

Management of the Asthma-COPD Overlap Syndrome (ACOS): a Review of the Evidence

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Abstract

Purpose of Review Examine the definition of the asthma-COPD overlap syndrome (ACOS) and current treatment strategies.

Recent Findings Patients with the ACOS have a lower quality of life and suffer from more complications than those affected by either disease alone. Diagnosis of ACOS is difficult because of the clinical similarities between the two diseases and the various phenotypes that comprise the syndrome. Defining treatment strategies for ACOS has been challenging because many clinical trials for asthma therapy have purposefully excluded patients with features of COPD, and COPD clinical trials have not included patients who might have an asthmatic component to their disease. Therefore, there are few randomized treatment trials which have included patients who have ACOS.

Summary Smoking cessation and appropriate vaccinations are cornerstone therapies, and pharmacologic therapy has focused on bronchodilators and inhaled corticosteroids. The role of biologics, such as omalizumab and IL-5 antagonists, in ACOS treatment is still being defined. As of now, with the paucity of randomized control trials guiding treatment strategies, the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD)

guidelines recommend treating ACOS according to the dominant phenotype.

Keywords COPD · Asthma · Eosinophil · Smoking · Pharmacotherapy

Introduction

Over the last 3 years, there has been a marked increase in interest in the intersection between the clinical entities of asthma and COPD. While clinicians have known for decades that patients who have asthma and smoke have more symptoms than those asthmatics who do not smoke [1–3], there has also been increased recognition that there are subsets of patients with asthma who have never smoked who have pathology consistent with COPD, just as there are patients who smoke who have inflammation that is usually characterized as allergic in nature [4•]. While the environmental and host factors driving these three scenarios are likely very different from each other, they have been grouped together as the asthma-COPD overlap syndrome (ACOS). As a result of the different pathophysiologies that result in ACOS, lumping such patients into one category has generated skepticism about the need for this terminology, and some experts argue that a patient with ACOS should be treated based on whether the clinical features of his or her disease are predominantly asthma or predominantly COPD, thus eliminating the need to characterize and define an independent condition of ACOS. A major concern is ACOS may discourage personalization of treatment by offering a simplistic, “one size fits all” approach to the management of pulmonary disease [5].

Despite this controversy, the presence of both asthma and COPD features in a single patient has implications on many aspects of care. Those patients with features of both COPD

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and asthma have a significantly lower quality of life compared to those with asthma or COPD alone [6•]. Similarly, those patients with ACOS also have a higher incidence of disease burden, including respiratory symptoms and activity limitation, independent of severity of airflow limitation [7]. Thus, it is not surprising to find that comorbidities are common in this disease group, and when compared to COPD, ACOS leads to more hospitalizations and ED visits [8•]. In one study, comorbid cardiovascular diseases in ACOS were the strongest factor for hospitalization [9]. Interestingly, ACOS has also been associated with significant societal disparities compared to other pulmonary diseases. In comparison to those with COPD alone, patients with ACOS in the USA have lower educational status, lower income, and higher BMI [8•].

Epidemiologic studies show that ACOS has a female predominance, and those diagnosed with the syndrome are typically younger than those with COPD, and older than those with asthma, with an average age of 64.0 years [8•, 9]. One Italian study of 1065 patients with spirometric data found the prevalence of ACOS to be 11.1%, compared to asthma (14.9%) and COPD (19.3%) [10]. A similar prevalence was noted at UC Davis Medical Center in the USA, which noted ACOS to be present in 15.8% of patients seen in their general pulmonary clinics [11]. More recently, the overall prevalence of ACOS in the USA was reported to be 3.2% [8•]. It is clear that identification and accurate diagnosis of ACOS is critical for patients with chronic pulmonary diseases.

Definitions and Diagnosis of ACOS

Longstanding guidelines exist for the diagnosis of asthma and COPD, but have only recently begun to take form for ACOS. Diagnosing ACOS is challenging because of the similarity between the clinical features of COPD and asthma and complicated by the fact that each disease has a different response to medications. Early definitions of ACOS simply relied upon making a determination whether the patient had a phenotype that was more similar to asthma or to COPD. This was done by assessing a patient's degree of reversibility of airflow obstruction, emphysematous changes, carbon monoxide diffusing capacity (D_LCO), and presence or absence of environmental allergies [11, 12]. More recently, multiple phenotypes of ACOS have been described, including patients who have both COPD and blood or airway eosinophilia, smokers with asthma, patients with a long history of asthma that have developed subsequent airway remodeling, and those with asthma and neutrophilic inflammation [13]. A global expert panel reviewed multiple trials and generated a working definition of ACOS comprised of major and minor criteria for diagnosis (Table 1) [14••].

