

Unmet needs in adult asthma

K. F. CHUNG

National Heart and Lung Institute, at Imperial College School of Medicine & Royal Brompton Hospital, London UK

Summary

Guidelines have been developed to provide an objective framework for the effective management of asthma. They are based on a mix of sound clinical practice and evidence-based medicine. The aims of asthma management are to ensure that the patient is symptom free and living an unrestricted life with normal physical activity, lung function normalized as much as possible, using minimum therapy, that exacerbations are kept to a minimum and mortality is reduced or abolished. In practice, however, these aims are not being met. Thus, unmet needs exist in asthma and need to be addressed. One particular unmet need is poor delivery of asthma care. Undertreatment of asthma is common, especially in severe asthma. However, studies suggest that some patients with severe asthma do not respond to any available treatments. Many outcome measures have been used in asthma and different outcomes will ensue according to which outcome measure is chosen, which in turn depends on the population studied. Asthma is a heterogeneous disease and there is heterogeneity in the response to treatment. However, at present there are no means to determine which patients will be a responder or non-responder to a particular treatment. In clinical trials of potential new asthma treatment we need to target the patient population more carefully according to the selected outcome measure, which should reflect the patient's perspective.

Keywords: asthma, adults, guidelines, undertreatment, outcome measures, heterogeneity

Introduction

Asthma guidelines have been distilled from a mix of sound clinical practice and evidence-based medicine. However, we must ask whether the guidelines have adequately addressed the needs of patients with asthma, and whether the proposed outcomes have been achieved. The goals of asthma management are wide-ranging and aim to ensure that the patient is symptom-free, living an unrestricted life with normal physical activity, with lung function normalized as much as possible, taking a minimal amount of asthma therapy with minimal adverse effects from medications, exacerbations are controlled or kept to a minimum, and that mortality is reduced or abolished (Table 1) [1]. In practice, these aims may not often be achieved, and the reasons for this may range from patient non-adherence to therapy to pathology unresponsive to current therapies. Therefore, although the asthma guidelines have been helpful in providing an objective framework or 'gold standard' for the management of asthma, we are clearly not meeting the gold standard, i.e. there are unmet needs. This article will

review some of these aspects in the light of recently available data.

Unmet needs in asthma

There are many areas where there may be unmet needs in asthma (Table 2). In particular, we appear to be very poor at delivering asthma care. Patients do not adhere well to treatment and should be encouraged to participate more in their own self-management plans. One area where there is a particular unmet need is among patients with difficult asthma who do not appear to respond to the available therapies.

Undertreatment of adult asthma

In a recent study in France, using a non-selected population of patients from the cities of Montpellier and Paris, patients had their asthma severity categorized as mild, moderate or severe, and the adequacy of their treatment assessed according to the International Consensus Report guidelines [2]. In both cities, there was substantial undertreatment of asthma, most notably among those with severe asthma where none of the patients from Paris and only 25% of those from Montpellier were treated correctly according to the guidelines.

Correspondence: Professor Fan Chung, Department of Thoracic Medicine, National Heart and Lung Institute, Dovehouse Street, London, SW3 6LY, UK.

Table 1. Aims of long-term management of asthma (British guidelines)

Minimal (ideally no) chronic symptoms
Minimal (infrequent) episodes
No emergency visits
Minimal need for prn beta-agonists
No limitations on activities, including exercise
PEF circadian variation of <20%
Minimal (or no) adverse effects from medicine

Table 2. Unmet needs in asthma

Drug delivery systems
Improving compliance
Delivery of asthma care
Education of patients/carers
Self management plans
Prevention of asthma exacerbations
Side-effects of medication (corticosteroids)

Therefore, the unmet need is that patients are not being matched in terms of treatment to the severity of their asthma. There may be many reasons underlying this.

