

challenge tests [editorial]. *Am J Respir Crit Care Med* 2018;198:988–990.

- Coates AL, Wanger J, Cockcroft DW, Culver BH, Carlsen KH, Diamant Z, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. *Eur Respir J* 2017;49:1601526.

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Reply to Amirav and Newhouse

From the Authors:

We thank Drs. Amirav and Newhouse for their letter and interest in our editorial on characterizing nebulizer performance for methacholine challenge tests (1). We respectfully disagree with the premise of their letter. We believe that the science and clinical relevance of the previous 1999 guidelines need to be updated. The main problem is that the English-Wright nebulizer is no longer widely available, and if pulmonary function labs were to use as a substitute currently available nebulizers that have much higher aerosol output than the English-Wright nebulizer, every concentration step would deliver a much higher stimulus dose than intended by the 1999 guidelines.

Regarding the need to calculate a delivered methacholine dose, the authors state that we offered no mechanism for how to compel nebulizer manufacturers to characterize the performance of their nebulizer. This was, in fact, the main purpose of our letter: to call out to the manufacturers to provide this essential service. We acknowledged that this would be beyond the capabilities of most pulmonary function labs, but it should be very much achievable by nebulizer manufacturers and aerosol scientists. Our hope was that this letter would emphasize to manufacturers that the American Thoracic Society and European Respiratory Society are counting on them to help the pulmonary function lab community.

The authors also suggest that the data cited regarding the comparison of the English-Wright nebulizer with other nebulizers should include information about other commonly used nebulizers. We certainly agree, and remain hopeful that such data will be forthcoming. The data we cited, including those obtained with a vibrating mesh nebulizer, were simply meant as examples of how dose, not concentration, should be the common unit of measurement across devices.

Regarding the point made about how the current recommendations might not provide more clinically relevant information, we would like to emphasize that at present there is significant variability in the way methacholine challenge tests are performed, resulting in the potential for imprecision and diagnostic error. No other diagnostic test in modern medicine would allow such a lack of rigorous standards or interlaboratory variation. With

better defined and updated methodology, physicians can now have more confidence in the results of testing. ■

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Reference

- Coates A, Culver B, Cockcroft D, Hallstrand T, Haynes J, Kaminsky D, et al. Characterizing nebulizer performance for methacholine challenge tests [editorial]. *Am J Respir Crit Care Med* 2018;198:988–990.

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Interstitial Lung Disease and Mediastinal Lymph Nodes: A Computed Tomography–based Biomarker beyond Nosological and Etiological Borders?

To the Editor:

We read with great interest the article by Adegunsoye and colleagues (1) recently published in the *Journal*. Using a rigorous

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multivaluated protocol, the authors demonstrate that mediastinal lymphadenopathy (MLA) is a strong predictor of clinical outcomes in interstitial lung disease (ILD), which is considered, in this article, to be a unique heterogeneous entity that includes idiopathic pulmonary fibrosis (IPF), interstitial pneumonia with autoimmune features, chronic hypersensitivity pneumonitis, connective tissue disease associated with ILD (CTD-ILD), and unclassifiable ILD. The strong prognostic value of MLA for survival in ILD could have important implications for patient stratification in the future. Nonetheless, considering ILD to be a unique entity may become partly irrelevant for the interpretation of results on plasmatic biomarkers. For example, based on their results and those of ongoing trials in IPF, the authors suggest that IL-6 might be protective in fibrotic ILD (1). This statement might be tempered, especially when considering CTD-ILD, as IL-6 may constitute a therapeutic target in scleroderma-associated ILD, with a recent clinical trial of tocilizumab reporting promising results regarding pulmonary involvement (2). From a pathogenetic and nosological viewpoint, separating each ILD subgroup may therefore remain relevant.

Beyond prognostic and therapeutic considerations, Adegunsoye and colleagues' results may have far-reaching heuristic consequences, and raise the issue of the precise etiology and pathogenesis of MLA in ILD. In their work, obvious causes of MLA were carefully ruled out, as sarcoidosis, drug toxicity-related ILD, and cancers were excluded. Nonetheless, although age and sex were included in the multivariable Cox regression model (Table 2 in Reference 1), the possible role of chronic heart failure as a concurrent etiology of MLA (3), as well as a cause of all-cause hospitalization and/or respiratory hospitalization and/or death, cannot be completely excluded. This hypothesis is supported by the significant difference ($P = 0.028$) in the prevalence of coronary heart disease between patients with and without MLA (Table 1 in Reference 1). This is particularly true when considering the association of MLA with greater aorta and pulmonary artery diameters, male sex, older age, and tobacco use. Although we do not assume that heart failure alone may explain the strong prognostic value of MLA in ILD, exploring the association of MLA with cardiac biomarkers such as N-terminal pro-B-type natriuretic peptide levels (3) and their respective prognostic values may help to clarify this issue.

