ones showed that long-term HFNC at home was feasible and safe with benefits in terms of reduction of exacerbation, leading to consideration of HFNC at home as a supplement to long-term oxygen therapy in the management of patients with severe COPD. ■

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Airway Mucus Dysfunction in COVID-19

Several anecdotal reports suggested the occurrence of excessive mucus production in coronavirus disease (COVID-19), but no systematic analysis had been published until the article by Kato and colleagues (pp. 1336–1352) in this issue of the *Journal* (1). In autopsy specimens, they found high degrees of production of the secreted airway mucin MUC5B and moderate amounts of MUC5AC. Strikingly, they also found occlusion of ∼50% of the small airways by mucus, as well as widespread aberrant expression of MUC5B within microcysts in damaged alveolar parenchyma. These findings have implications for understanding the pathophysiology and treatment of COVID-19 in particular and of viral pneumonia in general. Here, we address these implications in three sections.

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Airway Mucus Occlusion

The first important finding is widespread small airway occlusion by mucus. This is somewhat surprising because the cough that accompanies SARS-CoV-2 infection of the lower respiratory tract has generally been reported to be nonproductive (2, 3). However, mucus

occlusion of small airways often does not generate a productive cough, as also occurs in asthma or in chronic obstructive pulmonary disease with an emphysematous phenotype (4). The finding of small airway mucus occlusion also surprises because prior systematic analyses of lung pathology focused on alveolar injury, flooding, and endotheliitis without reporting airway mucus occlusion. However, the presence of excessive mucus can be missed with standard hematoxylin and eosin staining, where it appears blandly eosinophilic, similar to proteinaceous edema fluid. The presence of mucus is best identified with special histochemical stains such as Alcian blue and/or periodic acid–Schiff or with immunohistochemical staining. This in turn raises the question whether we have underestimated the role of mucus dysfunction in other viral pneumonias. The true importance of mucus occlusion in COVID-19 will not be known until the effects of targeted interventions such as mucolytics are determined, possibly with computed tomographic imaging of mucus plugs as an endpoint (5). Current *in vitro* evidence for the value of the mucus barrier in protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is contradictory (6, 7), but it will need to be considered in therapeutic interventions and might first be tested in animal models. Kato and colleagues provide *in vitro* evidence for the efficacy of dexamethasone, IL-1 antagonists, and epidermal growth factor receptor antagonists in reducing airway epithelial mucin production, all of which have been and/or are in clinical trials. Regarding epidermal growth factor receptor antagonists, preclinical studies in animal models of SARS-CoV-2 infection could be helpful in analyzing beneficial effects in reducing mucin production versus possible adverse effects in repair of lung injury (see below). In considering therapeutic intervention, it should be noted that airway mucus occlusion, besides being caused by increased mucin production, is most likely also due to impairment of ciliary beating (6, 8) and to mucus dehydration from activation of the epithelial apical sodium channel as in other respiratory viral infections.

MUC5B Predominance

A second important finding is that MUC5B expression is more highly increased than MUC5AC in COVID-19 (1). This is different from most well-studied respiratory viral infections in mice and humans, such as with paramyxoviruses, rhinoviruses, and influenza viruses, wherein MUC5AC is more highly upregulated (9–11). Accompanying this difference is evidence that mucin expression appears to be driven mostly by IL-1 signaling in COVID-19, in contrast to the prominent role of IL-13 in other respiratory viral infections in mice and humans. The *in vitro* studies of IL-1 signaling in epithelial cells by Kato and colleagues were performed in the absence of leukocytes, but epithelial cells have a critical role in biasing immune responses, so these are likely to be informative. Consistent with the findings of differential cytokine and mucin expression between SARS-CoV-2 and other respiratory viral infections, prior studies have shown that IL-1β increases expression of MUC5B moderately more than MUC5AC (12), whereas IL-13 increases expression of MUC5AC far more than MUC5B (9). Of interest, IL-13 attenuates SARS-CoV-2 infection (6, 7), raising the question whether deviation away from type 2 immunity is an evasion strategy of SARS-CoV-2.

