



## Editorial

 Frequent or Persistent Exacerbations: Identifying the Real Problem<sup>☆</sup>


## Agudizaciones frecuentes o persistentes: identificando el problema real

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It is well known that exacerbations of chronic obstructive pulmonary disease (COPD) represent a health problem of the first order in the clinical presentation of the disease. Current clinical guidelines acknowledge frequent exacerbations as a significant clinical presentation that needs a specific therapeutic approach.<sup>1</sup>

For some time, clinicians have known that some patients present more exacerbations than others. However, the concept of frequent exacerbator often reflected in the guidelines was based to a large extent on the “Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points” study (ECLIPSE). This was a large multicenter observational cohort study which followed 2164 COPD patients receiving active treatment, 337 smokers with normal lung function and 245 never-smokers, for a period of 3 years. The authors analyzed the frequency of exacerbations and identified a group (12%) that had 2 or more exacerbations every year, despite active treatment, another group (23%) who were persistently exacerbation-free, and a third group (65%) with a variable number of annual exacerbations.<sup>2</sup> This study also identified a history of previous exacerbations as the greatest isolated risk factor for predicting an exacerbation in the following year, thus establishing a pattern of clinical behavior among patients who were prone to exacerbations and consolidating the notion of a frequent exacerbator patient.

Therefore, 3 years of follow-up were needed to identify a group of patients who continue to have exacerbations despite medical treatment, and on this basis the current concept of an exacerbator patient was established. Current guidelines have simplified this concept by limiting the evaluation of the number of exacerbations to the previous year.<sup>1,3</sup> However, in the light of the ECLIPSE study results, limiting the analysis to the number of exacerbations in the previous year may lead to a misclassification of patients by number of exacerbations.

When considering this matter, it is important to scrutinize treatments and how they impact on the number of exacerbations. Currently, many treatments are available that are useful for reducing the number of exacerbations,<sup>4</sup> with a similar average impact. Accordingly, regardless of the debate about what treatment might be more effective depending on the type of exacerbation,<sup>5</sup> a patient who presented frequent exacerbations during the previous year may not constitute a major challenge for the clinician, since several effective treatments are available for reducing the rate of these events.<sup>4</sup>

Our real problem is the patient who continues having exacerbations despite appropriate medical treatment, a correct inhalation technique, and good treatment adherence. The persistent exacerbator should then be defined as the patient who continues to have exacerbations despite appropriate inhaled treatment. Due to the clinical implications of exacerbations in the clinical course of COPD,<sup>6</sup> these patients (12% in the ECLIPSE cohort<sup>2</sup>) constitute a real health problem and a major challenge to clinicians, since exacerbations are a clinical outcome which should improve with treatment.

Consequently, the diagnostic approach of the persistent exacerbator patient must be made using a systematic approach that can identify the conditions contributing to persisting exacerbations, thus enabling the physician to select the best preventive treatment possible. Because of its complexity, this process must be conducted in a specialized respiratory care setting. This systematic approach must include, but is not limited to, the following clinical considerations.

Firstly, the patient must avoid risk factors, particularly smoking which is the most significant risk factor, but also other possible factors including occupational exposures. In this respect, this clinical situation should be a motivation to help the patient advancing in the process of smoking cessation for which we have specific recommendations.<sup>1</sup>

Secondly, respiratory comorbidities that may impact on the appearance of exacerbations must be evaluated. The most significant of these is probably the presence of bronchiectasis. Bronchiectasis in COPD patients is associated with frequent exacerbations, isolation of a potentially pathogenic microorganism, severe respiratory obstruction, and mortality.<sup>7</sup> Another cause of infectious exacerbations is colonization or chronic infection of the

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airway, so it seems reasonable to recommend a high-resolution computed tomography scan and a microbiological study of sputum as part of the evaluation of these patients. Finally, the respiratory evaluation must include an investigation for the presence of an overlap syndrome with severe bronchial asthma<sup>8</sup> that might require specific treatment such as biologics.

Thirdly, potentially treatable extrapulmonary comorbidities that might be associated with the appearance of exacerbations must be studied. These include heart diseases which, given their obvious physiological relationship and symptomatic similarity to respiratory disease, can at times make it difficult to distinguish exacerbations of respiratory or cardiologic origin. Gastroesophageal reflux disease in COPD patients is associated with increased respiratory symptoms, poorer quality of life and more frequent exacerbations.<sup>9</sup> Although the efficacy of proton pump inhibitors in the reduction of exacerbations has been questioned,<sup>10</sup> it seems reasonable to take this comorbidity into account in the study of the persistent exacerbator. Finally, since exacerbations are mostly caused by infections,<sup>1</sup> immunodeficiency should also be ruled out.

In conclusion, there is no doubt that persistent exacerbations despite correct medical treatment are a challenge for the clinician, and must be approached systematically in a specialized respiratory medicine department. In remembrance of the famous novel of D. Miguel de Cervantes Saavedra (1547-1616), *The Ingenious Hidalgo Don Quixote*, this year we commemorate the 400th anniversary of his death, and instead of tilting at windmills when treating exacerbations, we should focus resources on identifying the real enemy, persistent exacerbators, and evaluate their determinant factors in order to offer the best preventive treatment possible in each case.

## Conflict of Interests

The authors state that they have no conflict of interests with regard to this manuscript.

## References

1. Miravittles M, Soler-Cataluna JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish guideline for COPD (GesEPOC). Update 2014. Arch Bronconeumol. 2014;50 Suppl. 1:1–16.
2. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363:1128–38.
3. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347–65.
4. Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015;147:894–942.
5. Lopez-Campos JL, Agusti A. Heterogeneity of chronic obstructive pulmonary disease exacerbations: a two-axes classification proposal. Lancet Respir Med. 2015;3:729–34.
6. Pavord ID, Jones PW, Burgel PR, Rabe KF. Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2016;11(Spec. Iss.):21–30.
7. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: a systematic review and meta-analysis. PLOS ONE. 2016;11:e0150532.
8. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. N Engl J Med. 2015;373:1241–9.
9. Martinez CH, Okajima Y, Murray S, Washko GR, Martinez FJ, Silverman EK, et al. Impact of self-reported gastroesophageal reflux disease in subjects from COPDGene cohort. Respir Res. 2014;15:62.
10. Baumeler L, Papakonstantinou E, Milenkovic B, Lacombe A, Louis R, Aerts JG, et al. Therapy with proton-pump inhibitors for gastroesophageal reflux disease does not reduce the risk for severe exacerbations in COPD. Respirology. 2016. <http://dx.doi.org/10.1111/resp.12758>.