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Treatment of COPD by clinical phenotypes. Putting old evidence into clinical practice.


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Running title: Treating COPD by phenotypes
ABSTRACT

The new GOLD update has moved forward the principles of treatment of stable COPD by including the concepts of symptoms and risks into the decision of therapy; however, no mention of the concept of clinical phenotypes was included. It is recognized that COPD is a very heterogeneous disease and not all patients respond to all the drugs available for treatment. The identification of responders to therapies is crucial in chronic diseases to provide the most appropriate treatment and avoid unnecessary medications. The classically defined phenotypes of chronic bronchitis and emphysema, together with the newly described phenotypes of overlap COPD-asthma and frequent exacerbator allow a simple classification of patients that share clinical characteristics and outcomes and, more importantly, similar responses to existing treatments.

These clinical phenotypes can help clinicians identify patients that respond to specific pharmacologic interventions. As an example, frequent exacerbators are the only subjects with an indication for anti-inflammatory treatment in COPD. Among them, those with chronic bronchitis are the only candidates to receive PDE4 inhibitors. Patients with overlap COPD-asthma phenotype show an enhanced response to inhaled corticosteroids and infrequent exacerbators should only receive bronchodilators. These well defined clinical phenotypes could potentially be incorporated into treatment guidelines.

Keywords: COPD; treatment; guidelines; phenotypes.
What is the relevance of clinical phenotypes in COPD?

The history of the guidelines of treatment of COPD is an example of the simplification of a complex reality. The Venn diagram included in the American Thoracic Society (ATS) statement for management of COPD in 1995 reflected the complexity of the disease and its different clinical presentations (1). However, the limited alternatives for pharmacologic treatment at that time made it unnecessary to identify the different types of patients for clinical practice. The evolution of the concept of one-treatment-fits-all led to the selection of the pharmacologic treatment based almost exclusively on the severity of airflow obstruction introduced in the GOLD document in 2001 (2) and successive revisions up to the last one in 2011 (3). The recent revision of the GOLD document has moved forward and changed the paradigm proposing a treatment directed by the intensity of symptoms (measured by the mMRC dyspnea scale and/or the COPD Assessment Test) and the risk of poor outcomes (identified by the degree of airflow obstruction and/or the frequency of exacerbations) (3) in a three-dimensional evaluation as previously suggested by Lopez-Campos (4). This is clearly a significant improvement in considering the patient as a whole and not only by the degree of airflow obstruction; nevertheless, there is no mention of differential treatment based on clinical characteristics of patients in the document.

The last decade has seen an exponential increase in research in the field of COPD and new options for treatment of the disease have successfully been developed (5), together with new evidence about the use of old drugs in certain types of patients with COPD (6). It has become increasingly evident that not all
patients respond equally to all drugs (irrespective of the severity of symptoms and/or the level of risks), and the need to identify “responders” is crucial (7,8). In this context, the concept of a clinical phenotype in COPD has emerged as "... those attributes of the disease alone or in combination that describe the differences between individuals with COPD in relation to parameters that have clinical significance (symptoms, exacerbations, response to treatment, rate of progression disease, or death)” (9). Therefore, the phenotype should be able to classify patients into subgroups with prognostic value and to determine the most appropriate therapy to achieve better results from a clinical standpoint.

How many clinical phenotypes are there?

Many previous studies have attempted to identify and quantify the prevalence of different phenotypes of COPD, using populations of various sources, severities and particularities (10). Yet there is still no consensus on the number and definition of the different COPD phenotypes, being anywhere from two to 210 million (the estimated number of patients worldwide) (11). However, there must be a compromise between the oversimplification of the term COPD, as a definition that encompasses the entire spectrum of patients with incompletely reversible airflow obstruction largely caused by smoking, and the complexity of considering each patient individually as an orphan disease (12). This intermediate step might arise by the identification and description of some phenotypes that not only have biological or epidemiological sense but also prognostic and therapeutic value, especially at the individual patient level.
**Which are the relevant clinical phenotypes?**

The old ATS Venn diagram already included all the clinical types of patients with COPD and their overlaps (1). If we want to define “clinically relevant” phenotypes we need to identify those phenotypes which, besides determining clinical outcomes, also characterise patients with a different or selective response to specific treatments and are prospectively validated. As an example, from the seminal study by Burrows et al (13) it is clear that patients can present with predominant emphysema or chronic bronchitis, and this now has an impact on treatment since it has been demonstrated that only patients with chronic bronchitis (and exacerbations) respond to the new PDE4 inhibitor roflumilast (5). Therefore, identification of patients with the phenotype of frequent exacerbations and chronic bronchitis is relevant in clinical practice. Other phenotypes with clinical or therapeutic implications include the frequent exacerbator and overlap COPD-asthma.

