A new approach to the classification and management of airways diseases: identification of treatable traits

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Introduction

The symptoms of asthma have been recognised and described at least since the time of the Ancient Egyptians, who used inhaled smokes of various plants as a treatment[1]. The first recorded use of the term asthma, from the Greek *aazein* for panting, was by Hippocrates (360-470 BC). It has, over time, evolved from a symptom-based descriptor to a more specific label encompassing symptoms, abnormality of airway function and airway inflammation. The asthma we recognise today is a common, chronic inflammatory condition of the airways which affects 5-10% of the UK population and over 300 million people worldwide[2]. It is characterised by episodes of shortness of breath, wheeze and cough due to airflow limitation as a result of an increased tendency of the airway to narrow (airway hyperresponsiveness), airway mucosal inflammation and increased airway mucus production. Chronic obstructive pulmonary disease (COPD) is a largely smoking related, inflammatory condition of the airways. It is the second most common respiratory condition in the UK after asthma and affects around 4% of the population aged over 40. The term COPD captures a range of conditions, mainly chronic bronchitis and emphysema. Conventionally a diagnosis of asthma requires demonstration of variable airflow obstruction, currently the defining abnormality for diagnosis, whereas COPD requires demonstration of fixed airflow obstruction These characteristics are also used for monitoring of the disease. Implicit in this approach, and in the step-wise, one-size-fits-all guideline-based management approach that follows, is the assumption that these components are homogeneous and causally linked (figure 1).

[Figure 1]

It is now clear that neither assumption is correct and that our current classification system of airways diseases over-generalises a complex and heterogeneous mix of pathophysiologically distinct mechanisms responsible for morbidity in patients. There is a concern that retaining these labels[3]

may be one of the reasons we have seen a stalling in improvements in key clinical outcomes[4] and poor progress in new drug discovery[5].

In this review we outline a new strategy to stratification which recognises the clinical and biological complexity of airways disease and its common comorbidities. It acknowledges that both clinical patterns of disease and mechanistic pathways can occur in isolation or in combination in any given patient and may change over time, either as a part of the natural history of the disease and/or as a consequence of therapy. It is clinically operationalised by treating, in a targeted fashion, components that can be recognised and modified (treatable traits). This approach avoids making unproven causal links and escapes the current rigid "diagnostic label" approach. We believe it paves the way for more precision, efficient and safe use of existing therapy and that it has been the key factor driving recent encouraging progress in new drug discovery.

Why change? Difficulties with the current taxonomy of airway disease

Incorrect assumptions

Two assumptions are commonly made when making a diagnosis of airways disease and planning treatment: first, that the condition is homogeneous and therefore suitable for one-size-fits-all type management; and second, that symptoms and abnormalities of airway function are directly and causally linked to eosinophilic airway inflammation. These assumptions underpin guidelines for the management of asthma (figure 2), which recommend a step-wise increase in anti-inflammatory medications to achieve control of symptoms and optimal lung function[6]. Current guidelines for COPD also suggest that treatments are increased based on symptoms, exacerbation history and lung function[7]. New insights gained from the widespread use of non-invasive measures of airway inflammation has shown that neither assumption is correct.

[Figure 2]

Unexpectedly these techniques have shown that 'asthma' and other airways diseases consist of a heterogeneous mix of pathologically distinct processes. For example, eosinophilic airway inflammation, hitherto regarded as a defining characteristic of asthma, is in fact present in only 40-50% of patients and its presence is not strongly associated with traditional measures including lung function and symptom scores. Moreover, the same pattern of airway inflammation can be identified in patients with COPD and chronic cough, conditions that are seen as distinct and are managed differently. The presence of eosinophilic airway inflammation is associated with the risk of attacks and the likely benefit of corticosteroid treatment[8-10] so misclassification of pathology on the basis of our current classification system could be associated with sub-optimal targeting of this treatment. In support of this, studies have shown that management guided by non-invasive measures of eosinophilic airway inflammation rather than traditional measures results in better outcomes and more economical use of treatment irrespective of the diagnostic label[8,11-13]. The benefit of inflammation control on the risk of future exacerbations is much greater than that seen with symptoms and measures of airway function, demonstrating that these features are to some extent disconnected (figure 3).

[Figure 3]

Stalling of progress

Patients with asthma are at risk of asthma attacks, where symptoms and airflow limitation worsen and become less responsive to bronchodilator therapy. These attacks are the most clinically important aspect of the disease as they can result in severe symptoms requiring unscheduled medical help, hospital admission and, in some cases, death. Hospital admission rates and deaths from asthma in most developed countries halved in the 10-15 years after the publication of the first asthma treatment guidelines advocating earlier and more aggressive use of inhaled corticosteroids

in 1989. However, it is of concern that these outcomes have not improved much over the last 10 years despite increased spending on treatment [14]. Asthma attacks still result in around 1200 deaths every year in the UK. The National Review of Asthma Deaths (NRAD), a multi-agency review of all suspected asthma mortality in the UK[15], looked in detail at 195 asthma deaths in the UK between 2012-2013 and concluded that the majority were the result of basic errors in asthma management and were thus readily preventable. It is hard to escape the conclusion that this reflects poor targeting of treatment and/or an inability to sell the concept of prophylactic treatment to patients. A key question is the extent to which this is a result of our current classification system, which takes no account of either the pathological heterogeneity of airway disease, or the disconnection between current symptoms and future risk of attacks. We suggest that 25 years after the introduction of guidelines we have reached a turning point where the clinical community need to decide whether we continue on our current path (more inhaled corticosteroids in more lungs), or adopt an alternative, precision-based strategy founded on a more detailed analysis of the mechanisms driving adverse asthma outcomes (more inhaled corticosteroids in the right lungs).

Hindering new drug discovery

The shortcomings of our current approach to the classification of airway diseases and the incorrect assumptions that are made when applying diagnostic labels is illustrated most compellingly by the history of new drug discovery in asthma. Oral corticosteroids are a lifesaving treatment and represent one of the mainstays of treatment today. However, a Medical Research Council study in 1956 of oral corticosteroids in asthma [16] showed no benefit over bronchodilator treatment. This was a surprise to experienced chest physicians, who had seen the beneficial effects of oral corticosteroids in their asthma patients. Dr Morrow Brown conducted a further trial of oral corticosteroids in asthma in 1958, this time also evaluating the sputum of subjects prior to treatment using his medical student microscope. He found the presence of eosinophils in sputum was associated with the response to oral corticosteroids and that treatment was clearly effective in

the subgroup with eosinophilic sputum[17]. It is of note, however, that nearly 60 years on from Dr Brown's seminal findings we are still using oral corticosteroids for all patients with the label asthma without any evaluation of the pattern of airway inflammation.

