

REVIEW

Phenotyping airways disease: an A to E approach

S. Gonem, V. Raj, A. J. Wardlaw, I. D. Pavord, R. Green* and S. Siddiqui*

Department of Infection, Immunity & Inflammation, Institute for Lung Health, University of Leicester, Leicester, UK

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Summary

The airway diseases asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous conditions with overlapping pathophysiological and clinical features. It has previously been proposed that this heterogeneity may be characterized in terms of five relatively independent domains labelled from A to E, namely airway hyperresponsiveness (AHR), bronchitis, cough reflex hypersensitivity, damage to the airways and surrounding lung parenchyma, and extrapulmonary factors. Airway hyperresponsiveness occurs in both asthma and COPD, accounting for variable day to day symptoms, although the mechanisms most likely differ between the two conditions. Bronchitis, or airway inflammation, may be predominantly eosinophilic or neutrophilic, with different treatments required for each. Cough reflex hypersensitivity is thought to underlie the chronic dry cough out of proportion to other symptoms that can occur in association with airways disease. Structural changes associated with airway disease (damage) include bronchial wall thickening, airway smooth muscle hypertrophy, bronchiectasis and emphysema. Finally, a variety of extrapulmonary factors may impact upon airway disease, including rhinosinusitis, gastroesophageal reflux disease, obesity and dysfunctional breathing. This article discusses the A to E concept in detail and describes how this framework may be used to assess and treat patients with airway diseases in the clinic.

Keywords asthma, chronic obstructive pulmonary disease, phenotype

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Correspondence:

Dr Salman Siddiqui, Respiratory
Medicine, Glenfield Hospital, Leicester,
LE3 9QP, UK.

E-mail: ss338@le.ac.uk

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Introduction

In 1961 the 'Dutch hypothesis' of airways disease was proposed, postulating that asthma, emphysema and chronic bronchitis were variants of the same disease, termed 'chronic non-specific lung disease' [1]. In subsequent years this view fell out of favour as it was felt that asthma and chronic obstructive pulmonary disease (COPD) – an umbrella term for emphysema and chronic bronchitis – could be clearly distinguished on the basis of aetiology, pathology, physiology and clinical features. Specifically, asthma was felt to be an atopic disorder mediated by mast cells, eosinophils and CD4⁺ cells, characterized by variable airflow obstruction, airway hyperresponsiveness (AHR) and episodic symptoms. On the other hand, COPD was considered to be mainly a smoking-related condition mediated by neutrophils, macrophages and CD8⁺ cells, characterized by fixed airflow obstruction (FAO), minimal AHR and little day-to-day variation in symptoms [2]. The contrasting

aetiological, physiological and immunopathological features of 'classical' asthma and COPD are illustrated in Fig. 1.

Although most clinicians will recognize the two extremes described above, it is increasingly recognized that a number of patients defy categorization into these classical asthma and COPD groups. For instance, only 30% of patients with asthma have classical bronchodilator reversibility [3], whereas up to 40% of patients with COPD may have a degree of reversible airflow obstruction [4]. In addition, patients with chronic asthma may develop FAO and have an accelerated rate of lung function decline [5]. Both asthma and COPD may be associated with exacerbations, in which symptoms of cough, wheeze or dyspnoea worsen significantly over a period of days. Furthermore, the airway inflammatory profiles of patients who behave clinically or physiologically as having asthma or COPD may not fit the expected pattern; some patients with asthma have predominant sputum neutrophilia [6] whereas a number of patients with COPD exhibit sputum eosinophilia [7]. This blurring of the boundary between the

*Co-senior authors.

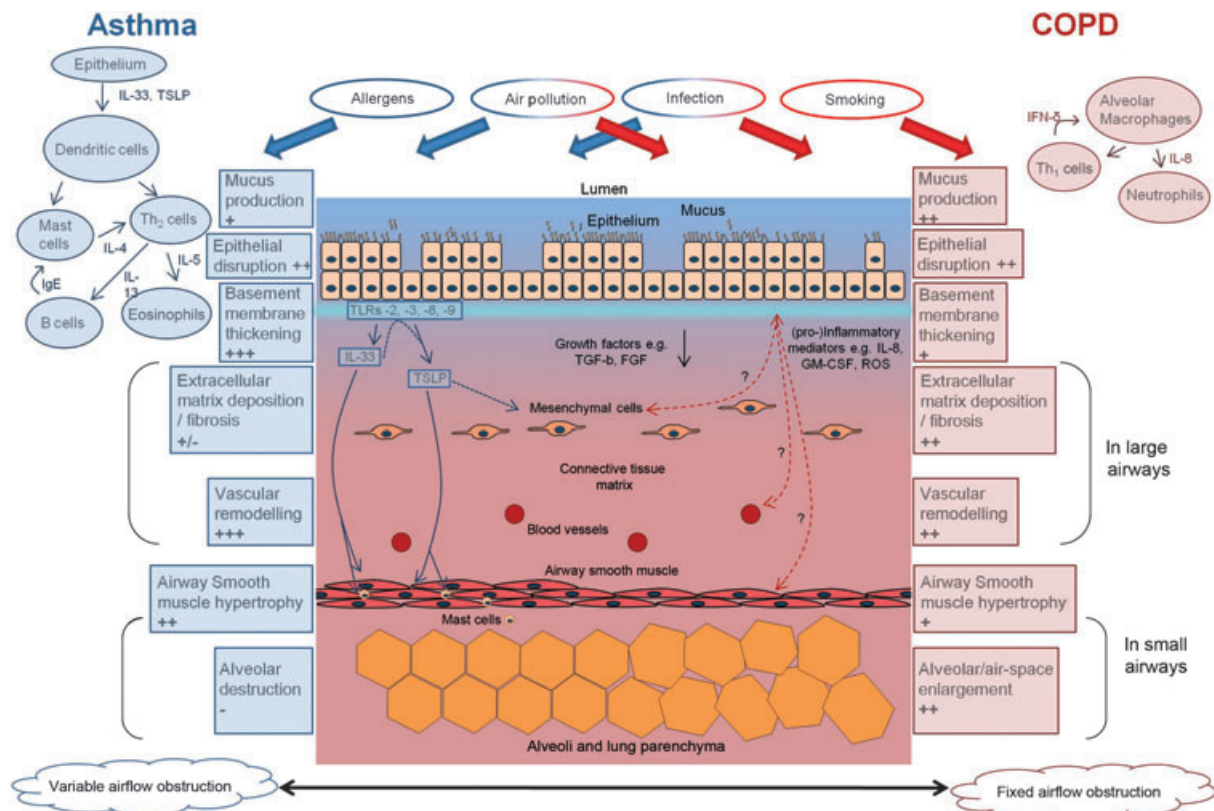


Fig. 1. Immunopathological mechanisms of asthma and COPD. The contrasting immunological, pathological and physiological abnormalities seen in asthma and COPD are compared. Although distinct in many ways, there is considerable overlap between the two conditions.

two conditions has re-awakened the debate around the Dutch hypothesis. The evidence in favour of and against the Dutch hypothesis was recently reviewed in a pair of opposing editorials [1, 8], and is summarized in Table 1.