From an etiological viewpoint, this specific focus on MLA may bring back into light neglected causes of ILD with MLA, such as dust exposures. No mention is made of pneumoconiosis in Adegunsoye and colleagues's work. The higher prevalence of MLA in men (Table 1 in Reference 1), in addition to the well-known association between occupational dust exposures and male sex, also highlights this issue. Recent studies have pointed out that the prevalence of crystalline silica exposure in CTD-ILD may be undervalued (4). There is growing interest in the involvement of environmental airborne contaminants in ILDs of unknown etiology, such as IPF (5), as well as in CTD-ILD (4) and other fibrotic ILDs such as pulmonary alveolar proteinosis with fibrotic features (6). Beyond size, location, and number, obtaining a thorough description of MLA, with specific attention paid to density and calcifications, may offer new insights into the complex relationship between exposure to airborne contaminants and ILD. Histological examinations of MLA in ILD may also help to clarify the immune processes at stake. As was

recently suggested with regard to pulmonary alveolar proteinosis of autoimmune origin, *dysimmune* is not synonymous with *idiopathic* (6). Therefore, further studies are needed to better elucidate the specific etiologies of MLA in ILD of unknown origin. In the end, this could help to refine the current nosological classification of these diseases and possibly improve the search for a proper cause, leading to efficient preventive measures. ■

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References

1. Adegunsoye A, Oldham JM, Bonham C, Hrusch C, Nolan P, Klejch W, *et al.* Prognosticating outcomes in interstitial lung disease by mediastinal lymph node assessment: an observational cohort study with independent validation. *Am J Respir Crit Care Med* [online ahead of print] 14 Sep 2018; DOI: 10.1164/rccm.201804-0761OC.
2. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, *et al.* Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016;387:2630–2640.
3. Ngom A, Dumont P, Diot P, Lemarié E. Benign mediastinal lymphadenopathy in congestive heart failure. *Chest* 2001;119: 653–656.
4. Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, *et al.* Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmun Rev* 2014;13:151–156.
5. Winterbottom CJ, Shah RJ, Patterson KC, Kreider ME, Panettieri RA Jr, Rivera-Lebron B, *et al.* Exposure to ambient particulate matter is associated with accelerated functional decline in idiopathic pulmonary fibrosis. *Chest* 2018;153:1221–1228.
6. Ronsmans S, Nemery B. The presence of autoimmune antibodies in pulmonary alveolar proteinosis does not necessarily imply idiopathic disease. *Lancet Respir Med* 2018;6:e48.

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Prognostic Impact of Mediastinal Lymph Nodes in Interstitial Lung Diseases: Is Environmental Exposure the Offender?

To the Editor:

We read with great interest the work of Adegunsoye and colleagues showing a significant association between enlarged mediastinal lymph nodes (MLNs) on chest computed tomography and survival in patients with interstitial lung diseases (ILDs) (1). They report a 66% prevalence of enlarged MLNs according the type of ILD, with various potential causes of development as previously pointed out. The authors raise the hypothesis that enlarged MLNs may be reflective of underlying immunologic phenomena in lung tissue, which in turn contribute to the pathophysiology of disease progression in pulmonary fibrosis. However, we suggest that the potential involvement of environmental exposures in ILDs, particularly anthracosis, should be discussed. Anthracosis caused by coal dust and other environmental factors such as air pollution, biomass fuels used extensively for cooking (“hut lung”), and cigarette smoking is also known to be a source of damage in MLNs (2).

A broad array of inhaled exposures are risk factors for developing an ILD, particularly idiopathic pulmonary fibrosis (IPF) in genetically susceptible patients (3). Inhaled agents are known to induce a series of lesions in alveolar epithelial cells, causing a

biochemical oxidant injury and thereafter an immunological response when healing mechanisms (e.g., inflammation, coagulation, and epithelial repair) are put in place, resulting in pulmonary fibrosis. It is very likely that MLNs are involved in this process. Indeed, autopsy studies have revealed higher levels of inorganic particles, such as silicon and aluminum, in the MLNs of patients with IPF compared with controls (3).

Interestingly, inhalation of occupational dusts may be an aggravating factor associated with a poor prognosis in several diseases, and particularly in IPF. In a large Korean cohort of patients with IPF, Lee and colleagues evaluated the prognosis of IPF according to the patients’ work and found that the wood or chemical dust–exposure group showed the worst outcomes (4). This group displayed a greater annual decline in FVC% and a higher mortality compared with nonexposed patients, with a hazard ratio of 1.813 (95% confidence interval [CI], 1.049–3.133, $P = 0.033$) (4). Based on U.S. death certificates from 1999 to 2003, Pinheiro and colleagues identified three industry categories with potential exposure to wood and metal dust that were associated with statistically significant risk estimates for IPF mortality: fabricated structural metal products (mortality odds ratio [MOR], 1.7 [95% CI, 1.0–3.1]), metal mining (MOR, 2.2 [95% CI, 1.1–4.4]), and wood buildings and mobile homes (MOR, 5.3 [95% CI, 1.2–23.8]) (5). Gold and colleagues examined potential associations of occupational exposures with the risk of mortality from systemic autoimmune diseases, using U.S. death certificates from 26 states (6). Farming occupation was associated with death from any systemic autoimmune disease (odds ratio [OR], 1.3 [95% CI, 1.2–1.4]), mining machine operators were at increased risk of death from systemic lupus erythematosus (OR, 1.8 [95% CI, 1.2–2.7]), and risk of death from systemic sclerosis was associated with usual occupation as industrial machinery repairers (OR, 2.3 [95% CI, 1.4–3.9]).

Enlarged MLNs in ILDs may be at least in part a marker of occupational or environmental exposure. Thus, we may hypothesize that the prognostic impact of MLNs observed in the study by Adegunsoye and colleagues could be related to the negative effects of unrecognized exposures. It would have been interesting to look at the patients’ occupational potential exposures, and ideally to perform a cytological analysis of MLNs to verify the presence or absence of lymph node anthracosis or anthracofibrosis in these patients. ■

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