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Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome

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Abstract

Overlap of asthma and chronic obstructive lung disease (ACO) in patients with obstructive lung disease is growing in recognition, though there is not consistent agreement on the diagnostic criteria for the disease process. Patients with ACO have distinct clinical characteristics and trajectories, which is representative of a heterogenous, multifactorial, and incompletely understood inflammatory pathophysiology. Current treatment strategies are focused on titration of inhaled therapies such as long-acting bronchodilators, with increasing interest in the use of targeted biologic therapies aimed at the underlying inflammatory mechanisms. Future directions for research will focus on elucidating the varied inflammatory signatures leading to ACO, the development of consistent diagnostic criteria and biomarkers of disease, and improving the clinical management with an eye towards targeted therapies.

Keywords

COPD; asthma; overlap

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are two of the most common forms of obstructive lung disease world-wide. Increasingly, patients with clinical characteristics of both asthma and COPD have been identified as a unique subset of obstructive lung disease. This was defined as “asthma-COPD overlap” (ACO), and it represents a spectrum of airway pathology rather than a singular disease process.[1] There are multiple phenotypes of ACO, from patients with COPD and long-smoking histories with peripheral eosinophilia to others with asthma with fixed obstruction on pulmonary function testing (PFT) and a significant smoking history. This heterogeneity is a result of variable host and environmental factors, making a singular designation of ACO a difficult, and

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controversial, diagnosis. Currently, there is no universal consensus on the diagnostic criteria. Despite this, there are important considerations for patients with clinical characteristics of both COPD and asthma, as they have significantly worse quality of life and more frequent healthcare contact than patients with either asthma or COPD individually.[2] In this review, we will summarize the most recent data regarding asthma-COPD overlap, including the epidemiology, diagnosis, pathophysiology, and recommend management strategies, highlighting both areas of new knowledge and ongoing controversy.

Diagnosis

The lack of a consistent case definition of ACO is a result of both the varying and incompletely understood pathophysiology of ACO. In 2015, the concept of “asthma-COPD overlap syndrome” was solidified in guidelines by the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD), referring to patients who had fixed airway obstruction and the presence of clinical features for both asthma and COPD.[3] In contrast, this approach to categorizing ACO was not endorsed by a joint American Thoracic Society/National Heart, Lung, and Blood Institute workshop report in 2017.[1] The GINA/GOLD report outlined a number of clinical characteristics suggestive of ACO. They defined ACO as occurring in adults older than 35–40 years of age who have evidence of airflow obstruction on spirometry that is, at least in part, reversible with bronchodilator challenge (Table 1), along with presence of other several clinical findings consistent with asthma, such as a history of atopy or allergic rhinitis, a previous diagnosis of asthma by a physician, or laboratory evidence of eosinophilia in the blood or sputum, in conjunction with clinical features consistent with COPD (Table 2).[3] These comprehensive guidelines provided broad guidance on the diagnosis of ACO but did not provide a specific outline needed for more definitive diagnosis.

In the last several years, a number of consensus panels have developed and proposed criteria for diagnosis of ACO to further delineate a concise yet thorough approach to diagnosis. [4,5] A diagnostic model from a global expert panel in 2016 provided specific criteria that encompasses both patients with COPD and asthma who have specific clinical features suggestive of the other disease process (Table 3).[4] Patients had to have all three major criteria and at least one minor criteria to be diagnosed with ACO. This system represents the most clearly defined diagnostic criteria for ACO that also captures the heterogeneity of the disease.

As diagnostic models are updated and improve, there may be variable concordance between the several previously proposed diagnostic criteria. One study evaluated the 2015 GINA/GOLD diagnostic criteria and other proposed systems in a cohort of over 1600 patients with either asthma or COPD, in which they identified 6 subpopulations with ACO.[6] This study found there was little agreement between the GINA/GOLD diagnostic criteria and other ACO definitions in addition to noting that prevalence varied based on the definition applied from 3.8% to 18.4% overall. Another study evaluated the role of bronchodilator response and imaging evidence of emphysema in better characterizing overlap features and disease severity in over 10,000 obstructive lung disease patients aged 45–80 with 10 or more pack years of smoking in the COPDGene study.[7] They found that when identifying patients

with ACO with additional bronchodilator and imaging criteria, ACO patients had less severe emphysema on imaging and less severe obstruction, but they had similar severity and rates of exacerbations. Other diagnostic testing, such as the use of blood eosinophil levels or fractional excretion of nitric oxide (FeNO), have been an active area of investigation, yet have not shown benefit in distinguishing between phenotypes of chronic obstructive airway disease.[8] These findings highlight both the heterogeneity of the disease and the difficulty of identifying a singular manifestation of ACO.

