

Seminar

Asthma

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Asthma is one of the commonest chronic diseases of affluent societies. The striking increase in prevalence of asthma over recent decades and the rarity of this disease in less affluent populations confirms the importance of environmental factors in the cause of asthma—although which environmental factors are responsible is still not clear. Family studies show that genetic factors are also important in determining individual susceptibility to asthma, with results of genetic studies suggesting that there are many genes with moderate effects rather than a few major genes. Asthmatic airways show inflammation and remodelling, with CD4+ helper cells, mast cells, and eosinophils characterising the inflammatory response. Inhaled corticosteroids remain the cornerstone of treatment with the addition of long-acting β agonists as the next step if symptoms continue. Leukotriene antagonists, the only new drugs to reach the market in the past decade, have modest effects. However, a better understanding of the mechanisms underlying asthma and the genetic and environmental factors that predispose individuals to asthma should lead to better preventative strategies and new therapeutic approaches.

The increasing prevalence of asthma and recognition of the burden it imposes on patients and health services has led to extensive research into its cause, pathophysiology, and management. Here, we review some of the most important research developments and highlight some clinical developments that have helped to improve management of asthma.

Epidemiology

Asthma is diagnosed clinically on the basis of symptoms of wheeze, dyspnoea, and cough, and by objective evidence of variable airflow obstruction. In developed countries, asthma is strongly but not exclusively associated with allergic sensitisation to *Dermatophagoides pteronyssinus* and other environmental allergens. Allergic asthma can present for the first time at any age, but incidence is highest in childhood.¹ Asthma presenting in childhood frequently remits during adolescence but can recur in adult life;² asthma in adults tends to persist for life and is probably associated with an accelerated decline in lung function.³ Wheezing with respiratory infection in very young children tends to occur in association with reduced lung function,⁴ usually resolves within the first 2 years of life,⁵ and is labelled as asthma or wheezy bronchitis. Deaths from asthma are now uncommon, especially in children and young adults; in the past they have occurred in epidemics thought to have been caused by use of high-dose formulations of relatively unselective β -agonist drugs.^{6,7}

Asthma has no standard definition. Attempts to define asthma have generally resulted in descriptive statements invoking notions of variable airflow obstruction over short

periods of time, sometimes in association with markers of airway hyper-responsiveness and cellular pathology of the airway;⁸ they have not, however, provided validated quantitative criteria for these characteristics to enable diagnosis of asthma to be standardised for clinical, epidemiological, or genetic purposes. Although asthma has no standard definition, a clinical diagnosis of asthma in young adults is a repeatable finding in populations with developed health services, and in such populations doctor-diagnosed asthma is typically reported by about 5% of those aged 20–44 years⁹ and in more than 10% of children.¹⁰ To avoid concerns about the reliability and validity of this marker of disease in different countries and cultures, and over different time periods, epidemiological studies generally use self-reported wheeze in the past year to identify asthma. Irrespective of the disease measure used, the evidence is consistent in showing a substantial increase in the prevalence of wheeze and diagnosed asthma over time in many populations.¹¹ Prevalence rates tend to be highest in economically developed countries with a temperate climate^{9,10} and low in rural subsistence and economically developing communities, and they increase with adoption of a more affluent lifestyle.^{12,13} The increased prevalence of asthma over time in the developed world seems to be part of a generalised trend of increasing prevalence of allergic sensitisation and allergic disease.

Although these findings provide clear evidence that environmental factors play a major part in the cause of asthma and allergy, family studies show that a strong component of asthma risk is genetically determined. This apparent inconsistency could be because, at least in the

Search strategy and selection criteria

Because about 6000 articles are published every year about asthma, we have done a non-systematic review of articles published in English and collected by the authors over many years. We gave priority to randomised controlled trials when available, to larger studies, and to articles published in high quality journals. We also drew on our own clinical experience when it seemed appropriate and to fill gaps in the published work.

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Panel 1: Examples of candidate genes implicated in development of asthma

Chromosome	Candidate genes
5q	Th2 cytokine cluster (interleukin 4, 5, 9, 13)
6q	Tumour necrosis factor α , MHC
11q	Clara cell secretory protein, high affinity IgE receptor β subunit ((Fc ϵ R1 β))
12q	Interferon γ
14q	T cell receptor α/δ complex
16q	Interleukin-4R α
20p	ADAM33

Data taken from references 18–20, 23–25.

developed world, exposure to the major environmental determinants of asthma is now relatively widespread and possibly ubiquitous, leaving genetic factors as the major detectable determinants of individual disease risk. In the developing world, however, the emergence of asthma probably reflects the strong effect of environmental exposures associated with economic development.

