Making Sense of Bronchoalveolar Lavage Lymphocytosis in Fibrotic Interstitial Lung Disease

Christopher J. Ryerson, M.D.*

Department of Medicine, University of British Columbia and Centre for Heart Lung Innovation, St. Paul's Hospital, Vancouver, British Columbia, Canada

Clinicians managing patients with fibrotic interstitial lung disease (ILD) exert substantial effort collecting and integrating various clinical, radiological, and serological data; however, these findings are frequently inconclusive even when comprehensively examined by a multidisciplinary panel of experts (1). It is often recommended that patients with an unclear etiology for their ILD undergo a surgical lung biopsy, but this is associated with significant potential complications, including a nonnegligible risk of death (2). Transbronchial lung cryobiopsy is a promising, less-invasive approach to sampling lung tissue (3), but this can yield misleading results in some settings and has variable risk of complications (4).

Bronchoalveolar lavage (BAL) is frequently used in patients with newly identified ILD, sometimes eliminating the need for a lung biopsy. There is little doubt that BAL is useful in patients with an abrupt onset of nonfibrotic ILD, with a variety of potential findings that are diagnostically informative (e.g., eosinophilia, alveolar hemorrhage) (5). BAL is also performed in this situation to identify or exclude active infections that could be causing or at least contributing to the clinical picture. BAL is similarly helpful for excluding infection in patients with a chronic fibrotic ILD who have rapid worsening and superimposed ground glass on chest imaging (6), but the utility of BAL cellular analysis in distinguishing various subtypes of fibrotic ILD is somewhat less certain.

The role of BAL in the evaluation of patients with ILD was one of the key questions addressed in a recent clinical practice guideline focused on the diagnosis of hypersensitivity pneumonitis (HP) (7). For each key question, a comprehensive systematic review was conducted to provide the guideline committee with available evidence on which to base recommendations for or against each diagnostic tool of interest. These recommendations are provided in the guideline itself, together with a brief narrative explaining the key findings of each systematic review and meta-analysis. In this issue of *AnnalsATS*, the purpose of the article by Patolia and colleagues (pp. 1455–1467) is to provide a more thorough description of the methods employed in the BAL component of the guideline as well as to provide a detailed description of the key findings from the 84 publications that provided data for various components of this key question (8). The separate publication of this article thus provides opportunity to explore the evidence in a way that is not feasible within a guideline that succinctly addresses a multitude of clinically relevant questions.

The guideline committee voted nearly unanimously in favor of performing BAL to help distinguish HP from other ILDs (7), with a stronger "recommendation" for patients with nonfibrotic disease (voting 30 in favor to 1 against) compared with the weaker "suggestion" for patients with fibrotic disease (voting 28 to 3). The recommendation to use BAL in nonfibrotic HP was based on the very high percentage for BAL lymphocytes in nonfibrotic HP, which is helpful in its own right, as well as on the potential for BAL to identify other nonfibrotic ILDs or an active infection that can present similarly. At first glance, the suggestion for BAL in fibrotic HP also makes perfect sense. In the 12 studies directly comparing fibrotic HP with idiopathic pulmonary fibrosis (IPF), which is commonly considered the most frequent and challenging diagnostic dilemma encountered by ILD clinicians, there was a relatively high mean difference of 21% in the BAL lymphocyte percentage (95% confidence interval, 14–27%). This difference seems large enough to be clinically useful, but diving into the details of this meta-analysis raises some interesting questions. Most notably, despite the substantial mean difference, the area under the receiver-operating-characteristic curve (AUC) is only 0.54 when data from these same studies were pooled for this purpose. This exceptionally poor AUC would suggest the contradictory conclusion that using BAL lymphocytosis to distinguish fibrotic HP from IPF is not much better than flipping a coin.

