

The Asthma COPD Overlap Syndrome (ACOS)

Stephen Bujarski · Amit D. Parulekar ·
Amir Sharafkhaneh · Nicola A. Hanania

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Abstract Asthma and chronic obstructive pulmonary disease (COPD) have traditionally been viewed as distinct clinical entities. Recently, however, much attention has been focused on patients with overlapping features of both asthma and COPD: those with asthma COPD overlap syndrome (ACOS). Although no universal definition criteria exist, recent publications attempted to define patients with ACOS based on differences in clinical features, radiographic findings, and diagnostic tests. Patients with ACOS make up a large percentage of those with obstructive lung disease and have a higher overall health-care burden. Identifying patients with ACOS has significant therapeutic implications particularly with the need for early use of inhaled corticosteroids and the avoidance of use of long-acting bronchodilators alone in such patients. However, unlike asthma and COPD, no evidence-based guidelines for the management of ACOS currently exist. Future research is needed to improve our understanding of ACOS and to achieve the best management strategies.

Keywords Asthma · Chronic obstructive pulmonary disease · COPD · Asthma COPD overlap syndrome · ACOS · COPD phenotypes

This article is part of the Topical Collection on *Asthma*

S. Bujarski · A. D. Parulekar · A. Sharafkhaneh · N. A. Hanania (✉)
Section of Pulmonary, Critical Care and Sleep Medicine, Baylor
College of Medicine, 1504 Taub Loop, Houston, TX 77030, USA
e-mail: hanania@bcm.edu

S. Bujarski
e-mail: bujarski@bcm.edu

A. D. Parulekar
e-mail: paruleka@bcm.edu

A. Sharafkhaneh
e-mail: amirs@bcm.edu

A. Sharafkhaneh
Section of Pulmonary, Critical Care and Sleep Medicine, Medical
Care Line, Michael E. DeBakey VA Medical Center, 2002 Holcombe
St., Bldg 100 (111i), Houston, TX 77030, USA

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases with significant public health impact. There is still debate about whether COPD and asthma are expressions of the same disease or whether asthma and COPD are completely independent disorders [1]. However, it is known that the predominant pathological changes, expected inflammatory processes, usual clinical presentation, and likely responses to therapeutics differ between the two. Typically, patients with asthma have a predominant Th2 cytokine-driven, CD4⁺ lymphocytic, and eosinophilic airway inflammation that is responsive to corticosteroids. In contrast, patients with COPD typically have a more Th1 cytokine-driven, cytotoxic CD8⁺ lymphocytic, and neutrophilic inflammation [2, 3].

For many years, evidence-based guidelines for asthma and COPD [4, 5, 6] have guided practitioners on the appropriate assessment and management of these two common diseases. These recommendations have generally focused on considering asthma and COPD as two distinct entities and stipulated the need for differentiating one from the other prior to implementing the recommended management approaches. However, real-world clinical practice has clearly demonstrated that features of these two conditions often overlap despite their distinct underlying pathophysiological mechanisms. Furthermore, there is strong scientific evidence that supports this clinical overlap. Given the recognized heterogeneity of clinical presentation, disease course, and response to treatment among asthma and COPD, multiple phenotypes of each of these two diseases have now been identified [7–9, 10, 11, 12, 13]. Phenotypic characterization of both these diseases and their overlap affords better understanding of the underlying disease processes with the overall goal to better define differences in prognosis and responses to therapeutic interventions [8, 9].

Recently, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) has recognized the above concept by

publishing guidelines which incorporate COPD phenotypes and suggest individualized specific therapeutic recommendations depending on phenotypic profiles [10•, 11•, 12••, 14•, 15•, 16•]. Based on current estimates, the largest of these proposed COPD phenotypes represents a population that has features and characteristics of both COPD and asthma; the mixed phenotype (COPD-asthma). This entity has also recently been recognized by a joint committee publication between the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Global Initiative for Asthma (GINA) and is described as the asthma-COPD overlap syndrome (ACOS) [17••]. Although no universally agreed-upon definition of ACOS or mixed COPD-asthma phenotype currently exists, available data can help identify features and characteristics of COPD and asthma patients that comprise this subgroup. In addition, while no randomized trials have specifically investigated this phenotype, available evidence suggests that it represents a population that has a different response to usual therapy and may have a different impact on health-care utilization. This review provides an updated, evidence-based overview of the topic of ACOS and proposes areas of future research need.

