macrophages (7), which are also elevated in the *Chlamydia* SRA model, but neutrophils themselves have also been reported to release IL-1β via this pathway (8, 9). In the current study, IL-1β expression correlates with neutrophilia in both murine models and clinical samples, but is this solely because the IL-1β is driving the neutrophilia or are neutrophils themselves also producing IL-1β, thereby promoting a vicious circle of inflammation? Given the abundance of neutrophils in the SRA models, it is pertinent that neutrophil-derived proteases can also activate any extracellular pro–IL-1β and enhance and amplify the initial caspase-1–mediated activation (10), and thus may further perpetuate IL-1β–driven inflammation. Furthermore, what are the signals that are driving both the expression and activation of the NLRP3 inflammasome complex within these infection-induced SRA models? It would be interesting to determine whether a similar mechanistic pathway underlies the severe pathology induced by viral exacerbations of asthma. It is estimated that the majority of exacerbations are induced by common respiratory viruses such as rhinovirus or respiratory syncytial virus—particularly in children. Although the immune response to viruses and bacteria are different, both types result in recruitment of neutrophils, and thus similar pathways may operate to induce pathology.

Severe, steroid-resistant, neutrophilic asthma remains a clear unmet need in asthma management, and thus these studies detailing the therapeutic potential of targeting the NLRPR3/IL-1β pathway are of clear translational interest. Kim and colleagues demonstrate the therapeutic efficacy of targeting the NLRP3 inflammasome pathway at various levels, be it inhibition of caspase-1 or NLRP3 itself or IL-1β antagonism (4). As with all antiinflammatory strategies, there is always an inherent risk of compromising host defense, and yet adverse infectious events are seemingly rare in patients in whom IL-1β signaling has been perturbed (11). Nonetheless, given the specific involvement of the NLRP3 inflammasome in driving SRA, it may be prudent to assess the therapeutic potential of selective NLRP3 inhibitors, such as MCC950, in the clinic rather than strategies that will affect global IL-1β production from all inflammasome complexes. Regardless, these exciting studies by Kim and colleagues highlight a clear rationale to reduce IL-1β availability to ameliorate neutrophilic SRA (4). ■

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Robert J. Snelgrove, Ph.D.
Clare M. Lloyd, Ph.D.
National Heart and Lung Institute
Imperial College London
London, United Kingdom

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One-off Spirometry Is Insufficient to Rule In or Rule Out Mild to Moderate Chronic Obstructive Pulmonary Disease

Making an accurate diagnosis of chronic obstructive pulmonary disease (COPD) matters. For those affected, it is the initial step in accessing appropriate interventions. First and foremost, this should start by minimizing future inhaled exposures. Similarly, for those not affected, excluding COPD avoids unnecessary prescription of drugs that would have no benefit, are costly, and may have side effects and can prompt a search for alternative diagnoses. Everyone, wherever they live in the world, deserves access to an accurate COPD diagnosis.

So far so good—but it turns out making an accurate diagnosis of COPD is not straightforward. First, COPD exists as part of a spectrum of lung disease arising when a genetically susceptible individual is exposed to sufficient inhaled environmental toxin. Large airway involvement is characterized by cough and sputum

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leading to the clinical diagnosis of chronic bronchitis. Destructive alveolar involvement results in the anatomical and, thus, radiological diagnosis of emphysema. COPD is a physiological diagnosis defined by, and therefore diagnosed when, there is poorly reversible airflow obstruction. This must be in the presence of exposure to sufficient recognized toxin, typically cigarette or biomass smoke, or increased susceptibility to such toxin, as in alpha-1 antitrypsin deficiency. The airflow obstruction results from mucus plugging and loss of alveolar attachments but also intrinsic involvement of the small airways with inflammation and fibrosis in the wall (1). Of note, there are other causes of poorly reversible airflow obstruction besides COPD, for example chronic asthma and bronchiectasis. Not everyone with poorly reversible airflow obstruction has COPD.

