

Chronic obstructive pulmonary disease phenotypes, biomarkers, and prognostic indicators

Christopher E. Brightling, M.B.B.S., Ph.D.

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease associated with significant morbidity and mortality. Current diagnostic criteria are based on lung function impairment, symptoms, and exacerbation frequency but do not capture the heterogeneity of the disease in terms of the complex pathologic changes that occur within lung, the different airway inflammatory patterns, or the airway microbial ecology. Recognition of the importance of defining the heterogeneity of COPD has led to the identification of important phenotypes with specific biomarkers, treatment responses, and underlying pathophysiologic mechanisms. This review summarized the presentation at the Eastern Allergy Conference 2016, which considered how multidimensional phenotyping provides important clinical insights that enable the clinician to move toward a precision medicine approach for COPD.

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Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality, and is predicted to become the third leading cause of mortality worldwide by 2030.^{1,2} COPD is defined by airflow obstruction that is not fully reversible, does not change markedly over time, and is usually progressive.^{1–3} Cigarette smoke is the main causative agent, although other exposures (e.g., occupational and biomass fuel) are increasingly being recognized as important. Exacerbations, an acute onset of sustained worsening of the patient's symptoms from a usual stable state, are particularly important because these exacerbations are associated with high economic costs and accelerated lung function decline as well as having a negative impact on quality of life and mortality.^{1–5}

Current diagnostic criteria do not fully capture the heterogeneity of COPD in terms of the complex pathologic changes that occur within lung, the different airway inflammatory patterns, or the airway microbial ecology. Considered herein was how recognition of the importance of defining the heterogeneity of COPD by using multidimensional phenotyping has led to the identification of important phenotypes, with specific biomarkers, treatment responses, and underlying pathophysiologic mechanisms.

MULTIDIMENSIONAL COPD PHENOTYPING

A phenotype is composed of the observable characteristics that result from gene-environment interactions. To fulfill clinical and research goals, it has been proposed that “COPD phenotypes” should also be able to classify patients into distinct subgroups, provide prognostic information, be prospectively validated for each outcome, and ultimately alter clinically meaningful outcomes.⁶ Most approaches to phenotyping have considered symptoms, e.g., chronic bronchitis. This approach is also reflected in guidelines that the Global Initiative for Chronic Obstructive Lung Disease categorizes COPD based on the degree of lung function impairment, symptoms, and exacerbation frequency into COPD A to D¹ (Fig. 1). However, this does not include remodeling, lung damage, or inflammation in its classification nor does it integrate interactions between the gene and airway environment, e.g., airway microbial ecology.

Airway Damage and Remodeling: Emphysema and Small Airway Obliteration

Chronic airflow obstruction is due to a combination of emphysema (tissue damage with permanent dilatation distal to the terminal bronchiole) and small airway obliteration.^{1–3} The distribution of emphysema can be centrilobular or panacinar. Small airways are the major site of airway obstruction in COPD. This small airways obliteration is due to a combination of remodeling and accumulation of inflammatory exudates within the airway lumen, both of which increase with disease severity (Fig. 2).^{7,8} Remodeling changes observed in COPD include disruption and loss of epithelial cilia, squamous metaplasia of the respiratory epithelium, goblet cell hyperplasia and mucous gland enlargement, bron-

From the Institute for Lung Health, National Institute for Health Research Respiratory Biomedical Research Unit, Department of Infection, Immunity and Inflammation, University of Leicester and University Hospitals of Leicester NHS Trust, Leicester, United Kingdom

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Address correspondence to Christopher E. Brightling, Ph.D., Institute for Lung Health, Clinical Science Wing, University Hospital of Leicester, Leicester, LE3 9QP, UK

E-mail address: ceb17@le.ac.uk

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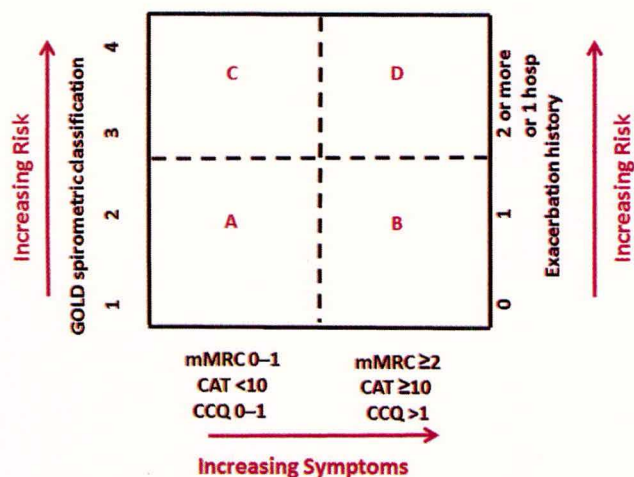


