

Editorial

Incorporating the airway microbiome into asthma phenotyping: Moving toward personalized medicine for noneosinophilic asthma

Juliana Durack, PhD,^a Homer A. Boushey, MD,^b and Yvonne J. Huang, MD^c San Francisco, Calif, and Ann Arbor, Mich

Key words: Airway microbiome, asthma, eosinophils, personalized medicine

Asthma is highly heterogeneous in severity and in patterns of airway immune responses.^{1,2} This heterogeneity, which was expressed as differences in asthma phenotypes, challenges the effectiveness of uniform management strategies. For example, it is clear that current therapies directed largely at ameliorating bronchoconstriction and airway inflammation with bronchodilators and inhaled corticosteroids do not work for all patients. A promising approach to this clinical dilemma lies in stratifying patients by markers of underlying airway inflammation, in particular neutrophilic and eosinophilic phenotypes. Such strategies have already identified patients with eosinophilic or type 2–driven inflammation as more likely to respond to corticosteroids or recently approved biologics and have prompted research on phenotypes unresponsive to such treatments, such as those with noneosinophilic inflammation or eosinophilic inflammation that persists despite high-dose inhaled corticosteroid treatment. Although many mechanisms underlying eosinophilic asthma have been delineated, the mechanisms driving neutrophilic or persistent eosinophilic inflammation remain poorly understood.

Severe asthma itself is heterogeneous based on differences in clinical, demographic, and inflammatory features. Recent findings indicate this heterogeneity extends also to the microbiome domain; differences in the composition of lower airway microbiota have been linked to distinct clinical and inflammatory features among patients with severe asthma.^{3–5} A new study by Taylor et al⁶ in this issue of the *Journal* based on analysis of sputum collected from 167 participants in the Asthma and Macrolides: the Azithromycin Efficacy and Safety Study (AMAZES) trial (ACTRN12609000197235) provides additional evidence linking characteristics of the airway microbiota to inflammatory phenotype in a large severe asthma cohort.

The findings by Taylor et al⁶ support growing evidence that perturbations in the airway bacterial microbiome can play a role in neutrophilic asthma. Compared with patients with eosinophilic inflammation, who actually comprised the greatest proportion (50%) of subjects in the study, those with neutrophilic inflammation harbored a less diverse bacterial community. Specifically, this subgroup demonstrated relative enrichment in the opportunistic pathogens *Haemophilus* and *Moraxella* species and a reduced relative abundance of *Streptococcus*, *Gemella*, *Rothia*, and *Porphyromonas* species, organisms typically viewed as nonpathogenic commensals. Overall, these results are in agreement with those of prior studies that have found collectively that members of the Gammaproteobacteria (the taxonomic class to which *Haemophilus* and *Moraxella* species and many other potential respiratory pathogens belong) become more dominant in the lower airways with increasing disease severity. Moreover, immune responses related to neutrophilic inflammation (eg, T_H17-associated epithelial gene expression⁴) have been associated with Gammaproteobacteria abundance.

These biological features might explain the ineffectiveness of corticosteroids in certain subsets of patients with steroid-refractory asthma, among whom it has been shown that the presence of *Haemophilus* but not *Prevotella* species can attenuate the macrophage response to dexamethasone.⁴ However, just as intriguing is the finding by Taylor et al⁶ of essentially no relationship between airway bacterial community composition and sputum eosinophil percentages. This is consistent with prior reports of inverse or negative relationships between airway biopsy or sputum eosinophil counts and bacterial burden in both patients with severe and those with mild asthma.^{4,7} These observations collectively suggest that other factors, including the potential role of nonbacterial microbiota, such as fungi, can drive the pathogenesis of eosinophilic asthma.

Of note, the subjects classified as having neutrophilic asthma in this study comprised only 8% (n = 14) of the 167 subjects analyzed compared with 50% classified as having eosinophilic asthma. Thus one might have expected associations to have been found between eosinophilic inflammation and the profiled sputum bacterial community. Instead, the opposite was observed. Moreover, paucigranulocytic inflammation was the second most common phenotype (36%) observed, and the absence of relationships to the bacterial microbiome implies that other mechanisms are involved in this subgroup. Finally, the assertion that neutrophilic asthma was characterized by “a greater frequency of taxa at high relative abundance” (namely, *Haemophilus* and *Moraxella* species) is weakened by the fact that less than 50% (6/14) of the subjects actually displayed this pattern and comprised only 4% of the total study cohort. This highlights the heterogeneity of the airway microbiome, at least compositionally, even within this severe asthma subgroup, as is evident from Fig 2 of the study.⁶

From the Divisions of ^aGastroenterology and ^bPulmonary & Critical Care Medicine, Department of Medicine, University of California, San Francisco, and ^cthe Division of Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor.

H.A.B. has received funding from grants from the National Institutes of Health (National Heart, Lung, and Blood Institute: 5U10HL098107; National Institute for Allergy and Infectious Diseases: P01AI089473 and UM1AI114271, sub A124789). Y.J.H. receives funding from IRO1 AI129958.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 19, 2017; accepted for publication May 3, 2017.

Corresponding author: Homer A. Boushey, MD, Division of Pulmonary/Critical Care Medicine, University of California, San Francisco, 505 Parnassus Ave, M1292, Box 0130, San Francisco, CA 94143. E-mail: homer.boushey@ucsf.edu.