Definition of ACOS

Existing guidelines provide formal definitions and outline diagnostic criteria for asthma and COPD. The GINA guidelines define asthma as a heterogeneous disease characterized by chronic airway inflammation presenting with episodic respiratory symptoms and expiratory airflow limitation which is variable and completely reversible [17••, 18•]. The GOLD guidelines and the American Thoracic Society/European Respiratory Society (ATS/ERS) statement define COPD as a preventable and treatable disease that is characterized by persistent airflow limitation, usually progressive, and associated with an enhanced chronic inflammatory response with exacerbations and comorbidities contributing to the overall severity. Whether using a fixed post-bronchodilator ratio of forced expiratory volume in 1 s and forced vital capacity (FEV1/FVC) or age-dependent cutoff values below the lower fifth percentile, objective criteria are established to diagnose and stage the disease [4•, 17••, 18•, 19, 20].

Unfortunately, there is no consensus on a unified definition or diagnostic criteria for ACOS. In fact, there is great variability in defining this population in the available literature. Criteria which have been used to define or differentiate individuals with ACOS in recent publications are detailed in Table 1. In addition, different methods have been used to make the diagnosis of ACOS, including the use of self-report of concomitant asthma and COPD diagnoses, retrospective identification using chart reviews and ICD-9 coding, magnitude of acute bronchodilator reversibility, and unique locally established criteria. Predictably, the inconsistencies

and discrepancies that exist with reported data on ACOS can be in part explained by the absence of a consistent definition and diagnostic parameters.

In an attempt to better define phenotypes and provide a starting ground for further research, SEPAR developed a new approach to COPD based on clinical phenotypes. These Spanish COPD Guidelines (GesEPOC) have provided a proposed definition of the mixed phenotype [COPD-asthma (ACOS equivalent)] as “an airflow obstruction that is not completely reversible, accompanied by symptoms or signs of increased obstruction reversibility [11•].” In addition, a panel of experts for GesEPOC proposed diagnostic criteria to help identify COPD patients that possess the accompanied symptoms and signs of increased reversibility consistent with ACOS. Two major criteria consisting of (1) a very positive bronchodilator test defined as an increase in FEV1 of $\geq 15\%$ and 400 ml, (2) eosinophilia in sputum, and (3) personal history of asthma or one major and two minor criteria consisting of (1) high total IgE, (2) personal history of atopy, and (3) positive bronchodilator test defined by an increase in FEV1 $\geq 12\%$ and 200 ml on two or more occasions are considered necessary to fulfill ACOS [12••]. Although founded on available evidence and consensus vote, the committee statement warns that prospective studies are required to validate this criteria-based definition and diagnosis.

In a similar attempt to recognize this entity, the scientific committees for GOLD and GINA recently released a joint statement in which they provided a consensus-based description for clinical use of ACOS: “ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD.” However, this statement emphasizes that the above description is merely intended to stimulate further study of the characteristics and treatments for this common clinical problem [17••]. This document provides a stepwise approach for patients with respiratory symptoms suggestive of chronic disease. It uses clinical, spirometric, and radiographic features to help delineate if an adult patient is most likely suffering from asthma or COPD or fulfills enough shared features to be considered within ACOS. Understanding that this distinction is often quite complex, and that there may be utility in diagnostic testing such as inflammatory biomarkers, high-resolution computed tomography (CT) scan, and more specific lung function parameters, it suggests possible further investigations that may be utilized to further distinguish these entities. In addition, it provides a general concept of initial therapeutic choices based on the most likely clinical syndrome. Lastly, it recognizes that patients with ACOS may warrant expert evaluation as they may have worse outcomes and greater health-care utilization.

