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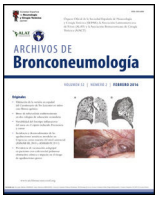

Editorial

The Exacerbation Conundrum

El embrollo de la exacerbación

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Acute exacerbations are common events in the natural course of COPD and are known to increase mortality and negatively impact patient's quality of life and lung function.[1,2] The economic cost of treating acute exacerbations contributes to more than half of the expenditure spent on care of COPD patients.[3] So far, however, there is no single biomarker that can consistently predict exacerbations.[4] In 2010, the ECLIPSE study which was a cohort of GOLD 2–4 individuals identified a subgroup of individuals, termed "frequent exacerbators" defined as those who had two or more exacerbations annually.[5] Roughly 12% of the ECLIPSE population had two or more events each year for three years. Since then, the "frequent exacerbator "has been accepted as a COPD phenotype and has been incorporated into the current GOLD guidelines multidimensional assessment of COPD.[6]

However, a recently published analysis of the SPIROMICS cohort highlights the challenges clinicians and researchers still face in identifying those most at risk.[7] In this study, that also included patients with GOLD 1 disease, only 2% of subjects qualified as "frequent exacerbator" during three years of follow-up. The most common phenotype was subjects with no exacerbations (51%) followed by subjects with inconsistent exacerbations (those with events in some years and not in other years, 41%). The results of the ECLIPSE and SPIROMICS studies are in some ways more similar than they appear at first glance. In neither study is the "frequent exacerbator" as defined by ≥2 events per year on a consistent basis actually that common (12% and 2%, respectively).

The SPIROMICS analysis did identify a slightly larger a subset of "consistently" exacerbating individuals with ≥1 event per year for each of three years of follow-up. While this represented only roughly 7% of the population studied, examination of these individuals did identify some potentially new biomarkers that may help to identify and understand the biology of such individuals including a CT metric of small airway abnormality (Parametric Response Mapping functional small airways disease), IL-15 and IL-8.

Both studies also highlight the inconsistency of events in a single individual over time. Between Years 1 and 2 in ECLIPSE, 39% of patients changed from a frequent exacerbator (≥2 AECOPD) to infrequent exacerbator (0–1 AECOPD); 17% changed from infrequent exacerbator to frequent exacerbator. In the SPIROMICS GOLD 2–4 population, between Years 1 and 2, 52% of frequent exacerbators became infrequent exacerbators while 14% of infrequent exacerbators became frequent exacerbators. It is the inherent randomness of exacerbation events which is challenging to model and points to the fact that there are likely both individual factors that we are not adequately capturing (such as the contribution of comorbidities, for instance) as well as factors outside the individual such as seasonal variation in viral infections, allergen and air pollution exposures.

These data also point to another group that deserves further study but often is overlooked, the exacerbation resistant group. Of particular interest are those with GOLD 3–4 spirometric severity who do not exacerbate. Twenty nine percent of SPIROMICS GOLD stage 3–4 had no exacerbations over 3 years period. There may be factors related to the microbiome or immune function of these individuals that make them exacerbation resistant. A better understanding of this group could provide insights into the treatment of the group who do exacerbate. For instance, non-culture based studies of exacerbations demonstrate dynamic changes in the lung microbiome (in the absence of a dominant pathogen) before and during exacerbations suggesting a role for a dysregulated lung microbial ecosystem in the pathogenesis of exacerbations.[8] It has been hypothesized that differences in the composition of the respiratory microbiome in terms of species density and diversity might explain differences in the rates of exacerbation between groups of patients with otherwise similar clinical characteristics.[9] A complex bidirectional adaptive relationship between the lung microbiome and host response may contribute to maintaining homeostasis and clinical stability in exacerbation resistant individuals. Gastroesophageal reflux disease (GERD), which has been shown to be associated with exacerbation,[5] could potentially alter the equilibrium by introducing new gut microbes, thereby, triggering an exacerbation. In

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addition, GERD might influence the baseline composition of the lung microbiome.

Until a better understanding of exacerbations is reached, from a practical standpoint, there are a few easily assessed clinical factors that have been identified as predictors of future events in multiple studies including prior event history, symptoms (assessed by CAT or SGRQ), GERD and lower FEV_1% predicted. The use of two or more exacerbations in the prior year to identify high risk patients may be overly stringent. Reported exacerbation rates from the population based CanCOLD study suggest a much lower event rate (0.39 events per patient year) among the general COPD patient population as compared to ECLIPSE (0.85–2.00 events per patient year) but comparable to SPIROMICS (0.37 events per patient year).[10] Conversely, it may also be fair to say that patients who consistently experience no exacerbations are more likely than not to remain exacerbation free. In those with inconsistent exacerbations, meticulous exclusion of competing diagnoses (CHF, depression) along with reducing symptom burden should remain the cornerstone of COPD care. A search for avoidable external triggers may also provide valuable information in patient with multiple exacerbations.

As we move forward, future studies of exacerbations will hopefully help us better understand the relationship between baseline patient phenotype, triggers and exacerbation subtypes. To that end, a better understanding of lung microbial ecosystem and host immune response on altered homeostasis may also provide the essential knowledge needed to explain the origins and unpredictability of exacerbations.

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