American Thoracic Society/National Heart, Lung, and Blood Institute Asthma–Chronic Obstructive Pulmonary Disease Overlap Workshop Report

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent chronic obstructive lung diseases with an associated high burden of disease. Asthma, which is often allergic in origin, frequently begins in infancy or childhood with variable airflow obstruction and intermittent wheezing, cough, and dyspnea. Patients with COPD, in contrast, are usually current or former smokers who present after the age of 40 years with symptoms (often persistent) including dyspnea and a productive cough. On the basis of age and smoking history, it is often easy to distinguish between asthma and COPD. However, some patients have features compatible with both diseases. Because clinical studies typically exclude these patients, their underlying disease mechanisms and appropriate treatment remain largely uncertain. To explore the status of and opportunities for research in this area, the NHLBI, in partnership with the American Thoracic Society, convened a workshop of investigators in San Francisco, California on May 14, 2016. At the workshop, current understanding of asthma–COPD overlap was discussed among clinicians, pathologists, radiologists, epidemiologists, and investigators with expertise in asthma and COPD. They considered knowledge gaps in our understanding of asthma–COPD overlap and identified strategies and research priorities that will advance its understanding. This report summarizes those discussions.

Keywords: asthma; chronic obstructive pulmonary disease; overlap

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent and heterogeneous conditions with an associated high disease burden. Physiologically, asthma displays bronchial hyperresponsiveness (BHR) and variable expiratory airflow limitation, which is partially or fully reversible with a bronchodilator, whereas COPD displays chronic airflow limitation that is not fully reversible with a bronchodilator. A patient's age and smoking history often easily separate asthma and COPD, but some patients have features compatible with both diseases. To describe this condition, investigators

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At a Glance Commentary

Scientific Knowledge on the Subject: Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent conditions, with an associated high disease burden. On the basis of age and smoking history, it is often easy to distinguish between asthma and COPD. However, some patients have features compatible with both diseases. Because clinical studies typically exclude these patients, their underlying disease mechanisms and appropriate treatment remain largely uncertain. To explore the status of and opportunities for research in this area, the NHLBI, in partnership with the American Thoracic Society, convened a workshop of investigators.

What This Study Adds to the Field: At the workshop, current understanding of asthma–COPD overlap was discussed among clinicians, pathologists, radiologists, epidemiologists, and investigators with expertise in asthma and COPD. They considered knowledge gaps in our understanding of asthma–COPD overlap and identified strategies and research priorities that will advance its understanding. One of the major conclusions of the workshop was that this condition does not represent a single discrete disease entity.

introduced the term "ACOS" (asthma–COPD overlap syndrome) (1). Because one of the major conclusions of the workshop was that this condition does not represent a single discrete disease entity, the modified term "asthma–COPD overlap" (ACO) will be used throughout this report.

ACO may be used to describe patients with asthma who have features of COPD, specifically incompletely reversible (i.e., fixed) airflow obstruction, as was observed in up to 20% of patients with asthma (2). Such nonsmoking patients with asthma with fixed airflow obstruction may appear comparable to patients with COPD, with a greater rate of decline in lung function over 5 years than patients with asthma with reversible obstruction (3). However, nonsmoking patients with asthma with fixed airflow obstruction demonstrate significantly more blood, sputum, and bronchoalveolar lavage fluid eosinophilia than similarly obstructed patients with COPD (4). In that study, higher sputum eosinophil counts predicted greater lung function decline in asthma, whereas higher sputum neutrophils were associated with lung function decline in COPD.

ACO may also be used to describe patients with COPD with features of asthma, such as bronchodilator responsiveness (BDR) and/or BHR. About 50% of patients with COPD show significant BDR (5), but up to 90% have BHR, especially women with COPD (6). BDR may predict the response to treatment in patients with COPD. For example, FEV_1 improved to a larger extent after 8 weeks of treatment with fluticasone/salmeterol in patients with COPD with versus without BDR (7) and after 2 to 3 months of inhaled corticosteroids (ICS) in a computed tomography (CT)-defined nonemphysema phenotype with greater BDR than in two emphysema phenotypes (8). Although BHR is clearly influenced by FEV_1 itself (9), multivariate regression analyses showed that more severe BHR in COPD was independently associated with airway inflammation (6). Results from two large cohorts demonstrated that BHR is associated with greater mortality and rate of FEV_1 decline and markers of systemic inflammation in COPD (10). Thus, patients with COPD who have features of asthma may have a poorer long-term clinical course than those without.