Another near miss is the case of the anti-IL-5 monoclonal antibody treatment, Mepolizumab. Two of the earlier trials of Mepolizumab showed that it dramatically reduced the blood and sputum eosinophil count in patients with asthma but did not improve airway responsiveness, lung function or quality of life [18,19]. The disappointing clinical effect of treatment led many to question whether eosinophilic inflammation played as important a role in asthma as previously thought. However, other potential explanations for the observed lack of clinical efficacy was that the drug was being used in patients who did not have active eosinophilic inflammation, and that the trials were looking at the wrong outcomes. Patients with active eosinophilic disease are at risk of exacerbations and this increased risk is relatively independent of symptoms or decreased lung function. It follows that reducing the amount of eosinophilic inflammation may not improve symptoms as much as exacerbation rate. This change in thinking led to the design and development of appropriate trials, in the right subjects looking at the most responsive clinical outcomes. These have shown dramatic improvements in exacerbation rates in subjects with eosinophilic asthma who are treated with Mepolizumab.

Practical difficulties

The demonstration of variable airflow obstruction remains the cornerstone of a diagnosis of asthma. Airflow obstruction can be measured by spirometry at the GP surgery or in a hospital clinic, and peak flow meters which patients can use at home are particularly suited for the demonstration of variability over time. There are, however, a large number of patients who have acquired a label of asthma without any objective confirmation of variable airflow obstruction [20]. There are a number of reasons why this is the case. Firstly, there is not a single, agreed way of demonstrating variable

airflow obstruction; methods range from documenting peak flows at home over time, spirometry and bronchodilator reversibility and bronchial provocation tests. Secondly, tests such as bronchial provocation tests, the most sensitive tests for demonstrating variable airflow obstruction, are not practical to do in primary care settings because of their complexity, the time needed, the volume of patients seen with symptoms that are possibly due to asthma, and the potential adverse effects that may require further immediate treatment. These considerations have meant that a pragmatic 'trial of treatment' is often used as a diagnostic tool. This has resulted in a large number of patients who have had transient symptoms, for example viral bronchitis with wheeze, being labelled as having asthma and continuing on treatments long-term. Finally, using variable airflow obstruction alone to diagnose asthma and to modify treatment does not assess the risk of asthma attacks optimally, and indeed 58% of asthma deaths studied in the NRAD report were labelled as having 'mild' or 'moderate' asthma. To make a diagnosis of COPD, fixed airflow obstruction needs to be demonstrated by spirometry. This definition can also cause diagnostic uncertainty, for example how much bronchodilator reversibility is allowed before airflow obstruction is labelled 'fixed'? Clearly, we need better tools to diagnose and risk assess patients.

There are additional practical difficulties in discriminating patients with asthma and a degree of fixed airflow obstruction from those with COPD. This is an important consideration as current guideline-based strategies for use of inhaled corticosteroids differ markedly, with early use advocated for the former and late, risk-directed use advocated for the latter. Traditionally these conditions are discriminated on the basis of demographics (atopy, smoking history, age of onset of symptoms) and the demonstration of variable airflow obstruction. However, there is no evidence that these characteristics are linked to the presence of eosinophilic airway inflammation and thus the risk of preventable exacerbations. The current approach therefore has the potential to lead to inappropriate use of our most effective risk reduction strategy. Only a minority of patients with a diagnosis of asthma or COPD in the community have classic features as set out in guidelines and as

required for participation in key clinical trials that have informed these guidelines [21]. These trials are therefore poorly generalisable to the wider population with airway disease.

A new approach

By deconstructing the umbrella terms 'asthma' and 'COPD' into their component parts, with differing underlying mechanisms, treatments can be targeted to the processes that are active and relevant to that individual patient. This approach requires recognising traits that are a) identifiable and b) treatable. The identification of eosinophilic airway inflammation as a readily identifiable and treatable trait is a good example of this. To adopt this approach we need to remove the false assumptions that all of the symptoms of asthma or COPD are due to one underlying process, and will be amenable to one treatment paradigm. The identification of biomarkers that reflect underlying disease processes are crucial in this process. We strongly believe that with this "label-free" personalized approach can be applicable and adaptable to all patients with airways disease in both primary and secondary care.

Treatable traits

The Oxford English dictionary defines a trait as a "distinguishing quality or characteristic, typically one belonging to a person or a genetically determined characteristic". In our context, this would translate to disease attributes which are recognizable and irrefutably associated with relevant clinical outcomes in subgroups of patients with airways diseases. More importantly, these attributes should be modifiable or treatable, to the point where clinical benefit occurs when this is done.

Table 1 lists some potential treatable traits and, in the following section, we discuss the most recognisable and treatable of these. It is important to stress that our current view does not, and should not, preclude subsequent addition or sub-division of traits that are detectable and treatable. One example is mucus hypersecretion, which we have not listed here as we currently lack

knowledge on how to detect or treat it. The treatable traits that we have mentioned here are neither new nor revolutionary, instead, they stem from examining the limited archetypal responses that can occur in a biological tube in the face of adverse events such as exposure to environmental stimuli like allergens, air pollution, smoking and infections [22]. It is also important to note that these proposed treatable traits are neither disjunctive nor static. Patients could have a single predominant or multiple traits at the same time, and with further pressure from changing environmental stimuli, aging or other developing comorbidities, could also have different trait(s) identified at different time-points of their airways disease. The identification of these treatable traits should therefore be based on an iterative process involving repeated observations and measurements as traits may change over time. The concepts could be extrapolated to aid in management of episodes of exacerbations of airway diseases.

[Table 1]

Airflow limitation

Before the advent of biomarkers and advanced imaging techniques, spirometry was the only objective means to assess airway diseases. Although the repertoire of spirometric abnormalities cannot reflect the complexity and heterogeneity of airway diseases there is still merit in using spirometry to identify airflow limitation, which can be episodic and variable or largely fixed and persistent. It is also important to define the best achievable function for individual patients.

Traditionally airflow limitation is sub-classified as variable or fixed with the former often assumed to be due to a reversible process of repeated contraction of hyper-reactive airway smooth muscle, sometimes referred to as airway hyperresponsiveness. However, there could be other potentially treatable factors contributing to variable airflow limitation, including but not limited to sensitization

of airway nerves and release of airway inflammatory mediators that affect airway smooth muscle contractility, intrinsic abnormality of airway smooth muscle and structural changes to the airway.

Airway smooth muscle hyperresponsiveness can be targeted and inhibited by treatment including inhaled beta2(β2)-agonists by β2 receptor-induced airway smooth muscle relaxation [23-25] and inhibition of mast cell mediator release, albeit imperfectly due to the development of tachyphylaxis. Anti-muscarinic antagonists reduce airflow limitation by inhibiting intrinsic vagal tone to the airway. These agents are potentially less able to prevent bronchoconstriction mediated by inflammatory mechanisms such as mast cell mediator release although in practice seem to be as effective as beta2-agonists in most patients with established airflow limitation. In this population, the combination of long-acting beta2agonists and anti-muscarinic agents produced additive benefits and this is increasingly regarded as the optimum treatment. Regular inhaled corticosteroids [26,27] also reduce airway hyperresponsiveness when given to patients with the right pattern of disease probably via multiple mechanisms including reduction in eosinophilic airway inflammation [28], upregulation of β2 receptor numbers and reduction in inflammation-induced airway remodelling in the long term [29].

