"To define is to limit": perspectives on asthma–COPD overlap syndrome and personalised medicine

Vanessa M. McDonald[1,2] and Peter G. Gibson[1,2]

Affiliations: [1]Priority Research Centre for Healthy Lungs and Centre of Excellence in Severe Asthma, Faculty of Health and Medicine, The University of Newcastle, New Lambton Heights, Australia. [2]Dept of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, Australia.

Correspondence: Vanessa M. McDonald, Centre of Excellence in Severe Asthma and Priority Research Centre for Healthy Lungs, The University of Newcastle, 1 Kookaburra Circuit, New Lambton Heights NSW 2305, Australia. E-mail: Vanessa.McDonald@newcastle.edu.au

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both common and usually distinct airway diseases. However, it is now well recognised that many patients, particularly those aged over 55 years, have features of both asthma and COPD [1–5]. This may occur in up to 20% of patients [3]. In recent years there has been intense interest in the coexistence of asthma and COPD, as evidenced by the proliferation of reviews and editorial space dedicated to the topic [1, 3, 6–9]. It has even been given a new name: asthma–COPD overlap syndrome, or ACOS.

Despite this interest, knowledge of the exact prevalence of ACOS remains elusive, and this is in part related to the lack of a precise definition. It is agreed that demonstration of both an "asthma component" and a "COPD component" is necessary to receive an ACOS label [10]. However, despite the increasing number of asthma–COPD overlap studies that have emerged in recent years, the components of ACOS are not agreed upon between studies.

The evidence base to support treatment recommendations in patients with features of both asthma and COPD is also scarce. Whilst there has been a proliferation of publications relating to asthma–COPD overlap, these have been limited to reviews, cross-sectional studies, cohort studies and population-based studies. There are few robust clinical trials that have evaluated pharmacological interventions for this population. Indeed, the majority of regulatory studies in either asthma or COPD exclude patients with features of both diseases [11, 12].

In recognition of the paucity of evidence and the challenges of managing patients, learned societies throughout the world have developed consensus documents [10, 13–15] in an attempt to provide clinicians with advice in relation to the assessment and management of patients with coexisting asthma and COPD.

Most recently, the *European Respiratory Journal* published the proceedings of round-table discussions that aimed to develop a consensus definition and to advance the field both scientifically and clinically [6]. Through discussions, global experts proposed major and minor criteria for a diagnosis of ACOS. To

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confirm a diagnosis, the committee recommends that three major criteria (persistent airflow limitation in those aged >40 years, ⩾10-year smoking history or equivalent air pollution exposure, and documented history of asthma before the age of 40 years or a bronchodilator response (BDR) of >400 mL in FEV_1 (forced expiratory volume in 1 s)) are met, with the addition of one minor criterion (history of atopy or allergic rhinitis, or BDR of FEV_1 ⩾200 mL and 12% from baseline values on two or more visits, or a peripheral blood eosinophil count of ⩾300 cells·μL^{-1}) [6].

What is the impact of different definitions of ACOS?

In this edition of the *European Respiratory Journal*, Bonten *et al.* [16] seek to answer this question by evaluating the impact of six different definitions of ACOS, in their report of results from a population-based cohort study of individuals. The Netherlands Epidemiology of Obesity study involved the general population aged 45–65 years, with an oversampling of individuals with a body mass index (BMI) of ⩾27 kg·m^{-2}. These analyses were adjusted to account for the oversampling of increased-BMI participants. A subpopulation of people with asthma and/or COPD was identified. The aims of the study were to assess the impact of a range of different ACOS definitions in terms of the prevalence of ACOS, patient characteristics and exacerbation risk.

Throughout 2008–2012, individuals were assessed and completed questionnaires on demographics, lifestyle and clinical information including comorbidities, and underwent a series of investigations involving spirometry and anthropometric measures. In 2013, the primary care electronic medical records (EMR) register was used to gather medical history and medication prescription data, including prescription of airway-related antibiotics, oral corticosteroids or the combination of both in order to assess exacerbations of airways disease.

