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Editorial

Why understanding the asthma chronic obstructive pulmonary disease overlap syndrome (ACOS) is important to the clinician

Many common chronic diseases are clinically very heterogeneous with novel and genetically complex mechanisms that significantly interact with environmental forces. The chronic airway syndromes of asthma and chronic obstructive pulmonary disease (COPD) are excellent examples of such diseases where the environment, genetics and epigenetics contribute to a wide spectrum of phenotypes[1-4]. Asthma and COPD are both airway obstructive diseases and the two most common respiratory diseases worldwide with millions of patients suffering from these syndromes[1]. Because these both are so common, probability would suggest that there would be patients that could have both diseases or at least elements of both syndromes. In 2004, Guerra noted that it was common in clinical practice to see patients with asthma that also showed COPD-like phenotypes and vice versa[5]. The overlap of asthma and COPD in adults was also suggested by the observation than adult patients with active asthma were 12 times more likely to acquire COPD over time than patients without active asthma[5]. Gibson and Simpson noted in 2009 that epidemiological studies have shown as many as half of the older patients with obstructive airway disease have overlapping diagnoses of both asthma and COPD[6]. They named this the "overlap syndrome".

In a cross-sectional study of patients with overlap of asthma and COPD compared to COPD alone, these patients were found to be younger, have lower lifetime smoking, to be more likely African-American and to have worse disease-related quality of life[7]. The asthma-COPD overlap syndrome is common and has been reported worldwide[8-10]. It was first abbreviated as "ACOS" in 2013[11]. ACOS has been recognized as a phenotype of both asthma and COPD[12]. Recently, international efforts for improving the management of both asthma and COPD have incorporated guidelines into their recommendations that recognize and offer guidelines for the treatment of ACOS[13,14]. A consensus document and review on ACOS has also been published[15]. It has been pointed out that ACOS patients demonstrate significant heterogeneity[6,16,17]. Similar to asthma and COPD, no single phenotype or endotype defines all ACOS patients[17].

So why is knowledge about ACOS important to the practicing clinician? The prevalence of the ACOS from a variety of studies of patients with obstructive airway disease examining either asthma or COPD cohorts has been found to be approximately 20 per cent[6]. A recent study used the GINA/GOLD (Global Initiative for Asthma/Global Initiative for Obstructive Lung Disease) joint project definition of ACOS which included age >40 years, post bronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) <0.7 and history of significant cigarette smoke exposure[18]. Among these patients with COPD major criteria used to classify them as ACOS were *(i)* a previous history of asthma, *(ii)* bronchodilator response to albuterol >15 per cent and 400 ml in FEV_1. Minor criteria included *(i)* IgE levels >100 IU, *(ii)* history of atopy, *(iii)* blood eosinophils >5 per cent, and *(iv)* two separated bronchodilator responses to albuterol with FEV_1 >12 per cent and 200 ml[18]. At least one major or two minor criteria were required for the diagnosis of ACOS and 15 per cent of the cohort of 831 patients with COPD met this ACOS definition[18].

In addition to the high prevalence of ACOS, significant health consequences exist for ACOS patients. A recent systematic review and meta-analysis of 19 ACOS studies concluded that the overall