The main importance of identifying fixed airflow obstruction is to avoid over-treatment in a patient with airflow limitation who is constantly symptomatic. The difficulty in this situation lies mainly in the fact that there is no agreed definition of the point when airflow limitation becomes fixed and what constitutes an adequate treatment trial for these patients. The next consideration is whether the development of airflow limitation is due to an ongoing active process, or is the result of burnt out disease in early life that has affected normal lung development [30]. Currently we have few reliable ways of doing this prospectively and, as a result, there are few treatment options. Smoking cessation [31-33] and the use of inhaled corticosteroids in patients with evidence of eosinophilic airway

inflammation [34] have both been shown to result in a reduced rate of decline in lung function and therefore represent potential treatable factors responsible for progressive airflow limitation.

Airway inflammation ("bronchitis")

Airway inflammation is integral in the pathogenesis of airways diseases including asthma and COPD. Despite treatment guidelines[35] considering asthma as an inflammatory disease, it remains the case that characterising and quantifying the inflammatory component of asthma is not actively promoted in these consensus documents. Inflammation in the airway is driven by two main pathophysiological themes, namely T-helper 2 driven mechanisms resulting in eosinophilic inflammation and non-T-helper 2 mechanisms often resulting in neutrophilic inflammation (figure 4). A sub-group of patients with asthma have no demonstrable airway inflammation (paucigranulocytic asthma)[36].

Of the measurements currently available to assess and characterise airway inflammation, quantitative sputum cell count (total cell count as well as the differential cell count) is the most specific, discriminative and well-validated [37-42]. Normal values have been well-documented [43]. The principal application of sputum cell counts is in guiding treatment based on the predominant cellular nature of airway inflammation, specifically, differentiating eosinophilic and non-eosinophilic airway inflammation.

[Figure 4]

However, there are important limitations to the use of induced sputum to assess airway inflammation, including technical difficulty of sputum processing, a 10-20% failure rate, and the lack of an immediately available result [44]. Researchers have therefore been interested in simpler, more clinically accessible methods. Bafadhel and colleagues demonstrated that patients with a peripheral blood eosinophil count of <2% of the total white cell count (equivalent to a total eosinophil count of

around 0.15 x 10^9/L) at the time of an exacerbation of COPD were very unlikely to have a raised sputum eosinophil count [45] and went on to show that this cut point effectively stratified patients' response to oral prednisolone given to treat the exacerbation, with all the benefit occurring in patients with a blood eosinophil count > 2% [13]. This cut point has since been shown to be a reliable marker of response to mepolizumab in severe asthma [46] and inhaled corticosteroids in patients with COPD [9,47,48] with no evidence of clinical efficacy in the 30-40% of patients with blood eosinophil counts <2% of the total white cell count.

There are other biomarkers available for assessment of eosinophilic airway inflammation, including but not limited to blood indices such as the total and allergen-specific IgE, and exhaled breath nitric oxide [41,49]. The testing of exhaled breath nitric oxide requires little training and can be easily performed in day-to-day clinical practice in primary care and hospital outpatient settings. A cautionary aspect of exhaled breath nitric oxide interpretation in smokers merit comment as smoking exposure, whether active or passive, via conventional or electronic cigarettes, tends to reduce nitric oxide readings, irrespective of duration of the exposure [50-56]. Hence, this limits the value of this test in current smokers [57,58] .

The presence of eosinophilic inflammation is associated with an increased risk of future exacerbations and a positive response to corticosteroid-based anti-inflammatory treatment[39]. It is therefore an archetypal treatable trait, easily recognizable in patients. It is thought that two different pathways, differing in their relationship to allergy, generate eosinophilic airway inflammation via common effector cytokines IL-5 and IL-13[59]: Allergen-specific adaptive Th2 cells and allergen-independent type-2 response, possibly involving innate lymphoid cells type-2. These different pathways may result in different clinical responsiveness to treatment with inhaled corticosteroids and it is possible that more severe asthma, which is less responsive to inhaled corticosteroids, is particularly associated with the second, non-allergic pathway. Many of these

patients respond well to treatments that deplete circulating eosinophils (i.e. oral corticosteroids and anti-IL-5 monoclonal antibodies) and it may be that the airway mucosal process resulting in type-2 cytokine production is not inhibited by corticosteroids and that clinical benefit can only be achieved by reducing the response to this signal.

It is important to note that increased eosinophilic airway inflammation typically precedes future exacerbations as demonstrated in a 12-month follow-up after cessation of Mepolizumab where it was found that there was a rebound in blood eosinophil count soon after stopping therapy which progressively rose back to baseline over 6 months[60]. These findings highlight the importance of maintaining suppression of eosinophilic airway inflammation in patients with severe eosinophilic asthma and recurrent exacerbations. Serial biomarker measurements can guide adjustments in anti-inflammatory treatment and identify the minimum corticosteroid dose required to maintain control of the eosinophilic inflammation [8,11].

Most patients with eosinophilic airway inflammation respond well to inhaled corticosteroids but a minority require maintenance oral corticosteroids. This treatment clearly has a beneficial role in eosinophilic airways disease, but benefit is offset by morbidities related to oral corticosteroid usage. Fortunately, we have within our sights biological treatments that offer potential as better alternatives to oral corticosteroids. Anti-eosinophil biological agents such as that targeting IL-5 (Mepolizumab) [46,61,62], IL-5 receptor (Benralizumab) [7], alpha chain of the IL-4 receptor (Dupilumab) [63], and IL-13 (Lebrikizumab) [64] are all showing encouraging signs of efficacy and Mepolizumab is now an approved treatment. Non-biological treatments targeting specific eosinophil related pathways are also of interest, with antagonists of the Chemoattractant Receptor-homologous molecule expressed on T-Helper type-2 cells (CRTH2) prostaglandin D2 receptor showing particular promise[65,66].

On the contrary, the presence of non-eosinophilic (neutrophilic or pauci-granulocytic) inflammation, a recognisable and stable trait, is more poorly understood compared to eosinophilic inflammation and hence more difficult to treat. The term "neutrophilic" asthma is generally applied to patients with asthma whose sputum neutrophil count is abnormal with reference to established normal values in sputum of healthy adults [43], either a sputum neutrophil count of >65% or >500 x 10^4/ml, although it needs to be emphasized that there is no consensus on this definition at present. This pattern of airway inflammation is not responsive to treatment with corticosteroids [67-69]. Evidence suggests that neutrophilic airway inflammation can contribute to the development of fixed airflow obstruction in asthma [70-72] and hence increased severity of asthma and resultant deviation towards an "asthma-COPD overlap" label. Fortunately, a non-eosinophilic phenotype of asthma indicates low risk of serious asthma attacks[8], hence this group of patients may well be better served by reduced corticosteroid treatment and introduction of alternative therapies such as long-acting bronchodilators [73,74].

