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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. ■

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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. Dickson RP, Schultz MJ, van der Poll T, Schouten LR, Falkowski NR, Luth JE, *et al.*; Biomarker Analysis in Septic ICU Patients (BASIC) Consortium. Lung microbiota predict clinical outcomes in critically ill patients. *Am J Respir Crit Care Med* 2020;201:555–563.
3. Sulaiman I, Chung M, Angel L, Tsay JJ, Wu BG, Yeung ST, *et al.* Microbial signatures in the lower airways of mechanically ventilated COVID-19 patients associated with poor clinical outcome. *Nat Microbiol* 2021;6: 1245–1258.
4. Leisman DE, Mehta A, Thompson BT, Charland NC, Gonye ALK, Gushterova I, *et al.* Alveolar, endothelial, and organ injury marker dynamics in severe COVID-19. *Am J Respir Crit Care Med* 2022;205: 507–519.
5. Saris A, Reijnders TDY, Nossent EJ, Schuurman AR, Verhoeff J, Asten SV, *et al.*; ArtDECO consortium and the Amsterdam UMC COVID study group. Distinct cellular immune profiles in the airways and blood of critically ill patients with COVID-19. *Thorax* 2021;76:1010–1019.
6. Boers LS, de Brabander J, Nossent EJ, Heunks LMA, Vlaar APL, Bonta PI, *et al.*; ArtDECO consortium Amsterdam UMC COVID study group. Sustained alveolar hyperinflammatory response in critically ill COVID-19 patient [abstract]. *Am J Respir Crit Care Med* 2022;205: A3539.

Erratum: Antihistone Properties of C1 Esterase Inhibitor Protect against Lung Injury

The authors wish to inform the readers that there is an error in their article published in the July 15, 2017 issue of AJRCCM (1). It was brought to their attention that they had inadvertently duplicated a representative image in Figure 2F ($B1^{-/-}B2^{-/-}$ mice, Bleomycin + Veh) in Figure 6A (wild-type mice, Bleomycin + Veh). A revised version of Figure 6A is published here with the correct Bleomycin + Veh panel (Figure 2F, which is unchanged, is also included for comparison).

These corrections do not affect the interpretation of the data or the conclusions of the paper. The authors deeply apologize for any inconvenience caused. ■

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Reference

1. Wygrecka M, Kosanovic D, Wujak L, Reppe K, Henneke I, Frey H, Didiasova M, Kwapiszewska G, Marsh LM, Baal N, Hackstein H, Zakrzewicz D, Müller-Redetzky HC, de Maat S, Maas C, Nolte MW, Panousis C, Schermuly RT, Seeger W, Witzenrath M, Schaefer L, Markart P. Antihistone properties of C1 esterase inhibitor protect against lung injury. *Am J Respir Crit Care Med* 2017;196:186–199.