Does the asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) exist? A narrative review from epidemiology and practice

David L. Hahn

Intracell Research Group, Town of Wake Forest, NC, United States

Received 21 May 2022; Accepted 21 August 2022
Available online 1 November 2022

Abstract
Asthma and chronic obstructive pulmonary disease (COPD) have traditionally been approached as separate entities that must be researched and treated separately. There is growing recognition, however, that a substantial proportion of patients with obstructive lung disease have characteristics of both asthma and COPD (termed the asthma-COPD overlap syndrome (ACOS)). Lung disease experts have difficulty defining ACOS, and many still resist accepting the possibility that asthma and COPD may be linked. It is likely that practicing clinicians may be equally confused about how to identify and treat ACOS. This narrative review aims to clarify concepts of ACOS definition, argues that the best way to understand ACOS is to view the chronic lung disease process longitudinally rather than cross-sectionally, and presents evidence that ACOS can be the end result of the natural history of severe asthma. The review also points out the serious gaps in knowledge regarding therapy for ACOS and presents emerging data supporting the intracellular respiratory pathogen Chlamydia pneumoniae as a possible common etiologic agent in severe asthma and ACOS.

© 2022 Codon Publications. Published by Codon Publications.

KEYWORDS
Asthma; Asthma-COPD overlap syndrome (ACOS); Chlamydia pneumoniae; Chronic obstructive pulmonary disease (COPD)

Introduction
Splitting vs lumping

Most lung disease experts have traditionally adopted a “splitting” approach to the diagnosis, treatment, and research of asthma and chronic obstructive pulmonary disease (COPD). Asthma is conventionally defined as an episodic symptomatic condition (wheezing, shortness of breath, cough, chest pain, etc.) triggered by a variety of stimuli (inhaled allergens, cold air, exercise, viral infections, etc.) whose cardinal physiologic features are bronchial hyperresponsiveness and completely reversible airway obstruction. COPD is characterized as persistent respiratory symptoms (dyspnea, cough, sputum production, etc.) plus irreversible airway obstruction defined by postbronchodilator FEV1/FVC ratio <70%. The “splitting” view—that asthma and COPD are seen as distinct entities generated by different mechanisms—has become known as the “British hypothesis.” An alternate view to the splitting...
approach is that “pure” asthma and “pure” COPD represent clearly defined entities only at either extreme of a chronic lung disease spectrum that has been termed “chronic non-specific lung disease” (CNSLD). This “lumping” approach was first articulated by Orie and has become known as the “Dutch hypothesis.” The Dutch hypothesis posits that all obstructive lung diseases are manifestations of the same basic underlying disease process involving the eosinophil. That all obstructive lung diseases have the same underlying mechanism has proven to be an oversimplification. Airway eosinophilia was once considered a cardinal physiologic feature of asthma, but this paradigm is now recognized as an incomplete picture. Sputum inflammatory patterns in asthma are heterogeneous and may include, in addition to elevated eosinophils alone, elevated neutrophils alone, both elevated eosinophils and neutrophils, and even normal levels of both eosinophils and neutrophils. Likewise, COPD is a heterogeneous condition, with multiple underlying etiologies, many of which have been systematically ignored in favor of focus almost exclusively on smoking-associated COPD. For example, it has been written that COPD is the “only disease characterized by a single risk factor” (smoking). However, this belief is not tenable, as population-based epidemiological studies consistently report that 23–40% of patients within COPD cohorts are never-smokers.

The splitting versus lumping debate rages on. In 2015, a joint guideline from the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) emphasized the existence and importance of the asthma-COPD overlap syndrome (ACOS) by acknowledging that “...people with overlapping asthma and COPD form a sizeable and clinically important proportion of those with airflow limitation....”. In 2021, however, the updated GOLD guideline (page 81) stated “We no longer refer to asthma & COPD overlap (ACO), instead we emphasize that asthma and COPD are different disorders, although they may share some common traits and clinical features (e.g., eosinophilia, some degree of reversibility).” These competing lumping/splitting statements from the same expert bodies are certain to sow confusion among lung specialists and other practicing clinicians alike regarding optimum diagnosis and treatment for chronic lung diseases. The aim of this narrative review is to paint a picture based on existing (but often neglected) epidemiological and clinical evidence regarding the topic of ACOS.