ACO: Clinical Features

Although classical asthma and COPD are easily distinguished, patients often present to primary care providers with nonspecific respiratory symptoms or with similarly reduced lung function despite differing clinical histories, including severe childhood asthma with impaired lung development, asthma in a smoker, long-standing asthma with irreversible airflow obstruction, and emphysema with atopy and variable symptoms of airway disease. This variability suggests that multiple different mechanisms may drive the presentation of these phenotypes of airway disease.

Patients with features of ACO have greater symptom burden and physical impairment, more hospitalizations (11), and a worse quality of life (12) than those with asthma or COPD alone. In the COPDGene study, the 13% of patients with COPD who reported having had a doctor diagnosis of asthma at younger than 40 years of age had similar lung function to those with COPD alone but had worse quality of life, more frequent exacerbations, and more gas trapping on CT scan (13). However, despite this clinical significance, asthma and COPD guidelines can only poorly address this population, because they are based on studies from which most patients with ACO were excluded. Indeed, guidelines provide opposite safety-based recommendations about pharmacotherapy. In asthma, ICS are recommended to reduce the risk of exacerbations and mortality, but in COPD, ICS are reserved for patients with a history of repeated exacerbations. Long-acting bronchodilators (without ICS) are initial therapy in COPD, but long-acting β-agonists alone are contraindicated in asthma because of the risk of death. Few pharmacotherapy studies are underway in overlap populations. Although this evidence is being obtained, clinicians must be provided with interim clinical advice on the basis of safety considerations (14), such as was published by the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (15).

It is hence proposed to use the term ACO as an interim clinical label, to identify at-risk patients on the basis of clinical features of both asthma and COPD to safely manage patients until evidence about mechanisms and targeted treatments emerges. For clinical practice, GINA and GOLD suggested a syndromic approach to identify patients with typical asthma, typical COPD, and overlap, on the basis of the relative number of clinical features of asthma and COPD and results from spirometry (15). That approach was not endorsed by the discussants of this workshop.

In many retrospective studies, the distinction of asthma from COPD was based on spirometry, including bronchodilator reversibility and post-bronchodilator FEV_1/FVC less than 0.70 or less than the lower limit of normal. Most have limited

"asthma" to lifetime nonsmokers, or ex-smokers with less than 5 to 10 pack-year history. With physiological criteria alone, the prevalence of ACO may be overestimated, because up to 50% of patients with COPD have bronchodilator reversibility greater than 200 ml and greater than 12% (5, 7). In addition, patients with asthma whose physiology does not revert to normal despite multiple treatments have been long recognized. These patients, described as having "fixed" airflow limitation, have been identified objectively with unbiased clustering approaches in the Severe Asthma Research Program (SARP). In SARP, fixed obstruction is associated with a mixed inflammatory process and high inhaled and systemic corticosteroid use and side effects (16). Despite this inability to improve to "normal" with bronchodilators, more than 12% reversibility is sometimes present.

One approach to minimizing the effect of preconceptions about classification of airway disease and to develop "unbiased" subgroups is to apply cluster analysis. One analysis of adults with symptomatic airway obstruction identified two distinct clusters of patients with marked bronchodilator reversibility and peak flow variability; one had late-onset disease, a heavy smoking history, and emphysema, and the other had moderate to severe allergic asthma (17). In SARP, cluster analysis identified five clusters of nonsmoking patients with asthma, where cluster 5 had characteristics associated with COPD (18). More studies of mechanisms or endotypes driving these phenotypes are needed.

Role of Imaging in ACO

Imaging can contribute to the evaluation of asthma and COPD by assessing airway narrowing and wall thickness and the presence, pattern, and severity of emphysema and identifying and quantifying expiratory air trapping. Although CT is the most widely used technique, magnetic resonance imaging (MRI) can provide additional information about the size of distal airspaces and the presence of ventilation defects. Primary measures of emphysema are the percent of lung voxels less than −950 Hounsfield units (LAA−950 HU) and the 15th percentile of lung attenuation (PERC15) (19). Imaging can be used for disease identification and stratification and for exploring image-based biomarkers or as an efficacy outcome in therapeutic trials in patients with ACO.

Small airways less than 2 mm in diameter are believed to be the primary site of airflow obstruction in both asthma and COPD (20, 21). These small airways include a portion of both the conducting airways and the acinar airways and are currently below the limit of CT resolution.

Analyses of large airway morphology, measures of central airway wall thickness, lumen area, and the wall area percent (100 × wall area/total bronchial area) have consistently demonstrated in smokers and those with COPD to be associated with histopathologic measures of remodeling and highly correlated with relevant measures of disease severity (22). The strength of these correlations increases when more peripheral airways are measured (22), possibly reflecting either small airway disease or native airway structure (23) important to disease pathogenesis.

