

Reply to “Chronic Obstructive Pulmonary Disease Lung Microbiota Diversity May Be Mediated by Age or Inhaled Corticosteroid Use”

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We thank Pragman et al. for their [comments on our recently published paper](#) (1), pointing out that the relationships found between the bronchial microbiome and severity in COPD patients may be partly mediated by covariates like age and treatment, which are closely related to severity. The points that Pragman et al. raise are of great interest, and at the current stage of research cannot yet be satisfactorily answered; studies on the human microbiome have only recently focused on the respiratory system, and knowledge of the field is still limited.

The potential impact of inhaled corticosteroids on microbial diversity needs to be evaluated. In COPD, corticosteroid use is recommended for patients with frequent exacerbations (www.goldcopd.org), and in our study we were unable to assess the effect of this prescription because our sample included mainly patients who have criteria for the chronic use of this treatment. Most of our COPD patients have followed daily inhaled-corticosteroid treatment for over 1 year (14 out of 17 [82%]), and the prevalence of corticosteroid use was not significantly lower in patients with moderate to severe disease (62%) than in patients with advanced disease (100%). The effect of inhaled corticosteroids on the respiratory microbiome probably may be more accurately addressed in patients with mild asthma, who are usually treated with inhaled-corticosteroid treatment but do not use it during long periods of stability.

The relationship between the respiratory microbiome and ageing mentioned by Pragman et al. (2) is not well established yet, and further research in this field is needed. The authors reported age-related changes in the respiratory microbiome of COPD patients, but since age was also related to disease severity in their population sample, it is difficult to determine whether the changes that they observed are attributable to severity or to ageing. In our study, patients with moderate to severe and advanced disease were of similar ages ($P = 0.059$, Mann Whitney test), and we did not observe a relationship between age and alpha-diversity (age versus Shannon diversity [$\rho = -0.165$, $P = 0.526$]; age versus Chao 1 index [$\rho = -0.284$, $P = 0.270$]), suggesting that the effect of age on the characteristics of the microbiome in our population must be minimal. However, studies including subjects with a wide age range would be needed to clarify the effect of ageing on the respiratory

microbiome, both in healthy subjects and in patients with chronic disease.

Finally, we should stress that Pragman et al.'s study was performed using bronchoalveolar lavage samples, while in our study sputum samples were used. Although both samples provide information on the respiratory microbiome, they represent two different compartments of the respiratory airway. Bronchoalveolar lavage samples the distal airway at the alveolar level, while bronchial secretions recovered from sputum are representative only of the bronchial flora in the proximal tracheobronchial system. A recent study by Cabrera-Rubio et al. (3) found that the respiratory microbiomes in bronchoalveolar lavage and sputum show clear-cut differences, with higher microbial diversity in the bronchoalveolar lavage specimen. Accordingly, it might be hypothesized that in advanced COPD, the bronchial flora changes to a restricted microbiome, as we showed in our study of sputum, while the distal microbiome shows a different pattern of development, as suggested by the data obtained with bronchoalveolar lavage fluid.

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