The COPD exacerbator phenotype refers to patients with two or more exacerbations annually (14,15). This phenotype is based on clinical records and/or patient recall, and it has been shown that diagnosis based on patients reporting their history of exacerbations is reliable (16). The COPD exacerbator phenotype implies a worse prognosis (17) and underscores the importance of asking and recording the history of exacerbations in the clinical record and identifies patients who may require anti-inflammatory treatment added to bronchodilators.
On the other hand, epidemiological studies of COPD incidence show that young asthmatics who smoke and develop not fully reversible airflow obstruction (i.e. COPD by definition) have a disease with different characteristics to those with chronic airflow obstruction but no history of asthma. In the first case allergic rhinitis, bronchial hyperresponsiveness, and the presence of wheezing, together with higher plasma concentrations of IgE are significantly more frequent, indicating that this is an overlap phenotype between asthma and COPD (18). The overlap COPD-asthma phenotype has been defined as an incompletely reversible obstruction of airflow accompanied by symptoms or signals of increased reversibility of the obstruction (19,20) or as the diagnosis of COPD in a patient with a history of previously diagnosed asthma before the age of 40 (21). These patients share characteristics of both diseases and represent a challenge in differential diagnosis, particularly in primary care (22). The prevalence of this mixed phenotype is unknown, but there are different estimates of its importance in the context of COPD. The COPD Gene cohort found this in 13% of their sample (21). Soriano et al (10) estimated that approximately 23% of COPD patients of ages from 50 to 59 years could have a mixed phenotype, with this percentage increasing with age. The relevance of this phenotype, already described in the Canadian (23) and Japanese (24) guidelines, is its enhanced response to inhaled corticosteroids (23-26),

These phenotypes identify patients with different response to the treatments available and allow a more personalized approach to treatment, which is modulated according to COPD severity.
Other COPD phenotypes have been proposed, but their importance when directing treatment is not established. As an example, the fast decliner is a patient with a greater than average fall in FEV\textsubscript{1}. A practical problem is that this phenotype is impossible to identify without close monitoring of lung function for at least three years (27), and no specific treatment for these patients is currently available. Similarly, an “inflammatory phenotype” has been described in patients with persistently elevated serum concentrations of inflammatory markers (28). They are associated with poorer clinical outcomes, but as yet no specific treatment has been identified for these patients. Current smokers may also represent a different phenotype with worse outcomes and poorer response to treatment, but we consider that current smokers must be identified across all phenotypes and intensive smoking cessation strategies must be adopted in these individuals. Moreover, a phenotype called "systemic" or with significant comorbidity, being either cardiovascular, metabolic or otherwise, has been identified (29). However, we believe that comorbidity should always be considered as a feature in all patients and in all stages or grades, which may accompany or complicate any of the clinical phenotypes. In addition to this, there is no specific or differential treatment for COPD with or without comorbidity (or comorbidities).

**How can we treat COPD based on clinical phenotypes?**

According to the different responses to pharmacologic treatment, the recent Spanish Guideline for Treatment of COPD (Guía Española de la EPOC – GesEPOC) has proposed four different phenotypes characterized by the combination of the classical types of emphysema, chronic bronchitis,
exacerbators and patients with overlap COPD-asthma (30). The proposed phenotypes in GesPOC are: A) Infrequent exacerbator, with either chronic bronchitis or emphysema; B) Overlap COPD-asthma; C) Frequent exacerbator with predominant emphysema; D) Frequent exacerbator with predominant chronic bronchitis (31).

Following the GOLD proposal the frequent exacerbator is defined as having 2 or more exacerbations per year (3), based, among others, on the results of the ECLIPSE study (14). The COPD exacerbator frequently presents chronic bronchitis, defined as the presence of productive cough or expectoration for more than three months a year and more than two consecutive years (32,33). Bronchial hypersecretion in COPD has been associated with increased airway inflammation and increased risk of bronchial colonization and respiratory infection, which may explain why patients with chronic bronchitis have an increased frequency of exacerbations (32-34). These patients may be treated with bronchodilators, inhaled corticosteroids, and they respond to treatment with the PDE4 inhibitor roflumilast (5). Selected cases of frequent exacerbators may respond to long-term treatment with macrolides (6), quinolones (particularly if they produce dark sputum) (35), and when inhaled corticosteroids cannot be used, mucolytics may be effective in reducing exacerbations (36-38).

