(SARS-CoV-2) outbreaks and has had markedly high mortality (1). Therefore, we read with great interest in a recent issue of the *Journal* the study by Kullberg and colleagues describing the potential role of lung microbiota in nonresolving coronavirus disease (COVID-19)-associated ARDS (2). In this observational cohort study, regularly collected BAL fluids from mechanically ventilated patients with COVID-19 were analyzed for bacteria and fungi using the 16S sequencing technique and related to outcome. We would like to raise three points.

First, the authors reported at the group level that an increased bacterial and fungal load led to a prolonged duration of mechanical ventilation, higher mortality, and more microbiotic dysbiosis such as pneumonia and COVID-19–associated pulmonary aspergillosis. In addition, this microbiotic load was also associated with an increased inflammatory response. Unfortunately, the authors failed to discriminate the patients with a low or high proinflammatory response related to the microbiological burden. This could have played an important role in the outcomes reported. Second, at an individual level, the initial load of bacteria and fungi was insufficiently distinctive for daily clinical practice. Not to mention that 16s sequencing is (not yet) available in all hospital laboratories. Third, the application of selective decontamination of the digestive tract is supposed to be routine care in the Netherlands according to Dutch guidelines (3). However, the results indicate a persistent carrier state of gram-negative bacteria, which is surprising and worrying at the same time.

The authors are to be congratulated on this scientific approach to a relevant clinical problem. But how may we translate this observational study into our daily practice? The strict monitoring of infections, including COVID-19–associated pulmonary aspergillosis in COVID-19–associated ARDS, is correctly stressed, given that early recognition and timely treatment likely improves the patient outcome (4). In addition, the importance of recognition and suppression of a secondary immunological disorder, whether or not caused by a low-grade infection, cannot be emphasized enough (5). Hopefully, the techniques used in this study will enable early diagnosis and treatment of pulmonary infections in the foreseeable future. Until then, we probably need additional approaches, including selective decontamination of the digestive tract and patient-tailored immune modulation to further improve outcomes in COVID-19–associated ARDS. ■

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Efficacy of High-Flow Nasal Cannula Oxygen Therapy in Reducing Future Exacerbations for Patients with Stable Hypercapnia with Chronic Obstructive Pulmonary Disease

To the Editor:

We have read with great interest the article by Nagata and colleagues (1) published in this issue of the *Journal*, "Home High-Flow Nasal Cannula Oxygen Therapy for Stable Hypercapnic COPD: A Randomized Trial," which provided positive results for long-term high-flow nasal cannula oxygen therapy (HFNC) in reducing the risk of moderate/severe exacerbations in patients with stable hypercapnia and chronic obstructive pulmonary disease (COPD). We congratulate Nagata and colleagues for this excellent work that provides more choices for this population. Compared with previously published studies, several advancements, such as controlling the adherence to HFNC and recruiting only patients with hypercapnia, have been made in their work. Nevertheless, the study has some flaws that deserve more discussion.

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First, we address the inclusion criteria. This study recruited patients with COPD with $Pa_{CO_2} > 45$ mm Hg; the final mean value was 50 mm Hg, which is relatively lower (around 10 mm Hg) than many past studies (2, 3) assessing the efficacy of noninvasive ventilation for this population, indicating that the included patients presented a lower severity of disease. In addition, HFNC presented a weak performance in lowering the Pa_{CO_2}. Thus, the conclusion should be extrapolated with caution to those patients with higher Pa_{CO_2} to avoid delaying the initiation of noninvasive ventilation for this population.

Moreover, long-acting beta agonist (LABA) and long-acting muscarinic agent (LAMA) were prescribed more frequently in the HFNC/LTOT group and may play a role in reducing the risk of exacerbations. In addition, the long-term oxygen therapy (LTOT) group showed a higher rate of inhaled corticosteroids (ICS) use, suggesting the presence of eosinophilic inflammation in this group, which indicated a higher risk of future exacerbations (4).

Second, patients in the HFNC/LTOT group showed a lower Pa_{O_2} at baseline but a higher Pa_{O_2} at the 12-month visit, indicating that HFNC exerted more impact on the improvement of Pa_{O_2} than Pa_{CO_2}. It is reasonable to attribute the benefit of HFNC to providing more adequate oxygen therapy. Moreover, the published data did not display the adherence to conventional oxygen therapy, and we are concerned that inadequate oxygen therapy in the LTOT group may increase the difference between these two groups.

Third, the main outcome of exacerbations relied highly on patient dairies, and the sham device was not blinded for patients. A lower level of self-assessment may exist for patients in the control group, which may result in misdiagnosis of exacerbations for daily fluctuation of symptoms. The limitations of the original data may not be compensated for by inviting a third blind team to complete the final diagnosis.

Moreover, we noticed that a few subjects reported more than 10 counts, and even 18 counts, of exacerbation in the LTOT group. In the situation of a relatively small sample size and exacerbation counts, these patients provided close to one-third of the total number of exacerbations in the control group. Although the investigators included patients with at least one moderate/severe exacerbation in the past year before enrollment to assure a high risk of future exacerbation, hospitalizations due to severe exacerbation may predict worse outcomes than a moderate exacerbation, and frequent exacerbations in the past year may contribute to more exacerbations in the future than those who reported only one or two exacerbations in the past year (5). Therefore, the number and the severity of exacerbations in the past year should also be listed as a potential confounding factor, and it is necessary to confirm the presence of other potential lung diseases, such as bronchiectasis, because the latter may contribute to a great number of exacerbations (6).

In conclusion, we believe that future studies are important to evaluate the efficacy of HFNC in patients with a higher degree of hypercapnia, with better control of enrollment criteria. ■

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