



# Chronic obstructive pulmonary disease phenotypes: imprint on pharmacological and non-pharmacological therapy

Mostafa Bakeer<sup>1,2^</sup>, Georg-Christian Funk<sup>2</sup>, Arschang Valipour<sup>2</sup>

<sup>1</sup>Chest Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt; <sup>2</sup>Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology, Vienna, Austria

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*Correspondence to:* Dr. Mostafa Bakeer. Chest Medicine Department, Faculty of Medicine, Mansoura University, 35516 Mansoura, Egypt.  
Email: mbekeer10@hotmail.com.

**Abstract:** Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease associated with significant morbidity and mortality. Over the past few years, there has been cumulating interest in describing this heterogeneity and using this information to group patients into different COPD phenotypes. The term phenotype is defined as single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes. It describes also the physical appearance or biochemical characteristics which result from the genotype-environment interaction. Furthermore, it clearly identifies subgroups with a significant impact in the prognosis. Recently, approaches to COPD phenotyping have been significantly enhanced in tandem with developments in understanding the disease's various pathological, clinical and genetic features. This knowledge inspired the researchers to investigate more tailored therapeutic strategies that could not only give a more potent effect but also help to avoid the traditional therapy's undesirable side effects. Eventually, it could be said that the phenotypic approach to COPD in the last decade had a huge impact on daily practice and management delivered to COPD patients. In this review, we highlight the impact of pharmacological and non-pharmacological treatment options on COPD outcomes, using a personalized treatment strategy based on different phenotypes.

**Keywords:** Chronic obstructive pulmonary disease (COPD); phenotypes; therapeutics

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## Introduction

Chronic obstructive pulmonary disease (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 and influenced by host factors

including abnormal lung development (1). The diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough and/or sputum production, and a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis, however there may be significant lung pathology (e.g., emphysema) in the absence of airflow limitation that needs further evaluation. Drawbacks of the current diagnostic criteria include the fact

<sup>^</sup> ORCID: 0000-0001-7673-3065.

that they do not reflect the heterogeneous histopathological or pathophysiological background observed in COPD (2).

### Approaches to COPD phenotyping

Over recent years, the term “phenotype” has been introduced to help clinicians better to identify different types of COPD subgroups. “Phenotype” refers to a set of observable characteristics with which individuals can be grouped. The purpose of such grouping is to define clusters of patients with common characteristics that relate to clinically meaningful outcomes such as symptoms, prognosis and response to therapies (3).

In 1955, the earliest phenotypic classification of COPD was introduced to classify patients into two groups based on physical examination, the “Pink Puffers” and the “Blue Bloaters” (4). As spirometry came into routine use it was recognized that chronic airflow obstruction could be seen in a variety of overlapping conditions, such as chronic bronchitis, emphysema and asthma (5).

In more recent years, “cluster analysis” has been performed in an attempt to better characterize patient groups with specific baseline features beyond classical disease characteristics, such as age, gender, body-mass-index, and/or smoking exposure (6-12).

These groupings are constructed such that the degree of association is strong between members of the same cluster and weak between members of different clusters (6).

While some of these clusters may use a single-scale, others may use a multi-dimensional approach (13). For instance, a “whole-person scale” is based on clinical symptoms (e.g., chronic bronchitis). An “organ scale” is based on lung function or radiology, such as description of emphysema or bronchial wall thickening. Others, such as the “cell tissue scale” or a “genetic scale” use either biological samples or genetic mutational analysis. These approaches however, did not integrate information from other scales of COPD which is critical to improve understanding of the disease (2).

In 2012, the Spanish Society of Pulmonology and Thoracic Surgery published the first clinical guideline using a multi-dimensional based approach of phenotyping and phenotype-based tailored treatment in COPD. Four clinical phenotypes were introduced based on exacerbation frequency and dominant clinical manifestations: non-exacerbators, asthma-COPD overlap (ACO), exacerbators with emphysema, and exacerbators with chronic bronchitis (14).