There is a link between smoking exposure and the development of neutrophilic airway inflammation and this pattern of neutrophilic airway inflammation seems to improve with smoking cessation [75,76]. Furthermore, Simpson *et al* have demonstrated evidence of persistent innate immune activation in neutrophilic asthma resulting in production of pro-inflammatory cytokines such as IL-8 and IL-1β [77,78]. It is unclear why there is persistent activation but it may be related to endotoxin exposure or chronic bacterial colonisation of the lower airways with bacteria such as *Haemophilus influenzae* [79]. With this link to chronic bacterial colonisation, there is a pertinent role for long-term low-dose macrolide treatment in patients with neutrophilic inflammation in asthma and COPD by modulating key inflammatory mediators and reducing the rate of severe exacerbations [80,81 82-84]. In addition, trials investigating novel CXCR2 (IL-8 receptor type 2) receptor antagonists showed promising results in reducing sputum neutrophils in patients with moderate-severe COPD and severe asthma, albeit with lesser clinically important effects such as improvement in FEV_1 or quality of life scores [85,86]. This

gives us hope that more treatment could be available for this group of patients in future and further research is required to refine the role of such treatment.

Impaired airway defences predisposing to airway infection

There is a relationship between viral and bacterial infections and exacerbations of airway disease. Major causes of asthma exacerbations in children include respiratory syncytial virus and human rhinovirus [87,88]; in adults Influenzae virus and metapneumonvirus are also important [89]. It was found that *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the major causes of bacterial infections in the respiratory tract, but only *Haemophilus influenzae* was detected from stable asthmatic outpatients[89] suggesting that modulation of *Haemophilus influenzae* infection or colonisation might be important in the management of patients with stable asthma [90-92]. Bacteria other than *Haemophilus influenzae* might contribute to increased risk for asthma exacerbations, although it is uncertain whether early detection via sputum culture and multiplex polymerase chain reaction analysis and treatment of these bacterial infections might be useful in preventing asthma exacerbations.

One difficulty in this area is that infection might have different effects at different stages in the development of airways disease. For example the "hygiene hypothesis" suggests that exposure to microbial infections during early childhood protects against subsequent development of atopy and asthma. There is also a view that exposure to microbial infection during early childhood provokes the development of atopy and asthma[93,94] and that the composition of the airway microbiome is important in the development of atopy and asthma [95,96]. Finally, atopy and asthma are thought to increase the individual's susceptibility to airway infections and colonisation[97-101]. The increased risk of infections may reflect the negative effects of inflammation on airway architecture and biological barriers. More fundamental immune dysfunction, beginning even before the clinical onset of asthma, is also likely to be important. One such factor is the deficient airway epithelial interferon

response to viral infection seen in patients with asthma [102]. This may represent a treatable trait as the first study of inhaled interferon in asthma showed a reduced rate of asthma exacerbations following a cold in patients with severe asthma [103]. This treatment approach is being evaluated currently in larger, more definitive clinical trials.

Altered cough reflex sensitivity

Cough is an important airway defence mechanism mediated by a neuro-immune interaction [104]. A dysregulation of either or both of the airway immune or nervous system could lead to an altered (frequently increased) cough reflex sensitivity and increased coughing. Up to 10% of patients presenting to secondary care in the UK do so because of a cough lasting more than 8 weeks (chronic cough) and 75% of us will, at some time in our life, present to primary care because of a prolonged cough. Chronic cough is particularly prevalent in middle aged females[105]. Cough associated with corticosteroid responsive eosinophilic airway inflammation is present in only 12% of patients [106] and, when present, is often associated with normal airway responsiveness. Despite this, many patients are treated with inhalers on the assumption that they have cough variant asthma or eosinophilic bronchitis [107], reflecting the difficulties in excluding asthma highlighted earlier.

The initial approach to altered cough reflex sensitivity would require treatment of any detectable underlying cause(s) such as airway inflammation, airflow limitation and/or stopping of any causative agent such as angiotensin converting enzyme inhibitors used for the treatment of hypertension. However, a significant proportion of patients have no obvious cause found after extensive assessment and the best approach would then be to target the cough reflex hypersensitivity itself. Although it is possible to measure sensitivity of the cough reflex by provocation with inhaled tussive agents such as capsaicin, cough challenge tests are currently used only in animal and human research studies as they are unable to discriminate patients with abnormal cough from healthy subjects [108]. Also, although studies have shown that cough challenge test results are reproducible

and responsive to change in patients after interventions, they may not reflect the patient's subjective perception of benefit after treatment of cough [108]. Other potentially more applicable and responsive measures of cough are available including 24 hour cough count monitors and cough-specific quality of life questionnaires.

Purinergic signalling, a form of extracellular signalling mediated by purine nucleotides and nucleosides such as adenosine and ATP, plays a role in cough reflex hypersensitivity. Purinergic P2X receptors are a family of ligand-gated, non-selective cation channels that open in response to extracellular ATP and comprises seven members termed $P2X_1$-$P2X_7$ [109]. $P2X_3$ receptors, now recognized as major players in mediating primary sensory effects of ATP, are found in airway nociceptive fibres which are crucial in the activation of our cough reflex [110-114]. A novel $P2X_3$ receptor antagonist (AF-219) has shown promising results in significantly reducing cough frequency in patients with unexplained chronic cough suggesting that this might be an important treatable trait in patients with airway disease [115,116]. In addition, treatments that modify the influence of higher centre control on the cough reflex, such as gabapentin, can also be useful [117]. A systematic review of non-pharmacological interventions for patients with refractory chronic cough also suggest benefit in the use of two to four sessions of a combination of education, cough suppression techniques, breathing exercises and counselling to achieve improvements in cough reflex sensitivity and cough-related quality of life for these individuals [118]. Further research is needed to more comprehensively establish effective components, treatment duration and frequency of this package.

Altered cough reflex sensitivity could also manifest as a reduced sensitivity or effectiveness of the cough reflex such as in relation to an underlying neuromuscular disease or medication. Such patients may benefit from cough augmentation techniques[119].

Fungal Hypersensitivity

Allergic bronchopulmonary aspergillosis is an allergic lung disease that occurs in individuals with severe allergic asthma or cystic fibrosis. It is mediated via a T-helper 2 dominant immune response to growth of fungi in the airways and can lead to progressive, permanent structural damage with bronchiectasis and fibrosis if unrecognised and left untreated [120].

