



The asthma–COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases?

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Most research of treatments for airways diseases has been restricted to patients who meet standard definitions of either chronic obstructive pulmonary disease (COPD) or asthma, yet to distinguish COPD from asthma in adult patients who have clinical features of both can be challenging. Treatment guidelines provide scant advice on how such patients should be managed. With increasing recognition that asthma and COPD are heterogeneous diseases, attention has been directed to the needs of a group of patients with what is now termed asthma–COPD overlap syndrome (ACOS), particularly in view of the high morbidity in this population. This Review considers the epidemiology, mechanisms of disease, current attempts to define and diagnose ACOS, existing and potential treatment options, and new approaches to the phenotyping and taxonomy of airway diseases.

Introduction

In respiratory medicine, the term overlap syndrome has been applied both to the association between obstructive sleep apnoea and chronic obstructive pulmonary disease (COPD)¹ and to patients with features of both asthma and COPD (asthma–COPD overlap syndrome [ACOS]).^{2,3} In 2014, this syndrome was the topic of a joint publication by the Global Initiative for Asthma (GINA)⁴ and the Global initiative for Obstructive Lung Disease (GOLD),^{3,5} and is beginning to appear in national clinical practice guidelines.^{6–9} These developments have been prompted by the following considerations: the recognition that ACOS represents a form of airways disease that is associated with a disproportionate number of exacerbations,^{10,11} hospital admissions, and use of health-care resources;¹² the fact that patients with ACOS are generally excluded from most trials of new treatments for asthma or COPD; the realisation that asthma and COPD themselves are heterogeneous disorders and that new insights are emerging into the gene–environment interactions involved in different forms of airways diseases and resultant phenotypes; and the emergence of new treatments for asthma and COPD that target specific biological mechanisms of disease (ie, endotypes).¹³ However, some commentators question whether the description of ACOS as a clinical entity is valid or a useful concept. To address these concerns, this Review discusses the epidemiology, mechanisms of disease, current attempts to define and diagnose ACOS, existing and potential treatment options, and new approaches to the phenotyping and taxonomy of airway diseases.

Epidemiology of ACOS

The reported prevalence of ACOS in different studies varies according to how asthma and COPD were defined, the population sampled (random population samples vs asthma or COPD cohorts), and age group (all adults or older adults [eg, aged >40 years]). When ACOS is defined on the basis of a doctor diagnosis of both asthma and COPD, its prevalence in different cohorts of patients aged 40 years and older with chronic airways disease—including the US NHANES III study,¹⁴ the UK GP

Research Database,¹⁵ and other studies in the USA,¹⁶ Italy,¹¹ and Finland¹²—is in the range of 15–20%. However, in patients with chronic asthma, physicians are probably biased towards adding a diagnosis of COPD with increasing age and in those who have features of chronic irreversible airflow limitation, are symptomatic with this disease and therefore need additional treatment.¹⁷ This tendency is suggested by the lower proportions diagnosed with asthma alone in older age groups (eg, 65–84 years) than in younger age groups (eg, 20–44 years).¹¹

However, when the diagnoses of asthma, COPD, and ACOS have been based on lung function criteria, the estimated prevalence of ACOS has varied from 17% in a retrospective study of hospital records¹⁸ to 60% in non-smokers with severe asthma in prospective studies.^{19,20} Predictors for incomplete reversibility of airflow limitation in patients with asthma include male sex,^{19,21} increasing age,^{19–21} asthma diagnosis as a child,²¹ hospital admission in infancy,²¹ increased duration of asthma,^{19,20} adult-onset asthma,²⁰ atopy,^{19,21} early-onset asthma with blood eosinophilia,²² sputum eosinophilia,²⁰ a history of smoking (even low pack-years),^{18,19,22} low baseline forced expiratory volume in 1 s (FEV₁),²³ airway

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Key messages

- Asthma–COPD overlap syndrome (ACOS) is not a disease entity but a term applied to patients with clinical features of both asthma and chronic obstructive pulmonary disease (COPD)
- ACOS is associated with greater morbidity than asthma and COPD alone, and with relative treatment refractoriness, but since most clinical studies have excluded such patients, information is sparse
- The clinical usefulness of ACOS is predominantly in non-specialist practice where detailed diagnostic tests are not available
- Recommendations based on consensus suggest that patients with suspected ACOS should be given both a long-acting bronchodilator (the cornerstone of COPD treatment) and an inhaled corticosteroid (the cornerstone of asthma treatment)
- Evolving concepts of gene–environment interactions in the natural history and pathogenesis of chronic airways diseases point to the need for a revised and expanded taxonomy based on phenotyping and endotyping rather than clinical descriptions alone, in which inclusive terms like ACOS might not be needed

