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ASTHMA AND COPD OVERLAP SYNDROME

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Asthma-COPD overlap syndrome (ACOS) has a higher disease burden than either condition alone.
Patients with ACOS have frequent exacerbations, poor quality of life, a more rapid decline in lungfunction, and high mortality.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common obstructive airway diseases frequently seen by clinicians in practice. Approximately 25 million Americans are reported to have asthma, and 15 million Americans have been diagnosed with COPD. An additional 24 million American adults have evidence of impaired lung function, suggestive of an under diagnosis of COPD.3 According to the National Heart, Lung and Blood Institute, the costs of COPD and asthma totaled $68.0 billion in 2008, of which $53.7 billion were direct costs. A subset of patients with asthma and COPD have characteristics of both disorders and are described clinically as having asthma-COPD overlap syndrome (ACOS). Patients with ACOS have a higher burden of disease and health care utilization and increasing recognition of this condition is critical. This article will review the identification, epidemiology, diagnostic evaluation, and basic treatment strategy for ACOS. This information should assist the primary care physician (PCP) in his or her approach to this condition. The distinction between asthma and COPD is usually most evident to the clinician at the extremes of age. Asthma typically develops in childhood, manifests with classic symptoms of recurrent chest tightness, cough, wheeze, and dysponea., and tends to be associated with atopic disorders. Chronic obstructive pulmonary disease typically manifests later in life, is insidious with productive cough and dyspnea being prominent symptoms, and tends to be associated with tobacco smoking. In addition, asthma is characterized by intermittent, reversible airflow obstruction, whereas COPD has persistent and irreversible airflow obstruction. As such, a nonsmoking atopic younger patient with a history of recurrent childhood wheezing with reversible airflow obstruction would favor a diagnosis of asthma. In contrast, an older patient with a history of tobacco smoking with chronic cough and dyspnea with evidence of fixed obstruction would favor a diagnosis of COPD.

According to the **Dutch Hypothesis,** asthma and airway hyper-responsiveness predispose patients to COPD later in life, and asthma and COPD are different expressions of a single disease. This theory is supported by a long-term cohort study in the U.S., which indicated asthma as a risk factor for the future development of COPD.Patient groups that have features of ACOS include smokers with asthma and nonsmokers with longstanding asthma who progress to COPD. Although asthma and COPD can present “classically,” many clinicians recognize that these disorders may present with overlapping features that make distinguishing between the two diagnostically challenging. Soriano and colleagues succinctly outlined the difficulties in distinguishing between asthma and COPD:-

- The conditions are viewed as part of a disease continuum;
- They have strong overlapping features
- There is no incentive to differentiate whether their treatment and prognosis are the same
- There are a lack of clear guidelines as to how the distinction can be made in clinical practice
- Uncertain criteria are used by physicians to classify patients as having asthma or COPD

The term ACOS is a clinical descriptive one and has not been clearly defined as evidenced by the multitude of descriptions in the literature. Solera-Cataluña and colleagues defined the clinical
phenotype as "overlap phenotype COPD-asthma" based on the presence of major and minor criteria.
Major criteria consisted of a postbronchodilator increase of forced expiratory volume in 1 second (FEV1)
≥ 12% and ≥ 400 mL, and eosinophilia in sputum in addition to a personal history of asthma. Minor criteria included high total immunoglobulinE (IgE), personal history of atrophy, and a postbronchodilator increase of FEV1 ≥ 12% and ≥ 200 mL on ≥ 2 occasions. Zeki and colleagues defined ACOS as: (1) asthma with partially reversible airflow obstruction, with or without emphysema or reduced carbon monoxide diffusion capacity (DLCO) to < 80% predicted; and (2) COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced DLCO.10 Louie and colleagues proposed the following major criteria for ACOS: a physician diagnosis of asthma and COPD in the same patient, history of evidence of atrophy, elevated total IgE, aged ≥ 40 years, smoking > 10 pack-years, postbronchodilator FEV1< 80% predicted and FEV1/forced vital capacity (FVC)
< 70%.11 Minor criteria consisted of a postbronchodilator increase of FEV1 by ≥ 15% or ≥ 12% and ≥ 200 mL following albuterol.The Global Initiative for Asthma/Global Initiative for Chronic Obstructive Lung Disease published a joint consensus document on ACOS, which described a stepwise approach to diagnosis based on defining characteristics.5 To distinguish between the diagnosis of asthma, COPD, and ACOS in an adult patient, the guideline focuses on the features that are felt to be most helpful in distinguishing the syndromes in stepwise fashion. The physician should first assemble the features that favor a diagnosis of asthma or COPD, then compare the number of features in favor of a diagnosis of asthma or COPD, and finally consider the level of certainty around the diagnosis of asthma or COPD or whether there are features of both, suggesting ACOS.