Epidemiology

Given the heterogenous nature of ACO and the lack of a consistent case definition, estimates of its prevalence are limited and difficult to ascertain, though it is a significant contributor to the overall burden of obstructive lung disease globally. Often, the reported prevalence of ACO in a given study is dependent on the population that was evaluated. In a survey sample in a general United States population, ACO was estimated to occur in approximately 2–4% of the population.[9] In estimates derived from cohorts of patients diagnosed with asthma or COPD, prevalence varies even further. In pooled cohorts of patients with COPD or asthma, it is estimated that approximately one-quarter of patients have ACO.[10,11] In a large, cross-sectional study of over 2000 primary care patients in the United Kingdom with a diagnosis of COPD, asthma, or both, 15% of patients met criteria for ACOS.[12] Definitive measures of prevalence for ACOS will remain elusive in the absence of unified diagnostic criteria that allows for standardized identification of the disease.

In patients identified as having ACO, a number of unique clinical characteristics have been identified. In a large Spanish cohort of patients with COPD and/or asthma, patients determined to have ACO were more likely to be younger and female than patients with COPD alone.[13] These findings were similar to those from a multinational cohort of COPD patients in the ECLIPSE study, where patients with ACO were more likely to be female and younger.[14] Notably, patients in this cohort were also more likely to have a diagnosis of COPD for more than 10 years compared to patients with COPD without asthma overlap. Among primary care patients in the United Kingdom, patients with ACO were more likely to have multiple comorbidities, including obesity, hypertension, gastroesophageal reflux disease, a finding also replicated in ACO patients from the ECLIPSE study.[12,14] In a U.S. cohort, ACO patients were also more likely to have lower income and lower education, and this population also has greater exposure to environmental triggers for asthma and COPD such as biomass and tobacco smoke.[15]

In addition to demographic differences, patients with ACO have been noted to have a distinct clinical trajectory. COPD patients with a history of childhood asthma or a diagnosis of asthma prior to 40 years of age have more severe and more frequent exacerbations, though they did not have a greater decline in pulmonary function.[16] Similarly, being in the lowest quartile of lung function by spirometry at age 7 was associated with the development of ACO as an adult.[17] Patients with ACO with “late onset of asthma”, however, (after age 40) were found to have a more rapid decline in forced expiratory volume in one second (FEV_1), as a marker of disease progression, than those patients with COPD or asthma alone.[18] Similarly, ACO patients in this cohort had more exacerbations than patients with COPD

alone, and ACO patients with late onset asthma had a higher mortality. The evidence for increased mortality, however, is not consistent, with other studies demonstrating no difference in mortality.[14,19] Additionally, ACO is associated with greater healthcare utilization due to emergency department visits and hospital admissions, suggesting that the disease manifests with a greater number of exacerbations.[2] Longer term studies with standardized diagnostic criteria are needed to clarify the overall clinical course and natural history of asthma-COPD overlap.

Pathophysiology

The underlying pathophysiology of ACO remains an active area of debate and investigation. Originally presented in the early 1960's, the "Dutch hypothesis" proposed that both asthma and COPD arise from a common pathophysiology with the ultimate phenotype of asthma or COPD being influenced strongly by environmental exposures and individual genetics, such that ACO is along a spectrum of disease from asthma to COPD. The alternate "British hypothesis" proposes that asthma and COPD are distinct pathophysiologic entities with unique inflammatory milieus, such that ACO develops from a unique inflammatory insult to the airways, separate from COPD or asthma alone.[20]