Figure 1. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of chronic obstructive pulmonary disease (COPD) based on severity of symptoms (by using the modified Medical Research Council [MRC] or COPD assessment test [CAT] score), lung function (forced expiratory volume in 1 second [FEV₁] % predicted), and exacerbation frequency to derive GOLD stages A–D (adapted from Ref. 1).

cholar smooth-muscle hypertrophy, airway wall fibrosis, and inflammatory cell infiltration.^{9,10}

Analysis of data from computed tomography (CT) and micro-CT demonstrated a reduction in the number and luminal area of terminal bronchioles in COPD of varying severities,¹¹ which has led to the suggestion that narrowing and the disappearance of small conducting airways can explain the increased peripheral airway resistance reported in COPD.¹¹ Quantitative CT has demonstrated that gas trapping more than emphysema is related to lung function impairment but has also underlined the heterogeneity of proximal airway remodeling, gas trapping and emphysema in COPD, and severe asthma (Fig. 3).¹² In addition, CT can show other common pathologies that coexist with COPD, such as bronchiectasis and interstitial lung abnormalities, can be identified.^{13,14} Of note, CT lung densitometry has benefits over lung function in terms of its sensitivity for detecting emphysema progression¹⁵ and provides regional data,¹⁶ which has led to the suggestion that CT may be more useful than lung function to assess emphysema progression in clinical trials.

Airway Inflammation

The presence of airway inflammation in both stable COPD and exacerbation episodes is well recognized, with severity of airflow obstruction that correlates with airway inflammation, and with severe airflow obstruction associated with increased neutrophils, macrophages, and CD8+ lymphocytes in the bronchial mucosa.¹⁷ Noninvasive measures of airway inflammation, most notably sputum cytology, has identified different

sputum phenotypes determined by granulocyte composition termed neutrophilic, eosinophilic, mixed granulocytic, and paucigranulocytic.^{18,19} Although sputum cytology has underscored that neutrophilic inflammation is most commonly observed in COPD, a sputum eosinophilia is present in 10–40% of patients with COPD.^{20–23} In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End Points cohort, repeated blood eosinophil counts were available in 1483 subjects over 3 years.²⁴ By using a cutoff for blood eosinophils of 2%, 37% of subjects had persistently elevated eosinophils, 49% were intermittent, and the remainder were noneosinophilic. The persistently eosinophilic group were older, predominantly male, with milder disease and fewer symptoms. Emphysema progression was greater in the noneosinophilic group,²⁴ and, in contrast to severe asthma, there were no differences in lung function decline among the groups.

To further inform the understanding of the heterogeneity of COPD in a stable state, unbiased statistical approaches, e.g., cluster analysis, have been applied to large clinical data sets.^{25–28} Interestingly, these have underscored the importance of eosinophilic airway inflammation in asthma, COPD, and the asthma-COPD overlap syndrome.²⁹ Ghebre *et al.*³⁰ combined data from asthma and COPD, and identified three clusters. Cluster 1 consisted of subjects with asthma and with increased interleukin (IL) 5, IL-13, and CCL26 mediators, and eosinophil predominance. Cluster 2 consisted of an overlap between asthma and COPD, with neutrophil predominance, with 11% of patients with asthma having sputum eosinophilia. Cluster 3 consisted mainly of patients with COPD and with mixed granulocytic airway inflammation. The differences seen between neutrophilic COPD in cluster 2 and eosinophilic COPD in cluster 3 included the presence of increased bacterial colonization in the former and increased CCL13 in the latter, possibly explaining the observed airway inflammation differences seen among these clusters.

