The Impact of Bronchoalveolar Lavage Cell Analysis on Clinicians' Diagnostic Reasoning About Interstitial Lung Disease*

James K. Stoller, M.D.; John A. Rankin, M.D., F.C.C.P.; and Herbert Y. Reynolds, M.D., F.C.C.P.

To assess the impact of bronchoalveolar lavage (BAL) on clinicians' diagnostic reasoning, we administered serial telephone questionnaires to all pulmonary physicians submitting BAL specimens to our laboratory from nonimmunocompromised patients with diffuse interstitial lung disease. Questionnaires were completed when the lavage specimens were first submitted and again after the results were reported to referring physicians. We recorded the clinicians' ordered list of likeliest diagnoses for the patient, a level of confidence in each diagnosis mentioned, and any proximate plans for further diagnostic tests. Of 78 patients in the study, information from the BAL fluid cell analysis caused clinicians to change their diagnostic thinking in 46 (59 percent). These changes were far more frequently appropriate (52 percent) than not (9 percent), and clinically impressive changes did occur but were infrequent (3 of 78 [4 percent]) in this series. Specifically, BAL permitted the unexpected diagnosis of Pneumocystis carinii in a patient not previously suspected to have acquired immune deficiency syndrome (AIDS) and appropriately encouraged clinicians to avert planned surgical biopsies in two patients subsequently found to have sarcoidosis. These findings suggest that when used to evaluate nonimmunocompromised patients, BAL fluid cell analysis can have an important impact on clinicians' diagnostic reasoning about their patients' interstitial lung diseases.

Since the first analytic descriptions1-5 of bronchoalveolar lavage (BAL), this procedure has been used extensively to characterize the cellular and soluble components of alveolar lining fluid in many interstitial lung diseases.6-12 Although investigators now believe that BAL fluid cell analysis can only rarely identify a specific interstitial lung disease, little attention has been given to whether BAL fluid analysis affects clinicians' diagnostic reasoning or streamlines the clinician's approach to individual patients with interstitial lung disease. Several published reports have examined the diagnostic usefulness of BAL in interstitial lung disease,13,14 but these analyses have been limited because conventional test measures—like sensitivity, specificity, and predictive values—often fail to answer the questions that concern the clinician about a diagnostic test: How does the test result affect the relative likelihood of contending diagnoses? Does the test result indicate a modification in further plans for tests and treatment? To more directly appraise the impact of BAL fluid analysis on clinicians' reasoning, the current study asked: Did learning the results of BAL cell analysis alter clinicians' diagnostic impressions or test ordering, or both, in evaluating nonimmunocompromised patients with diffuse interstitial lung diseases?

METHODS

Questionnaires

Serial telephone questionnaires (called QST 1 and QST 2) were administered to all pulmonary physicians who submitted BAL specimens from eligible patients to our laboratory between June 1984 and September 1985.15 For each physician, two questionnaires were completed, each at a separate time: (1) when the BAL fluid specimen was first submitted for analysis (QST 1), and (2) again immediately after the BAL results were reported to the referring physician (QST 2). Each questionnaire was administered by one of the investigators (J.A.R.) and recorded four physician responses, including (1) an ordered list of up to three specific and most likely diagnoses, (2) a level of confidence in each listed diagnosis, (3) any proximate plans for further diagnostic tests, and (4) whether any test results other than BAL analysis had become available in the interim between QST 1 and QST 2. Because the serial questionnaires were usually completed within 24 hours of one another, few interim test results became available to clinicians. Also, although transbronchial biopsies were frequently done after the BAL (63 of 78 [81 percent]), these biopsy results most often were still unknown when the second questionnaire was completed (54 of 63 [86 percent]). Among the nine cases for which transbronchial biopsy results were known when QST 2 was completed, the biopsy specimen was nondiagnostic in seven (78 percent). Therefore, because the BAL analysis was almost always available to the referring physician within two to 24 h of submission and because a specific final diagnosis was rarely known before QST 2

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*MFrom the Department of Medicine, Pulmonary Section and Robert Wood Johnson Clinical Scholars Program, Yale University School of Medicine, New Haven, CT; and the Research Service, West Haven Veterans Hospital, West Haven, CT.

