Asthma guidelines: recommendations versus reality

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Summary
Highly effective treatments for asthma are now available, but many patients with asthma are still poorly controlled. Guidelines for asthma therapy are widely disseminated, but they may be considered too complex for general use, and clinical studies used to support the guidelines are not indicative of 'real life'. In the 'real' world, patients frequently cannot use their inhaler correctly, particularly pressurised metered-dose inhalers (pMDIs) which require good coordination between inhaler activation and patient inhalation. Breath-activated inhalers and dry powder inhalers (DPIs) are much easier to use and result in better lung deposition of the inhaled drug. Surprisingly, two recent Cochrane meta-analyses recommended that pMDIs should be preferentially prescribed, as they have similar efficacy to breath-activated inhalers and DPIs and are cheaper. In reality, DPIs are more cost-effective as they deposit more drug in the lungs, may improve compliance and result in more effective asthma control. Improvements in inhaled drug delivery will continue to be paramount in improving asthma management.

Introduction
Asthma is a chronic inflammatory airway disorder that is a serious public health problem in countries throughout the world. In 1993, the Global Initiative for Asthma (GINA) was formed and its goals and objectives were described in the 1995 Workshop Report Global Strategy for Asthma Management and Prevention. This report has been widely distributed and translated into several languages.

In January 2000, the GINA Executive Committee suggested that the Workshop Report be updated to incorporate the several advances in the fields of asthma pathology, genetics, diagnosis, assessment and treatment detailed in scientific publications since 1995.1

The aim of the present article was to review asthma management guidelines and their aims, discuss how well these aims are being met, detail any guideline limitations and outline possible future therapies for asthma.

Asthma management guidelines
Asthma guidelines are now used in virtually every country and have had important benefits in improving the management of asthma. The principles of modern asthma therapy, and overall goal of every asthma management programme, is
to achieve control of the disease. According to the GINA guidelines the goals for successful management of asthma are: to achieve and maintain control of symptoms (including nocturnal symptoms); to minimise use of rescue β2-agonists; to prevent asthma exacerbations; to maintain pulmonary function as close to normal levels as possible (peak expiratory flow (PEF) circadian variation <20%); to maintain normal activity levels (including exercise); to avoid adverse effects due to asthma medications; to prevent development of irreversible airflow limitation; and to prevent asthma mortality.

The updated guidelines are evidence-based, ranking evidence in four levels of importance from randomised controlled studies (evidence A) to panel consensus (evidence D). The newly formed Science Committee will also update the guidelines every year (instead of every 5 years) ensuring that the guidelines are always up to date, so providing the best possible advice on asthma management.

The GINA guidelines recommend a stepwise approach to pharmacological therapy. The selection of pharmacological treatment options is made on the basis of asthma severity, the patient’s current treatment, pharmacological properties and availability of anti-asthma medication, as well as economic considerations. The stepwise approach to therapy recommends that the number and dose of asthma medications are increased with increasing asthma severity. The aim is to accomplish the goals of therapy with the least possible medication. The premise of the GINA approach to therapy is that as asthma severity increases, the dose of inhaled corticosteroids (ICSs) is stepped up and other classes of drugs are added, particularly long-acting β2-agonists (LABAs). Once control of asthma has been achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

Are asthma guidelines improving asthma control?

Despite the implementation of both national and international guidelines and the availability of highly effective medication to combat both asthma symptoms and the underlying inflammatory component of the disease, asthma remains poorly controlled, indicating that guideline recommendations are not being adequately implemented. This state of affairs is global and does not appear to be due primarily to financial factors; ICSs are relatively inexpensive. The current level of asthma control in Europe falls far short of the goals for long-term asthma management (Fig. 1A). Rabe and colleagues showed that of 2803 patients with asthma, 46% reported daytime symptoms, and 30% reported asthma-related sleep disturbances at least once a week. Over the course of a year 25% of patients reported an unscheduled urgent care visit, 10% reported one or more emergency room visits and 7% reported overnight hospitalisation due to asthma. Most shocking of all was the fact that less than one-third of these patients, including those with severe persistent asthma, were taking ICSs (Fig. 1B). Levels of asthma control were even worse in the USA for every parameter assessed (Fig. 1A), indicating that this lack of control is not cost-related, but rather due to poor compliance to therapy.