Creation of documents by such large committees as GINA, GOLD, and SEPAR establishes the importance and recognition

Table 1 Criteria used to define or differentiate individuals with ACOS in recent publications

Citation	ACOS criteria or definition utilized	
Marsh et al. [8]	COPD per GOLD and any of the following: 1. BDT FEV1 $\geq$ 15 % 2. Peak flow variability $\geq$ 20 % during 1 week 3. Physician diagnosis of asthma and either symptoms (wheeze or nocturnal SOB and wheeze or nocturnal chest tightness in the last 12 months) or use of an inhaler in the last 12 months	
Blanchette et al. [2]	ICD-9 Claim COPD and ICD-9 Claim Asthma in the same patient	
Gibson et al. [22]	COPD per GOLD and increased variability of airflow evidenced by provocation dose of hypertonic saline that induces a 15 % fall in FEV1 of <12 ml	
Kauppi et al. [27]	COPD per ATS/ERS criteria and 1 or more of the following findings: 1. Positive BDT (increase in FEV1 of ≥ 12 %) 2. BD response of ≥ 15 % or diurnal variation of ≥ 20 % in PEF 3. Moderate to severe bronchial hyperreactivity 4. Decrease in FEV1 of ≥ 15 % on exercise test	
Hardin et al. [1]	COPD per GOLD stage II or worse and subject report of physician diagnosis of asthma before age 40	
Zeki et al. [3]	1. COPD per ATS/ERS and allergic disease consistent with asthma, that is, variable airflow obstruction or AHR that is incompletely reversible with or without emphysema or reduced DLCO or 2. COPD with emphysema accompanied by reversible or partially reversible airflow obstruction	Reversible airflow obstruction defined as FEV1 or FVC ≥ 200 ml and 12 % post-BDT AHR defined by positive MCT
Soler-Caraluna et al. [12•, 16•] GesEPOC/SEPAR Consensus Guideline (2012)	COPD per GOLD and either 2 major criteria or 1 major and 2 minor criteria are met Major criteria: 1. Very positive BDT (increase in FEV1 >15 % and >400 ml) 2. Eosinophilia in sputum 3. Personal history of asthma	Minor criteria: 1. High total IgE 2. Personal history of atopy 3. Positive BDT (increase in FEV1 >12 % and >200 ml) on two or more occasions
Kitaguchi et al. [32•]	COPD per GOLD at least moderate with asthmatic symptoms such as episodic breathlessness, wheezing, cough, and chest tightness worsening at night or in the early morning	
De Marco et al. [33•]	Self-reported, physician diagnosis of COPD and asthma in the same patient	
Louie et al. [24••]	Major criteria: 1. Physician diagnosis of asthma and COPD in the same patient 2. History or evidence of atopy—such as hay fever and elevated total IgE 3. >40 years old 4. Smoking >10 pack years 5. Post-Bronchodilator FEV1 <80 % predicted and COPD per GOLD definition.	Minor criteria: 1. ≥ 15 % increase in post-bronchodilator FEV1 or 2. ≥ 12 % and ≥ 200 ml in post-bronchodilator FEV1
Menezes et al. [23••]	COPD per GOLD or COPD per lower limit of normal derived from own population and either: 1. Wheezing in the last 12 months in self-report survey plus positive BDT (post-BD increase in FEV1 or FVC of ≥ 200 ml and 12 %) or 2. Self-reported prior diagnosis of asthma	
GINA/GOLD ACOS Consensus Statement [17••]	Characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD ACOS is therefore identified by the features that it shares with both asthma and COPD	

COPD chronic obstructive pulmonary disease, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *BDT* bronchodilator testing, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *ICD* International Classification of Diseases, *ATS/ERS* American Thoracic Society/European Respiratory Society, *AHR* airway hyperresponsiveness, *DLCO* carbon monoxide diffusing capacity, *MCT* methacholine challenge test

of ACOS; however, the definitions and criteria will need to be validated to ensure their application.

Impact and Epidemiology of ACOS

The overlapping concept within the umbrella term of COPD is not new. Soriano et al. established that 19 % of patients with

airflow obstruction had at least two or more conditions, the most common of which were asthma and COPD [21]. Therefore, ACOS, or the mixed phenotype, provides a special area of importance as it comprises a large portion of all adults with obstructive lung disease.

The exact prevalence of ACOS is unknown. It is very difficult to accurately assess its prevalence due to variable definitions that exist throughout the literature. However, an

estimated 13–55 % of all COPD patients fulfill potential criteria for ACOS [1, 8, 22, 23•, 24•, 25•]. Some reports suggest that at least 50 % of individuals over the age of 60 with obstructive airway disease [22] and approximately 25 % of adult patients with severe asthma fulfill ACOS criteria [24•].