Poorly reversible airflow obstruction is defined by a reduced post-bronchodilator ratio of FEV_1 to (F)VC. Even here, the picture is complex. This is not the platform to rehearse arguments for and against the approach of defining COPD using a fixed FEV_1/(F)VC ratio less than 0.70 or defining abnormality using the lower limit of normal (LLN; less than the fifth percentile) (2). Note that both approaches, by necessity, have a hard threshold defining normal from abnormal. Whichever approach is used, an unanswered problem has been how to handle those people with a ratio at the boundary of normal. In this issue of the *Journal*, Aaron and colleagues (pp. 306–314) examine this question and therefore inform on diagnostic uncertainty in COPD (3).

Aaron and colleagues (3) provide an analysis of "diagnostic instability" in COPD, defined as crossing and recrossing the diagnostic FEV_1/(F)VC threshold. The study also examined "diagnostic reversals," defined as subjects meeting criteria for COPD at study onset then normalizing and remaining normal over the subsequent period of observation. A total of 7,412 patients were studied across two established cohorts over 4 to 5 years. The bottom line is a significant risk of diagnostic instability, particularly (and predictably) greatest for those patients closest to the threshold. The instability rate was 19.5% in the Lung Health Study (LHS) cohort and 6.4% in the Canadian Cohort of Obstructive Lung Disease (CanCOLD). There were differences between the cohorts in the number of visits and in smoking status, both of which likely contributed to the observed differences in diagnostic instability rate. The instability rate estimate was similar using fixed ratio compared with LLN in the larger and therefore more accurate LHS cohort. Diagnostic reversal occurred in 12.6 and 27.2% of subjects in these cohorts and was commonest in subjects who quit smoking during the study. Diagnostic change was unusual after two confirmatory tests in people continuing to smoke.

If COPD is progressive, why does "diagnostic instability" occur? As discussed by the authors, respiratory infections and exposure to inhaled irritants can both cause transient changes in spirometry (3). Moreover, the view that COPD is always progressive has been challenged (4). Patients with asthma are characterized by variable airflow obstruction. Perhaps some patients had asthma? A self-report of physician-diagnosed asthma was an exclusion to entry in the LHS but not the CanCOLD study. However, removal of these subjects from the analysis did not materially affect the results, and therefore this explanation seems unlikely.

The implication of these results is profound: a single post-bronchodilator spirometry test is insufficient to confirm or exclude COPD when the FEV_1/(F)VC ratio is close to the threshold, and certainty in diagnosis only becomes possible with more severe airflow obstruction. This is of relevance both in the clinic and in the context

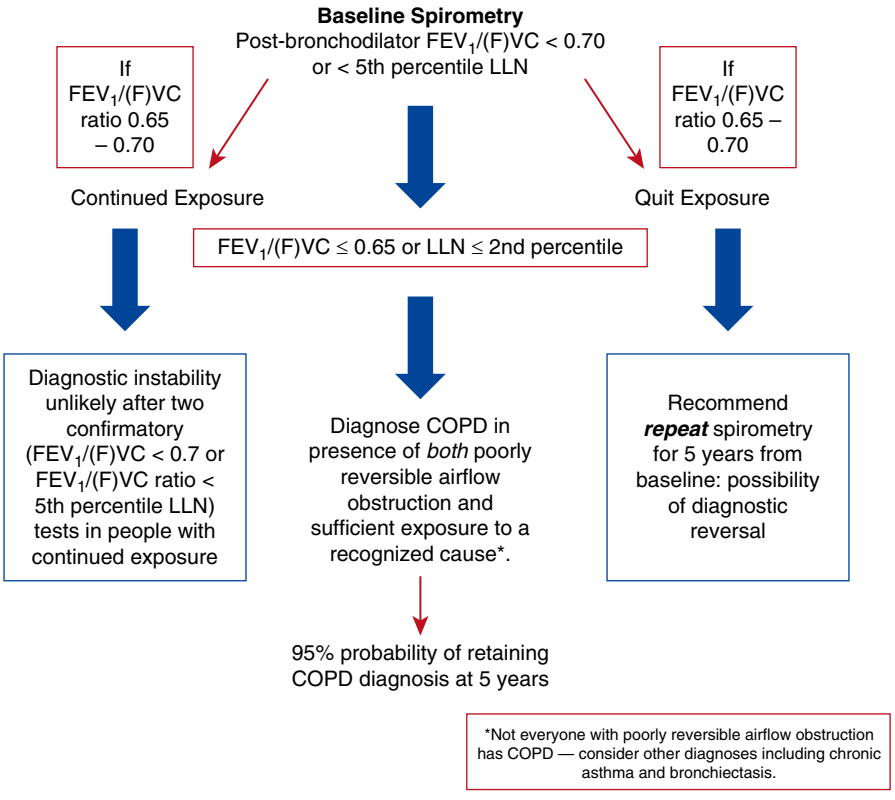

Figure 1. A suggested approach to the diagnosis of chronic obstructive pulmonary disease (COPD). LLN = lower limit of normal.

