

Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



COPD9USA Session Summary

COPD Overlap Syndromes: Asthma and Beyond

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This article serves as a CME-available enduring material summary of the following COPD9USA presentations:

- “COPD and Asthma” *Presenter:* Prescott Woodruff, MD, MPH
- “COPD and Lung Cancer” *Presenter:* William Bulman, MD
- “COPD and Bronchiectasis” *Presenter:* Jeremy Clain, MD
- “COPD and Interstitial Lung Disease” *Presenter:* George Washko, MD

Abbreviations: chronic obstructive pulmonary disease, **COPD**; asthma-COPD overlap syndrome, **ACOS**; computerized tomography, **CT**; Global Initiative for Asthma, **GINA**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points, **ECLIPSE**; intensive care unit, **ICU**; lung volume reduction surgery, **LVRS**; high resolution computerized tomography, **HRCT**; combined pulmonary fibrosis and emphysema, **CPFE**

Citation: Lambert AA, Dransfield MT. COPD overlap syndromes: Asthma and beyond. *Chronic Obstr Pulm Dis (Miami)*. 2016;3(1):459465. doi: <http://dx.doi.org/10.15326/jcopdf.3.1.2015.0176>

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Keywords:

COPD; overlap; asthma; lung cancer; bronchiectasis; interstitial lung disease

Introduction

Chronic obstructive pulmonary disease (COPD) affects 15 million Americans and became the third leading cause of death in the United States in 2011.¹ Comorbidities are increasingly recognized to play an important role in the management and outcomes of patients with COPD.^{2,3} COPD phenotypes have been proposed to facilitate patient classification for

prognostic, therapeutic, and research purposes.⁴ Proposed phenotypes have been expanded beyond subtypes of COPD to include overlapping pulmonary disease.⁵ Overlapping diagnoses with COPD complicate the diagnosis and management of this disease but may also pose an opportunity to identify distinct and modifiable pathophysiology. We summarize here 4 of these overlapping syndromes that were reviewed at the 2015 COPD9USA conference.

COPD and Asthma

The overlap of COPD with asthma is referred to as asthma-COPD overlap syndrome (ACOS). ACOS represents a clinical diagnosis and should be considered among patients with persistent airflow limitation and a combination of features typically associated with both asthma and COPD.⁶ Examples of features more typical of asthma than COPD that may be present include: childhood symptoms, significant day to day variability of symptoms, known triggers for symptoms, personal or family history of atopy, or more pronounced reversibility of airflow obstruction. Despite these characteristics, classic COPD features may still be present, such as hyperinflation or computerized tomography (CT)-defined emphysema. Identification of patients with

ACOS is critical because outcomes for patients with ACOS may be worse than those for patients with COPD or asthma alone;⁷ as a result, subspecialty referral is often required to ensure appropriate diagnosis and treatment.

Although the Global Initiative for Asthma (GINA) and the Global initiative for chronic Obstructive Lung Disease (GOLD) recommend a clinical definition of ACOS,⁶ characterizing ACOS by these clinical features may not represent the distinguishing underlying pathophysiology and may inappropriately categorize patients. Therefore, distinguishing ACOS from singular COPD may be more appropriately performed by utilizing biological features that may reflect the underlying disease pathology and the response to therapy.⁸

Eosinophilia may represent the appropriate surrogate to distinguish these clinical diseases. A subset of patients with COPD are known to exhibit eosinophilic, rather than neutrophilic, inflammation.⁹ The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort observed 37% of participants to have persistently elevated blood eosinophil counts ($\geq 2\%$) over 3 years and reported that these patients demonstrated distinct characteristics, including older age, male gender, fewer symptoms and less airflow obstruction.¹⁰ Importantly, ECLIPSE found that blood and sputum eosinophilia were correlated. Sputum eosinophilia has been found to correlate with responsiveness to both systemic^{11,12} and inhaled^{13,14} corticosteroids among COPD patients. Additional targeted therapy beyond corticosteroids has been suggested for eosinophilic COPD patients with the medication benralizumab, a monoclonal antibody that inhibits interleukin-5.¹⁵

In summary, ACOS represents a distinct disease process with both unique pathophysiology and responsiveness to therapy. As opposed to traditional clinically-driven phenotypes, ACOS may be better defined by biological tools, such as blood or sputum eosinophil count. Use of these biologic markers may more accurately characterize the underlying pathophysiology and predict targeted therapeutic responsiveness.

