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# The Many Faces of Chronic Obstructive Pulmonary Disease: Moving Towards Precision Medicine

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## ABSTRACT

When the term chronic obstructive pulmonary disease (COPD) was first used in 1970s, it included two main phenotypes: the "*blue bloater*" (chronic bronchitis) and "*pink puffer*" (emphysema). Recently, as our current knowledge on the disease has progressed, the attention has been drawn to very diverse subtypes of chronic airflow obstruction characterised by different causes, age of onset, pathological and clinical manifestations. Over the years, "recommendations" have been generated for the clinicians on how to manage the patients with COPD, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations. Although the GOLD recommendations had the great merit to draw attention onto the COPD severity and its clinical management, they are now less suitable to address the extremely diverse nature of COPD. This review will give an overview of the history of COPD, and the many faces of COPD over the years to date. **(BRN Rev. 2019;5(2):90-103)**

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## INTRODUCTION

In the era of precision medicine, the observable differences between patients with chronic obstructive pulmonary disease (COPD) are calling into question the current way of classifying subjects with COPD based solely upon their lung function. Recent research advances point toward different diseases currently being encompassed under the same umbrella named "COPD" rather than the existence of one single disease, COPD, with several causes, pathogenesis, clinical manifestations, and therapeutic options[1,2] (Fig. 1). In this review, we will discuss the story of COPD as a clinical entity, the way our knowledge of COPD developed over the years, and our current understanding of the many faces of the disease.

## HISTORICAL INSIGHT INTO CHRONIC OBSTRUCTIVE PULMONARY DISEASE

### COPD - the Dawn

Physicians have been tracking the symptoms of COPD for around 200 years. In 1679, Swiss physician Théophile Bonet referred to "voluminous lungs". In 1769, Italian anatomist Giovanni Morgagni reported 19 cases of "turgid" lungs. In 1814, British physician Charles Badham identified chronic bronchitis as a disabling health condition and used the term "catarrh" to describe an ongoing cough and excessive mucus. In 1821, the physician René Laënnec, inventor of the stethoscope, recognised emphysema as another component of COPD[3].

Interestingly, back in the 1800s, the leading causes of the development of COPD were indicated as environmental factors such as air pollution or genetic conditions, as cigarette smoke was not prevalent at the time. In 1846, John Hutchinson invented the spirometer, which allowed the measurement of "vital lung capacity". Approximately 100 years later Robert Tiffeneau, a French pulmonologist, created a more complete diagnostic instrument for the measurement of all the lung volumes[3]. In 1953 (Fig. 2), Oswald described in Lancet the clinical features of "chronic bronchitis" and "emphysema" based on his observations of 1000 patients[2]. Thus, in 1959, a gathering of medical professionals called the Ciba Guest Symposium helped defining chronic bronchitis, emphysema, and asthma associated with chronic airflow limitation. Soon after, in the October 1962 issue of the *Archives of Environmental Health* appears a definition and classification of three common respiratory diseases: chronic bronchitis, asthma, and emphysema. William Briscoe is thought to be the first person to use the term "chronic obstructive pulmonary disorder" at the 9th Aspen Emphysema Conference in June 1965[3]. In 1977, Fletcher and Peto[4] provided a description of the natural history of COPD, which dominated the view of the lung function decline in COPD until recently. In 1987, the word COPD first appeared on a document by the American Thoracic Society board of directors.

### COPD - the Rise

Even if the existence of "inflated lungs" which made it difficult to breath was well known since a long time, it was only in the late 90s that the research community started focusing on COPD, its pathogenesis, its clinical presentation, and how to treat it.