Using a cross-sectional Spanish cohort of patients with COPD, Miravittles and co-workers (15) demonstrated that non-exacerbators were the most prevalent phenotype, comprising about two-third of the overall patient population studied. Since then, the Spanish classification has also been adopted by others. The POPE study (16,17), a cohort of 3,362 patients from Central and Eastern Europe, confirmed the high prevalence of non-exacerbators found in the Spanish cohort, but also observed differences in the prevalence of these phenotypes between countries. Furthermore, exacerbators with or without chronic bronchitis had a higher symptom load and more frequent comorbidities compared to other phenotypes of interest. Both above-mentioned reports were further able to demonstrate that patients with COPD appear to receive inhaler treatment independent of their predominant clinical phenotype.

In the following section, we will review some of the evidence regarding phenotype-based treatment strategies. In addition to the conventional therapeutic options we also provide an overview of evolving, mainly endoscopic treatment approaches in selected patient groups and their impact on clinical course and outcomes. General recommendations, such as smoking cessation, vaccination, pulmonary rehabilitation, and identification and treatment of comorbidities should be applied to every patient with COPD, regardless of the phenotype, and thus will not be discussed here. We further acknowledge that there may be an overlap between phenotypes, thus therapeutic strategies mentioned below may be directed towards the predominant phenotype in individual patients. Strategies of the phenotype-based treatment of COPD are summarized in *Table 1*.

### Phenotype-based conventional management of COPD

#### Non-exacerbator phenotype

By definition, these patients are characterized by presenting a maximum of one episode of moderate exacerbation in the previous year. In large COPD cohorts this is the most frequent COPD phenotype and comprises about two-thirds (60%) of patients with COPD (15,16).

Non-exacerbators have a lower risk of deterioration in quality of life, loss of lung function and mortality compared with the exacerbator phenotype (18). The majority of COPD patients with this phenotype remain in the same phenotype after 1 year follow up (19). The main focus of treatment is thus to ensure clinical stability by providing

**Table 1** Phenotype-based management of COPD

Management	Non exacerbator	ACO	Emphysema exacerbator	Chronic bronchitis exacerbator
General measures	Vaccination			
	Smoking cessation			
	Pulmonary rehabilitation			
	Treatment of comorbidities			
Pharmacological	Mono or dual BD	ICS + LABA ± LAMA	Dual BD	Dual BD ± PDE-4 Inhibitors ± ICS
	–	Anti-IgE	Mucolytics	Mucolytics
	–	Anti-IL 5	–	Macrolide therapy
Non pharmacological	–	BT	LVRS	Mechanical mucus clearance
	–	–	ELVR	TLD (experimental)
	–	–	–	Bronchial rheoplasty (experimental)

COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; BD, bronchodilator; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; PDE-4, phosphodiesterase-4; BT, bronchial thermoplasty; LVRS, lung volume reduction surgery; ELVR, endoscopic lung volume reduction; TLD, targeted lung denervation.

appropriate inhaler therapy. Depending whether or not patients with COPD present with a high or low symptom load, mono or dual bronchodilator (BD) treatment should be the initial treatment and inhaled corticosteroid (ICS) treatment should be rather avoided in the absence of concomitant asthma (1,20). Long-acting bronchodilators (LABD) are required in the majority of symptomatic patients. They enable better control of symptoms, and improve lung function (21,22) in addition to reducing number of exacerbations (23). As mentioned above, non-pharmacological management should involve smoking cessation counseling, self-management, and rehabilitation efforts.

### Emphysema exacerbator phenotype

This phenotype represents a smaller proportion of COPD patients with less than a 10% prevalence rate (15,16). An exacerbator phenotype is defined as any patient with COPD who presents two or more moderate exacerbations (that require at least outpatient treatment with systemic corticosteroids and/or antibiotics) in the previous year, or at least one severe exacerbation that requires hospital admission (24). In order to differentiate a new event from a treatment failure, an acute episode either 4–6 weeks from the beginning of an original exacerbation or 4 weeks after the completion of its treatment is suggested as a definition for “recurrence” of COPD exacerbation (25).

Patients with an emphysema exacerbator phenotype

demonstrate the highest mortality rate compared with other COPD phenotypes (19,26). Due to the differential management, it is important to differentiate exacerbator patients with predominant emphysema from those with predominant symptoms of chronic bronchitis. In contrast to patients with chronic bronchitis, the emphysema phenotype appears to be experiencing exacerbations mainly due to hyperinflation rather than infection or inflammation. Identification of emphysema should be facilitated by measurement of gas trapping using static lung volumes and carbon monoxide diffusing capacity (DLCO) testing. In clinical routine, chest computed tomography (CT) is the diagnostic approach of choice, and may be used for treatment selection in advanced disease (27).