COPD and Lung Cancer

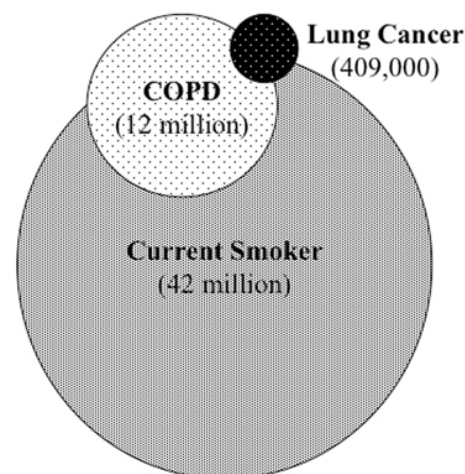
Lung cancer is the leading cancer cause of death among both men and women in the United States¹⁶ and kills more people annually than colorectal, breast, prostate and pancreatic cancers combined.¹⁷ More

men are diagnosed with lung cancer each year but the incidence among women has been rising, related to changing smoking patterns over the last century. Approximately 42 million American adults currently smoke cigarettes,¹⁸ 12-15 million have COPD,^{1,19} and approximately 400,000 have lung cancer.²⁰ Figure 1 illustrates the prevalence of these overlapping diagnoses.

Approximately 50%-80% of patients with lung cancer had pre-existing COPD prior to their cancer diagnosis.²¹⁻²³ Comorbid COPD and lung cancer is prevalent due to the shared risk factor of tobacco use however, the risk for lung cancer among patients with COPD exceeds expected rates based upon age or extent of tobacco exposure.²⁴⁻²⁶ Specifically, COPD is independently associated with a 2.5-fold increase in the odds of lung cancer, after adjusting for age, gender, and extent of tobacco use.²⁷ COPD patients with CT-defined emphysema have a nearly 4-fold independent increase in the odds of lung cancer.²⁸ This independently elevated risk for lung cancer among COPD patients is therefore not likely driven by tobacco use or age alone, but rather other processes such as chronic inflammation, amplified carcinogenic effects from tobacco exposure, impaired mucociliary clearance or shared genetic susceptibility.²⁹

Not only do patients with COPD experience increased risk for lung cancer compared to their smoking, age-matched peers, but they also suffer worse prognosis from

Figure 1. Prevalence of Smoking, COPD and Lung Cancer



Graphic illustrates prevalence of cigarette smoking (42.1 million in 2013), COPD diagnosis (12 million in 2010) and lung diagnosis cancer (408,808 people in 2012) among adults in the United States.

lung cancer with approximately doubled mortality.^{30,31} GOLD guidelines suggest that patients with comorbid COPD and lung cancer should receive the same treatment for each condition as would be recommended for patients with either diagnosis alone³²; however these recommendations are often limited by the severity of underlying respiratory disease including surgical, chemotherapeutic and radioablative thresholds.^{29,33} An increasing number of studies are now focused on expanding application of these therapies beyond traditional thresholds or identifying less invasive or aggressive treatment regimens that may still afford benefit in those with advanced chronic pulmonary disease.^{34,35} Curative surgical resection for early stage lung cancer has been an area of focus because it offers the greatest mortality benefit for patients with early disease,³⁶ may preserve lung function in those with limited reserve and may provide benefits similar to lung volume reduction surgery (LVRS) in select candidates. LVRS showed the greatest benefit for patients with upper lobe predominant emphysema and poor exercise capacity following pulmonary rehabilitation³⁷; therefore these COPD patients who have resectable lung cancer in an upper lobe may derive dual benefit from surgery.

Given the known poor prognosis for lung cancer among COPD patients and the many limitations to providing standard therapies for these patients, prevention and screening are critical components of care. Aggressive tobacco cessation efforts³⁸ and targeted screening chest CT scans³⁹ are imperative in the care of COPD patients. Importantly, COPD patients in the CT arm of the National Lung Screening Trial did not experience overdiagnosis with CT screening but rather a shift towards a more favorable stage at the time of cancer diagnosis.⁴⁰

COPD and Bronchiectasis

Bronchiectasis, a suppurative lung disease with radiographically defined airway dilation, is common among patients with advanced COPD and is distinct from airway wall thickening which is a common finding in obstructive lung diseases.⁴¹ Comorbid bronchiectasis has been reported in 28%-58% of COPD patients with moderate to severe airflow obstruction⁴²⁻⁴⁴ with increasing prevalence as degree of airflow obstruction increases.⁴⁵ These reports may underestimate the true burden of bronchiectasis because bronchiectasis is a radiographically-defined diagnosis that exhibits clinical overlap with COPD; therefore, COPD patients may not

be appropriately evaluated for comorbid bronchiectasis. As the performance of chest CTs increases for the purposes of lung cancer screening, bronchiectasis will likely become increasingly recognized.