In light of the above, some authors have suggested abandoning the terms 'asthma' and 'COPD' altogether [9], whereas others have proposed that they should be

retained but only used to refer to patterns of physiological abnormality, namely reversible or FAO respectively [10]. Regardless of the terms used, it remains clear that patients with airway disease form a heterogeneous group and a number of disparate factors may contribute to disease activity and symptoms at a given time in any given individual. Delineating these factors accurately for each particular patient will become increasingly important as

Table 1. Evidence in favour of and against the Dutch hypothesis

Evidence in favour	Evidence against
Asthma and COPD cannot be clearly distinguished physiologically. Patients with severe asthma may develop fixed airflow obstruction over time, whereas patients with COPD often have an element of variable airflow obstruction.	Most patients with asthma and COPD can be readily distinguished on the basis of their clinical features, with an early onset and episodic symptoms in asthma, and a late onset with progressive symptoms in COPD.
Patients with asthma may exhibit neutrophilic airway inflammation whereas some patients with COPD have eosinophilic airway inflammation.	Asthma and COPD have different aetiologies, with atopy being a key driver of asthma, and smoking being the primary cause of COPD.
Asthma and COPD often overlap in their pathological features, with mucous metaplasia and vascular remodelling occurring in both conditions.	Although their pathological features may overlap, asthma is mainly characterized by basement membrane thickening and airway smooth muscle hypertrophy, while in COPD there is prominent goblet cell hyperplasia and alveolar destruction (emphysema).
Airway hyperresponsiveness is a common feature of both asthma and COPD.	COPD is generally far less responsive to corticosteroids than asthma.
Asthma and COPD respond to similar treatments such as inhaled bronchodilators and corticosteroids.	

a number of expensive and novel therapies emerge that are highly efficacious in selected patients, but of little net benefit in others. A schema for assessing each of these factors systematically in the clinic has been proposed previously [9]. This incorporates the following five factors, conveniently labelled A to E:

- A – Airway hyperresponsiveness
- B – Bronchitis (airway inflammation)
- C – Cough reflex hypersensitivity
- D – Damage to the airways and surrounding lung parenchyma
- E – Extrapulmonary factors

These five factors together encompass the main clinico-pathological dimensions of airway disease. In particular, airway disease pathology may be described in terms of airway inflammation (bronchitis), and structural and remodelling changes (damage), whereas airway hyperresponsiveness and cough reflex hypersensitivity account for the day-to-day clinical symptoms of airway disease. Finally, a variety of extra pulmonary factors may impact upon the clinical expression of airway disease, including rhinosinusitis, gastroesophageal reflux disease and obesity.

This review focuses on each of these domains in detail, discussing how each may be assessed and treated in an airway disease clinic, with a particular emphasis on new and emerging investigations and treatment modalities. Each section will end with a short clinical summary, detailing recommendations for practical management and future research. The review concludes with a summary of the A to E approach and a description of how it may inform an integrated and individualized approach to patient management. Throughout the article, we highlight that although relationships certainly exist between the five domains, they are relatively independent of each other in terms of pathophysiology and response to treatment. As such it is likely that they are underpinned by different genetic and environmental factors.

A – Airway hyperresponsiveness

Airway hyperresponsiveness is a fundamental feature of the asthma paradigm and is characterized by the capacity of the airway to narrow in response to a host of direct and indirect stimuli to the airway smooth muscle (ASM). Direct challenge agents such as histamine and methacholine act via receptors located on ASM involved in the regulation of airway calibre. Indirect agents such as cold air, adenosine, mannitol and exercise induce bronchoconstriction by the release of mediators from resident airway cells.

Airway hyperresponsiveness has two relatively independent components, airway sensitivity and airway reactivity. Airway sensitivity refers to a left-shift of the

dose-response curve such that bronchoconstriction begins to occur at lower concentrations of the irritant substance, whereas airway reactivity refers to a steepening of the dose-response curve such that small increments in the concentration of the irritant substance cause a greater degree of bronchoconstriction [11]. Niimi *et al.* investigated the relationship between airway sensitivity and reactivity, and both the degree of airway inflammation and the degree of bronchial wall thickening, as measured by computed tomography (CT) [12]. They found that airway sensitivity, but not airway reactivity, was correlated with eosinophilic airway inflammation. Furthermore, bronchial wall thickening was found to be negatively correlated with airway reactivity. This contrasted with the previously held view that in the presence of bronchial wall thickening a given degree of ASM shortening would cause greater bronchoconstriction through geometrical effects [13]. This observation may explain the apparent discordancy between AHR and airway inflammation that has previously been reported, and highlights the importance of considering these two domains of AHR in studies that utilize it as a biomarker in asthma [14, 15].

Despite the complex relationship between AHR and airway inflammation, measurements of AHR have been proposed as a tool to titrate anti-inflammatory therapy. Sont *et al.* [16] investigated this approach and found that the strategy of stepping up corticosteroid therapy in response to a reduction in methacholine PC₂₀ appeared to reduce mild exacerbations compared with a reference strategy of titrating therapy based upon a composite control measure of symptoms, variable airflow obstruction and FEV₁%. In addition, over a 2-year follow-up period, the AHR group demonstrated a reduction in basement membrane thickening compared with the reference strategy, suggesting that targeting AHR in asthma may modulate factors that drive disease persistence, such as airway remodelling.

Indirect challenge tests, using stimuli such as exercise or inhaled mannitol, are less sensitive, but more specific for clinical asthma than direct challenge tests [17]. Furthermore, although both direct and indirect tests correlate with the degree of eosinophilic airway inflammation, the correlation is stronger with indirect tests [18]. Moreover, treatment with inhaled corticosteroids (ICS) can abolish AHR to indirect stimuli, but a degree of AHR to direct stimuli remains [19]. More recently, a study comparing the titration of ICS against inhaled mannitol PD10 and an asthma symptom-based approach (reference group) demonstrated a significant reduction in mild asthma exacerbations, with a corresponding improvement in symptoms, salivary ECP and methacholine PC₂₀ in the mannitol group [20]. Further studies are required to establish the clinical utility of biomarkers of AHR in titrating asthma therapy and reducing exacerbations.

A number of epidemiological studies have suggested that AHR may be an independent risk factor for the development of FAO in asthma [21–23], suggesting that AHR may be associated with the development of disease persistence. Indeed a recent study examining the role of repeated direct bronchial challenge vs. allergen challenge in asthma has demonstrated that the former may induce structural airway remodelling with thickening of the basement membrane, increased epithelial mucin expression and increased epithelial TGF- β expression (which occurred in the repeated challenge group only), independently of airway inflammation [24]. These observations suggest that AHR may contribute directly to disease persistence in asthma, and that targeting AHR by maintaining bronchoprotection may be an important strategy in disease management. Long-acting β -agonists (LABAs), in combination with ICS, now comprise an important component of asthma and COPD management. Ultra long-acting β -agonists (ultra-LABAs) such as indacaterol, and ultra-long-acting antimuscarinic agents such as aclidinium, have recently been developed, allowing the convenience of once-daily administration [25, 26]. Indacaterol is currently licensed for COPD, and combinations of ICS and ultra-LABAs are in development. Long-acting muscarinic agonists are established in the treatment of COPD, and may have an important role in severe asthma [27]. Further research is required to establish the utility of these agents in the long-term management of airways disease.

Further evidence to support the concept of bronchoprotection in airways disease comes from the observation that AHR is related to the inability of patients with airways disease to dilate their airway in response to a deep inspiration [28]. It is speculated that the loss of these protective effects may contribute to AHR in asthma and may be partly driven by the presence of mast cells within the ASM bundle [29]. The infiltration of ASM by mast cells appears to be an important mechanism of AHR [30], and is linearly related to the degree of AHR [31]. Thus, targeting mediator released by mast cells in the ASM bundle may have utility in the management of patients with airways disease.

