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CLINICAL PERSPECTIVES

An update on asthma management

C. JENKINS

Department of Thoracic Medicine, Concord Hospital; Woolcock Institute of Medical Research, Royal Prince Alfred Hospital and Co-operative Research Centre for Asthma, Sydney, New South Wales, Australia

Abstract
Asthma remains a major cause of morbidity in the Australian community, despite enhanced strategies and interventions for achieving optimal outcomes. Although there is some evidence of over use of high doses of inhaled corticosteroids (ICS), there is also evidence for under use of ICS, despite long-term data demonstrating clear benefits of low doses. The present paper briefly discusses some of the issues that are pertinent to the development of sensitization and atopic disease, but focuses mainly on the current understanding of best clinical practice for adults with asthma and the optimal approach to management. A clear definition of asthma control and a systematic approach to down-titration to minimize ICS doses is crucial to achieving better outcomes. Patient self-management education and optimal therapy are the keys to achieving better outcomes, although uncertainty remains about recommendations for mild asthma, despite new data. (Intern Med J 2003; 33: 365–371)

Key words: asthma control, asthma management, inhaled corticosteriods.

ASTHMA IN AUSTRALIA: THE CURRENT PICTURE

Asthma is a common disease in Australia and, according to the National Health Survey (NHS), the self-reported prevalence of asthma increased from 8% in 1989–1990 and 11% in 1995, to 12% in 2001.[1,2] Hence, in 2001, there were approximately 2.2 million people in Australia with asthma as a current and long-term condition (11% of males and 13% of females). The prevalence of wheezing illness and asthma in children has increased dramatically over the last 20 years, but in adults has changed only a little.[3–5] Australia has one of the highest rates of asthma in the world, together with countries such as the United Kingdom, New Zealand and the Republic of Ireland.[6]

The reasons underlying the high prevalence of asthma in Australia are not well understood, although genetic predisposition, a westernised lifestyle and high allergen exposure (especially to house dust mites and fungi) are considered to be important factors. Recent evidence suggests that nonallergic environmental factors significantly modify the risk of developing asthma, particularly in the first years of life.

It is sometimes said that the increased awareness of asthma in our community may be causing over-diagnosis. While it is certainly true that there are individual cases in which transient or recurrent respiratory symptoms are misdiagnosed as asthma, there is convincing evidence that asthma is still under-treated and morbidity is high for the community as a whole. The International Study of Asthma and Allergy in Children indicated that 8% of 6–7 year olds and 12.2% of 13–14 year olds have >12 episodes/year, while 11.2% of 6–7 years olds and 9.8% of 13–14 year olds experience sleep disturbance ≥1 nights/week due to asthma.[7] The New South Wales (NSW) Health Survey in 1997[8] and the 1992–1995 South Australian Health Omnibus Survey (SAHOS)[9] both indicated high levels of morbidity. In both studies, less than half of those surveyed with asthma were taking preventative medications (preventers). The following conservative criteria were applied in the NSW Health Survey to identify the 54% for whom preventers were indicated: (i) frequent night waking from asthma, (ii) at least three general practitioner (GP) visits for asthma attacks in a 12-month period, (iii) moderate interference with daily activities or (iv) reliever use on ≥50% days in the last month. These criteria probably underestimate the number of people for whom use of preventers would result in significant benefit and in this survey only 42.5% of this group were taking regular preventers. In the SAHOS, the great proportion of people with asthma (approximately 80% of both adults and children) still do not have written action plans or undertake peak expiratory flow (PEF) monitoring.[5]

Due to treated and untreated disease, the burden of asthma in Australia is significant, with direct and indirect costs totalling in excess of $A700 million per year. More than 60 000 Australians are admitted to hospital annually due to asthma. During 1997–1998, asthma was

Correspondence to: Christine Jenkins, 702/26 Ridge St, North Sydney, NSW 2060, Australia. Email: crj@med.usyd.edu.au

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the principal diagnosis in 60 280 hospital separations, or 1.08% of all hospital separations, with an average length of stay of 3.5 days.[10] Asthma is the most common chronic childhood disease in Australia and one of the most common reasons for emergency department admissions.[11] Asthma is presently the sixth most frequent problem managed by GPs (28 per 1000 encounters), accounting for 2.0% of problems managed in 2000–2001.[12]

THE SIX-STEP ASTHMA MANAGEMENT PLAN

Although the six-step asthma management plan (Table 1) was an expert consensus statement and may appear 'old hat',[13] the underlying principles remain essentially unchallenged. The availability of newer medications has altered the means by which best lung function is achieved and maintained, but not the underlying concepts of the plan.

