Recent developments in asthma management

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Asthma is a common chronic heterogeneous condition with several characteristic features (fig 1). It can present in early childhood as well as in adulthood, and it varies markedly in severity, clinical course, subsequent disability, and response to treatment. In common with other atopic disorders such as allergic rhinitis, atopic dermatitis, and food allergy, the prevalence of asthma has risen over the past few decades in both developed and developing countries.¹ The increasing burden of asthma in primary and secondary care has led to extensive research into its genetics, pathophysiology, and treatment. In this review, we highlight some of the recent developments in the clinical management of asthma and identify key areas in which further research is needed.

Methods

We did a comprehensive literature search using Medline, Clinical Evidence, the Cochrane Library, and Embase. We used the following keywords in the search: acute asthma, chronic asthma, leucotriene receptor antagonist, long acting β_2 agonist, inhaled corticosteroid, action plans, allergen, diet, magnesium, vitamin, Buteyko, anti-immunoglobulin E, and interleukin. We selected and extracted recent articles from 2000 onwards that we felt to be of relevance or interest to practising clinicians, as well as choosing topics that we were aware of being potentially important. All the authors are respiratory physicians with an interest in airways disease.

Chronic asthma

Non-pharmacological management

Allergen avoidance

Atopy and asthma are separate conditions with differing genetic and epidemiological associations.

Fig 1 The key components of asthma

Summary points

No strong, evidence based data suggest that dietary manipulation or the Buteyko technique is of great benefit in the clinical management of asthma

Further studies are needed to establish exactly what patients should do when asthma becomes less well controlled

Inhaled corticosteroids at smaller doses can be combined with long acting β_2 agonists to provide effective and safe asthma control

Intravenous magnesium and leucotriene receptor antagonists may confer some benefit in acute asthma, but further evaluation is needed

Whether asthma treatment in the future can be adjusted with the aid of an inflammatory biomarker or knowledge of a patient's genotype remains to be seen

Although atopic sensitisation increases the likelihood of asthma, this is not an absolute association. Allergen avoidance is commonly recommended in patients with asthma, especially those who show type I hypersensitivity to common aeroallergens.^{1 2} However, a surprising lack of evidence based data exists to substantiate the effectiveness of this approach. Several major studies have specifically evaluated allergen avoidance and its impact on asthma control. In a double blind randomised placebo controlled study involving 1122 adults with asthma, Woodcock et al evaluated the effects of avoidance of house dust mite with the use of allergen impermeable bed coverings.³ Even though more than 60% of patients in both groups were sensitised to house dust mite, this commonly advocated avoidance measure was not associated with beneficial effects in peak expiratory flow or other measures of asthma control. However, some benefits have been observed with more complex, intrusive, and expensive modalities combining avoidance of aeroallergens with other measures such as behavioural adaptation and environmental intervention.⁴ To effectively treat asthma in terms of aeroallergen avoidance, a multifaceted approach may have to be adopted, which not only

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involves reducing the exposure to a particular aeroallergen but also provides an environment in which triggers of asthma are kept to a minimum.

Dietary manipulation

In recent years, the increasing prevalence of asthma and atopic diseases has been hypothesised at times to be a consequence of changes in diet associated with affluence. Typical examples are the decreasing dietary intake of antioxidants (found in fresh fruit) and changes in intake of dietary fat (more margarine and less butter and oily fish). Indeed, several studies have shown associations between atopy and asthma and increased intake of dietary margarine and polyunsaturated fatty acid and reduced intake of butter and fish.⁵ This in turn has led to investigations evaluating whether other dietary manipulation can influence parameters of asthma control. Despite the promising results of epidemiological studies, dietary supplementation studies in adults have concluded that vitamins C and E, magnesium, and fish oil are not associated with clinically significant beneficial effects.⁶⁻⁹ For example, in a study involving 300 people with asthma, the effects of daily vitamin C and magnesium were evaluated over a 16 week period. Compared with placebo, supplementation conferred no benefit on lung function, airway hyper-responsiveness, symptoms, or use of reliever drugs.⁹ However, if people who are particularly susceptible to the beneficial effects of antioxidants or lipids can be identified, dietary supplementation may have a future role in specifically targeted patients.

