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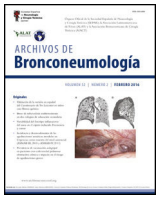

Editorial

Heterogeneity and Complexity in Bronchiectasis: A Pending Challenge☆

Heterogeneidad y complejidad del síndrome bronquiectasias: un reto pendiente

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I think the next [21st] century will be the century of complexity

Stephen Hawking (1942–2018)

Although bronchiectasis was initially defined as an apparently simple structural alteration (permanent dilation of the airways), it in fact constitutes a syndrome, understood by Scadding[1] as a set of interrelated signs and symptoms that do not necessarily share a single identifiable pathogenesis. In this respect, the bronchiectasis syndrome is both heterogeneous (the components appear in some but not all patients and can, moreover, change over time in a given patient)[2] and complex (where complexity is understood as the existence of a dynamic non-linear relationship between the multiple components).[2] Unfortunately, our current knowledge of the bronchiectasis syndrome is still limited and, consequently, treatment offered on the basis of the small number of clinical trials published is often insufficient. The challenge, then, is how to more effectively deal with this heterogeneity and complexity.

Dealing With Heterogeneity in the Bronchiectasis Syndrome

In the first place, bronchiectasis should no longer be considered as mere bronchial dilation. Instead, a diagnosis of bronchiectasis syndrome must also require the presence of relevant clinical manifestations; this would drastically reduce diagnostic heterogeneity by ruling out all forms of asymptomatic bronchial dilation that might appear in the healthy population.[3] Another important step has been the publication of scales, such as the (E)-FACED or Bronchiectasis Severity Index (BSI), that use a combination of variables (clinical, microbiological, and radiological) to quantify the severity and prognosis of the disease and indicate the level of care most suitable for the management of each patient.[4] Finally, another important factor has been the recognition of the existence of homogeneous groups of patients with bronchiectasis (or clinical phenotypes), such as the chronic *Pseudomonas aeruginosa* bronchial infection phenotype,[5,6] the exacerbator phenotype,[7,8] and the COPD overlap phenotype.[9] All these phenotypes are associated with differences in clinical presentation, prognosis, and therapeutic response.[10]

Integrating most of these key variables in a single multicomponent tool that provides a more global vision of the disease would be another important step to help address the heterogeneity of the bronchiectasis syndrome. This tool should combine at least the 3 main (and treatable) aspects of bronchiectasis: severity (multidimensional scores), impact (quality of life and other psychosocial aspects), and activity (biomarkers).[11] From a therapeutic point of view, one of the most interesting recent initiatives in the field of chronic airway disease addresses the so-called treatable traits. This paradigm shift considers airway diseases as a single spectrum of varying alterations: traits for which treatment is available are treated, and the "diagnostic label" is of secondary importance. For example, it is common to find patients with bronchiectasis that also have treatable traits of COPD (smokers or non-reversible airflow obstruction) or asthma (bronchial hyperreactivity or eosinophilia), so a treatable-traits approach would target each of these features.[2,12]

Dealing With the Complexity of the Bronchiectasis Syndrome

The complexity of the syndrome (defined as the dynamic non-linear relationship between its components) is more difficult to tackle than its heterogeneity, as it is determined by the interaction between the patient's genome and their environment via epigenetic changes. However, the identification of this biological complexity forms the basis of precision medicine, defined as therapeutic intervention that targets the needs of an individual patient on the basis of the genetic differences, biomarkers, phenotypic presentation or psychosocial characteristics that differentiate one patient from another with similar diseases.[13] Although we are still far from treating the bronchiectasis syndrome with precision medicine, at no other time in history has such rapid progress been observed in the 3 main areas that would make it possible:

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diagnostic imaging (it is estimated that only 1% of the data provided by CT is currently exploited), the development of "omic" techniques (including genomics, proteomics, metabolomics, and microbiomics) which will help us better understand the multiple endotypes (mechanisms) and biomarkers associated with the syndrome,[14,15] and bioinformatics (computational capacity that allows the processing of vast amounts of data, known as big data).[16] All these advances may eventually help identify new therapeutic targets in different groups (ideally, individuals) with the bronchiectasis syndrome.

As the recently deceased Stephen Hawking predicted, the 21st century will undoubtedly be the century of complexity. In the medical field, the outcome will be precision medicine (as is already occurring in some specialties such as oncology). The bronchiectasis syndrome cannot be left on the sidelines.

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