

Asthma-COPD Overlap Syndrome: A Review of Current Knowledge and Future Directions

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Abstract

Asthma and chronic obstructive pulmonary disease are common diseases both characterised by airflow obstruction. Over recent decades the prevailing belief was that asthma and COPD were distinct diseases that can be easily distinguished and require different treatments. This stimulated basic scientific research aimed at obtaining a better understanding of both diseases, particularly COPD that had been neglected. The downside of this approach was that it resulted in the exclusion of patients from clinical trials that exhibited features of both diseases. However, it has been increasingly recognised that these patients are common in everyday clinical practice and that their exclusion from clinical trials meant that therapeutic decisions were not evidence based. The concept of the asthma COPD overlap syndrome is an attempt to develop diagnostic criteria for patients with features of both asthma and COPD. This is a necessary starting point from which to design studies to investigate the clinical features, aetiology, pathophysiology and prognosis of these patients, and ultimately determine treatment strategies. However, from the outset the concept of asthma COPD overlap syndrome has been controversial and has not gained universal acceptance.

In this review we will describe current definitions and concepts of the asthma COPD overlap syndrome and explore how our understanding of this syndrome may develop in the future.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are chronic pulmonary diseases with similar clinical features and both are characterised by varying degrees of airflow obstruction. However, their aetiologies, pathology, progression and treatment responses differ markedly and guidelines produced by expert bodies have stressed the differences between the 2 diseases and the importance of diagnostic clarity. The Global Initiative for Asthma (GINA) defines asthma as ‘a heterogenous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.’¹ The Global Initiative for Obstructive Lung Disease (GOLD) defines COPD as ‘COPD is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.’² These definitions are deliberately broad so as to be applicable in a wide range of countries and healthcare settings, including resource-poor environments where access to more sophisticated diagnostic tools may be limited. However, the disadvantage of such broad definitions is that patients may have clinical features that are included in the definitions of both asthma and COPD. For example some patients with a diagnosis of asthma may have ‘persistent airflow obstruction’ rather than ‘variable expiratory airflow limitation’ and patients with COPD can have symptoms that vary and variable airflow obstruction.³ Clinicians face

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considerable diagnostic and therapeutic confusion when managing patients who have features of both asthma and COPD. Patients also face confusion when given different diagnostic labels of asthma or COPD by different clinicians. Therefore, experts have attempted to reach consensus regarding the diagnostic labels and clinical features that can be used to describe patients with features of both asthma and COPD. However, this approach remains controversial and the topic of fierce debate.

Asthma COPD overlap syndrome (ACOS)

Various terms have been used to describe patients with features of both asthma and COPD including asthma with chronic bronchitis, combined asthma and COPD, mixed asthma and COPD, asthma with irreversible airflow obstruction, COPD with asthmatic features and COPD with a reversible component. It was recognised that there are patients with features that ‘overlap’ both asthma and COPD as far back as 1995 in the COPD guidelines of the American Thoracic Society.⁴ However over the next two decades both clinical and basic science research focused on defining the unique clinical, pathological and inflammatory features of asthma and COPD, resulting in the prevailing view that they are two clearly distinct diseases. This was reflected in the design of clinical trials in which patients with overlapping features of both diseases were excluded and only patients with ‘pure’ asthma or COPD were included. However it became increasingly clear that such an approach resulted in only a minority of patients with asthma and COPD fulfilling the inclusion criteria for clinical trials.⁵⁻⁶ A large number of patients were excluded because they had clinical features of, or risk factors for, both asthma and COPD. A review published in 2009 by Gibson et al exploring this issue coined the term the ‘overlap syndrome of asthma and COPD.’⁷ This triggered a host of studies and expert reviews over the following years and in 2015 GINA and GOLD published a joint document proposing the term asthma COPD overlap syndrome (ACOS).⁸ However there has not been universal acceptance of the term or even the need for another diagnostic label in addition to asthma and COPD.⁹⁻¹⁰ Therefore debate continues how best to describe the range of patients with obstructive airway disease, particularly those that do not fit classical descriptions of asthma and COPD.

Definitions of ACOS

The GINA/GOLD document has described ACOS as ‘characterised by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD’ (8). The document emphasized that this is not a definition of a new disease but a ‘description for clinical use’, and that a specific definition cannot be developed until more is known about underlying mechanisms. It listed features that are individually characteristic of asthma and COPD and recommended that if a patient has features of both, this is suggestive of ACOS. So for example early age of onset, variable airflow obstruction, normal lung function between symptoms and symptoms that vary seasonally would favour asthma, whereas later age of onset, persistent airflow limitation and exposure to a risk factor such as tobacco smoke would favour COPD. While this is an easy to use pragmatic approach to the problem it has several drawbacks. Firstly the document did not define how many shared clinical features of asthma and COPD are required to diagnose ACOS, therefore this remains a subjective assessment on the part of the clinician. Secondly it is clear that patients with very different phenotypic (and probably mechanistic) features can be included under an umbrella of ACOS. For example a patient with lifelong asthma who has never smoked and has persistent symptoms and airflow obstruction would have features of both asthma and COPD. Equally a patient with a personal and family history of asthma and a smoking history with some variability in symptoms and airflow obstruction would tick different boxes but also fulfil criteria for ACOS.