The discrepancy in these measurements prompted the authors to check their results multiple times, with the suggested primary explanation being the high standard deviations (SDs) observed for the BAL lymphocyte percentage in both the population with fibrotic HP and the population with IPF within each study. This high SD results in substantial overlap of the BAL lymphocyte percentage in these two populations, thus limiting the potential use of this measure to distinguish these two diagnoses, despite the impressive mean difference. An additional likely contributing factor is the variable BAL lymphocyte percentages across the included studies. We can consider two hypothetical studies as a

*C.J.R. is Deputy Editor of *AnnalsATS*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

DOI: 10.1513/AnnalsATS.202007-818ED

simple example. In one study, patients have a mean BAL lymphocyte percentage of 15% in fibrotic HP compared with 5% in IPF, with a mean difference of 10%. In a second study, these same values are 45% and 15%, with a mean difference of 30%. A crude pooling of the mean difference of these two studies yields an average mean difference of 20%, similar to what was observed on the basis of the real data. However, if we consider a single patient with a lymphocyte percentage of 15%, the first study would suggest a diagnosis of HP, whereas the second would suggest a diagnosis of IPF. This type of variability in the lymphocyte percentages across the meta-analyzed studies, in addition to the high SD within each ILD subtype, thus results in the calculated AUC from these pooled studies being much lower than what might be expected.

What do these findings mean to clinicians and their patients? First, they suggest that the average patient with fibrotic HP does in fact have a higher BAL lymphocyte percentage than the average patient with IPF. However, there is also sufficient variability in the BAL lymphocyte percentage within and across studies that prohibits identification of a specific threshold that consistently distinguishes fibrotic HP from IPF. This limitation indicates the need for clinicians to consider any recommendation for a specific BAL lymphocyte threshold within the context of their own patient population (9), requiring a thorough understanding of the local performance characteristics of this test. For example, different causes and acuities of HP may have different BAL lymphocyte percentages, with these factors likely varying from one region to another. There are also frequent differences in how BAL is performed that might similarly impact findings (e.g., instilling a minimum volume, preferential sampling of specific areas, discarding the first returns). Finally, it is also important for clinicians to understand that incorporation bias and confirmation bias can lead to overly optimistic estimates of local performance characteristics as easily as they can bias studies.

Although BAL was recommended by the guideline committee, the results of this systematic review and meta-analysis show that BAL findings can be highly variable in fibrotic ILD and confirm that BAL should only be considered one piece of the diagnostic puzzle. Additional high-quality data are therefore still needed to help standardize BAL and demonstrate its performance characteristics in patients with fibrotic ILD. Completing such a study, which is made more feasible with the increasing use of cryobiopsy, would help convince remaining skeptics and allow all clinicians to more fully appreciate the advantages and potential limitations of BAL cellular analysis in the evaluation of patients with fibrotic ILD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Guler SA, Ellison K, Algamdi M, Collard HR, Ryerson CJ. Heterogeneity in unclassifiable interstitial lung disease: a systematic review and meta-analysis. *Ann Am Thorac Soc* 2018;15:854–863.
2 Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States: 2000 to 2011. *Am J Respir Crit Care Med* 2016;193: 1161–1167.
3 Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, *et al*.; Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance (COLDICE) Investigators. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020;8:171–181.
4 Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease: a systematic review and metaanalysis. *Ann Am Thorac Soc* 2016;13:1828–1838.
5 Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, *et al*.; American Thoracic Society Committee on BAL in Interstitial Lung Disease. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012;185: 1004–1014.
6 Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis: an international working group report. *Am J Respir Crit Care Med* 2016; 194:265–275.
7 Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, *et al*. Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020;202: e36–e69.
8 Patolia S, Tamae Kakazu M, Chami HA, Chua A, Diaz-Mendoza J, Duggal A, *et al*. Bronchoalveolar lavage lymphocytes in the diagnosis of hypersensitivity pneumonitis among patients with interstitial lung disease. *Ann Am Thorac Soc* 2020;17: 1455–1467.
9 Morisset J, Johannson KA, Jones KD, Wolters PJ, Collard HR, Walsh SLF, *et al*.; HP Delphi Collaborators. Identification of diagnostic criteria for chronic hypersensitivity pneumonitis: an international modified Delphi survey. *Am J Respir Crit Care Med* 2018;197: 1036–1044.