Not only does ACOS represents a large proportion of COPD patients, but also this group has a higher health-care burden, both in terms of cost and utilization. Patients within this phenotype have more frequent exacerbations, are more likely to have a severe exacerbation requiring hospitalization, use more respiratory medications, and have the highest reported pulmonary symptoms [1, 2, 23•, 26•]. More importantly, patients with ACOS also report worse quality of life than those with either disease alone [27].

Unfortunately, this large cohort of patients poses a problem to clinicians who are attempting to apply evidence-based guidelines. Most prior therapeutic trials included highly selected, clearly defined patient populations. Typically, smokers with asthma and COPD patients with a history of asthma have been excluded from asthma and COPD clinical trials, respectively. Travers et al. questioned the external validity of existing randomized controlled asthma and COPD clinical trials. He concluded that over 90 % of COPD and asthma patients were taking medication based on data from trials for which they themselves would not have been eligible for enrollment [28, 29]. Ultimately, a large group of individuals, many with features consistent with ACOS, that smoke and have asthma [30, 31] or COPD and a history of asthma have not been well studied.

Identifying the Patient Population

In general, the literature on ACOS has been mostly retrospective and observational. Nevertheless, the diagnosis of ACOS should be considered in certain patient populations listed in Fig. 1. Clinically, patients fulfilling ACOS are younger than those with COPD but older than those with asthma. In the U.S., they are more likely African American and have less smoking history than typically seen in traditional COPD. They commonly have features associated with asthma including wheezing, atopy, elevated total IgE levels, and allergic problems such as allergic rhinitis, positive skin prick testing, and hay fever [1–3, 32•, 33•]. Furthermore, airway inflammation in this population tends to be more eosinophilic than the usual neutrophilic inflammation described in COPD patients [32•, 34]. Lung function testing in patients with ACOS often reveals a higher carbon monoxide diffusing capacity (DLCO) and a more pronounced acute bronchodilator reversibility than COPD patients [23•, 32•, 34]. On high-resolution computerized tomography (CT) scan of the chest, patients with ACOS have more gas trapping, less

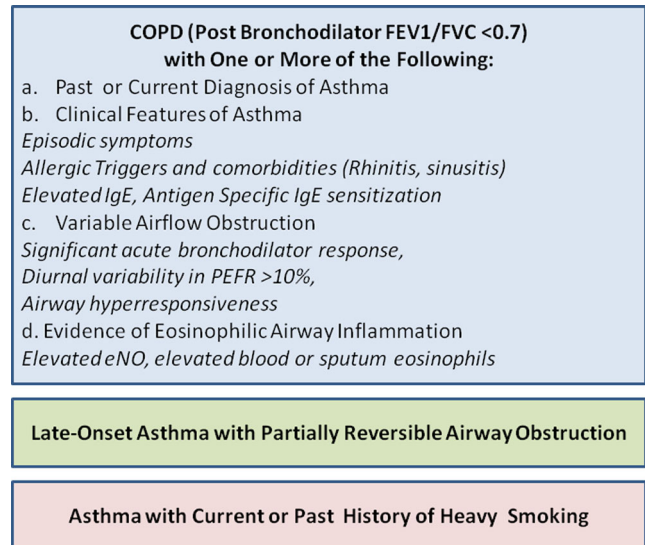


Fig. 1 Clinical populations where ACOS should be considered

emphysema, and greater bronchial wall thickening when compared to patients with COPD [1, 35].

A history of asthma, either self-reported or physician-documented, is strongly associated with ACOS. It is well known that asthma patients are at higher risk for developing COPD [36–38]; however, it is sometimes very challenging to diagnose COPD patients with chronic asthma once fixed obstruction is present on spirometry. This is particularly true in patients with undiagnosed asthma who smoke or those who develop fixed airway obstruction regardless of smoking history. These nuances leave a large proportion of patients with asthma to be poorly characterized.

Epidemiologic studies of COPD demonstrate that patients with asthma who develop fixed airflow obstruction have different baseline clinical and immunologic characteristics than those patients with COPD and no history of asthma [39]. In addition, patients who develop COPD and have a history of asthma maintain differences once the fixed obstruction is evident. Markers of eosinophilic inflammation including serum and sputum eosinophilia and fraction of exhaled nitric oxide (FeNO), characteristics typically associated with asthma, are often found in patients with fixed airflow obstruction secondary to asthma [40–42].