Genetics

Genome screens with classical linkage and fine mapping approaches suggest that susceptibility to asthma is determined by many genes that have a moderate effect.^{14–17} Identification of the precise loci involved has been difficult but, important loci are thought to exist on chromosomes 5q23–31,¹⁸ 11q,¹⁹ and 12q.²⁰ Classical positional cloning approaches have led to identification of new genes of potential importance on chromosome 14q24 and chromosome 20p13 (ADAM33).^{21,22} Studies^{18–20,23–25} of polymorphic variation within genes likely to be involved in disease pathophysiology have also identified a number of candidate genes which could affect the risk of developing asthma (panel 1). However, most of these genes have been identified in studies in which asthma has been defined as being present or absent rather than in quantitative terms, and these studies might therefore have tended to identify genes involved in disease initiation rather than in severity or progression. A major challenge for the future is to identify how genes that predispose individuals to asthma interact with environmental factors to cause disease.

Knowledge of the genes important in the initiation or natural history of asthma will prove to be valuable only if it can be used to prevent disease or improve patient care. At present it is far from clear that early treatment of asthma modifies natural history to any clinically relevant extent. Gene therapy is unlikely to be a sensible approach for most patients for a disease that can usually be controlled with simple and safe drugs. This approach could however be worthwhile for some patients with severe disease, perhaps by use of over-expression of anti-inflammatory mediators in the lung. It could also be possible to use genetic information to predict treatment response, since a number of targets for commonly used asthma drugs show substantial genetic variability,²⁶ the best examples being the β_2 adrenoceptor and enzymes in the 5-lipoxygenase pathway. Individuals with the Arg-Gly-16 β_2 adrenoceptor variant have been shown to have changed responses to bronchodilators,²⁷ whereas the number of repeats of an Sp1 recognition sequence in the 5-lipoxygenase promoter partly determines responses to drugs affecting responses in the airways that are mediated by leukotrienes.²⁸ In reality, the differences in clinical response in relation to these polymorphisms is quite small, although combinations of polymorphisms within a gene (haplotypes) might prove to be more important than individual polymorphisms.

Environment

A more affluent and educated lifestyle has many characteristics that could be involved in the cause of asthma and allergy, but which of these are responsible has not been clearly established. Exposure to *D pteronyssinus* from living in warm and insulated housing and sleeping on soft pillows and mattresses is associated with more severe asthma symptoms in sensitised individuals,²⁹ but such an association does not account for the more general increase in prevalence of sensitisation to other allergens or explain why, in less affluent populations, sensitisation to *D pteronyssinus* can be common but have little relation to the risk of asthma.^{30–32}

That allergic sensitisation and, to a lesser extent, asthma, is less common in children with older siblings has given rise to the hygiene hypothesis—ie, that children growing up in modern affluent societies could be exposed to lower levels of infection, which in turn cause their immune system to polarise towards a Th2 rather than a Th1 lymphocyte phenotype and hence pose a greater risk of allergic disease.³³ Possible reasons for this effect include increased exposure to infection, acquisition of different intestinal commensal bacteria,^{34,35} and higher exposure to bacterial endotoxins,³⁶ and these mechanisms could also explain why allergy is less common in children brought up on farms or with early exposure to animals.³⁶ Intestinal parasite infection, particularly by parasites that have a systemic phase in their lifecycle, could also be associated with reduced risk of asthma. This protective effect may be greatest in individuals sensitised to allergens, and is probably driven by end-organ suppression of Th2-mediated immunity by mechanisms that have evolved in the parasite to protect it against host immunity.^{37,38}

Results from observational studies³⁹ have shown that diets low in foods providing vitamin E, vitamin C, magnesium, and ω -3 polyunsaturated fats, or high in sodium and ω -6 polyunsaturates, are associated with increased risk of asthma. So far, however, investigators of intervention studies have failed to provide consistent evidence of a causal association, either for individual nutrients or the foods that contain them. Obesity is an independent and reversible risk factor for asthma, more so in women than men, and apparently without any effect on allergy.^{40,41}

Ambient pollutants have a complex role in asthma. Asthma symptoms are exacerbated to varying degrees by exposure to particulates, sulphur dioxide, and nitrogen oxides, but the substantial reduction in ambient levels of these pollutants over a period in which asthma prevalence has increased in many countries, including the UK,⁴² argues against a major causal effect, as does the low prevalence of allergic asthma in East Germany before unification⁴³ and in other eastern European countries when ambient levels of these pollutants were high.⁴⁴ An alternative interpretation of these data, that particulate pollution protects against incidence of allergic disease while exacerbating symptoms in sensitised individuals, is supported by the observation that allergic sensitisation is less common in adults whose parents were smokers,⁴⁵ and the lower incidence of sensitisation in smokers.⁴⁶ If a causal association with pollution exists, the major source of pollution will probably be from the indoor rather than the outdoor environment, with exposure to nitrogen oxides, particulates, and volatile organic compounds including formaldehyde, moulds, and other biological or synthetic exposures being important. Asthma arising from these and other exposures in the occupational environment is well recognised and accounts for a small but important proportion of cases of incident asthma in adults.