Panel 1: A clinical description of the asthma–COPD overlap syndrome

- Age 40 years or older (usually)
- Airflow limitation persistent and not fully reversible, but often with existing or historical variability or airway hyper-reactivity, or both
- Respiratory symptoms, including exertional dyspnoea, are persistent but variability can be prominent
- Might have had symptoms in childhood or early adulthood
- Frequently a history of doctor-diagnosed asthma (existing or previous), allergies, a family history of asthma, or a history of noxious exposures—or any of these features
- Symptoms are partly but substantially reduced by treatment
- Exacerbations can be more common than in COPD but are reduced by treatment
- Symptoms worsen over time
- Treatment needs are high
- Comorbidities can contribute to impairment
- Chest radiograph—as for COPD (eg, hyperinflation or bullae might be seen)
- Increase in eosinophils or neutrophils, or both, in sputum

hyper-responsiveness,²⁰ low usage of inhaled corticosteroid,²³ and aspirin hypersensitivity.¹⁹ Likewise, studies investigating bronchodilator responses in patients with COPD report significant responses²⁴ that range from 439 (24%) of a population of 1831 in the ECLIPSE study,²⁵ 3007 (52%) of 5783 in the UPLIFT trial,²⁶ and 225 (49%) of 462 in a Finnish study.¹⁸ Notably, however, bronchodilator response alone is viewed as too unreliable for defining clinical phenotypes of COPD.^{25,27}

A third context in which prevalence of ACOS has been reported is when spirometry testing has been done in population-based samples. The Wellington Respiratory Survey²⁸ studied 3500 participants aged 25–75 years, randomly selected from the electoral register in Wellington, New Zealand. 469 of these participants, aged 50 years or older, completed questionnaires and underwent comprehensive lung function testing, measurement of fractional exhaled nitric oxide, blood eosinophil count, and CT imaging of the lungs. By usual definitions (spirometry, CT, or both), 20·5% of participants with chronic airflow limitation qualified for a diagnosis of COPD; of these, 55% also satisfied widely used criteria for a diagnosis of asthma,²⁸ and would therefore be deemed to have ACOS.

Definitions and descriptions of asthma, COPD, and ACOS

When considering how to define ACOS, existing definitions of asthma and COPD would seem the logical place to begin, but they provide little help to the clinician.

In 2014, GINA defined asthma as “a heterogeneous disease, usually characterized 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”.⁴ The GOLD definition of COPD describes “a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases” and that “exacerbations and comorbidities contribute to the overall severity in individual patients”.⁵ Similarities between these definitions are obvious, but a notable feature in the COPD definition is an exposure history. However, exposure history is not stated as a requirement, and asthma is not mentioned as an additional risk factor for COPD, which is at variance with evidence based on epidemiological studies.^{11,14–16,29} Furthermore, variable airflow limitation also occurs in COPD, albeit of a lesser magnitude than in asthma, and exacerbations occur in both diseases. Further comparisons of the usual features of the diagnoses for each disorder pose difficulties for the clinician. Panel 1 provides a description of ACOS based on published reports and the table compares data from studies in asthma, COPD, and ACOS, in which different definitions of ACOS were used. None of the features of asthma or COPD is pathognomonic, and all might be present in individual patients. For this reason, pending further research about underlying mechanisms (so-called endotypes),³⁹ some pragmatism is necessary for clinical management—at least for the non-specialist physician without access to specialised investigations.

Rather than attempting to define ACOS, the GINA–GOLD report³ provides a description: “ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD”. In this context, a subtle difference exists between a description and a definition. The 2015 update⁴⁰ of this joint document clarifies that, because up to now ACOS has generally not been studied in broad populations, “a specific definition for ACOS cannot be developed until more evidence is available about its clinical phenotypes and underlying mechanisms”. The document⁴⁰ emphasises that this description is intended for use in primary care as a starting point for the recognition, initial treatment, and further investigation of ACOS, but is clearly inadequate from the perspective of understanding the biology of ACOS.

Diagnosis of ACOS

Until the past few years,^{5,41–43} clinical practice guidelines have been relatively silent on how to diagnose and manage patients with features of both asthma and COPD (ie, ACOS), except to advise that the two disorders might coexist. Several groups have proposed a more structured approach.^{31,44,45} In 2013, Louie and colleagues⁴⁴ suggested