There is evidence for both these predominant hypotheses. Asthma patients who smoke or have substantial exposures to pollutants can develop a neutrophilic airway inflammatory response similar to COPD, mediated through cytokines such as interleukin (IL)-17, leading to fixed obstruction.[21] As compared to patients with asthma alone, ACO patients who smoked greater than 10 pack years have higher levels of blood neutrophils and IL-6, suggesting a unique inflammatory pattern to that of asthma.[22] Similarly, patients with a diagnosis COPD can develop a T-helper type 2 (Th2) inflammatory phenotype with significant eosinophilia and IgE production, very similar to inflammatory profile of asthma.[23] Genetic signatures common to asthma can be seen in patients with COPD and are associated with features of ACO.[24] In both scenarios, persistent inflammation is the root etiology. The use of blood biomarkers linked to these inflammatory pathways for diagnosis, such as serum YKL-40 and periostin, is an important and ongoing avenue of research to help delineate the pathobiology of ACO.[25]

It is likely that both patients with asthma and those with COPD can have substantial overlap in inflammatory mechanism. One study delineated 3 endotypes of patients diagnosed with severe asthma or moderate to severe COPD – severe asthma with elevated eosinophils and Th2 cytokines, COPD predominant patients with elevated eosinophils and neutrophils, and a mixed asthma-COPD phenotype that was predominantly.[26] The inflammatory profiles in individual patients, in addition to specific environmental exposure, help explain the heterogeneity of ACO and may serve as a better guide for understanding the pathophysiology and diagnosis than current diagnostic taxonomy.

Therapeutic Management

Scientific evidence directing treatment and management of ACO is limited. Often, patients who have ACO are excluded from both clinical trials of asthma and COPD patients. This

reality leaves clinicians deciding upon therapeutic options based on the patient's predominant phenotype (predominantly asthma and predominantly COPD) and titrating medications based on clinical response. The mainstays of treatment are inhaled therapies as well as biologic therapy targeted at underlying inflammatory processes.

Inhaled Therapies

Guideline driven therapy for both COPD and asthma include inhaled medications, ranging from long-acting bronchodilators such as anti-muscarinic agents (LAMA) and beta-adrenergic antagonists (LABA), as well as inhaled corticosteroids (ICS). Treatment of asthma emphasizes early use of ICS, whereas COPD treatment emphasizes long-acting bronchodilators, but the overlap of asthma and COPD may benefit to the early use of both ICS and long-acting bronchodilators. Biomarkers such as blood eosinophils may also help dictate therapeutic response and guide treatment decisions such as early use of ICS.[27,28] In COPD patients with the greatest elevation in blood eosinophils, which are a surrogate of airway eosinophilia often seen in asthmatics, the use of an ICS, in addition to LABA, was associated with reduced exacerbation rates.[29–31] Similarly, the withdrawal of ICS therapy in COPD patients with significant eosinophilia may be harmful and related to an increase in exacerbations.[32] In older adults with COPD and concurrent asthma, the use of ICS was associated with fewer hospitalizations.[33] While not all studies have seen a consistent relationship with ICS use and exacerbation rate in COPD patients with eosinophilia,[34] in a study of COPD patients with severe airflow obstruction and a history of exacerbations, triple therapy with ICS/LABA/LAMA did reduce moderate to severe exacerbations compared to LABA/LAMA combination therapy alone.[35] Similarly, the effectiveness of long-acting muscarinic agents has been demonstrated in poorly-controlled asthma, as well as severe asthma with emphysematous changes on imaging or a concurrent diagnosis of COPD.[36,37] The addition of tiotropium in ACO patients improved both spirometric measures as well as patient-reported symptom control and quality of life.[38,39]

Biologics

Given the increasing understanding of the inflammatory pathways implicated in ACO as well as success in asthma, there has been increasing interest in the use of targeted therapies, including biologic antibodies, against cytokines and inflammatory precursors in patients with ACO. Omalizumab, an anti-IgE monoclonal antibody (mAb) and the first biologic therapy approved for use in severe asthma in the United States, was retrospectively evaluated in patients with severe asthma and overlapping COPD and found to be associated with significant improvements in symptom control and quality of life.[40] However, in a post-hoc analysis of a larger, observational cohort of patients treated with omalizumab for asthma, both those with ACO and those without demonstrated similar improvements after treatment.[41] Another biologic, mepolizumab, which is a mAb that blocks the action of IL-5 in the eosinophilic inflammatory pathway, reduced moderate to severe exacerbations in patients with eosinophilic COPD.[42] In this study, higher levels of eosinophils at screening were associated with greater reduction in exacerbations with use of mepolizumab. In contrast, the use of benralizumab, a mAb directed against the alpha-subunit of the IL-5 receptor, did not improve exacerbation rates in patients with COPD and a history of exacerbation, regardless

of eosinophil level.[43] Given these findings, it remains a question as to the future role biologics play a role in the management of ACO.