Many other factors have been implicated in the cause of asthma and allergy, including lower maternal age, maternal diet and smoking, duration of breastfeeding, prematurity, and low birthweight, but none of these factors has been shown to contribute substantially to the rise in asthma prevalence over recent decades in the UK. Thus, despite extensive investigation and clear evidence of the importance of environmental effects, the major environmental causes of asthma have still to be identified. If, as suggested above, exposure to the major environmental determinants of asthma is now almost uniform in the developed world, then the focus of investigation of environmental causal factors might need to shift towards the developing world where asthma and allergic disease are still rare but are emerging as clinical problems in conjunction with changes in lifestyle and environmental exposures. To identify environmental causes, epidemiological studies need populations with heterogeneity of exposure and disease prevalence; sufficient heterogeneity might no longer exist in the developed world.

Asthma pathogenesis

The pathology of asthma is characterised by various changes in the airways including mucus plugging, shedding of epithelial cells, thickening of the basement membrane, engorgement of the vessels, and angiogenesis, inflammatory cell infiltration, and smooth muscle hypertrophy and hyperplasia.⁴⁷ The pathogenesis of asthma can be broadly subdivided into inflammatory and remodelling components.

Inflammatory component

The inflammatory features of asthma consist of a dense inflammatory infiltrate in which eosinophils, mast cells, and CD4+ helper T lymphocytes predominate.⁴⁷ Neutrophilic infiltration also arises during asthma exacerbations⁴⁸ and in the late response to allergen challenge. Dendritic cells seem to be the key cells for antigen presentation in asthma.⁴⁹ Antigens then cause cross-linking of IgE and as a consequence mast cells are activated and degranulate. Mast cells are important in the acute airway responses to allergens and may also contribute to remodelling in chronic asthma.⁵⁰ Interest in the mast cell will probably increase with the recent report that the presence of mast cells in the smooth muscle layer in bronchial biopsies helps to differentiate asthma from eosinophilic bronchitis, suggesting that interactions between mast cells and smooth muscle are important in asthma pathogenesis.⁵¹ Such an observation is consistent with results of studies of sensitised human airway smooth muscle *in vitro* where the degree of contraction to antigen is related to the number of mast cells present.⁵²

A defining characteristic of asthma is the presence of many activated eosinophils,⁵³ which are thought to contribute to airway epithelial damage by release of products such as eosinophil major basic protein. However, the central role for eosinophils as effector cells in asthma has been challenged. Administration of antibodies against interleukin 5 to patients with asthma greatly reduces systemic and sputum eosinophilia, but has a negligible effect on airflow and airway hyper-responsiveness.⁵⁴ Similarly, administration of interleukin 12, which drives differentiation of T cells to a Th1 rather than a Th2 phenotype, reduced eosinophil numbers, but not airway responsiveness in patients with asthma.⁵⁵ Furthermore, a study⁵⁶ in MBP-1 knockout mice suggested that this protein does not contribute to airway hyper-responsiveness.

The role of T lymphocytes is less controversial. T lymphocytes seem to be essential cells in the orchestration of the airway inflammation that characterises asthma.^{57,58} T-helper lymphocytes differentiate into two main phenotypes, Th1 and Th2, which produce distinct profiles of cytokines and chemokines. Th1 cells produce interferon γ whereas Th2 cells produce interleukin 4, 5, and 13. Th2 cells are potent stimulators of IgE production from B lymphocytes. Results of studies^{59,60} in mice have suggested that Th2 cytokines have key roles, and results of bronchoscopic lavage studies⁶¹ in human beings have shown increased concentrations of these cytokines. Asthma is probably not due to Th2 driven inflammation alone however, and studies⁶² in mice suggest that Th1 cells also contribute.

Inflammatory cells are recruited into the airways by chemokines, which exert some degree of selectivity in the cells they attract. Eosinophil chemottractants include eotaxin, interleukin 5, RANTES (ie, regulated by activation, normal T-cell expressed and secreted), and monocyte chemottractant proteins 3 and 4, whereas neutrophils are recruited mainly by interleukin 8.⁶³ These chemokines are produced by inflammatory and structural cells such as airway smooth muscle cells and airway epithelium.⁶³⁻⁶⁵ Inflammatory cells bind to adhesion molecules on bronchial vessel endothelium and subsequently undergo a process of transmigration into the airway interstitium.⁶⁶ Adhesion molecules that are important in this process include ICAM-1, VCAM-1, and E-selectin. Airway cells also release survival factors, such as granulocyte macrophage colony stimulating factor (GM-CSF), which extend the life of inflammatory cells at the site of inflammation.⁶⁷

Remodelling component

Acute inflammatory diseases usually resolve with repair processes restoring normal structure and function. In chronic asthma, this process becomes disturbed and ineffective repair leads to remodelling involving several structures.⁶⁸ Epithelial damage and loss of its protective barrier function exposes the deeper airway structures to environmental insults, and both inflammatory and structural cells produce several growth factors that lead to angiogenesis, proliferation of smooth muscle in the airway, thickening of basement membranes, and fibrosis.⁶⁸ The increase in the mass of smooth muscles in the airway increases bronchial responsiveness by increasing force in response to bronchoconstrictor stimuli and by reduction of the airway's diameter.⁶⁹ Smooth muscle in the airways of patients with asthma proliferates excessively *in vitro*.⁷⁰ Important cytokines and enzymes during the remodelling process include transforming growth factor β , epidermal growth factor, and matrix metalloproteinases.⁶⁸