J Allergy Clin Immunol 2017;■■■:■■■-■■■.
0091-6749/\$36.00

© 2017 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaci.2017.05.026>

An important strength of the study is the relatively large number of patients with severe asthma studied, representing one of the largest investigations to date that corroborates previous findings of airway bacterial microbiota associations with diminished or absent eosinophilic inflammation in asthmatic patients. However, it remains unclear whether and, if so, to what extent patterns of airway microbial dysbiosis actually drive rather than merely reflect associated patterns of immune response. Mechanistic studies will be necessary to elucidate how members of the airway microbiota induce or modulate inflammatory responses in asthmatic patients. Compositional profiling needs to be complemented with function-oriented analyses of both the host and microbial sides because interactions between the host and microbiome are almost certainly bidirectional, with species- and strain-specific behaviors shaped by the microenvironment in which they exist. Thus the surrounding physiologic, biochemical, and microbial milieu shapes both the composition and function of a microbial community.

Of relevance to this discussion, byproducts of host inflammation can serve as growth factors for Gammaproteobacteria. These include reactive oxygen and nitrogen species produced by neutrophils and other cell types that can be converted by members of the Gammaproteobacteria to support their anaerobic respiration in inflamed obstructed airways.⁸ This reflects the versatility of microbes to adapt and even thrive under a variety of conditions, invoking mechanisms like those demonstrated in Gammaproteobacteria, such as *Pseudomonas*, *Moraxella*,⁹ and *Haemophilus*¹⁰ species.

Although obvious, it should be kept in mind that the conditions shaping microbial behavior include administration of treatments intended to ameliorate asthma. An example is the finding that exposure to corticosteroids alters the physiology and gene expression profiles of *Haemophilus influenzae* to induce biofilm formation and resistance to macrolide antibiotics.¹¹ Conversely, it should also be kept in mind that subject-specific microbiomes can shape the efficacy of therapeutics, as has been best shown in the gut.¹²

The clinical promise of this study is its suggestion of the possibility of developing personalized treatments for neutrophilic asthma through antimicrobial or microbiome-modifying approaches.

Whether such strategies will be effective and result in sustained improvement in outcomes remains uncertain. Some clues as to the effectiveness of antimicrobial treatment might be provided by the trial into which the subjects of this study were enrolled (ie, the AMAZES trial of the benefits of sustained treatment of

noneosinophilic asthma with azithromycin). Other approaches, such as probiotic or prebiotic administration to revert pathogen overgrowth, might also be effective. However, it is likely that patient-specific factors will affect the success of attempts to modify their microbiome. Longitudinal studies will be necessary to understand the dynamics of the airway microbiome in asthmatic patients and the extent to which changes are accompanied by shifts in patterns of airway inflammation. It is clear that more studies will be needed to achieve the goal of truly personalized treatment strategies for asthma, a goal whose achievement is well served by the attention of Taylor et al⁶ to the airway microbiome as a possible phenotypic feature that might help identify the patients with asthma best suited for particular treatments.

REFERENCES

1. Durack J, Boushey HA, Lynch SV. Airway microbiota and the implications of dysbiosis in asthma. *Curr Allergy Asthma Rep* 2016;16:52.
2. Ndum O, Huang YJ. Asthma phenotypes and the microbiome. *EMJ Allergy Immunol* 2016;1:82-90.
3. Goleva E, Jackson LP, Harris JK, Robertson CE, Sutherland ER, Hall CF, et al. The effects of airway microbiome on corticosteroid responsiveness in asthma. *Am J Respir Crit Care Med* 2013;188:1193-201.
4. Huang YJ, Nariya S, Harris JM, Lynch SV, Choy DF, Arron JR, et al. The airway microbiome in patients with severe asthma: associations with disease features and severity. *J Allergy Clin Immunol* 2015;136:874-84.
5. Simpson JL, Daly J, Baines KJ, Yang IA, Upham JW, Reynolds PN, et al. Airway dysbiosis: *Haemophilus influenzae* and *Tropheryma* in poorly controlled asthma. *Eur Respir J* 2016;47:792-800.
6. Taylor SL, Leong LEX, Choo JM, Wesselingh S, Yang IA, Upham JW, et al. Inflammatory phenotypes in patients with severe asthma are associated with distinct airway microbiology. *J Allergy Clin Immunol* 2017;140:XXX-XXX.
7. Durack J, Lynch SV, Nariya S, Bhakta NR, Beigelman A, Castro M, et al. Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. *J Allergy Clin Immunol* 2016 [Epub ahead of print].
8. Huffnagle GB, Dickson RP, Lukacs NW. The respiratory tract microbiome and lung inflammation: a two-way street. *Mucosal Immunol* 2017;10:299-306.
9. Wang W, Reitzer L, Rasko DA, Pearson MM, Blick RJ, Laurence C, et al. Metabolic analysis of *Moraxella catarrhalis* and the effect of selected in vitro growth conditions on global gene expression. *Infect Immun* 2007;75:4959-71.
10. Othman DS, Schirra H, McEwan AG, Kappler U. Metabolic versatility in *Haemophilus influenzae*: a metabolomic and genomic analysis. *Front Microbiol* 2014;5:69.
11. Earl CS, Keong TW, An SQ, Murdoch S, McCarthy Y, Garmendia J, et al. *Haemophilus influenzae* responds to glucocorticoids used in asthma therapy by modulation of biofilm formation and antibiotic resistance. *EMBO Mol Med* 2015;7:1018-33.
12. Spanogiannopoulos P, Bess EN, Carmody RN, Turnbaugh PJ. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. *Nat Rev Microbiol* 2016;14:273-87.