Without going into each step in detail, the six-step plan encompasses the major aspects of asthma care, and emphasizes all the vital elements. The first step, 'assessment of severity' (both of an acute presentation and of the disease in its long-term manifestations), is still vital in determining the likely level of treatment required. 'Achieving best lung function' (step two) is not the only goal, and if this step were rewritten today, achieving optimal symptom control would probably be added to lung function. It is now known that improvements in different lung function measures occur at different rates (Fig. 1), and that there are uncertainties regarding the best summary measure of asthma control. Whereas the rational first step in good management is 'avoidance of triggers' (step three), this is still not achievable to the extent that the disease becomes inconsequential, and almost all patients require some form of pharmacotherapy. Persistent asthma in adults – whether mild, moderate or severe – requires long-term treatment, and there is level 1 evidence indicating that inhaled corticosterioids (ICS) are the optimal treatment choice; superior to all other preventer medications. Controversy presently revolves around the management of mild asthma, the point at which long-acting bronchodilators should be added to ICS, and the means by which good asthma control is assessed and treatment reduced.

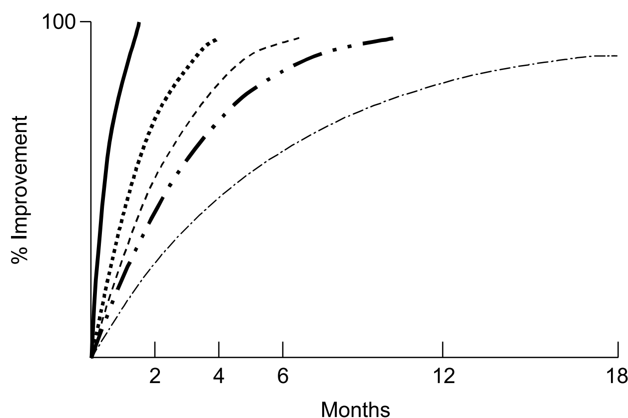

Figure 1. Time course of changes with ICS treatment in different measures of asthma control over 24 months. (–) no night symptoms; (…) FEV1; (- - -) amPEF; (- . . -) no SABA use; (– · –) AHR. The percentage improvement is relative to the maximal value achieved. This may be a normal value (i.e. no AHR, or the best possible for an individual). These curves are derived from data collected during a long-term study of initially poorly controlled asthma with budesonide.[27]

The fifth step, 'develop an action plan', can be interpreted in several different ways. It was initially intended to mean an individualized written plan that facilitated recognition of deteriorating asthma and outlined appropriate treatment and action. The rate of ownership of written action plans is as low as 20% (for both adults and children) in some surveys[5] and up to 50% in others. Recent Australian evidence suggests that ownership of action plans is a marker for reduced risk of death from asthma.[14] Ideally, patients should participate in formulating a plan that is tailored to their preferences (either PEF- or symptom-based) and to their previous history. Simply handing over a written plan without engaging patients in the process of optimal self management will not achieve better outcomes. Action plans can be based on symptoms or PEF, but should be kept clear and simple, and should be tailored to the patient's level of literacy, visual acuity and understanding.

The results of a systematic review of the sixth step, 'educate and review regularly', support this approach.[15] The review indicated there is level 1 evidence that optimal self-management education (i.e. regular medical review, self-management education, a written action plan) results in better asthma outcomes, such as: (i) fewer days lost from school or work, (ii) better lung function and (iii) fewer out-of-hours presentations. This is the scientific basis of the Commonwealth's Practice Incentive Program for the proactive management of asthma, and is a clear example of the way in which evidence-based medicine can drive better practice. The initiative was introduced in November 2001, and reimburses GPs for undertaking planned review and for educating patients with moderate to severe asthma in three visits over a period of 4 weeks to 4 months. The

Table 1 The Australian six-step asthma management plan

Step 1	Assess asthma severity
Step 2	Achieve best lung function
Step 3	Maintain best lung function: identify and avoid triggers
Step 4	Maintain best lung function: optimize medication
Step 5	Develop an action plan
Step 6	Educate and review regularly

important components of this are: (i) assessment of asthma severity, (ii) review of medication and triggers and (iii) self management education and provision of a written action plan. It is anticipated that spirometry will become a mandatory component for reimbursement in the future.