Diagnosis and assessment

Ascertainment of whether asthma is present is usually straightforward, and is based on a characteristic history and variability in lung function. Delays in diagnosis are not uncommon, however, especially when cough is the presenting symptom. In young children it can take some time to ascertain whether the child has persistent asthma rather than wheezy bronchitis.⁵ In older patients, distinguishing severe chronic asthma from chronic obstructive pulmonary disease can be difficult and the two disorders sometimes merge in those who have smoked cigarettes. Asthma can also be diagnosed incorrectly, especially in patients with inappropriate hyperventilation, dysfunction of the vocal cords, or obstruction of the upper airway. Unusual features and any suggestion of upper airway obstruction requires further investigation.

Panel 2: At-risk signs in a patient with asthma**On routine review**

Previous visit to intensive-care unit or cardiorespiratory arrest from asthma

Frequent admissions or visits to an accident and emergency department

Excessive use of β agonists by nebuliser or inhaler

Failure to take inhaled corticosteroids despite symptoms or exacerbations

Large fluctuations in peak-flow rate

During an exacerbation

A quiet chest, distress, and difficulty in speaking

Tachycardia and an unrecordable peak-flow rate

High arterial carbon dioxide tension and low arterial oxygen tension or oxygen saturation measurement when breathing air

Objective diagnosis of asthma still relies on demonstration of variability in lung function over time or improvement after a bronchodilator, prednisolone, or high-dose inhaled corticosteroid. Such variability can be measured with spirometry in the clinic or by regular peak-flow measurements at home, with regular peak-flow measurements usually giving a better overall measure of asthma severity. Demonstration of bronchoconstriction after vigorous exercise can be useful in young people, whereas an increase in blood eosinophils could point to asthma in older patients. Other features associated with asthma, such as non-specific bronchial hyper-responsiveness to agents such as methacholine, are not specific enough to be a useful diagnostic test.

Acute exacerbations of asthma need to be assessed rapidly and accurately to enable life-saving treatment to be implemented promptly, and guidelines are available.^{8,71-73} Patients at increased risk of dying from asthma (panel 2) need particular care. Asthma attacks can be subdivided according to severity but since most attacks are managed initially in busy admission units, assessment and management should be kept simple, so that essential first-line drugs (oxygen, nebulised β_2 agonists, and oral or intravenous corticosteroids) are given rapidly to all patients. The severity of acute asthma is still underestimated on occasions, sometimes with fatal consequences, and usually because objective measurements of severity have not been made. Oxygen saturation measurements are also useful when vocal cord dysfunction mimics an asthma attack, when values are usually (though not invariably) normal.

Factors that provoke asthma

The factors that commonly provoke asthma are well known—allergens, upper respiratory tract infection, exercise, perfume and fumes, and changes in temperature and humidity. Some agents provoke asthma less frequently, but are important to exclude. These include drugs (aspirin and other non-steroidal anti-inflammatory drugs, β -blockers), food additives (eg, metabisulphite, tartrazine), and food and drinks (eg, peanuts, alcohol,⁷⁴ Cola⁷⁵). Some premenstrual deterioration in asthma control is not uncommon in younger women, but it is not usually severe, and treatment with progesterone or gonadotropin-releasing hormone analogues are rarely needed.^{76,77}

Some substances found in the workplace cause asthma because of specific sensitisation, and occupational asthma accounts for up to 10% of asthma in young adults in Europe.⁷⁸ Panel 3 shows some of the commoner substances, although more than 200 sensitising agents

Panel 3: Occupational agents causing asthma for which patients in the UK can get industrial injuries benefit

Agents	Some occupations at risk
Isocyanates	Plastic foam, ink, paints, adhesives
Platinum salts	Platinum refining
Acid anhydride and amine hardening agents, including epoxy resin curing agents	Many industries using adhesives, plastics, resins, etc
Soldering flux	Electronics industry
Proteolytic enzymes	Biological washing powder manufacturing
Small animals, including insects	Research laboratories
Dust, meal, or flour from barley, oats, rye, wheat, and maize	Bakers, flour milling
Antibiotics, cimetidine, ispaghula powder, ipecacuanha	Drug manufacturing
Wood dusts	Working with hard woods
Castor bean dust	Oil industry, merchant seamen
Azodicarbonamide	Blowing agent, foam plastics

have been identified.⁷⁹ Occupational asthma is preventable and can lead to severe irreversible airway obstruction if the patient is not removed from the sensitising agent. An occupational history should be taken from all patients with asthma and the history should be supplemented, when occupational asthma is suspected, with frequent peak-flow measurements during days when the patient is and is not at work and referral for a specialist opinion.

A few patients have asthma as part of a wider problem such as allergic bronchopulmonary aspergillosis, Churg Strauss syndrome,⁸⁰ and aspirin-induced asthma.⁸¹ Panel 4 shows the main features of these disorders.