	Asthma	Overlap	COPD	Source
Childhood onset atopic asthma	Usually present	Compatible with diagnosis	Rarely present	Sears et al (2003) ³⁰
Atopy, allergies, and family history	100%	64%	25%	Gibson et al (2009) ³¹
Occupational asthma	Compatible with diagnosis	Occasionally present	Rarely present	..
Allergic rhinitis	59% ..	55%; 57%	25% 28%	de Marco et al (2013) ¹¹ Hardin et al (2011) ¹⁰
FEV ₁ reversibility tests and airway hyper-responsiveness	Usual or very commonly encountered	Compatible with diagnosis	66%	Tashkin et al (2008) ³²
Sputum eosinophilia	Usually present	Compatible with diagnosis	Rarely present	Fu et al (2014) ³³
Non-eosinophilic or neutrophilic sputum	Occasionally present	Usually present	Usually present	Gibson P et al (2009) ³¹ Fu et al (2014) ³³
Recurrent exacerbations	Usually present	Usually or very commonly encountered; 43%	Compatible with diagnosis 18%	Hardin et al (2011) ¹⁰
Severe exacerbations (emergency unit or hospital admissions)	Occasionally present	Usually present; 33%	Compatible with diagnosis 18%	de Marco et al (2013) ¹¹ Hardin et al (2011) ¹⁰
Chronic bronchitis	Occasionally present	Compatible with diagnosis	Compatible with diagnosis	Johannessen et al (2005); ³⁴ Ohar et al (2010); ³⁵ de Marco et al (2007) ³⁶
Systemic inflammation (C-reactive protein, interleukin 6)	Rarely present	Compatible with diagnosis	Compatible with diagnosis	Fu et al (2014) ³³
Multimorbidity or comorbidity	Compatible with diagnosis	Usually present	Usually or very commonly encountered	Soriano et al (2005) ³⁷
Relative corticosteroid insensitivity (higher doses needed)	Occasionally present	Usually present	Usually present	..
Chronic airflow limitation	Occasionally present	Usually present	Usually present	Soriano et al (2003) ³⁵
Smoking exposure (pack-years; relative risk ratio)	1.27	1.70	3.16	de Marco et al (2013) ¹¹
Smoke, biomass, or occupational exposure	Rarely present	Compatible with diagnosis	Compatible with diagnosis	Golpe et al (2014) ³⁸

Prevalences are estimates based on available scientific literature. As few studies have compared the three diagnostic categories, in most cases, these estimates of prevalence are based on the authors' assessment of results of published studies. Where available, actual reported percentage prevalence from the associated reference is provided.
COPD=chronic obstructive pulmonary disease. FEV₁=forced expiratory volume in 1 s.

Table: Prevalence of phenotypic features of asthma, COPD, and asthma-COPD overlap syndrome in adults

the diagnosis of ACOS be applied to patients with a doctor diagnosis of both asthma and COPD, a history or evidence of atopy (eg, hayfever or raised total IgE concentrations), a smoking history of more than 10 pack-years, and a fixed airway obstruction. Minor criteria included an increase in baseline FEV₁ after bronchodilator of 15% or more, or of 12% or more, and 200 mL or more, from the baseline value. A Spanish consensus statement⁴⁵ proposed that patients with COPD should be deemed to have “overlap phenotype COPD–asthma” if they satisfied two major criteria (increase in FEV₁ of 15% or more and 400 mL or more, sputum eosinophilia, or a personal history of asthma), or one major and two minor criteria (high total IgE, personal history of atopy, or an increase in FEV₁ of 12% or more and 200 mL or more on two or more occasions). A limitation of this proposal is that its usefulness in a wider range of patients with chronic airways disease has not yet been tested. Furthermore, the validity of the weighting applied to different features requires confirmation.⁴⁵

Some authors have included use of specialised tests for defining ACOS. For example, Zeki and colleagues²

described ACOS in two ways: first, patients with allergic disease consistent with asthma (ie, variable airflow limitation or airway hyper-responsiveness), with incomplete reversibility, with or without emphysema on CT scans or reduced carbon monoxide diffusion capacity; or secondly, COPD with emphysema accompanied by reversible or partly reversible airflow limitation, with or without an allergic syndrome or reduced carbon monoxide diffusing capacity. Using these definitions, Zeki and colleagues² diagnosed ACOS in 15.8% of a small group of patients with chronic airways disease attending an academic pulmonary referral clinic and in 19.9% of a small group of patients attending a network of severe asthma clinics.

A clinical approach to the diagnosis of chronic airway diseases, including ACOS

In clinical practice, for a clinician to make a diagnosis in patients with chronic airways disease, they need to weigh features of typical asthma or typical COPD that are present against those that are absent. Several of these features call for a quantitative judgment; for example,

what level of smoking history (number of pack-years) would change the diagnosis from asthma to COPD if all other features favoured asthma? In the global context, how much exposure to biomass or other risk factors should lead to a designation of COPD? Should late-onset asthma after middle age only be deemed to be asthma if the patient has no or only a trivial smoking or biomass exposure history? Could patients with the same risk factors also have common pathological changes? The GINA–GOLD approach to ACOS,^{3,40} mainly intended for non-specialist clinicians, comprises five steps: recognition of patients with chronic airways disease; a syndromic assessment to guide the clinician towards a diagnosis of asthma, COPD, or ACOS; use of spirometry at the earliest opportunity to support the diagnosis and gauge severity; initiation of treatment with a focus on safety; and if needed and feasible, referral for additional investigations. This approach recognises that, like asthma and COPD, ACOS also comprises a heterogeneous group of disorders that—in time and with the aid of detailed methods of endotyping and phenotyping³⁹—will be further split into subtypes, often with overlapping features (figure 1). The GINA–GOLD approach is thus deliberately descriptive and inclusive for clinicians, but also encourages researchers to closely examine these overlapping phenotypes. The term ACOS could therefore be viewed as a place-marker or holding position for further research.