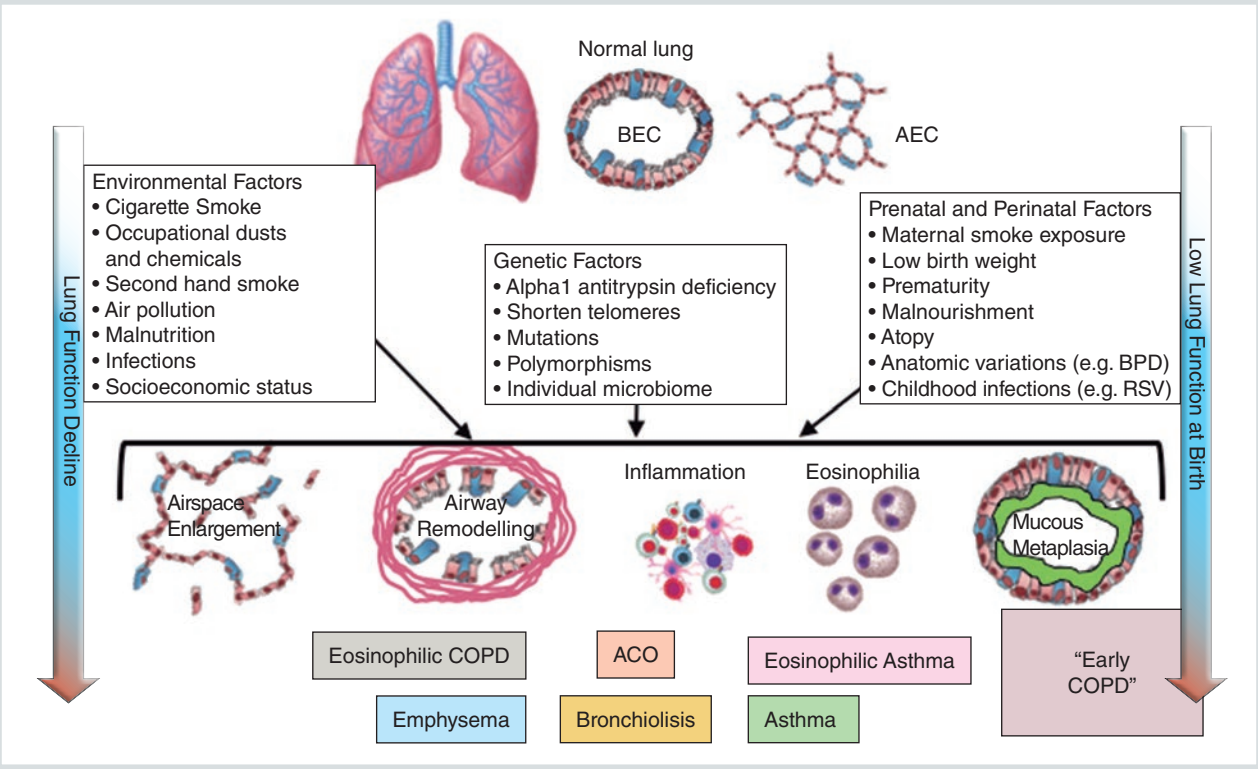


**Figure 1.** Pathobiology of COPD and its subsets: pre/perinatal factors can determine low lung function at birth and environmental factors can determine an accelerated lung function decline, whereas genetic factors contribute to both low lung function at birth and accelerated lung function decline. The final result is a cascade of pathologic events which lead to airflow limitation and often overlap each other from clinical and pathologic standpoints.
ACO: asthma COPD overlap; AEC: alveolar epithelial cells; BEC: bronchial epithelial cells; BPD: bronchopulmonary dysplasia; COPD: chronic obstructive pulmonary disease; RSV: respiratory syncytial virus.

In March 1995, a document titled "Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease" was published on the American Journal of Critical Care Medicine where the characteristics, the clinical presentation, and the treatment options of COPD were explained[5]. In January 1997, a number of COPD experts from around the world met in Brussels to explore the possibility of developing a global initiative for COPD, which was named Global Initiative for Chronic Lung Disease (GOLD)[6] (Fig. 2). This initiative was created as a joint activity between the U.S. National Heart, Lung, and Blood Institute and the World Health Organization and it was composed by experts in the fields of respiratory medicine, epidemiology, socioeconomics, public health, and health education[7]. The central objectives of GOLD were to increase awareness of COPD, to help patients with COPD, and to provide comprehensive recommendations on the clinical management of COPD. From that moment until now, the GOLD recommendations, followed by others, such as the National Institute of Clinical Excellence (NICE) in the United Kingdom, have guided the diagnosis and the management of COPD, progressively including

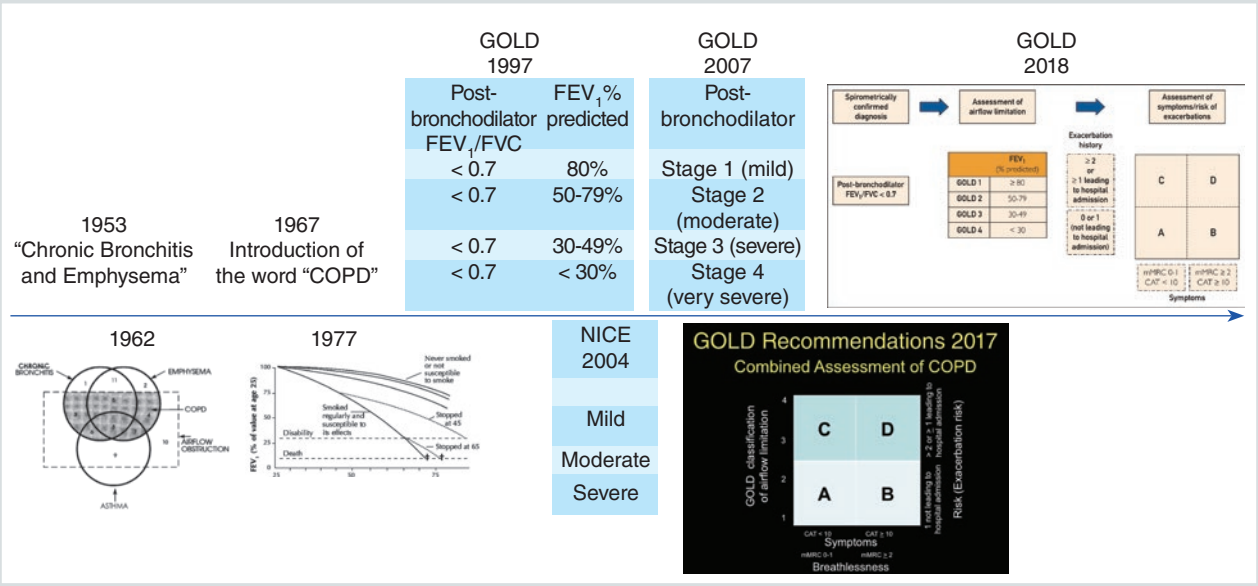


**Figure 2.** The history of COPD.
COPD: chronic obstructive pulmonary disease; $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; NICE: National Institute for Health and Clinical Excellence.

more refined criteria for diagnosis and treatment of COPD as the knowledge on the disease advanced[8]. Over the years, the GOLD recommendations have evolved to mirror the increasing knowledge of COPD. In fact, the first GOLD recommendations proposed that the diagnosis of COPD requires solely the presence of incompletely reversible airflow obstruction to be confirmed by spirometry. However, the current GOLD classification of COPD includes, after spirometric assessment of airflow limitation, a multidimensional approach to the disease which includes symptom-/exacerbation-based assessments of the patients. A major contributor to this advancement is due to the introduction of the BODE index in 2004 by Celli et al[9]. The BODE index included for the first time not only pulmonary but also systemic variables in the assessment of patients with COPD: body mass index (B of body mass index [BMI]), airflow obstruction (O of obstruction), dyspnoea (D of dyspnoea) and exercise capacity (E of exercise). The BODE index, together with other seminal studies showing a higher prevalence of comorbidities in COPD patients compared with healthy subjects, represented a turning point in the diagnosis and management of COPD.