The level of asthma control in general practice is also poor. A high proportion of patients with typical symptoms of asthma complained of wheezing, chest tightness, cough and breathlessness, which
significantly impacted on their lifestyle and activities. Even patients who felt well had asthma symptoms, showing that patients underestimate their own symptoms, and suggests that asthma control is even worse than anticipated. Frequent use of short-acting β₂-agonists (SABAs) has also been associated with poor asthma control and an increased risk of death due to asthma. Interestingly, addition of ICSs to SABA therapy reduced the risk of death due to asthma by 60%. Therefore, if physicians and patients adhere to asthma management guidelines, deaths due to asthma should be markedly reduced.

Problems associated with guidelines

Inherent flaws with asthma management guidelines

Not only are physicians and patients not adhering to asthma management guidelines, but the guidelines themselves suffer from inherent limitations. Fixed international guidelines and rigid scientific protocols do not take account of individual differences in response to treatment and severity of adverse effects. The guidelines take account of neither the availability or cost of pharmacological treatments in different countries, nor give advice on the best device for delivery of drug to the lungs. Secondly, for the time-limited general practitioner, the complexity and length (>170pp.) of the guidelines are not conducive to rapid understanding and effective implementation into their treatment schedules. As 95% of patients with asthma are treated in general practice, it is vital that doctors understand the guidelines in order to prescribe the most effective treatments to their patients. Most importantly, although the guideline recommendations are based on the best available scientific evidence, including randomised controlled studies, systematic reviews and meta-analyses, each of these types of study have disadvantages associated with them.

Perhaps the most powerful evidence used when reviewing guidelines is systematic reviews and meta-analyses. These summarise the results of several studies and therefore, obtain evidence which would be too weak with individual studies alone. Of particular importance are the Cochrane Library Reviews which are now published freely so that everyone has access to them. However, several systematic reviews and meta-analyses have serious flaws. They may bias opinion; in some of them there has been a powerful influence from pharmaceutical companies, where certain studies have been included but not others. In assessing systematic reviews there are several questions which need to be addressed. It is important to see if any bias is apparent in the selection of studies, whether the criteria used for assessing the validity of included studies are reported, the methods used to combine the findings were appropriate and whether the conclusion(s) are actually supported by the data. Jadad and colleagues carried out a systematic review of 50 systematic reviews and meta-analyses of asthma treatment published between 1988 and 1998. They showed that 40 of these had serious flaws; all of the reviews from the pharmaceutical industry had serious flaws because they all favoured the sponsors product.

Randomised controlled clinical studies have traditionally been considered the pinnacle in evidence based asthma management excellence, as they minimise bias and the placebo effect. However, they do have limitations associated with them which should be taken into consideration. For almost all of these studies there are strict exclusion and inclusion criteria. It is common to find in large studies that only 10% of the screened patients are included in the study. Patients are commonly excluded if they smoke, are elderly or have a concomitant disease. Patients are also frequently required to show a predefined bronchodilator response, have stable asthma, be compliant with the medication and be able to correctly use inhalers. All these factors ensure that the study population, from which we extrapolate to all patients, is not representative of patients with asthma in the ‘real world’. Indeed, these limitations of randomised controlled studies may account for some of the marked discrepancies which have been observed between clinical studies and patient reality.