MRI using inhaled hyperpolarized helium or xenon offers the ability to directly visualize pulmonary ventilation, and apparent gas diffusion can provide a measurement of the size of distal airspaces in emphysema (24). MRI may therefore provide a sensitive marker of early small airway abnormality.

Indirect assessment of the small airways via CT scan has also been investigated. One option is to measure gas trapping by quantifying the percent of voxels less than −856 HU on expiratory CT scan (25). Another method to measure gas trapping is to compute the ratio of expiratory to inspiratory mean lung density (26). Both methodologies in COPD cannot completely distinguish areas of small airway disease from areas of emphysema. Image registration that matches inspiratory and expiratory lung helps to overcome this problem (27), although this approach increases radiation exposure. Measurement of functional small airway disease using this technique can predict progression of airflow obstruction in COPD (28).

Although CT measures of decreased lung attenuation are often used as a surrogate for emphysema, patients with asthma may also have decreased lung attenuation (29), presumably because of overinflated lung parenchyma. This technique can differentiate asthmatic subgroups with distinctive clinical phenotypes (30).

Although imaging is unlikely to provide all the information needed to stratify a patient as having asthma, COPD, or overlap, CT evidence of significant small airway abnormality in the setting of supportive clinical characteristics and lack of significant emphysema would be consistent with overlap. Quantitative CT metrics using inspiratory and expiratory images may also hold promise as a surrogate endpoint in ACO. In the future, MRI may also provide useful information regarding the nature of airway obstruction.

Is ACO Traceable to Early Infancy?

Regardless of whether ACO develops in individuals with severe asthma who advance to fixed obstruction or in adult smokers who had childhood asthma, its origins may begin in childhood (31). In the Childhood Asthma Management Program (CAMP) study, FEV_1/FVC ratio was significantly lower in subjects with asthma than in control subjects, and deficits were already present at age 6 years (32). Interestingly, 11% of CAMP participants with asthma had a level of lung function consistent with COPD in early adult life. The Busselton longitudinal study suggested that smoking may have more severe effects on lung function in subjects with a baseline history of asthma (33).

In a long-term cohort study, children with asthma were six times more likely to have airflow limitation consistent with COPD at age 60 to 65 years than those without childhood asthma (34). The extent of fixed airflow obstruction in nonsmoking adults who had childhood asthma was equivalent to that observed with a 33 pack-year history of smoking (35). In subjects with asthma in the Tucson Children's Study, post-bronchodilator FEV_1/FVC ratio at age 22 years was linearly related to age of onset of the disease (36). The lowest lung function in patients with current asthma was observed in those who were first diagnosed before age 6 years Airflow limitation and BHR were already observed by age 6 years in subjects with onset of asthma in early adult life (36). These observations lead to the questions of when fixed obstruction starts, how frequent it is in this population, and if

preventing childhood asthma could have a substantial impact on ACO and long-term survival.

Adults with a history of wheezing lower respiratory illnesses due to respiratory syncytial virus (RSV) and who smoked are 1.6 times more likely to have a diagnosis of asthma than those without a smoking history (37). Early life RSV-related events may thus synergize with smoking in predisposing to ACO. Interestingly, wheezing lower respiratory illnesses due to RSV in early life may predispose to harboring RSV chronically (38), and RSV has been detected in the airways of patients with COPD (39), suggesting that cigarette smoke may reactivate RSV, enhancing its deleterious effects. Additional data link respiratory viral infections to persistent airway inflammation and mucus production in mouse models of postviral airway disease. One model, using mouse parainfluenza virus, has identified three new immune pathways of airway disease (40) and showed that IL-33/IL-33 receptor signaling was required for *Il13* and mucin gene expression and that *Il33* gene expression was localized to a virus-induced subset of airway epithelial cells linked to progenitor function (41). Patients with COPD tissue samples confirmed *IL33* gene expression associated with *IL13* and mucin gene expression. A similar cascade has been found in virus-induced asthma exacerbations (42). These findings support a unified model that links the acute antiviral response to persistent and progressive chronic airway disease.

Another model using mice deficient for the myeloid receptor TREM-2 (triggering receptor expressed on myeloid cells) and the mouse parainfluenza virus showed that soluble TREM-2 prompted feed-forward expansion of immune cells required for IL-13 production. This mechanism may explain how infection leads to type 2 immune disease (43). Finally, a third model revealed that the mouse chloride channel accessory 1 gene was associated with increased mucin (*MUC5AC*) gene expression, and studies in humans defined a signaling pathway from human Clca1 to mitogen-activated protein kinase 13 that was responsible for IL-13–driven mucus production in human airway epithelial cells (44). These results revealed a new pathway for regulating mucus production and suggest that development of a distinct type 2 immune response may drive both asthma and COPD.

