate approaching that of TBB in the investigation of pulmonary infiltrates in immunocompromised patients, without entailing TBB-associated complications.10,13-18 There are, however, several specific issues for each subset of patients considered, which make questionable some of the conclusions drawn from these series.

In patients with HIV infection, BAL has been shown to be nearly of the same value of TBB in the diagnosis of Pneumocystis carinii pneumonia (PCP),10 the former most common pulmonary disease in this setting. This is not too surprising since in PCP there is a significant alveolar component, and BAL, which samples the alveolar space, is likely to provide diagnostic material. However, following the successful adoption of various chemoprophylactic regimens, PCP is now far less frequent than before.20 Furthermore, administration of aerosolized pentamidine, one of the currently used chemoprophylactic methods, may be followed by the development of atypical and localized forms of PCP, which are unlikely to be diagnosed by BAL as easily as the classic variety of the disease.21 In opposition to the declining tendency of PCP, tuberculosis is increasingly reported in HIV-infected subjects. Diagnosis of HIV-associated tuberculosis often may be difficult, since patients frequently present with nonspecific or even normal chest x-ray films and their sputum specimens are negative for acid-fast bacilli in a relevant proportion of cases.22 In the case of HIV-associated tuberculosis, TBB has been reported to provide incremental diagnostic rates, leading authors to draw different and conflicting conclusions about the usefulness of this procedure in such diagnostic settings.23-25 While in the case of other opportunistic pathogens, the importance of a higher diagnostic yield lies only on a possible benefit for individual patients, which may eventually arise from a more precise diagnosis, with Mycobacterium tuberculosis the environmental spread of the organism also must be considered. As a consequence, in case of tuberculosis attention should be paid not only to the crude diagnostic yield respectively attainable by more or less invasive investigations but also to the time elapsing before a conclusive diagnostic piece of information is achieved. In case of sputum-negative active tuberculosis, unless acid-fast bacilli are seen in the BAL specimen, no diagnostic findings are obtained until bacillary growth becomes detectable in culture, after 10 to 12 days with the most sensitive methods (radiometric culture technique) and at least 3 weeks with ordinary culture media (Lowenstein-Jensen). Transbronchial biopsy may well provide, in these cases, diagnostic information, which makes it possible to start antituberculous chemotherapy earlier as well as adopt nosocomial isolation precautions.

Delayed diagnosis of HIV-associated tuberculosis followed by a delay in beginning chemotherapy has been the most relevant causative factor of the many nosocomial outbreaks, which occurred in the AIDS wards.26,27 Such an issue is becoming even more urgent in these times, due to the diffusion of multidrug-resistant strains of M tuberculosis, which have been reported often to circulate among HIV-infected patients in nosocomial settings.28

Focal and diffuse pulmonary involvement of HIV-infected subjects by Kaposi's sarcoma (KS) are not easily recognized, unless endobronchial macroscopic lesions are seen and a tentative diagnosis is allowed. In previous studies, TBB was shown to be an insensitive diagnostic procedure for the detection of KS,29 but more recent findings,30 as well as the investigation here concerned, provided substantial evidence on the usefulness of TBB for the diagnosis of KS, while BAL has virtually no diagnostic value here.

In our series, neoplastic lung lesions were as frequent as fungal infections in patients with hematologic malignancies. This was an unexpected finding, since fungi are the most common causes of pulmonary infiltrates in this clinical context.31,32 Lesions due to the underlying hematologic malignancy are more easily diagnosed by TBB than BAL; the cytologic examination is of little value in this case.10 In these patients, fungal pneumonia are mainly due to Aspergillus and Candida species. In the case of aspergillosis, both culture and microscopic examination of tissue provide the most firm diagnosis. Aspergillus species has been implicated in invasive pneumonia, or alternatively it may be present as a saprophytic entity. The simple examination or culture made on BAL specimens may not be appropriate for establishing the diagnosis of the invasive form of aspergillosis; the pathologic landmark of blood vessel invasion with hemorrhagic alveolar infarction is hardly detected by BAL.33

A slightly better diagnostic power of BAL has been claimed in the case of pneumonia caused by Candida species.33 However, since this fungus is often present as a saprophytic organism, it is not usual to demonstrate a causative role for Candida in these cases by relying only on BAL.34

Many are the pulmonary disorders occurring in renal transplant recipients. Pneumocystis carinii
pneumonia, pneumonia caused by Aspergillus species, as well as tuberculosis and pulmonary KS are recognized in these patients, but the most frequent pulmonary disease in this setting is reported to be cytomegalovirus (CMV) pneumonia.\textsuperscript{35}

The diagnosis of CMV pneumonia is established in the presence of typical clinical findings with positive cultures for CMV, the histopathologic evidence of CMV cytopathic changes in lung tissue, and exclusion of other etiologic agents. Bronchoalveolar lavage culture is highly sensitive but poorly specific, while the finding of CMV inclusions in a BAL specimen is a rare event, so that examination of lung tissue is still required to establish with confidence that CMV is the cause of pneumonia,\textsuperscript{36,37} and TBB was proved to be the preferred procedure in this specific setting.\textsuperscript{38}

According to our experience, TBB seems able to improve the diagnostic power of BAL, mainly in fungal infections, the reemerging tuberculosis and malignant underlying disease. Unless a diagnosis has been obtained by sputum-based analyses, TBB should routinely be performed in immunocompromised patients whose conditions are worsening after empirical antimicrobial therapy has failed and the diagnostic process has been oriented to bronchoscopy.

Bronchoalveolar lavage and TBB may be complementary in their ability to diagnose or exclude infectious and noninfectious complications in immunocompromised patients and they may well obviate the need for open-lung biopsy.

References

11. CDC. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults. MMWR 1992; 41:1-19