## COPD -The Fall

More and more, COPD is being seen as a more complex disease, placing a magnifying glass on the unexplored multifaceted effects of air pollutants such as cigarette smoke on the lung and the whole body. Also, studies showing that pre- and perinatal determinants of low lung function at birth can lead to airflow obstruction at early age even in absence of cigarette

smoke, have called into question whether we are currently missing a big piece in our understanding of COPD. As our scientific knowledge of COPD progresses, the causes, clinical phenotypes, and pathological events underlying airflow limitation are becoming too heterogeneous to be encompassed under the definition of what today we call COPD.

## THE MANY FACES OF COPD

### Emphysema versus airway disease

Computed tomography (CT) has been instrumental in identifying COPD sub-phenotypes, such as airway disease (bronchitis and bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which varies from patient to patient. This classification is not new since classically, the "*blue bloaters*" and the "*pink puffers*"[10] were considered the two most common phenotypes of COPD, but with the premise that they could overlap each other. Recent basic and translational studies have highlighted some major differences in the pathobiology of emphysema versus chronic bronchitis, such that they are now thought to be two different entities and not two manifestations of the same disease. Network analysis of lung transcriptomics showed that bronchiolitis and emphysema have distinct molecular signatures, independently of the grade of airflow limitation[11]. In fact, emphysema involves a prominent immune response with evidence of B-cell activation and lymphoid follicle formation, which is absent in bronchiolitis. The pathobiology of emphysema seems much more closely related to an activation of the adaptive immune compartment, with autoimmune features characterised by the presence of anti-elastin antibody and T helper type 1 (TH1) responses, which correlate with emphysema severity more than airflow limitation[12-14]. Also, emphysematous lung harbours Th1 and Th17 cells secreting cytokines and chemokines that further enhance the release of matrix metalloproteinases, unlike bronchiolitis[15]. Interestingly, it has been recently shown that the loss of terminal bronchioles, highlighted by microCT scan analyses of lung tissue, is an early event in the pathogenesis of both emphysema and chronic bronchitis, and occurs before the lung function starts declining[16] (Fig. 3).

Cross-sectional analyses have shown that emphysema is often associated with less tissue in other body compartments, which translates into lower BMI, skeletal muscle measured as a lower fat-free mass index (FFMI), as well as bone density (osteopenia and osteoporosis)[17,18]. Likewise, longitudinal studies have identified that patients with emphysema have an accelerated loss of lung function. Interestingly, this progressive loss of lung tissue that characterises emphysema is associated with the synchronous and also enhanced loss of tissue mass in several other body compartments because of generalised abnormal tissue maintenance and repair, and not just to inflammation. In fact, the progression of CT scan-defined emphysema over time is associated with lower levels of soluble receptor for advanced glycation end product (sRAGE) and surfactant protein D (SP-D), two molecular biomarkers related to lung tissue damage and regeneration[17]. Moreover, the presence of emphysema is associated with less cardiovascular disease and diabetes (which are characterised by low-grade systemic inflammation) but more osteoporosis (which indicates a systemic loss of tissue)[17,19].