Mucociliary Clearance, Chronic Bronchitis, and ACO

COPD and asthma share chronic bronchitis (CB) as a common clinical-pathological component. CB presents clinically with cough and sputum production and exhibits features of airway remodeling, inflammation, and mucus obstruction. This suggests that failure of mucociliary clearance is central to CB pathogenesis. It has recently been proposed that the mechanisms underlying successful mucus clearance rely on the airway mucociliary apparatus being comprised of two hydrogels: (*1*) a tethered mucin periciliary layer (PCL), and (*2*) a mobile secreted mucin (MUC5AC and MUC5B) mucus layer located on top of the PCL (45). The two hydrogels compete for water as a function of their relative osmotic pressures (water-drawing powers). In health, the PCL gel is more concentrated than the mucus layer, ensuring that the PCL is well hydrated and lubricates mucus flow over airway surfaces. In disease, a decrease of airway surface liquid or mucin hypersecretion onto airway surfaces produces a "hyperconcentrated" (dehydrated) mucus layer. In this diseased state, the mucus layer draws water from the PCL, producing osmotic compression of cilia that can lead to mucus transport cessation, chronic inflammation, obstruction, and bacterial infection.

There is promise in defining features of ACO on the basis of the mucin characteristics that are features of cigarette smoking–induced COPD versus asthma. Biochemical studies have identified MUC5B as the dominant secreted mucin in cigarette smoke–induced COPD (46), and a fraction of patients with asthma have been reported to exhibit high airway mRNA expression levels of MUC5AC with evidence for a reduction in MUC5B (47). To better understand the contributions of mucins to ACO, it will be necessary to know the specific features of mucins that are characteristic of CB in "pure" COPD and asthma.

ACO: Cell and Molecular Biomarkers and Their Therapeutic Implications

Sputum cytology has identified four major phenotypes of cellular inflammation in airway disease: neutrophilic, eosinophilic, mixed granulocytic, and paucigranulocytic. COPD is typically more neutrophilic and asthma more eosinophilic. However, there is heterogeneity with each condition and overlap between both conditions. For example, in asthma, some phenotypes are eosinophilic and others are neutrophilic or combined eosinophilic and neutrophilic (16, 48), whereas in COPD, 10 to 40% of subjects have sputum eosinophilia (49). With some variability over time and in response to therapies, many subjects exhibit relative phenotype stability, suggesting consistent underlying molecular mechanisms. To further understand the inflammatory networks, cluster analysis of sputum cytokines has been undertaken in asthma and COPD alone and in combination (50). This research has revealed three biological clusters: a type-2 inflammatory group, which, although asthma predominant, includes patients with COPD; a proinflammatory group driven largely by IL-1β and tumor necrosis factor-α which is present in both asthma and COPD; and a COPD-predominant group characterized by a mixed granulocytic response with elevated sputum IL-6 and C-C motif chemokine ligand 13 (50). In the stable state, the inflammatory pattern predicts response to therapy with a higher blood and sputum eosinophilia associated with greater short-term response to inhaled (51) and oral corticosteroids (52) and novel biologics targeting IL-5 (53). Management algorithms using sputum eosinophil counts to guide corticosteroid therapy reduce exacerbations in both asthma and COPD (54, 55). In contrast, lack of a blood eosinophilia was associated with an improved response to macrolide antibiotics in asthma (56). These findings point to the potential for targeted treatment in the future.

As in COPD, numerous studies have shown that some patients with severe asthma have neutrophilic airway inflammation with air trapping and higher levels of proteases associated with COPD (57). Additional studies have reported neutrophilia, either alone or in combination with eosinophilia, in asthma (16, 48). The majority of patients with asthma and sputum neutrophilia are taking high-dose inhaled or even systemic corticosteroids, which prevent apoptosis of neutrophils, potentially contributing to their presence, and making it more difficult to address causality (58). In addition, neutrophilia appears to be highly

variable and not consistently associated with smoking (59), and studies aimed at reducing neutrophilia in severe asthma have not shown efficacy (60).