Mast cell-derived mediators, such as tumour necrosis factor- α (TNF- α) may modify ASM contractile function and hence increase AHR [32]. An initial randomized controlled trial of etanercept, an anti-TNF- α agent, in refractory asthma showed a significant improvement in methacholine PC₂₀ and asthma quality of life score in the active treatment group [33]. These effects were more marked in the subgroup of patients with high expression of membrane-bound TNF- α by peripheral blood monocytes at baseline, identifying a potentially important biomarker to stratify response. The largest study to date of anti-TNF- α therapy in asthma was a

randomized controlled trial of golimumab in severe persistent asthma [34]. In this study, there were no significant differences between the active and placebo groups with respect to the co-primary endpoints of pre-bronchodilator FEV₁ and the number of severe exacerbations, although post-hoc analysis revealed a significant reduction in exacerbations with active treatment in the subgroup of patients with FEV₁ reversibility greater than 12% at baseline. However, this trial was halted at Week 24 due to excess cases of malignancy and serious infections in the treatment group.

An alternative approach to the management of AHR is to target the ASM itself. A large body of mechanistic evidence supports the notion that the ASM has a number of intrinsic abnormalities in asthma including increased velocity shortening [35], loss of length adaptation [36, 37] and altered calcium signalling [38]. Collectively these processes may contribute to both AHR and the attenuation of deep breath-induced bronchodilatation in asthma. It is likely that targeting these intrinsic abnormalities may lead to novel therapies for AHR. For example, a recent mechanistic study has demonstrated that bitter taste receptors (TAS2Rs) are expressed on human ASM. Activation of these receptors caused relaxation of isolated ASM, attenuation of AHR and dilatation of airways that was threefold greater than that elicited by β -adrenergic receptor agonists (mediated via a large conductance calcium channel) in animal models of allergic asthma [39]. Further studies are required to establish the role of both novel mast cell stabilizing agents and mediator inhibitors in managing AHR in asthma. In addition, establishing sustained bronchoprotection may be an important paradigm in targeting disease persistence in asthma.

Although AHR is usually associated with asthma, it has been known for some years that it is also a common feature of COPD [40]. Airway hyperresponsiveness in COPD is strongly associated with increased mortality (up to 16-fold), independent of baseline lung function [41], suggesting that it may be an important prognostic biomarker. Lung parenchymal destruction in COPD causes a reduction in the tethering forces keeping airways open, resulting in greater airway reactivity [42]. Although at least some of the AHR in COPD may be explained by the long-term structural changes and FAO in this condition, there is evidence that, as in asthma, indirect tests of AHR may correlate with eosinophilic airway inflammation in COPD [43]. Further studies are required to establish the role of AHR in predicting disease risk and response to therapy in COPD.

Clinical summary

Airway hyperresponsiveness is an important diagnostic criterion for asthma and also occurs in COPD, although

the mechanisms may differ. Targeting AHR with ICS may reduce asthma exacerbations, although further research is required in this area. The co-localization of mast cells in the ASM bundle is associated with AHR in asthma and the loss of deep breath-induced bronchodilatation in both asthma and COPD, suggesting that targeting the mast cell-ASM axis may provide novel therapies for asthma/COPD management in the future.

Finally there is emerging evidence linking AHR to airway damage in asthma thus providing a mechanistic link between AHR and disease persistence in asthma. Clinical studies are required to establish the role of sustained bronchoprotection in preventing the development of FAO.

B – Bronchitis

Airway inflammation is a characteristic feature of both asthma and COPD, and as discussed below, treatments that modify airway inflammation result in improved outcomes such as a reduction in acute exacerbations. Therefore, the measurement and treatment of inflammation in both the large and small airways is a key step in patient management. Airway inflammation may be directly measured through microscopic examination of induced sputum. Four main inflammatory subtypes have been identified on the basis of microscopy, namely eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic [reviewed in (44)], as shown in

Fig. 2. Sputum eosinophilia is normally defined as an eosinophil percentage (as a proportion of the total cell count) greater than 3%. This is partly based on data in healthy non-smokers in which the value for mean plus two standard deviations was 2.2% [45, 46]. Simpson *et al.* recommended a cut-off value of 3% to distinguish eosinophilic from non-eosinophilic asthma as this provided optimal reproducibility [47]. A normal range for sputum neutrophil percentage is less easy to define as there is greater variability in this parameter among normal subjects. Furthermore, it is known that sputum neutrophil percentage rises with increasing age [48].

A recent study investigated patterns of induced sputum gene expression at the RNA level in asthmatic and control subjects [49]. Unsupervised hierarchical cluster analysis techniques were used to derive three clusters of gene expression, designated transcriptional asthma phenotype (TAP) 1, 2 and 3. TAP1 and TAP2 corresponded to sputum eosinophilia and neutrophilia respectively. TAP3 corresponded to paucigranulocytic asthma and was similar to the gene expression in normal controls. Interestingly, mixed granulocytic inflammation on sputum microscopy did not map to a distinct TAP, and these patients were mainly grouped under TAP1. On this basis, the authors suggested that mixed granulocytic inflammation may represent a transitional rather than a distinct phenotype. In this study, patients with TAP3 had normal mean FEV₁ and FVC values, in contrast with the TAP1 and TAP2 patients who displayed

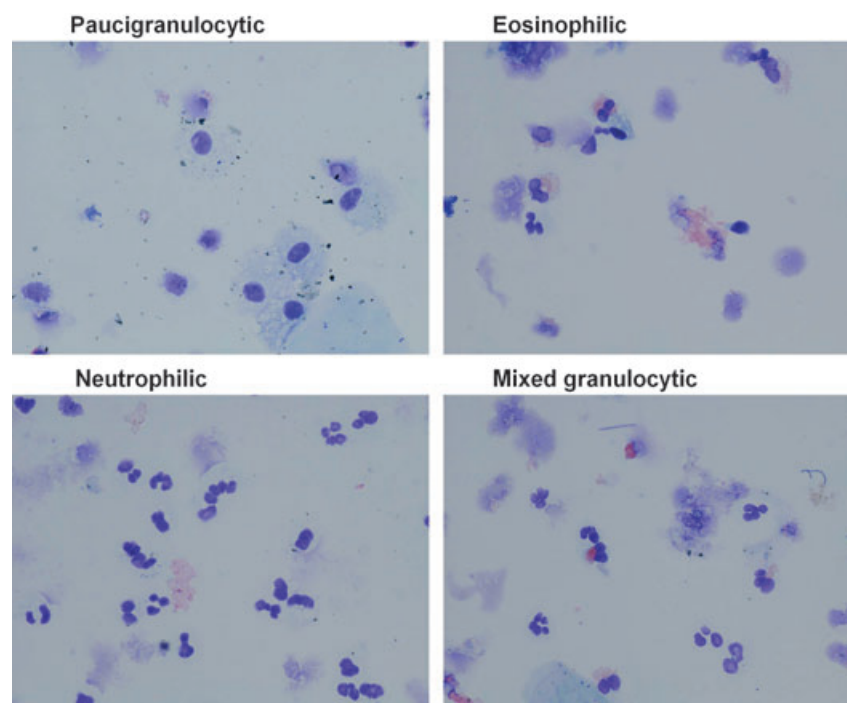


Fig. 2. Phenotyping airway inflammation using induced sputum. The four primary sputum inflammatory phenotypes are illustrated. The slides were produced using a variant of the Romanowsky stain and the images captured at $\times 400$ magnification.

obstructive deficits on spirometry, suggesting that paucigranulocytic asthma may represent a mild asthma phenotype with quiescent airway inflammation. This notion is supported by a recent study comparing inflammatory phenotypes in adults and children with stable or acute asthma [6]. These investigators found that paucigranulocytic asthma was the most common phenotype in both adults and children with stable asthma. In contrast, the inflammatory phenotype was predominantly eosinophilic in children with acute asthma and neutrophilic in adults with acute asthma.