A reported history of asthma is often insufficient to differentiate ACOS from COPD because not all asthmatics fit the typical eosinophilic, steroid-responsive profile. Smoking induces considerable overlap between asthma and COPD, clinically, and in regard to inflammation and airway pathology. Smoking asthmatics fit a profile more consistent with the traditional COPD patient. These patients are often less responsive to inhaled corticosteroids (ICS), likely related to the more neutrophilic airway inflammation that is often seen in their airways [43–45].

Differentiation of airway inflammation plays an additional key role in identifying individuals with ACOS. Eosinophilic airway inflammation frequently suggests asthma but does not necessarily exclude COPD. Indeed, many patients with COPD and fixed airflow obstruction on spirometry display eosinophilic airway inflammation and respond well to both inhaled and systemic steroids [46]. These patients do not necessarily represent asthma patients who developed fixed airflow obstruction [34, 47]. It remains unclear why some patients with COPD have a predisposition to develop an eosinophilic airway response. Some hypotheses have been described which are beyond the scope of this review [46]. Many recent studies attempting to better clarify ACOS focus on this important concept. Not only is it believed that eosinophilic inflammation is associated with COPD exacerbations but that the group with this inflammatory profile is more responsive to steroids [32, 46, 48, 49]. In addition, this may represent a subset of patients that should be treated early with ICS and not have ICS withdrawn due to potential worsening [50].

Traditionally, measuring eosinophilic inflammation has been done with sputum or bronchial lavage cellular analysis, which can be difficult to obtain. More recently, FeNO levels have been shown to correlate with airway inflammation characterization in COPD, similar to what has been demonstrated in patients with asthma [51]. In addition, it has been shown that a normal FeNO level predicts lack of steroid response [52]. It is widely believed that higher FeNO levels occur more frequently in patients with ACOS compared with other COPD phenotypes [34].

A large group of COPD patients have partial reversibility demonstrated by positive bronchodilator testing (BDT) [53–56]. Although partial reversibility among COPD patients is unlikely to identify asthma patients accurately, it likely has some clinical relevance for prognosis, therapeutic intervention, and identifying individuals with ACOS. In addition, the lack of standardized BDT procedures and criteria for positivity has created confusion and difficulty comparing studies. Given the unclear nature of this concept, it has often been accepted that lack of response to short-acting bronchodilators (BD) does not preclude potential long-term benefits of bronchodilators in individuals with COPD. Some studies demonstrated COPD patients with positive BDT have an increased mortality; others question this finding [57–59]. Recently, subgroups of COPD patients with positive BDT have been shown to have an improvement in FEV1 after treatment with ICS/long-acting beta2-agonist (LABA) combination [60]. Despite the uncertainty of the overall clinical importance, a significant improvement in lung function during BDT helps distinguish ACOS as a group of COPD patients that have the potential to act more like asthma patients and benefit from ICS.

More recently, research has demonstrated the potential for biomarkers such as surfactant protein A (SP-A), soluble receptor for advanced glycation end products (sRAGE),

myeloperoxidase (MPO), and neutrophil gelatinase-associated lipocalin (NGAL) in sputum and serum as well and genetic variants in differentiating asthma, COPD, and ACOS [61, 62]. These markers will likely serve as important specific indicators but need future exploration prior to clinical application.

Therapeutic Implications

ICS therapy constitute the foundation for management of persistent asthma. Inhaled long-acting bronchodilator therapy constitutes the cornerstone for management of stable COPD. No large randomized controlled trials have been conducted involving therapeutic interventions targeting patients specifically with ACOS. Therefore, more data are needed to help guide how to best optimize this patient population. In the interim, existing and emerging data can be utilized to make a general construct for therapeutic management and develop concepts for potential future research.

The current concept of identifying asthma and COPD phenotypes revolves around individualizing therapeutic and management strategies. Based largely on the evidence from ISOLDE trials [63, 64], current recommendations are made to utilize ICS in COPD patients with exacerbations and FEV1 < 50 % to reduce future exacerbations. However, as noted by others [56], COPD exacerbations were prevented in many with FEV1 > 50 %. Therefore, the utilization of ICS in patients with COPD may not be dependent on severity based on FEV1, but instead on features which may reflect a population that is more steroid responsive. This steroid-responsive subpopulation of COPD is thought to be in large part made up of individuals with ACOS. This concept is advocated by some experts in the field and is currently reflected in the Canadian and Spanish COPD guidelines [16, 56, 65–67]. Although the lowest dose of ICS that achieves response is advocated, some evidence suggests patients with ACOS should not have the ICS withdrawn due to greater number of exacerbations [50]. Along the same lines, avoiding ICS in those that are less likely to derive benefit may have just as large of an impact, mitigating some of the potential complications of ICS use such as pneumonia [68].