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prevalence among COPD cohorts was 27 per cent[19]. ACOS patients have more frequent exacerbations and hospitalization, worse health-related quality of life, higher healthcare costs and were younger with higher BMI than other COPD patients[19]. In a large 17,088 COPD patients study from Taiwan, ACOS patients had almost twice as many acute respiratory events (pneumonia, acute exacerbation, acute respiratory failure and cardiopulmonary arrest) than did the rest of the COPD cohort[20]. The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) is a multicenter population study of 5,044 patients, 40 yr or older with 12 per cent found to have COPD, 1.7 per cent asthma and 1.8 per cent ACOS. The ACOS subjects had more respiratory symptoms, had worse lung function, used more respiratory medications, had more exacerbations and hospitalizations and had a worse perception of general health status than the COPD or asthma patients[21]. Rhee *et al*[22] found in a large study of 185,147 COPD patients that those with ACOS had more emergency department visits, hospital admissions and intensive care unit visits than those COPD patients without an asthma component. Medical utilization and costs were significantly higher both for outpatient and inpatient care for the ACOS patients compared to those with COPD or asthma. A retrospective cohort analysis of administrative data of commercial health plans in the United States evaluated patients 6 years and older with asthma and without COPD and those with ACOS[23]. Among matched patients, the average age was 61.7 ± 16 yr for ACOS and 38.4 ± 20.1 yr for asthma patients without COPD. All-cause health care costs were twice as high for patients with ACOS. Asthma related costs were about twice as high for ACOS patients compared to asthma patients and represented 29 per cent of total healthcare costs[23]. In contrast, a study of older adults (>55 yr) with progressive obstructive airway disease found that COPD patients had a poor prognosis compared to asthma or ACOS patients[24]. This Australian study had groups of similar age, gender, body mass index and atopic status. They reported that the BODE (Body-mass index, airflow Obstruction, Dyspnoea, and Exercise) index, quality of life scores and hospitalization within the last 12 months along with the diagnosis of COPD versus asthma or ACOS predicted a significantly higher 4-year all-cause mortality. A retrospective single center Japanese trial of elderly adults found that the most frequent cause of death in patients with asthma and ACOS was not directly related to their airway disease but was malignant diseases[25]. In general, a high and increased disease burden is seen in patients diagnosed as ACOS.

In addition to the high incidence of ACOS and its increased disease burden, a third reason for the clinician to be aware of and to understand ACOS is the limited data that support its treatment. Most drugs approved by regulatory agencies have a COPD, an asthma or both COPD and asthma indications. Most clinical trials focusing on these approvals have excluded ACOS patients. GINA/GOLD guidelines[13,14] for the treatment of ACOS are vague and lack specificity. Expert opinion has resulted in treatment guidelines but with little evidence to support specific treatments[11,26]. Because data supporting the concept of ACOS as a heterogeneous inflammatory disorder of the airways are strong, there appears to be an increased response to inhaled corticosteroids[6]. Unlike in asthma, the uses of long-acting beta-2 agonists have not been shown to date to have a detrimental effect in ACOS. New biologicals approved already or soon to be approved for asthma are likely to have a potential role in selected endotypes of ACOS with appropriate biomarkers. Both anti-IgE and anti-eosinophilic therapies against airway inflammation may work in some ACOS patients and be predicted because some ACOS patients show the appropriate biomarkers and respond to high dose inhaled corticosteroids. Although not formally studied, these ACOS patients may be candidates for the use of anti-IgE and new anti-cytokine antibody therapies[16].

There are some efforts to study and expand the limited information on ACOS treatment options. A review of the long-acting muscarinic receptor antagonist tiotropium bromide recently has advocated its use in COPD, asthma and ACOS patients but without specific trials in ACOS patients[27]. A Japanese study with either COPD, asthma or ACOS patients found that those with COPD had significantly lower antioxidant levels than matched normals but those with asthma and ACOS did not have lower levels[28]. Findings like this can generate trials that are based on phenotypes and biomarkers for each of these syndromes and will result in future specific treatment recommendations for ACOS patients. Finally, a recent trial of a new albuterol dry powder using the Easyhaler Delivery System demonstrated that airway reversibility was seen in asthmatics, COPD and ACOS patients[29]. More formal pharmacological studies that show efficacy in treatments in defined phenotypes of ACOS patients are needed particularly if genetic biomarkers can be identified to guide therapeutic choice and give more

precision to the treatment selection for these patients. Because of the wide range of phenotypes that make up asthma, COPD and ACOS, biomarkers and endotyping will be needed to define the best medication approaches and reach the goal of precision medicine. Currently, the clinician is forced to use trial and error to find the best treatment approaches for ACOS patients.

In summary, the busy clinician treating asthma patients needs to be aware of ACOS because of its frequency and prevalence, its significant health consequences and expense and the limited specific data on treatment. Further knowledge about the intermediate pathophenotypes or endotypes and the genetic or biomarkers to define them for the clinician coupled with future rigorous pharmacological clinical trials that include ACOS patients are needed to insure the best and most cost-efficient treatments in the future. Epidemiological studies to define potential environmental alterations other than avoiding cigarettes are needed to better understand if early environmental exposures alter the epigenetics that increase the risk of ACOS. ACOS is a syndrome made up of many different phenotypes just as are asthma and COPD. The busy clinician needs to be aware of the evolving understanding of obstructive airway diseases and how these various phenotypes including ACOS affect individual patient treatments.

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