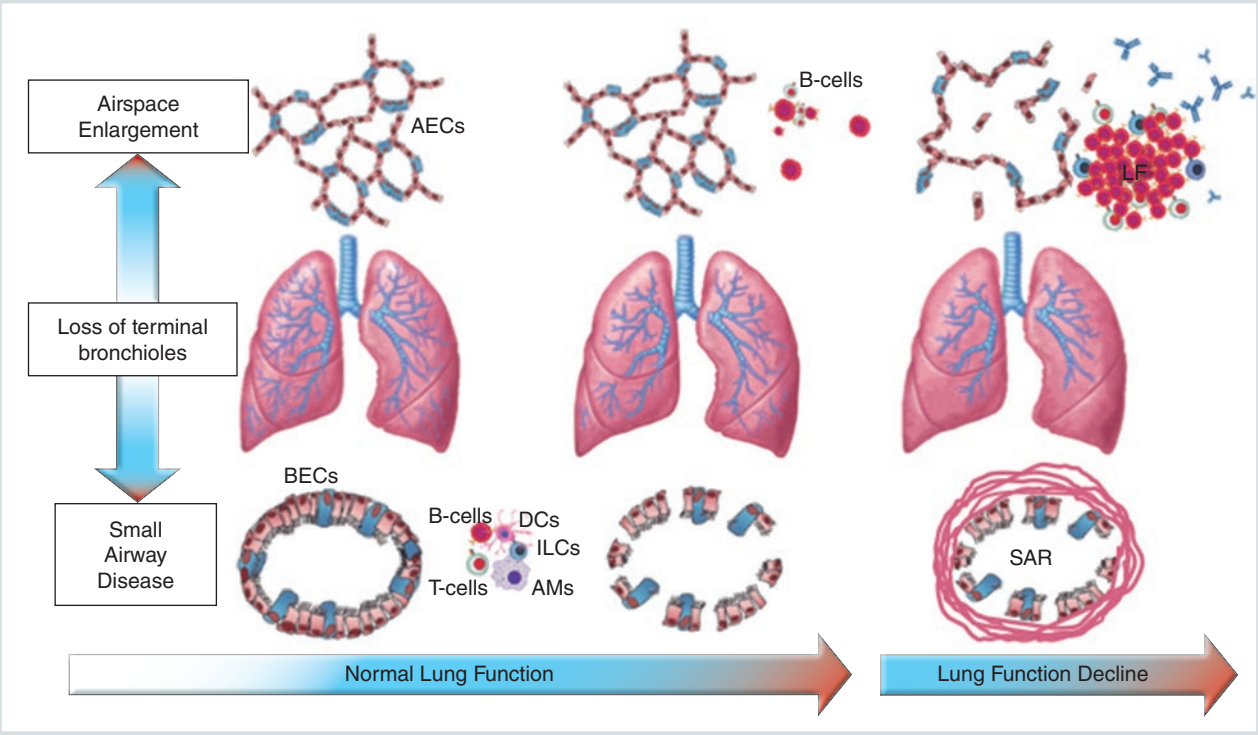


**Figure 3.** Pathobiology of emphysema-predominant versus airway disease-predominant COPD: emphysema involves a prominent immune response with evidence of B-cell activation, lymphoid follicle (LF) formation and generation of autoantibodies against lung tissue, which are absent in bronchiolitis. The loss of terminal bronchioles is an early event in the pathogenesis of both emphysema and chronic bronchitis and occurs before the lung function starts declining.
AECs: airway epithelial cells; AMs: alveolar macrophages; BECs: bronchial epithelial cells; COPD: chronic obstructive pulmonary disease; DCs: dendritic cells; ILCs: immune lymphoid cells; SAR: small airway remodelling.

From a clinical standpoint, proper identification of these patients is relevant because patients with severe emphysema have more exacerbations and are more likely to be hospitalised and die within three years than patients without this phenotype[20]. In the daily clinical practice, both visual and quantitative CT scans have become instrumental in the diagnosis and management of patients with COPD[21]. Quantitative CT provides useful information regarding emphysema, airways, and gas trapping and provides a means of objectively characterising and following these pathological processes. Also, quantitative CT scan has been instrumental in showing that small airways disease/loss is evident even in early disease stages and correlates with disease progression[22,23]. More recently, high-resolution CT scan (HRCT) has allowed a more in-depth assessment of the emphysema and gas trapping subphenotypes. National Institute of Health (NIH)-funded cohorts, such as COPDgene (www.copdgene.org) and SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS, www.spiromics.org), have been using HRCT scans to differentiate COPD sub-phenotypes even further. The main sub-phenotypes which have emerged with the contribution of HRCT

are: (1) chronic airflow obstruction (CAO) defined by a low post-bronchodilator forced expiratory volume in one second ($FEV_1$)/forced vital capacity (FVC), (2) HRCT-defined emphysema (low attenuation at maximal inhalation, total lung capacity), (3) hyperinflation or gas trapping on HRCT, defined as low attenuation of the lungs at low lung volume (around functional residual capacity), and (4) airway inflammation (defined by bronchial wall thickening on HRCT, also known as bronchiectasis). Thus, HRCT scan allows a more in-depth phenotypisation of the COPD lung. However, a comparison of CAO versus emphysema showed "striking disagreement" between spirometric CAO (regardless of how mild airway obstruction was defined) and HRCT-defined emphysema[24], underlining some knowledge gaps on the relative use of HRCT scans versus other more commonly used diagnostic tools for COPD[25]. Also, the use of HRCT scan is still associated with high costs, radiation exposure, and a high incidence of false positive findings (e.g., nodules). Although the criteria to use HRCTs versus. low regular CT scan in the clinical practice have to be further defined, the use of CT scan to image the lung is undoubtedly becoming a first-line choice in the phenotypisation of emphysema versus airway disease-predominant COPD.

## Early versus late COPD

To date, COPD has always been considered a disease of the elderly, and little attention has been paid to the individuals at risk before they develop clinically evident COPD. Until recently, the prevailing idea was dominated by the Fletcher and Peto curve of lung function declines, indicating that during development (from birth to approximately 25 years of age), all people reached the same plateau for lung function as measured by the $FEV_1$[26]. According to this theory, what determined whether the development of COPD was the rate of subsequent decline in the $FEV_1$ level. Emerging evidence, however, called into question this concept. Long-term cohorts have shown that the majority of patients do not progress to the most advanced phases of COPD, although the presence of mild obstruction predisposes to a more rapid fall of $FEV_1$, and that the combination of low lung function at birth and rapid decline results in a higher risk of development of COPD compared to subjects having only one or none of these traits[27,28]. These findings suggest that low $FEV_1$ in early adulthood is essential in the genesis of COPD and that accelerated decline in $FEV_1$ is not an obligate feature of COPD[29].

Thus, recently the term "early COPD" has entered the COPD glossary, indicating the presence of COPD in younger individuals, but a unanimous consensus on the exact definition of early COPD has not been reached yet. Martinez FJ et al.[30] defined early COPD as ever-smokers (≥ 10 pack-years), younger than 50 years, and with any of these abnormalities: (1) $FEV_1$/FVC < lower limit of normal; (2) compatible CT abnormalities (airway abnormality and/or emphysema); or (3) $FEV_1$ decline (≥ 60 mL/year). According to this definition, the only differentiator between early and mild COPD is the temporal information. However, the recommendation that persons less than 50 years old should be considered to have an early disease does not take into consideration that a majority of smokers start in their teens and hence would already have accumulated a substantial number of pack-years of smoking burden by the time they are in their forties. Additionally,

the terms "early" and "mild" should be used with caution when talking about COPD pathogenesis[31]. According to the current state of the art, "mild" COPD is based on a spirometric measurement, whereas "early" relates to the time when COPD is diagnosed or studied for the first time, and both may not be coincident in the same individual. Also, "early" versus "late" COPD belong to a timescale, which does not necessarily mirror the time when the pathogenesis of the disease started. Part of the confusion is that, at present, it is not possible to differentiate mild COPD of recent onset from earlier onset COPD that does not progress to a more severe stage[31,32].