To assist syndromic diagnosis, the GINA–GOLD document presents in table form a checklist of features that, when present, are most characteristic of asthma or of COPD, so that patients with multiple (empirically ≥ 3)

features characteristic of asthma are recognised and treated appropriately and patients with multiple features characteristic of COPD are treated for COPD. ACOS should be considered in patients who have a similar number of features of asthma and COPD. A weakness of this empirical recommendation is that each feature is given an equal status in predicting the presence of asthma or COPD, yet the absence of exposure to tobacco smoke or other noxious inhalant makes the diagnosis of COPD improbable, and a bronchodilator response of more than 400 mL is more predictive of asthma.^{46,47} An increased weighting of such features might improve the validity of the GINA–GOLD table for identifying ACOS. Data on which to base these weightings should come from unbiased phenotyping studies of broad populations with chronic airways disease, which will also prove useful for identifying phenotypes of ACOS (figure 1).

Approach to treatment in ACOS

Although overlapping or mixed asthma and COPD are described in some recent national COPD guidelines^{6,7,9} and the GINA⁴ and GOLD⁵ strategy documents, almost no high quality data exist on which to base treatment recommendations, because patients with ACOS have been specifically excluded from trials investigating treatments for asthma or COPD. However, many clinicians have experience of empirical treatment of such patients with drugs approved for asthma or COPD. At present, the GINA–GOLD document⁴⁰ recommends that the initial treatment of ACOS default towards treating for severe asthma on safety grounds, specifically avoiding the prescription of monotherapy with a long-acting bronchodilator, which, although acceptable in COPD, is associated with a substantial risk of severe life-threatening exacerbations in asthma.⁴ The recommendation in the Spanish consensus guideline⁴⁸ for patients with overlap phenotype COPD–asthma is to add inhaled corticosteroid to the treatment for COPD. No evidence is available for the safety of withholding inhaled corticosteroid from patients with ACOS. In clinical practice, if the asthma diagnosis preceded that of COPD, clinicians will probably view such patients as at least partly refractory to inhaled corticosteroid, fulfilling criteria for severe asthma. Thus, many of these patients will also have received second and third line controller drugs for asthma (such as add-on inhaled long-acting β_2 -agonists [LABA], long-acting muscarinic antagonists [LAMA], omalizumab, leukotriene receptor antagonists, or slow-release theophylline), which is equivalent to steps four to five in the asthma treatment recommendations of GINA⁴ and the British Thoracic Society.⁴⁶ However, if a patient is first deemed to have COPD, they might have been given an inhaled LAMA or LABA, or both, before the addition of an inhaled corticosteroid, according to the GOLD recommendations.⁵

The treatment approach for ACOS is poised to change as phenotypes are identified (figure 2) and, in the absence of specific studies in ACOS, as evidence is extrapolated

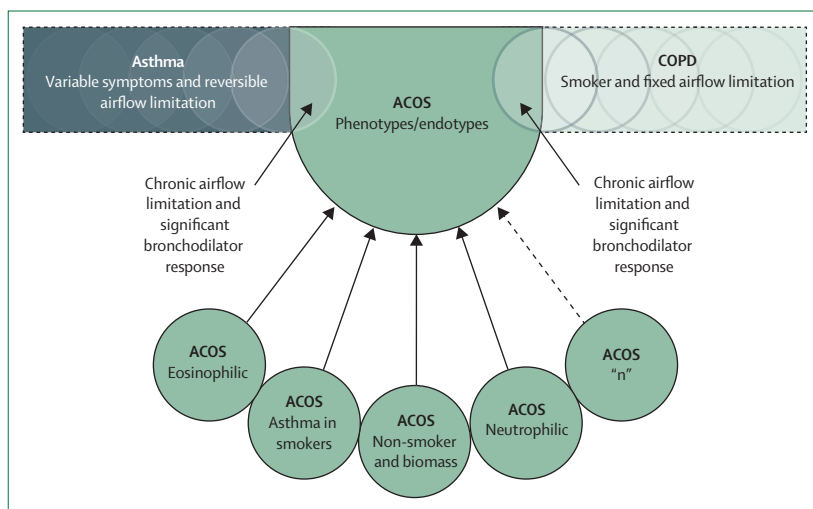


Figure 1: Phenotypes of asthma, COPD, and ACOS

The relation between asthma, chronic obstructive pulmonary disease (COPD), and asthma–COPD overlap syndrome (ACOS) and possible phenotypes of these disorders that might be identified by comprehensive phenotyping. Both asthma and COPD are heterogeneous diseases and comprise several phenotypes. Some patients (those with chronic airflow limitation and a substantial bronchodilator response) can be viewed as having ACOS, as might patients with several features of both asthma and COPD, which, in time, might be identified as specific phenotypes of ACOS. Some suggested phenotypes of ACOS are presented as clear circles. ACOS “n” are hypothesised additional phenotypes of ACOS that might be identified in the future. Dotted arrow represents that ACOS “n” is not a single phenotype but consists of an unknown number of phenotypes.