Technologies to profile whole genomes, proteomes, and metabolomes are evolving quickly and have the potential to distinguish subgroups within these complex diseases on a molecular level (47, 61). Gene expression microarray studies suggest an asthma subgroup that has airway epithelial gene expression markers of a heightened type-2 immune response, classically believed to be the main inflammatory pathway in asthma (47). This subgroup, called "type-2–high asthma," manifests exaggerated airway hyperresponsiveness and a better response to ICS. Similar analyses applied to COPD cohorts show significant concordance in gene expression changes in lung tissue between asthma and COPD (62). This overlap in gene expression changes suggests shared mechanisms may be leading to airflow obstruction in the two diseases. Given that the type-2 immune response is more typical of asthma, investigators assessed whether a type-2 gene expression signature identifies a molecular phenotype of COPD with asthma-like characteristics, which would represent a biologically defined ACO subgroup. In these studies, increased airway obstruction, airway tissue, and blood eosinophils and greater response to inhaled corticosteroids were associated with epithelial and tissue markers of asthmatic type-2 inflammation in COPD. Importantly, these patients did not bear a clinical history of asthma. These findings are promising, as they show that type-2 eosinophilic inflammation is a useful biomarker to guide consideration of ACO in patients otherwise believed to have COPD. Analysis and integration of large, longitudinal datasets of molecular, immunologic, and metabolic characteristics, coupled with measures of airway exposures and the microbiome, hold promise for identifying new shared biomarkers and treatment targets for both asthma and COPD. With this understanding, precision medicine may be realized for individuals with ACO.

Conclusions

Participants to the workshop did not think it useful at this time to develop a single, universal definition of ACO for diagnosis and treatment. Instead, discussions focused on reviewing the evidence that features of asthma and COPD may coexist at epidemiological, phenotypic, and biological levels and that the presence of overlapping

Table 1. Workshop Recommendations

Epidemiological and clinical research
- Undertake longitudinal studies in broad populations to better define the prevalence of ACO and its course.
- Phenotype asthma and COPD with respect to specific cellular or biologic processes.
- Clinical trials should include and stratify smoking patients with asthma, especially for studies involving targeted therapies.
- Assess inhaled corticosteroid efficacy in patients who have asthma and persistent airflow limitation.
- Investigate which COPD subgroup(s) has favorable response to ICS.
- Determine when fixed airflow limitation develops (i.e., childhood, adulthood, or both) and what drives its development.
- Assess structural and functional airway disease using imaging and investigate how these features relate to diagnosis and responsiveness to interventions in asthma, ACO, or COPD.
- Study the applicability of imaging measures as surrogate endpoints in clinical trials.
- Perform MRI studies of the nature of airway obstruction in ACO.
- Link respiratory health with genetic ancestry and the effects of acculturation to better understand respiratory health in underrepresented populations.
- Consider the effects of social determinants of health, both individually and at the population level, and socioeconomic inequality in driving asthma, COPD, and ACO.
- Understand the role of comorbidities in ACO.

Basic and applied research
- Identify specific gene signatures in lung cells that are associated with "fixed" airflow limitation, neutrophilia, and smoking.
- Conduct mechanistic studies to better understand the interplay of inflammatory and remodeling pathways and their functional impact in ACO.
- Investigate the role of RSV and other respiratory viral infections in airflow limitation.
- Address the role of respiratory viral infections in initiating the type-2 immune response and mucus cell metaplasia.
- Use multilevel systems biology approaches (including genetics, gene expression, and proteomics) to provide insights into disease mechanisms underlying ACO and inform phenotyping.
- Understand the utility and role of mucin subtypes (especially MUC5AC and MUC5B) in defining and contributing to airway disease in asthma, COPD, and ACO.
- Determine the influence of host genetics and the environment on the development of biological phenotypes.
- Investigate the stability of phenotypes of airway disease.
- Define whether these phenotypes confer a different natural history/future risk and response to therapies.
- Discover and develop new and more precise therapeutics for the airway disease in ACO.

Definition of abbreviations: ACO = asthma–chronic obstructive pulmonary disease overlap; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; MRI = magnetic resonance imaging; RSV = respiratory syncytial virus.

features has clinical significance. Several research themes emerged, mainly driven by the need to better understand the biology and pathophysiology of ACO and develop precise treatments for subtypes. In addition to biological factors, it will be important in future studies to address the role of race and ethnicity, socioeconomic status, and acculturation, considering that genetic ancestry, a proxy for genetic variation, can possibly be leveraged to improve diagnostic clinical accuracy and identify new genetic risk factors (63). The participants of the workshop identified high-priority research needs and developed specific research recommendations that could foster rapid advances toward disease preemption and personalized therapy. These recommendations are described in Table 1 as a guideline for further studies of ACO. ■

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