Asthma morbidity in relation to treatment guidelines

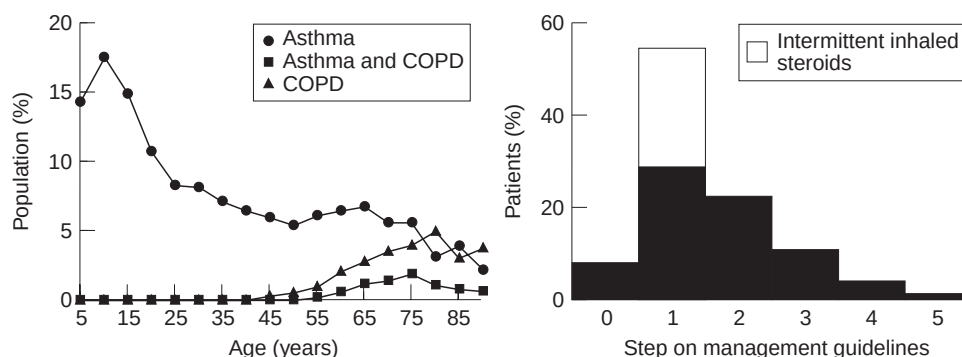
In a recent study in Nottinghamshire [3], involving about 4000 patients with asthma in a general practice population, various aspects of patients' treatment were related to their step on the British guidelines for asthma management, which range from step 0 (no treatment) to step 5 (maximal treatment). Figure 1 shows that the majority of patients were at step 1 or step 2 (i.e. mild to moderate asthma) and only a minority of patients were at the more severe end of the disease spectrum. Interestingly, when beta-agonist inhaler

use was related to the step on the asthma management guidelines, patients who took more treatment (i.e. those at steps 4 and 5) were the ones who used more beta-agonist inhalers (Fig. 2). The same pattern was seen with the number of oral steroid courses taken in the previous year. Of course, this study does not explain why this pattern occurs. However, one interpretation of this data is that perhaps those patients with more severe asthma do not respond to any treatments available. Moreover, it is possible that those patients in step 2 or 3 were still using their beta-agonist inhalers because they were not very adherent to their anti-inflammatory treatment.

Outcome measures in asthma

The outcome measures used in clinical trials have conventionally been based on symptoms and some measure of lung function, whereas more recent studies have used exacerbation and quality of life as outcome measures. Other possible outcome measures are listed in Table 3. Different outcomes will ensue according to the outcome measure chosen, which in turn depends on the population studied.

What outcome measure should be the primary end-point? We have to choose end-points from the patient's point of view: symptoms, exacerbation, limitations of daily life, and lung function. From the patient's perspective, perhaps the greatest concern is the ability not to have exacerbation of asthma for which they need to take oral steroids and to take time off work or school. Other issues from the patient's perspective include duration of treatment necessary, the variability of the response to existing therapies, and the side-effects from therapies. The value of surrogate biomarkers is unclear. Are they more/less sensitive to therapy than clinical markers? It will be of value if, for convenience, the biomarker is a faithful marker of some of the above end-points, e.g. rate of decline of lung function. It is in the area of the long-term outcome that we have relatively few data. However, at present, we do not know which particular outcome measure to choose over any other.

**Fig. 1.** Distribution of patients in a community-based study. Reproduced with permission of the BMJ Publishing Group from ref [3].