What does epidemiology tell us about ACOS?

What can epidemiology tell us about the relative merits of the splitting vs lumping concepts? A simple calculation can help distinguish whether “splitting” or “lumping” applies to ACOS. If asthma and COPD are indeed independent, then the prevalence of ACOS should approximate the product of asthma prevalence and COPD prevalence. For example, if asthma prevalence in an adult cohort is 7% and COPD prevalence is 11%, then by random chance the appearance of asthma and COPD in the same person should approximate 0.07 x 0.11 = 0.0077 or roughly 0.8%.

ACOS prevalence was actually more than five times higher (4.3%) than what would be expected by random association in this actual epidemiologic study. A 2019 systematic review and meta-analysis of global population prevalence reported similar results: 6.2% for asthma only, 4.9% for COPD only, and 2% for ACOS. Random association would have yielded an ACOS prevalence of 0.3% (0.062 x 0.049 = 0.003, or 0.3%). Instead, the actual prevalence of ACOS was 2% or 6.7 times (0.02/0.003 = 6.67) what would be expected by random association alone. This apparent nonrandomness of the link between asthma and COPD is completely consistent with the results of prospective epidemiological studies conducted over the past half century. These prospective studies show that previous asthma is a very strong risk factor for development of subsequent COPD, independent of the smoking status. Table 1 presents the results of the five identified prospective, population-based studies of various populations (e.g., clinic asthma patients, random population samples of healthy people, birth cohorts) followed for variable periods of time (range 9-53 years). Prior to the results of these prospective studies, the Tucson Epidemiologic Study of Obstructive Airways Diseases, TESOAD, published cross-sectional observations documenting three separate categories of obstructive airways: (1) asthma, (2) asthma with chronic airway obstruction (abbreviated as AS-CAO in TESOAD, an earlier term for what is now called ACOS), and (3) smoking-associated COPD (comparable to COPD of the emphysematous type prevalent in smokers). TESOAD was ultimately a large, population-based 20-year prospective study of non-Hispanic households in Tucson, Arizona, begun in the 1970s. Subsequent results from this and other prospective cohort studies show strong relationships between asthma and the subsequent development of COPD (Table 1). In addition to asthma as a predictor of subsequent COPD, some studies also reported that early life infections (bronchitis and pneumonia) were also predictors of subsequent COPD. This latter observation may have relevance to the discussion later in this review concerning potential common etiology for asthma and ACOS. The epidemiological evidence appears to favor lumping over splitting in the sense that asthma and COPD appear as different manifestations of the same natural history of obstructive airway disease over time, at least in a subset of the population. The remainder of this review assumes that ACOS exists and that at least one ACOS syndrome is part of the natural history of asthma.

Clinically useful ACOS definition

A nominal definition of ACOS is simply a patient who has incompletely reversible airflow limitation and who also exhibits features of asthma. The prevalence of ACOS by this definition is around 20% in patients with obstructive airways disease, irrespective of the study design (i.e., the prevalence of ACOS is around 20% in epidemiologic studies or studies of selected populations: severe asthma, adult asthma, or COPD). The features of asthma do not need to be fully present concurrently, that is to say, the asthma may have been present historically and the cardinal feature of reversibility (e.g., ≥12% and ≥200 mL change in FEV1 spontaneously or following bronchodilator) may presently be blunted or absent, due to airway damage from lung remodelling. It has been recognized that ACOS may
Table 1 Prospective studies of asthma and the risk for subsequent COPD