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Reprint requests: Dr. Stoller, Department of Pulmonary Disease, 9500 Euclid Avenue, Cleveland 44106.
was completed, changes in suspected diagnoses and planned tests or treatments between QST 1 and QST 2 could be confidently ascribed to learning the fluid cell analysis results.

Eligibility Criteria

Because BAL has already been shown to be helpful in diagnosing infections in immunocompromised patients,1,13 this study did not evaluate BAL in this clinical setting. Instead, patients were eligible for this study if (1) BAL was performed to evaluate a diffuse interstitial infiltrate on the chest roentgenogram, and (2) the patient was not suspected to be immunocompromised at the time BAL was performed (eg, without acquired immune deficiency syndrome [AIDS], known cancer, or immunosuppressive treatment).

Final Diagnoses

To assess whether diagnostic changes between QST 1 and QST 2 were appropriate, definitive final diagnoses were sought in all patients. Except for one patient with mixed connective tissue disease (whose final diagnosis was established from a compatible clinical picture and serologic results), all final diagnoses (available in 51 patients) were based on available tissue biopsies. Five patients underwent two biopsy procedures. Diagnostic procedures included open lung biopsy (11 patients), transbronchial biopsy (36 patients), lymph node biopsy (six patients), renal biopsy (one patient), skin biopsy (Kveim, one patient), and percutaneous lung aspiration (one patient).

Bronchoalveolar Lavage

Techniques for BAL did not vary significantly among the 32 physicians who submitted specimens.14 All BAL fluid analysis reports were uniform and included: (1) total cells retrieved, (2) cell differential counts, (3) results of any incidental microscopic findings (eg, organisms apparent during examination of stained specimens), and (4) routine interpretation of the differential cell count as consistent with granulomatous or nongranulomatous disease. Notably, BAL fluid was not prepared with any specific microbiologic stains (eg, silver methenamine). Also, soluble components (eg, immunoglobulins) were not analyzed immediately and lymphocyte subtyping was not routinely performed. Therefore, results of such analyses were not available in the reports to submitting physicians.

Definitions

Several definitions were used in this analysis. A diagnostic change (QST 2 vs QST 1) occurred when (a) a diagnosis was either newly considered or deleted, (b) the order of likeliest diagnoses changed, or (c) the level of confidence in a diagnosis changed. Changes were deemed appropriate if, after learning the BAL results, the physician either more strongly suspected the correct final diagnosis or less avidly suspected an incorrect diagnosis.

Changes were clinically impressive if they newly suggested the correct final diagnosis or caused its elimination from consideration. Also, changes in planned diagnostic tests were deemed impressive when invasive tests (eg, open lung biopsy, lymph node biopsy) were avoided.

Results

Between June 1984 and September 1985, 93 eligible patients’ BAL fluid specimens were submitted for analysis. Paired telephone questionnaires were successfully completed for 78 of these patients (78 of 93 [84 percent]), which comprised the study patient population. Unavailability of the referring physicians or investigators precluded completion of the remaining 15 patients’ questionnaires. Altogether, 32 physicians (six full-time Yale pulmonary faculty members, four Yale pulmonary fellows, and 22 private pulmonary physicians) submitted BAL specimens. Fifty-seven patients were referred to the study by private pulmonary physicians, 15 by faculty, and six by fellows.

Final diagnoses in the 78 study patients are listed in Table 1. Of the 18 represented causes of interstitial lung disease, pulmonary sarcoidosis was most frequent (29.5 percent) and idiopathic pulmonary fibrosis was the second most common diagnosis (9.0 percent). Notably, of the 27 patients whose diagnoses were considered either uncertain or unknown, most (22) had transbronchial biopsies that showed nonspecific fibrosis. In the remaining five patients, no tissue biopsies were available.