The Bonten *et al.* [16] study involved 5675 out of 6671 individuals with complete datasets and a subpopulation of 846 participants with asthma or COPD. Asthma and COPD were identified by self-report or by documentation in the EMR using codes from the International Classification of Primary Care. The authors used six different definitions to apply a label of ACOS. Using these definitions, they reported the prevalence of ACOS in the general population and in the subpopulation of participants with asthma and COPD. They found that the actual prevalence was sensitive to the definition that was used. The greatest agreement between the definitions was with definition one "COPD and asthma in the registry" and definition two "COPD and asthma in the registry or ACOS as text in the EMR". The highest prevalence (4.9% and 38.3% in the total and asthma/COPD population respectively) was reported in definition six: "COPD in the registry *or* self-report *or* FEV_1/FVC <0.7 *and* asthma in the registry *or* F_{ENO} ⩾45 ppb".

Whilst these data highlight the impact of the absence of a precise definition, it should be noted that the majority of the definitions used by Bonten *et al.* [16] would not measure up favourably to the diagnostic criteria proposed by Sin *et al.* [6] or those of international guideline committees [10, 13–15]. Instead, the definitions rely on a registry entry, a clinical notation or self–report, or a combination of these. One definition involved a combination of these criteria with airflow limitation, another involved the addition of F_{ENO} (exhaled nitric oxide fraction) and another used the presence of airflow limitation, age and smoking history. Interestingly, the authors also report that airflow limitation was present in only one-third of the group that used self-report and in only half of the registry definition group, highlighting the limitations and inconsistency in the application of such definitions.

The reported impact of ACOS was also sensitive to the different definitions. Rates of moderate exacerbations over a median follow-up period of 1.8 years were examined, and again these differed according to the definition used. Previous studies report that patients with features of both asthma and COPD experience an increased disease burden. Compared with those with either asthma or COPD alone, such patients experience greater impairment to their health status, more severe airflow limitation, and increased exacerbations and hospitalisations [2, 17–21]. Bonten *et al.* [16] also report a higher exacerbation burden for ACOS patients compared with asthma-alone patients, but not compared with COPD-alone patients. This may be related to the fact that Bonten *et al.* [16] only assessed moderate exacerbations, or it could be related to the imprecision of the definitions used.

The results of this study do trigger thought as to what is the best way forward. The argument for a consensus definition is clear, for without this it will continue to be difficult to understand the prevalence of ACOS, the clinical course, and how this patient group responds to therapy. But would such a definition advance management and improve patient outcomes? COPD and asthma are both heterogeneous diseases. In both diseases there is an overlap of airway inflammatory granulocytes, in both conditions patients may be atopic and hyperresponsive, and a reasonable proportion of patients with asthma have a smoking history [22]. Given the limitations of different definitions, is it necessary to define the overlap of features as a new disease entity? In addition to ACOS we are now starting to see reference to BCOS (bronchiectasis–COPD overlap syndrome), CCOS (cardiac–COPD overlap syndrome), and so on, so do we

continue through the alphabet of syndromes? Or should we abandon ACOS, as has been previously proposed [3, 7] and opt for treating the patient and their problems irrespective of their disease label: that is, use a personalised medicine approach [4, 7, 23–26]? With this approach, a diagnosis of obstructive airway disease is confirmed or considered highly probable following a clinical history and examination, and assessment of spirometry, airway inflammation and risk factors, and then, when a diagnosis of airways disease appears highly likely, the multiple clinical traits that manifest in individuals with airways diseases are assessed and targeted therapies applied [23–25, 27]. This approach, as proposed recently in the *European Respiratory Journal,* paves the way for a label-free personalised medicine approach to diagnosis and management by recognising the clinical and biological complexity of asthma and COPD and offers a rational and safe approach to the use of existing therapies [24]. Early studies of personalised medicine suggest that the application of a multidimensional assessment identifies many untreated clinical management problems or traits within the domains of the airways, self-management, comorbidities and risk factors [28], and that these traits are similar irrespective of a label of asthma, COPD or ACOS [28]. Furthermore, when patients with COPD and ACOS receive individualised therapy that is targeted to their individual traits, health outcomes are improved [27].

Oscar Wilde said "to define is to limit", and so, by placing a label on an individual, does this limit, confine and restrict the treatment approach? Should we not optimise the wellness of individuals through personalised medicine rather than simply treating the label?

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