of clinical trials. Subjects with a fixed ratio less than or equal to 0.65 or LLN less than or equal to 0.2% had a 95% chance of retaining a COPD diagnosis at 5 years. For subjects above these limits, repeat testing is required, likely more than once in those who quit smoking.

This is not the first study to report such findings. Perez-Padilla (5) reported a similar diagnostic instability rate of 11.7% (using fixed ratio) in 2,026 patients enrolled in the Projeto Latino-Americano de Investigação em Obstrução Pulmonar (PLATINO) studies. Others have examined this too (6). The current study is valuable because of its size and therefore measurement precision, the replication of findings, and the explicit description of appropriate cutoffs permitting security in diagnosis.

There are some further limitations. LHS and CanCOLD are both North American cohorts, where tobacco smoke is the principle inhaled toxin; globally, COPD is a condition associated with biomass exposure. In addition, normal spirometry does not exclude other smoking-related lung conditions, such as emphysema (7). However, this study and others (5, 6) provide solid ground for a new paradigm in the diagnosis of COPD. We propose:

1. COPD requires the presence of both poorly reversible airflow obstruction and sufficient exposure to a recognized cause. The Global Initiative for Chronic Obstructive Lung Disease (8) also emphasizes the importance of symptoms.
2. Not everyone with poorly reversible airflow obstruction has COPD; consider other diagnoses, including chronic asthma and bronchiectasis.
3. People can have smoking-related lung disease with normal spirometry; consider whether there may be emphysema, chronic bronchitis, or smoking-related interstitial disease.
4. Whichever approach is used, fixed $FEV_1/(F)VC$ ratio or LLN, be wary of making and excluding the diagnosis of COPD in those people close to the threshold. A "watch and repeat" policy may be best, especially for patients who successfully quit smoking (Figure 1).

The Global Initiative for Chronic Obstructive Lung Disease states "the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation" (8). Well, no, it does not. Caution is necessary around the threshold, whether it be LLN or fixed ratio. Hypertension treatment would not be started on the basis of one moderately elevated reading. We have to get the basics right in COPD too: accurate diagnosis and exposure reduction for all. ■

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Shumonta Quaderi, B.Sc., M.R.C.P.
John R. Hurst, Ph.D., F.R.C.P.
UCL Respiratory
University College London
London, United Kingdom

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Myeloid-derived Suppressor Cells in Sepsis

When the innate immune response triggered by a pathogen fails to prevent or resolve infection, it can become unbalanced and harmful to the host, which results in a failure to return to normal homeostasis and the clinical syndrome of sepsis (1). In sepsis, the host response is disturbed in two seemingly opposite directions characterized by concurrent hyperinflammation and immune suppression. Sepsis-induced immune suppression involves both the innate and adaptive immune system. Hallmark features are diminished expression of human leukocyte antigen-DR on blood monocytes, a diminished capacity of monocytes and macrophages to release proinflammatory cytokines upon stimulation, and a strong depletion of $CD4^+$ and $CD8^+$ T cells, B cells, and dendritic cells due to apoptosis (1). The sustained immune suppression that accompanies sepsis has been implicated as a causal factor in late sepsis mortality due to secondary infections (1).

In this issue of the *Journal,* Uhel and colleagues (pp. 315–327) provide observational data that support a role for expansion of myeloid-derived suppressor cells (MDSCs) in immune suppression and enhanced susceptibility to nosocomial infections in patients with sepsis admitted to the intensive care unit (ICU) (2). MDSCs are a mixed population of predominantly immature myeloid cells that suppress effector immune cells, in particular, T cells (3).