

make a confident provisional clinical diagnosis (1) (with confirmation by mandated follow-up), thus sparing individuals with S1S, who comprise the vast majority of subjects presenting with ABHL, from an invasive procedure. In the 50+ years since its publication, to my knowledge, not a single verified exception has been published. The decision to proceed thus rests on a quantitative assessment: What proportion of ABHL is caused by AD? What is the benefit of their earlier ascertainment? How many persons with ABHL must undergo an invasive procedure to confirm an AD? What are the harms and costs of a confirmatory invasive procedure?

I reviewed the abstract or text of the case series cited by the authors of the guideline policy (2) and found that most confounded their analysis by conflating BHL with cases demonstrating radiographically evident mediastinal lymphadenopathy, a feature characteristic of lymphoma. Collectively, they reported 1.96% with an AD, more than 100-fold a prior estimate in which ADs presented as ABHL (3). None furnished a documented instance. Some guideline authors commented on rare reports of metastatic hypernephroma presenting in this fashion. Because earlier diagnosis confers no material benefit, we did not consider it an AD. Based on the product of the incidence and radiographic presentation of AD, we estimated that they comprise $\leq 0.05\%$ of persons presenting with ABHL (3). We reported that a delay in diagnosis of lymphoma would have, at most, a trivial effect on its course, that primary TB was typically unilateral and self-limited in 95% of cases, and that both lymphoma and progressive primary TB would become evident during mandated follow-up.

Major complications of transbronchial needle aspiration (TBNA) appear to be infrequent, but, absent a reporting requirement or incentive, they cannot be quantified.

Under the assumption that our estimate of the positive predictive value of a clinical diagnosis of S1S based on ABHL underestimated AD by a twofold order of magnitude (i.e., $\leq 0.05\%$ vs. 1.96%), that TBNA is 100% sensitive for AD and sarcoidosis, that it is complication free, and that the procedural (99–232) charge is \$5,000, if 102 persons with ABHL were submitted to TBNA, the net charge would be a half-million dollars, 100 would receive no offsetting, tangible benefit, and 2 would be found to have a lymphoma or TB. Under our estimate of $\leq 0.05\%$ AD, under the same assumptions, if 10,005 persons with ABHL underwent TBNA, the net charge would be 50 million dollars, 10,000 would receive no tangible benefit, and, at most, 5 persons with an AD might be marginally benefitted by an earlier diagnosis (vs. mandated clinical follow-up).

Tissue confirmation of S1S is indicated in the occasional patient with high-risk history (e.g., lymphoma, renal cell carcinoma, or TB exposure), but, because of the extreme rarity with which an AD (whose earlier diagnosis would be materially beneficial) presents in this fashion, tissue confirmation is not required; it imposes numerous individuals destined to spontaneous resolution to an invasive and costly procedure not offset by commensurate benefit. In the exquisitely rare individual (none have been reported!) with an AD simulating S1S, the diagnosis will become evident with routine, mandated follow-up with trivial to no harm imposed by the diagnostic delay.

The disproportion between potential benefits versus collective harms (including the procedure as a harm) and costs strongly favor a provisional clinical diagnosis of S1S over tissue confirmation. ■

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References

1. Winterbauer RH, Belic N, Moores KD. Clinical interpretation of bilateral hilar adenopathy. *Ann Intern Med* 1973;78:65–71.
2. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;201:e26–e51.
3. Reich JM, Brouns MC, O'Connor EA, Edwards MJ. Mediastinoscopy in patients with presumptive stage I sarcoidosis: a risk/benefit, cost/benefit analysis. *Chest* 1998;113:147–153.

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Reply to P. B. et al., to Fahim and Rosewarne, and to Reich



From the Authors:

The American Thoracic Society (ATS) Sarcoidosis Diagnosis and Detection Guideline Committee relishes the engagement of the sarcoidosis community and would like to sincerely thank correspondents of these three letters for their care of patients with sarcoidosis, contributions to sarcoidosis research, and raising these excellent discussion points.

Notably, ATS guideline development follows strict Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology to ensure that the highest level of evidence is reviewed and synthesized. As a corollary to this rigorous method, a limited number of key questions with highest clinical impact to the field of sarcoidosis and for which sufficient supportive data were available were selected for a comprehensive search and review of the literature. Therefore, a number of compelling questions, such as the utility of cervical lymph node biopsy, were not selected for review. In this regard, we are indebted to the ATS methodologists and ATS librarian who searched and reviewed thousands of publications for this guideline.