One concept which has now been widely accepted is that the spectrum of patients presenting with chronic respiratory symptoms and irreversible airway obstruction is much more heterogeneous than previously thought. Also, only approximately 10–15% of smokers develop COPD[33,34]. According to this novel view, there is an entirely different pathway leading to the diagnosis of COPD from the rapid-decline form, one in which smoking can undoubtedly play a role, especially in the clinical expression of the disease, but in which the central derangement is already present in early life. COPD pathogenesis may begin much earlier, even before birth, as passive foetal smoke exposure in utero is associated with increased adult COPD risk, independently of either active or passive smoke exposure in childhood, adolescence or adulthood. Individuals sustaining childhood respiratory impairment are also at increased risk of reduced adult lung function. Similarly, other pre-, peri- and post-natal factors can determine the lung function at birth and its decline, such as second-hand smoke, maternal smoke, infections in childhood, prematurity, anatomic variations of the lung, childhood atopy and/or asthma, and malnutrition[35] (Table 1).

Right now, only very few well-characterised longitudinal cohorts around the world include follow-up times long enough to address the exact effects of the pre- and perinatal events determining the lung function at birth and the consequent development of COPD early in life[36,37]. One of the significant challenges so far has been to detect early disease and not just mild disease at an earlier chronological age. Early COPD indicates a COPD diagnosed in younger individuals who likely had low lung function already in their first years of life. Thus, "early origin COPD" might be a more suitable definition to define this type of onset. Importantly, to have COPD at a young age does not necessarily mean that the subjects will have a fast lung function decline and will progress into more severe stages of COPD with age[38]. This phenotype should be differentiated from a mild COPD diagnosed when the subject is still young, but which will progress to severe COPD with age. The difference between the two presentations is not subtle but still hard to distinguish based on our current knowledge. It is worth mentioning that one of the most interesting pages of the GOLD recommendations has been the definition of "GOLD 0 COPD". In this scientific era when "early COPD" is gaining enormous attention, the concept of "GOLD 0 COPD" returns to the limelight. The GOLD 0 was first introduced in the GOLD recommendations in the early 2000s and comprised patients who are "at risk" for the development of COPD[39]. The existence of a real "GOLD 0 patient" has been area of

**Table 1.** Risk factors of early COPD

| Prenatal | Perinatal | Childhood and early life |
|---|---|---|
| • Family history of COPD and/or asthma/ atopy<br>• Atopy<br>• Genetic factors<br>• Anatomic variations of the lung: bronchopulmonary dysplasia | • Maternal smoking and/or exposure to pollution<br>• Antibiotic use<br>• Non-vaginal birth<br>• Preterm birth<br>• Undernourishment<br>• Low lung function at birth and/or ARDS at birth<br>• Low birth weight | • Lower respiratory tract illnesses (especially respiratory syncytial virus)<br>• Air pollution<br>• Childhood asthma<br>• Active smoking during adolescence<br>• Second-hand smoke exposure<br>• Psychosocial stress |

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease.

controversy for several years. Can a patient really have "chronic airflow obstruction" with normal lung function? What is sure is that, even if patients do not progress to airflow limitation, symptoms, exacerbations and radiographic abnormality are present in GOLD 0. Even if GOLD 0 did not stay long into the GOLD recommendations, it had the undeniable value of raising interest on the subjects with symptoms of COPD before they develop airflow limitation, suggesting a preventative therapeutical approach in these individuals. Thus, future research is needed to characterise the risk factors further and the subjects at risk of developing COPD early in life, how to diagnose, when and if to start treating subjects at high risk of developing COPD early in life.

## Asthma-COPD overlap syndrome versus high eosinophil COPD

Asthma and COPD appear as a result of different pathobiological mechanisms, and although they present diverse features and symptoms of airway inflammation and airway obstruction, they also share common features. In 2014 the Global Initiative for Asthma (GINA) and GOLD Joint Committee came out with the definition: "Asthma-COPD overlap syndrome" (ACOS) is characterised by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. It is therefore identified by the features that it shares with both asthma and COPD"[40]. Subsequently, the term "syndrome" came to be considered inappropriate in this context. The reasons included the fact that asthma and COPD have different pathogeneses which encompass a variety of mechanisms, and the clinical features are often highly diverse. As a result, it has been recommended that the term "syndrome" be dropped and that the disease name is changed to "asthma and COPD overlap (ACO)"[41]. The disease then was described as follows: "Asthma-COPD overlap is characterised by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Asthma-COPD overlap is therefore identified in clinical practice by the features that it shares with both asthma and COPD. This is not a definition, but a description for clinical use, as ACO includes several different clinical phenotypes and there are likely to be several different underlying mechanisms"[40].

Over the years, there have been several attempts to explain the mechanism underlying a disease with the characteristics of both asthma and COPD — one major hypothesis in the Dutch Hypothesis[42]. The Dutch researcher Dick Orie first proposed this hypothesis in 1961. He hypothesised that "asthma, chronic bronchitis, and pulmonary emphysema (COPD) is a single disease (chronic non-specific disease) that occurs as a result of the same genetic factors (atopic status, promotion of airway hyperreactivity), and only presents different clinical phenotypes due to different environmental factors (allergens, smoking, and infections)" [40]. This hypothesis was later reworked by Fletcher, who introduced the concept of chronic non-specific lung disease (CNLD). According to this hypothesis, an individual with certain genetic factors presents the clinical phenotype of COPD when exposed to smoking and the clinical phenotype of asthma when exposed to allergens. Thus, if the subject has been exposed to both environmental factors and therefore the two cannot be separated, he will develop a form of overlap of the two diseases (ACO)[40].