from phenotype-directed specific treatments for severe asthma and COPD.^{49–52} The value of phenotyping in severe asthma is already well established in treatments targeting specific endotypes (eg, anti-IgE antibody treatment for patients with raised serum IgE [omalizumab therapy] and anti-interleukin 4, anti-interleukin 5, and anti-interleukin 13 in patients with a T-helper-2 cell allergic phenotype of severe asthma).^{49,53} Some of these mechanisms might have a role in phenotypes of ACOS and might prove helpful for treatment of ACOS and possibly for treatment of some patients with COPD as well. In both ACOS and COPD, a subset of patients with raised blood or sputum eosinophils seem to be more responsive to inhaled corticosteroids than those without raised blood or sputum eosinophils.⁵⁴ These patients might also be responsive to other anti-allergy drugs.

Nonetheless, treatments that target neutrophil-related pathways in asthma⁵⁵ and COPD⁵⁶ might also be effective in ACOS. At present, the only phenotype-directed treatment for COPD is the phosphodiesterase 4-inhibitor roflumilast, which is effective in patients with chronic bronchitis.⁵⁵ Roflumilast has also been effective in unselected patients with asthma,⁵⁶ and, because it targets predominantly neutrophil-driven mechanisms, is being assessed for efficacy in combination with the leukotriene receptor antagonist montelukast in severe asthma (ClinicalTrials.gov NCT01765192). If roflumilast proves effective in asthma, a use in the treatment of ACOS is also

possible. Studies that have led to the approval of tiotropium for the treatment of patients with asthma receiving an inhaled corticosteroid⁵⁷ and patients with more severe asthma whose symptoms remain uncontrolled on inhaled corticosteroid and LABA,⁵⁸ further blur the distinction between treatments for asthma and COPD and suggest potential approaches to ACOS treatment. The efficacy of anticholinergics in asthma, which in some studies was shown to be similar to that of LABA for both bronchodilation and symptom control,⁵⁷ suggests that not only does cholinergic tone have a role in asthma, but it also provides the basis for the use of a combination of LABA and LAMA in patients with ACOS. So far, no clinical feature that identifies patients who will have a favourable response to tiotropium has been reported, although a trend toward a numerically higher bronchodilator response associated with older age and increasingly severe airflow limitation was reported.^{57,58} Atopy and eosinophilia do not predict the tiotropium response.

The present approach to pharmacotherapy for ACOS includes trial and error, and extrapolation from results of trials in highly selected patients with asthma or COPD, with those with ACOS specifically excluded. From a practical point of view, the concept of a control panel that considers the treatable clinical traits present in an individual patient with airway disease has been proposed as a way to implement a personalised management of patients with airway diseases.^{59,60}