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Population studied</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| Vonk, et al. \(^1\)  
Asthma patient cohort | Asthma clinic patients seen at a single site in the Netherlands (Beatrixoord Hospital) between 1962 and 1970 (median age 23) were reexamined between 1991 and 1998 (median age 49.5) (median follow-up 26 years) | At follow-up, 41% did not have airway obstruction, 43% had reversible airway obstruction (RAO), 16% had irreversible airway obstruction (IAO), and 23% had abnormal DLCO. Patients with RAO had asthma-like symptoms (wheezing, asthma attacks, bronchial hyperresponsiveness), whereas patients with IAO had COPD-like symptoms (cough, phlegm, dyspnea). |
| Silva et al. \(^1\)  
Population-based cohort | Random, stratified cluster sample of white, non-Mexican-American households in Tucson, AZ, followed for 20 years beginning 1972-1973 | In the cohort of 3,099 adults, subjects with active asthma (n=192) had significantly higher hazard ratios for acquiring COPD than inactive asthma (n=150) or nonasthmatic subjects (n=2751). (COPD was supported by DLCO (diffusing capacity of the lungs for carbon monoxide) data.) Compared with nonasthmatics, active asthmatics had a 10x higher risk for chronic bronchitis (95% CI 4.94–20.25), 17x higher risk for emphysema (95% CI 8.31–34.83), and 12.5x higher risk of fulfilling COPD criteria (95% CI 6.84–22.84). |
| Tai et al. \(^1\)  
Population-based cohort | A 1957 birth cohort was followed from the age of 7 to age 50 | A total of 346 (76%) subjects were evaluated at age 50. Compared with children without symptoms of wheeze to the age of 7 (nonasthmatics), children with severe asthma had a 32x higher risk of developing COPD (95% CI 3.4–269). In this cohort, 43% of the COPD group had never smoked. |
| De Marco et al. \(^1\)  
Population-based cohort supplemented with additional asthma patients | International multicenter study performed on random samples of young adults (ages 20-44 years) followed for 9 years from 1991-1993 to 1999-2002 and supplemented by additional subjects with recent asthma-like symptoms. | Asthma alone (n=941), COPD alone (n=166), ACOS (n=216), none of these (n=5659). Subjects with ACOS shared risk factors and clinical characteristics with subjects with asthma alone but had an earlier age of asthma onset. ACOS seemed to represent a form of severe asthma, characterized by more frequent hospitalizations, and to be the results of early-onset asthma that had progressed to fixed airflow obstruction. |
| Bui et al. \(^1\)  
Population-based cohort study with multiple assessments of lung function. | A 1961 birth cohort of 8583 Tasmanian children were followed until age 53 years. A total of 2438 had at least two waves of lung function data at ages 7 and 53. | Six trajectories were identified: (1) early below average, accelerated decline, (2) persistently low, (3) early low, accelerated growth, normal decline, (4) persistently high, (5) below average, and (6) average. The trajectories that increased risk of COPD at age 53 were (1), 46% COPD; (2), 13%; and (5), 8%. By far, trajectory (1) had the highest risk for COPD (46%) and also the highest risks for ever asthma at age 7 (37%), active asthma at age 53 (58%), and the overlap syndrome at age 53 (26%). Early-life predictors of the three trajectories included childhood asthma, bronchitis, pneumonia, allergic rhinitis, eczema, parental asthma, and maternal smoking. |

DLCO: diffusing capacity of the lungs for carbon monoxide.

logically consist of three distinct syndromes: (1) severe asthma with incomplete airflow reversibility, (2) childhood asthma and coincidental adult smoking, and (3) eosinophilic COPD.\(^2\) These three syndromes represent, respectively, (1) the longitudinal natural history of severe asthma, (2) coincidental asthma and smoking-associated COPD (often of the emphysematous type), and (3) a previously nonasthmatic COPD patient who somehow or the other acquires features of asthma via the eosinophil.\(^3\)