Allergic bronchopulmonary aspergillosis is an under-diagnosed condition characterised by varied clinical and radiological manifestations including recurrent pulmonary infiltrates with or without bronchiectasis[121] and uncontrolled asthma[121] as evident in a series of 155 such cases where only 19% had well-controlled asthma[122]. Fungal exposure, to *Aspergillus fumigatus* in particular, has been linked to loss of asthma control, lower lung function and increased severity of asthma [123]. It is characterized by presence of elevated levels of Aspergillus-specific IgE antibodies in the blood, elevated total IgE levels (frequently > 1000 IU/mL) and other supporting evidence including radiographic changes consistent with allergic bronchopulmonary aspergillosis and *Aspergillus fumigatus*-specific precipitins (IgG antibodies). Pooled prevalence of sensitization to *Aspergillus fumigatus* is seen in an estimated 28% of asthma patients in specialty clinics[124]. It is considered that having severe asthma and evidence of fungal sensitization but without the other clinical manifestations amounting to the full diagnosis of allergic bronchopulmonary aspergillosis as a separate entity known as Severe Asthma with Fungal Sensitization (SAFS)[121] although these conditions are probably a continuum of fungal hypersensitivity severity.

Treatment options for allergic bronchopulmonary aspergillosis or severe asthma with fungal sensitization are limited and the chronic relapsing nature of this disease further complicates management. Corticosteroids, which suppress the hypersensitivity reaction, and anti-fungal drugs are regarded as first and second line agents respectively. Biological therapy might have a role but has not been evaluated extensively. Omalizumab, an anti-IgE monoclonal antibody and the first biologic therapy used in asthma, has been used to treat severe atopic asthma. Unfortunately, most

patients with allergic bronchopulmonary aspergillosis have blood IgE levels that are above the current prescription dosing range imposed for clinical use of Omalizumab, so it has not been clear whether Omalizumab may be effective in this condition. Published case series of instances when Omalizumab has been used have reported reduced steroid requirement, exacerbations and steroid-related toxicity [125-131] [132]. Further validation of efficacy is needed. Similarly, there could be a role for other biological therapies targeting T-helper 2-high disease but this needs to be studied.

Increased Body Mass Index

Epidemiological studies have identified an association between obesity defined as body mass index of ≥ 30kg/m^2 and risk of asthma or asthma-like symptoms, with the latter increasing with increasing body mass index [133-135]. Furthermore, obesity is associated with a lower likelihood of achieving well-controlled asthma and less-favourable response to current asthma therapy, in particular glucocorticoids [136-142].

Emerging data suggest at least two possible distinct phenotypes of obese asthma patients: early-onset, atopic asthma that is complicated by coexisting obesity (found in both sexes) and late-onset, non-atopic asthma that is caused by obesity (found predominantly in women). The causal mechanism(s) resulting in obesity-related asthma is poorly understood [143,144]. It is important to note that clinical evaluation of obese patients with asthma-like respiratory symptoms can be confounded by that fact that obesity alters lung physiology principally through reduction in functional residual capacity with resultant downstream mechanical effects that result in symptoms that resemble asthma or make asthma symptoms more pronounced.

Obesity is increasingly regarded as a chronic low-grade pro-inflammatory state [145-148] but how this systemic inflammation modulates airway inflammation and asthma is not fully understood. Current evidence suggests that obesity does not increase the degree of eosinophilic airway inflammation and

that obesity-related asthma is mediated primarily via non-eosinophilic pathways. There is also evidence to suggest presence of increased systemic oxidative stress in obesity and increased systemic and airway oxidative stress in patients with asthma, too. However, based on conflicting currently available data, it is still unclear if increased airway oxidative stress as a result of increased systemic oxidative stress in obesity is a direct causative factor for asthma. Changes in the levels of adipokines with obesity, via an increase in leptin or a reduction in adiponectin, favour a pro-inflammatory state and hence have also been implicated in the causation of asthma in obesity. Because both asthma and obesity appear to have their roots in utero and in early childhood, common exposures such as in prenatal and early-life diet and nutrition that predispose individuals to both these conditions may also be part of epigenetic mechanisms linking obesity and asthma. These are likely modulated further by sex hormones on expression of asthma in obesity as obesity seems to have a greater effect on women than men. More research is clearly required in obese patients with asthma to fully characterise this trait properly in order to facilitate better treatment and even prevention of asthma in this group of patients.

Fortunately, the obese asthma trait seems to be treatable to some extent by losing weight with corresponding improvements in lung function, severity of asthma symptoms, overall asthma control, comorbidities and resultant decreased medication utilization and hospitalizations [149-153].

Poor treatment adherence

Although not a biological process, poor adherence to prescribed inhaled steroid treatment in asthma is responsible for worsening asthma control, an increased risk of asthma attacks and is associated with a higher death rate [154,155]. With the clear benefit of inhaled steroids in patients with eosinophilic airways inflammation, it is key to understand and attempt to break down the barriers to good treatment adherence which include social circumstances, problems with the inhaler devices and side effects of medications.

There are a number of ways to assess adherence to treatment including asking the patient in the clinic and tracking prescriptions from writing to when (if) they are filled in the pharmacy. These approaches can come with a large margin of error, with one study reporting 35% of subjects from a difficult asthma clinic had filled less than 50% of their prescriptions and 88% admitted low adherence after initially denying it [156]. This study also found that 50% of patients said to be taking oral steroids were non-adherent when checked by blood level assay. Other studies, also in a difficult asthma clinic settings, showed that over 60% of patients had filled less than 80% of their prescriptions [157].

Electronically chipped inhaler devices that can measure and record the doses taken and the efficacy of the inhalation are now available for use in clinical trials. A trial using a chipped device coupled with clinician feedback on the results improved adherence by 30% over 10 weeks [158]. A more robust approach may be to monitor individual treatment doses, and link this with the expected biological response of reduced airways inflammation. This is now possible with the increasing availability of portable exhaled nitric oxide testing. Using this approach poor adherence can be identified by delivering high dose inhaled steroids and measuring the exhaled nitric oxide response [159], and differentiate this from treatment refractory disease. A similar approach could be undertaken with long-acting intramuscular steroid injections, rather than oral steroids, and measuring biological responses such as the exhaled nitric oxide, asthma attack rate, lung function and blood eosinophil level.

How might personalised, mechanism based management work in practice?

Proof of concept studies have shown that this type of approach results in better patient outcomes and more economical use of treatment [8,11,160-162]. It will also be necessary if we are to make the most of the opportunities presented by the new biological era in severe asthma as all these agents require a personalised, biomarker directed approach to patient selection. The approach need not add to the complexity of management of airway diseases as it could be adapted to different levels of care. For example, in primary care the focus could be on the two major treatable traits in patients with airway disease: eosinophilic airway inflammation and airflow limitation. The management algorithm would look similar to that suggested in the 2011 GOLD treatment pathway [7] with the crucial difference that the focus will be on risk of exacerbations as a result of eosinophilic airway inflammation and symptoms due to airflow limitation (figure 5). This would result in more personalised and potentially more effective treatment but would also highlight cases where neither pathway is active early on in the diagnostic process rather than after many months of fruitless asthma treatment. Two immediately obvious scenarios are the patient with symptoms not due to airflow limitation and a patient with recurrent exacerbations with low biomarkers of eosinophilic airway inflammation. Cough reflex hypersensitivity is the most important cause of the former and infection-related neutrophilic airway inflammation is an important cause of the latter.

