Don't Inhale: Acute Respiratory Distress Syndrome Risk and Tobacco Exposure in Patients with Sepsis

Tobacco smoke exposure is a well-documented risk factor for acute respiratory distress syndrome (ARDS) in trauma patients, burn patients, and transfusion recipients, as well as lung transplant recipients, where donor tobacco use is associated with primary graft dysfunction, a form of ischemia-reperfusion injury in the allograft after lung transplantation (1–6). In this issue of the *Journal*, Moazed and colleagues (pp. 927–935) have made a substantial addition to this body of literature with a well-designed, multicenter prospective cohort study identifying a strong association between biochemically defined tobacco exposure in patients with sepsis, importantly including those with pulmonary sepsis, and substantially increased odds of ARDS (7).

This study adds to a growing body of literature highlighting the remarkable heterogeneity of ARDS. Despite a lower level of illness severity and a lower level of biochemically determined systemic inflammation as determined by plasma levels of IL-8 and soluble tumor necrosis factor receptor 1, the authors identified that septic patients with either active or passive tobacco exposure had increased odds of ARDS. This level of syndromic heterogeneity at the level of the patient highlights the need to integrate more precision into the design of clinical trials (a one-size-fits-all approach for ARDS therapeutics will not work). Different phenotypes of ARDS will likely require different therapeutics targeting distinct pathways to be effective. Several of the authors on this study were involved in prior latent class analysis of the large well-phenotyped ARMA (ARDS Clinical Trials Network Low-Tidal-Volume [V_T] Trial) and ALVEOLI (Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury) cohorts demonstrating two distinct ARDS phenotypes with both divergent underlying biochemical and clinical characteristics as well as distinct clinical outcomes, including mortality and ventilator-free days. Notably, smoking status was not included in those analyses as this information was not available either from history or using biomarkers. Based on the current sepsis study, the inclusion of smoke exposure status, using biochemically determined tobacco exposure, should be added to future assessments of clinical phenotyping of ARDS patients as was done in a recent similar assessment of the EARLI (Early Assessment of Renal and Lung Injury) and VALID (Validating Acute Lung Injury Markers for Diagnosis) ARDS cohorts (albeit, only with current smoking status assigned from history) (8).

Furthermore, the results emphasize the need for precise patient risk factor identification and phenotyping; simply asking a patient (or their surrogate) whether they smoke is likely insufficient. Electronic health record documentation of smoking status is inaccurate and often contains discrepant data, including patients with reports of both current and never smoking in the same record (9). However, the use of highly sensitive biomarkers greatly improves our ability to identify both passive and active smokers in the critical care setting when accurate patient histories are difficult to obtain (10). Precise assessment of tobacco exposure with both nicotine and tobacco combustion product biomarkers is one of the real strengths of this study.

The results of this study also have significant public health ramifications. The majority of tobacco cessation efforts are focused on reducing the level of risk to the smoker; studies aimed at reducing secondhand smoke exposure are typically aimed at reducing pediatric tobacco smoke exposure (11). The finding that passive smoke exposure is associated with an odds of ARDS nearly identical to that of active smoke exposure highlights that any smoke exposure, not necessarily through active or heavy smoking, increases ARDS risk. Based on this finding, a significant percentage of the population may be at increased risk of ARDS. In their 2019 Report on the Global Tobacco Epidemic, the World Health Organization highlighted the significant morbidity and mortality associated with secondhand smoke exposure and emphasized, "The only way to adequately protect both smokers and nonsmokers from secondhand smoke is to fully eliminate indoor smoking" (12). Increased ARDS risk in patients with sepsis should be added to the substantial list of rationale for aggressive smoking cessation efforts. The potential impact of any significant tobacco exposure is especially important during the current coronavirus disease (COVID-19) pandemic. Smoke exposure results in overexpression of angiotensin-converting enzyme 2, the primary receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the human respiratory tract, on the apical surface of bronchial epithelial cells (13). Furthermore, there is a preponderance of data demonstrating that active tobacco smoking likely significantly increases the risk of death from COVID-19 (14). Interestingly, Sinha and colleagues (15) utilized latent class analysis and demonstrated that clinically determined current or former smoke exposure was associated with a more hyperinflammatory ARDS phenotype, different than the findings in the current study. Further study is needed to assess whether the findings of Moazed and colleagues of the strong association of ARDS in sepsis patients with passive smoke exposure is mirrored in the passive smoke-exposed COVID-19 patient population.

The potential importance of passive smoke exposure as a risk factor for ARDS also has implications in lung transplant donor assessment. As mentioned above, we have demonstrated that donor smoking history is associated with severe primary graft dysfunction after lung transplant (3). Most of the focus has been on surrogate reported smoking history, likely even less accurate than electronic medical record-obtained smoking status in critically ill patients. Based on the results from Moazed and colleagues, better characterization of donor smoke exposure using biochemically determined smoking history may lead to better primary graft dysfunction risk assessment. Additionally, donor smoking history may have a more significant impact on primary graft dysfunction risk in higher-risk recipients based on pulmonary diagnosis, body mass index, and pulmonary

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hypertension (16). A more precise assessment of donor smoke exposure, passive or active, may provide more information for safer donor-recipient matching.

Overall, this study provides guidance for the design of future ARDS therapeutic drug trials. This study adds to the preponderance of evidence suggesting that clinical trials must begin to integrate precise phenotyping of ARDS patients into patient selection, including their tobacco exposure, to identify effective patient-specific therapeutics for ARDS. Finally, and perhaps most importantly, ongoing public health efforts to highlight the profound impact of tobacco smoke exposure on ARDS risks are integral to decreasing the population-based risk of a syndrome with high morbidity, mortality, and societal cost. ■

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The Shorter, the Better: Can We Improve Efficiency of Idiopathic Pulmonary Fibrosis Trials?

Idiopathic pulmonary fibrosis (IPF) is the prototypic fibrosing lung disease, characterized by relentless progression and poor prognosis (1). Patients gradually deteriorate despite treatment with the current standard of care, nintedanib or pirfenidone (2). These drugs have been approved after decades of failed trials and heated discussion on the choice of the best efficacy endpoint. Endpoints have been investigated in thousands of patients before it was decided that the change of FVC over 1 year was the right one, a decision based mainly on the correlation between FVC changes and mortality and accepting that studies with mortality as endpoint were not feasible (3).

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