Eosinophilic inflammation is also increased at exacerbations, as evidenced in studies of sputum,³¹ bronchoalveolar lavage,³² and bronchial biopsy specimens.³³ Indeed, eosinophilic, but not neutrophilic, inflammation increased at exacerbation in bronchoalveolar lavage of patients with chronic bronchitis. Attempts have similarly been made to phenotype the biologic profiles of COPD exacerbations. Hurst *et al.*³⁴ studied 36 plasma biomarkers in 90 patients with COPD by looking at paired baseline and exacerbation samples. C-reactive protein, a nonspecific marker of infection, inflammation, and injury, was the most selective but not sufficient alone to confirm an exacerbation diagnosis. None of the systemic biomarkers examined in this study were useful to predict exacerbation severity. After a proteomic analysis of serum from patients with an exacerbation of COPD, serum amyloid

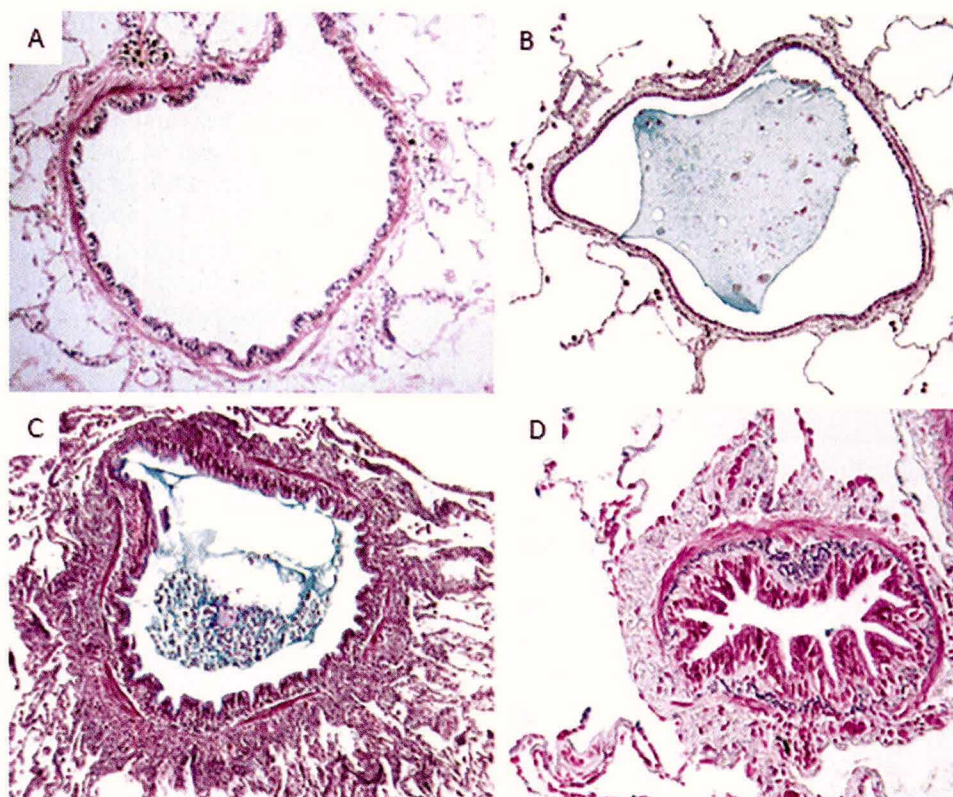


Figure 2. Example photomicrographs of (A) a normal small airway and different processes of small airway obliteration, (B) mucus plugging, (C) airway inflammation and inflammatory exudates, and (D) subepithelial fibrosis and increased airway smooth-muscle mass (adapted from Ref. 7).

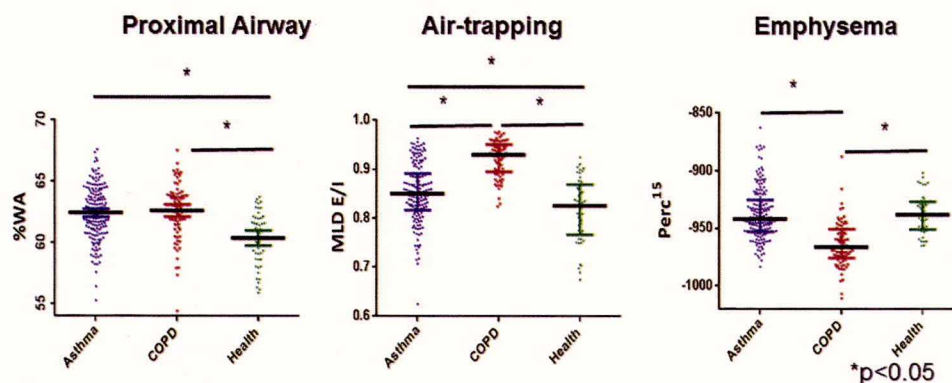


Figure 3. Heterogeneity of computed tomography (CT) derived remodeling in asthma, chronic obstructive pulmonary disease (COPD), and healthy controls. Proximal airway wall thickening (%wall area [WA]), air-trapping (mean lung density expiratory–inspiratory [MLD E/I]), and emphysema (15th percentile of the Hounsfield units as a measure of lung density [Perc 15]) (adapted from Ref. 12).