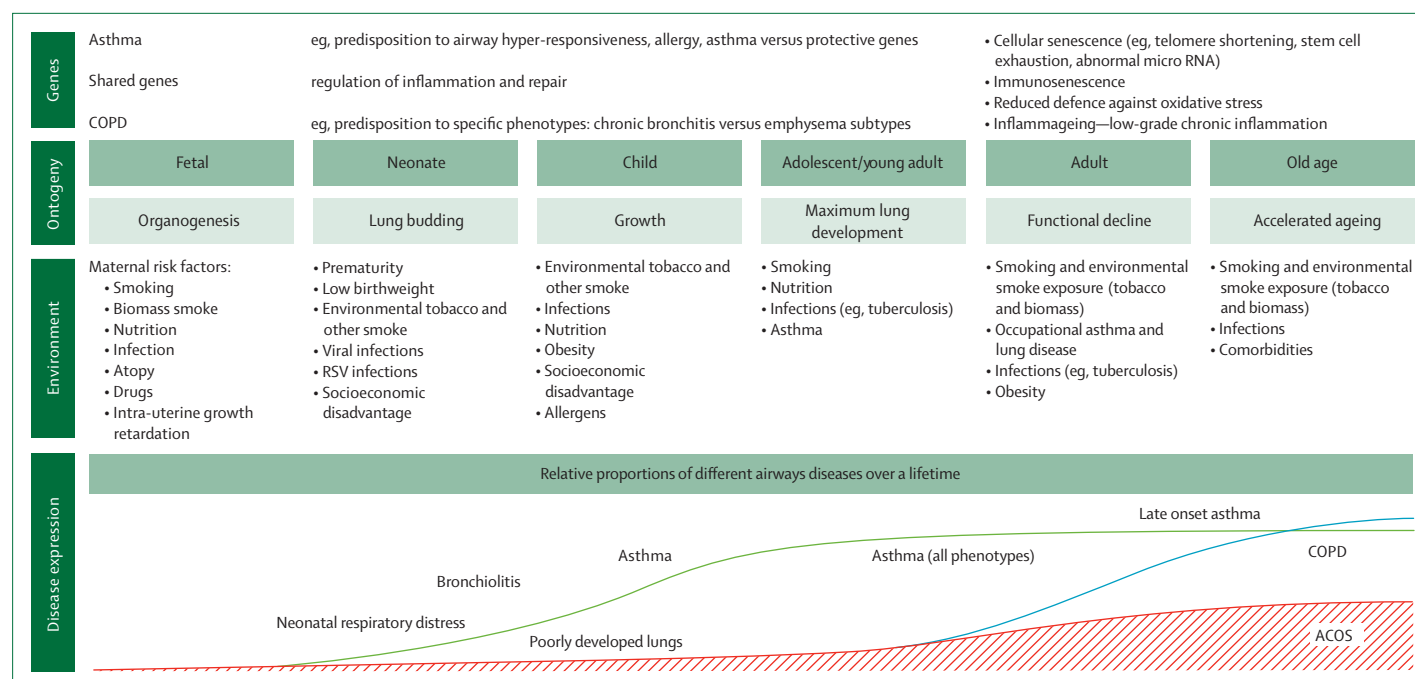


Figure 2: Interplay of genetic and environmental factors of airway diseases throughout the lifecourse

The potential complex interplay of genetic and environmental factors during the different stages of lung growth and decline, and resultant airway diseases. The origins of chronic lung disease are during organogenesis and periods of lung growth, but continue through further exposures and environmental factors during childhood, adolescence, and adulthood. Finally, loss of protective mechanisms have an important role in old age. The stage at which different airway diseases present is also determined by the effect of life changes, such as the development of allergies (atopy). The presentation of asthma–COPD overlap syndrome (ACOS) could be viewed as the combined effect of factors that lead to chronic obstructive pulmonary disease (COPD) and others that relate to asthma. RSV=respiratory syncytial virus.

Need for a new taxonomy of airways diseases based on progress in endotyping and phenotyping

The argument for a new taxonomy for chronic airways diseases is compelling.^{61,62} The creation of a new taxonomy is not an academic exercise, but is essential for an improved understanding of the natural histories and pathogenesis of these disorders, and as part of the personalised (precision) medicine approach to find treatments for unmet needs, particularly for severe forms of disease.^{59,63,64}

The existing classification of airways disease into asthma and COPD involves a-priori assumptions from historical definitions. An alternative approach is to base classification on evidence from broad populations by use of techniques such as cluster analysis. For example, the use of cluster analysis in 175 patients aged 25–75 years who had airway obstruction, or wheeze within the past 12 months, or both, identified five distinct clusters (ie, phenotypes), two of which fitted the description of ACOS.⁶⁵ The first of these clusters, cluster 1 (8% of the cohort), had atopic asthma, symptoms of chronic bronchitis, and emphysema on CT imaging. The patients in this cluster had severe airflow limitation, the greatest degree of bronchodilator reversibility and peak flow variability, concomitant eczema and rhinitis, a history of heavy cigarette smoking, and substantially reduced quality of life. The second cluster, cluster 5 (22% of the cohort), had a combination of airflow limitation, chronic bronchitis without emphysema, no major history of smoking, rhinitis, eczema, blood eosinophilia, and mildly increased fractional exhaled nitric oxide.⁶⁵ However, results of this and other studies based on cluster analysis should be viewed as preliminary in view of their differing populations (some have involved non-random populations sourced from specialist clinics, thereby with inherent biases) and differing inclusion criteria, number and nature of variables included, and clinical endpoints studied. For example, studies in COPD have considered phenotypes that relate to selected clinically meaningful outcomes such as symptoms, exacerbations, lung function, response to therapy, rate of disease progression, and death. Some studies have included clinical,⁶⁶ physiological,⁶⁷ and lung imaging findings^{68,69} and evidence for systemic inflammation, exacerbation proneness, and the presence of comorbidities in the assessment of phenotypes.^{63,70,71} A cluster analysis⁷² published in 2015 of patients with COPD in the ECLIPSE study identified five clusters with different clinical features that, importantly, were associated with different inflammatory biomarkers and outcomes.