We certainly appreciate the suggestion to consider cervical lymph node biopsy in patients suspected of having sarcoidosis as proposed by Fahim and Rosewarne. Lower procedure risk and cost

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The authors are the co-chairs of the official American Thoracic Society Document entitled, "Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline."

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to the patient as well as potentially lower risk of infectious exposure to health care providers are important aspects of this approach. Addressing cervical lymph node biopsy for the diagnosis of sarcoidosis is an excellent suggestion for future guidelines. In the interim, we encourage the accumulation of data from additional studies to provide a more robust evidence base to evaluate the procedure in the context of a guideline.

The committee further notes that the ATS standard for guideline rigor includes tightly framing each research question using patient/intervention/comparator/outcome (PICO) methodology. Thus, the recommendation for endobronchial ultrasound–guided transbronchial needle aspiration over mediastinoscopy did not include review of all possible alternative methods of endoscopic ultrasound technique. We appreciate and agree with the benefits raised by P. B. and colleagues of potentially improved procedural tolerance of esophageal endoscopic approaches such as endoscopic ultrasound with fine needle aspiration (EUS-FNA) compared with bronchoscopic approaches. We note that three of the studies selected for the question about mediastinal/hilar lymph node sampling versus no sampling featured EUS-FNA studies (1–3). Compared with endobronchial ultrasound, the number of thoracic lymph nodes that can be sampled via an esophageal approach is more limited. In addition, the majority of interventional pulmonologists do not routinely perform EUS-FNA or endoscopic ultrasound using echobronchoscope. For these reasons, we did not feel it reasonable to include these modalities in our recommendation on endoscopic approaches to biopsy in comparison to traditional mediastinoscopy. Advances in the evidence base for the safety and efficacy of these varied approaches could be addressed in future guidelines.

We also appreciate Dr. Reich's contributions to the field of sarcoidosis, including the nuanced risk and cost analysis in his letter to the editor favoring no biopsy of asymptomatic bilateral hilar lymphadenopathy (ABHL) based on his original meta-analysis of the sarcoidosis literature of the 20th century, in which higher risk mediastinoscopy of mediastinal lymph nodes present at the time of ABHL was the biopsy technique (4). The challenge for clinicians and patients remains that not a single clinical study has been published in the contemporary literature on the narrowly defined topic of ABHL in the absence of mediastinal lymphadenopathy. Thus, the committee considered 16 studies that enrolled a total of 425 patients with asymptomatic radiographic stage I sarcoidosis, comprising patients who have ABHL and who may also have asymptomatic mediastinal lymph node enlargement. These studies capture center-to-center variation in practice and patient populations as well as a range of techniques to sample lymph nodes. They adequately document the existence of alternative diagnoses that mimic stage I sarcoidosis. The rate of alternative diagnoses (8 of 425, or 1.9%) is low, yet it is not trivial, and the alternative diagnoses of tuberculosis (TB) and lymphoma are of particular import to patients, who were represented by a patient advocate on the clinical practice guideline committee. In addition, the presumptive diagnosis of sarcoidosis engenders lifelong screening and clinical follow-up for emergence of multisystemic disease, prompting significant concern for some patients and thus reduction in long-term quality of life and increased cost to patients. Thus, the clinical practice guidelines committee did not make a recommendation for or against biopsy in the setting of ABHL, and our recommendations conform with those of Dr. Reich's based on the premise that close clinical follow-up is the key to safely recommending a nonbiopsy

approach. However, we also recognize that some patients have limited access to health care because of socioeconomic healthcare disparities and the decentralized nature of our American health system, such that close follow-up may not be realistic in all cases.

In sum, we have found an overall paucity of high-quality evidence for or against biopsy of stage I sarcoidosis, with an overall detection rate of 85% for sarcoidosis, 11% nondiagnostic, and 2% alternative diagnosis including TB and lymphoma, using the full range of contemporary biopsy techniques (5). The present guideline is rooted in a decision by our multidisciplinary committee to recommend that an individualized patient/healthcare provider choice regarding biopsy can be made. Key factors guiding this personalized decision include the risk profile of the preferred/available biopsy technique; patient preference; the community prevalence of alternative infectious disease such as TB, histoplasmosis, or coccidioidomycosis; the patient's cancer and occupational/exposure history; and the ability to closely follow for development of symptoms if biopsy is not performed. We acknowledge in research statements throughout this guideline that more high-quality data is sorely needed to guide these important decisions. We encourage members of the sarcoidosis research community to address these questions in future publications to inform future sarcoidosis clinical practice guidelines. ■

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References

1. Oki M, Saka H, Kitagawa C, Kogure Y, Murata N, Adachi T, *et al*. Transesophageal bronchoscopic ultrasound-guided fine needle aspiration for diagnosis of sarcoidosis. *Respiration* 2013;85:137–143.