A (SAA) protein was identified as a putative biomarker.³⁵ SAA, as with C-reactive protein, is increased at exacerbation onset compared with the stable state but is more sensitive than C-reactive protein alone. The SAA concentration was also related to the severity of the COPD exacerbation but was poorly related to etiology, which indicated that it has limited value to directing therapy. Whether SAA has utility in predicting a future risk of severity and poor outcomes requires further study.

These studies^{34,35} compared the stable state with exacerbations but did not fully classify the exacerbation event based on its potential etiology. Bafadhel *et al.*³¹ recruited 145 patients into an observational study with biomarkers from blood and serum assessed at stable state and during exacerbations for 1 year to define biomarkers to identify bacterial, viral, or eosinophilic-associated exacerbations. In this study, 55% of exacerbations were associated with bacteria, 29% with virus, and 28% with sputum eosinophilia. From a compre-

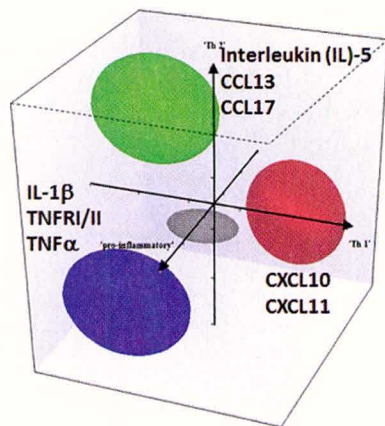


Figure 4. Biologic clustering of chronic obstructive pulmonary disease (COPD) exacerbations. Cartesian plot, showing four clusters "Th1-predominant," "Th2-predominant," "proinflammatory," and "pauci-inflammatory" in gray. Each ellipsoid is proportional to the number of subjects in each cluster (adapted from Ref. 31).

hensive biomarker panel of >30 mediators, differential cell counts in blood and sputum, and clinical variables, the biomarkers that best identified these clinical phenotypes were sputum IL-1 β , serum CXCL10, and percentage peripheral blood eosinophils, respectively. The observation that CXCL10 was the best biomarker for identifying viral exacerbations (sensitivity 80%, specificity 60%) is consistent with previous findings that CXCL10 increases between baseline and exacerbation in COPD exacerbations due to human rhinovirus.³⁶ When using unbiased cluster analysis, four biologic exacerbation clusters were identified, and these validated the *a priori* etiologic groups: "Proinflammatory" bacterial-predominant, "T-helper lymphocyte type 1 viral-predominant," "T-helper lymphocyte type 2 eosinophilic-predominant," and a fourth group that was termed "pauci-inflammatory" because this was associated with limited changes in the inflammatory profile (Fig. 4). Disease severity according to the Global Initiative for Chronic Obstructive Lung Disease criteria was not different among these biologic clusters, and the biomarkers were associated with their respective potential etiologies, independent of disease severity.

These findings supported the concept of different "exacerbation phenotypes." Interestingly, the eosinophilic and bacterial-associated phenotypes were also observed in stable disease and predicted the future exacerbation phenotype. Patients experienced more bacterial exacerbations if their stable sputum samples contained bacteria and experienced more eosinophilic exacerbations if eosinophilic inflammation was present in the stable state, which indicates that these biomarkers, in addition to directing therapy during the exacerbation event, might identify subgroups to target therapy with the aim of reducing future risk.

