

The A to E of airway disease

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Summary

The terms asthma and chronic obstructive pulmonary disease have evolved from their original very specific physiology-based definition to describe additional disease entities such as symptoms, airway inflammation and airway structure. We argue that as a result there is widespread confusion about what the terms mean. This has become a significant hurdle to optimal disease management and drug development. We propose that these disease labels should be replaced with a new alphabetical assessment tool for characterizing airway disease, which provides a checklist of five relatively independent factors potentially responsible for morbidity in patients with airway disease: Airway hyperresponsiveness, Bronchitis, Cough reflex hypersensitivity, Damage to the airway and surrounding lung and Extrapulmonary factors. We speculate that the use of this system to characterize airway disease will improve outcomes by promoting better targeting of new and existing treatments.

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Introduction

While some conditions such as TB and cystic fibrosis map precisely to an underlying disease process, many including asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis refer to complex phenotypes without a single, well-defined pathogenetic process, where it is unclear if there is one disease presenting heterogeneously or several diseases with common features (Fig. 1). The term asthma has been used for centuries to describe a certain pattern of breathlessness, although in the modern era it has become a term to describe variable airflow obstruction and airway hyperresponsiveness (AHR). COPD refers to a fixed obstructive spirometric defect. As new information about the physiology, biology and response to treatment of airway disease has emerged, the terms have evolved to encompass a sprawling mix of clinical features, abnormal physiology and pathology that defy a single definition. It has been cogently argued in a recent issue of the journal [1] and earlier [2] that it is time to bring these terms back to their original meaning, and that the other aspects of airways disease should be given different names. We go further than this, arguing that confusion about the meaning of the terms asthma and COPD has got in the way of an understanding of the

pathogenesis and treatment of airway disease to such an extent that the terms should now be abandoned. Others have a similar view on the basis that overlapping features are common, pathogenic pathways may be similar, many patients have a disease that is difficult to classify and relatively few patients with airway disease meet the diagnostic criteria for clinical trials [3–5]. Our principal concern is that use of the terms asthma and COPD leads to inappropriate focus on only one aspect of inflammatory airways disease: disordered airway physiology. While there is no doubt that airflow obstruction is a central feature of many airway diseases, all too often, its demonstration is seen as an end rather than the beginning of a search for causes and associated factors. There is also evidence that variable airflow obstruction is most amenable to therapy, and thus unlikely to be relevant to the majority of patients who present to clinics with continued morbidity despite treatment [6]. The inappropriate emphasis on impairment of lung function means that other factors such as persistent airway inflammation, a heightened cough reflex, airway damage and extrapulmonary factors are not given sufficient emphasis when evaluating patients.

We believe a better approach to the description of complex conditions such as asthma and COPD is to view

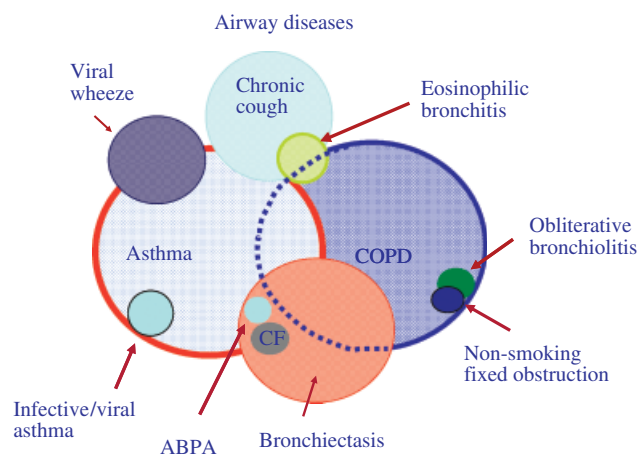


Fig. 1. Venn diagram showing the complex relationship between different airway diseases. ABPA, allergic bronchopulmonary aspergillosis.