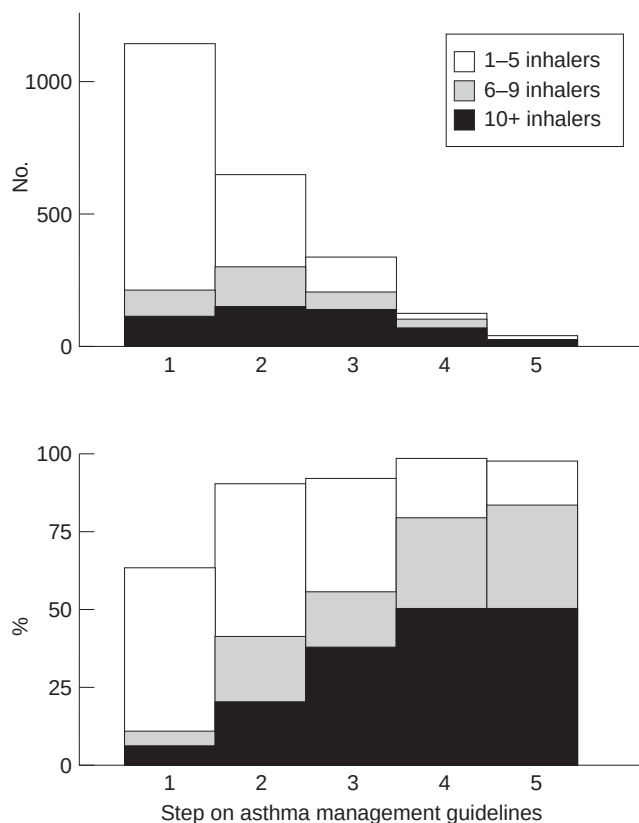


Fig. 2. Number of patients requesting 1–5, 6–9 and 10+ β -agonist inhalers over the previous year in relation to the step on the asthma management guidelines. The data are expressed in absolute numbers and as a percentage of patients on each step of treatment. Reproduced with permission from the BMJ Publishing Group from ref [3].

Sont *et al.* [4] determined whether there was more effective asthma control or a greater improvement of airways function when using a treatment strategy based on the usual outcome measures such as symptoms, bronchodilator usage, PEF variability, and baseline FEV₁ vs a strategy that also included airway hyperresponsiveness (AHR). They found that a higher

Table 3. Outcome measures in asthma

Short-term lung function
Quality of life
Symptoms and limitations
Psychosocial impact
Exacerbations
Sputum eosinophils and exhaled nitric oxide
Bronchial hyperresponsiveness
Cost-effectiveness
Use of a short-acting beta-agonist
Long-term lung function

daily dose of inhaled steroids was needed to keep AHR at a certain level compared with the reference strategy, which used symptoms and lung function as the outcome measure (Fig. 3). Not surprisingly, this study also showed that patients treated according to the AHR strategy had a lower rate of mild asthma exacerbation and greater improvements in FEV₁. In addition, and in contrast to earlier studies, the subepithelial reticular layer thickness was reduced in the AHR strategy group. The results of this study raise the issue of whether we should aim to use higher doses of inhaled steroids or any inhaled anti-inflammatory drug for treating asthma, rather than the strategy given in the guidelines, which is to give the minimal amount of steroids necessary to control asthma symptoms.

Assessment of asthma therapies

All asthma is not similar in terms of clinical presentation (frequency of exacerbation, long-term decline in lung function, diurnal variability, severity of disease, etc.); the underlying mechanisms may be different (atopy vs non-atopy, different triggers, rapidity of onset, effect of smoking, etc.), hence perhaps the variability in responses to treatment.

Thus, there are different populations of asthma patients. It may be important to divide the asthma population into various subtypes, especially in order to look at the effect of a particular treatment in a specific target group. For example, to examine if a drug prevents or controls asthma exacerbation, it would be necessary to use a population that has exacerbation. Perhaps it is not surprising to find out that there is a gradation of therapeutic response to treatments given to a group of asthmatic patients. In a study comparing the cysteinyl leukotriene receptor antagonist montelukast with low-dose beclomethasone dipropionate (BDP), Malmstrom *et al.* [5] showed that there is a normal distribution of the response (change in FEV₁) for both treatments (Fig. 4). This sort of assessment of the data is rarely done but illustrates that there are some patients who are actually worsened by

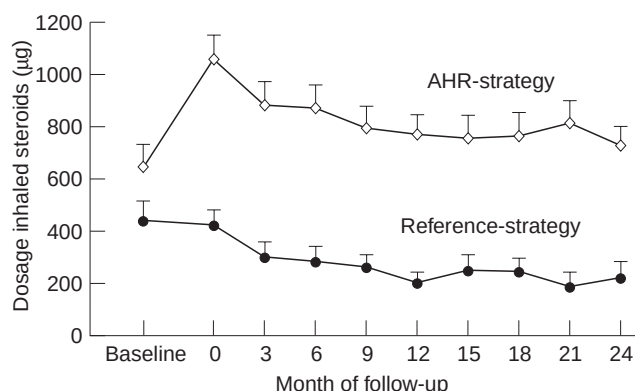


Fig. 3. Dose of inhaled corticosteroids needed to control asthma according to different strategies. Reproduced with permission of the American Thoracic Society from ref [4].