Despite this clinical overlap, recognition of bronchiectasis among patients with COPD is important because its presence is associated with worse outcomes. Specifically, outpatients with comorbid bronchiectasis and COPD suffer more frequent respiratory exacerbations, higher rates of potentially pathogenic microorganisms isolated in their sputum, and increased mortality.⁴⁶ Intubated intensive care unit (ICU) patients with overlapping bronchiectasis and COPD experience prolonged courses of mechanical ventilation, extended ICU and hospital length-of-stay, and increased rates of ventilator-associated pneumonia.⁴⁷

In addition to prognostication and risk stratification, diagnosis of bronchiectasis may also carry therapeutic relevance regarding the approach to microorganisms isolated in sputum, the role for bronchial hygiene, and the possibility of targeted pulmonary resection. In non-cystic fibrosis-related bronchiectasis, colonization with *Pseudomonas aeruginosa* has been associated both with disease progression, defined by forced expiratory volume in 1 second decline,⁴⁸ and mortality.⁴⁹ Anti-pseudomonal treatment is recommended for non-cystic fibrosis patients with evidence of chronic colonization with *Pseudomonas aeruginosa*⁵⁰ and may also have a role for those with frequent exacerbations.⁵¹ Application of these findings to COPD patients with overlapping bronchiectasis and frequent exacerbations has been proposed but is not yet approved⁵²; therefore, individual practitioners may consider use of these therapies in a case-by-case fashion, without Federal Drug Administration approval.

In summary, bronchiectasis is prevalent among patients with advanced COPD and may represent a distinct phenotype that warrants targeted therapy.

COPD and Interstitial Lung Disease

Emphysema and fibrosis are radiographically and physiologically defined features that individually represent the extremes of lung disease but can coexist. Emphysema is characterized by a loss of lung tissue, decreased lung recoil and airflow obstruction; whereas fibrosis is characterized by a gain of lung tissue, increased lung recoil and airflow restriction. The overlap of these 2 conditions, likely related to the common exposure of tobacco smoke or other noxious

particles or gasses, results in pseudo-normalization of spirometry and lung volumes and an isolated, severely reduced diffusion capacity.⁵³ Resting and exertional hypoxemia are common,⁵⁴ with 1 study reporting 80% of combined pulmonary fibrosis and emphysema (CPFE) patients required supplemental oxygen.⁵⁵ The overlap of COPD and interstitial lung disease is often overlooked when imaging, specifically high resolution CT (HRCT), is not available to demonstrate the combination of radiographic pulmonary emphysema and fibrosis. CPFE was first recognized in 1990 but the prevalence of these overlapping diseases has become increasingly apparent as the performance of HRCTs increases.^{54,56} Despite this, targeted, specific therapy still does not exist.

Presently, research is focused upon identifying radiographic precursors of CPFE to identify those at risk for disease earlier, at which time interventions may afford greater benefit.^{57,58} COPD Genetic Epidemiology is a prospective cohort study that has obtained regular CT imaging on current and former smokers over time. At the time of enrollment into this study, 8% of participants demonstrated interstitial lung abnormalities.⁵⁹ These participants demonstrated reduced CT lung volume, less emphysema, greater symptoms, and reduced 6 minute walk distance as compared to their smoking counterparts without interstitial lung abnormalities on CT.⁶⁰ Shared genetic polymorphisms are being investigated to allow the identification of patients at risk for the overlap of emphysema with fibrosis, thereby enabling focused screening and therapy. The Muc5B promoter polymorphism, highly associated with idiopathic pulmonary fibrosis, is now recognized to be associated with interstitial lung disease in the general population.⁶¹

In summary, CPFE is a prevalent condition associated with worse outcomes in the COPD population. Radiographic and genetic methods are being developed to identify patients at risk for this manifestation of COPD. These tools will additionally allow the identification of optimal subpopulations for clinical therapeutic trials.

Conclusions

In conclusion, COPD is a prevalent and morbid condition, complicated by comorbid diseases and overlapping pulmonary syndromes. Better characterization of these overlapping syndromes may afford enhanced diagnostic methods, prognostication, and ultimately therapeutic intervention and outcomes.

Declaration of Interest

Dr. Lambert has served as a consultant for GLG Consulting and has received grants from the National Institutes of Health. Dr. Dransfield has received grants from GlaxoSmithKline and Forest and has been a contracted researcher for Boehringer Ingelheim, GlaxoSmithKline, Pulmonx, PheumRx, Otsuka, Pearl, Forest and AstraZeneca. Dr. Woodruff has served as an advisor for Janssen, Neostem and Genentech. He has been a consultant for Roche, Novartis and AstraZeneca and has received a grant from Genentech. Dr. Washko has served as a consultant for GlaxoSmithKline and his spouse is employed by Merck.

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