



Editorial

Non-exacerbator Phenotype in Chronic Obstructive Pulmonary Disease: Should We Go a Little Further?☆



El fenotipo no exacerbador en la enfermedad pulmonar obstructiva crónica: ¿es necesario ir un poco más allá?

Adolfo Balóira,* Nagore Blanco

Servicio de Neumología, Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain

It is beyond doubt that exacerbations are a fundamental aspect of chronic obstructive pulmonary disease (COPD), and this fact is reflected in the different guidelines and documents that address the management of this disease. Beyond this, however, everything becomes complicated. Starting with the imprecise definition of exacerbation, and continuing with the subjective nature of severity classifications (to treat or not to treat with antibiotics or systemic corticosteroids, to hospitalize or not to hospitalize), a hefty proportion of the variables associated with exacerbations fall within largely undefined limits. It is probably difficult to say much more about an event that, in many cases, is simply a continuum of the patient's underlying symptoms, and these are equally susceptible to variations associated with the multiple variables to which a patient is exposed on a day-to-day basis. The GesEPOC guidelines were produced with the aim of streamlining the different aspects involved in the management of a patient with this disease, and, as such, placed particular emphasis on classifying patients by clinical phenotypes and adapting treatment accordingly.¹ A phenotype is the result of the interaction between genetics and the environment – mainly exposure to cigarette smoke in the case of COPD, but also other important aspects, such as nutrition, socio-cultural setting, or the presence of other irritants or allergens. Hereditary alpha-1 antitrypsin deficiency is clearly documented as a genetic alteration that predisposes to a particular form of COPD, but it accounts for less than 1% of all cases. In recent years, numerous genome-wide association studies have been undertaken that are gradually identifying cellular pathways, the genetic expression of which may have great importance in the clinical phenotype of the disease.²

The phenotype-based classification initially proposed by GesEPOC clearly differentiates 2 groups, one with a tendency towards exacerbations and another that has no exacerbations or at most a limited number of events. The classification of the

exacerbator group is broken down further into 2 different phenotypes, in addition to the controversial mixed phenotype. However, the non-exacerbator group is not considered to possess different characteristics that may constitute separate clinical phenotypes. A priori, defining a phenotype exclusively on the absence of a certain element could be seen as too simplistic, but could be accepted if that element was found in most COPD patients, or rather, presented during exacerbations. However, as a patient with COPD is unlikely to be an exacerbator, this does not hold true. In the CHAIN cohort, for example, the percentage of non-exacerbators was 66.2%, i.e., 2/3 of patients were classified solely on the basis of this characteristic.³ It is difficult to accept that if the patient has exacerbations, the phenotype may be emphysema or chronic bronchitis, but if they do not have exacerbations, the distinction is irrelevant. Several studies have shown that, even in early stages, the course of emphysema and lung function decline differs according to whether it occurs predominantly in the upper or the lower lobes,⁴ regardless of the presence of exacerbations. Moreover, the presence of emphysema in patients with airflow obstruction might increase the risk of lung cancer.⁵ All this would appear to suggest a specific entity (a phenotype) for COPD patients with emphysema, even if they are non-exacerbators.

Another important issue is the possibility of the clinical phenotype changing during certain periods of time. During the natural history of any chronic disease such as COPD, clinicians often adjust the level of severity according to the patient's response to treatment. However, the phenotype, once assigned, is unlikely to change. The ECLIPSE study has shown the wide variability that exists in determining the threshold that defines the exacerbator phenotype.⁶ Forty percent of the patients who had at least 2 exacerbations in the first year presented 1 or fewer exacerbations in the second year, but among those who had 2 or more the 2 first years, 30% presented no exacerbations in the third year. This study also found that lung function was a very important variable for not being an exacerbator (78% in GOLD 2 and 53% in GOLD 4, in the first year of follow-up).

The definition of an exacerbator phenotype is also open to debate. There does not appear to be any major difference between the clinical and prognostic variables of the disease beyond a rate

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* Corresponding author.

E-mail address: adolfo.baloira.villar@sergas.es (A. Balóira).

of at least 2 exacerbations per year. Indeed, a subanalysis of the UPLIFT study found a more or less linear correlation between a greater number of exacerbations and worse quality of life, lung function decline, and increased mortality.⁷ When the GesEPOC guidelines were designed, the need to distinguish non-exacerbator phenotype from others was in large part due to the indication for treatment with inhaled corticosteroids to decrease the incidence of exacerbations in the exacerbator phenotypes. However, after the FLAME study⁸ (although only 19% of patients had at least 2 exacerbations in the previous year) and several post hoc analyses of other studies, the role of these drugs in preventing exacerbations is beginning to be questioned, since they do not seem to be superior to combined bronchodilators, except perhaps in the presence of eosinophilia.

In conclusion, classifying a COPD patient simply as a non-exacerbator may not entirely appropriate in the light of findings that have emerged in the past few years, in terms of both treatment and the natural history of the disease. Greater efforts should be made to further categorize around 60% of all COPD patients beyond simply calling them non-exacerbators.

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