The importance of including a representative section of the asthmatic population into clinical studies was examined in a recent study by Chalmers and colleagues (Fig. 2). They showed that cigarette smoking inhibited the inflammatory response to corticosteroids in patients with asthma. Non-smoking patients who received high dose fluticasone propionate (FP; 1 mg/day) showed a significant improvement in lung function, correlating to a concomitant reduction in sputum eosinophilia. But cigarette smokers had no response to high dose FP and no reduction in sputum eosinophils, indicating that cigarette smoking reduces steroid responsiveness. Normally, these cigarette smoking patients are excluded from any clinical study, which may lead to misleading results, and is one example where randomised clinical studies can give the
wrong answer. Viable alternatives to randomised controlled studies are 'real world' or effectiveness studies and 'n = 1' studies. A 'real world' study is more reflective of the population treated in clinical practice and mimics clinical practice as much as possible. Large numbers of patients are needed to account for the many variables which are factored out of the strictly controlled randomised clinical study, and there should be no, or minimal, exclusion or inclusion criteria. Therefore, a 'real world' study has a completely different population to that included in a randomised controlled clinical study. Another very valuable approach is the 'n = 1' study, where a single patient acts as his/her own control, treatment being sequentially changed in order to observe which is the best treatment for that particular patient.

The discrepancy in results obtained from randomised controlled studies and 'real-life' studies was demonstrated by Robinson and colleagues who examined the effectiveness of add-on montelukast therapy in a group of 72 patients with asthma (Fig. 3). The only inclusion criterion was that participants had to have asthma. The only exclusion criterion was that they should not be on an anti-leukotriene treatment already. The results showed that add-on montelukast therapy produced no improvement in lung function or asthma symptoms, and no reduction in β2-agonist use. To allow for any individual difference between patients, Robinson and colleagues also looked at those patients who had a large response (i.e. ≥15% increase in PEF). The results showed that patients in the placebo group more commonly had a large response, indicating that montelukast therapy had no value in that clinical setting. However, the study was carried out at a specialist hospital and so the results may not apply to the general population.

Recently, an effectiveness study has been done in the general population. A group of patients with controlled persistent asthma living in San Diego (n = 110) were prescribed montelukast (10 mg/day). 44% of them discontinued before completion of the study because they thought the treatment was ineffective and 56% continued for a year. At the end of a year the results showed that montelukast had a minimal effect, if any. Patients receiving montelukast showed no difference in the use of ICSs, systemic steroids or rescue β-agonist. These results are in marked contrast to results from a randomised double-blind controlled study in which montelukast therapy was superior to placebo. More of these studies are urgently needed to establish whether anti-asthma treatments are effective in the 'real world'.

**Non-compliance with asthma treatment regimen**

Asthma may still be poorly controlled because patients are non-compliant with their therapy. Reasons for non-compliance are complex and numerous and may be split into drug and non-drug factors. Drug factors include difficulty using the inhaler device, difficult regimens, adverse drug reactions, cost, reticence to take drugs or difficulty in acquiring drugs. Non-drug factors are also barriers to compliance and include such issues as not understanding the instructions; worrying about adverse effects; not trusting the doctor; no supervision so compliance is never checked; anger about being ill; and resentment. There may also be cultural, religious or ethical issues; dislike of being labelled with the disease; or simply forgetting to take the treatment.

One factor which is very important for compliance, particularly in severe asthma, is poor
perception of the disease. Obviously, if a patient cannot perceive how severe their symptoms are, then they are likely to under-estimate the level of treatment required and not comply with their management programme. Chetta and colleagues investigated patients’ perception of the severity of their asthma by assessing their perception of bronchoconstriction after methacholine challenge (Fig. 4). Results showed that in patients with severe asthma, the proportion of patients who could not perceive the severity of their asthma was higher than those who could perceive it. Therefore, it is important when assessing asthma control that an objective measure is used, as many patients (particularly patients with severe asthma) are unable to perceive how well their symptoms are controlled.

Lack of focus on device for drug delivery

As mentioned previously, one drawback of the guidelines is that while they focus on the pharmacological treatments available for the management of asthma, they neglect the delivery devices which are used to get these treatments into the lungs. This is highly surprising, given that inhaled therapy in asthma is likely to remain paramount for the next 10–15 years. When treating asthma, it is essential that sufficient drug is deposited to the lungs. The inhaled route of administration is preferred for many asthma medications, particularly corticosteroids and \( \beta_2 \)-agonists, as drug is targeted directly into the lungs. With inhaled therapy there is a faster onset of action time relative to oral administration and unwanted adverse effects are avoided, by virtue of the smaller doses and lower systemic bioavailability. Inhalation devices available for delivering drugs into the lungs include MDIs, dry powder inhalers (DPIs) and breath-activated inhalers.