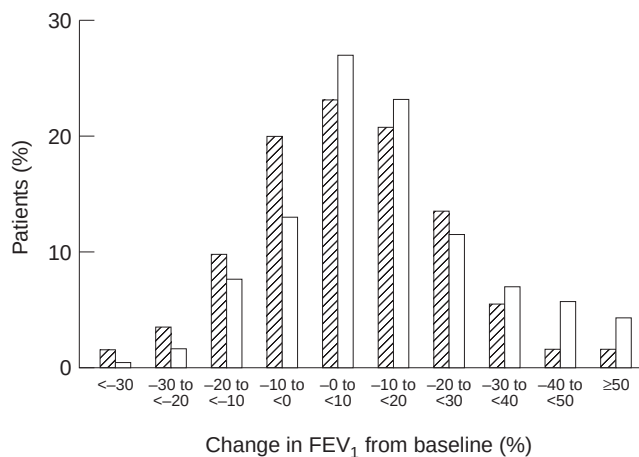


Fig. 4. Distribution of treatment responses for FEV₁ after treatment with either inhaled corticosteroids or montelukast. Reproduced with permission from the American College of Physicians from ref [5].

the treatment. Since this study was not a crossover study, we do not know whether those patients who did not respond to BDP were also unresponsive to montelukast and vice versa. It is likely that there are certain patient populations who respond better to one sort of treatment and other patient populations who respond to another type of treatment. One of the unmet needs in asthma is to determine how a particular asthmatic patient would respond to particular treatments. Moreover, it has direct implications for individual asthma patients in terms of which particular therapy should be prescribed for a certain type of asthma.

It does make sense to analyse results of clinical trials in terms of size of response, when heterogeneous populations are used. The FACET study looked at the effect of the long-acting beta-agonist formoterol in combination with inhaled corticosteroids in preventing exacerbation of asthma [6]. This study showed that a higher dose of budesonide (800 µg/day) and the combination of budesonide and formoterol reduced the exacerbation rate. However, the study needed about 200 patients in each group to show this effect because not all patients in this study had exacerbation. The rate of exacerbation was on average one exacerbation per patient per year.

In another study comparing the mean change in PEFR over time in patients treated with high-dose inhaled steroid vs low-dose inhaled steroid plus the long-acting beta-agonist salmeterol, the standard error bars were very large for a study with a large number of patients [7]. This implies that there are patients within this category who are responding and some who are not responding.

To summarize, some of the existing unmet needs in adult asthma are those that are related to the delivery of management care such as the problems of specific populations and age-groups, the lack of adherence and compliance, the need for the carer to provide a proper diagnosis and assessment of

asthma, and socioeconomic factors. Looking at how effective drugs are, there is the problem of which outcome measure to use, whether we should be looking at specific asthma populations and the problems of responders and non-responders, where perhaps the role of pharmacogenetics will come into play. Finally, there is a clear need for new drugs for those patients at the more severe end of the disease spectrum who do not respond well to current therapies [8].

While outcome measures will improve with better implementation of asthma care and education, one will have to look at advances in asthma biology to address some of these unmet needs. One thinks of genotyping the different 'phenotypes' of asthma and of pharmacogenetics, and of the possibility of new drugs with more specific targets (e.g. anti IL-5 therapies, anti-IgE, etc.). At the end of the day, we return to the issue of clinical and laboratory characterization, and of response to treatment and outcome measures. Although our understanding of the pathophysiology of asthma continues to improve, we have not yet reached a stage where effective measures can be taken to cure or even perhaps induce long-term remission using current asthma treatments.

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