Chronic obstructive pulmonary disease classification, phenotypes and risk assessment

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Abstract: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease. Various classification systems and phenotypes have been proposed. This review highlights the current classifications of COPD, describes the major phenotypes and provides a blue print for risk assessment of COPD. It is likely that more phenotypes and endotypes of COPD will be described paving the way to personalized medicine for patients with COPD.

Keywords: COPD classification; COPD phenotype

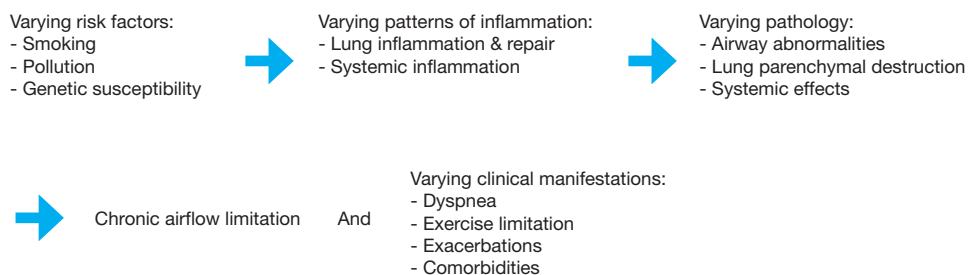## Chronic obstructive pulmonary disease (COPD) classification

COPD is defined as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (1). The diagnosis of COPD requires the spirometric demonstration of persistent airflow limitation, as defined by post bronchodilator FEV1/FVC <70%, in patients with appropriate symptoms and history of exposure to noxious stimuli (1). There is considerable heterogeneity in symptoms, disease progression, functional outcomes and response to therapies based on the etiology, pathogenesis and type of lung pathology (2,3) (*Figure 1*).

Various classification systems for COPD have been developed. The purpose of any classification is to allow categorization of patients in meaningful ways, so as to predict symptoms, functional outcomes, prognosis or response to therapies. The cardinal feature of COPD is airflow limitation. Therefore, the initial classification of COPD by GOLD (Global Initiative for Chronic Obstructive Lung Disease) was based solely on reduction in FEV1 (4). However, there is only a weak correlation between FEV1 and symptom severity, functional status

and prognosis (5-8). Dyspnea severity has been shown to better predictor of mortality than FEV1 alone in patients with COPD (9). Subsequently, a multidimensional grading system comprised of dyspnea score, exercise ability, body mass index and FEV1 (BODE Index) was shown to be better than FEV1 alone in predicting respiratory-related as well as all-cause mortality in patients with COPD (8,10). Further observations revealed that COPD exacerbations were an independent risk factor for mortality in patients with COPD (11,12). The 2011 GOLD guidelines combined FEV1 reduction, dyspnea and exacerbation history into classifying patients with COPD into Groups A–D. This created confusion since patient could qualify for a category based on either FEV1 reduction or exacerbation history (13-15). The more recent GOLD guidelines "grade" COPD severity based on percentage predicted FEV1. Separately, dyspnea severity and exacerbation history are incorporated into a 2×2 grid to form four "groups" A–D (*Figure 2*). This GOLD A-D grouping forms the basis for the most recent treatment recommendations (1,16).

COPD phenotypes and endotypes

It is clear that the COPD GOLD 2018 classification does not capture the heterogeneity of COPD. Different