Eosinophilic airway inflammation

There is compelling evidence that the presence of eosinophilic airway inflammation is associated with corticosteroid response [50, 51]. Thus, a natural strategy is to titrate corticosteroid treatment against a marker of eosinophilic airway inflammation, such as the sputum eosinophil count. For instance, Green et al. [52] used an algorithm in which corticosteroid dose was reduced if the sputum eosinophil count was < 1%, kept unchanged if it was 1–3% and increased if it was > 3%. There are four randomized controlled trials (three in asthma and one in COPD) that have compared a sputum-based treatment strategy with standard practice [52–55], as summarized in Table 2. A meta-analysis of the three studies in asthma concluded that sputum-based strategies were effective in reducing exacerbations in adults with asthma without a net increase in mean ICS dose [56]. In the COPD study [55], the rate of severe, but not mild or moderate, exacerbations was reduced in the sputum group compared with the control group.

Fractional exhaled nitric oxide (FeNO) is positively correlated with sputum eosinophilia [57], and thus

FeNO may appear to be an attractive tool for the monitoring of eosinophilic airway inflammation and titration of therapy, its main advantage being ease of measurement. However, clinical trials of this approach have yielded mixed results, with one study reporting a possible benefit [58] whereas others have been negative [59, 60]. A recent meta-analysis of six randomized controlled trials (two in adults and four in children/adolescents) concluded that a FeNO-based strategy did not result in a significantly different exacerbation rate compared with standard management [61].

Although most patients with eosinophilic airway inflammation respond well to ICS, there remains a group who are refractory to treatment and display persistent sputum eosinophilia, even after optimizing inhaler technique and ensuring patient adherence with therapy. The long-term use of oral corticosteroids is necessary in some of these patients, but has a number of significant side-effects including osteoporosis, weight gain, skeletal muscle wasting and steroid-induced diabetes. There is thus a need for effective alternative therapies for patients with refractory eosinophilic asthma.

Interleukin-5 is known to be an important mediator of eosinophilic airway disease. An initial randomized controlled trial of mepolizumab, a monoclonal anti-IL-5 antibody, in 362 unselected patients with persistent asthma found no statistically significant clinical benefit [62]. However, two later trials that specifically targeted patients with refractory eosinophilic asthma showed that mepolizumab significantly reduced exacerbation rates [63, 64], improved Asthma Quality of Life Questionnaire scores [63] and allowed oral prednisolone doses to be successfully reduced [64]. These studies suggest that sputum eosinophil counts may be useful to select appropriate patients for this therapy, although it should be noted that they did not include a comparison group with low sputum eosinophils. Nevertheless, these studies highlight the importance of careful clinical phenotyping to stratify medicines in airways disease [65]. Of note, approximately 30% of patient with COPD have a sputum eosinophilia [7], and targeting IL-5 in COPD warrants further investigation in clinical trials.

The humanized monoclonal anti-IgE antibody omalizumab is the only biological therapy for asthma currently licensed for use in the United Kingdom. A recent systematic review of eight randomized controlled trials concluded that omalizumab reduced the risk of asthma exacerbations in patients with moderate and severe allergic asthma, and allowed a reduction in the use of ICS [66]. Omalizumab has been shown to attenuate eosinophilic airway inflammation [67–69], and this is likely to, at least partially, underlie its beneficial effects.

There is increasing evidence that IL-13 may have a significant role in asthma [70, 71]. In particular, it

Table 2. Studies comparing sputum-based and standard treatment strategies in asthma and chronic obstructive pulmonary disease

Study	Subjects	Results
Green, 2002 [52]	Moderate or severe asthma (74 patients)	Significant reduction in severe exacerbations and hospitalizations in the sputum-based group.
Chlumský, 2006 [53]	Moderate or severe asthma (55 patients)	Significant reduction in exacerbations in the sputum-based group.
Jayaram, 2006 [54]	Asthma (117 patients)	Significant reduction in eosinophilic exacerbations in patients with moderate or severe asthma in the sputum-based group.
Siva, 2007 [55]	COPD (82 patients)	Significant reduction in severe, but not mild or moderate, exacerbations in the sputum-based group.

appears to be an important mediator of eosinophilic airway inflammation, promoting eosinophil transmigration into tissues [72], as well as their survival and maturation [73, 74]. A randomized controlled trial of lebrikizumab, an anti-IL-13 monoclonal antibody, in patients with uncontrolled asthma, showed a significant improvement from baseline in the primary outcome of pre-bronchodilator FEV₁ compared with placebo [75]. This difference was largely confined to patients with evidence of T-helper (T_H) 2 cell activation, evidenced by high levels of serum periostin, thus lending further support to the concept of treatment stratification based on inflammatory biomarkers.

Neutrophilic airway inflammation

It has been known for a number of years that neutrophils are an important effector cell in the chronic airway inflammation of COPD [76]. Moreover, evidence has accumulated for a distinct subtype of asthma characterized by neutrophilic airway inflammation [50, 77, 78]. Neutrophilic asthma is more common in smokers [79], and is associated with airflow limitation [80] and air trapping [81]. Recent evidence suggests that there may be an association between obesity and neutrophilic airway inflammation in women with asthma [82]. An added complexity is that treatment with ICS can produce sputum neutrophilia, potentially resulting in misclassification of the underlying inflammatory phenotype [83].

The mechanisms of neutrophilic bronchitis in asthma have been the subject of recent investigation, with evidence emerging for persistent activation of the innate immune response and persistent bacterial colonization. Simpson *et al.* [84] showed that mRNA expression of toll-like receptor (TLR)2, TLR4 and CD14 was increased in induced sputum from patients with neutrophilic asthma compared with other asthmatics, as well as levels of IL-8 mRNA. Levels of endotoxin, a bacterial product known to activate the innate immune system, were also increased in neutrophilic asthma, suggesting a role for chronic bacterial colonization in the pathogenesis.

Macrolide antibiotics possess anti-inflammatory properties over and above their anti-bacterial activity [85], and are of proven benefit in Japanese panbronchiolitis [86]. There is evidence that macrolides may specifically target neutrophilic airway inflammation. A recent study of 45 patients with refractory asthma found that 8 weeks of treatment with clarithromycin (500 mg twice daily) resulted in significantly reduced levels of sputum IL-8, reduced airway neutrophil numbers and improved quality-of-life scores, with the reduction in inflammatory markers particularly seen in the subgroup of patients with non-eosinophilic asthma.

However, these results should be interpreted with caution, as comparisons between the treatment and placebo groups were not reported [87].

There is increasing evidence that IL-17 produced by T_H-17 cells may play an important role in neutrophilic and corticosteroid-resistant asthma [88]. Elevated serum IL-17 was found to be a significant risk factor for severe asthma [89], and IL-17 mRNA is raised in sputum [90] and bronchial biopsies [91, 92] from patients with asthma. Anti IL-17 monoclonal antibodies have been developed, and at least one clinical trial in persistent asthma is currently underway.

Clinical summary

The optimal treatment of bronchitis (inflammation) forms a cornerstone of airway disease management. Sputum inflammometry is the gold standard for classifying patients' airway inflammatory profile and titrating treatment, and it should be available to all clinicians who manage airway disease. Titration of inhaled and oral corticosteroid therapy using sputum eosinophil counts is proven to improve outcomes and should be utilized in patients with refractory disease. Novel anti-eosinophilic therapies such as mepolizumab are not yet available for general use, but clinical trial data suggest that they are efficacious when targeted to patients with refractory eosinophilic airway inflammation. Once they are available, these therapies are likely to be particularly useful in patients who currently require oral corticosteroids to maintain control of their symptoms and eosinophilic airway inflammation. The evidence base for the treatment of neutrophilic asthma with macrolide antibiotics is currently weak. However, an empirical trial of low-dose antibiotic therapy may be considered in patients who manifest recurrent respiratory tract infections.