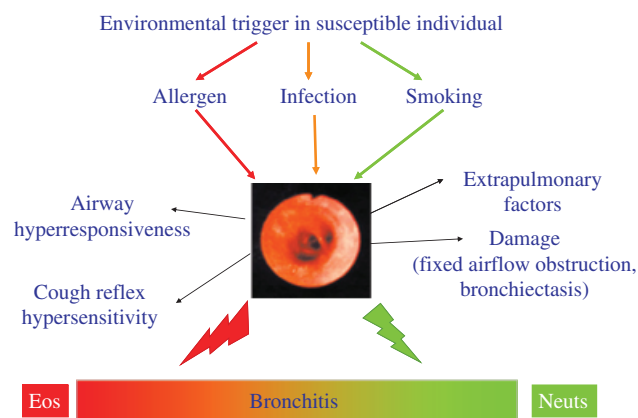


Fig. 2. Environmental stimuli in a susceptible individual leads to several relatively independent patho-physiological outcomes. Eos, eosinophilic; neuts, neutrophilic.

them as a collection of relatively independent patho-physiological abnormalities resulting from endogenous factors and exposure to noxious environmental stimuli such as allergens, cigarette smoke, infectious agents and air pollution. These results in different patterns of airway inflammation and a limited number of abnormal physiological responses (Fig. 2), which can be conveniently summarized using an A to E classification system: AHR, responsible for short-term, bronchodilator-responsive variable airflow obstruction; Bronchitis (eosinophilic or neutrophilic airway inflammation), responsible for a more gradual onset, relatively bronchodilator-resistant but potentially corticosteroid-responsive increases in airflow obstruction (exacerbations), particularly when occurring with A and/or D; Cough reflex hypersensitivity; and Damage, characterized by bronchodilator and corticosteroid resistant airflow obstruction as a result of airway and lung parenchymal damage. These abnormalities are associated with a number of more or less well-defined pathologies, patterns of clinical symptoms, physiological

abnormalities and treatment responses (Table 1). To add another layer of complexity, Extrapulmonary conditions linked to the inflammatory airway disease or independent of it may contribute to symptoms. Crucially, each of these components can, and often do, occur independently, controlled by distinct pathogenic pathways each with their own environmental, genetic, immunological and molecular signatures. Any one individual may have one or all of them. Some may remit over time while others appear.

Our paradigm is based on opinion; we acknowledge that there may be better, unbiased ways of deriving a classification system. However, it does provide a useful framework for further discussion. We do not exclude a causal relationship between one or more of the features shown in Table 1 and it remains possible that some or all of these abnormalities arise as a result of a common primary abnormality. D may be particularly associated with B, as eosinophilic airway inflammation is closely linked to thickening of the basement membrane [7] and chronic neutrophilic airway inflammation with the development of small airway fibrosis and emphysema [8, 9]. However, it cannot be assumed that inhibition of one pathway has beneficial effects on another. A good example of this faulty logic is the long-standing assumption that eosinophilic inflammation leads directly to airway hyperresponsiveness [10]. It is now clear that this is not the case [11]. The correlations between measures of airway dysfunction and the severity of eosinophilic inflammation, at least as measured by sputum eosinophilia, are weak [12, 13]. Careful observation in a clinical setting where sputum eosinophilia is routinely measured convincingly reveals that these two phenotypes can occur independently [7, 12, 14] and phenotyping using cluster analysis has shown that the two phenotypes fall into independent clusters, although they commonly occur together [15].

Phenotype-directed management

What do these insights mean for management? We believe that to effectively care for people with airway diseases, particularly those with the more severe and complex disease, it is necessary to determine as precisely as possible, the individual profile of patho-physiological abnormalities, which comprises that person's disease. This means assessing each of the patho-physiological abnormalities and addressing them in turn. The A to E checklist provides a structure for phenotype-directed management.