In line with other recommendations we suggest that the first line therapy of the emphysema phenotype should be dual BD treatment (18).

Given the risk of pneumonia and the absence of relevant airway inflammation in these patients, ICS treatment should be rather avoided and reserved for patients with a history of asthma, atopy, and/or blood eosinophilia (measured during stable state) (28). In our clinical experience patients with predominant emphysema rather rarely fulfill these criteria, but about one-third of patients may also have a relevant component of overlapping chronic bronchitis and bronchiectasis, more frequently found in lower lobes. These patients are usually characterized by chronic cough and sputum production, and may depict mucus in central and

peripheral airways and airway wall thickening on CT scans. Anti-inflammatory treatments may be an individual option in these patients as mentioned in the section on chronic bronchitis.

### **Chronic bronchitis exacerbator phenotype**

Chronic bronchitis is determined by the presence of cough and sputum production for at least 3 months per year in 2 consecutive years (18). The prevalence rate of this phenotype was found in approximately 20% of COPD patients (15,16).

Similar to the emphysema phenotype, patients with the chronic bronchitis are at an overall higher risk of moderate and severe exacerbations (19) in addition to worse respiratory symptoms (29). Patients with chronic bronchitis may undergo a high-resolution CT to rule out relevant bronchiectasis (30) and sputum cultures for identification of chronic microbial infection (31).

### ***Pharmacological management***

Similar to patients with emphysema, patients with a chronic bronchitic phenotype should also receive dual BD inhaler therapy. These patients, however, may further benefit from ICS (given above-mentioned criteria), and/or adding phosphodiesterase-4 (PDE-4) inhibitors (roflumilast) to inhaler therapy (32-34).

High-risk patients who had at least three exacerbations in the previous year and severe airflow obstruction despite adequate inhaler therapy may also be eligible for long-term treatment with macrolide antibiotics to reduce the number of exacerbations (35-37).

Similar to the use of macrolide antibiotics, data from randomized controlled trials may suggest the use of high dose mucolytics (e.g., N-acetylcysteine, 600 mg twice daily). Recent data suggests their benefits in reducing the number of exacerbations in high-risk patients, i.e., those with forced expiratory volume in 1 second ( $FEV_1$ ) <50% or with two or more exacerbations in the previous year, or both (38,39).

### ***Mechanical mucus clearance***

Patients with chronic bronchitis and bronchiectasis may also benefit from mechanical methods of mucus clearance, such as positive expiratory pressure, flutter valves, or high frequency chest compression vests; however, the evidence from these techniques usually do not stem from large, randomized clinical trials and thus should be applied critically (40). Similarly, other studies of chest physiotherapy or directed coughing techniques in COPD have shown some improvements in mucus clearance, but no changes in lung function (41).

### **ACO phenotype**

ACO phenotype can be diagnosed in a patient with COPD who also meet the diagnostic criteria for asthma or who present features considered as suggestive of asthma, such as: a strongly positive BD test (increase in  $FEV_1$  >400 mL and 15%), a history of atopy, and/or peripheral blood eosinophilia >300 cells per  $mm^3$  (14,42).

The reported prevalence of ACO greatly varies from 2% in a general population over 40 years of age, 11% to 56% among patients previously diagnosed with COPD and 13% to 61% among patients previously diagnosed with asthma (43). Epidemiologically, ACO patients have a female predominance, and affected patients appear to be younger compared to more “classic” COPD patients (44,45). Clinically, ACO exacerbations do not usually present with purulent sputum, but rather with symptoms of rhinitis, wheezing and cough with whitish sputum (46,47). The treatment of ACO consists of adding ICS to BD treatment, given an underlying high degree of bronchial eosinophilic inflammation with a subsequent marked clinical and spirometric response (48,49). Traditionally, ICS has been added to long-acting beta-agonist therapy, but more recently single-inhaler triple therapy with long-acting muscarinic antagonist (LAMA), may offer a step-up approach in more severe cases (50).

Patients with frequent exacerbations despite regular inhaler therapy may also be candidates for anti-IgE antibody treatment with biologicals, such as anti-IgE or anti-IL 5 (51). Previous studies have shown improvements in pulmonary function tests, decreased levels of fractional exhaled nitric oxide (FeNO), eosinophils, neutrophils, and interleukin-4 with the use of omalizumab (52). Studies also have showed its efficacy in decreasing rates of exacerbation and hospitalizations as well as improved asthma control and health-related quality of life (53,54).