FREQUENCY

In 1995, the American Thoracic Society guidelines defined 11 distinct obstructive lung disease syndromes and identified overlap syndromes in 6 of them.Soriano and colleagues quantified the subpopulations of these patients by analyzing the U.S. National Health and Nutrition Examination III survey and the U.K. General Practice Research Database and reported an increased frequency of overlapping diagnosis of asthma and COPD with advancing age, with an estimated prevalence for < 10% in patients aged < 50 years and > 50% in patients aged ≥ 80 years.8 A study of patients aged > 50 years by Marsh and colleagues reported a combined syndrome of asthma and COPD to be the most common phenotype as confirmed by spirometry.13 In this study, 62% of subjects with the combined asthma and COPD phenotype were current or former smokers. In a study of 44 adults aged > 55 years with stable asthma or COPD, Gibson and colleague reported that 16% and 21%, respectively, could be categorized as having overlap syndrome.14 As in previous studies, those with overlap syndrome and COPD were predominantly ex-smokers. Brahman and colleagues characterized asthma in subjects aged > 70 years.15 Compared with those who developed asthma at an advanced age, those with early onset asthma had a significantly greater degree of airflow obstruction on pre- and postbronchodilator testing. This study suggested that long-standing asthma may lead to chronic persistent airflow obstruction and mimic COPD. A longitudinal study by Vonk and colleagues reported that 16% of patients with asthma had developed incomplete airflow reversibility after 21 to 33 years of followup.16 De Marco and colleagues found the prevalence of asthma-COPD overlap to be 1.6%, 2.1%, and 4.5% in the 20 to 44, 45 to 64, and 65 to 84 years age groups, respectively, through a screening questionnaire of the general Italian population in concurrence with previous studies, noting an increased prevalence of ACOS in the elderly. Lee and colleagues described those with ACOS as older, male asthmatics, who have a higher lifetime smoking history and generally worse lung function.

QUALITY OF LIFE, MORBIDITY, AND MORTALITY

In addition to being more prevalent in the elderly, ACOS is associated with more severe symptoms, impairment in quality of life (QOL), more frequent exacerbations, and high health care utilization. The ACOS phenotype is also at risk for accelerated decline in lung function secondary to its association with advancing age, tobacco smoking, presence of bronchial hyper-reactivity, and exacerbations.Burrows and colleagues described the characteristics and course of asthma in subjects aged > 65 years and concluded that asthma in this group may be associated with severe symptoms, higher death rates, and chronic airway obstruction. In this study, the subjects with suspected ACOS smoked at least 20 pack-years and had a significantly

lower mean FEV1 (48.1% predicted ± 23.7) than any other group. Kauppi and colleagues reported on health-related QOL (HRQOL) and found that when compared to subjects with asthma or COPD only, the overlap group had the poorest HRQOL score. Chung and colleagues reported a similar reduction on self-rated health in the overlap group as well. Micaville's and colleagues reported that 17.4% of subjects previously diagnosed with COPD belonged to the COPD-asthma overlap phenotype.22 The overlap phenotype in this study had more dyspnea, wheezing, exacerbations, worse respiratory-specific QOL, and reduced levels of physical activity. Soriano and colleagues identified higher relative risks for pneumonia and respiratory infections in individuals aged > 65 years with asthma and COPD.In a study of hospital discharge registry data covering the Finnish population, Anderson and colleagues reported that the average numbers of treatment periods during 2000 to 2009 were 2.1 in asthma, 3.4 in COPD, and 6.0 in ACOS.Panizza and colleagues reported that long-standing asthma was associated with chronic airflow obstruction and increased risk of mortality.Although patients with both asthma and COPD are at risk for exacerbations, those with ACOS are at risk for more frequent and severe exacerbations. In the PLATINO study population, subjects with ACOS had higher risk for exacerbations, hospitalization, and worse general health status when compared with those with COPD.Frequent exacerbations of COPD leads to a greater loss of lung function compared with those who have infrequent exacerbations.14 A lower FEV1 is associated with increased disease severity in both asthma and COPD, and this is of particular concern to those with ACOS. Of significance is the association of the ACOS phenotype with tobacco smoking. Although asthma is a risk factor for accelerated lung function decline, smoking status significantly accelerates the decline, and the loss may be even greater in those with asthma who smoke. This can ultimately predispose patients to the ACOS phenotype. Fortunately, quitting smoking can slow the decline in lung function as reported in the Lung Health Study. The annual decline in FEV1 in subjects who quit smoking at the beginning of the 11-year study was 30.2 mL /year for men and 21.5 mL /year for women. For those who continued smoking, the decline in FEV1 was 66.1 mL /year in men and 54.2 mL /year in women. For those with ACOS, treating tobacco use and dependence should be regarded as a primary and specific intervention.