It is important to recognize that different drugs target different pathways. Most obviously, bronchodilators target variable airflow obstruction as a result of AHR and corticosteroids eosinophilic airway inflammation. If there is no eosinophilic airway inflammation, it is unlikely that corticosteroids will be effective [12, 16], and long-acting bronchodilators are unlikely to benefit patients with a

Table 1. The A to E of airway disease

	Clinical features	Definition	Physiology	Pathology	Mechanism	Existing treatments	Potential new treatments
Airway hyper-responsiveness	Short-term variable breathless, wheeze and chest tightness (i.e. over minutes or hours) Often exercise-induced and nocturnal	One or more of : methacholine $PC_{20} < 8$ mg/mL; > 12% improvement in FEV_1 after inhaled bronchodilator; > 20% within day variability in peak expiratory flow	Bronchodilator responsive airflow obstruction Exaggerated bronchoconstrictor response to constrictor stimuli Deep breath-induced bronchodilatation	Mast cell infiltration of airway smooth muscle [7] Increased airway smooth muscle mass [27]	Direct interaction between mast cells and airway smooth muscle involving multiple mediators, including histamine, cysteinyl-LT, PGD_2 Increased airway smooth muscle contractility Altered airway smooth muscle phenotype	Short and long-acting β_2 -agonists Anti-muscarinic agents Inhaled corticosteroids	Bronchial thermoplasty [17] TNF- α antagonists [18]
Bronchitis	Exacerbations, particularly when co-existing with an acute inflammatory stimulus and if A and/or D are present Cough with morning sputum May be clinically silent	Raised induced sputum eosinophil (> 2%) or neutrophil (> 61%) count Raised neutrophil and total inflammatory cell count may suggest infection Raised exhaled nitric oxide concentration suggests eosinophilic airway inflammation	Bronchodilator resistant corticosteroid responsive airflow obstruction (eosinophilic) Deep breath-induced bronchoconstriction	Eosinophilic or neutrophilic infiltration of mucosa Goblet cell hyperplasia	Allergic, Th2 cytokine driven (eosinophilic) or infection/innate immune response driven (neutrophilic) Airflow obstruction as a result of mucosal oedema and intraluminal impaction with mucus and cellular debris	Inhaled and oral corticosteroids for eosinophilic bronchitis; latter may be more effective for small airway disease Anti-leukotrienes Antibiotics for infective neutrophilic bronchitis	Eosinophilic: Omalizumab [28] Mepolizumab [23,24] Neutrophilic: long-term macrolide antibiotics [29]
Cough reflex hypersensitivity	Excess dry cough with changes in temperature, fumes, talking, laughing	Capsaicin cough reflex hypersensitivity	Heightened cough response to inhaled tussive stimuli such as capsaicin and citric acid	Increased sputum neutrophil numbers [30] BAL lymphocytosis in some [31] Sputum and airway mucosal eosinophilia in 10–15% [32]	Sensitization of sensory nerve endings by pro-tussive mediators such as histamine and PGE_2 [33]	Removal of aggravating factors (smoking, angiotensin converting enzyme inhibitor therapy, gastrooesophageal reflux, rhinitis) Inhaled and oral corticosteroids helpful in eosinophilic disease [34]	None
Damage	Non-variable breathlessness, wheeze and chest tightness Chest deformity	Post-bronchodilator and oral corticosteroid FEV_1 / FVC < 70% Impaired gas transfer CT criteria for emphysema and bronchiectasis	Bronchodilator resistant corticosteroid unresponsive airflow obstruction Impaired gas transfer Increased lung volumes	Emphysema Small airway fibrosis Thickening of basement membrane Increased lymphoid follicles Bronchiectasis	Likely a result of chronic airway inflammation, particularly if multiple inflammatory hits [35] Airflow obstruction as a result of progressive small airway constriction [36] and loss of airway support Reduction of area for gas exchange Damage induced by aspergillus sensitization and colonization	Smoking cessation	Lung volume reduction for emphysema [37]

Table 1. continued

Clinical features	Definition	Physiology	Pathology	Mechanism	Existing treatments	Potential new treatments
Extrapulmonary factors Episodic dyspnoea and chest tightness Weight loss or gain Rhinitis premature vascular disease	Specific to individual extrapulmonary factor	Altered vascular reactivity Muscle weakness	Increased systemic inflammation	Hyperventilation Upper airway obstruction and hypersensitivity Vocal cord dysfunction Insulin resistance Muscle wasting Loss of confidence Effect of obesity on lung function Poor adherence with therapy	Breathing retraining Nasal corticosteroids Modification of vascular risk factors Weight loss or dietary support Pulmonary rehabilitation	Anabolic agents

Factors potentially responsible for symptoms and morbidity in a patient with airway disease.