CURRENT ISSUES IN ASTHMA MANAGEMENT

The six-step asthma management plan remains the backbone of asthma care in clinical practice, however there have been several major changes in our understanding and approach to asthma in the last few years. The following sections will discuss several recent controversies and issues pertinent to best practice in asthma and, apart from the section on early life risk factors, refer to adult asthma management.

Environmental risk factors in early life

It is now believed that the process of atopic sensitization begins soon after conception and reaches its height in the early years of life. The TH2 immune system dominates at birth, but soon after, in response to environmental antigens, the infant's immune system has the potential to develop along the TH1 pathway, dominated by monocytic cell responses and interferon-γ, rather than TH2 immunity dominated by interleukins 2, 4, 5 and 10 and eosinophilic responses.

The triggers that facilitate the development of TH1 immune responses are the subject of intense research interest. Recently, epidemiologic studies have suggested that children growing up in environments where there is a high level of exposure to bacterial infections or frequent viral infection (i.e. children with siblings and those who attend child care early in life) are less likely to be atopic or to have a history of wheezing illness or asthma in later life than those with minimal exposure to infections in infancy.[16, 17] The concept that cleanliness and a low risk of early life infection may increase the risk of a persistent TH2-type response and the development of atopy and asthma has been dubbed the 'hygiene hypothesis'. The concept is illustrated by observations made in children from East and West Germany after unification. Despite a high level of atmospheric pollution, poorer living conditions and limited access to medical care, children from East Germany were less likely to develop asthma and wheezing than those from West Germany. The prevalence in East and West Germany of hay fever (2.7% *vs.* 8.6%, respectively) and airway hyperresponsivesness (AHR) (5.5% *vs.* 8.3%, respectively) among children aged 9–11 years follows a similar pattern, which is also seen in adults.[18] Ten years after re-unification and a progressive elevation of socioeconomic standards, East German children are now developing levels of wheezing illness that are similar to their Western peers.

Antibiotic use in early life is associated with increased risk of asthma and atopy in some (but not all) studies. The mechanism is unknown, however, because gut colonization by lactobacilli may be associated with reduced risk of atopy, it may be a result of altered gut flora reducing the stimulus to TH1 immunity. Children who are treated with antibiotics in the first year of life have higher prevalence of asthma, hay fever and eczema at the age of 8 years, particularly if there is a history of parental hay fever.[19] One study showed increased risk of asthma when antibiotics were administered in pregnancy.[19] A New Zealand study showed that the adjusted odds ratio (OR) for use of antibiotics in the first year of life was 4.05 for the development of asthma.[20] Having two or more older siblings is inversely related to use of antibiotics in early life, and is independently associated with a lower risk of developing asthma.

There is further *in vitro* and epidemiologic evidence suggesting that early life exposure to certain organisms may reduce asthma risk. Exposure to endotoxin and lipopolysaccharides (which are essential components of the bacterial cell wall) can elicit strong IL-12 responses which are important signals for the development of T cells into TH1-type cells. Endotoxin levels are particularly high in farm environments and where there is close contact with animals kept in the house. Children who grow up on farms, particularly those who live in houses with barns and who have close animal contact with milking cows or pigs in infancy, are less likely to be sensitized to inhaled allergens and are less likely to have asthma.[21]

Unfortunately, despite evidence of the impact of early life exposures on the risk of atopy and asthma, there are still few interventions that have been shown to prevent the development of asthma. Although some early life issues are clear – such as the benefits of a cigarette-smoke-free environment for reducing early-life wheezing in young children – it is now less clear what advice about allergen exposure should be given to parents in families where atopy and asthma are prominent. The benefits of exclusive breast feeding in preventing asthma are also less clear than they used to be. There are now several studies that show an increased likelihood of developing asthma in breast-fed children. This is particularly evident in longitudinal studies that followed children to older ages. However, a recent systematic review showed an overall reduced OR (0.7; 95% confidence interval 0.60–0.81) in children receiving at least 3 months exclusive breast feeding.[22] Should children grow up with dogs and cats? Some recent longitudinal and cross-sectional studies have shown reduced sensitization and asthma in children growing up with dogs and cats in atopic families.[23] Other studies have not shown a benefit, although exposure to other animals (livestock and poultry) appears to be protective. There are some unresolved issues regarding early life animal exposure and the relative importance of farm animals versus domesticated indoor pets, however results suggest that owning a cat or a dog is not harmful and could be protective against atopic disease. However, this must be balanced by the fact that these exposures can cause wheezing after sensitization has occurred. Timing, sequence of exposure and co-exposures to protective factors are probably crucial.