Management

A patient might have poorly controlled asthma due to poor management, severe asthma, or both. Panel 5 shows the aims of management. Poor compliance with treatment, especially inhaled corticosteroids, continues to be an important cause of poor asthma control and much effort is needed to ensure that patients understand why prophylactic treatment needs to be taken regularly and the dangers of poor compliance. Particular care is needed for patients who are more likely to be non-compliant such as adolescents, the poor and socially deprived,⁸³ and patients with psychosocial problems. Several developments have contributed to better asthma management including development of guidelines,^{8,71-73} better use of peak-flow meters, and recognition of the need to improve patient education and the involvement of respiratory nurses in asthma management. Patients now take more responsibility for assessing the severity of their asthma and adjusting treatment within limits using written personal guidelines and this makes sense for a disorder that can fluctuate rapidly.

Patients with asthma should be advised strongly not to smoke and to lose weight, if overweight, since these measures should improve asthma control.⁴¹ Inactivated influenza vaccine is recommended and is safe in patients with asthma.⁸⁴ Avoidance of allergens can be helpful for patients with specific allergen sensitivities, to an animal, for example. Whether and to what extent reducing the

Panel 4: Syndromes associated with asthma

Allergic bronchopulmonary aspergillosis

Asthma

High blood eosinophil count—usually $1-3 \times 10^9/L$

Recurrent pulmonary infiltrates

Positive skin prick test to *Aspergillus fumigatus*

Positive blood precipitins to *A fumigatus*

Proximal bronchiectasis

Responds to high dose prednisolone and often requires regular oral corticosteroids

Itraconazole might help⁸²

Churg-Strauss syndrome⁸⁰

Asthma, usually long standing, increasing in severity, and requiring oral corticosteroids

High eosinophil count (usually $>1.5 \times 10^9/L$)

Eosinophilic lung infiltrates, pleural effusion less common

Systemic vasculitis (mononeuritis multiplex, skin, gastrointestinal tract, kidneys, heart, and eyes)

In patients already taking corticosteroids the clinical features might be less florid

Responds to high-dose prednisolone and cyclophosphamide

50% of patients have a positive antineutrophil antibody,

specifically to myeloperoxidase

Has been reported after hyposensitisation injections and some drugs, including macrolide antibiotics and leukotriene antagonists, although a causal association is not established

Aspirin-sensitive asthma⁸¹

Bronchoconstriction occurs in response to aspirin and other non-steroidal anti-inflammatory drugs—the response can be rapid and life-threatening

Associated with nasal polyps and asthma is frequently chronic and severe

Some patients also bronchoconstrict in response to hydrocortisone

Some response to leukotriene antagonists

Patients should be told to avoid all non-steroidal anti-inflammatory drugs

Panel 5: Aims of management

To enable a patient with asthma to:

Achieve as normal a lifestyle as possible, including a normal exercise tolerance

Avoid night-time awakenings due to asthma

Avoid exacerbations

Avoid important adverse effects from treatment—now and in the future

Over the past two decades many groups have tried to develop new types of drug for asthma, but only the leukotriene modifiers are on the market. Patients have benefited, however, from several studies^{8,71-73} designed to assess the role and merits of the drugs presently available. Most asthma guidelines include a stepwise approach to asthma treatment, which ranges from β agonists alone for very mild intermittent asthma to oral corticosteroids for severe chronic asthma. The UK guidelines are being updated, but a schematic hierarchy of the drugs considered most appropriate for different levels of asthma severity is shown in figure 1. Treatment should be determined by symptoms, exacerbations, and lung function since the weight of evidence suggests that none of the drugs in use changes the natural history of asthma. There is some controversy about inhaled corticosteroids, which are very effective at suppressing inflammation in asthma. Symptoms and airway obstruction have usually recurred, however, when the drugs are discontinued.⁹⁰⁻⁹²

Inhaled corticosteroids

Inhaled corticosteroids are the cornerstone of treatment for asthma. They are especially helpful in patients with mild or moderate asthma, improving lung function, and reducing symptoms and exacerbations,⁹³⁻⁹⁵ and they have been shown to reduce readmissions for asthma⁹⁶ and asthma deaths.⁹⁷ Inhaled corticosteroids are recommended for all patients requiring more than one puff a day from their β -agonist inhaler.

concentration of house dust mite is feasible and worthwhile is still uncertain, but large trials are under way to assess its effectiveness. Complementary approaches to treatment, such as Yoga, help some patients, but overall, the effect seems to be small.^{85,86} Asthma control sometimes improves with allergen immunotherapy,⁸⁷ but for patients, other than those sensitised to wasp and bee venoms, the small benefit is outweighed by the occasional fatal reaction to the injection.⁸⁸ New approaches, including vaccination with allergen DNA conjugates, are under investigation.⁸⁹

Pharmacotherapy

Drugs should be given by inhalation when possible so that the same beneficial effect can be achieved with a much smaller dose, thus causing lower systemic drug concentrations and fewer systemic adverse effects. The large number of inhalation devices available causes confusion and asthma nurses can often help patients to find an inhaler that they can use effectively.

