Understanding of asthma has improved

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
- allergens-mediated occupational asthma
- post viral wheezing
- 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.

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 (IL2 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 secondary 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 disease.

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-allergic mediated, non-eosinophilic (predominantly neutrophilic) bronchial inflammation of the airways. Only 40 to 50 per cent of all asthma in the general population can be attributed to allergen-mediated eosinophilic inflammation. An equal proportion of asthma is based on non-eosinophilic (predominantly neutrophilic) airway inflammation which may account for the rise in prevalence of asthma worldwide, and why so many purported patients with asthma are suboptimally controlled on standard asthma therapies.

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Clinical update

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 diagnostic algorithms to give better direction to clinicians evaluating patients at a distance from sophisticated research labs.
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-asthmatic individuals, so 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 use of eNO alone for diagnosis and therapeutic dilemma. A proportion of such patients 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 treatment approaches.

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 pre-dominantly 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-responsive-ness, 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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