It is well known that the pattern of inflammation varies quite significantly between COPD and asthma. COPD is most often associated with a neutrophilic infiltration and an

Table 1 Sin et al. suggested criteria for diagnosis of ACOS [14••]

Major
1. Persistent airflow limitation ($FEV_1/FVC \leq 0.70$ despite bronchodilator therapy) in patients age 40 years or older
2. Significant smoking history of ≥ 10 pack-years or equivalent exposure to air pollution
3. Documented history of atopy/asthma or bronchodilator response ≥ 400 mL in FEV_1
Minor
1. Documented history of asthma or allergic conditions
2. Bronchodilator response of $FEV_1 \geq 200$ mL and 12% from baseline on two or more visits
3. Peripheral eosinophilia ≥ 300 cells/ μ L

To make a diagnosis of ACOS, all three major criteria plus at least one minor criterion must be present [14••]

increased number of macrophages, while asthma is generally eosinophilic, characterized by T helper type 2 (Th2) inflammation and IgE production in response to common aeroallergens which can sensitize mast cells [15]. Fractional exhaled nitric oxide (FeNO) has been recognized as a marker of eosinophilic inflammation and has been used in the diagnosis and monitoring of asthma. FeNO has been proposed as a test to distinguish COPD from ACOS. In one study, a cutoff value of greater than 22.5 ppb FeNO predicted an ACOS diagnosis instead of COPD with a sensitivity of 70% and specificity of 75% [16].

Until recently, ACOS had only limited molecular data to support its differentiation from COPD and asthma. Sputum biomarkers have been a topic of interest, and increased levels of chitinase-like protein (YKL-40), interleukin (IL)-6, and neutrophil gelatinase-associated lipocalin (NGAL) have been associated with ACOS, though only increased NGAL was shown to reliably differentiate ACOS from COPD and asthma [17]. Investigation into the role of oxidative stress and mitochondrial dysfunction in ACOS has demonstrated that the ratio of mitochondrial DNA to nuclear DNA is elevated in the overlap syndrome, compared to lower levels in asthma and higher levels in COPD [18]. While the diagnostic utility of mitochondrial DNA alteration is still unknown, other investigations have identified other genetic variations that are characteristic of ACOS. Single nucleotide polymorphisms in the genes *CSMD1*, *SOX5*, as well as *GPR65* are associated with ACOS specifically [19]. Perhaps in the future, diagnosis of ACOS will include genetic and molecular criteria in addition to the social, physiologic, and immunologic variables shown in Table 1.

Evidence for Management

From a therapeutic standpoint, ACOS is also a conundrum. Evidence supporting treatment strategies specifically for

ACOS is quite limited. Most of the randomized controlled trials supporting relevant pulmonary pharmacotherapy have been performed in either relatively pure COPD or asthma, and only recently has ACOS been a target of such research. For instance, most clinical trials for asthma have included relatively young patients with allergic disease who either never smoked or had less than a 10 pack-year history of tobacco use. Subjects enrolled in asthma studies typically have either bronchodilator reversibility or positive methacholine challenges. These criteria were set in place to exclude patients with COPD who might not respond to asthma therapy in a clinically significant manner. On the other hand, clinical studies in COPD have been more likely to enroll older subjects with fixed airway obstruction and an extensive history of cigarette smoking. As a consequence, focusing clinical trials on the extremes of either asthma or COPD has prevented “real world” studies that enroll patients who have features of both asthma and COPD. Therefore, there are a very limited number of trials that include such patients, resulting in questions about how to optimally treat them. This interest has certainly gained momentum as witnessed by the recent number of articles on ACOS. Using the search terms “asthma,” “COPD,” and “overlap,” there were 11 articles from 2000 to 2011, but 58 articles in 2015 and over 100 in 2016. This exponential increase in ACOS articles is even more interesting when one performs a PubMed search and finds that the number of review articles on ACOS from 2000 to 2016 was greater than the number of original research articles. Therefore, we have been relying on conjecture and expert opinion rather than an evidence-based approach to treatment of ACOS. Here, we outline the current evidence guiding pharmacotherapeutic strategies relevant to the management of ACOS.