Likewise, screening of the human genome (genome-wide association studies) has been applied to cohorts of patients with COPD and asthma independently, to search for shared genetic determinants and potential mechanisms of disease.⁷³ So far, such studies have had the inherent weakness of using doctor-diagnosed asthma and COPD. However, the desirability of changing the

taxonomy of airways diseases is supported by the finding of genotypes associated with different forms of emphysema identified on CT imaging and the chronic bronchitis phenotype.^{66,74,75}

If the assumption is correct that the identification of genetic predisposition or molecular mechanisms (ie, endotypes) will allow a personalised and more precise approach to the prevention and treatment of airways diseases, broad-based endotyping and phenotyping, constantly sharpened by an iterative process that includes increasing numbers of variables from different sources, has to be viewed as an essential process.³⁹ Besides providing a new, more appropriate, taxonomy than what exists at present, broad-based endotyping and phenotyping will lead to improved and more varied treatment options.^{62,70}

Pathways to ACOS and the Dutch hypothesis of chronic airways disease

ACOS is generally only used as a potential diagnosis in adults aged 40 years and older (midway through life). Detailed studies comparing elderly patients with chronic asthma and fixed airflow limitation with age-matched patients with COPD, confirm differences in airway morphology and inflammation, implying that lifelong asthma does not morph into the usual forms of COPD, but ageing inevitably plays a part in chronic airflow limitation.^{76,77} The origins of airway diseases in adulthood can be traced to infancy and even earlier (figure 2). Hence, consideration of potential pathways that might lead to the adult presentation of ACOS are essential to understand this disorder. One such pathway begins with childhood asthma, for which predictors of persistence of symptoms into adulthood and the development of fixed airway limitation are known. Longitudinal cohort studies^{30,78} have confirmed that airflow limitation in early life can persist through adolescence into adulthood. When assessed in adulthood, the person might be viewed as having either severe asthma or ACOS; ACOS is more likely if risk factors other than asthma are present (eg, concurrent smoking). A second potential pathway is represented by late-onset features of asthma in patients who have substantial smoking histories or other exposures that might have led to a diagnosis of COPD. Here the diagnosis of both asthma and COPD might be reasonable, but no methods exist at present to attribute the contribution of each to the clinical picture. A third pathway is represented by asymptomatic adults with airway hyper-responsiveness who progress to chronic airflow limitation compatible with a diagnosis of COPD.^{79,80} Finally, a fourth pathway recognises the link between early-life risk factors and small lungs, with an increased risk of development of fixed airflow limitation and asthma (figure 2).^{14,21,67}

More than 50 years ago, Orie and colleagues⁸¹ presented what came to be termed the Dutch hypothesis for the causation of airways diseases—long before most of the

methods described in this Review became available. The Dutch hypothesis addressed the need to adopt a broader view of airways diseases—unfettered by definitions of asthma and bronchitis (as COPD was then termed)—than existed at the time. Orie and colleagues⁸¹ proposed that these disorders were clinical expressions of endogenous or inherited factors, modified by age and sex, and exogenous environmental exposures to allergens, smoking, viruses, and air pollution. They proposed that, rather than lumping asthma and COPD together, these diseases—in recognition of their shared risk factors and the effects of ageing and sex—should be viewed as chronic, non-specific lung disease that represents, not two, but potentially several clinical entities that would need further study; effectively, a call for phenotyping and a revised taxonomy that would encompass patients with features of both asthma and COPD.^{82,83}

One approach to explore the Dutch hypothesis is to identify genes and mechanisms common to asthma and COPD. Candidate gene studies have identified shared genes, including MMP9 and TGFβ1,⁸⁴ which predict lung function in both asthma and COPD.⁶⁷ However, two genome-wide association studies,^{85,86} both published in 2014, that set out to compare single nucleotide polymorphisms associated with asthma and COPD, did not find any overlap. Although the first study⁸⁵ was negative, rare genetic variants might have been missed or, consistent with the Dutch hypothesis, population-specific environmental factors might have modified the phenotypic expression in different cohorts. The second study⁸⁶ compared single nucleotide polymorphisms associations between ACOS, (defined as COPD with an asthma diagnosis before the age of 40 years) and COPD in the ECLIPSE cohort, and also examined for single nucleotide polymorphisms previously associated with asthma or COPD. Again, although overall the findings were negative, in a subgroup analysis a weak association was reported between ACOS and the lung developmental gene *SOX5*, and with *GPR65*, a gene involved in eosinophil activation.⁸⁶ Thus, shared susceptibilities between COPD and asthma, affected by different environmental factors, could result in different clinical expressions of airways disease (figure 2). A report⁸⁷ published in 2015 identified a T-helper-2 cell signature in airway epithelial gene expression in patients the asthma–COPD overlap; further evidence of a mechanism common to asthma and ACOS.

Conclusions and future research

The understanding of chronic airways disease in adults with features both of asthma and COPD (so-called ACOS) is incomplete, and its treatment omitted from previous regulatory studies and treatment guidelines. Existing descriptions of ACOS are intended, in the first instance, as interim advice to assist clinical management of airways disease by non-specialist physicians, not as definitive statement. Preliminary advice in most

