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Hospitalization Outcomes for COVID-19 in Patients with Interstitial Lung Disease: A Potential Role for Aerodigestive Pathophysiology?

To the Editor:

We congratulate Drake and colleagues for their timely, international multicenter study of outcomes of hospitalization for coronavirus disease (COVID-19) in people with interstitial lung disease (ILD) (1). This found that 161 people with ILD were at increased risk of death compared with 322 propensity score–matched control subjects. The comparison group, people without ILD, or other chronic lung disease, was obtained from the valuable ISARIC 4C (International Severe Acute Respiratory and Emerging Infection Consortium Coronavirus Clinical Characterization Consortium) cohort. People with ILD and COVID-19 had higher mortality (hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.17–2.18; $P = 0.003$) compared with control subjects, with the greatest risk in idiopathic pulmonary fibrosis (IPF) (HR, 1.74; 95% CI, 1.16–2.60; $P = 0.007$). Furthermore, obese people with ILD had an elevated risk of death (HR, 2.27; 95% CI, 1.39−3.71).

Gastroesophageal reflux disease (GERD) is linked with obesity and is an important comorbidity in many chronic lung diseases (2) including ILD (3) before and after lung transplantation. The link between IPF and GERD has been identified as a research priority. GERD appears to be common in IPF, the largest ILD subgroup studied by Drake and colleagues, and GERD may be associated with adverse IPF outcomes.

GERD treatment in IPF ranges from conservative clinical strategies such as antacid strategies to consideration of surgical fundoplication (3). Conditional recommendations for treatment are incorporated into IPF current guidelines, and treatment with proton pump inhibitors (PPIs) is very common (3).

Excess lower respiratory tract infections are described as a concern in people prescribed PPIs. Prospective data are limited in ILD, but in a rare pilot randomized study of omeprazole therapy in IPF, there was a small excess of lower respiratory tract infections (4). We have also previously found that viable fungal and bacterial microorganisms can be isolated from gastric juice in people with lung disease, and in people without lung disease, when pH exceeds 4. Stomach acid may be considered an important element of gastric homeostasis and overall microbiological defense.

With regard to viral infection, PPIs are a putative risk for influenza, rotavirus, and Middle East respiratory syndrome coronavirus infection. In stringent mRNA and protein expression studies, one of the highest expression sites for angiotensin-converting enzyme 2 protein, a key protein involved in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) host cell entry, leading to COVID-19, is the upper gastrointestinal tract. An increased, dose-dependent risk of COVID-19 has recently been shown, among PPI users, in a substantial North American study of 53,130 people in which 3,386 reported a positive COVID-19 test (5). Regression analysis showed that individuals using PPIs up to once a day (odds ratio, 2.15; 95% CI, 1.90–2.44) or twice daily (odds ratio, 3.67; 95% CI, 2.93–4.60) had significant, PPI dose response–associated, increased odds for reporting a positive COVID-19 test (5). A Korean nationwide cohort study with propensity score matching studied a potential role for PPIs as a risk in severe COVID-19, including 132,316 people tested for SARS-CoV-2. In confirmed COVID-19, the current use of PPIs conferred a 79% greater risk of severe clinical outcomes (6).

We suggest that PPI treatment may have been taken by many of the people with IPF in the study from Drake and colleagues, with the potential that the control group systematically had less exposure. We wonder if the authors were able to consider this in their analyses or have data that might inform this. We would be very interested in the authors' expert opinion on the potential role of "aerodigestive" pathophysiology in their findings. ■

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Reply to Althuwaybi *et al.*

From the Authors:

Althuwaybi and colleagues propose an interesting hypothesis to explain the potential mechanism for increased risk of mortality following hospitalization for coronavirus disease (COVID-19) in patients with interstitial lung diseases (ILDs) (1). Unfortunately, in our study these data were not collected, and therefore, we cannot not make comparisons with the control population. Gastroesophageal reflux is strongly linked to hiatus hernia, which is twice as prevalent in patients with idiopathic pulmonary fibrosis (IPF) as the general population (2, 3). It is therefore plausible that proton pump inhibitors (PPIs) may have been prescribed in excess in patients with ILD.

However, the cited evidence for a putative role of PPIs in pathophysiology is inconclusive and likely does not overcome the residual effect of significant comorbidities in our cohort. In an unpowered pilot randomized controlled trial into the effect of omeprazole therapy on cough in IPF, Dutta and colleagues reported safety events including three respiratory tract infections in the placebo group compared with six using omeprazole, which could be explained by chance (4). In a large population-based study of patients with IPF in a real-world clinical practice setting, PPI use was not associated with a difference in survival or the incidence of respiratory-related hospitalization compared with those not using PPIs (5). Althuwaybi and colleagues describe a dose response of PPIs with risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection reported in a large North American survey, as well as a retrospective health insurance database study in Korea that observed an association of PPI use with COVID-19 severity (6, 7). In contrast, the same Korean study found no association of PPIs with risk of infection; further study and meta-analyses will be required to build certainty on an effect. Lee and colleagues did observe a significant association between PPI use and severe outcomes in an adjusted model, particularly for a subgroup with $<$30 days of PPI records (7). Although the study included 132,316 individuals, a more limited 267 were currently using PPIs and were positive for SARS-CoV-2. A 79% greater risk of severe intervention was observed from 24/267 people with current PPI use (18/175 with $<$30 d of records), in comparison with 14/267 propensity-matched controls. The propensity-matched group had fewer significant comorbidities, and analyses did not adjust for lung function or body mass index, which we identify as important predictors of hospitalization outcomes. PPI use was not available for the individuals included in the study by Drake and colleagues, although the cited studies suggested little effect in past users or those with $>$30 days of treatment. It is likely that disease status, enhanced respiratory support, and significant comorbidities had a more substantial impact than PPI on outcomes in our cohort.

Furthermore, the role of PPIs in IPF pathogenesis remains uncertain. *Post hoc* analysis from international trials in IPF reported that pulmonary infections were higher in patients with advanced IPF (i.e., FVC $<$70%) who were receiving antacids compared with those not treated with antacids (8). However, PPIs have pleiotropic activity including antiinflammatory and antiproliferative effects (9). It is also worth noting, however, that although hiatus hernia has been independently linked to mortality in patients with IPF (2) and almost 5,000 participants in the AGES-Reykjavic birth cohort (3), in these uncontrolled studies, no association was found between PPI prescription and outcomes. The potential of antacid drugs to contribute to viral infections including COVID-19 has been the subject of some discussion (10). Thus, until further data are available, the potential adverse or favorable effects of PPIs in ILDs during the current pandemic remain to be determined, but understanding the balance of benefits and potential harms from antacids is imperative.

There are also a number of other potential mechanistic explanations why patients with ILD may have had poor outcomes

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