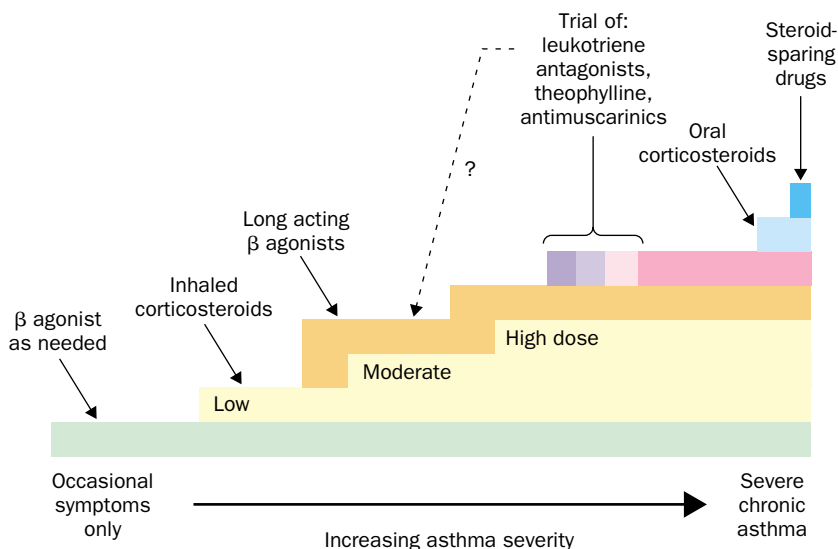


Figure 1: Treatment hierarchy used to add further drugs as asthma becomes increasingly severe

Two limitations of inhaled corticosteroids require comment. First, although small doses of an inhaled corticosteroid are very effective, the added benefit from higher doses is limited (figure 2). Doubling⁹³ or quadrupling⁹⁴ the dose of an inhaled corticosteroid can improve asthma control, but it is usually better to add in a long-acting β agonist.⁹³⁻⁹⁵ Second, long-term high doses of inhaled corticosteroids can cause systemic adverse effects, including reduced bone mineral density,^{98,99} which is likely to predispose patients to osteoporotic fractures as they get older, and an increase in cataracts¹⁰⁰ and glaucoma.¹⁰¹

Since inhaled corticosteroids reduce the need for oral corticosteroids, which have many more adverse effects, the goal of treatment is to give the minimum dose of inhaled corticosteroid to maintain good control. Most patients with asthma can be managed on a low dose, which will produce maximum or near maximum benefit with minimum risk of long-term adverse effects (figure 2). What this dose is will vary depending on the severity of asthma but will rarely be above 800 μg beclometasone or budesonide a day and usually less than 400 μg a day (equivalent to 400 μg and 200 μg fluticasone, respectively, since fluticasone is twice as potent as beclometasone and budesonide). Patients who need a higher dose should carry a steroid card and if the dose is maintained or they require courses of oral corticosteroids, the question of prophylaxis against osteoporosis needs to be considered.

β -agonists

Short-acting β agonists such as salbutamol and terbutaline are very effective in prevention of exercise-induced asthma and for relieving acute attacks of asthma. They do not provide benefit when given regularly¹⁰² and, although more debatable, some patients can even deteriorate,¹⁰³ particularly those with the Arg 16 β -receptor polymorphism.¹⁰⁴ Patients should therefore take short-acting β agonists only as required. Excessive use of β agonists is associated with asthma deaths¹⁰⁵ and any patient requesting inhalers frequently (more than one or two a month) should be assessed to ensure that they are taking their prophylactic treatment appropriately.

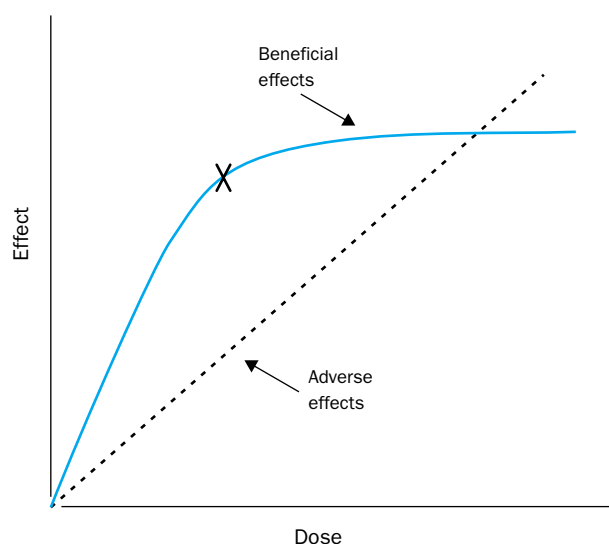


Figure 2: **Relation between beneficial and adverse effects with increasing doses of inhaled corticosteroids**

X=dose at which maximum benefit is achieved with minimum side-effects.