[Figure 5]

Conclusion

The current approach to classification of airways disease is, we believe, no longer fit for purpose. It is impractical, overgeneralises complex and heterogeneous conditions and results in management that is imprecise and outcomes that are worse than they could be. Importantly, the assumptions we make when applying a diagnostic label have impeded new drug discovery and will continue to do so unless we change our approach. We suggest a new mechanism-based approach where the emphasis is on identification of key causal mechanisms and targeted intervention with treatment based on

possession of the relevant mechanism rather than an arbitrary label. We highlight several treatable traits and suggest how they can be identified and managed in different healthcare settings. There are likely to be many more whose identification will follow once we remove the constraints imposed by our current outdated classification system.

Figures and boxes

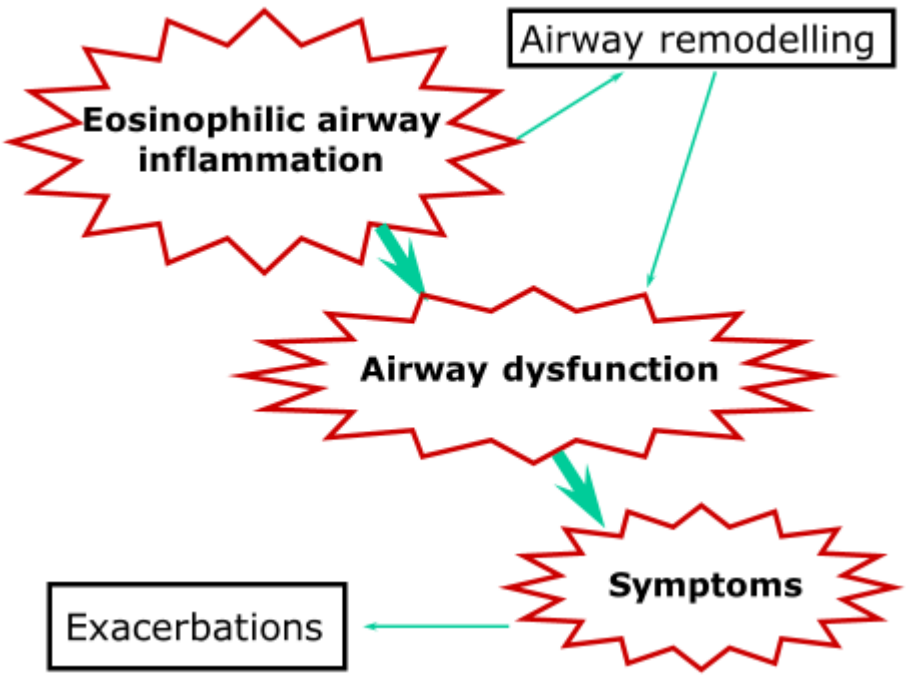

Figure 1. Previously assumed direct causal relationship between eosinophilic airways inflammation, airways hyperresponsiveness, symptoms and exacerbations.

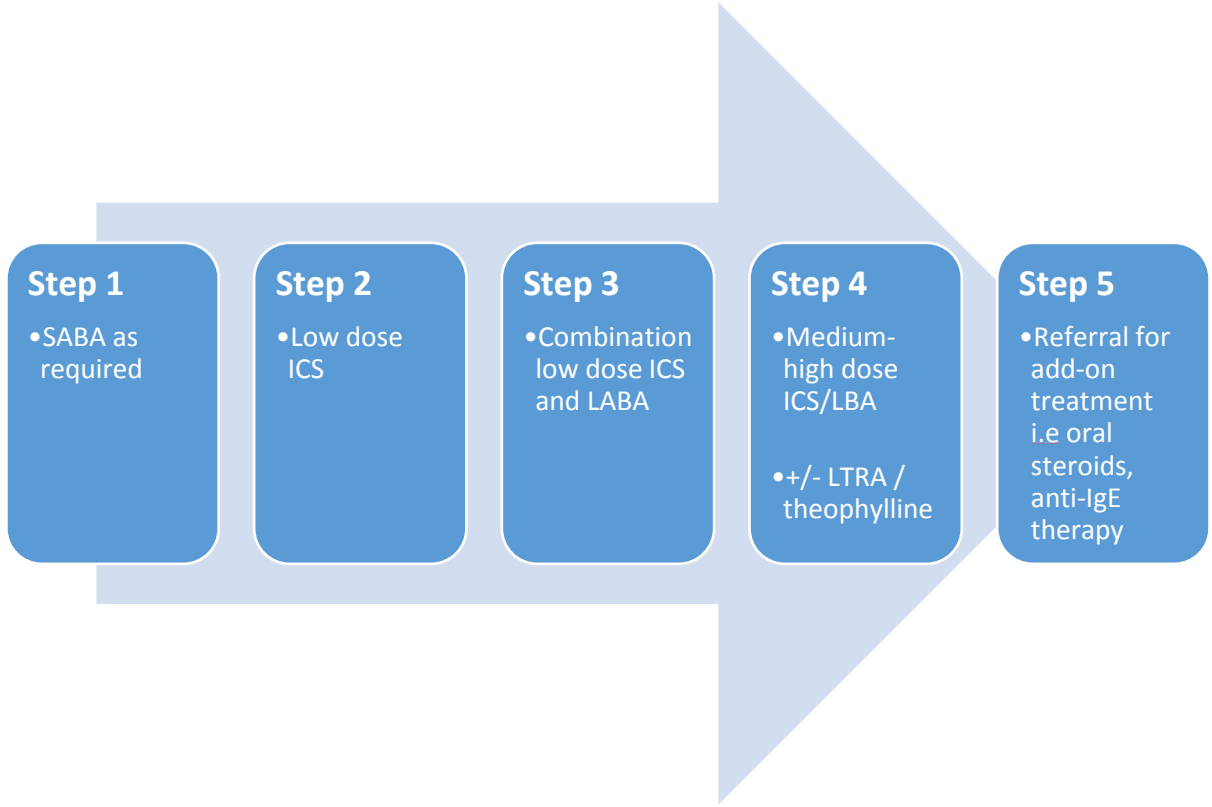

Figure 2. Stepwise approach to increasing asthma medications. Modified from GINA guidelines [6]. SABA – short acting beta-2 agonist, ICS – inhaled corticosteroid, LABA – long acting beta-2 agonist, LTRA – leukotriene receptor antagonist.

