propose new measures, we encourage them to ensure that their measures meaningfully capture OSA-specific risk and test whether treating OSA confers benefit in one group over another. We hope that, together, as a field, we will develop sound inclusion criteria for future CPAP trials, selecting patients whose physiologic data reveals high risk of adverse CV outcomes in OSA. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Ali Azarbarzin, Ph.D.*
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

Andrey Zinchuk, M.D.
Yale University
New Haven, Connecticut

Yüksel Peker, M.D., Ph.D.
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

Koc University
Istanbul, Turkey

University of Gothenburg
Gothenburg, Sweden

Lund University
Lund, Sweden

and

University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Scott A. Sands, Ph.D.
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

On behalf of all the authors

ORCID IDs: 0000-0002-4986-4753 (A.A.); 0000-0003-0488-9778 (A.Z.).

*Corresponding author (e-mail: aazarbarzin@bwh.harvard.edu).

References

1 . Azarbarzin A, Zinchuk A, Wellman A, Labarca G, Vena D, Gell L, *et al.* Cardiovascular benefit of CPAP in adults with coronary artery disease and OSA without excessive sleepiness. *Am J Respir Crit Care Med* 2022;206:766–773.
2. Huang Z, Qin L, Chen J, Wang L, Liu Z. Heart rate response in OSA: a clue to reveal cardiovascular benefit from CPAP? *Am J Respir Crit Care Med* 2022;206:1180–1181.
3. Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, *et al.* The sleep apnea-specific pulse-rate response predicts cardiovascular morbidity and mortality. *Am J Respir Crit Care Med* 2021;203:1546–1555.
4. Azarbarzin A, Ostrowski M, Moussavi Z, Hanly P, Younes M. Contribution of arousal from sleep to postevent tachycardia in patients with obstructive sleep apnea. *Sleep (Basel)* 2013;36: 881–889.
5. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, *et al.*; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007;50:823–830.
6. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care* 2003;26:1553–1579.

Check for updates

Microbial Burden-associated Cytokine Storm May Explain Nonresolving Acute Respiratory Distress Syndrome in Patients with COVID-19

To the Editor:

We read with great interest the article reported by Kullberg and colleagues in the *Journal* on the association of lung microbiota of critically ill patients with coronavirus disease (COVID-19) with nonresolving acute respiratory distress syndrome (ARDS) (1). The study enrolled patients with COVID-19 under mechanical ventilation, and the primary clinical outcome was successful liberation from mechanical ventilation on Day 60 after starting mechanical ventilation (1). The authors showed that successfully extubated patients with COVID-19 have significantly less alveolar microbial burden in the lower respiratory tract and significantly less mortality than deceased or intubated patients on Day 60 after initiation of mechanical ventilation (1, 2). Unfortunately, how the enhanced microbial burden affected the clinical outcome of patients with COVID-19 remains unclear. Several studies have documented the importance of increased systemic and intraalveolar concentrations of inflammatory cytokines in the pathogenesis of COVID-19 or sepsis-associated ARDS (3–5). Thus, the significant correlation observed by the authors between the microbial burden and the bronchoalveolar lavage fluid concentration of inflammatory cytokines points to intraalveolar cytokines as the potential factors mediating the detrimental effects of enhanced microbial burden in patients with COVID-19 with ARDS. However, Kullberg and colleagues assessed correlations in all (extubated and deceased or intubated) patients and in all (first and followed-up) BAL fluid samples. The two groups were not separately evaluated. In addition, the difference in the BAL fluid concentrations of inflammatory cytokines between the two groups of patients was not evaluated. Therefore, it is difficult to determine whether inflammatory cytokines played some pathogenic role in the (deceased or intubated) group of patients with COVID-19 with poorer clinical outcomes.

To clarify the potential implication of excessive cytokine secretion as the process mediating the pathological effects of the enhanced lung bacterial or fungal burden in patients with COVID-19 with nonresolving ARDS, the BAL fluid concentrations of inflammatory cytokines and the strength of correlation of microbial burden with inflammatory cytokines should be separately evaluated and compared between the extubated and deceased or intubated groups. Addressing the above questions will provide important and original information on whether increased lung microbial burden–associated "cytokine storm" may explain nonresolving ARDS in critically ill patients with COVID-19. ■

Author Contributions: Approval and writing the draft of the letter: T.Y., C.N.D.-G., H.F., T.K., and E.C.G.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Taro Yasuma, M.D.
Corina N. D'Alessandro-Gabazza, D.M.D.
Tetsu Kobayashi, M.D.
Esteban C. Gabazza, M.D.*
Hajime Fujimoto, M.D.
Mie University
Tsu, Mie, Japan

ORCID ID: 0000-0001-5748-1499 (E.C.G.).