Buteyko technique

The Buteyko technique encourages patients with asthma to control their rate of breathing and is based on the proposition that symptoms are due to hyperventilation and hypocapnia. Cooper et al evaluated 69 patients in a randomised controlled study examining the effects of twice daily breathing exercises for six months.¹⁰ No differences were observed in lung function or airway hyper-responsiveness to methacholine, although some reduction in symptoms and use of reliever drugs was noted. Similarly, a Cochrane review failed to find any improvement in lung function when the Buteyko technique was incorporated into the routine care of asthmatic patients.¹¹

Asthma action plans

One of the main goals of asthma management is the prevention and prompt treatment of exacerbations. Some patients have an abrupt deterioration in control over a couple of days, whereas others develop an exacerbation on a background of chronically poorly controlled asthma. In addition to regular medical review, availability of easily accessible information, and self monitoring, all patients should be given an asthma action plan.² A written plan aids detection of deteriorating asthma control and offers straightforward advice in terms of appropriate drug treatment. Such plans must be devised on an individual basis and formulated according to personal best peak expiratory flow, symptoms, or both. Box 1 outlines the key components of a successful asthma action plan—one that results in consistently improved outcomes.¹²

The widely held belief is that during periods of deteriorating asthma control, patients should be

encouraged to at least double their dose of inhaled corticosteroid. However, two recent studies have shown no apparent benefit of doing this.^{13 14} In both of these randomised controlled double blind trials, increasing the inhaled corticosteroid dose was no more successful than keeping to a maintenance dose in preventing subsequent deterioration. However, doubling the dose of inhaled corticosteroid may become successful only when incorporated into a written asthma action plan in “real life” settings.

Pharmacological management

Combined inhaled corticosteroids and long acting β_2 agonist inhalers

Asthma is increasingly considered to be a multifaceted disease process in which intermittent smooth muscle contraction causing airflow obstruction is almost as important as underlying endobronchial inflammation. The dose-response curve for the effect of inhaled corticosteroids on lung function becomes flat at only moderate doses, indicating that giving higher doses may worsen the overall therapeutic ratio.¹⁵ This has led to the more widespread use of lower doses of inhaled corticosteroid in combination with long acting β_2 agonists (formoterol, salmeterol). Combined products containing inhaled corticosteroid and long acting β_2 agonist have the potential advantage of improving patients' adherence to drugs, as fewer inhalations and inhaler devices are needed. Moreover, the fairly rapid relief of symptoms conferred by the long acting β_2 agonist moiety (especially with formoterol) may inextricably enhance adherence to anti-inflammatory treatment and lead to a reduction in exacerbations.¹⁶ In addition, for reducing the risk of local (fig 2) and systemic adverse effects, combination treatment is generally more effective than increasing the dose of inhaled corticosteroid in patients with mild, moderate, or severe symptomatic disease.¹⁷⁻¹⁹ Bronchial biopsy data are needed to evaluate fully the effects of combination inhalers versus more aggressive anti-inflammatory treatment, such as doubling the dose of inhaled corticosteroid or adding a leucotriene receptor antagonist. This is vital to ensure that prolonged treatment with smaller doses of inhaled corticosteroids (in conjunction with a long acting β_2 agonist) does not have less favourable long term effects on airway remodelling.

In vitro data show synergy between inhaled corticosteroids and long acting β_2 agonists in terms of enhanced nuclear glucocorticoid receptor translocation and reduced smooth muscle proliferation.^{20 21} However, little evidence suggests that these in vitro findings translate into beneficial in vivo effects.^{22 23} Nevertheless, combination inhalers provide patients

Box 1: Key components of a written asthma action plan

- Peak expiratory flow based on personal best values and not predicted values
- Two to four levels of intervention in terms of symptoms or lung function
- Advice as to when to use oral corticosteroids or increase the dose of inhaled corticosteroids (and for how long)

with a convenient way of ensuring delivery of two different types of drug to the endobronchial tree, with commensurate improvements in asthma control. Moreover, in a recent case-control study, initial concerns about the safety of more widespread use of long acting β_2 agonists were not substantiated in terms of effects on mortality.²⁴

Leucotriene receptor antagonists

Leucotriene receptor antagonists exhibit dual anti-inflammatory and bronchodilator properties. They are useful across a broad range of severity of asthma and are of some benefit in patients with aspirin induced asthma, exercise induced symptoms, and concomitant allergic rhinitis.^{1 2}

Leucotriene receptor antagonists are positioned at step 4 of the UK asthma guidelines,² or in other words when patients have symptoms despite treatment with inhaled corticosteroids and long acting β_2 agonists. Two recent studies (published after the dissemination of these guidelines³) have compared the addition of either montelukast or salmeterol in patients with symptoms who are taking only inhaled corticosteroids (that is, at step 3).^{25 26} Neither of these multicentre trials found significant differences in frequency of exacerbations between randomised treatments. For example, after a year of treatment, 20.1% of patients in the montelukast group compared with 19.1% in the salmeterol group had an exacerbation of asthma.²⁵ Moreover, improvements in asthma specific quality of life were also similar. In the same study, add-on montelukast 10 mg daily showed superior anti-inflammatory efficacy, whereas salmeterol gave greater improvements in parameters of lung function. These studies highlight the importance of evaluating more long term outcomes such as exacerbation frequency, rather than lung function alone, when comparing the clinical effects of anti-asthma treatment.

