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Chronic obstructive pulmonary disease phenotypes: Are they really useful in clinical practice?

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Abstract:

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. It is a complex and heterogeneous disease. In recent years, studies showed that forced expiratory volume in 1 s solely was not enough to describe heterogeneity of COPD patients, and subsequently, phenotypes of COPD were identified. The aim of phenotyping is the classification of patients into distinct subgroups according to the prognosis and response to therapy so that the selection of optimal therapy can be possible, and this clinical approach may improve prognosis. In the assessment and management of the disease, it is important to consider phenotype of a COPD patient. The aim of this article is to review predefined COPD phenotypes, their clinical and epidemiological features, and usefulness in clinical practice for accurate diagnosis and appropriate treatment of COPD patients.

Keywords:

Chronic obstructive pulmonary disease, epidemiology, phenotypes, treatment

Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of mortality and morbidity worldwide.[1] Postbronchodilator forced expiratory volume in 1 s (FEV_1) is a diagnostic criterion and also it helps grading the disease severity. COPD is a very complex and heterogeneous disease in the means of symptoms, prognosis, and course of the disease. FEV_1 is not solely sufficient to explain this heterogeneity. Snider presented some overlapping subgroups such as asthma, emphysema, and chronic bronchitis (BC) in Venn diagram and subsequent studies also supported this overlap.[2] Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, which is a milestone showing heterogeneity of COPD within each GOLD stage, revealed apparently that FEV_1 does not capture the complexity of the disease, and the clinical management of patients with COPD needs more than spirometry.[3] Phenotype of COPD is currently defined as a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes such as symptoms, exacerbations, response to therapy, rate of disease progression, or death.[4] Relief of symptoms and prevention of exacerbations are two main goals of COPD management.[5] By means of phenotypes, treatment can be personalized considering not only severity of airflow limitation but also clinical features of patients.[6]

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Phenotypes of Chronic Obstructive Pulmonary Disease

Nonexacerbator phenotype

A nonexacerbator phenotype is defined as any patient with COPD who presents <2 exacerbations in the previous year.[7]

Frequent exacerbator phenotype

In the ECLIPSE study, it was shown that in each category of airflow limitation, number of exacerbations of COPD patients varied widely.[3] This result was suitable with suggestions of the UK National Institute for Clinical Excellence in that exacerbations, symptoms, and comorbidities should be considered in the clinical assessment of COPD patients to manage their treatment more appropriately.[8]

An exacerbator phenotype is defined as any patient with COPD who presents 2 or more moderate exacerbations in the previous year, defined as those that require at least outpatient treatment with systemic corticosteroids and/or antibiotics, or a severe exacerbation that requires hospital admission.[7]

The analyses of results of ECLIPSE study made evident that having two or more exacerbation per year seemed a stable phenotype during 3 years in a group of patients (12% of the study population). This proportion was found 2% in SPIROMICS cohort.[3,9]

Patients with an exacerbator phenotype have a higher risk of hospitalization, while patients with severe exacerbations have a higher risk of mortality. Due to the different response to pharmacological treatments, it is important to differentiate patients with an emphysematous or Chronic bronchitis phenotype.[7]

Chronic bronchitis phenotype

Definition of CB firstly made by British physicians in Ciba symposium in 1959.[10] Subsequently, the World Health Organization (WHO) and the American Thoracic Society (ATS) defined CB.[11,12] ATS definition of CB is made based on the symptoms of a cough that produces mucus or phlegm on most days, for 3 months, for two or more years (after other causes for cough have been excluded).[12] The prevalence of CB is higher in patients with COPD, affecting 14%–74% of all patients with COPD.[13] In the ECLIPSE study, 34.6% of the 2161 participants reported CB.[3] For identification of CB phenotype of COPD, Spanish COPD Guideline suggested that the patient must be asked about the presence of cough with expectoration for at least 3 months of the year in 2 consecutive years. In the case of patients with the exacerbator phenotype with BC, high-resolution computed tomography (HRCT) should be carried out to check whether the patient has bronchiectasis.[7]

Emphysema phenotype

Similar to CB, emphysema also primarily defined in Ciba symposium in 1959.[10] It was defined as enlargement of the acinus that might or might not be accompanied by destruction of respiratory tissue. Subsequently, the WHO and ATS limited the term emphysema to enlargement of any part or all of the acinus accompanied by destruction of respiratory tissue.[11,12]

The emphysema can be better characterized by measurement of gas trapping using static lung volumes and the carbon monoxide diffusing capacity test. Chest CT will be necessary when considering the possibility of surgical treatment or if the patient presents frequent exacerbations.[7]