*Corresponding author (e-mail: gabazza@doc.medic.mie-u.ac.jp).

References

1. Kullberg RFJ, de Brabander J, Boers LS, Biemond JJ, Nossent EJ, Heunks LMA, *et al.*; ArtDECO consortium and the Amsterdam UMC COVID-19 Biobank Study Group. Lung microbiota of critically ill COVID-19 patients are associated with non-resolving acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2022;206: 846–856.
2. Barnett CR, Segal LN. Untangling lower airway dysbiosis in critically-ill COVID-19 patients. *Am J Respir Crit Care Med* 2022;206: 806–808.
3. Hue S, Beldi-Ferchiou A, Bendib I, Surenaud M, Fourati S, Frapard T, *et al.* Uncontrolled innate and impaired adaptive immune responses in patients with COVID-19 acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;202:1509–1519.
4. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, *et al.* Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020;8:1233–1244.
5. Peukert K, Fox M, Schulz S, Feuerborn C, Frede S, Putensen C, *et al.* Inhibition of caspase-1 with tetracycline ameliorates acute lung injury. *Am J Respir Crit Care Med* 2021;204:53–63.

Reply to: Microbial Burden-associated Cytokine Storm May Explain Non-Resolving ARDS in COVID-19 Patients

From the Authors:

We thank Yasuma and colleagues for their interest in our study and appreciate the opportunity to elucidate the complex interplay between lung microbiota, alveolar inflammation, and clinical outcomes in critically ill patients with coronavirus disease (COVID-19) (1). In line with recent studies in critically ill patients both with and without COVID-19 (2, 3), we found that patients with an increased microbial burden had a lower incidence of liberation from invasive mechanical ventilation, higher mortality, and increased alveolar concentrations of proinflammatory cytokines.

In their letter, the authors raise an interesting question regarding differences in the inflammatory response to an increased lung microbial burden between patients with a better (extubated on Day 60 after intubation) and worse outcome (deceased or still intubated). First, we included these outcome groups as interaction terms in linear regression models with the $\log_{10}$-transformed microbial burden as a dependent variable and concentrations of cytokines as independent variables (tumor necrosis factor-α, IL-6, IL-1β, and transforming growth factor-α for the bacterial burden and tumor necrosis factor-α, IL-12p70, IL-17A, and transforming growth factor-α for the fungal burden). In these analyses, no statistically significant interaction terms were found. Next, when we performed stratified analyses for the outcome groups, as suggested by Yasuma and colleagues, the strength of correlation of microbial burden with inflammatory cytokines was similar between the two groups, although not always statistically significantly in patients who were extubated at Day 60 after intubation. The absence of a significant effect could very well be a consequence of the lower number of extubated patients ($n = 44$) compared with deceased or still intubated patients ($n = 70$) at Day 60. Taken together, the data in our study showed no evidence for a different relationship between pulmonary microbial load and alveolar inflammation depending on the clinical outcome.

Previous studies have shown that the alveolar immune response during COVID-19 strongly differs from the systemic response and that both contribute to disease severity (4, 5). However, whether ongoing alveolar inflammation, potentially mediated by the lung microbiome, is responsible for persistent acute respiratory distress syndrome (ARDS) and poor outcomes remains unclear. We have recently described (in a conference abstract) that patients with COVID-19 with nonresolving ARDS had a sustained alveolar hyperinflammatory state, and we hope to expand on the clinical consequences of such pulmonary hyperinflammation in the near future (6).

Overall, we found that the alveolar inflammatory response to an increased microbial burden did not differ between outcome groups. Lung microbiota are a potential source of sustained pulmonary inflammation in critically ill patients and could represent an important contributor to clinical heterogeneity in COVID-19–related ARDS. ■

Supported by the Nederlandse Organisatie voor Wetenschappelijk Onderzoek under Vidi grant 91716475 (W.J.W.) and Veni grant 016.1860.046 to JanWillem Duitman and by an Amsterdam University Medical Center PhD Scholarship to R.F.J.K. and an Amsterdam University Medical Center fellowship to L.D.J.B.

Originally Published in Press as DOI: 10.1164/rccm.202207-1346LE on July 22, 2022

Author disclosures are available with the text of this letter at www.atsjournals.org.

Robert F. J. Kullberg, M.D.*
Justin de Brabander, M.D.‡
Leonoor S. Boers, M.D.‡
Lieuwe D. J. Bos, M.D., Ph.D.§
W. Joost Wiersinga, M.D., Ph.D.§
Amsterdam University Medical Centers
Amsterdam, The Netherlands

ORCID IDs: 0000-0001-8269-9887 (R.F.J.K.); 0000-0001-7852-7994 (L.S.B.).