Figure 1 Factors that contribute to the heterogeneity in COPD. COPD, chronic obstructive pulmonary disease.
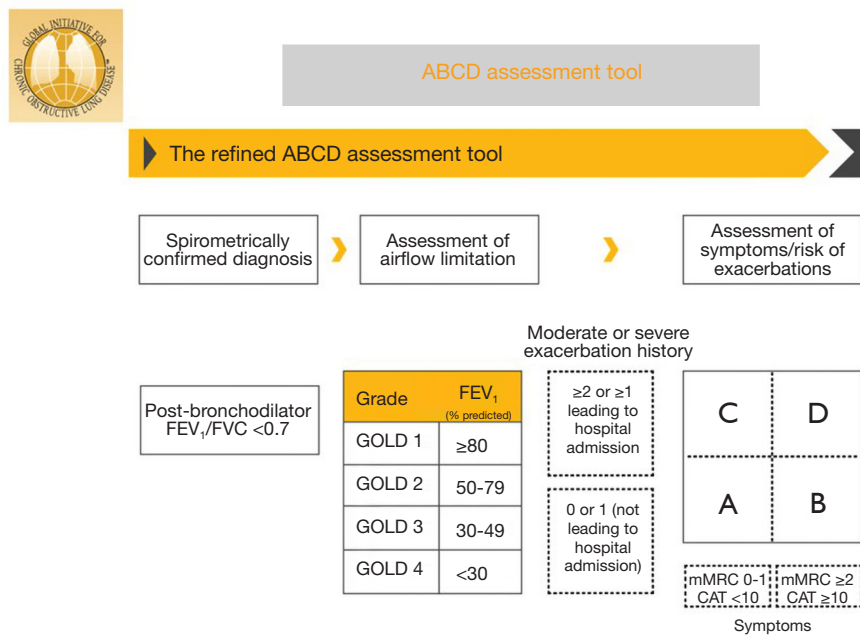
Figure 2 COPD GOLD ABCD Assessment tool (reproduced with permission from Global Initiative for Chronic Obstructive Lung Disease). COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

phenotypes of COPD have been proposed. "Phenotype" refers to a set of observable characteristics with which individuals can be grouped. The purpose of such groupings is to define clusters of patients with common characteristics that relate to clinically meaningful outcomes such as symptoms, prognosis and response to therapies. Phenotypic grouping is essential when researching the pathophysiologic pathways in a disease as heterogeneous as COPD.

The earliest phenotypic classification of COPD separated them into two groups based on physical examination, the "Pink Puffers" and the "Blue Bloaters" (17). As spirometry came into routine use it was recognized that chronic airflow obstruction could be seen in a variety of overlapping conditions, most notably in patients with chronic

bronchitis, emphysema and asthma (18,19) (*Figure 3*). Within this paradigm, the overlap of asthma and COPD and the presence of chronic bronchitis have been proposed as distinct COPD phenotypes.

Asthma-COPD overlap (ACO)

ACO is a term is used for a phenotype that combines features of both disorders (20,21). ACO is diagnosed when a patient has the defining characteristic of COPD, namely persistent airflow limitation as well as features of asthma (22). It is estimated that between 10–20% of patients with COPD have features of asthma as well (22,23). ACO is not a single uniform entity but comprises multiple sub-phenotypes,

such as patients with asthma who have irreversible airway obstruction due to structural changes, patients with asthma and severe disease or asthmatics who smoke and have predominantly neutrophilic inflammation, and patients with COPD and eosinophilic inflammation (23) (*Figure 4*). Not surprisingly, there are varying definitions of ACO (24,25). ACO patients have not been well studied because they are typically excluded form randomized controlled trials in patients with COPD (22). In general, patients with ACO have more symptoms, more frequent exacerbations, increased risk of hospitalization and a worse quality of life (26-28). On the other hand, patients with ACO appear to have a lower mortality (21,29).

The identification of this subset of patients is important because of the therapeutic implications (24,30,31). Patients with ACO may derive greater benefit from inhaled corticosteroids (ICS), regardless of FEV1 or exacerbation frequency (24). In studies of ICS in COPD, patients with

ACO features had a greater reduction in exacerbation rate (30). Given the variability in the diagnosis of ACOS, some have focused on one easily available biomarker, blood eosinophilia. Blood eosinophilia predicts greater benefit from ICS in patients with COPD, specifically in reduction of exacerbations (32-34). Therapy with mepolizumab, which blocks the interleukin-5 (IL-5) pathway, was associated with a reduction in exacerbations in COPD patients with eosinophilia when compared with placebo (35). On the other hand, a study of benralizumab in patients with COPD and sputum eosinophilia did not reduce the rate of acute exacerbations of COPD (36).

Chronic bronchitis COPD phenotype

Individuals with COPD and chronic bronchitis have increased exacerbation frequency, accelerated decline in lung function, worse health-related quality of life and trend to higher mortality as compared with COPD patients without chronic bronchitis (37,38). Among COPD patients with exacerbations, those with chronic bronchitis symptoms, had a higher mortality than those with emphysema (29). This phenotype has therapeutic implications. Roflumilast, an oral phosphodiesterase-4 inhibitor, has been found to be most effective in patients with a chronic bronchitis phenotype and a history of frequent exacerbations (39,40).

