

Understanding of asthma has improved



'Asthma' describes a host of conditions

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Traditionally, airways disorders have been loosely divided into asthma and COPD. Asthma is widely believed to be an allergen-mediated bronchial inflammation causing reversible and steroid-responsive airflow obstruction, while COPD is mainly caused by smoking-related bronchial inflammation contributing to partial or non-reversible airflow obstruction which is only occasionally responsive to steroids.

This simplistic concept does not explain the large number of patients who present with adult onset symptoms of cough and/or wheeze, without a history of atopy or heavy smoking, who develop airways obstruction which does not respond particularly well to steroids.

This group includes patients with functional small airways damage and/or bronchiectasis, who often present with cough and/or wheeze associated with airflow obstruction which may be helped by oral and/or inhaled steroids, but more particularly by antibiotics.

Over recent years, there has been a major shift towards considering airways disorders as a broader category, with more attention on identifying the specific inflammatory cell involved in the hope of targeting therapy better.

It is now widely accepted asthma is probably not a single disease, but rather a complex of multiple, separate entities that overlap and allergic mechanisms are only one of a number of mechanisms contributing to what is loosely labelled as asthma.

The challenge is to define better the characteristics of patients

with airflow obstruction to help guide us with the treatment options. While the use of bronchial provocation testing, expired nitric oxide (eNO) measurement, induced sputum analysis and high resolution expiratory CT (HRCT) scans of the chest have allowed much better characterisation of patients, they are not uniformly available to GPs. We must therefore, review treatment and diagnosis algorithms to give better direction to clinicians evaluating patients at a distance from sophisticated research labs.

Different asthma phenotypes

Asthma is a chronic inflammatory disease of the airways. Until recently, asthma phenotypes have been largely defined on clinical grounds using, eg, age of onset, severity of symptoms, degree of airflow obstruction, frequency of exacerbations, triggers, and steroid responsiveness and dependence. From a therapeutic perspective, asthma phenotypes are better defined according to number and type of inflammatory cells in the airways, ie, whether inflammation is eosinophilic or neutrophilic (see panel).

To complicate things, mixed inflammatory patterns can occur from coexistence of stimuli which cause both neutrophilic and eosinophilic inflammation.

Non-eosinophilic asthma is an inflammatory phenotype of asthma with non-allergen mediated, non-eosinophilic (predominantly neutrophilic) bronchial inflammation of the airways.

Only 40 to 50 per cent of all asthma in the general population is attributable to allergen-mediated eosinophilic inflammation. An equal proportion of asthma is based on non-eosinophilic (predominantly neutrophilic) airway inflammation which may account

Key points

- Asthma is now regarded as a complex of multiple, separate entities that overlap, and allergy is only one contributory factor.
- Modern airways disease management incorporates clinical characteristics, secondary tests of atopy and airway hyper-responsiveness, the newer tests of eNO and induced sputum, along with discretionary use of HRCT.
- An updated algorithm-based approach to diagnosis and treatment of airways disease is presently being trialled at Middlemore Hospital, and it is hoped to have the results available for publication by the end of 2007.

Defining asthma phenotypes

Eosinophilic v neutrophilic airways inflammation

Eosinophilic inflammation is dominant in:

- typical atopic ("extrinsic") asthma
- allergen-mediated occupational asthma
- post viral wheeze
- eosinophilic bronchitis
- non-atopic ("intrinsic") asthma (some cases)

Neutrophilic inflammation is dominant in:

- non-atopic ("intrinsic") asthma (most cases)
- smoking-related airways disease
- bronchiectasis
- functional small airways damage
- asthma caused by certain occupational irritants.

for the rise in prevalence of asthma worldwide, and why so many purported patients with asthma are suboptimally controlled on standard asthma therapies.