Asthma–chronic obstructive pulmonary disease overlap syndrome

Overlap of COPD and asthma was firstly presented in Venn diagram by Snider and Kleinerman.[2] However, definition and clinical importance of Asthma–COPD Overlap Syndrome (ACOS) were stated primarily 30 years later, in 2014, in GINA/GOLD guideline. In this guideline, ACOS was defined as persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is, therefore, identified in clinical practice by the features that it shares with both asthma and COPD.[14] More recently, the ATS and the National Heart, Lung, and Blood Institute issued a workshop statement concluding that ACOS should not be considered a discrete disease entity, but rather an airways disease phenotype of mixed features.[15] According to the recent GesEPOC-Guidelines for the Management of Asthma consensus, ACO can be diagnosed in a patient with COPD who also meets the diagnostic criteria for asthma according to the current guidelines or who presents features considered as suggestive of asthma, such as a strongly positive bronchodilator test (increase in FEV_1 >400 mL and 15%) and/or peripheral blood eosinophilia >300 cells per mm^3.[7]

There are many other definitions of ACOS in different studies, and they share several key obligatory features that patients should be 40 years or older, have persistent airflow obstruction, and a history of asthma or evidence of bronchodilator reversibility.[16]

COPD phenotypes and their definitions were summarized on Table 1.

Bronchiectasis in chronic obstructive pulmonary disease

Overlapping of bronchiectasis and COPD was firstly described by Barker in 2002.[17] Subsequently, the rates

Table 1: Chronic obstructive pulmonary disease phenotypes and their definitions

Phenotype	Definition
Nonexacerbator	COPD patient who presents <2 exacerbations in the previous year
Frequent exacerbator	COPD patient who presents 2 or more moderate exacerbations in the previous year or a severe exacerbation that requires hospital admission
CB	COPD patient who had cough with expectoration for at least 3 months of the year in 2 consecutive years
Emphysema	COPD patient who had gas trapping using static lung volumes and the carbon monoxide diffusing capacity and/or emphysema on HRCT
ACOS	COPD patient who had persistent airflow limitation with several features usually associated with asthma or who presents features considered as suggestive of asthma, such as a strongly positive bronchodilator test (increase in FEV_1 >400 mL and 15%) and/or peripheral blood eosinophilia >300 cells per mm^3

HRCT: High-resolution CT, CT: Computed tomography, FEV_1: Forced expiratory volume in 1 s, CB: Chronic bronchitis, ACOS: Asthma-COPD overlap syndrome, COPD: Chronic obstructive pulmonary disease

of bronchiectasis described on HRCT were reported in different studies ranging from 4% to 57.6% of COPD patients.[18] The rate of bronchiectasis was found relatively lower than other studies (4%) and increased with GOLD stages in ECLIPSE study.[3] The presence of bronchiectasis causes longer and more frequent exacerbation and increased mortality.[5] COPD patients who were mechanically ventilated had longer intensive care units stay and hospitalization in the case of associating bronchiectasis.[19] COPD patients who have bronchiectasis had poorer lung function and higher risk of complication, and it was proposed that it should be considered a phenotype of COPD.[20,21] Bronchiectasis with COPD is not still yet defined as a phenotype in a guideline.

Epidemiology of chronic obstructive pulmonary disease phenotypes

Epidemiological studies about COPD phenotypes have been performed. One of these studies is FENEPOC study from Spain, that contained 647 COPD patients, and the authors investigated frequency of phenotypes, their clinical characteristics, and the availability of diagnostic tools. Nonexacerbator phenotype was the most frequent phenotype in Spain and ACOS was the least frequent. Diagnostic tools were available to classify COPD phenotypes in clinical practice and pharmacological treatment of patients showed variability considering the phenotype of patients.[22] Another epidemiological study of COPD phenotype from Spain showed uneven distribution of COPD phenotypes in a large cohort (n = 831) stable COPD patients, nonexacerbator phenotype was the most frequent phenotype similar to FENEPOC study, but frequent exacerbator emphysema was the least frequent one and distribution of phenotypes was stable during 1-year follow-up.[23] Soler-Cataluña *et al*. found that frequent exacerbators have worse survival than nonexacerbator patients.[24] Exacerbations became more frequent and more severe as the severity of COPD increased and that the single best predictor of exacerbations, across all GOLD stages, was a history of exacerbations in ECLIPSE cohort.[25] COPDGene and PLATINO studies showed that patients with BC have worse respiratory symptoms and higher risk of exacerbations.[26,27] Classification of COPD patients according to the clinical phenotypes is useful to differentiate groups of patients who had different mortality risk. Execerbator emphysema is associated to the highest risk of mortality in COPD patients.[28,29] ACO phenotype had the best long-term prognosis.[28] POPE study from Poland showed that nonexacerbator phenotype was the most frequent phenotype, while BC with BC was the most symptomatic phenotype.[30]