The dose of ICS: when is enough enough?

Although there are now several new treatments available for asthma, ICS remain the most effective preventative medications available. They improve symptoms and lung function, prevent lung function decline and reduce the risk of hospital admission and death from asthma. Although asthma management guidelines recommend progressive increases in dose of ICS (up to fluticasone 1000 μg equivalent) if asthma is persistently symptomatic or suboptimally controlled, evidence in favour of a dose–response benefit over 500 μg/day is scant. Studies suggest that for lung function measures (FEV1, morning and evening PEF) the dose–response curve for ICS flattens off at approximately 500 μg fluticasone equivalent daily, and further dose increases achieve very little, although the risks of side-effects from systemic absorption increase dramatically.[23,24]

A recent meta-analysis indicated that in most patients, 90% of the possible benefit of ICS was achieved at a dose equivalent to fluticasone 200 μg daily.[25] Further increases in dose >500 μg daily could achieve small increments in benefit, however this will only be necessary in a minority of patients. However, the studies included in the study of Holt *et al.* were 6–12 weeks in duration, and may not have captured vital information that should influence treatment decisions about long-term management. In particular, although ICS reduced asthma exacerbations, there were very few in total and some studies suggest the dose–response curve for prevention of exacerbations may be different, with higher doses required to achieve this benefit more effectively[26] and rapidly.[27] Overall, the case for higher starting doses above fluticasone 500 μg daily is weak,[28] particularly if long-acting beta agonists (LABA) are also used.

Static lung function measures (clinic FEV1 and daily PEF) are only one aspect of asthma control. Many consider that, in addition, modifying AHR is a crucial part of achieving optimal asthma control. This view is strongly supported by studies that demonstrate better outcomes, including reduced exacerbation rates, when AHR (or an indirect measure of airway inflammation such as sputum eosinophils)[29] is included in assessments of control and ICS doses are adjusted accordingly. An important Australian study recently showed that lung function improves as airway inflammation is controlled, but that improvements in AHR reflect the longer-term reversal of basement membrane thickening.[30] This is considered to reflect airway remodelling, which if not controlled can result in fixed, irreversible airflow limitation.

Another crucial issue affecting optimal use of ICS is the necessity for back titration to the minimum effective dose that maintains optimal asthma control. The timing and magnitude of ICS dose reductions are unclear from current evidence. Because AHR may take 1–2 years to normalize or reach maximum benefit,[28] and because a higher maintenance dose achieves better control of AHR, exacerbation rate and basement membrane thickness,[27] it may be inappropriate to reduce ICS too quickly or to too low a dose. More studies will be needed before this is clarified, but treatment algorithms which include AHR or an indirect measure of inflammation are likely to achieve better outcomes. The 'holy grail' of asthma will be the identification of a simple, non-invasive marker that can be used as a surrogate for AHR, obviating the need for bronchial provocation tests.

Combination therapy: when are two better than one?

LABA have had a significant impact on asthma management, their role being defined by a series of carefully conducted randomized controlled trials, showing clear benefit over increased doses of ICS for suboptimal asthma control. Added to ICS in symptomatic asthma, LABA improve: (i) clinic lung function, (ii) daily PEF, (iii) symptom control and (iv) quality of life (QOL). They reduce short-acting beta agonist (SABA) use and reduce mild and severe asthma exacerbations. There is a strong rationale for combining ICS and LABA from *in vitro*, as well as clinical, studies which demonstrate the benefits of their complementary action.[31,32] *In vitro*, beta-2 agonists can enhance the anti-inflammatory effects of ICS, while ICS can reverse the reduction in beta-2 receptor numbers that occurs with chronic beta-2 agonist exposure.

The two LABA in current use are formoterol and salmeterol. Both have a 12-h duration of clinically significant bronchodilatation, and differ mainly in rapidity of onset, formoterol taking 2–5 min and salmeterol taking 20–30 min to achieve this.