When the frequent exacerbator does not present with chronic cough and sputum production and the typical clinical and radiological signs of emphysema can be identified, this constitutes the exacerbator with an emphysema phenotype (39). The basis of pharmacologic treatment in these patients is long-acting bronchodilators and, in some cases, inhaled corticosteroids.
New studies have identified phenotypes of exacerbations: bacterial, viral, eosinophilic and pauciinflammatory. These phenotypes are quite stable and related to the clinical phenotype in stable state (40,41). For example, individuals with eosinophilic exacerbations usually have increased concentrations of peripheral eosinophils, even in stable state (40), and their exacerbations respond to systemic corticosteroids, in contrast to non-eosinophilic exacerbations that may have a poorer evolution with systemic corticosteroids compared to placebo (42). It is tempting to associate infective exacerbations with the exacerbator with chronic bronchitis phenotype, eosinophilic exacerbations with the overlap COPD-asthma phenotype, and pauciinflammatory exacerbations with the exacerbator with an emphysema phenotype, but confirmatory studies are needed.

On the contrary, the infrequent exacerbator is defined as any patient experiencing less than two exacerbations per year. The importance of identifying this phenotype is that there is currently no anti-inflammatory treatment indicated or licensed for infrequent exacerbators, irrespective of having predominant emphysema or chronic bronchitis. The treatment of this phenotype is based on long-acting bronchodilators, alone or in combination, and the possible addition of theophyllines in the more severe cases (43).

Finally, the overlap COPD-asthma phenotype is associated with enhanced response to inhaled corticosteroids due to the predominance of eosinophilic bronchial inflammation (44,45). Therefore, these patients should be prescribed inhaled corticosteroids together with long-acting bronchodilators irrespective of the severity of the airflow obstruction, as recognized in some previous
guidelines (23,24). The Spanish guidelines have also recognized this phenotype (31) and a consensus document has been generated with diagnostic criteria to identify patients with overlap COPD-asthma. Among these criteria, the most important are the history of previous asthma before the age of 40, the demonstration of eosinophilic inflammation in sputum or increased peripheral eosinophilia and enhanced reversibility in airflow obstruction after the bronchodilator test. Due to the poor reproducibility of bronchodilator response, marked response (>400 mL in FEV1) or at least two positive bronchodilator tests is required (46). A simplified scheme of pharmacologic treatment guided by clinical phenotypes is depicted in Figure 1.

This review is focused on pharmacologic treatments, but we should not forget that comprehensive treatment of COPD must include smoking cessation strategies, pulmonary rehabilitation, exercise, management of comorbidities and surgical options for selected patients.

Where do we go from here?

It is clear that the approach to treatment according to clinical phenotypes represents a significant change in the management of COPD, from treatment focused on the severity of the airflow limitation to a more personalized approach directed by clinical features. Large pharmacological clinical trials have included unselected populations of patients with COPD and analyzed the results as comparisons of mean values between treatment groups without considering the possibility of the existence of different populations of responders and non responders to a given drug (47). New studies need to incorporate subgroup analysis of response by clinical characteristics (5,6) or even be restricted to
particular phenotypes to investigate the response to therapy of a group of patients with common characteristics (48). The results of these trials will help to personalise treatment for this complex disease. In the meantime we can use the classical phenotypes described here to easily identify subgroups of patients that will respond to different treatments. We believe that including these rapidly recognizable clinical phenotypes in management guidelines would help clinicians to select the most effective treatments for their patients. Nonetheless, this approach should be validated in future clinical studies.

REFERENCES:


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Figures

Figure 1. Proposal of pharmacologic treatment of COPD according to clinical phenotypes.

Figure 1

<table>
<thead>
<tr>
<th>No exacerbator</th>
<th>Overlap COPD-asthma</th>
<th>Exacerbator with emphysema</th>
<th>Exacerbator, with chronic bronchitis</th>
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<tr>
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<td>Long-acting bronchodilators</td>
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<td>Macrolides</td>
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Footnote: Bronchodilators are the basis of treatment of COPD irrespective of the clinical phenotype. Inhaled corticosteroids are indicated in frequent exacerbators and patients with the overlap COPD-asthma phenotype. Mucolytics can be used in frequent exacerbators, particularly if they have predominant chronic bronchitis and/or inhaled corticosteroids are not prescribed. Roflumilast is indicated in frequent exacerbators with chronic bronchitis. Finally, selected cases of patients with chronic bronchitis and frequent exacerbations, despite optimal therapy, may be candidates for
treatment with long-term antibiotics under close follow-up in reference centers.

The order of the bars does not represent the order of preference for treatment.