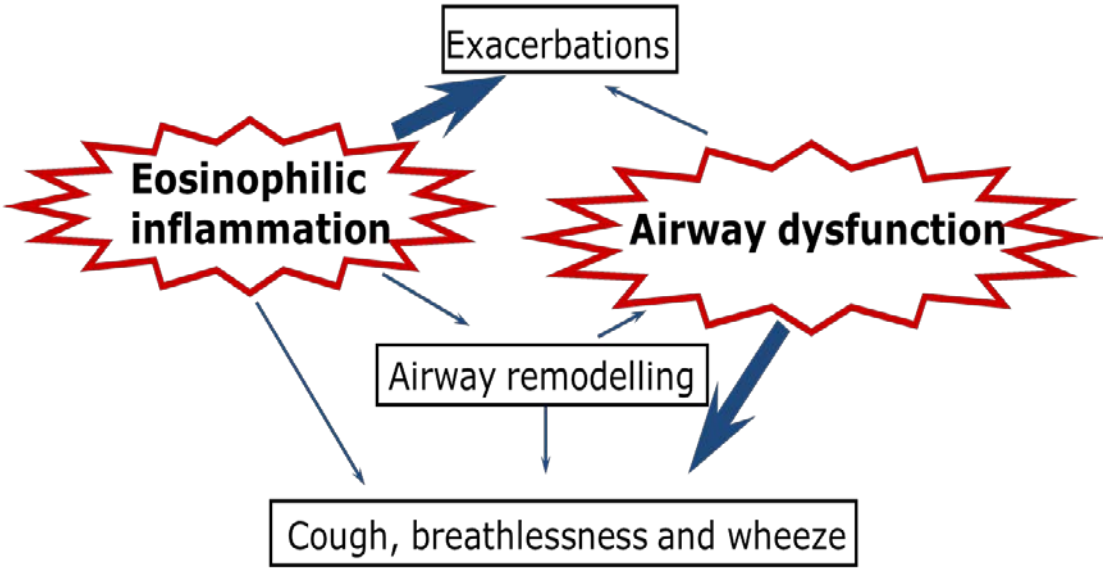

Figure 3. Dissociation between airways inflammation, airway dysfunction and clinical outcomes in severe asthma

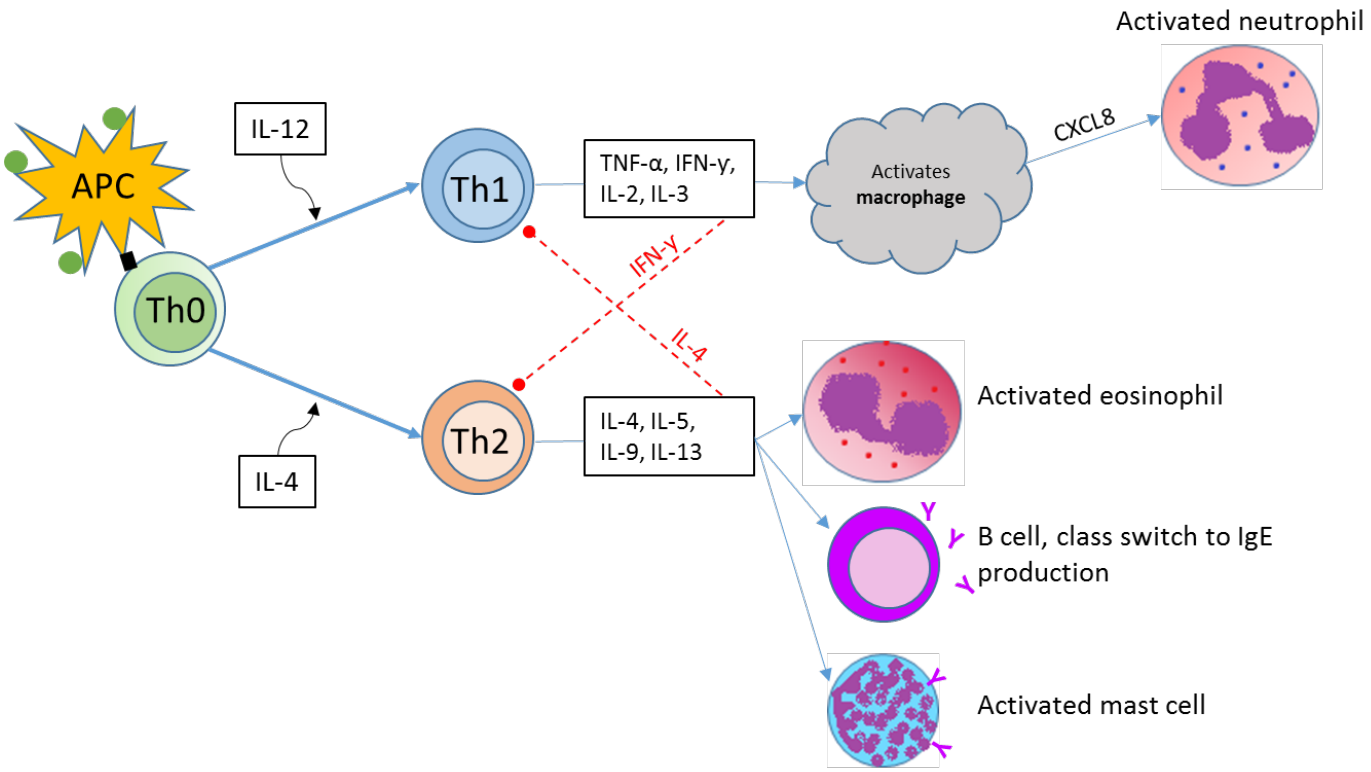

Figure 4. Pathways leading to Th1 (neutrophilic) and Th2 (eosinophilic) inflammation. Naïve Th0 cells differentiate following interaction with antigen bound APCs and cytokine influence. The subsequent cytokine cascades recruit white blood cells, causing inflammation. The Th1 and Th2 pathways inhibit each other via IFN-γ and IL-4 respectively meaning that one type of inflammation predominates. APC – antigen presenting cell, Th – T-helper, IL - interleukin