Anti-immunoglobulin E

The link between coexisting inflammation of the upper and lower airway is well recognised; at least 40% of people with asthma have evidence of allergic rhinitis, and an even greater proportion have allergy driven disease. Recent work has explored attenuating the effects of IgE, a molecule that tends to define and mediate type 1 hypersensitivity and allergic reactions. Omalizumab is a recombinant humanised monoclonal antibody that has been shown to be useful in patients with allergic asthma and concomitant allergic rhinitis. For example, omalizumab was given to 405 patients with allergic asthma plus allergic rhinitis in a double blind randomised placebo controlled fashion.²⁷ A prerequisite to study entry was an elevated IgE concentration plus at least one positive skin prick test. Patients given active treatment (parenterally) over a 28 week period had fewer asthma exacerbations (21% *v* 30%, $P=0.02$) and an improvement in asthma and rhinitis quality of life questionnaires (58% *v* 41%, $P<0.001$). In another study of patients with poorly controlled moderate to severe allergic asthma, omalizumab was given every four weeks for 12 months.²⁸ Patients had a mean forced expiratory volume in one second of approximately 70% predicted and a median beclomethasone dipropionate equivalent daily dose of 2000 μ g. Compared with standard care, omalizumab signifi-

Fig 2 Oropharyngeal candidiasis as a consequence of high dose inhaled corticosteroid treatment

cantly improved the number of incidents related to asthma deterioration, exacerbation rates, ventilatory function, and symptom scores. Further studies are needed to evaluate the real life effectiveness and acceptability to patients of omalizumab. Moreover, this treatment needs to be compared with more conventional treatments that attenuate the effects of cysteinyl leucotrienes and histamine in allergic airways disease (such as leucotriene receptor antagonists and antihistamines).

Anti-interleukin 5 and interleukin 12

Eosinophils—whose development, synthesis, migration, and survival are directly under the influence of interleukin 5—are one of the main effector cells implicated in asthma. After synthesis in the bone marrow, they migrate to the systemic circulation and on to the lung. In a study of patients with mild allergic asthma who were randomised to receive a single dose of either parenterally administered monoclonal antibody to interleukin 5 or placebo, patients in the treatment arm were found to have significantly lower eosinophil counts in sputum and peripheral blood.²⁹ This reduction in blood eosinophils was sustained over a 16 week period. Similar reductions in eosinophils in sputum and blood have also been observed in patients with mild allergic asthma who were given recombinant human interleukin 12.³⁰ However, both studies found a consistent dissociation in response between effects on eosinophils and lack of effect on airway hyper-responsiveness. Thus, although such agents are novel and specifically designed to disrupt the asthmatic inflammatory cascade, these preliminary studies suggest that they may not offer clinically significant therapeutic benefit.

Acute asthma

Acute asthma is a relatively common medical emergency and causes at least 1000 deaths each year in the United Kingdom. Box 2 shows factors associated with fatal or near fatal episodes. The main drugs used in the management of acute asthma are nebulised β_2 agonists and oral or parenteral corticosteroids. Guidelines also suggest concomitant treatment with ipratropium and aminophylline if a patient fails to respond to initial treatment.²

Magnesium

Magnesium has been shown to act as a bronchodilator in patients with asthma, although results from clinical

Box 2: Medical and psychosocial features associated with a fatal or near fatal episode of asthma

- Misuse of alcohol or drugs
- Psychiatric illness
- Denial
- Non-concordance with prescribed drugs
- Learning difficulties
- Income and employment difficulties
- Previous self discharge from hospital
- Social isolation
- Previous admission to intensive care for asthma
- Brittle asthma

trials have been variable. In a randomised placebo controlled trial of 248 patients with acute asthma with mean forced expiratory volume in one second (FEV₁) 23% predicted, Silverman et al evaluated the effects of 2 g of intravenous magnesium.³¹ Patients given active treatment had a greater FEV₁ after four hours: 48.3% predicted compared with 43.5% in placebo treated patients ($P=0.045$ for the difference). Moreover, in patients presenting with an FEV₁ < 25% predicted, the final difference in FEV₁ in magnesium treated patients was even greater (45.3% *v* 35.6% with placebo, $P=0.001$). Intravenous magnesium has shown less promising results in other trials.³² Thus, although further data are needed, intravenous magnesium may be of some benefit in patients with acute asthma and severely impaired FEV₁ who have not had a good initial response to conventional treatment. Large prospective placebo controlled randomised trials are needed to compare magnesium and aminophylline in acute asthma. This in turn would be of use in deciding the potential role of each drug in the acute setting.