C – Cough reflex hypersensitivity

Chronic dry cough that is out of proportion to other symptoms may occur in isolation, or in association with asthma or COPD. Patients manifesting this symptom often present a difficult clinical problem, particularly once common causes, such as rhinosinusitis, gastroesophageal reflux disease and angiotensin converting enzyme inhibitor use have been excluded. Chronic cough may be associated with considerable impairment of quality of life that may be measured using standardized questionnaires, such as the Leicester Cough Questionnaire [93].

The sensitivity of the cough reflex may be measured objectively using the capsaicin (or citric acid) challenge test, in which different concentrations of capsaicin or citric acid are inhaled, followed by counting the number

of coughs in the 10 s following inhalation. Dose-response curves can be derived from this data, giving the concentration required to produce two coughs and five coughs, designated D2 and D5 respectively [94]. Digital cough monitors have been developed to assess the frequency of cough on a day-to-day basis. These consist of a portable microphone connected to a digital sound recorder. Once the recording is complete it is downloaded to a computer to be analysed by an automated cough detection algorithm. One such digital cough monitor, the Leicester Cough Monitor, showed good sensitivity and specificity when validated against the gold standard of manual cough counting by a trained observer [95]. The value of objective measures of cough reflex sensitivity and cough frequency was demonstrated by the study of Decalmer et al. [96] who found a moderate correlation between objective and subjective measures of cough frequency.

It is well-established that a subgroup of patients with chronic cough has demonstrable eosinophilic airway inflammation, a condition known as eosinophilic bronchitis (EB) [13]. Eosinophilic bronchitis is characterized by eosinophilic airway inflammation, but an absence of AHR [14], thus distinguishing this condition from asthma, including cough-variant asthma. EB has emerged as powerful disease-control model to study the immunopathological mechanisms of AHR in asthma. We have identified that mast cell infiltration of the ASM in central airways [97] and reduced luminal patency [98], as well as the expression of IL-13 in tissue and sputum [99, 100], are the key features that differentiate asthma from EB without asthma. This would indicate that AHR is driven by the interaction of mast cells with the ASM [which are intimately juxtaposed (101)], and altered luminal patency. Indeed we have recently demonstrated that ASM cells co-cultured with human lung mast cells have increased contractile protein expression [102]. Studies comparing structure and function in EB and asthma have provided unique insights into the immunopathological mechanisms of AHR in asthma (Fig. 3). Patients with EB usually respond well to ICS, with a marked reduction in both sputum eosinophilia [103, 104] and cough reflex sensitivity [104]. However, a small proportion may go on to develop FAO which resembles the phenotype of patients with COPD and sputum eosinophilia [105].

It has recently been established that in some cases, chronic cough may be an upper airway disorder closely related to vocal cord dysfunction (VCD) [106]. A study of 25 adults with chronic persistent cough and 11 healthy controls found that 14 of 25 patients with chronic persistent cough exhibited paradoxical vocal cord movement on laryngoscopy (56%), compared with 1 of 11 healthy controls (9.1%), a statistically significant difference [107]. Moreover, a randomized

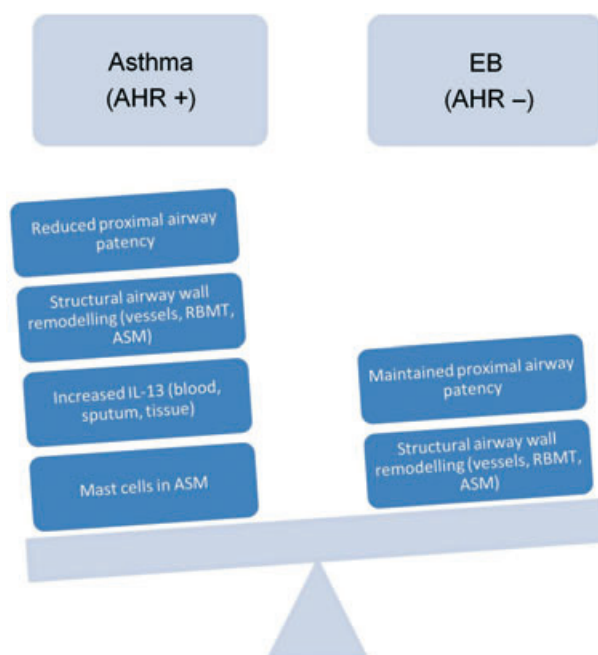


Fig. 3. Non-asthmatic eosinophilic bronchitis: towards understanding the mechanisms of airway hyperresponsiveness. Asthma is distinguished from eosinophilic bronchitis by the respective presence or absence of airway hyperresponsiveness (AHR), thought to be mediated by mast cell infiltration of airway smooth muscle in the presence of reduced proximal airway patency. This concept highlights the independence of AHR and airway inflammation (bronchitis). AHR, airway hyperresponsiveness [(+) present, (–) absent]; ASM, airway smooth muscle; EB, non-asthmatic eosinophilic bronchitis; RBMT, reticular basement membrane thickening.

controlled trial of speech therapy in 87 patients with chronic cough reported improved symptom scores in both the placebo and treatment groups, but with significantly greater improvement in the treatment arm compared with the placebo arm [108].

There is some evidence for an association between chronic cough and organ-specific autoimmune disease. Birring et al. [109] found that both self-reported autoimmune disease and organ-specific autoantibodies were more common in patients with idiopathic chronic cough than in age and sex-matched controls. A further study found that women with treated hypothyroidism had increased cough reflex sensitivity compared with age and sex-matched normal controls [110]. The finding of bronchoalveolar lavage fluid lymphocytosis in some patients with idiopathic chronic cough lends further support to an autoimmune aetiology [111].

Cough reflex hypersensitivity may be considered a neuropathic disorder. A syndrome of hereditary sensory neuropathy, chronic cough and gastro-oesophageal reflux disease (GORD) has been linked to chromosome 3p22–p24 [112]. Furthermore, a family has been

described in which a mutation in the peripheral myelin protein zero gene resulted in late-onset sensorimotor neuropathy, tonic pupils and chronic paroxysmal cough [113]. Chronic cough may be caused by sensory neuropathy of the superior or recurrent laryngeal nerve, with one study reporting that gabapentin may give symptomatic relief in these patients [114]. A small study of 28 patients with post-viral cough, presumed to be due to post-viral vagal neuropathy, showed improved symptomatic relief with low-dose amitriptyline compared with codeine/guaifenesin [115]. Furthermore, there is evidence that vitamin B₁₂ deficiency may contribute to chronic cough, perhaps due to sensory neuropathy, and that replacement therapy in vitamin B₁₂-deficient patients with chronic cough can lead to symptomatic improvement [116].

Although the cough reflex is clearly an important protective response, in some patients it is so sensitive as to impact on day-to-day activities and sleep, without serving any useful purpose such as the expectoration of sputum. Unfortunately, there is a paucity of effective therapies for suppression of the cough reflex. Although opiates have some efficacy through central actions, their side-effects, including sedation and dependence, make them an undesirable long-term option. A more attractive solution would be to selectively target the vagal afferent nerves responsible for mediating the cough reflex. There are at least two types of nerve fibre involved. Rapidly conducting myelinated A- δ fibres mediate the involuntary protective cough that is triggered by aspiration, whereas slowly conducting unmyelinated C-fibres mediate the characteristic itchy urge-to-cough sensation that is associated with respiratory tract infections, and culminates in a voluntary cough [117]. It is speculated that suppression of the C-fibre mediated pathway may be of clinical benefit in patients with chronic cough. Two transient receptor potential (TRP) channels, TRPV1 and TRPA1 appear to be particularly important stimulators of this pathway [117], and future therapies for chronic cough may target these receptors specifically.