### ***Phenotype-based interventional treatment options for COPD***

#### **Lung volume reduction procedures**

Given that lung hyperinflation is the driving component of symptoms and exercise limitation in patients with emphysema phenotype, lung volume reduction procedures in advanced disease may offer relieve. The landmark National Emphysema Treatment Trial (NETT) reported that lung volume reduction surgery (LVRS) in carefully selected patients with upper lobe predominant emphysema, led to durable improvement in exercise capacity, symptoms,

and oxygen use (55). However due to the associated risks and costs, LVRS it is not commonly offered (56). More recently, endoscopic approaches to lung volume reduction have been adopted by the clinical community.

In fact, patients with emphysema phenotype may experience improvements in clinical outcomes (dyspnea score, exercise capacity and lung function) by endoscopic lung volume reduction (ELVR) using endobronchial valves, coils and thermal vapor ablation (57-60). Compared with surgical lung volume reduction, endoscopic treatment may also be applicable to patients with lower lobe emphysema. In fact, Eberhardt *et al.* were able to demonstrate similar improvements in clinical and functional outcomes following endobronchial valve therapy in upper versus lower lobe emphysema (61).

In addition to emphysema distribution, disease heterogeneity might also play a role in treatment selection. Heterogeneity is the relative difference in the emphysema scores between ipsilateral lobes. Heterogenous emphysema is generally defined as more than a 10% to 20% difference in the proportion of emphysema measured at -910 HUs or a >10% difference in the proportion of pixels of less than -950 HU (62). While treatment with endobronchial valves has also been successfully performed in patients with homogenous emphysema (63), data from randomized controlled trials using other techniques such as coil treatment or vapor ablation have yet to confirm clinically meaningful efficacy in homogenous emphysema.

### Targeted lung denervation (TLD)

Since a large subset of patients with bronchitic COPD remain symptomatic and continue to experience frequent exacerbations and symptoms despite optimal medical treatment, novel endoscopic approaches may apply to this patient group.

TLD has been developed with the intention of disruption of the peribronchial vagal innervation of the lungs and its downstream effects on mucus hypersecretion, bronchoconstriction, and airway hyperresponsiveness. While previous studies of TLD in COPD have predominantly focused on proof of concept, optimal dosing, an extended safety profiling (64,65), the most recent AIRFLOW-2 trial prospectively evaluated the safety of this intervention, with the effect on respiratory adverse events as the primary outcome, in patients with symptomatic moderate to severe COPD (66). The authors of this report were able to demonstrate that TLD on top of maintenance inhaler therapy was associated with fewer respiratory

adverse events in the primary endpoint time window and hospitalization for COPD exacerbations over 1 year of follow-up compared with control patients who underwent a sham procedure. The ongoing AIRFLOW-3 trial is a randomized controlled trial of TLD vs. sham with COPD exacerbation rates as a primary outcome.

### Bronchial rheoplasty

Another endoscopic technology that may apply to chronic bronchitis patients is bronchial rheoplasty. It is a novel procedure in which pulsed electric fields are delivered to the airways via an endobronchial catheter, with the intention of ablation of mucus producing airway cells. First-in-man results from a recent multi-center study confirm safety and initial clinical outcomes of bronchial rheoplasty (67). In fact, treated patients had a substantial improvement in COPD symptoms, which were accompanied by changes in airway histology, i.e., a reduction in the number of mucus-producing cells.

### Bronchial thermoplasty (BT)

BT is an approved technique that involves the application of high radiofrequency energy through a fiberoptic bronchoscopic catheter approach to selectively ablate airway smooth muscle in the proximal airways. BT has only been studied in severe asthma and the results showed a significant improvement in asthma control and quality of life in addition to reduction in the numbers of severe exacerbations, and the needed dose of oral corticosteroids (68,69).

While patients with an explicit diagnosis of ACO have yet not been studied systematically (51), the underlying pathobiology and first case reports appear to underline the potential of BT in this patient group (70-72).

### Conclusions

The application of the concept of phenotyping has resulted in a more individualized treatment approach in patients with COPD and appears to be increasingly adopted by guidelines and the clinical community.

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