Eosinophilic asthma is an entity distinct from non-eosinophilic asthma, both immunologically and pathologically. Eosinophilic asthma involves activation of the acquired immune response with Th2 lymphocyte-mediated cytokine release (IL5 in particular) causing eosinophilic inflammation and IgE-mediated mast cell release. Non-eosinophilic asthma, in contrast, involves activation of the innate immune response, with Th1 lymphocyte-mediated cytokine release (IL8 in particular) causing influx of neutrophils. Pathologically, eosinophilic asthma causes subepithelial basement membrane thickening and mast cell infiltration of the airway smooth muscles, whereas non-eosinophilic asthma is quite distinct with a normal basement membrane thickness.

Known triggers

Unlike eosinophilic asthma which is allergen-mediated, non-eosinophilic asthma is triggered by environmental exposure to: bacterial endotoxins; ozone; smoke; viral infections; endotoxins in house dust mites; occupational irritants; and particulate air pollutants, for example, diesel exhaust.

This may also explain the renewed interest in the suspected association between chlorinated indoor swimming pools and asthma, possibly due to neutrophilic inflammation from exposure to trichloramines derived from reaction of chlorine with organic substances in the pools.

Different clinical presentations

Non-eosinophilic asthma commonly presents as difficult-to-control, adult onset asthma with chronic persistent symptoms. There is often fixed airflow obstruction on spirometry or evidence of small airway narrowing (downward scalloping of the expiratory flow volume loop), with symptoms and airflow obstruction being poorly responsive to steroids.

Non-eosinophilic asthma can also present as occupational asthma. Although work-related exposures can cause allergic asthma with eosinophilic inflammation, a substantial proportion is non-allergic. In contrast with allergic asthma, previously unexposed subjects can develop symptoms and airflow obstruction without prior sensitisation or latency, and the underlying inflammation is non-eosinophilic (neutrophilic).

Making a diagnosis

Diagnosis and control of asthma, until recently, was largely based on patient history, symptoms and peak flow measurements. Bronchodilator reversibility testing and tests for airway hyper-responsiveness and atopy are used as second-line tests where control has been difficult to achieve, but in truth they have not been particularly helpful, except in the occasional patient.

More recently, non-invasive ways to measure airway inflammation have been developed, and include induced sputum and eNO. These tests not only help to differentiate eosinophilic from non-eosinophilic airways inflammation, but can also be used to monitor the extent of inflammation and response to treatments. HRCT scans are also being used to look for evidence of small airways

damage and to exclude bronchiectasis.

Induced sputum is a reproducible and non-invasive method for measuring airways inflammation. It is obtained by hypertonic saline nebulisation using a special type of ultrasonic nebuliser. It needs to be performed in a carefully supervised environment because hypertonic saline can sometimes induce bronchospasm, and sputum analysis needs to be performed by a trained technologist within two hours of collection. While induced sputum testing has been shown to improve asthma control when done longitudinally, the cost and time required to undergo testing makes it currently impractical outside asthma research trials.

In contrast, eNO is easy and non-invasive, but requires a chemiluminescence breath analyser. It has been confirmed as a marker of airway inflammation, although there are many factors (eg, use of steroids, leukotriene antagonists and long-acting beta-agonists, upper respiratory tract infection, reflux, smoking and presence of airflow obstruction) which can impact on the results. There is also considerable overlap between levels of eNO in asthmatic versus non-asthmatics, with some debate over the acceptable cut-off to correctly diagnose asthma.

Hence, the precise role of eNO as a diagnostic test for asthma remains debatable. It is accepted as an asthma control test and, when used longitudinally, rising levels of eNO are accurate at predicting loss of control of asthma. However, for the reasons mentioned above, the authors would caution about using eNO in isolation without also performing an induced sputum evaluation.

Clinical implications

Treatment choices in asthma are mainly centred on whether corticosteroids should be used or not, and, if the patient is already on corticosteroids, whether the dose should be increased, decreased or held constant. Inflammatory phenotyping as a guide to therapy is valuable in differentiating between patients with poorly suppressed eosinophilic inflammation, who would be more likely to benefit from increased steroid dose, and those with non-eosinophilic inflammation who require alternative treatment approaches.