Clinical summary

Chronic dry cough that is out of proportion to other symptoms may occur in both asthma and COPD, or in isolation. Specific treatment options are currently lacking, and the mainstay of therapy is the management of co-morbid conditions, such as rhinosinusitis and gastroesophageal reflux disease. Chronic cough appears to be related to VCD in some cases, and speech therapy may be helpful in these instances. Future therapies for chronic cough may specifically target the transient receptor potential channels TRPV1 and TRPA1.

D – Damage

A hallmark of both asthma and COPD is progressive alteration in the architecture of the airways and surrounding lung parenchyma. Classical manifestations of this include basement membrane thickening and ASM hypertrophy in asthma [31]. Chronic obstructive pulmonary disease is characterized pathologically by airway wall thickening, due to connective tissue deposition and the accumulation of inflammatory exudate in the airway lumen [118], as well as by lung parenchymal destruction (emphysema). Recently it has been appreciated that small airway remodelling and obstruction occurs early in the natural history of COPD, before the development of frank emphysema [119].

Fixed airflow obstruction is an important feature of both COPD and severe asthma [120–122], although the link between FAO and specific remodelling changes has not been definitively proven. Fixed airflow obstruction is a predictor of mortality in patients with airways disease [123, 124], and population studies have shown an association between reduced FEV₁, regardless of cause, and cardiovascular mortality [125]. The rate of decline of FEV₁ in patients with asthma and FAO is positively correlated with baseline FeNO and sputum eosinophil counts, whereas in patients with COPD, the rate of decline is positively correlated with baseline sputum neutrophil count and exacerbation frequency [5]. These data suggest that there is a link between airway inflammation and progressive airflow limitation, although this remains to be proven by longitudinal mixed effects studies linking serial eosinophil counts in sputum with lung function decline. Interestingly, it has been shown that poor airway function in infancy strongly predicts airflow obstruction in young adulthood [126]. Thus, early life events may predispose to the development of COPD in adulthood.

It has been established that smoking cessation markedly slows the rate of decline of FEV₁ in patients with COPD [127]. There is conflicting evidence as to whether the rate of decline can also be influenced by pharmacotherapy. A recent systematic review concluded that long-term ICS did not significantly affect the rate of FEV₁ decline in patients with COPD [128]. However, a recent large study of tiotropium in COPD showed an improvement in FEV₁ following 48 months of treatment, compared with placebo [129].

Advanced imaging and physiological techniques are currently being developed to enable the non-invasive assessment of large and small airway remodelling in asthma and COPD. Quantitative CT scanning may be used to derive standard measures of large airway remodelling, such as the wall area percentage (WA%), luminal area and wall thickness [130], as well as the degree of air trapping [131] (see Fig. 4). A recent series

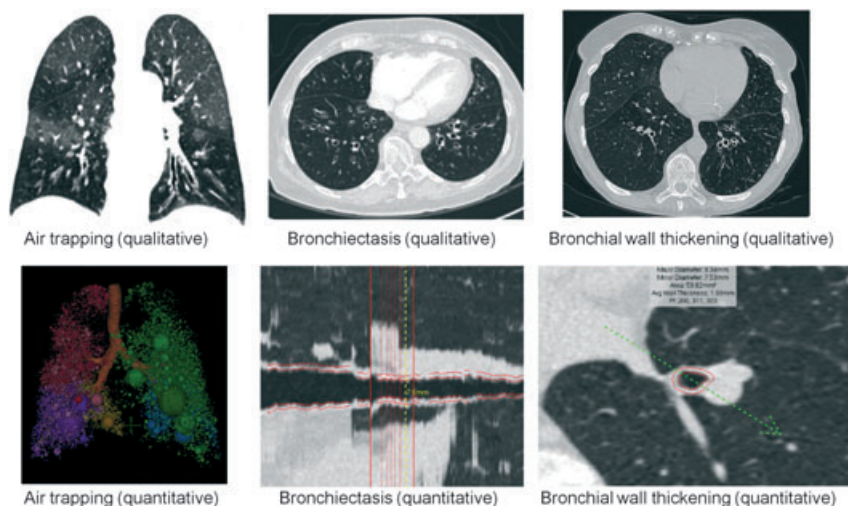


Fig. 4. Qualitative and quantitative analysis of computed tomography images in patients with airways disease. Air trapping, bronchiectasis and bronchial wall thickening may be assessed qualitatively using standard expiratory and inspiratory computed tomography (CT) scans. Quantitative assessment of these features may also be performed using specialized software. The images shown were produced using Pulmonary Workstation 2.0 (VIDA Diagnostics Inc., Coralville, IA, USA).

of high-resolution CT scans in patients with severe asthma showed bronchial wall thickening in 62%, bronchiectasis in 40% and radiological emphysema in 8% of cases [132]. Radiological abnormalities can be correlated with physiological and immunopathological changes. For instance, a study of quantitative CT in patients with severe asthma found that bronchial wall thickening was associated with persistent airflow obstruction and neutrophilic airway inflammation [133]. Few longitudinal studies have assessed the role of CT metrics as biomarkers in airways disease. Haldar et al. demonstrated that 12 months of therapy with mepolizumab reduced airway wall area when compared with placebo [63]. However, few studies have defined the minimal important difference required for interventional studies using CT metrics, and radiation exposure is likely to limit the use of longitudinal imaging in airways disease [134]. Computational fluid dynamics is an emerging technique which allows modelling of airflow through obstructed airways [135]. It is currently a research tool and not yet in widespread clinical use, but it may offer promise in studies predicting drug deposition and response to bronchial thermoplasty by identifying flow-limiting airway segments.

A number of tools have been proposed to specifically assess small airway structure and function, including both radiological and physiological techniques. Busacker et al. demonstrated that air trapping on expiratory CT scans, measured quantitatively, correlated with severe exacerbations and ITU admission in asthma [81]. MRI following inhalation of hyperpolarised ^3He is an alternative imaging technique that allows the assessment of molecular diffusion to characterize alveolar

airspace size [136]. Although it provides less morphological information than high-resolution CT, it may be a more sensitive measure of alveolar destruction [137], and has the advantage of not subjecting the patient to ionizing radiation. Emerging physiological tools for the assessment of small airway function include forced oscillation at low frequencies [138, 139], and single or multiple-breath gas washout techniques [140]. Further clinical studies are required to assess the analytical and clinical validity of these emerging small airway biomarkers.

Although both asthma and COPD are underpinned by chronic inflammation, the resulting structural abnormalities are a prime cause of morbidity and mortality in these conditions. Bronchiectasis often occurs in conjunction with COPD and severe asthma. As it cannot be reversed, the mainstays of therapy are supportive. Physiotherapy should be provided and patients taught effective sputum clearance techniques. Antibiotics should be used early to treat exacerbations, with the choice of agent based on recent sputum cultures. Long-term antibiotics may be considered in refractory cases. Allergic bronchopulmonary aspergillosis (ABPA) is a condition in which long-term colonization of the airways with, and sensitization to, the fungus *Aspergillus fumigatus* results in airway inflammation and bronchiectasis in patients with asthma. A number of studies have shown that patients with ABPA benefit from treatment with itraconazole [141–143].

Fungal sensitization in the absence of ABPA is common in severe asthma, particularly to *Aspergillus* and *Penicillium* spp. which are found indoors and are thermophilic, allowing them to colonize the airways. We

have found that patients with asthma who are IgE-sensitized to *A. fumigatus* have both a lower post-bronchodilator FEV₁ than non-sensitized asthmatics of similar severity, and high rates of positive sputum culture for *A. fumigatus* [144]. This observation has also been noted in a cross-sectional study of a severe asthma clinic in which an increased rate of bronchiectasis was seen in sensitized patients [145]. This raises the possibility that chronic colonization of the airways with fungi is a significant cause of lung damage.