- von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, in 't Veen JC, *et al.* Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. *JAMA* 2013;309:2457–2464.
- Iwashita T, Yasuda I, Doi S, Kato T, Sano K, Yasuda S, *et al.* The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis. *Endoscopy* 2008;40:400–405.
- Reich JM, Brouns MC, O'Connor EA, Edwards MJ. Mediastinoscopy in patients with presumptive stage I sarcoidosis: a risk/benefit, cost/benefit analysis. *Chest* 1998;113:147–153.
- Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, *et al.* Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;201:e26–e51.

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Short-Acting β_2 -Agonist Use Could Be a Confounding Factor for Interpreting Increased IL-6

To the Editor:

The proinflammatory cytokine IL-6 is upregulated approximately threefold during naturally occurring asthmatic attacks (1). Importantly, in relation to overuse of β_2 -agonists in the context of asthma exacerbations, IL-6 induction by rhinovirus was further augmented by β_2 -agonists (2). *In vitro* studies on bronchial epithelial cells demonstrated that IL-6 is upregulated by β_2 -agonists (3).

SARP (Severe Asthma Research Program) enrollment procedures determined that participants maintained medications for asthma as prescribed by their care provider (4). I could not find details on the asthma medications use in the SARP III trials (4, 5). Peters and colleagues (5) did not address the possibility that β_2 -agonist use might be confounding the association between plasma IL-6 and higher asthma exacerbation rates. Knowledge about the asthma medication and ideally about the blood levels of β_2 -agonists is needed to exclude any influence of β_2 -agonists on the increment of IL-6 increase before adopting it as an exacerbation-prone biomarker.

Jevnikar and colleagues (6) recently described a subset of patients with asthma and high IL-6TS. This subset constitutes a novel asthma phenotype associated with frequent exacerbations, eosinophilia, airway inflammation, remodeling, and impaired epithelial integrity. It was noted that 86% of the patients of U-BIOPRED (Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes) cohorts used short-acting β_2 -agonists and that 98% of the patients used long-acting β_2 -agonists (7), but the authors did not take into account this probable confounding factor.

I would like to alert the authors of both studies that IL-6 could be upregulated by overuse of β_2 -agonists. ■

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References

- Yokoyama A, Kohno N, Fujino S, Hamada H, Inoue Y, Fujioka S, *et al.* Circulating interleukin-6 levels in patients with bronchial asthma. *Am J Respir Crit Care Med* 1995;151:1354–1358.
- Ritchie AI, Singanayagam A, Wiater E, Edwards MR, Montminy M, Johnston SL. β_2 -agonists enhance asthma-relevant inflammatory mediators in human airway epithelial cells. *Am J Respir Cell Mol Biol* 2018;58:128–132.
- Johnston SL, Edwards MR. Mechanisms of adverse effects of β -agonists in asthma. *Thorax* 2009;64:739–741.
- Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, *et al.* Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract* 2018;6:545–554, e4.
- Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, *et al.*, NHLBI Severe Asthma Research Program. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. *Am J Respir Crit Care Med* 2020;202:973–982.
- Jevnikar Z, Östling J, Ax E, Calvén J, Thörn K, Israelsson E, *et al.*; Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes study group. Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation. *J Allergy Clin Immunol* 2019;143:577–590.
- Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, *et al.*; U-BIOPRED Study Group. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015;46:1308–1321.

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Systemic IL-6 and Severe Asthma

To the Editor:

We read with interest the findings of Peters and colleagues in patients with severe asthma who reported that an increase in baseline circulating IL-6 levels of 1 pg/ μ l was associated with a 10% increased risk of an exacerbation over 3 years and was 14% when excluding patients on oral corticosteroids (1). Elevated levels of IL-6 in induced sputum in patients with asthma are related to impaired lung function (2, 3).

IL-6 is also a key component of the cytokine response in viral illness. For example, in hospitalized patients with severe coronavirus disease (COVID-19), circulating levels of IL-6 are the strongest predictor of the need for mechanical ventilation. In the *in vitro* murine model of acute lung

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