In contrast, the British Hypothesis, first proposed in 1965 by Charles Fletcher, described ACO as "a disease in which asthma and COPD occur as a result of different mechanisms triggered by different pathogeneses". Unlike the Dutch Hypothesis in which asthma and COPD are described as being impossible to separate, the British Hypothesis proposes that ACO develops when factors such as smoking contribute to asthma and when factors related to asthma, including antigen sensitisation, contribute to COPD[43]. To date, whether one hypothesis is closer to the reality than the other is still unclear. However, we know that some factors can predispose to the development of both asthma and COPD simultaneously. Among these factors, airway hyperreactivity, genetic background, low lung function at birth, maternal smoke exposure, and viral infections in childhood play a major role. Interestingly, most of these factors are the same ones determining early origins of COPD[29]. Thus, it would be interesting to know which one of these factors contributes to the shift towards the asthmatic phenotype versus the COPD phenotype and whether ACO represents a clinical subset per se, or is a feature of "COPD of early origin."

The picture changes if we look at the immunopathology of COPD versus asthma. Until recently, the two diseases were thought to have completely different inflammatory hallmarks. On one side, the innate immune system (macrophages and neutrophils) was considered the key player in the milder stages of COPD, whereas T and B cells were considered the critical players of the more severe stages of COPD[44,45]. On the other side, asthma was considered a TH 2-prevalent disease with high eosinophils infiltrate[46]. Eosinophils were also known to get into the lower airways of patients with COPD, but their role was unknown and considered marginal. However, recent studies have shown that increased sputum eosinophils were present in both stable and exacerbation phases of patients with COPD, implying the potential role of eosinophils in the pathogenesis of COPD[47,48]. Eosinophilia is generally defined as greater or equal to 2% eosinophils in either blood or sputum, or an absolute blood eosinophil count of $0.34 \times 10^9$ cells per litre. Peripheral blood eosinophil count is highly associated with eosinophilia of the respiratory tract[49]. This blood biomarker has also been shown to reflect submucosal eosinophilia of

the lung and reticular basement membrane thickening[50]. A subset of COPD patients presents 2% or more of blood eosinophils, which has been called "high eosinophil-COPD". From a clinical standpoint, the exact meaning of high versus low eosinophil count is still unclear. Some studies suggest that high count of eosinophils in blood is predictive of favourable response to steroidal and bronchodilator therapies in patients with stable COPD, whereas some other suggest that high eosinophil count in COPD patients does not contribute to exacerbation risk, in-hospital mortality, and length of hospital stay. However, high eosinophil count in the outpatient COPD patients with higher eosinophil count demonstrated an increased risk of exacerbation by 18%[47,48]. Interestingly, consistently in both asthma and COPD, sputum eosinophilia is associated with an excellent response to corticosteroid therapy and strategies aimed to normalise sputum eosinophils reduce exacerbation frequency and severity[51]. Thus, the new GOLD recommendations have been updated to mirror the recent increased knowledge on the presence of eosinophils in COPD, and suggest that high blood eosinophil counts (≥ 300 eosinophils/μL) are used to identify patients with a greater likelihood of a beneficial response to inhaled corticosteroids (ICS)[47,52].

Eosinophil inflammation might be a common mechanism underlying the pathogenesis of ACO, or might identify a subset of COPD patients with asthmatic features or vice-versa. Thus, further studies are needed to clarify our understanding of the role of eosinophil recruitment to the airway, and the consequence of such eosinophil infiltrate, in order to develop new therapies to target these molecular pathways.

## GOLD 1 versus GOLD 4 COPD

The GOLD recommendations have dominated the COPD scene for more than one decade, and they are currently the most widespread way of classifying patients with COPD. Indeed, the GOLD recommendations have given a significant contribution in approaching the patients with COPD and in providing guidance for their therapeutic management. Also, the evolvement of the GOLD recommendations over the years mirrors the evolvement of our understanding of the disease. Before the 2011 update of the GOLD recommendations, therapy recommendations were based primarily on lung-function values[53]. Current treatment recommendations are based on a combination of lung function, symptoms and number of exacerbations in the previous year. The new grading for COPD begins with mild (1) through to very severe (4) stages using post-bronchodilator $FEV_1$ and adds the impact of symptoms using the modified Medical Research Council (MRC) dyspnoea scale or the COPD Assessment Test (CAT) with a final additional stratification based on the number of COPD exacerbations in the previous 12 months. The final categories are A–D (https://goldcopd.org). As one would expect, not everyone fits into these four categories. Also, the higher is the category of severity from A to D, the more therapeutic options are listed. This need of including such a high number of therapeutic options probably mirrors the increasing difficulties of including an increasing number of clinical manifestations, and the relative treatments, under the same umbrella of COPD. One significant advancement of the current GOLD recommendations compared to the past is that the current system does recognise the fact that $FEV_1$ alone

cannot define the severity of the disease, and is therefore not an adequate predictor of the therapeutic needs of people with COPD[54].

More and more, science is moving towards a more personalised approach to the patient with COPD, where the focus has shifted from the clinical presentation (airflow obstruction) to the pathobiological mechanism, or "endotype" [55] underlying the disease[56]. Exposure to noxious stimuli such as cigarette smoke, biomass smoke or traffic emissions may affect different cell types in the lung depending on susceptibility. Individuals will respond to these insults in many different ways according to their susceptibility. Some subjects with susceptible airway epithelial cells may be prone to increased mucin gene expression that leads to phlegm production and airway disease (airway endotype); in some others, susceptible endothelial cells of the lung and/or systemic vasculature may lead to pulmonary and renal endothelial cell injury, resulting in albuminuria or pulmonary vascular disease and emphysema[57]. Others may have susceptible hematopoietic cells of the lung that initiate abnormal response of B cells[58,59], ultimately leading to the destruction of the alveolar structures and emphysema. According to this new view, in order to reliably sub-phenotype COPD, it is critical to study younger cohorts of subjects at risk for developing COPD so that the endotypes can be identified[31]. The advantage of looking at upstream cohort is that, while the pathology and clinical presentation of the established COPD may be identical, the pathobiological origins of the disease are different. Therefore, early endotyping is necessary in order to have the tools to stratify and treat COPD in a more personalised fashion[55].