Initial concerns regarding LABA – and their potential for tolerance, masking of asthma severity or long-term effects that might increase asthma severity – have been allayed by an excellent track record in clinical practice. However, a recent large US safety study (n = 25 858) was stopped after interim analysis showed that salmeterol use was associated with a trend to increased asthma-related, life-threatening experiences, including death.[33] This was only statistically significant in African Americans, who were found to have more severe asthma at baseline and a very low level of ICS use (38%). The current guideline for LABA use (that they must not be used as monotherapy) is strongly supported by these findings.

At several different ICS doses (200–1000 μg budesonide or beclomethasone equivalent), the addition of LABA has been shown to be superior to doubling the dose of ICS. One of these studies,[34] showed that budesonide 800 μg/day alone achieved greater reduction in asthma exacerbations than 200 μg/day in combination with formoterol, however the best outcome was achieved when formoterol was added to budesonide 800 μg/day. Hence, there may still be a dose–response for ICS when LABA are added and further studies are awaited. The addition of a LABA allows reductions in ICS dose in well-controlled asthma, thus minimizing risk of ICS systemic effects. At present, a LABA added to ICS is the best option for patients who are symptomatic on ICS alone. Theoretically, another option is to add the leukotriene inhibitor montelukast, however results have

varied, with one study showing no effect and another showing inferiority to salmeterol when added to ICS to improve asthma control.[35,36]

Combination therapy with ICS plus LABA in one single inhaler, is available as fluticasone and salmeterol or budesonide and formoterol. This is now the 'gold standard' treatment for moderate to severe asthma, although many patients can be optimally controlled on ICS alone.[28,34] There is no role for LABA as single therapy, nor as replacement for SABA for relief of asthma symptoms. Although formoterol has a rapid onset and a significant dose–response (6 μg–48 μg), it is more expensive than SABA and no studies have yet shown superiority in treatment of acute asthma.[37]

Treatment of mild asthma: does it matter?

Mild asthma can be considered as intermittent or persistent. Some adults experience seasonal or intermittent asthma symptoms and are completely well for the remainder of the year. In general, it is accepted that mild, intermittent asthma requires treatment on the basis of symptom frequency which can be ceased when patients are asymptomatic and have normal lung function. The relatively low use of spirometry in general practice means that most patients do not have their lung function measured and assumptions are made that it is normal or optimal, when in fact it may be significantly below best. These patients should not be thought to have intermittent asthma, even if they don't appear to have troublesome symptoms for significant periods of time.

The Asthma Management Handbook 2002 recommends low-dose ICS for patients who use SABA three or more times per week (excluding for exercise).[38] By consensus, this is the symptom threshold that warrants maintenance preventative medication, but many patients self-titrate and stop preventative medication when they feel well. What is the evidence that mild asthma should be treated with maintenance preventative medication?

Estimates of the spectrum of asthma severity in Australia suggest that approximately 70% of those affected have mild disease.[39] Definitive studies are needed concerning the natural history of mild asthma, either untreated or treated with intermittent ICS. However, several lines of reasoning suggest that mild asthma is not an entirely benign disease. For some time it has been recognized that delays in commencement of treatment with ICS result in poorer outcomes (such as reduced improvement in lung function and AHR) in mild and moderate asthma.[40,41] In asthma mortality studies, 'mild' asthmatics account for approximately 30% of subjects and attacks may occur without warning.[42] Recent studies with ICS and LABA indicate that, when treated, patients with mild asthma perform better in terms of lung function, symptoms and exacerbations than those receiving placebo.[43,44] In a recent large study of mild asthma ($n = 7241$), budesonide 200 μg daily in children or 400 μg daily in adults reduced the severe exacerbation rate by 44% and reduced the rate of life threatening events by 64%. The 3-year cumulative probability of a severe asthma related event was low at 6.5%, however, budesonide improved symptom-free days and reduced the need for systemic glucocorticoids. Mild asthmatics may have airway inflammation and basement-membrane thickening, which – along with symptoms, exacerbation rates and lung function – also improves with ICS treatment.[27,30,45]