Inflammatory phenotyping helps guide whether patients should have their steroid dose increased or not

In non-eosinophilic (neutrophilic) asthma, reduction of steroids may sometimes help to improve symptoms, as prolonged use of corticosteroids can mobilise and prolong the survival of neutrophils by decreasing neutrophil apoptosis. A significant subgroup of patients with non-eosinophilic asthma with functional small airways damage or bronchiectasis may also benefit from a minimum of six to 12 weeks of macrolide antibiotic therapy. Debate remains as to whether this is as a consequence of an antibiotic or an immunomodulatory effect. It is our premise that the effect is predominantly an antibiotic one and that the stimulus for neutrophilic inflammation is colonisation of damaged airways by pathogenic bacteria caused by a reduction in local host defence mechanisms.

Occupational asthma which can account for almost 15 per cent of adult onset asthma can be difficult to diagnose and can be associated with either eosinophilic or neutrophilic inflammation depending on the nature of exposure (a less than 0.1 per cent incidence in New Zealand based on ACC figures suggests we are grossly underdiagnosing the condition). Until recently, monitoring of peak expiratory flow performed during two weeks at work and away from work was used for the diagnosis of work-related asthma. The addition of induced sputum counts, at and away from work, improves the specificity and sensitivity of the diagnosis.

Patients presenting with chronic cough can cause a diagnostic and therapeutic dilemma. A proportion of such patients will have eosinophilic inflammation causing cough variant asthma. Others will have undiagnosed bronchiectasis or functional small airways damage. Therefore, eNO, induced sputum and sometimes HRCT may be essential in patients who do not respond to straightforward measures.

Future directions

The challenge is to develop an algorithm-based approach to airways disease management which incorporates clinical characteristics, secondary tests of atopy and airway hyper-responsiveness, and the newer tests of eNO and induced sputum, along with discretionary use of HRCT. This is the current research focus of our team at Middlemore Hospital and we hope the results will be available for publication by the end of the year. This should improve the clinician's ability to differentiate between eosinophilic and non-eosinophilic asthma and thus better guide therapeutic intervention, with optimal use of inhaled and/or oral steroids, antibiotics and long-acting beta-agonists, along with preventative strategies.

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WORLD NEWS

GPs told to up steroids in asthmatic smokers

Many patients with asthma who smoke need higher-than-usual doses of inhaled steroids, UK GPs have been warned in new guidelines.

But experts say smokers should be encouraged to quit and offered add-on therapy before doses of inhaled steroids are increased, to reduce the risk of serious side effects.

Recommendations from the Scottish Intercollegiate Guidelines Network/British Thoracic Society (SIGN/BTS) on pharmacological management of asthma have been updated after evidence emerged that smoking reduced the benefits of inhaled

steroids. The guidance recommends: "Clinicians should be aware that higher doses of inhaled steroids may be needed in patients who are smokers or ex-smokers."

But specialists say evidence inhaled steroids are less effective in previous smokers is sparse.

Martyn Partridge, professor of respiratory medicine at Imperial College, London, and an advisor on the guidance, says, "Smoking specifically interferes with inhaled steroids gaining access to glucocorticoid receptors in the airways – meaning, in effect, that smokers potentially need more treatment to achieve the same effect. This does not

appear to be widely known by doctors or patients."

Neil Thomson, professor of respiratory medicine at Glasgow University, has published research showing non-smokers with mild asthma responded better to doses of 400µg of inhaled steroid daily than smokers. The differences in improvement were reduced when the dose of inhaled steroid was increased to 2000µg daily.

The guidance advises GPs to warn patients smoking reduces effectiveness of therapy.

It also warns that children on high steroid doses should be monitored by specialists, and that increasing doses in adults was often ineffective. Pulse

How UK guidance has changed

- Specific written advice about steroid replacement in the event of a severe intercurrent illness should be part of the management plan for children treated with 800µg per day of BDP or equivalent.
 - Any child on this dose should be under the care of a specialist paediatrician.
 - In adults, doubling the dose of inhaled steroids at the time of exacerbation is not effective.
 - Anti IgE monoclonal antibody: the guideline concludes that as there are no active comparative studies it is not possible to place omalizumab in the stepwise treatment of asthma.
- Source: SIGN/BTS