The following clinical section will focus on the first syndrome (the natural history of severe asthma) because severe asthma appears to account for the majority of ACOS\(^4\) and because prospective asthma management is a major focus for clinicians who follow their patients longitudinally. Barrecheguren et al.\(^5\) performed a multicenter, observational, cross-sectional study on 3,125 COPD patients (smokers or ex-smokers of at least 10 pack-years) who were recruited in primary care and specialty clinics. ACOS was defined in two ways: (1) ACOS 1 patients fulfilled Spanish consensus ACOS diagnostic criteria consisting of two major or one major and two minor criteria (major criteria: very positive bronchodilator test, sputum eosinophilia, or previous diagnosis of asthma before age 40; minor criteria: elevated IgE, history of atopy, or positive bronchodilator test) and (2) ACOS 2, the remaining patients with ACOS, diagnosed only on the basis of a history of asthma before
age 40 without fulfilling the Spanish consensus criteria. Of the total COPD cohort, ACOS 1 prevalence was 5.1% and ACOS 2 prevalence was 10.8% (68% of all ACOS). Because the enrolled cohort excluded nonsmokers, it is possible that the proportion of ACOS patients with prior asthma in the general population might be even greater than the two-thirds documented in this study.

Natural history of severe asthma in the clinical setting

As reviewed above, there is now consistent evidence from prospective epidemiological studies that a significant proportion of severe asthma will develop irreversible airflow limitation and will eventually be classifiable as COPD (or even chronic bronchitis). Overlapping diagnoses in patients who do not meet criteria for textbook diseases are common occurrences in medical practice and represent treatment challenges. ACOS is a classic example. Indeed, longitudinal clinical observations of the same patient have documented new-onset severe refractory asthma at the onset of the natural history and “burnt out” COPD at the time of the patient’s demise 17 years later. Could specific treatment directed against severe refractory asthma and/or ACOS have nudged this natural history toward a more benign outcome? This question is unanswerable at the present time because evidence does not exist.

ACOS therapy

Asthma and COPD efficacy trials upon which the respective treatment guidelines are based have traditionally excluded ACOS. Asthma trials systematically exclude smokers and those with pulmonary function evidence for COPD; conversely, COPD trials systematically exclude nonsmokers and those with a history of asthma and/or significant airway reversibility. Therefore, treatment of ACOS depends on extrapolation from asthma and COPD studies and is based on consensus and expert opinion rather than on evidence from randomized treatment trials. The 2022 Global Initiative for Asthma (GINA) guidelines (page 142) recommend that ACOS should be treated like asthma. However, in practice, the majority of patients with ACOS currently appear to be treated similarly to COPD. One large observational study of ACOS patients in the USA, France, Germany, Italy, Spain, and the UK found that the most commonly prescribed regimens for ACOS were inhaled corticosteroids/long-acting beta2 agonist (ICS/LABA) plus long-acting muscarinic antagonist (LAMA) (ACOS 30%, asthma 1.4%, and COPD 32%), ICS/LABA (19%, 41.5% and 17%, respectively), and LAMA (6%, 0.4%, and 19%, respectively). Many studies report that, despite treatment, ACOS patients suffer more symptoms, exacerbations, hospitalizations, worse lung function, and greater decline in FEV1 than either “pure” asthma or “pure” COPD patients. In addition to this impressive list of morbidities, patients with ACOS (and late-onset asthma) suffer increased mortality compared to asthma and COPD alone patients. A recent prospective population-based 24-year Finnish study also found that, in addition to increased overall mortality, ACOS was also associated with significantly increased coronary artery disease compared to asthma alone, COPD alone, ever-smokers without asthma or COPD, and never-smokers without asthma and COPD. The association of ACOS and coronary artery disease may also be relevant to the discussion of common etiologies for asthma and ACOS discussed later in this narrative review. Given the significantly worse prognostic course for ACOS compared to either asthma or COPD alone, there is a clear need for better treatment for ACOS patients, who should be included in rather than excluded from future efficacy and effectiveness treatment trials.