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PC₂₀, the provocative concentration required to cause a 20% fall in FEV₁; PG, prostaglandin; LT, leukotriene; BAL, bronchoalveolar lavage; Th2, T-helper type 2.

highly eosinophilic phenotype who do not have much in the way of variable airflow obstruction. This is becoming an urgent issue as a number of novel (and often very expensive) drugs enter drug development, which specifically target one cellular pathway linked to one pathophysiological abnormality. Most modify A and/or B; hence, clinicians and investigators prescribing and evaluating these treatments need to ensure that the subjects recruited display the relevant abnormality and do not have symptoms exclusively due to C, D and/or E. The primary outcome also needs to be chosen after careful consideration of the clinical features most closely associated with that abnormality (Table 1).

An example where this has been carried out well is the AIR 1 trial of bronchial thermoplasty in moderate and severe asthma [17]. Bronchial thermoplasty is thought to selectively target airway smooth muscle and reduce A. In order to ensure that a potentially responsive population was recruited, entry criteria included characteristics associated with A including current symptoms, a large acute bronchodilator response to inhaled salbutamol and clear deterioration when long-acting β_2 -agonists were withdrawn. The primary outcome was a composite measure of asthma control, consisting of measures associated with A assessed during a period when long-acting β_2 -agonists were withdrawn. An example of a less successful clinical trial design is the phase 3 development of anti-TNF- α agents. Early pilot studies had suggested a clinically important effect on A but not B in patients with refractory asthma and evidence of marked AHR [18, 19]. However, a subsequent large clinical trial of the anti-TNF- α monoclonal antibody golimumab in refractory asthma, recruited patients on the basis of a history of asthma exacerbations (most closely linked to B) and chose exacerbation frequency as the primary outcome [20]. Participants had noticeably less AHR than those participating in the earlier pilot studies and many were obese, raising the possibility that E might be contributing to symptoms. Interestingly, golimumab was effective when analysis was restricted to subjects who had a large acute bronchodilator response (a feature of A).

The archetypal example of drug development being adversely effected by unhelpful disease labels is the story of the clinical development of blocking antibodies against IL-5, in particular mepolizumab, which very specifically ablates eosinophils. Eosinophilic airway inflammation, which is often clinically silent most of the time, is associated with exacerbations of asthma and COPD, but not with AHR, which causes most asthma symptoms. Yet for 10 years, mepolizumab was tested exclusively in asthma against outcomes related to AHR in patients identified by the presence of variable airflow obstruction and/or AHR [21, 22]. It is therefore, not, surprising that the results were negative. When the drug was tested in patients with eosinophilic airway inflammation against

outcomes associated with an airway eosinophilia, it worked [23, 24]. The benefits of the treatment were particularly obvious in a subset of patients who had a large improvement in forced expiratory volume in 1 s after 2 weeks of treatment with prednisolone. In contrast, those with a large response to bronchodilator therapy responded poorly [25]. Thus, the population who do well with mepolizumab can be recognized by identifying those patients where corticosteroid responsive airway inflammation is making a large contribution to airflow limitation. Despite this, and despite evidence that eosinophilic airway inflammation contributes to exacerbations of COPD [26], regulatory agencies still appear to be insisting on traditional markers of variable airflow obstruction being used to identify patients and measure the efficacy of anti-eosinophilic drugs and do not appear to be comfortable with a drug that only targets one aspect of the disease, even when it is the one which causes death.

Conclusion

The current classification of airways disease is confused, not inclusive and inappropriately emphasizes impairment of lung function such that other factors such as persistent airway inflammation, a heightened cough reflex, airway damage and extrapulmonary factors are not given sufficient consideration when evaluating patients. We believe that the A to E checklist is a better system for assessment of patients with airways disease as it embraces the diversity of clinical expression of the disease and encourages analysis of the mechanisms of symptoms and disordered airway function. It will be particularly useful in patients with severe disease as the stakes are higher and phenotypic diversity is greatest. We speculate that widespread adoption of this system will improve outcomes in airway diseases by promoting better targeting of existing and new treatments.

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