Conclusions

Asthma-COPD overlap represents a unique, heterogenous form of obstructive lung disease, manifesting in patients who have features of both asthma and COPD. Estimates of prevalence vary given the lack of uniform diagnostic criteria, and patients with the disease tend to be younger, female, and have more co-morbidities than either asthma or COPD alone. The pathophysiology varies with both Th2 high and Th2 low pathways acting differentially in patients with variable environmental and genetic contributions. At the root of the pathology, however, is ongoing airway inflammation. The cornerstone of therapeutic management remains inhaled therapies, with evidence for use of inhaled corticosteroids as well as long-acting bronchodilators. Ongoing research into the mechanisms of inflammation and the utility of targeted biologics will be an important avenue of research to improve the outcomes of patients with asthma-COPD overlap.

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Highlights

- Asthma-Chronic Obstructive Pulmonary Disease Overlap (ACO) represents a unique disease entity with patients manifesting characteristics of both asthma and chronic obstructive pulmonary disease.
- ACO is the result of the intersection of varying inflammatory processes manifesting in the common outcome of symptomatic obstructive lung disease.
- The mainstays of treatment continue to be inhaled medications with growing interest in, but currently limited evidence for, the use of targeted biologic therapies.

Table 1:

Spirometry Characteristics between Asthma, COPD, and ACO

Spirometry	Asthma	COPD	ACO
Normal FEV_1/FVC pre- or post BD	Compatible with diagnosis	Not compatible with diagnosis	Not compatible with diagnosis
Post BD FEV_1/FVC <0.7	Indicates airflow limitation, but may improve spontaneously	Required for diagnosis (GOLD)	Usually present
Post BD increase in FEV_1≥12% and 200ml	Usual in course of asthma, but may not be present when well controlled	Common and likely when FEV_1 is low	Common and likely when FEV_1 is low
Post BD increase in FEV_1≥12% and 400ml	High probability of asthma	Unusual in COPD and consider ACO	Compatible with diagnosis of ACO

Abbreviations: FEV1 – forced expiratory volume in one second; FVC – forced vital capacity, BD – bronchodilator

Table 2:

Common Clinical Characteristics of Asthma-COPD Overlap Syndrome

Characteristics of Asthma-COPD Overlap Syndrome	
Feature	Clinical Manifestation
Age	Usually > 40 years of age
Spirometry	Obstruction (FEV_1/FVC) < 70%
	Partial Reversibility of Obstruction with Bronchodilator
Clinical History	Atopy or Allergic Rhinitis
	Prior Diagnosis of Asthma
Exposures	Tobacco or Biomass Smoke
	Allergen Exposure
Laboratory Findings	Blood and Sputum Eosinophilia
	Elevated IgE
	Asthma patients may have neutrophilic sputum
Imaging Findings	Emphysema
	Hyperinflation

Abbreviations: FEV_1/FVC – Forced expiratory volume in one second to forced vital capacity

Table 3:

ACO Diagnostic Criteria Consensus Definition (adapted from Sin et al.)[4]

Major Criteria	Minor Criteria
Persistent airflow limitation (post-bronchodilator FEV1/FVC < 0.7 or LLN) in patients 40 years of age or older	History of atopic disease or allergic rhinitis
Smoking history of at least 10 pack years or air pollution/biomass exposure equivalent	Bronchodilator response of ≥ 200 mL and 12% of baseline on ≥ 2 office visits
Bronchodilator response of ≥ 400 mL or documented/physician diagnosed history of asthma before age 40 years	Peripheral eosinophil count of ≥ 300 cells/uL

Abbreviations: LLN – Lower Limit of Normal; FEV1/FVC – forced expiratory volume in one second to forced vital capacity; mL – milliliters; uL – microliters