Other expert societies have produced their own definitions of ACOS. In 2016 a global expert panel of specialists and generalists from North America, Western Europe and Asia proposed a set of diagnostic criteria consisting of 3 major criteria (1: Persistent airflow limitation (post-bronchodilator FEV₁/FVC <0.70 or < lower limit of normal) in individuals 40 years of age or older; 2: ≥10 pack years of smoking or equivalent and 3: A documented history of asthma before 40 years of age or bronchodilator response ≥400 mL) and three minor criteria (1: Documented history of atopy or allergic rhinitis; 2: A bronchodilator response of ≥200 mL and 12% or greater on 2 different occasions and 3: A peripheral eosinophil count of 300/μL or greater).¹¹ Patients who meet all 3 major

criteria and at least 1 minor criterion should be considered as having ACOS. Other national societies have also produced diagnostic criteria.¹² Therefore it is clear that although there is broad agreement on what constitute the key clinical features of ACOS, as yet there is still no universally agreed definition. In the absence of such a definition epidemiological, mechanistic and therapeutic studies will continue to be difficult and plagued by the use of different definitions.

Epidemiology

As there is no agreed definition of AOCs, its prevalence in studies will depend on which definition is used. Most epidemiological studies have simply determined the proportion of patients with a physician diagnosis of both asthma and COPD and used this as a measure of the prevalence of ACOS. A review of general population studies from a number of different countries estimated the population prevalence of ACOS to range from 1.6% to 4.5%.¹³ In the USA the prevalence of patients with a physician diagnosis of both asthma and COPD has been reported as 2.7%.¹⁴ The prevalence of ACOS defined in this way appears to increase with age. In a survey of a random sample of the Italian population the prevalence of patients with a dual diagnosis was 1.6% in the 20-44-year age group, 2.1% in the 45-64-year age group and 4.5% in the 65-84-year age group.¹⁵ Among people aged > 40 years in five Latin American cities the prevalence of patients with a dual diagnosis was 1.7%.¹⁶

Other studies have investigated the prevalence of dual diagnoses in patients with an existing diagnosis of asthma or COPD. A systematic review of five studies reported that the mean prevalence of ACOS defined in this way among patients with asthma or COPD was 20%.¹⁰ In a survey from the USA of 3,486 patients, 1,585 (45.4%) had asthma alone, 1,294 (37.1%) had COPD alone, and 607 (17.4%) had ACOS.¹⁷ In a literature review the prevalence of ACOS among patients with COPD ranged from 12.1% to 55.2%, and the prevalence of ACOS among asthma patients ranged from 13.3% to 61.0%.¹³ A meta-analysis of 27 studies identified COPD patients with a physician diagnosis of asthma or evidence of reversible airflow obstruction ($\geq 12\%$ and at least 200ml change in FEV₁ from baseline, or $\geq 20\%$ change in PEF or airway hyper-responsiveness).¹⁸ Using these criteria 27% of

COPD patients were diagnosed with ACOS. Compared with patients with COPD only, ACOS subjects were younger, had a shorter smoking history and a higher BMI, but there were no differences between the groups in spirometry and the 6-minute walking distance. Among 1,488,613 adults in the USA with a diagnostic code of either COPD or asthma, 21.3% had a diagnosis of both asthma and COPD.¹⁹ Considering that these studies were carried out in diverse populations and used different definitions of asthma, COPD and ACOS, it is not surprising that the results are so varied. More definitive epidemiological data on the prevalence of ACOS will be impossible to obtain before a stringent, universally-agreed definition is available.

Burden of disease

Although the prevalence of ACOS continues to be debated, epidemiological studies have consistently demonstrated that patients with a dual diagnosis of asthma and COPD have worse outcomes compared with those with a single diagnosis. Studies from a number of different countries have reported that ACOS is associated with greater symptoms,^{15,20-21} worse lung function,²² more frequent exacerbations,²⁰⁻²² more hospitalisations,^{15,17,19,23} greater prevalence of anxiety and depression,^{17,19} impaired activity^{15,17} and more comorbidities.¹⁹⁻²⁰ Some of these findings may relate to the increased diagnosis of ACOS with increasing age. However, it is clear that the burden of disease associated with a dual diagnosis of asthma and COPD is high and needs to be addressed.