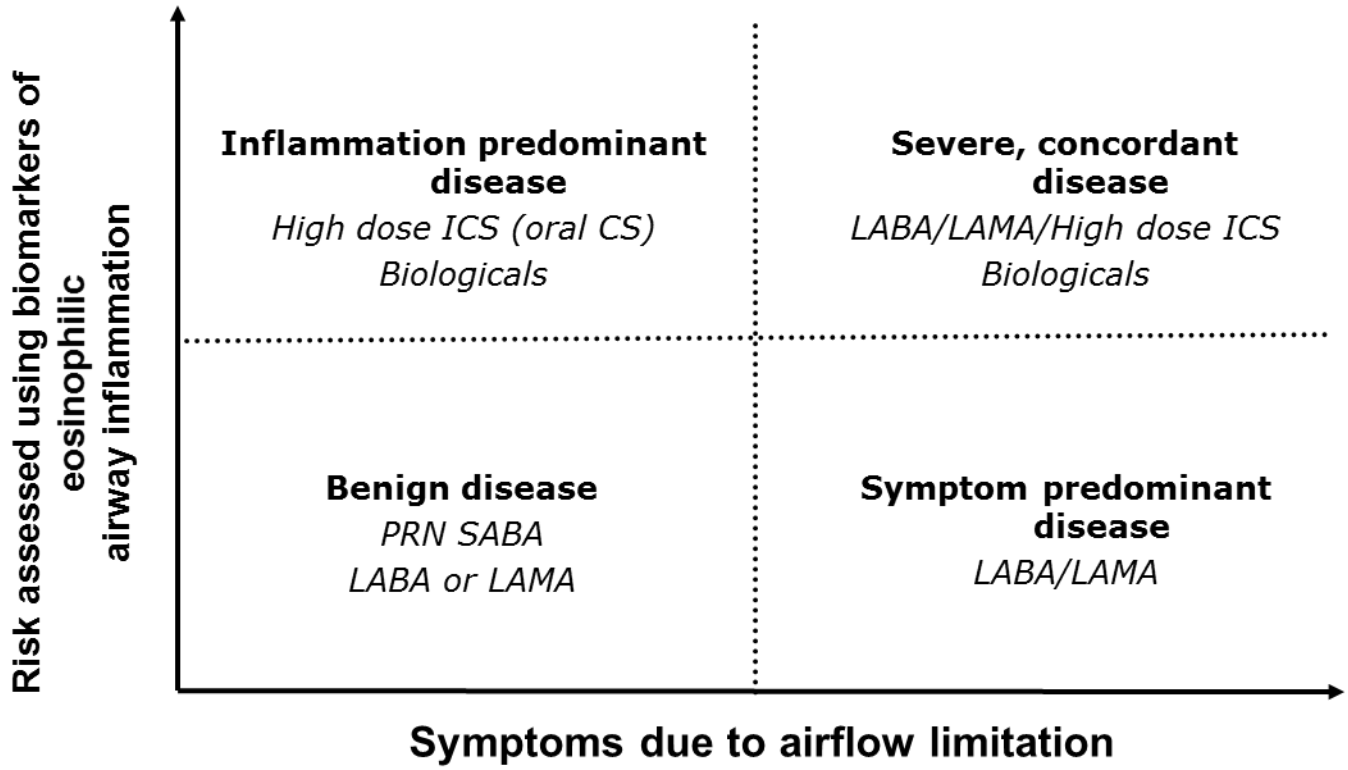

Figure 5. Proposed classification of airways diseases incorporating measures of eosinophilic airways inflammation and symptoms due to airflow obstruction, and appropriate therapies based on this. PRN – as needed, ICS – inhaled corticosteroids, LABA – long-acting beta-agonist, SABA – short-acting beta-agonist, LAMA - long-acting muscarinic receptor antagonists

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Trait	How to measure	Definition	Treatment	Clinical effect	Strength of effect
Airflow limitation	Spirometry (primary care, respiratory clinic or lung function lab)	FEV1/FVC ratio of < 0.7	1. Bronchodilators (LABA, LAMA or LABA/LAMA)[163] 2. ICS[164] 3. Bronchial thermoplasty[165]	Improved daily symptoms, reduction in exacerbations, improved lung function	1. +++ 2. +++ 3. +
Airway hyperresponsiveness	Methacholine challenge Bronchodilator reversibility	PC20 < 8 mg/ml Improvement in FEV1 of 15% and/or 200ml	As above		
Eosinophilic airway inflammation	A. Induced sputum B. Blood C. FeNO	A. Eosinophil count ≥ 3% in sputum B. Eosinophil count ≥ 2% in blood C. FeNO > 25ppb	1. Corticosteroids (inhaled or oral)[8,166] 2. Biologics (anti-IL5, anti-IgE)[46,167,168]	Reduced exacerbations and improved daily symptoms	1. +++ 2. +++
Chronic airway infection	Sputum microscopy, culture and sensitivity	Colonisation of the airways by bacteria	Long-term low dose macrolide antibiotics[82]	Reduced exacerbations	++
Bronchiectasis	CT scan	Abnormal dilation of the small airways predisposing to excess sputum production and infections	1. Airway clearance techniques (eg physiotherapy)[169] 2. Mucolytics 3. Macrolides[170] 4. Surgery in single lobe bronchiectasis	Reduction in daily sputum production and number of exacerbations	1. + 2. + 3. ++ 4. +++ (in selected patients)
Cough reflex hypersensitivity	A. Cough questionnaire B. Cough counts C. Capsaicin challenge	A&B. > 100 coughs/day C. Research tool, no defined 'normal' value	1. Speech and language therapy[171] 2. Gabapentin[117]	Reduction in cough frequency +/- patient awareness of cough	1. ++ 2. +
Obesity	Weight in kilograms over height in metres squared	BMI > 30 kg/m2	Weight loss by[149-151,153] 1. Diet 2. Exercise 3. Bariatric surgery	Improved daily symptoms and lung function, reduction in severe exacerbations	++
Gastro-oesophageal reflux	A. Patient account B. Oesophageal pH monitoring	A. Symptoms B. Significant drops in oesophageal pH	1. Proton pump inhibitors / H2 antagonists 2. Surgery	Improved daily symptoms	1. + 2. +
Upper airways disease (eg vocal cord dysfunction)	A. Laryngoscopy B. Flow-volume loop	A. Paradoxical adduction of vocal cords during inspiration, expiration or both B. Flattened inspiratory curve	1. Speech and language therapy[172] 2. Psychotherapy	Improved daily symptoms and fewer exacerbations	1. ++ 2. +
Deconditioning	Cardiopulmonary exercise testing	Reduced exercise capacity with no pulmonary or cardiac limitation	Exercise and education	Improved daily symptoms Unknown effect on exacerbation	+
Poor treatment adherence	A. Prescription monitoring B. Chipped inhaler devices C. FeNO suppression testing	A/B. < 80% adherence = poor adherence < 50% adherence = very poor adherence C. FeNO value change over a week when monitored inhaler is used	1. Education[154] 2. FeNO suppression test as educational tool[159] 3. IM corticosteroids in those with eosinophilic disease and poor adherence	Improved daily symptoms, reduction in exacerbations, improved lung function	1. + 2. ++ 3. +++ (in selected patients)
Aspirin sensitivity / Aspirin induced asthma	A. Aspirin challenge B. Prior history	Acute asthma symptoms on taking aspirin / NSAID drugs	1. Aspirin desensitisation[173] 2. Leukotrine receptor antagonists[174]		1. ++ 2. ++

+ Some effect of treatment or limited evidence of effect, ++ Moderate effect of treatment, +++ Good effect of treatment

FEV1 Forced expiratory volume in one second (litres), FVC Forced vital capacity (litres), LABA Long acting beta agonist, LAMA Long acting muscarinic antagonist, ICS inhaled corticosteroid, PC20 Provocative concentration, IL-5 Interleukin-5, IgE Immunoglobulin E, FeNO Fractional exhaled nitric oxide, ppb Parts per billion, NSAID non-steroidal anti-inflammatory drugs