Bronchial thermoplasty is an emerging technique that involves the application of thermal energy to the bronchial walls. It may ameliorate AHR in asthma by reducing ASM mass. Bronchial thermoplasty has been evaluated in three randomized controlled trials [146–148]. The most recent of these, the AIR2 Trial [148], found that patients who received the active treatment had improvements in asthma-specific quality of life and had fewer exacerbations in the period from 6 to 52 weeks after the procedure, compared with those who received sham bronchoscopy. However, there was a 6% rise in hospitalizations among treated patients during the 6 weeks immediately following the procedure. Furthermore, it should be noted that in this study, exacerbations were assessed as a secondary outcome measure, so the finding of reduced exacerbations in the period from 6 to 52 weeks should be considered hypothesis-generating. The two previous studies, designated AIR1 and RISA [146, 147], examined the role of bronchial thermoplasty in moderate to severe and severe persistent asthma respectively. Neither of these studies was sham thermoplasty-controlled. Interestingly the RISA study failed to identify significant improvements in direct AHR post-thermoplasty, in contrast with a preliminary study that identified a significant (approximately three doubling dose) improvement in AHR at 1 year post thermoplasty [149]. AIR1 identified a significant improvement in morning peak flow in the thermoplasty group, but AHR was not assessed. These results call into question the putative mechanism of efficacy of bronchial thermoplasty, and further studies evaluating targeted thermoplasty to proximal airways that are maximally thickened (identified using CT) or that exhibit flow limitation identified using functional magnetic resonance imaging, may allow more accurate stratification of thermoplasty patients. Future studies of thermoplasty should also assess the effects of the treatment on histological outcomes and airway inflammation.

Lung volume reduction surgery (LVRS) is now a well-established treatment modality for selected patients with COPD. By surgically resecting emphysematous lung tissue, hyperinflation is ameliorated, thus allowing the respiratory muscles to once again act at a mechanical advantage. A recent large trial of LVRS showed

functional and symptomatic benefits in patients with heterogeneous upper-lobe-predominant emphysema, with additional mortality benefits in those patients who also had low exercise capacity at baseline [150]. However, correct patient selection is critical as the risk of death following LVRS is markedly increased in patients with FEV₁ < 20% predicted and either homogeneous emphysema or carbon monoxide diffusing capacity < 20% predicted [151].

Novel bronchoscopic therapies are emerging that may provide valid alternatives to LVRS. Endoscopic lung volume reduction (ELVR) involves the bronchoscopic placement of one-way valves within segmental and sub-segmental bronchi that supply hyperinflated areas of lung, thus causing their collapse. A recent large clinical trial of this technique found that in patients with heterogeneous emphysema, ELVR produced modest improvements in FEV₁ and 6-min walk test, but at the expense of a greater frequency of pneumonia, exacerbations of COPD and haemoptysis [152]. Endoscopic airway bypass is a further technique that is still in its infancy [153]. Stents are inserted through the bronchial wall at the level of the segmental bronchi, creating an internal bronchopulmonary channel and allowing trapped air to escape. A randomized sham-controlled trial is currently underway in patients with homogeneous emphysema [154]. It is thought that this technique makes use of collateral ventilation, the movement of air along non-anatomical pathways [155], and it is possible that potential responders could be identified by assessing the extent of collateral ventilation, for instance using a technique, such as xenon-enhanced dynamic dual-energy CT [156].

Clinical summary

Structural changes associated with airway disease that may be apparent on a CT scan include bronchiectasis, bronchial wall thickening and emphysema. Bronchiectasis is managed supportively with physiotherapy and prompt treatment of exacerbations with antibiotics. ABPA is a common co-morbid condition which should be screened for and treated with antifungal agents if diagnosed. Lung volume reduction surgery may provide symptomatic improvement in carefully selected patients with upper lobe-predominant emphysema and reduced exercise capacity, while novel endoscopic alternatives appear promising, but are not yet in common use. Bronchial thermoplasty appears to reduce asthma symptoms and exacerbations for a period of up to 1 year, but at a cost of increased hospitalizations in the 6 weeks immediately following the procedure. Further studies are required to determine which patients are most likely to benefit from this procedure, and whether outcomes can be improved further by targeting thermoplasty to

airways in which the ASM is most thickened. Finally, biomarkers of small airway dysfunction such as air trapping on expiratory CT imaging and airway closure markers measured using inert gas washout may prove to have utility in predicting severe asthma exacerbations, and further studies are required to assess the clinical utility of these imaging and physiological biomarkers in predicting outcomes in airways disease.

E – Extrapulmonary factors

Common extrapulmonary factors that may modify the clinical expression of airway disease include GORD, allergic rhinitis and obesity. A recent placebo-controlled trial of esomeprazole in patients with poorly controlled asthma and minimal or no symptoms of GORD produced no improvement in asthma control, despite the high prevalence of asymptomatic gastro-oesophageal reflux, as ascertained by ambulatory pH monitoring, in this group of patients [157]. Other studies have demonstrated some clinical benefit, particularly in patients with symptoms of GORD, although such benefits were generally modest [158, 159]. Allergic rhinitis and asthma often co-exist, and there is some evidence that treatment of allergic rhinitis with intra-nasal corticosteroids may improve asthma control [160, 161]. Obesity appears to be associated with a more severe asthma phenotype [162]. Possible mechanisms for this include an alteration in lung mechanics, an increase in systemic inflammation or glucocorticoid insensitivity. In some cases, obstructive sleep apnoea may contribute to the clinical picture – a recent study found that obstructive sleep apnoea-hypopnoea was more common in patients with severe asthma than in patients with moderate asthma, or in control subjects matched for age and BMI [163]. Although few studies have been performed in this area, there is some evidence that weight loss may result in improved asthma control in some obese asthmatic patients [164].

Although it is well-established that asthma and atopy are strongly associated, it is not known whether or not allergen exposure can trigger exacerbations. Murray et al. found that in children with asthma, allergen sensitization and exposure, in combination with viral infection but not alone, was associated with a markedly increased risk of admission to hospital due to an exacerbation of asthma [165]. The triad of asthma, aspirin-sensitivity and nasal polyposis has been recognized for at least 40 years [166] and is thought to be mediated by the over-production of cys-leukotrienes in response to cyclo-oxygenase inhibition [167]. Anti-leukotriene drugs are certainly effective in patients with aspirin-intolerant asthma, but it remains unknown if their efficacy is greater in this group than in patients with asthma in general [167].

Functional and psychological factors often complicate the clinical picture in patients with airway disease. Vocal cord dysfunction refers to inappropriate adduction of the vocal cords, resulting in partial airway obstruction [168]. It may masquerade as or co-exist with asthma, often resulting in a fruitless escalation of therapy and recurrent emergency department visits. The diagnostic gold standard is laryngoscopy and direct visualization of the vocal cords during symptoms, but this is rarely practical. Speech therapy is the mainstay of management. Dysfunctional breathing is an abnormal pattern of breathing often associated with hyperventilation. It may be confused with, or occur in association with, asthma and other airway disorders. Thomas et al. [169] found a prevalence of 29% among patients with asthma in a primary care setting, using the Nijmegen questionnaire as a screening tool. Among subjects without asthma, the prevalence was significantly lower, being 14% in women and 2% in men [170]. Once recognized as a contributory feature in a particular individual, dysfunctional breathing may respond to breathing retraining provided by a specialist physiotherapist [171, 172].

Despite advances in therapy over the past two decades, asthma continues to cause hundreds of preventable deaths among young people each year in the United Kingdom. These deaths are often associated with adverse psychosocial factors, such as psychosis, alcohol or drug abuse, financial or employment problems and learning difficulties [173]. Asthma death is also related to reduced use of primary care services [174] and poor adherence with therapy [175]. It has been shown that non-adherence with prescribed treatment is common among patients with difficult asthma [176]. Thus, objective measures of adherence, such as general practitioner repeat prescription records, should be routinely consulted in patients with refractory asthma.