The uncertainty and carelessness around the definition of mild asthma contributes to the problem of determining the best treatment. At present, guideline-defined mild asthma covers a spectrum of severity that ranges from trivial, very infrequent symptoms to symptoms several times per week with or without normal lung function, making this a very diverse group of subjects. In clinical trials, patients who take only SABA are often said to have 'mild asthma', despite the fact that mean FEV1 for this group may be as low as 70% predicted,[46] and it may be a requirement for entry to the study that patients have symptoms several times a week. Such patients actually have moderate disease, and do best when taking regular preventative medication. Results from these trials are wrongly interpreted to mean that mild asthma should be treated, when in fact the patients did not have 'mild asthma' in the first place. However, definitive studies concerning the natural history of true mild asthma, either untreated or treated with intermittent ICS, are needed so that the long-term consequences of this severity of disease are better understood.

Because this group constitutes the majority of those with asthma in Australia, there will be important health and economic implications if we do not clarify these issues by conducting careful studies to examine the natural history of mild disease. It is not known which features distinguish the subject with mild asthma who is at risk of a life threatening attack from the subject who never has more than occasional symptoms. It may be that mild asthma does not warrant regular preventative medication unless lung function is below best. This requires competent performance and interpretation of spirometry in general practice, and regular assessment, just as a patient at risk of diabetes or coronary artery disease would be reviewed annually or with any change in clinical status.

Asthma control: does it have to be perfect?

Asthma severity and asthma control are terms that are often used as if they were synonymous, which they are not. Asthma control is an assessment of the current situation, including: (i) lung function, (ii) symptoms, (iii) control of exacerbations, (iv) achievement of normal activity levels and (v) QOL. Asthma control should be assessed at each visit so that the adequacy of treatment can be judged and adjustments can be made. Asthma severity can only be adequately assessed by achieving optimal control and then determining the amount of preventer medication required to sustain control. Assessment of severity also includes past history, including significant events (such as previous hospitalization), severity and frequency of exacerbations. As clearly stated in the *Asthma Management Handbook 2002*,[38] asthma severity applies to overall disease severity, not to the severity of an acute attack. It should be assessed when the patient is stable.

Ideal asthma control is the goal of treatment. This is defined as: (i) no symptoms, (ii) no exacerbations, (iii) no impact on daily activities and (iv) normal or best lung function. A validated composite measure of control would be of great value for clinical practice because it would standardize asthma assessment and help give an overview that would encompass lung function, symptoms, impact and prognosis. Clinical assessment alone does not reduce exacerbations as well as assessment that includes an indirect measure of inflammation (i.e. sputum eosinophilia or AHR).[27,28,46] Scores have been proposed and prospective studies on control assessed using composite measures derived from accepted asthma guidelines are needed.[45]

Achievement of optimal asthma control is a stated aim of asthma management, but even in clinical trials, ideal control is rarely achieved.[47] Optimal control may be impossible all of the time and, at present, best treatment cannot prevent all exacerbations.[34,46] Even the absence of exacerbations doesn't guarantee good asthma control and objective measures are mandatory as lung function in adults may insidiously decline over many years.[41]

FUTURE DIRECTIONS

There are many important research questions yet to be answered. There are many different phenotypic expressions of asthma and it is unlikely that a single gene is responsible. The identification of different genetic factors contributing to different asthma phenotypes and the complexities of the interaction between the environment and genetic predisposition are areas of intense research activity.

Of the new methods of treatment, omalizumab or anti-IgE shows benefit given by injection every 2–4 weeks versus placebo in improving asthma control over 6–12 months. Its benefit beyond the period of treatment, and in comparison to low-dose ICS, has yet to be defined. New phosphodiesterase-4 inhibitors (given orally) are currently being trialed and show promise as non-steroid anti-inflammatory agents, which may potentially be added to ICS or a substitute for them. Targeted anti-inflammatory medications (such as anti-IL-4 and 5) have been disappointing so far, and more specific anti-inflammatory treatments (such as activators of IL-10 and 12) are only just entering clinical trials and have yet to be fully assessed. Advances are under development for formulations of currently used drugs that permit: (i) once-daily dosing, (ii) more effective inhaler use, (iii) better delivery to small airways and (iv) reduced risk of systemic activity. However, the impressive track record of ICS, with or without long acting bronchodilators, means they are likely to remain the mainstay of therapy for several years to come. More effective management of asthma may come in the short term from a better understanding of the issues that influence health beliefs and behaviour, a fertile area of research applicable to a wide range of diseases.

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