Airway Exposome: Microbial Ecology

The airway is continuously exposed to a variety of insults, which include pollutants (e.g., cigarette smoke), allergens, and pathogens. Infection caused by pathogens, such as bacteria, viruses, or a combination of these, is thought to have an important role in COPD pathogenesis. In nonexacerbating patients bacteria can be identified using traditional culture methods to identify presence of bacterial colonization.^{31,37,38} This colonization is associated with increased airways inflammation, poorer health status, and more rapid lung function decline.^{39–41} Molecular techniques that use pathogen-specific quantitative polymerase chain reaction^{42,43} and sequencing⁴⁴ provide insights into the microbial ecology and have demonstrated that, in stable disease, *Haemophilus influenzae* is associated with neutrophilic inflammation and increased proinflammatory cytokines.^{45,46} Interestingly, at exacerbation, *Moraxella catarrhalis* increases in association with concomitant amplification of inflammation.⁴²

CLINICAL APPLICATIONS OF MULTISCALE COPD PHENOTYPING

Combinations of inhaled glucocorticoids, long-acting β -agonists, and long-acting muscarinic antagonists have been shown to improve symptoms and exercise tolerance as well as reduce exacerbations.^{1–3} Increasing knowledge of disease pathology at multiple scales improves our understanding of COPD and enables phenotype-specific clinical management. Inhaled and oral corticosteroids decrease eosinophilic bronchial mucosal inflammation⁴⁵ and induced sputum differential eosinophil count^{20–23}, and the presence of sputum eosinophilia (>3%) in COPD is a good predictor of the short-term response to oral and inhaled corticosteroid treatments in stable disease. Importantly, a blood eosinophil count is also associated with a greater reduction in exacerbation frequency in response to inhaled corticosteroids,^{46,47} and, in an inhaled corticosteroid withdrawal trial, a higher blood eosinophil count was associated with increased exacerbations.^{48–50}

IL-5 is an obligate cytokine in the maturation and survival of eosinophils. Anti-IL5 has demonstrated clinical efficacy in severe asthma with reduction in severe exacerbations.⁵¹ Recognition that eosinophilic inflammation is important in a subgroup of patients with COPD has led to the study of anti-IL-5 targeted biologics. Benralizumab is a human afucosylated monoclonal antibody that targets IL-5R α expressed by eosinophils and basophils, and, after receptor blockade, initiates antibody-dependent cell-mediated cytotoxicity.⁵² Benralizumab improved lung function but did not decrease exacerbation rates, although there was a trend toward reduction in ex-

acerbations and improvement in health status in those subjects with COPD and with higher baseline blood and sputum eosinophil counts.⁵³ These encouraging findings have supported progression to phase III studies.

In stable disease, macrolide antibiotics reduce exacerbation frequency in COPD and asthma.^{54,55} In asthma, benefit was best in those individuals without evidence of eosinophilic inflammation. In COPD, response to macrolide therapy was not observed in current smokers, but, to date, no biomarker of inflammation or bacterial colonization has been used to direct macrolide therapy in stable disease. The international challenge to reduce inappropriate antibiotic usage to minimize antibiotic resistance means that there is an urgent need to undertake biomarker-directed studies of macrolides and other antibiotics in COPD.

An exacerbation diagnosis is currently based on symptoms, with guidelines that recommend treatment with systemic corticosteroids, along with antibiotics if there is increased sputum purulence.^{1,2} In acute exacerbations of COPD, systemic corticosteroids reduce treatment failure and length of hospital stay but do not reduce mortality and are associated with significantly more adverse events.⁵⁶ Antibiotics reduce hospital readmission rates, mortality, and treatment failure⁵⁷ but have disadvantages in terms of increased rates of antibiotic-related diarrhea, including emergence of *Clostridium difficile* infection. Moreover, the benefit of antibiotics in terms of reduced treatment failure and mortality reduction may be limited to those patients who experience severe exacerbations.⁵⁷

In acute exacerbations of COPD, targeting oral corticosteroid treatment to those patients with evidence of eosinophilic airways inflammation can lead to a safe reduction in oral corticosteroid prescriptions.^{58,59} Moreover, those patients who do not receive prednisolone with eosinophilic inflammation have poor outcomes, and, in contrast, those who receive oral corticosteroids, but without an eosinophilia, may experience more adverse events and poorer recovery rates.^{58,60} Procalcitonin, a peptide released in bacterial infections, has potential in identifying bacterial exacerbations of COPD and in guiding treatment duration. A procalcitonin algorithm (predefined criteria for starting and/or stopping antibiotics) reduced the duration of antibiotic courses, without increasing adverse events.⁶¹ Thus, use of procalcitonin to guide treatment could reduce inappropriate antibiotics in acute exacerbations of COPD.

CONCLUSION

There is increasing recognition that COPD is a heterogeneous disease and that current approaches do not

fully address this issue. Identification of important COPD phenotypes with specific biomarkers, treatment responses, and underlying pathophysiologic mechanisms will help the clinician to move toward a precision medicine approach for COPD.

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