Finally, a consequence of the GOLD recommendations has been the fact that, when talking about the pathogenesis of COPD, one assumes that the events occurring in the lung during COPD follow an exact temporal sequence, from GOLD 1 to 4. Due to the unlikelihood, apart from rare cases, to get repeated sampling of lung specimens from the same subject longitudinally, it is hard to determine whether in COPD innate immune responses always precede the adaptive immune responses, or whether small airway disease is always preceding emphysematous destruction in the course of COPD[60]. Indeed, the airway endotype is often associated with mild airflow obstruction, whereas the emphysematous endotype is associated with more severe airflow obstruction[11]. However, there is a knowledge gap about the temporal sequence and the extent of the overlap of the pathologic manifestations occurring throughout COPD.

Future studies are very much needed to clarify the time course and the relative contribution of endotypes underlying COPD onset and progression in order to allow early COPD diagnosis and intervention on the basis of the endotype involved. As with all newly developed models for the conceptualisation of obstructive lung disease, the GOLD model will undoubtedly be further modified over time to be much more patient-oriented than the older system of mild-to-very-severe classification according to $FEV_1$ alone.

## CONCLUSIONS

Over the last two decades, substantial progress has been made in defining and understanding COPD. From a lung-centred view of

the disease, it is now clear that COPD is an umbrella under which several pathologic manifestations stand, sometimes affecting the body as a whole. Also, until recently, COPD was considered a disease of the elderly, whereas now it is known that lung function is affected by several factors established in the prenatal and perinatal periods. Thus, specific individuals develop airflow limitation at a young age, and cigarette smoke exposure is only one causative factor of such decline in lung function. The GOLD recommendations, which are still a milestone in the diagnosis and treatment of COPD, are adjusting to the increased knowledge of the disease. Further studies are needed to clarify the heterogeneous nature of airflow limitation which we now call "COPD" (Fig. 1), and to better cluster the patterns of airflow limitation under the right umbrella. Airflow limitation is becoming too big of a giant whose feet don't fit anymore into the shoes of COPD. Thus, will we still be calling it "COPD" in 50 years? Probably not (author's opinion).

## DISCLOSURES

Dr. Polverino has no conflict of interest to disclose.

## REFERENCES


1. Polverino F, Celli B. The Challenge of Controlling the COPD Epidemic: Unmet Needs. Am J Med. 2018;131:1-6.
2. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. Am Rev Respir Dis. 1987;136:225-44.
3. Petty TL. The history of COPD. Int J Chron Obstruct Pulmon Dis. 2006;1:3-14.
4. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1:1645-8.
5. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med. 1995;152:S77-121.
6. Rodriguez-Roisin R, Rabe KF, Vestbo J, Vogelmeier C, Agustí A. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 20th Anniversary: a brief history of time. Eur Respir J. 2017;50.
7. Rabe KF. Guidelines for chronic obstructive pulmonary disease treatment and issues of implementation. Proc Am Thorac Soc. 2006;3:641-4.
8. Gruffydd-Jones K, Jones MM. NICE guidelines for chronic obstructive pulmonary disease: implications for primary care. Br J Gen Pract. 2011;61:91-2.
9. Celli BR, Cote CG, Marin JM et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005-12.
10. Johnson MA, Woodcock AA, Rehahn M, Geddes DM. Are "pink puffers" more breathless than "blue bloaters"? Br Med J (Clin Res Ed). 1983;286:179-82.
11. Faner R, Cruz T, Casserras T et al. Network Analysis of Lung Transcriptomics Reveals a Distinct B-Cell Signature in Emphysema. Am J Respir Crit Care Med. 2016;193:1242-53.
12. Kheradmand F, Shan M, Xu C, Corry DB. Autoimmunity in chronic obstructive pulmonary disease: clinical and experimental evidence. Expert Rev Clin Immunol. 2012;8:285-92.
13. Xu C, Hesselbacher S, Tsai CL et al. Autoreactive T Cells in Human Smokers is Predictive of Clinical Outcome. Front Immunol. 2012;3:267.
14. Bhavani S, Yuan X, You R, Shan M, Corry D, Kheradmand F. Loss of Peripheral Tolerance in Emphysema. Phenotypes, Exacerbations, and Disease Progression. Ann Am Thorac Soc. 2015;12 Suppl 2:S164-8.
15. Di SA, Caramori G, Gnemmi I et al. T helper type 17-related cytokine expression is increased in the bronchial mucosa of stable chronic obstructive pulmonary disease patients. Clin Exp Immunol. 2009;157:316-24.
16. Koo HK, Vasilescu DM, Booth S et al. Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study. Lancet Respir Med. 2018;6:591-602.
17. Celli BR, Locantore N, Tal-Singer R et al. Emphysema and extrapulmonary tissue loss in COPD: a multi-organ loss of tissue phenotype. Eur Respir J. 2018;51.
18. MacNee W, Murchison JT. Small Airway Disease or Emphysema: Which Is More Important in Lung Function and FEV1 Decline? An Old Story with a New Twist. Am J Respir Crit Care Med. 2016;194:129-30.
19. Hersh CP, Make BJ, Lynch DA et al. Non-emphysematous chronic obstructive pulmonary disease is associated with diabetes mellitus. BMC Pulm Med. 2014;14:164.
20. Mullerova H, Maselli DJ, Locantore N et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. Chest. 2015;147:999-1007.
21. Lynch DA, Al-Qaisi MA. Quantitative computed tomography in chronic obstructive pulmonary disease. J Thorac Imaging. 2013;28:284-90.
22. Lynch DA, Austin JH, Hogg JC et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. Radiology. 2015;277:192-205.
23. Hogg JC, Chu F, Utokaparch S et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:2645-53.
24. Enright P. HRCT-defined emphysema is not COPD to be treated with inhalers. Thorax. 2014;69:401-2.
25. Washko GR, Hunninghake GM, Fernandez IE et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011;364:897-906.
26. Rennard SI, Vestbo J. Natural histories of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5:878-83.
27. Lange P, Celli B, Agusti A et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. N Engl J Med. 2015;373:111-22.
28. Bui DS, Burgess JA, Lowe AJ et al. Childhood Lung Function Predicts Adult Chronic Obstructive Pulmonary Disease and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. Am J Respir Crit Care Med. 2017;196:39-46.
29. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2016;375:871-8.