Figure 1 shows that when QST 1-QST 2 pairs were compared, at least one diagnostic change had occurred in most of the patients (46 of 78 or 59 percent). Of the 46 patients in whom changes occurred, two changes

Table 1—Final Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary sarcoidosis</td>
<td>23 (29.5)</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>7 (9.0)</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>2</td>
</tr>
<tr>
<td>Lipoid pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatoid lung</td>
<td>2</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td>Vasculitis, unspecified</td>
<td>1</td>
</tr>
<tr>
<td>Chronic eosinophilic pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Talcosis</td>
<td>1</td>
</tr>
<tr>
<td>Silicosis</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia (AIDS)</td>
<td>1</td>
</tr>
<tr>
<td>Gold lung</td>
<td>1</td>
</tr>
<tr>
<td>Furadantoin lung</td>
<td>1</td>
</tr>
<tr>
<td>Final diagnosis unknown or uncertain</td>
<td>27 (34.6)</td>
</tr>
<tr>
<td>Total</td>
<td>78 (100)</td>
</tr>
</tbody>
</table>

FREQUENCY OF DIAGNOSTIC CHANGES

(N = 78 PATIENTS)

41% n=32 No diagnostic change occurred

59% n=46 Diagnostic change occurred

Figure 1
occurred in 13 (17 percent of 78) and three changes occurred in nine (11 percent of 78), for a total of 77 diagnostic changes in these 46 patients.

Figure 2 shows the types of diagnostic changes that were observed, most of which (38 of 77 changes or 49 percent) were changes in the level of confidence attached to a particular diagnosis. Least frequent were changes in the relative order of diagnoses considered (10 of 77 changes or 13 percent).

Figure 3 shows the frequencies with which the diagnostic changes made in 46 patients were appropriate. Most commonly (24 of 46 patients or 52 percent), all recorded changes were deemed appropriate. In four patients (9 percent), none of the changes in diagnosis was appropriate, and in 13 (28 percent) the appropriateness of diagnostic changes could not be assessed because the patients' final diagnoses were uncertain.

Of the 24 patients in whom all diagnostic changes were appropriate, changes were clinically impressive in three (12.5 percent). Specifically, in one patient initially thought to have sarcoïdosis, examination of a Wright's stained preparation of the BAL fluid (for differential cell count) incidentally revealed clusters suggestive of Pneumocystis carinii pneumonia. A subsequent workup (initiated because of this unexpected finding from BAL) revealed that the patient had AIDS and pulmonary infections with both P. carinii and Cryptococcus neoformans. In two other patients, physicians appropriately cancelled planned surgical biopsies (ie, open lung biopsy and mediastinoscopy for lymph node biopsy) when the results of BAL proved to be consistent with a suspected diagnosis of sarcoidosis. In both instances, transbronchial biopsy results were available only after the BAL results were reported and the second questionnaire was completed. In both instances, the transbronchial biopsy results later confirmed the diagnosis of sarcoidosis.

Among the four patients in whom inappropriate diagnostic changes occurred after BAL, none of the changes was clinically impressive; in no instance was the final correct diagnosis eliminated from consideration by the BAL fluid analysis results. Finally, no clinically impressive change occurred in five patients for whom some diagnostic changes were appropriate and others not.

**DISCUSSION**

The results of this study show that when clinicians used BAL differential cell counts to evaluate patients with interstitial lung disease, diagnostic impressions were changed frequently (59 percent of the time) by learning the results of the available BAL fluid analysis. Most changes (52 percent) in physicians' diagnostic impressions or plans, or both, were appropriate, as were all the clinically impressive changes. Although infrequent, these impressive changes included the surprise diagnosis of P. carinii pneumonia in a patient not suspected to have AIDS, and the avoidance of unnecessary invasive tests (ie, open lung biopsy and mediastinoscopy). It is noteworthy that because clinicians' answers to the follow-up questionnaires were elicited before the results of transbronchial biopsies became available, this study isolates the impact of BAL results, which was clinically impressive in these three cases. Although transbronchial biopsies also were done (two patients) and confirmed the suspected diagnoses, the clinicians had already decided to forego subsequent invasive tests by the time the confirmatory biopsies became available. Although these decisions would have remained appropriate had the transbronchial biopsies not been done, the current data do not infer that BAL makes transbronchial biopsy unnecessary. Overall, our findings suggest that BAL cell analysis can sometimes improve physicians' evaluations of diffuse interstitial lung disease in their nonim-
munocompromised patients.