Macrolide antibiotics are now included as treatment options for both severe asthma and for smoking-associated COPD. Although none of the randomized trials upon which these macrolide recommendations are based include patients with ACOS, there are some data from clinical experience. A large clinical case series reported that a subset of ACOS patients responded dramatically to azithromycin, doxycycline, or a combination of these agents with some patients experiencing prolonged remissions after completing a year-long course of treatment. Of 79 severely uncontrolled ACOS patients in this clinical case series treated with long-term macrolides or tetracyclines, 51 (64.6%) became controlled at follow-up, and of these 51, 27 (52.9%) continued to take antibiotics while 24 (47.1%) had discontinued antibiotics earlier yet remained controlled. Remarkably, 14 (58%) of 24 remained in complete symptom remission off antibiotics. The results of this clinical case series underscore the relevance and the importance of the British Thoracic Society expert asthma guideline (discussing macrolide treatment for severe asthma) recommending that clinical response should guide continued macrolide therapy, with breaks in treatment being considered if/when the desirable clinical outcome is obtained. Collectively, these clinical data strongly support the need for further research into underlying mechanisms that include appropriate infection biomarkers, as treatment duration and success may depend on the mechanism.

Asthma and ACOS: a common etiology?

Underlying etiologies for asthma remain mysterious and the same can also be said for ACOS. Proven efficacy of macrolides for severe asthma may provide some clues. Macrolides, particularly azithromycin, are now included as a treatment option for both severe asthma and COPD without an understanding of the underlying mechanism of action (non-antimicrobial anti-inflammatory vs antimicrobial). That underlying infections may be causal is plausible. Worldwide increases in asthma prevalence noted in recent decades can only be explained by relatively powerful environmental causal factors, among which are unrecognized infectious disease pandemics. There is growing interest and research into the microbiome’s role in asthma. The microbiome consists of bacteria, fungi, and viruses that colonize body surfaces exposed or open to the outside environment, such as the skin, lung, oral cavity, and the gut. There are no current therapeutic applications of conventional microbiome research relevant to asthma management.

Less attention has been paid to the possibility that specific obligate intracellular microbes could be etiologically...
involved in severe asthma and its progression to ACOS.\textsuperscript{43} The obligate intracellular respiratory pathogen \textit{Chlamydia pneumoniae} has been associated with severe asthma and its progression to ACOS.\textsuperscript{44, 46} \textit{C. pneumoniae} is well known to be a common cause of a wide variety of acute respiratory illnesses and can also often infect the lung asymptomatically.\textsuperscript{43} \textit{C. pneumoniae} can chronically infect the lung in a persistent state that is biologically refractory to antibiotic killing, especially by conventional courses of antibiotics.\textsuperscript{43} \textit{C. pneumoniae} infection biomarkers are associated with asthma\textsuperscript{44} and with the development of irreversible airflow limitation in asthma.\textsuperscript{44, 47} A recent meta-analysis found that the population attributable risk (i.e., the proportion of disease attributable to the risk factor) for \textit{C. pneumoniae}-specific IgE in chronic asthma was 47% and was even higher in severe asthma (a risk factor for ACOS).\textsuperscript{45} Irreversible airflow limitation in asthma is associated with seroreactivity against chlamydial heat shock protein 60 (chsp60),\textsuperscript{47} and the association is quite specific, as there is no comparable association with seroreactivity against the closely related \textit{Chlamydia trachomatis} hsp60 molecule.\textsuperscript{46} Chlamydial heat shock protein 60 is responsible for the scarring sequelae of other chronic chlamydial diseases such as trachoma and tubal infertility. \textit{C. pneumoniae}-specific hsp60 is produced in large quantities during chronic persistent infection, and it is biologically plausible that this hsp60 production could be the pathogenetic mechanism linking severe asthma and ACOS. Recalling the association of ACOS and coronary artery disease alluded to earlier,\textsuperscript{38} it is worth noting that \textit{C. pneumoniae} biomarkers are also associated with atherosclerosis in epidemiologic studies, and chronic \textit{C. pneumoniae} infection, likely migrating from the lung via the bloodstream, is also commonly detected in coronary arteries.\textsuperscript{43} It is therefore plausible to suggest that one common underlying etiology that links asthma, ACOS, and coronary artery disease is chronic infection by this obligate intracellular respiratory pathogen.