Beta-Agonists and Inhaled Corticosteroids

The underlying pathophysiology of ACOS, which shares features of both asthma and COPD, predicts that patients with ACOS should have a robust response to beta-agonists and inhaled corticosteroids (ICS). In one study, cluster analysis identified five distinct phenotypes of airway disease, and each phenotype was evaluated for its responsiveness to the primary medications used in the treatment of asthma and COPD [20]. For all identified phenotypes, including ACOS, bronchodilation was greater after salbutamol compared to ipratropium, and after 12 weeks of treatment with ICS, those with ACOS demonstrated a significantly greater improvement in SGRQ score as well as reduction in peak flow variability compared to other phenotypes [20]. Similarly, in COPD patients with airway epithelial cell gene expression of Th2 inflammation, an immune response typically associated with asthma, higher levels of Th2 inflammation correlated with increased bronchodilator response and improvement in hyperinflation after fluticasone treatment [21].

Serum markers such as blood eosinophil count, serum IgE, and FeNO have also been suggested as tools to stratify COPD patients and predict positive response to ICS treatment [22, 23]. Benralizumab, a monoclonal antibody antagonist to the IL-5 receptor, has been investigated as a possible therapeutic to add to the treatment of patients with COPD and eosinophilia. Interestingly, however, after 56 weeks of treatment with benralizumab, patients with COPD and eosinophilia showed slight, but not significant, improvement in the number of acute exacerbations and FEV₁ [24]. It is worth noting that this trial had a relatively small sample size, and perhaps clinically significant differences would be observed in a larger patient population.

A post hoc analysis of data from two randomized controlled trials investigated the utility of blood eosinophil count as a biomarker of response to ICS and found that in patients with moderate-to-severe COPD treated with an ICS-LABA combination, increasing eosinophil counts correlated with more significant reductions in exacerbations [22]. Similarly, a post hoc analysis of the FORWARD study found that while those with the highest eosinophil counts ($\geq 279.8/\mu\text{L}$) had the most exacerbations while on long-acting beta-agonist (LABA) monotherapy, this group benefitted the most from the addition of beclomethasone to formoterol for the treatment of severe COPD [25, 26].

Specifically in a patient population with ACOS and mild symptoms, after 8 weeks of treatment with an ICS-LABA, there was significant improvement in the spirometry parameters vital capacity, FEV₁, and peak expiratory flow [27]. In a patient population with mild-to-moderate airflow limitation, those with ACOS had a significantly greater improvement in FEV₁ after 3 months of ICS-LABA treatment compared to those with COPD alone [28]. However, in those with severe to very severe airflow limitation, no significant difference was noted in treatment response [28]. Despite multiple studies confirming improvement of FEV₁ in ACOS with the use of ICS, little data exists on the long-term effects of ICS-LABA treatment in ACOS. One observational, 12-year retrospective cohort study found ICS/ICS-LABA use in ACOS to not be significantly beneficial with regard to mortality, annual rate of FEV₁ decrease, and incidence rates of severe exacerbations [29]. This study was limited, however, in that the patients were defined as “ICS-treated” if they had received at least one dose of ICS, and discontinuation of the medication was not considered [29]. These findings verify that further research is needed to clarify the exact role and benefit of ICS/ICS + LABA in ACOS.

Anticholinergics

Although patients with ACOS have less bronchodilation with tiotropium monotherapy compared to that observed with salbutamol monotherapy, there is still the benefit of FEV₁ improvement and better symptom control following tiotropium administration in patients with combined COPD

and concomitant asthma [20, 30]. In a study comparing ICS-treated asthmatics with and without emphysematous changes, tiotropium increased FEV₁ by 12.6 percentage points (173 mL) in those with emphysematous changes 60 min after inhalation compared to placebo [31•]. An increase of only 5.4 percentage points at 60 min was noted for those without emphysema [31•]. Those with emphysema had persistent FEV₁ improvement and decreased SABA use after 2 months of treatment with tiotropium [31•]. These results suggest that there is a role for anticholinergic therapy in the treatment of ACOS, perhaps in combination with other therapies, and more information is needed.