While many investigators have evaluated the characteristics of BAL fluid in patients with opportunistic infections and in a variety of noninfectious interstitial lung diseases, we can identify only a single study that considers the impact of BAL on clinicians' diagnostic reasoning. Unlike our analysis, Studny and co-workers performed a Bayesian analysis to assess the predictive value of BAL differential cell counts for diagnosing sarcoidosis and tuberculosis. The current study examines the diagnostic impact of BAL in a different way and in a broader array of interstitial processes.

Impressive diagnostic changes were infrequent in this report, but two study conditions may have caused these results to underestimate the full diagnostic value of analyzing BAL fluid. First, the BAL fluid analyses that were performed in this study were limited to total cell counts, differential cell counts, and any incidental microbiologic findings. However, many other reports suggest that characterizing immunoglobulin levels and lymphocyte subpopulations in BAL fluid may add further diagnostic information. For example, sarcoidosis and hypersensitivity pneumonitis may share a lymphocytic alveolitis but may be differentiated by additional features, eg, lavage fluid in hypersensitivity pneumonitis, but not sarcoidosis, usually shows an increase of suppressor lymphocytes. Other recent reports suggest that the hyaluronate content of lavage fluid may be a useful marker for sarcoidosis. Thus, more extensive analysis of the specimens may have provided more discriminating information.

A second reason that this study may have underestimated the diagnostic value of BAL is that for 40 of the 51 patients whose final diagnoses were determined (23 of whom had sarcoidosis), the clinician already favored the correct final diagnosis even before the lavage was done. Under circumstances where the correct final diagnosis was favored even before lavage was done, the BAL fluid analysis had limited opportunity to advance the correct diagnosis, so the study may underestimate the impact of BAL. The study also does not permit conclusions about the diagnostic impact of BAL in those 27 patients for whom a final diagnosis remained unknown.

Although impressive changes following BAL were infrequent in this series, those patients who were spared surgical biopsies benefited substantially; the results of BAL fluid analysis obviated their physicians' plans for more invasive and morbid procedures.

An important goal of the current research is to identify patients for whom the results of BAL fluid analysis are most likely to be useful in directing the diagnostic evaluation. The study confirms that BAL is a simple addition to planned bronchoscopy in patients with suspected sarcoidosis, but the findings suggest that a major impact on physicians' diagnostic thinking may be limited to a minority of such patients. In other circumstances—as when the clinician must decide between several equally likely diagnoses—our experience suggests that lavage will be most useful for patients whose contending diagnoses are likely to have different BAL profiles, eg, a lymphocyte-predominant alveolitis vs a neutrophil-eosinophil alveolitis. For example, in the older patient for whom nongranulomatous and granulomatous disease are equally contending possibilities, BAL may be the least invasive, nonserologic way to attempt to distinguish these two diagnostic possibilities. In such a patient, the safety of BAL performed at the time of transbronchial biopsy, especially when compared to the risk of more invasive procedures, makes lavage an especially attractive procedure.

It is important to assess the issue of cost vs benefit before advocating a procedure for evaluating patients. Our study does not answer definitely whether pulmonary physicians should perform BAL as a routine part of their evaluation of patients with interstitial lung disease. In our laboratory, patients are not charged for the BAL differential cell counts, and we believe that performing BAL is clinically justified when bronchoscopy is already planned to evaluate interstitial lung disease. However, if patients were to be charged, a more detailed cost-benefit analysis would be necessary before a broader recommendation could be made.

In addition to these conclusions about BAL, this study contributes a new method for evaluating diagnostic tests. Unlike sensitivity, specificity, or predictive values, the method used here assesses whether test information actually advances the clinician's correct diagnosis or appropriately changes plans for further testing or treatment. Also, unlike more conventional test measures, this new approach examines the effect of test information on the perceived likelihood of contending diagnoses. Knowing patients' final pathologic diagnosis made it possible to determine the appropriateness of any diagnostic change that occurred in this study.

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