At the present time, there are no treatments conclusively proven to halt the progression of asthma to ACOS, although clinical observations of asthma remission and/or dramatic improvement after azithromycin treatment of asthma suggest that halting the natural history progression of asthma to ACOS may be possible.\textsuperscript{48, 49} A review presented evidence supporting the suggestion that clinicians might consider prescribing a limited (-3 months) course of azithromycin for new-onset asthma, particularly when the asthma begins during or after an acute lower respiratory tract infection (C-level recommendation).\textsuperscript{49} Evidence for this suggestion included a clinical case series of 46 \textit{C. pneumoniae} seroreactive patients with moderate to severe asthma.\textsuperscript{50} Four patients with documented acute \textit{C. pneumoniae} infections developed new-onset asthma that disappeared after antichlamydial antibiotic treatment. Of the remaining 42 seroreactive asthma patients who were treated a mean of 6 years after development of chronic asthma, 21 (50%) had either complete remission (n=3) or lasting major clinical improvement (n=18) after antibiotic treatment. Clinical improvement in asthma after antibiotic treatment in the case series was significantly more likely in patients with early disease (P=0.01) and before the development of fixed obstruction (P=0.01), that is, before the development of ACOS. These clinical observations should be followed up by the performance of rigorous, inclusive randomized trials that so far have been unfundable due to the dogmatic beliefs engendered by the splitting approach to the study of asthma and COPD. The many evidence gaps surrounding prevention and treatment of ACOS call for concerted research efforts in this field of study.

Future perspective

Epidemiologic and clinical evidence supports the view that most ACOS is a consequence of severe asthma that develops a component of irreversible airflow limitation as a result of lung remodeling. ACOS appears to be frequent but may be under-recognized, and ACOS treatment is definitely underresearched. There is evidence to support the contention that unrecognized chronic intracellular lung infections by \textit{C. pneumoniae} could play a significant role in causing severe asthma and its progression to ACOS. Pending the results of further research and if conventional guideline treatments for asthma and/or COPD are ineffective in severe asthma and ACOS patients, clinicians might consider a long-term trial of azithromycin or doxycycline prior to referral for consideration for immunomodulatory therapies.\textsuperscript{46} Clinicians should also evaluate their COPD patients for characteristics of asthma in order to better classify them as ACOS or smoking-associated COPD. Clinicians should be aware that azithromycin has also shown demonstrated efficacy in smoking-associated COPD.\textsuperscript{3, 51} These are B- and C-level recommendations,\textsuperscript{46, 49} and further research including, rather than excluding, ACOS needs to be performed.

Conclusions

Prospective population-based epidemiologic evidence points to a significant amount of ACOS as being a consequence of lung remodeling in patients with severe asthma. ACOS patients suffer more morbidity and mortality than do patients with either “pure” asthma or “pure” COPD. ACOS patients have been systematically excluded from both asthma and COPD clinical treatment trials; therefore, it is unclear whether ACOS should be treated like asthma, like COPD, or warrants novel therapies such as against atypical infections. Clinical treatment trials that include ACOS patients are urgently required.

Conflicts of interest

Dr. Hahn is a member of the Scientific Advisory Board of the Intracell Research Group (IRG) (www.intracellresearchgroup.com). The position is not compensated. The mission of IRG is to disseminate evidence on associations of chronic infection in chronic diseases.

References

2. Sherrill D, Guerra S, Bobadilla A, Barbee R. The role of


36. Jalasto J, Kauppi P, Luukkonen R, et al. Self-Reported Physician Diagnosed Asthma with COPD is Associated with...