DIAGNOSIS

Spirometry is required for the appropriate diagnosis of obstructive lung disease and should be performed at least annually for assessment of control and disease progression.5,31,32 Postbronchodilator spirometry is necessary to determine whether obstruction (ie, FEV1/FVC < 0.7), if present, is reversible.32 In asthma, airway obstruction following bronchodilator administration is typically fully reversible.5 In COPD, patients will remain obstructed following postbronchodilator administration regardless of the FEV1 response.32 In ACOS, the postbronchodilator FEV1/FVC typically remains obstructed. A normal postbronchodilator FEV1/FVC is not compatible with the diagnosis of ACOS unless there is other evidence of chronic airflow limitation. Although spirometry confirms the presence of chronic airflow obstruction, it is of limited value in distinguishing between asthma with fixed airflow obstruction, COPD, and ACOS. At times, specialized investigations, such as carbon monoxide diffusion capacity on pulmonary function testing and chest imaging, may also be used to help distinguish between asthma and COPD.

TREATMENT

Although much has been published on the recognition and identification of ACOS, there is a paucity of information on the effectiveness of therapeutics for this population. Patients with ACOS are frequently excluded from clinical studies involving asthma and COPD, which limits the generalization of findings from these trials to these patients. Although a comprehensive review of the available treatments for obstructive airway disease is beyond the scope of this article, some management tenets will be discussed. In general, inhaled corticosteroids (ICS) are the cornerstone of the pharmacologic management of patients with persistent asthma, whereas inhaled bronchodilators (beta 2-agonists and anticholinergics) are the therapeutic mainstay for patients with COPD.31,32 In those with ACOS, the default position should be to start treatment with low or moderate dose ICS in recognition of the role of ICS in preventing morbidity and mortality in those with asthma.5 Depending on severity, a long-acting beta 2-agonist (LABA) could be added or continued if already prescribed for those with ACOS.5 Patients should not be treated with a LABA without ICS if there are features of asthma.5 Treatment of ACOS should also include advice about other therapeutic strategies such as smoking cessation, pulmonary rehabilitation, influenza and pneumococcal vaccinations, and treatment of other comorbid conditions.5 The treatment goals of ACOS are similar to those of asthma and COPD in that they are driven by controlling symptoms, optimizing health status and QOL, and preventing exacerbations. Although there are currently no disease-modifying medications that can alter the progression of

airway obstruction in either asthma or COPD, smoking cessation is an essential component of the successful management of all obstructive airway disorders, because it is a modifiable risk factor. The initial management of asthma and COPD can be carried out at the primary care level. All current guidelines for asthma, COPD, and ACOS providerecommendations for specialty referral for further diagnostic and therapeutic consideations.5,31,32 As ACOS is associated with more severe disease and greater health careutilization, specialty referral for this subgroup should be considered.

CONCLUSION

Although there is no generally agreed term or defining features for ACOS, it is commonly recognized that a proportion of older patients who present with symptoms of chronic airway obstruction have features of both asthma and COPD. It is broadly recognized that distinguishing asthma from COPD can be problematic, particularly in smokers and the elderly. In addition, as these patients have frequent exacerbations, a poor QOL, a more rapid decline in lung function, and high mortality, identification of this subgroup is important. The lack of clinical trials to help guide therapeutic interventions in this syndrome is problematic as the extrapolation of data from asthma and/or COPD trials may not be applicable. Further studies in therapeutics for those with ACOS are warranted. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy

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