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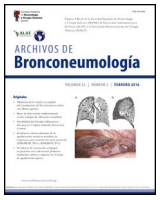

Editorial

Microbiome, Metabolome and Complexity in Bronchiectasis: The Future is Here

Many of the research articles currently being conducted on bronchiectasis begin with a compelling statement: "*Bronchiectasis is a complex and heterogeneous disease*."[1–3] These two attributes can probably also be applied to any of the most common airway diseases such as COPD[4–6] and asthma.[7] In bronchiectasis, this heterogeneity is commonly attributed to the large number of symptoms and signs that may accompany it,[8] while the complexity is attributed to the large number (more than a hundred) of pulmonary and extrapulmonary etiologies and comorbidities that may cause it and that appear clinically in a different way, from a phenotypic point of view.[9] However, the real complexity of bronchiectasis (and also of other airway diseases) does not lie only in its varied etiology but also in other aspects that have gained many points in recent years in view of the published information. These include the complexity of the changes in the lung microbiome,[10–12] its relationship with the metabolome[12–15] and in turn the relationship of the interaction between both these aspects and the clinical and prognostic variables of the disease.[12,15] This complexity is only enhanced by analysis of these same concepts and multiple relationships in any of the syndromes overlapping with bronchiectasis (those with asthma[7] or COPD[4] are the most usually studied).

Despite all this, in the present issue of *Archivos de Bronconeumología* Zhang et al.[16] have dared to publish some aspects of the difficult relationship of the metabolome and microbiome with important outcomes such as the risk of exacerbation of the overlap of the relationship between asthma and bronchiectasis and of each of its components separately. This is a truly complex article, and it could not be otherwise, but at the same time it is exhaustive and well written. It uses terms, relationships and interaction graphics that most readers are not used to but that they will have no choice but to familiarize themselves with in the near future since they mark, without a doubt, the basis of what we have been calling for years now personalized medicine.[17]

The authors, in a prospective cohort of 247 patients (99 with overlap asthma-bronchiectasis (ABO) with both eosinophilic and non-eosinophilic endotypes, 61 asthmatics without bronchiectasis and 87 bronchiectasis without asthma), assessed the differences between groups in the composition of the microbiota and the different metabolic pathways found, and they observed that these varied significantly, even in the clinical stability phase in the three groups. Thus, both the Shannon-Wiener Diversity Index (SWDI), a marker used to calculate the diversity in the microbiome and therefore the presence or absence of dysbiosis (understood as pathological changes in its composition), and the enormous variety of related metabolites (always measured in sputum) were different both between the three study groups formed, as well as in the two endotypes analyzed, depending on the count of the number of eosinophils in sputum. More specifically, among other multiple findings, the authors observed that the diversity in the microbiota was greater in asthma and ABO; that the presence of *Pseudomonaceae* and *Rothia* had a good discriminatory power of ABO with respect to asthma and bronchiectasis separately; that the abundance of *Pseudomonas* correlated negatively with other microorganisms present in the ABO-non-eosinophilic group; and that the composition of the metabolome in the ABO-eosinophilic differentiated it from the ABO-non-eosinophilic forms. In relation to the metabolome-microbiome interaction, the relative abundance of *Enterobacteriaceae* correlated negatively with the concentration of some metabolites such as 15-hydroxylated eicosatetraenoic acid, which in turn was more abundant in patients with ABO-eosinophilic, and finally, and most importantly from the clinical point of view, greater diversity of the microbiota was associated with a shorter time to the first exacerbation. If readers have managed to get to this part of the editorial without losing their breath or being able to retain so much information in such a short space of writing, we encourage them to continue reading the remaining part of the editorial. They will notice something obvious: the complexity of this form of study contrasts enormously with the relative simplicity of the current usual practice based on the measurement of some simple metabolites in sputum, related above all to the study of endotypes (neutrophilic or eosinophilic), the staining and culture of sputum to determine the presence and quantity of a certain microorganism to which we attribute the clinical state of the patient, and with which we establish the treatment that we believe to be most adequate,[18,19] and the use of parameters generally related to cell counts from peripheral blood that can, to a certain extent, give us some clue as to what is happening with local bronchial inflammation and that can serve as markers that are easy to obtain and cheap.[20]

As authors of this editorial, we will not be the ones to write against this way of doing things that we currently fear, since thanks to it we have managed to improve the health of many patients with asthma, bronchiectasis and overlap syndromes. However, it is evident, as clearly concluded by the study by Zhang et al.[16] that the simple staining and culture of sputum with a microbiologi-

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cal character or to obtain the concentration of certain molecules or the number of cells is a vague approximation of what actually occurs in the depths of our airways. However, although the future of these techniques is getting closer, we must be aware that the complexity that they handle is very difficult to integrate with respect to the attainment of a reliable, understandable, enduringly stable and cheap way of working with clear results in relation to clinical and prognostic aspects, which are the ones that ultimately determine the treatment to be established in a given patient. It is only necessary to think how it has been proven that the pulmonary microbiome can change due to the impact of multiple circumstances, both pathological (in the present study it has been observed in patients with asthma and bronchiectasis) and non-pathological, such as diet, different treatments (especially inhaled medication and antibiotics), and even the time of measurement in the day. Furthermore, it is likely that we find different microbiomes depending on the pulmonary lobe from which they come, while the whole system is complicated the most by the fact that everything changes in a short space of time, i.e., the degree of dynamism of these interactions is high.[21] And something similar could be said about metabolites or cell counts. All this leads to an unavoidable question. How are we going to manage this immense dynamic and changing amount of information and capture it in therapeutic clinical guidelines that inform physicians in a concise and clear way of what type of personalized treatment they should give their patients? It is clear that we have not yet reached this point, but we are on the way, and more than ever in this era of possible management of large amounts of information and the establishment of patterns via big data or machine/deep-learning techniques, we can make great progress in simplifying information to make it understandable and usable.[22] Therefore, it is important that these types of studies incorporate the figure of the professional involved in the management of information, in order to understand how to extract the best conclusions in the simplest possible way but without losing relevant information along the way. No one can deny that the future has arrived as regards the understanding of the endotypic complexity of these airway diseases, and there will undoubtedly be no other choice but to update our knowledge to better understand and become more familiar with this type of concept, whose purpose will be none other than to personalize the treatment of our patients as much as possible.

Use of artificial intelligence

No.

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Conflict(s) of interest

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