Frequent exacerbator COPD phenotype

COPD exacerbations have been associated with more rapid decline in lung function, worse quality of life and higher
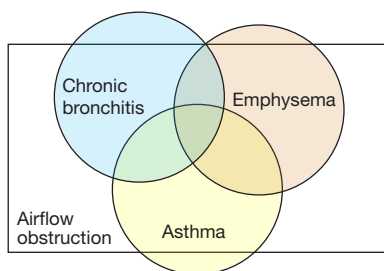
Figure 3 Non-proportional Venn diagram of COPD. COPD, chronic obstructive pulmonary disease.
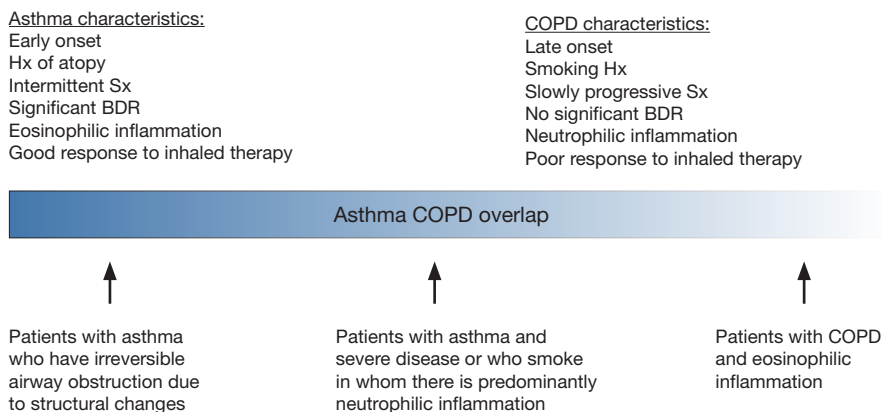
Figure 4 Asthma COPD overlap. COPD, chronic obstructive pulmonary disease.

Table 1 COPD risk assessment

Spirometry
FEV1/FVC <70%
FEV1% predicted
Bronchodilator response
Symptoms
Dyspnea: COPD Assessment Test (CAT) or MRC Dyspnea Scale
Chronic bronchitis
Asthma features
Exacerbation risk
History of prior exacerbations
Blood eosinophilia
Asthma COPD overlap
Blood eosinophilia as biomarker
Identify
Alpha-1-antitrypsin deficiency
Patients with emphysema & low BMI
Patients with high BMI & comorbidities
Upper lobe predominant emphysema

COPD, chronic obstructive pulmonary disease; BMI, body mass index.

healthcare costs (41). Severe COPD exacerbations are associated with a high mortality (11,42). An "Exacerbator" COPD phenotype has been proposed used to identify patients with COPD who are at high risk for exacerbations. The best identifier of the exacerbator phenotype appears to be a history of prior exacerbations (43,44). The frequent exacerbator phenotype is incorporated into the latest COPD GOLD treatment guidelines (1) (*Figure 2*). The Spanish COPD guidelines (GesEPOC 2017) include the ACOS, chronic bronchitis and exacerbator phenotypes in their treatment algorithm (45).

Other phenotypes have been proposed (46): "*Upper lobe-predominant emphysema phenotype*" may be considered for lung volume reduction surgery. "*Comorbid phenotype*" identifies a group of COPD patients that have high BMI, high prevalence of diabetes and heart disease, and higher mortality (46-48). There also appears to be group of patients with emphysema and hyperinflation, and low body mass index who have higher mortality despite having low rates of cardiovascular comorbidities (48).

COPD endotypes

An endotype is a subtype of a condition, which is defined by a distinct pathobiological mechanism. An example of a COPD endotype would be Alpha-1-antitrypsin (A1AT) deficiency. It is responsible for only a small proportion of patients with COPD, but is important to recognize important given the therapeutic option of A1AT replacement. There is ongoing research into classifying COPD based on the underlying disease mechanisms to guide therapy (49).

Future

As we continue to refine our understanding of the different disease mechanisms that contribute to COPD ("endotypes"), the future of assessing and managing patients with COPD may extend beyond simple classifications or phenotypic grouping. The future may be in personalized or precision medicine, where we are able to stratify an individual patient based on their phenotype and endotype to tailor their therapy (50,51). But for now, a practical, clinically relevant risk assessment is presented in *Table 1*.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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