Omalizumab

The anti-IgE antibody omalizumab has been used for years in the treatment of allergic asthma. A small sample of patients with ACOS, after 12 months of omalizumab treatment, had improved pulmonary function tests in addition to decreased levels of FeNO, eosinophils, neutrophils, and IL-4 [32]. In this study, these patients were defined as having ACOS based on clinical features of low lung function, limited reversibility of airway obstruction, hyperinflation, abnormal body composition, dyspnea, and episodic wheezing in addition to laboratory criteria not clearly defined [32]. A case report of three patients with ACOS on maximal therapy that underwent omalizumab treatment for 1 year had significantly lower rates of exacerbation and fewer hospitalizations compared to before initiation of omalizumab [33]. A recent, retrospective study showed that after 6 months of treatment with omalizumab, asthma control and health-related quality of life were significantly improved in patients with both asthma and COPD [34•]. Interestingly, however, no significant improvement in lung function was observed in this same population [34•].

Montelukast

After 8 weeks of treatment, montelukast, a leukotriene receptor antagonist, significantly increased daily morning peak flow in patients with asthma who smoked, but not in those who were tobacco-free [35]. In nonsmokers, treatment with montelukast did not cause any statistically significant change in the variables tested after 8 weeks of treatment [35]. In contrast, nonsmokers had significant improvement in FEV₁, peak expiratory flow rate, daily morning peak flow, Asthma Quality of Life (AQOL) score, as well as a significant reduction in % sputum eosinophils after 8 weeks of treatment with beclomethasone, while only morning peak expiratory flow rate and % sputum eosinophils was significantly changed in smokers after the same treatment [35]. This suggests that those with ACOS may derive benefit in pulmonary function with montelukast treatment. In experiments on mouse models with asthma and pancreatic elastase-induced emphysema,

montelukast reduced airway hyperresponsiveness and both eosinophilic and neutrophilic airway inflammation [36]. Randomized controlled trials are needed to quantify the potential benefit of montelukast in ACOS.

Antibiotics

Azithromycin is commonly added to the treatment regimen of severe COPD with the goal of decreasing the number of acute exacerbations. While no trials evaluating the efficacy of antibiotics in the treatment of ACOS could be identified, a single randomized trial of azithromycin in the treatment of asthmatic patients who smoke revealed that after 12 weeks of azithromycin 250 mg daily, morning peak flow and FEV₁ did not significantly differ from those patients treated with placebo [37].

Suggested Approaches to Treatment

Diagnosis of ACOS is challenging, and once a diagnosis is made, there are few evidence-based recommendations to guide management. The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) still recommend treating ACOS according to the dominant phenotype. In patients with asthma symptoms, low- or moderate-dose ICS is the preferred initial treatment, while COPD symptoms warrant first-line bronchodilator therapy [38•]. In those patients that have an equal number of asthma and COPD features, the recommendation is to start treatment for asthma with an ICS [38•]. While the addition of LABA or an anticholinergic is often necessary for ACOS, one should be careful to avoid LABA monotherapy in patients with asthma-dominant symptoms given the concern for increased asthma exacerbations and risk of asthma-related death found by the SMART study [38•, 39]. This is in alignment with the FDA recommendation of LABA use only in conjunction with an asthma-controller medication [39]. Given the lack of efficacy in managing symptoms, ICS monotherapy is not recommended for management of COPD [40•]. For every patient with ACOS, risk factor modification such as smoking cessation should be pursued, as well as staying up to date on recommended vaccinations and pulmonary rehabilitation [38•, 40•, 4••]. Given the complexity of ACOS management and the risk of poor outcomes in this population, experts recommend early referral to clinicians with more experience treating this population [4••].

Conclusions and Future Directions

ACOS is prevalent among patients diagnosed with asthma and COPD. It is challenging to accurately diagnose as it is not

reflective of a single disease, but phenotypes depending on the ratio of asthma and COPD characteristics. There is limited data to support a universal treatment strategy, and most evidence at this time supports the use of medications depending on whether a patient has symptoms more typical of asthma or of COPD. Current research indicates that other therapies such as omalizumab and montelukast may have a more defined role in the future. Additionally, genetics and molecular biomarkers are gaining recognition as a means to distinguish ACOS from other pulmonary diseases and may serve as potential therapeutic targets. Finally, research elucidating the specific endotype that leads to the clinical presentation of ACOS in an individual patient will further refine therapy.

Compliance with Ethical Standards

Conflict of Interest Drs. Peebles and Hines declare no conflicts of interest relevant to this manuscript.

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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