By contrast with short acting β agonists, regular use of the long-acting β agonists, salmeterol and formoterol, improves asthma control and reduces asthma exacerbations.^{93,94,106} Both drugs are effective for longer than 12 h and should be taken twice daily. The main clinical difference between the two drugs is that formoterol has a rapid onset of action, similar to that of salbutamol, raising the possibility that formoterol could be used for symptom control in addition to regular administration. Asthma control was better with formoterol when compared with terbutaline for relief of asthma¹⁰⁷ and it is now licensed for up to 72 μg a day. Because the long-acting β agonists improve asthma control and early safety concerns have been allayed by large clinical trials,^{93-95,106} they are now introduced at an earlier point in asthma management—ie, for patients who remain symptomatic despite 400–800 μg of an inhaled corticosteroid; results of one study⁹⁵ suggest that these drugs should be introduced even earlier. Both long-acting β agonists can now be given in combination with an inhaled corticosteroid and this could improve patient compliance.

Theophylline, ipratropium, cromoglycate, and nedocromil

Theophylline is effective in asthma and has some anti-inflammatory activity.¹⁰⁸ It is less effective than the long-acting β agonists¹⁰⁹ however, and its narrow therapeutic window and interactions with other drugs make it a less attractive option. More selective phosphodiesterase inhibitors have been developed¹¹⁰ but have not yet shown clear benefit over theophylline. Ipratropium and oxitropium are also effective bronchodilators but usually add little in patients with stable asthma who are already taking a β agonist. Sodium cromoglycate and nedocromil have been largely superseded by low-dose inhaled corticosteroids.

Prednisolone and steroid-sparing drugs

Although the proportion of patients with asthma who require regular prednisolone is small (around 1%), it accounts for some 50 000 patients in the UK and a further half a million patients need at least one course of oral steroids each year.¹¹¹ Oral corticosteroids cause much morbidity and patients on long-term oral steroids need careful assessment to be sure that such treatment is necessary. For those who require prednisolone, prophylaxis against osteoporosis needs to be considered, ideally with a measure of bone mineral density. Bisphosphonates and hormone replacement therapy decrease the loss of bone mineral density seen with oral corticosteroids, although the evidence for an effect on fracture is limited.¹¹²

Some immunosuppressive drugs (methotrexate, ciclosporin, and gold) reduce oral steroid requirements in patients with severe asthma, usually by 5.0–7.5 mg a day on average.^{113,114} Whether such a reduction is worthwhile has to be assessed for each patient against possible adverse effects and risks from the replacement drugs.

New drugs—Leukotriene modifiers consist of the lipoxigenase inhibitors such as zileuton, and the leukotriene antagonists such as montelukast and zafirlukast. The drugs are given orally and a single drug can therefore treat both rhinitis and asthma. Both types of drug are effective in patients with mild or moderate asthma.¹¹⁵ Leukotriene antagonists cause some bronchodilatation within an hour of administration¹¹⁶ and results of long-term studies^{115,117} have shown a reduction in symptoms and exacerbations. Most of the studies have been in

patients who were not taking an inhaled steroid, although both drugs have shown efficacy when added to an inhaled corticosteroid.¹¹⁵ The changes have been small, however, and less than those seen with a low dose of inhaled corticosteroid.¹¹⁸ Montelukast was ineffective when added to other treatment in a pragmatic study of patients with more severe asthma.¹¹⁹ Leukotriene antagonists should theoretically be useful in aspirin-induced asthma, but their effectiveness in these patients has been limited.¹²⁰

Churg-Strauss syndrome has occurred in association with use of the leukotriene antagonists, but whether it is due to a direct drug effect or unmasking of the syndrome as inhaled or oral corticosteroids are reduced is still uncertain.^{121,122}

Asthma and pregnancy

Several investigators^{123,124} have assessed the outcome of pregnancy in patients with asthma and although the outcome is usually fine, it is worse for both mother and fetus when asthma is not controlled well. Compliance with treatment could be reduced if the mother is concerned about the effect of drugs on the fetus. A historical cohort analysis¹²⁵ of 447 963 singleton deliveries in the USA showed a very small increase in congenital malformation in babies born to mothers with asthma; this could have been due to uncontrolled asthma since it did not relate to any specific drug. None of the drugs usually used to treat asthma has been shown to cause congenital malformations, but inhaled drugs should be used when possible to reduce systemic drug concentrations. Leukotriene modifiers should be avoided because of the limited safety information in this situation.

Asthma can improve or deteriorate during pregnancy, but problems with asthma during delivery are extremely rare. Exacerbations should be treated conventionally.

