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Research Bronchoscopy Standards and the Need for Noninvasive Sampling of the Failing Lungs

To the Editor:

We read, with great interest, "Research Bronchoscopies in Critically Ill Research Participants: An Official American Thoracic Society Workshop Report" (1), which outlined research practice standards for bronchoscopy that serve as the reference methodology for sampling of the lower respiratory tract (LRT). We echo the Workshop Report conclusions that research bronchoscopy in the intensive care unit is valuable, safe, and feasible. However, we further highlight the practical challenges and study design considerations associated with bronchoscopy-based research. In response, we propose that ongoing evaluation of the reliability of noninvasive sampling methodologies has the potential to enhance critical care research utilizing LRT specimens. These alternative methods may offer utility beyond resource-limited settings that was pointed out in the Workshop Report.

First, research bronchoscopy may be deferred in the sickest subpopulations with severe hypoxemia or hemodynamic instability, as even the slightest risks of bronchoscopy may be deemed as unacceptable. In contrast, noninvasive samples, such as endotracheal aspirates (ETAs), are part of routine medical care and can be collected through minimal-risk protocols even in the most unstable patients. Noninvasive methods do not require the presence of a study physician, thus allowing for wider reach of enrollment across more study sites. Research bronchoscopy typically requires dedicated informed consent from legally authorized representatives, a process that can pose logistical challenges, hampering early biospecimen collection in the hyperacute phase of critical illness. Therefore, cohorts that include noninvasive LRT sampling may be less prone to selection biases and more representative of the broad patient populations with acute respiratory failure. Furthermore, noninvasive collections can be repeated *ad libitum* to follow biological trajectories in the LRT. Approaches such as ETAs, exhaled breath condensates, or fluid analysis from routinely discarded heat moisture exchange filters (2, 3) would allow for repeated or even near-continuous assessment of the LRT and may, thus, augment our understanding of the temporal dynamics of LRT biology beyond cross-sectional research bronchoscopy.

Although there are limitations to noninvasive methods, they can capture many features observed in bronchoalveolar lavage (BAL) samples, including cellular heterogeneity, as well as distinct transcriptional (4) and protein signatures (5). For example, ETAs collected without cellular filtration can reveal heterogeneous LRT cellular populations, including neutrophils (6). ETA protein content may reflect important signals from the distal airspaces, as it contains measurable quantities of surfactant protein D (W.B. and G.D.K., unpublished results) and soluble receptor of advanced glycation end products—proteins associated with the distal airspaces (5)—even if their concentrations in ETA may not directly represent BAL levels. The analytical validity of noninvasive biospecimens remains to be consistently demonstrated, yet there is proof-of-concept evidence that rigorous protocols for noninvasive sputum samples can replicate BAL findings in patients with cystic fibrosis (7). Noninvasive sampling is the guideline-recommended method for pneumonia diagnosis in mechanically ventilated patients (8), and microbiome signatures in ETA samples predict patient-centered outcomes (9). Finally, the coronavirus disease (COVID-19) pandemic highlighted the importance of pragmatic LRT sampling across diverse healthcare systems and practices, because bronchoscopies were severely limited by increased clinical demands and heightened infection prevention precautions during the early phases of the pandemic.

Further work is necessary to compare the benefits and limitations of noninvasive methods to the gold standard of bronchoscopy. We recall that, nearly 50 years ago, the diagnostic value of BAL for pneumonia was established through meticulous comparisons against the reference standard of tissue sampling through invasive biopsies or autopsy. We propose that similar meticulous study of noninvasive methods against the current reference standard of bronchoscopy may also allow for development of scalable, reliable, and generalizable approaches for biological study of the LRT and rapid diagnostics during acute respiratory failure. ■

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Reply: Research Bronchoscopy Standards and the Need for Noninvasive Sampling of the Failing Lungs

From the Authors:

We appreciate the comments from Dr. Bain and colleagues regarding our recent American Thoracic Society Workshop Report titled "Research Bronchoscopies in Critically Ill Research Participants" (1). They highlighted the main goals of our proposal, which were to provide considerations regarding procedural standardization of bronchoscopy with bronchoalveolar lavage (BAL) and to summarize the existing evidence that this procedure is valuable, safe, and feasible in critical illness.

We agree that bronchoscopy is the gold standard for sampling of the lower respiratory tract (LRT) but that limitations remain. As suggested, there are challenges to feasibility due to a high resource burden and the potential for selection bias based on the severity of illness. For these reasons, it is important to continue to develop alternative strategies for evaluating the LRT beyond direct alveolar sampling with bronchoscopy.

Substances derived from the respiratory tract obtained via exhaled breath condensates or through discarded heat moisture exchange filters have shown important correlations to protein measurements in directly aspirated edema fluid (2, 3). However, the cellular content and anatomic source of any recovered cells from these samples remain uncertain. As this field moves forward, protocols that assess paired exhaled breath fluid and directly sampled alveolar fluid may provide good protein correlates of cellular inflammation or injury.

Tracheal aspirates (TA) have become more commonly used for microbial assessment of the LRT. The recent Infectious Diseases Society of America guidelines have supported TA as a reasonable option for diagnosis of ventilator-associated pneumonia, although the poor specificity of TA-derived microbial assessments may lead to overdiagnosis and misclassification of pneumonia status in research participants (4). One study has shown differences in microbial diversity between tracheal aspirates and mini-BAL specimens in mechanically ventilated patients, particularly in subjects without pneumonia (5). TA have also been increasingly studied to assess cellular inflammation during hypoxemic respiratory failure. During the coronavirus disease (COVID-19) pandemic, TA provided an opportunity to collect samples of convenience in the setting of increased clinical demands. These samples have provided insight into COVID-19 pathogenesis (6). However, direct comparisons between the cellular milieu and microbial composition found in TA and BAL are limited. Proportions of macrophages, monocytes, and