There is a high prevalence of depression among patients with COPD. In one large study, 26% of patients with COPD were depressed, compared with 12% of smokers without COPD and 7% of non-smokers [177]. Depression in patients with COPD was significantly associated with fatigue, poor quality-of-life score, younger age, female gender, history of cardiovascular disease and current smoking status. Therefore, screening for depressive illness in patients with chronic airways disease should be more widely adopted.

Advanced COPD is characterized by severe and distressing exertional dyspnoea due to dynamic hyperinflation. This results in avoidance of physical activity and subsequent deconditioning, with associated skeletal muscle atrophy and weight loss. The remaining skeletal muscle is also dysfunctional, and although the precise mechanisms of this are not completely understood, systemic inflammation, malnutrition and tissue hypoxia

are thought to play a role [178]. Pulmonary rehabilitation is a well-established treatment for COPD, and has been defined by the American Thoracic Society and the European Respiratory Society as an 'evidence-based, multidisciplinary and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities' [179]. Although pulmonary rehabilitation is a comprehensive intervention incorporating diverse components, such as self-management education and psychological counselling, its primary focus is on exercise training, particularly with the aim of improving skeletal muscle function and strength. It is not yet known whether pulmonary rehabilitation can be effectively delivered at home, or whether it is beneficial in the acute post-exacerbation setting. Creatine supplementation during pulmonary rehabilitation has been investigated, but does not appear to improve outcomes [180]. The role of pulmonary rehabilitation in asthma is not currently established since there are few studies that have addressed this question.

Clinical summary

The treatment of extrapulmonary factors that may impact upon airway disease is a crucial component of management that is often rewarded by symptomatic improvement. Rhinosinusitis may be treated with intra-nasal corticosteroids, and referral to an otorhinolaryngologist may be required if nasal polyps are a troublesome feature. Gastroesophageal reflux disease often responds to a combination of a proton pump inhibitor and a prokinetic agent, such as metoclopramide. Obesity is a common feature of severe asthma,

and although there is little positive evidence that weight loss improves asthma symptoms, it is reasonable to refer patients to a dietician for advice on losing weight, as this is likely to have additional health benefits. Respiratory physiotherapists also have much to offer the patient with airway disease, including the management of dysfunctional breathing and vocal cord dysfunction. Pulmonary rehabilitation is proven to improve outcomes in patients with COPD. A role for pulmonary rehabilitation in asthma has not yet been established, but it may be particularly beneficial in patients who are chronically limited by reduced exercise capacity. Finally, the role of psychosocial factors should not be underestimated. Poor adherence with therapy is common, and should be formally assessed by the inspection of repeat prescription records in patients with refractory asthma, particularly if immunosuppressive or biological therapies are under consideration. The involvement of psychologists or psychiatrists may assist with problems such as anxiety or depression.

Summary of the integrated A to E approach

Airway disease is a heterogeneous condition with multiple domains that may be conveniently labelled A to E, as illustrated in Fig. 5. Although these domains are relatively independent, they can interact to a certain extent. For instance, B (bronchitis) may lead eventually to remodelling and structural changes (D – damage), whereas structural changes that precipitate airway remodelling and reduced luminal patency may in turn contribute to A (AHR). Table 3 summarizes the investigations and treatment options available in the management of patients with difficult-to-treat airway disease.

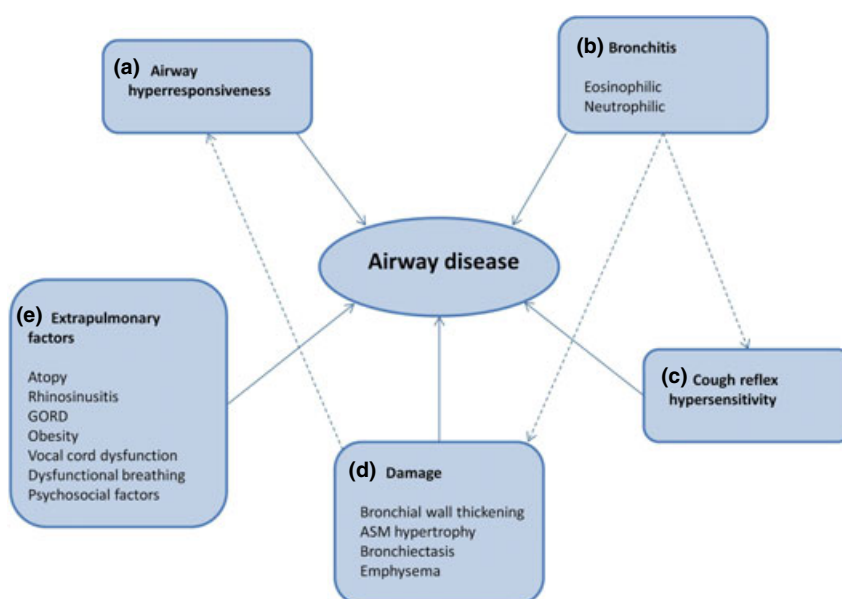


Fig. 5. The A to E approach to airway disease.

Table 3. Summary of the A to E approach to refractory airway disease

Domain	Key investigations	Current treatment options	Emerging treatment options
Airway hyperresponsiveness	Methacholine PC ₂₀	SABAs and LABAs, antimuscarinics	Ultra LABAs, bronchial thermoplasty
Bronchitis	Induced sputum cell count Fractional exhaled nitric oxide	Inhaled corticosteroids Oral corticosteroids Anti-leukotrienes Anti-IgE Antibiotics	Anti-IL-5 Anti-IL-13 Anti-IL-17
Cough reflex hypersensitivity	Capsaicin (or citric acid) challenge Digital cough monitor	Simple linctus Opiates Speech therapy	TRPV1/TRPA1 antagonists
Damage	High resolution quantitative CT	Smoking cessation Antifungal agents (ABPA) Antibiotics (bronchiectasis) Lung volume reduction	Bronchoscopic LVRS Bronchial thermoplasty
Extrapulmonary factors	Skin prick and RAST allergy tests Nasopharyngoscopy Oesophageal pH monitoring Objective adherence checks	Allergen avoidance Nasal corticosteroids Proton pump inhibitors Dietician advice Breathing retraining Pulmonary rehabilitation	Acute post-exacerbation pulmonary rehabilitation

ABPA, allergic bronchopulmonary aspergillosis; LABA, long-acting β -agonist; LVRS, lung volume reduction surgery; TRP, transient receptor potential.

These should be integrated into a personalized management plan for each patient.

Conclusion

It is overly simplistic to divide airway disease into two categories, asthma and COPD. Patients are best served by separately considering a number of dimensions that may affect the clinical expression of disease and providing individualized care accordingly. This review has presented a convenient and easy to remember schema that may be used in clinical practice to direct investigations and guide appropriate therapy. Although others may certainly be devised, the authors feel that the A to E approach has merit and should be adopted more widely. It is likely that such an approach will further drive the much-needed stratification of existing and emerging therapies in airways disease.

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Conflict of interest

AJW has sat on advisory boards for GSK and TEVA, and has received funding for research from GSK and Pfizer. RG has received support for attendance at meetings from Novartis and Pfizer, and a fee from Astra Zeneca for speaking at meetings. In the last 5 years IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Ingelheim and GSK. He has received honoraria for attending advisory panels with Almirall, Astra Zeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey and Napp. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca and Napp. He is Chief Medical Advisor to Asthma UK, a member of the BTS/SIGN Asthma Guideline Group, and joint Editor-in-Chief of Thorax. Neither IDP nor any member of his family has any shares in pharmaceutical companies. VR, SS and SG have no competing interests to declare.

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