30. Martinez FJ, Han MK, Allinson JP et al. At the Root: Defining and Halting Progression of Early Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018;197:1540-51.
31. Soriano JB, Polverino F, Cosio BG. What is Early COPD and Why is it Important? Eur Respir J. 2018.
32. Celli BR, Agusti A. COPD: time to improve its taxonomy? ERJ Open Res. 2018;4.
33. Terzikhan N, Verhamme KM, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. Eur J Epidemiol. 2016;31:785-92.
34. Siafakas NM, Tzortzaki EG. Few smokers develop COPD. Why? Respir Med. 2002;96:615-24.
35. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2016;375:871-8.
36. Bui DS, Lodge CJ, Burgess JA et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. Lancet Respir Med. 2018.
37. Guerra S, Halonen M, Vasquez MM et al. Relation between circulating CC16 concentrations, lung function, and development of chronic obstructive pulmonary disease across the lifespan: a prospective study. Lancet Respir Med. 2015;3:613-20.
38. Rossi A, Butorac-Petanjek B, Chilosi M et al. Chronic obstructive pulmonary disease with mild airflow limitation: current knowledge and proposal for future research - a consensus document from six scientific societies. Int J Chron Obstruct Pulmon Dis. 2017;12:2593-610.
39. Mannino DM. GOLD stage 0 COPD: is it real? Does it matter? Chest. 2006; 130:309-10.
40. Hikichi M, Hashimoto S, Gon Y. Asthma and COPD overlap pathophysiology of ACO. Allergol Int. 2018;67:179-86.
41. Nelsen L, Gater A, Panter C, Tolley C, Lee L, Pascoe S. Understanding and measuring symptoms and health status in asthma COPD overlap: content validity of the EXACT and SGRQ. J Patient Rep Outcomes. 2017;2:18.
42. Postma DS, Weiss ST, van den Berge M, Kerstjens HA, Koppelman GH. Revisiting the Dutch hypothesis. J Allergy Clin Immunol. 2015;136:521-9.
43. Chambliss JM, Sur S, Tripple JW. Asthma versus chronic obstructive pulmonary disease, the Dutch versus British hypothesis, and role of interleukin-5. Curr Opin Allergy Clin Immunol. 2018;18:26-31.
44. O'Donnell R, Breen D, Wilson S, Djukanovic R. Inflammatory cells in the airways in COPD. Thorax. 2006;61:448-54.
45. Polverino F, Seys LJ, Bracke KR, Owen CA. B cells in chronic obstructive pulmonary disease: moving to center stage. Am J Physiol Lung Cell Mol Physiol. 2016;311:L687-L95.
46. Nair P, O'Byrne PM. Measuring Eosinophils to Make Treatment Decisions in Asthma. Chest. 2016;150:485-7.
47. Casanova C, Celli BR, de-Torres JP et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. Eur Respir J. 2017;50.
48. Kolsum U, Ravi A, Hitchen P, Maddi S, Southworth T, Singh D. Clinical characteristics of eosinophilic COPD versus COPD patients with a history of asthma. Respir Res. 2017;18:73.
49. O'Connell EM, Nutman TB. Eosinophilia in Infectious Diseases. Immunol Allergy Clin North Am. 2015;35:493-522.
50. Eltboli O, Mistry V, Barker B, Brightling CE. Relationship between blood and bronchial submucosal eosinophilia and reticular basement membrane thickening in chronic obstructive pulmonary disease. Respirology. 2015;20: 667-70.
51. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. Ther Adv Chronic Dis. 2016;7: 34-51.
52. Cheng SL. Blood eosinophils and inhaled corticosteroids in patients with COPD: systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018;13:2775-84.
53. Hsieh MJ, Huang SY, Yang TM et al. The impact of 2011 and 2017 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines on allocation and pharmacological management of patients with COPD in Taiwan: Taiwan Obstructive Lung Disease (TOLD) study. Int J Chron Obstruct Pulmon Dis. 2018;13:2949-59.
54. Cabrera Lopez C, Casanova Macario C, Marin Trigo JM et al. Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197:463-9.
55. Petersen H, Vazquez Guillamet R, Meek P, Sood A, Tesfaigzi Y. Early Endotyping: A Chance for Intervention in Chronic Obstructive Pulmonary Disease. Am J Respir Cell Mol Biol. 2018;59:13-7.
56. Agusti A, Celli B, Faner R. What does endotyping mean for treatment in chronic obstructive pulmonary disease? Lancet. 2017;390:980-7.
57. Polverino F, Laucho-Contreras ME, Petersen H et al. A Pilot Study Linking Endothelial Injury in Lungs and Kidneys in COPD. Am J Respir Crit Care Med. 2017.
58. Polverino F, Baraldo S, Bazzan E et al. A novel insight into adaptive immunity in chronic obstructive pulmonary disease: B cell activating factor belonging to the tumor necrosis factor family. Am J Respir Crit Care Med. 2010; 182:1011-9.
59. Polverino F, Cosio BG, Pons J et al. B Cell-Activating Factor. An Orchestrator of Lymphoid Follicles in Severe Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2015;192:695-705.
60. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med. 2009;360:2445-54.