As mentioned, ACOS represents the group of COPD patients who are more likely to receive greater benefit from ICS, regardless of FEV1 severity and exacerbation history. This theory is based on extrapolated data from COPD patients that fulfill the above ACOS characteristics. COPD patients with a positive BDT or hyperreactivity test or sputum eosinophilia have been shown to be more responsive to ICS than those without these features [49, 69–74]. In addition, a study by Siva et al. demonstrated a reduction in the number of severe exacerbations when titrating steroid and BD therapeutics to achieve a reduction in sputum eosinophilic inflammation compared to those treated according to

current British Thoracic Society guidelines [75]. This finding may give some basis for optimal dosing of ICS in ACOS.

Because airway inflammation in patients with ACOS resembles that seen in patients with asthma, it has been suggested that the use of long-acting BD alone in this population should be avoided [16•]. Instead, ICS should be used in combination with BD. While LABA have long been the preferred bronchodilators in asthma, recent literature has demonstrated the efficacy of long-acting muscarinic antagonists (LAMA) such as tiotropium [76•, 77]. In addition, some data suggests the effects of tiotropium in regard to improvement in FEV1 and FVC may be more pronounced in asthmatics with smoking history and emphysematous changes on CT scan [78•]. In one clinical trial in patients with COPD and concomitant asthma, the use of tiotropium had a beneficial effect in improving lung function [79]. These trials provide a foundation to further explore the role of existing and future LAMA agents in individuals with ACOS.

It is unknown whether other specific therapeutics have greater benefit in patients with ACOS. Given the similar characteristics to asthma, unexplored options with therapeutics generally being used clinically or studied in asthma patients may benefit patients with ACOS. Options such as monoclonal antibodies against IgE, IL-5, and IL-13 may have a role in patients with features of ACOS and warrant further investigation [80•, 81•]. Furthermore, existing or future oral or inhaled anti-inflammatory agents such as PDE4 inhibitors, 5-lipoxygenase inhibitors, and MAP 38 kinase inhibitors may be beneficial in such a population [82•].

Future Needs

Existing data defining ACOS are very limited. Given that this population represents a large phenotype of asthma and COPD, identifying easy-to-use diagnostic criteria is essential. Specifically, it is necessary to validate currently proposed criteria set forth by SEPAR and GOLD-GINA to ensure diagnostic sensitivity and specificity. Identification of inexpensive and reproducible tests and biomarkers that help differentiate this phenotype from asthma and COPD are critical to ensure a better therapeutic approach. Finally, randomized clinical trials evaluating the use of current and emerging therapeutics on outcomes such as lung function, exacerbations, quality of life, and mortality are needed to facilitate the establishment of evidence-based guidelines for this group of patients historically excluded from clinical trials.

Conclusions

Defining the differences or various phenotypes of asthma and COPD is more than an academic principle. It holds clinical

relevance, affects patient outcomes, and provides great research potential. ACOS, although not universally defined, recognizes a previously neglected but a commonly encountered group of individuals that impose a major burden on the health-care system. While the definition and diagnostic criteria of ACOS are evolving, it clinically includes several potential patient populations. It represents many individuals with asthma who smoke or have developed fixed airway obstruction and COPD patients with eosinophilic airway inflammation. Clinical features and utilization of certain diagnostics testing can aid in differentiating individuals with ACOS. ICS should likely be considered as part of the first line of therapeutics for individuals with ACOS. Ultimately, future research is needed to better delineate this group and further establish best appropriate therapeutic interventions.

Compliance with Ethics Guidelines

Conflict of Interest Stephen Bujarski, Amit Parulekar, and Amir Sharafkhaneh declare that they have no conflicts of interest. Nicola Hanania served as consultant to Boehringer Ingelheim (BI), Novartis, Pfizer, Sunovion, and Genentech has served on the speaker bureau for Genentech, and his institution has received research grant support on his behalf from BI, Genentech, GSK, Sunovion, Mylan, Novartis, Pfizer, and Pearl.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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