Leucotriene receptor antagonists

The cysteinyl leucotrienes (C4, D4, and E4) are eosinophil chemoattractants with a range of effects implicated in the asthmatic inflammatory process. For example, they are potent bronchoconstrictors, cause mucous hypersecretion, recruit inflammatory cells, increase vascular permeability, impair mucociliary clearance, and cause proliferation of airway smooth muscle. Several studies have shown that pretreatment with a leucotriene receptor antagonist shortens the time taken to recover after bronchial challenge,^{22–33} implying that cysteinyl leucotrienes are important in sustaining the bronchoconstrictor response. Indeed, the real life implication of this was seen in a placebo controlled randomised study that evaluated 194 patients admitted to hospital with acute asthma.³⁴ Intravenous montelukast 7 mg or 14 mg, in addition to standard treatment, gave a more rapid recovery ($P=0.007$) in FEV₁ over a two hour period than did placebo. Montelukast treated patients also needed less β_2 agonist, and fewer treatment failures occurred compared with placebo. In another study, Silverman showed that addition of zafirlukast to the standard care of patients with acute asthma reduced the risk of relapse over one month compared with placebo ($P=0.047$).³⁵ Ipratropium was not included as part of

“standard care” in either of these studies, so further prospective data are needed before leucotriene receptor antagonists are incorporated into the routine care of patients with acute severe asthma.

Non-invasive ventilation

Non-invasive ventilation is useful in patients with chronic obstructive pulmonary disease admitted with decompensated hypercapnic respiratory failure.³⁶ Few data are available supporting its use in respiratory failure due to asthma, so intubation and mechanical ventilation remains the “gold standard” management. However, non-invasive ventilation may be tried in the intensive care setting under specialised supervision as long as the threshold for switching to more conventional ventilation is low. The use of non-invasive ventilation should be regarded as an alternative to mechanical ventilation in some patients with acute severe asthma, although criteria for its use in an exacerbation are far from clear.

Future treatments

Despite major advances in the understanding of the immunological and inflammatory processes associated with asthma, these factors alone may not explain many of its features. The accelerated decline in ventilatory function reported in adults with asthma has been attributed to airway remodelling (collagen deposition, smooth muscle hyperplasia, and blood vessel proliferation). Remodelling has usually been considered to be a consequence of the inflammatory process associated with asthma. However, it is now apparent that abnormalities in airway integrity are fundamental to the pathogenesis of asthma and possibly equal in importance to immunological and inflammatory responses. The finding that the asthma susceptibility gene ADAM33 is preferentially expressed in smooth muscle, myofibroblasts, and fibroblasts, but not in T cells or inflammatory cells, has strengthened this argument. ADAM33 is the focus of research with the ultimate aim of identifying novel therapeutic agents that specifically target the processes associated with airway remodelling.³⁷

Recent studies have shown that titrating asthma treatment according to inflammatory biomarkers or airway hyper-responsiveness in conjunction with more conventional parameters such as lung function and symptoms leads to better control than the use of the conventional parameters alone.^{38–39} Monitoring sputum eosinophils and serial assessment of airway hyper-responsiveness have been shown to be advantageous in reducing exacerbations and titrating anti-inflammatory treatment. Whether measuring the concentrations of an inflammatory biomarker or extent of airway hyper-responsiveness is incorporated into future algorithms guiding physicians in the clinical management of asthma remains to be seen.

Knowledge and understanding of various polymorphisms, including that of the β_2 adrenoceptor and leucotriene C4 synthase, has led to the study of pharmacogenetic determinants that may influence the response to treatment in asthma. Clinical trials could be expanded to evaluate any preferential response according to the presence or absence of various polymorphisms such as that of arginine and glycine

Additional educational resources

British guideline on the management of asthma. *Thorax* 2003;58(suppl 1):i1-94 (www.brit-thoracic.org.uk)

Global Initiative for Asthma (GINA). *Global strategy for asthma management and prevention: updated 2004*. NIH Publication No 02-3659 (www.ginasthma.com)

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Websites for patients

Asthma UK (www.asthma.org.uk)—A patient friendly website giving general advice and information about asthma

Allergy UK (www.allergyuk.org)—A website designed to increase awareness and understanding of allergies
British Lung Foundation (www.lunguk.org)—Providing information and support to people with respiratory disorders

Lung and Asthma Information Agency (www.laia.ac.uk)—Offers fact sheets and charts of the epidemiology of respiratory and allergic diseases

substitutions at amino acid residue 16 of the $\beta 2$ adrenoceptor. Treatments of asthma in the future could conceivably be tailored depending on a patient's specific genotype.

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