Current Treatment Approaches in Chronic Obstructive Pulmonary Disease Phenotypes

Nonexacerbator phenotype

Long-acting beta-2 agonist or long-acting antimuscarinic (LABA or LAMA) are choices of treatment in patients with nonexacerbator phenotype.[5] LABA/LAMA is suggested in nonexacerbator phenotype COPD patients with high risk.[7]

Frequent exacerbator

LAMA is the first choice in patients with frequent exacerbator phenotype. İf patient is highly symptomatic LABA/LAMA combination is first choice for the treatment. Inhaler corticosteroids (ICS) are indicated in patients who present frequent exacerbations despite optimal bronchodilator treatment. Recent studies showed that blood eosinophil counts predict the magnitude of the effect of ICS. The threshold of a blood eosinophil count >300 cells/μl can be used to identify patients with the greatest likelihood of treatment benefit with ICS.[5] In high-risk patients who do not present good control of exacerbations with two drugs (either two long-acting bronchodilators [LABDs] or an LABD + ICS), triple therapy with LAMA/LABA/ICS can be used. Long-term use of carbocysteine significantly reduces the number of exacerbations, delays worsening of symptoms, and improves quality of life in patients with COPD, compared to placebo. N-acetylcysteine (NAC) at doses of 600 mg daily can reduce the number of exacerbations in patients not treated concomitantly with ICS. More recent studies with high-dose NAC (600 mg twice daily) have shown a significant reduction in exacerbations, especially in high-risk patients (those with FEV_1 <50% or with 2 or more exacerbations in the previous year, or both).[31]

Long-term treatment with macrolides is indicated in high-risk patients with at least three exacerbations in the previous year despite adequate inhaled therapy. Macrolides administered on a long-term basis have been shown to significantly reduce the number of exacerbations in stable patients with severe COPD. Azithromycin (250 mg/day or 500 mg three times per week) for 1 year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care.[5,32,33]

Chronic bronchitis

Addition of roflumilast in patients with FEV_1 <50% and BC phenotype who have at least one hospitalization for an exacerbation in the previous year despite triple treatment may be considered. Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with BC, severe-to-very severe COPD, and a history of exacerbations. In this group of patients, addition of macrolide also may be considered.[5,7]

Asthma–chronic obstructive pulmonary disease overlap syndrome phenotype

The presence of ACOS indicates higher eosinophilic airway inflammation so that higher response to ICS. Current guidelines suggested ICS in a low or moderate dose according to symptoms of the patient; usually, the addition of LABA improves lung function and respiratory symptoms and reduces exacerbations. Triple ICS/LABA/LAMA treatment may be required in more severe cases[7,14] (GINA/GOLD 2015, Spanish guideline). Although ICS/LABA is the first choice in the treatment of ACOS, risk-benefit ratio of long-term treatment is not yet clear. These patients may benefit from omalizumab or montelukast treatment, but there is not adequate data about the efficiency of these drugs in ACOS treatment.[34]

Table 2 summarizes treatment of COPD phenotypes.

Table 2: Treatment of chronic obstructive pulmonary disease phenotypes

Phenotype	Treatment
Nonexacerbator	LABA or LAMA
	LABA/LAMA
Exacerbator with emphysema	LAMA
	LAMA/LABA*
	ICS/LABA**
	LAMA/LABA/ICS
	Carbocysteine, NAC
	Macrolides
Exacerbator with CB	LAMA
	LAMA/LABA*
	LABA/ICS**
	LAMA/LABA/ICS
	Roflimulast
	Carbocysteine, NAC
	Macrolides
ACOS	LABA/ICS
	ICS/LABA/LAMA

*Consider if highly symptomatic (CAT >20), **Consider if eosinophil >300 cells/μl. LABA: Long-acting beta-2 agonist, LAMA: Long-acting antimuscarinic antagonist, ICS: Inhaler corticosteroids, CB: Chronic bronchitis, ACOS: Asthma-COPD overlap syndrome, COPD: Chronic obstructive pulmonary disease, NAC: N-acetylcysteine, CAT: COPD assessment test

Future Directions and Conclusion

Although definition of COPD phenotypes and specific treatment considering phenotype of patient is currently possible in clinical practice, all patients in one phenotype were not identical and same patient could have more than one phenotype. In current literature, the definition of ACOS is not unique, many of these definitions do not consider environmental exposures (either cigarette smoke or biomass fuel) despite such exposures are very important in development of COPD. This uncertainty in diagnosis of ACOS causes variations in the prevalence in different studies. Treatment of ACOS also is controversial. Beyond this, it will be necessary in the future to consider not only phenotype of COPD patient but also basis of genetic, biomarker or psychosocial characteristics, treatable traits that distinguish a given patient from other patients with similar clinical presentations.

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Conflicts of interest

There are no conflicts of interest.

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