Drugs in development

The suggestion that the anti-inflammatory effects of corticosteroids are due to gene silencing (transrepression), whereas the adverse effects are due to gene activation (transactivation)¹²⁶ has led to interest in dissociated steroids that have only transrepression properties and should therefore have fewer adverse effects. Dissociated steroids produced unwanted effects on bone in animals, however, suggesting that some of their adverse effects are linked to transrepression.¹²⁷ The role of glucocorticoid receptor polymorphisms in determining the response to corticosteroids is also being investigated,¹²⁸ as is whether long-acting β agonists enhance the anti-inflammatory effects of corticosteroids in vivo as shown in vitro.¹²⁹

Panel 6: New therapeutic approaches to treatment of asthma

PDE4 inhibitors

Inhaled ciclosporin A

Monoclonal antibodies against IgE, CD4 cells, and Th2 cytokines (eg, interleukin 4 and 5)

Modulation of Th1/Th2 balance through vaccination

(*Mycobacterium vaccae*, DNA CPG vaccines) or promotion of Th1 related cytokines (interferon γ , interleukin 12 and 18)

More specific immunotherapy

Antagonists to chemokines, adhesion molecules, proinflammatory cytokines, tumour necrosis factor α , interleukin 1

Antisense oligonucleotides and gene therapy

Inhibitory cytokines interleukin 10

Increased understanding of the role of various cytokines and chemokines and the imbalance between Th1 and Th2 cells in asthma raises the possibility of interventions at different sites in the inflammatory cascade¹³⁰ (panel 6). Some improvements in asthma control have been seen in early studies of soluble interleukin 4 receptors¹³¹ and selective Th2 cytokine inhibitors.¹³²

Clinical studies of humanised monoclonal antibodies to IgE, CD4 cells, and interleukins 4 and 5 are under way. Antibodies to IgE caused a large reduction in circulating free IgE without major safety problems.¹³³ The first large-scale clinical study¹³³ with an IgE monoclonal antibody, omalizumab, in selected patients showed some clinical benefit and it enabled the dose of inhaled corticosteroid to be reduced. The effects of antibodies to interleukin 5¹³⁴ and interleukin 12¹³⁵ on clinical features of asthma have been disappointing. The need for regular injections to administer monoclonal antibodies is likely to restrict their role to patients with troublesome asthma.

The completion of the human genome project is likely to fuel a new and important period of research into asthma therapy. At present, all the drugs used to treat human disease target the products of around 500 genes, whilst the human genome contains some 32 000 genes. Development of expression profiling approaches at the genomic (RNA) and proteomic level is likely to lead to many new targets and therapeutic opportunities. The real difficulty is dealing with the bioinformatic challenge presented by use of these expression profiling approaches. One possible approach is to combine expression profiling approaches with classic genetic approaches.

Conflict of interest statement

The respiratory division has funding from AstraZeneca, GlaxoSmithKline, Novartis, Inflazyme, BykGulden, Ramer Health Care, Pharmacia Upjohn, Merck and Lambert Health Care for studies. A Tattersfield has a consultancy for a safety committee for Schering-Plough who also supported travel to a meeting. A Knox has received travel support from 3M and AstraZeneca and has given talks and taken part in advisory boards for AstraZeneca, Merck Sharp and Dohme, 3M, Pharmagene, and GlaxoSmithKline. J Britton has had support for travel from GlaxoSmithKline. I Hall has a consultancy for a novel target project with Roche.

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Uses of error

Series of errors

Mary E Hannah

I had been in consultant practice for 2 years. I arrived in the operating room on an Easter Monday morning to perform an elective repeat caesarean section. A few minutes after waiting for the anaesthetist to establish an epidural anaesthetic, I was asked to quickly scrub and begin the surgery.

On entering the operating room the woman was intubated and appeared to be asleep. The anaesthetist urged me to proceed with the surgery as quickly as possible and as I did so, he reported that my patient had become anxious following insertion of the intravenous needle, claiming she couldn't breathe, and he had proceeded to intubate her. The caesarean section was uneventful and a healthy baby was delivered. Afterwards I learned that my patient had felt all of the surgery, from the initial cut of the scalpel to the final suturing of the skin. She could hear and feel but was unable to speak or move. It sounded as if she had been paralysed but not anaesthetised. I was devastated to think that I had inflicted such a trauma on another human being. The anaesthetist admitted he had not given my patient any anaesthesia because he did not know the cause of her breathing difficulty. To investigate this further, the bottle of intravenous fluid she had received was sent to the laboratory for analysis.

At my patient's 6-week postpartum visit, she complained of recurrent panic attacks. She continued to ask me for answers but all I could do was apologise for the lack of anaesthesia. I arranged for psychiatric counselling and booked a return visit.

Several days later I received a lawyer's request for a detailed account of what had transpired in the operating room. On advice from counsel, I reported as little as possible and only what I knew to be fact. My patient did not return.

I learned several months later that the intravenous fluids had in fact contained succinylcholine, thus explaining completely my patient's reaction. The infusion that was started on this woman was from a bottle in the operating room that had been prepared and hung the night before. Apparently a case the previous evening had been cancelled after the bottle and tubing had been set-up. Succinylcholine had been inserted into the bottle but the bottle had not been labelled. Thus, when the anaesthetist had come in on the Monday morning, he had assumed this was a new bottle of intravenous fluids and had no reason to suspect it contained a potentially lethal drug. When the woman became paralysed, we never thought of the potential for someone else's error.

Fearing legal repercussions and on continuing advice from counsel, I did not contact my patient to provide her with this information. How reassuring she might have found it to know that she had not dreamt up this horrible experience, to learn there was a clear explanation for her symptoms, and to have us acknowledge that she had suffered a grievous injury for which a sincere apology was in order. I regret my silence.

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