Therapeutic Implications

Ascribing a diagnosis of asthma, COPD or ACOS to individual patients is not just of semantic or academic interest, but has a direct impact on treatment decisions. Clinical trials in asthma and COPD have utilised strict inclusion and exclusion criteria to ensure that a relatively 'pure' population is recruited. Patients with clinical features of both asthma and COPD have been excluded from clinical trials, resulting in a patient population that is not representative of the wider population seen in routine clinical practice. Halpin et al reported that the median eligibility of 36 893 patients with COPD for participation in 31 randomised controlled trials was only 23%.²⁴ Other studies have reported

eligibility rates ranging from 17% to 42%.²⁵ The commonest reason for exclusion was a history of asthma, allergic conditions or atopy. In asthma even lower rates of suitability have been recorded with a lack of reversibility and a smoking history being common reasons for exclusion.⁵⁻⁶ These data suggest that the majority of 'real life' patients have features of, or risk factors for, both asthma and COPD, but are excluded from clinical trials. The systematic exclusion of these patients from clinical trials means that the effects of treatments in this population are unknown. In view of the high burden of symptoms, exacerbations and hospitalisations among these patients clinical trials are urgently needed that include these patients to determine the optimum treatment strategies.

Until relatively recently there appeared to be increasing convergence in treatments for asthma and COPD, with clinical trials reporting that inhaled corticosteroid (ICS)/long-acting β_2 -agonists (LABA) are beneficial in COPD,²⁶ and long-acting muscarinic antagonists (LAMA) improve symptoms and lung function in asthma.²⁷ Therefore such a convergence would suggest a diminished importance for distinguishing asthma, COPD and ACOS. However, a number of recent clinical findings have changed treatment recommendations in asthma and COPD, particularly regarding the role of ICS in COPD. There is evidence that ICS are inappropriately overprescribed in COPD, and current treatment guidelines are not being adhered to.²⁸ This has become of growing concern as evidence has emerged of an increased risk of pneumonia associated with ICS use in COPD.²⁹ At the same time as evidence has emerged of potential adverse effects of ICS in COPD, studies have reported that ICS withdrawal is safe in COPD,³⁰ and that LABA/LAMA are equivalent to ICS/LABA in regards to exacerbation reduction.³¹ Together these emerging data have led to efforts to reduce inappropriate use of ICS in COPD.³² However, this could lead to underuse or withdrawal of ICS in patients with ACOS, with potential detrimental effects. For now this remains a hypothetical concern but it highlights the importance of including patients with features of both asthma and COPD in clinical trials and the danger in extrapolating the results of trials that recruit a highly select group of patients to the wider population seen in clinical practice.

Future directions

Although the concept of ACOS has helped to focus research attention on a previously neglected group of patients, concerns remain about adding another diagnostic label to an increasingly confusing landscape of airway diseases, phenotypes and endotypes.⁹ An alternative approach that has been proposed is to treat patients based on a personalised medicine approach and abandon disease labels.³³⁻³⁴ Under such an approach patients' history and risk factors would be assessed through a comprehensive history and examination and the presence of airflow obstruction confirmed with spirometry. The focus would then be on identifying 'treatable traits' and comorbidities, rather than basing treatment on a diagnostic label.³⁵ These traits may be pulmonary (e.g. eosinophilic airway inflammation, airflow obstruction, bacterial infection, chronic bronchitis), extra-pulmonary (e.g. obesity, gastro-oesophageal reflux disease, upper airway disease) or behavioural/lifestyle factors (e.g. smoking, allergen exposure, air pollution).³⁵ There is evidence that current diagnostic labels are inadequate in describing and distinguishing inflammatory patterns in patients with chronic airway disease³⁶ and therefore the alternative approach has the advantages of recognising the clinical and biological complexity of chronic airway disease. It is hoped that this will then have the potential to offer an evidence-based and cost-effective approach to treatment.

However, a personalised medicine approach to airway disease also has potential disadvantages in that it is likely to require increased and more sophisticated diagnostic testing leading to increased costs. Such an approach may not be achievable in resource-poor settings or in primary care even in high-income countries where many such patients are currently managed. Such an approach also requires a better understanding of the biology of airway diseases to select the best biomarkers that can correctly phenotype diseases and predict treatment response. The recent failure of a biomarker-directed treatment to reduce exacerbations in asthma highlights the need for further research into understanding the biology of chronic airway diseases.³⁷

Conclusions

Many patients with chronic airflow limitation seen in routine clinical practice do not fit easily into

neat definitions of asthma and COPD. As these patients were excluded from clinical trials the optimum treatment for these patients is not known. Characterisation of these patients as having asthma-COPD overlap syndrome has focussed attention on a previously neglected group of patients, but widespread acceptance of the term ACOS has been hampered by the inability to agree on a standardised definition. Debate continues as to whether a personalised medicine approach is superior to the use of diagnostic labels such as asthma, COPD and ACOS. It may be that currently ACOS is a useful concept but as our understanding of the biology and mechanisms of chronic airway diseases increases and robust biomarkers are discovered, then it may become either much better defined, or possibly, redundant.

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