Alveolar Microcysts

A third important finding is the presence of numerous mucin-expressing microcysts in the lung parenchyma. These bear pathological and molecular resemblance to "pods" observed as a sequela of respiratory viral infections in mice and to the "honeycomb cysts" of advanced idiopathic pulmonary fibrosis (IPF). The most relevant comparison would appear to be with postviral pods in mice because of the shared viral infection pathogenesis. Severe viral injury mobilizes rare $P63^+$ cells in distal airways, which quickly proliferate and invade alveolar regions to restore the damaged epithelial barrier, then persist as $SOX2^+$ airway cells without differentiation into gas-exchanging alveolar cells (13–17). These epithelial pods polarize and form microcysts, possibly either by self-organization around an expanding lumen as in cultured organoids or by spreading along remaining basement membrane surrounding destroyed alveoli. Molecularly, their $P63^+$ cell origin imparts postviral pods a basaloid signature, including the master transcriptional regulator P63, as well as KRT5, ITGB6, and EPHB2, as also noted in the COVID-19 microcysts by Kato and colleagues. The resemblance between COVID-19 microcysts and IPF honeycomb cysts could reflect a limited repertoire of repair processes in injured lungs or might point to a role for viral respiratory infections interacting with genetic predisposition in IPF pathogenesis.

Conclusion

In summary, COVID-19 has only been with us a short while; yet, it is now perhaps the best-studied human viral pneumonia. Further analysis of similarities with and differences from other viral pneumonias should provide us new insight into cellular and molecular mechanisms of lung immunity, injury, and repair to guide diagnosis and treatment. ■

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Understanding Sex-based Differences in Intensive Care Unit Mortality: Moving Beyond the Biology

Many observational studies have pointed to survival differences between critically ill men and women with varying directionality depending on the disease state (1–3). Women, as compared with men, have displayed worse outcomes in coronary artery disease, cardiac surgery, and after cardiac arrests (4, 5). However, women are more likely to survive than men with certain conditions such as chronic obstructive pulmonary disease and respiratory viral diseases (6, 7).

Although the interplay between the patient's biological and immunological factors has been speculated as the potential unmeasured drivers for observed sex-based differences in care outcomes (8, 9), the potential contributions of systemic and implicit biases and cognitive errors have been largely understudied. Other factors historically overlooked, such as care environment, caseload, and team dynamics, are being independently investigated and increasingly recognized as important determinants of outcome, particularly for those at a high baseline risk of death (10–12). Similarly, exploring the variation in intensive care unit (ICU) mortality outcomes by the sex of the patient will require dedicated investigation that transcends the lens of acute physiology and comorbidity and other host factors.

In this issue of the *Journal*, Modra and colleagues (pp. 1353–1360) report their findings from a large, cross-sectional study of adult patients admitted to ICUs in Australia and New Zealand. Modra and colleagues took a deep dive into understanding variation in hospital mortality in men and women on the basis of how frequently a given condition occurred within each sex. The primary exposure variable was "sex balance", defined as the percentage of patients in a diagnostic group who were women, and the primary outcome was sex difference in adjusted hospital mortality by ICU admission diagnosis. The study was large, encompassing over 1.4 million ICU admissions between 2011 to 2020 in the ANZICS APD (Australia and New Zealand Intensive Care Society Adult Patient Database) (13). Using mixed-effects logistic regressions, the authors adjusted for severity of illness, hours of hospitalization before ICU admission, and year of admission, with hospital site as a random effect.

The key findings were that women displayed better risk-adjusted survival than men in sepsis, respiratory disorders, and in the combined category of metabolic/renal and hematological disorders. On the other hand, women fared worse than men in burns and cardiovascular disorders, with the most marked sex difference

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