Panel 2: Some questions for future research on asthma–COPD overlap syndrome

- Unbiased endotyping and phenotyping of adult patients with chronic airflow limitation, including patients with evidence of emphysema on high-resolution CT scan and a normal ratio between forced expiratory volume in 1 s and forced vital capacity.
- Development of an approach or method, or both, to identify phenotypes and endotypes of asthma and chronic obstructive pulmonary disease (COPD), and to find out which of these phenotypes or endotypes might be considered to qualify for a diagnosis of asthma–COPD overlap syndrome (ACOS); for example, to distinguish eosinophilic or high T-helper-2 cell severe asthma from COPD with sputum eosinophilia, and neutrophil-predominant severe asthma from ACOS and COPD.
- Agreement on the features that, although not pathognomonic, are essential for the diagnosis of asthma and COPD, and on the possible alignment of components of the definitions of each.
- Weighting of non-essential features that support the diagnosis of either asthma or COPD.
- Evidence-based agreement on the number of features of asthma and of COPD that have to be present for the syndromic diagnosis of ACOS. Longitudinal cohort studies to examine the development of chronic airflow limitation in asthma to study the effects of ageing and of concurrent exposure to smoke and other noxious agents, including biomass in developing countries.
- Longitudinal cohort studies to examine mechanisms resulting in late-onset features of asthma and whether they should be classified as ACOS.
- Further genetic studies of determinants of different phenotypes of chronic airways diseases and gene–environment interaction studies.
- Treatment trials for patients fulfilling the description of ACOS, preferably with additional phenotypic characterisation for the presence of airway hyper-responsiveness or bronchodilator response, T-helper-2 cell high or low status, tobacco smoke or biomass exposure, and history of asthma or other childhood respiratory diseases.
- Comparative trials examining the efficacy and safety of the following treatment options, alone and in combination: long-acting β_2 -agonists, long-acting anti-muscarinics, inhaled corticosteroids, leukotriene modifiers, selective phosphodiesterase 4 inhibitors, theophylline, macrolides, bronchial thermoplasty, biologicals (both those like anti-IgE that are approved for asthma, and those in development—eg, inhibitors of interleukin 5, interleukin 4, interleukin 4–receptor, interleukin 13, and interleukin 8).

Search strategy and selection criteria

We searched the Cochrane Library (Jan 1, 2001, to Dec 31, 2015) and Medline (Jan 1, 1970, to Dec 31, 2015) for manuscripts published in English, using the medical subject heading (MeSH) search terms “Asthma” OR “COPD” OR “chronic obstructive airway disease” OR “chronic obstructive pulmonary disease” OR “chronic obstructive lung disease” AND “overlap”. We prioritised publications from the past 5 years. We also searched the reference lists of articles identified by this search strategy and selected those we deemed relevant. Review articles and book chapters are cited to provide readers with more details and references than could be provided in this Review.

publications is to treat patients with suspected ACOS with both a long-acting bronchodilator (the cornerstone of COPD treatment) and an inhaled corticosteroid (the cornerstone of asthma treatment).

However, we believe that, rather than inhibiting progress in defining phenotypes of asthma and COPD, the concept of ACOS will hopefully focus attention on the need to accelerate research beyond the information available at present on populations with physician diagnoses of asthma or COPD (ie, non-experts using present accepted definitions and methods for diagnosing these disorders). In this context, some urgent research questions are presented in panel 2. These questions aim to identify endotypes and phenotypes that might be better described as a form of ACOS, and help develop targeted treatments for patients across the range of chronic airways disease. We believe that modern methods of analysing complex biological networks⁸⁸ will help further understanding of the gene–environment interactions that lead to complex airway diseases in general, and ACOS in particular. Hence, we expect that the umbrella term ACOS might eventually be replaced as new phenotypes and underlying endotypes are identified and a new taxonomy (ie, classification) of airway diseases is generated.

Contributors

All authors contributed to the preparation and completion of each draft of this Review, and approved the final draft. RNvZ-S did the scientific literature search.

Declaration of interests

EDB reports personal fees for consulting and advisory board membership from Actelion, Almirall, AstraZeneca, Boehringer Ingelheim, and F Hoffman-La Roche; for advisory board membership from ALK-Abello, Chiesi, Elevation Pharma, Forest, GlaxoSmithKline, Napp Pharma, Navigant Consulting, Novartis, Pfizer, IMS Consulting Group, Takeda, and ICON; for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Novartis, Pfizer, and Takeda; for educational materials from PeerVoice and Indegene; grants to his institution for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Cephalon, Chiesi, GlaxoSmithKline, F Hoffman-La Roche, Merck, Nycomed, Takeda, TEVA, and Sanofi-Aventis, outside of the submitted work; and membership of the board of Global Initiative for Asthma. HKR reports grants, personal fees, and non-financial support from AstraZeneca and GlaxoSmithKline; personal fees from Novartis, Merck, Mundipharma, and Teva, outside of the submitted work; personal fees and non-financial support from Boehringer Ingelheim; and is chair of the Global Initiative for Asthma Science Committee. RNvZ-S reports personal fees for advisory board membership and lectures from ASPEN, Pfizer, Novartis, and AstraZeneca, outside of the submitted work. AA reports grants and personal fees from AstraZeneca, Chiesi, GlaxoSmithKline, Merck, Novartis, and TEVA, outside of the submitted work.

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