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Reply to Nett *et al.*

From the Authors:

We appreciate the perspective shared by Nett and colleagues regarding the potential utility of registries to assess the contribution of occupational and environmental exposures to the development and outcomes of idiopathic pulmonary fibrosis (IPF). We agree that exposures constitute an important source of risk for patients with IPF, and also perhaps for susceptible individuals at risk for developing clinically overt fibrosis. In this regard, expanding occupational assessments to include cohorts of patients with interstitial lung abnormalities may facilitate easier identification of exposure relationships through the sheer proportions of patients with interstitial lung abnormalities compared with narrowly defined IPF.

Measuring exposure relationships with IPF poses several challenges, which unfortunately have not yet been overcome. However, our plea for future IPF registries to consider investigating novel aspects of pulmonary fibrosis certainly accords with the idea of more in-depth occupational assessments (1). Given the small numbers of patients in any given occupation, collaborations among registries, as has been proposed for several European registries, may enhance the likelihood of identifying culpable exposures (2).

The absence of validated exposure tools that can be completed by patients and harried clinicians is a current difficulty. There are several other barriers to identifying occupational relationships with pulmonary fibrosis, many of which are not easily addressed with registries that focus on disease manifestations and patient-centered outcomes. These barriers include nagging issues regarding the aggressiveness of exposure assessments, poor recall in an elderly population, latency, the complex effects of gene–environment interactions, and potentially modifying effects of evolving environmental controls in a disease that typically requires many years to fully develop.

IPF is widely regarded to be due to deranged wound-healing responses to epithelial cell injury. The label "idiopathic" is probably no longer appropriate, as a variety of nonoccupational lung exposures have been linked to the development and prognosis of IPF, including tobacco use, gastroesophageal reflux, and air quality (3, 4). It is unsurprising, therefore, that any occupation that involves the generation of respirable particles may be a risk factor for IPF. Epidemiologic data are indeed necessary to help clinicians and policy-makers identify which particle types are likely to injure the epithelium the most, driving the progression of fibrosis. Moreover, further elucidation of gene–environment relationships in pulmonary fibrosis may eventually allow for better screening of at-risk workers.

We welcome continued dialogue among pulmonologists, epidemiologists, industrial hygienists, occupational medicine specialists, preclinical scientists, and patients. We agree that collaboration among all relevant parties will be instrumental in further refinement of historical and future IPF risk factors. ■

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Hyperoxemia and Death of the Critically Ill: Is There a Problem of Confounding by Indication or Outcome?

To the Editor:

Palmer and colleagues present findings using data and tools from the National Institute of Health Research Critical Care Health Informatics Collaborative in five United Kingdom university hospitals (1). This publication now makes a second recent database report that seemingly indicates an association between exposure to hyperoxemia and death during critical illness (1, 2). In the current report, the authors found an association between "any hyperoxemia" exposure and increased ICU mortality over the first week (Days 0–7). Rather intriguingly, there was no effect of "hyperoxemia dose" (time integral of Pa_{O_2} >100 mm Hg per epoch) in this relationship, which challenges a causal relationship but indicates a potential all-or-nothing problem, such as confounding by indication.

For example, confounding by severity is the problem whereby patients with more severe illness are likely to receive a hyperoxemia exposure; the authors site the issue of unstable patients undergoing multiple transfers and procedures that necessitate being placed in high $F_{I_{O_2}}$ for transfer. Another confounding by severity might be use of supplemental oxygen during resuscitation, with such sick patients often receiving an $F_{I_{O_2}}$ of 1.0. The hyperoxemia exposure will appear to result in poorer outcomes because degree of severity affects both the exposure and the patient outcome and is not an intermediate between the exposure and outcome (3). The authors have used methods to minimize this problem but, as they say, "at the expense of reducing the number of cases from which to learn."

There is, however, another confounder not considered in the report (1): The hyperoxemia exposure is independently associated with the definition of the outcome (death). For example, in the patient undergoing apnea testing as part of the assessment of death by neurological criteria (DNC), the test is started after a period of preoxygenation (10 min with $F_{I_{O_2}}$ 1.0) with an arterial blood gas (ABG) test result confirming an appropriate starting Pa_{CO_2}. In the United Kingdom, two sets of tests with separate evaluation of apnea are performed (i.e., at least two ABG tests, by definition, with hyperoxemia). After determination of DNC, there may be further ABG tests with hyperoxemia in the instances in which lung organ donation is being considered. The so-called standard criteria for choosing lungs are to ventilate with $F_{I_{O_2}}$ 1.0 and positive end-expiratory pressure 5 cm H_2O and then check that Pa_{O_2} is >300 mm Hg. Palmer and colleagues do not provide the number of deaths (outcomes) meeting DNC or the number of instances in which lung organ donation was considered. Also, it is not clear from the supplementary methodological references about the National Institute of Health Research Critical Care Health Informatics Collaborative database (4, 5) how ABG test results up to the first apnea test can be identified or how time of death can be differentiated from time of "discharge" in organ donors. I wonder whether the authors would consider restricting their statistical procedures by stratifying according to criteria for death (cardiac vs. DNC) and reexploring the associations between "any hyperoxemia," "hyperoxemia dose," and death. ■

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The views expressed are those of the author.

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