A systematic review of 24 randomised controlled studies which compared MDIs, DPIs and breath-activated inhalers, concluded that there was no difference between them, recommending that every patient should use the cheap pressurised metered dose inhaler (pMDI). This is a typical example of how misleading systematic reviews can be, as they do not take into account all the issues that are important. For example, although pressurised metered-dose inhalers (pMDIs) may be cheaper than DPIs, DPIs are easier to use, are environmentally friendly, do not produce a cold sensation upon inhalation and deposit more drug into the lungs. As many as 90% of patients use their MDI incorrectly, as the device requires good coordination between activation and inspiration, an optimal inspiratory flow rate and effective training. Misuse of pMDIs is frequent and associated with poorer asthma control in ICS-treated patients. Common mistakes when using a pMDI include failure to inhale slowly and continuously after activation of the inhaler, failure to exhale fully before inhaling the medication, activating the inhaler before inhalation or at the end of inhalation and concluding inhaler activation while holding breath. Even with instruction, only half of patients can use an MDI correctly compared with almost 90% of patients using a breath-activated inhaler or DPI. In addition, as airway inflammation in the lungs of patients with asthma extends to the smaller airways, it is important that inhalation devices can deliver anti-inflammatory drug to all sites of inflammation in the lungs. Many of the old inhalers, like pMDIs, deliver most of the drug to the large airways, it is important that inhalation devices can deliver anti-inflammatory drug to all sites of inflammation in the lungs. Many of the old inhalers, like pMDIs, deliver most of the drug to the large airways. There is no doubt that the type of inhaler is just as important as the class of drug in the long-term management of asthma.

Mis-classification of asthma severity

Asthma severity is also frequently mis-classified which means that patients are not adequately treated. A large study in general practice in the UK enrolled patients with mild intermittent asthma based on symptoms and forced expiratory volume in 1 s (FEV\(_1\)). However, when these patients were re-assessed for diagnosis of asthma severity based on symptoms, FEV\(_1\) and medication use, 22% of them had mild persistent asthma, 15% had moderate persistent asthma and 3% had severe persistent asthma.
Future asthma therapy

Current asthma therapy is highly effective which poses a challenge for the development of new treatments, since they will need to be safer and more effective than existing treatments, or offer some other advantage in long-term asthma management. What kind of asthma treatments might we expect in the future? Many specific inhibitors for systemic treatment are currently being considered. Since release of mediators from mast cells in asthma is Immunoglobulin (Ig)-E-dependent, an attractive approach is to block the activation of IgE using blocking antibodies that do not result in mast cell activation. Clinical studies with anti-IgE (omalizumab) show a steroid sparing effect in patients with severe asthma, indicating that this treatment might be useful in the control of patients with allergic asthma who have problems with adverse effects of oral steroids. However, this treatment is expected to be expensive. Tumour necrosis factor (TNF) antibodies (infliximab) or soluble TNF-receptors (etanercept) are another logical approach to asthma therapy, since TNF-α may play a role in amplifying atopic inflammation through the activation of nuclear factor (NF)-κB and other transcription factors.

Inhibition of interleukin (IL)-5 is another potential approach to asthma management, as it is essential for eosinophilic inflammation. Humanised monoclonal blocking antibodies to IL-5 have been developed, and a single injection reduced blood eosinophils for over 3 months and prevented eosinophil recruitment into the airways after allergen challenge. However, this treatment had no effect on the early or late response to allergen challenge or on airway hyperresponsiveness, suggesting that eosinophils may be less important for these responses than previously believed. Long-term clinical studies have also shown lack of clinical efficacy. Infusion of the inhibitory cytokine human recombinant IL-12 has an inhibitory effect on eosinophils in patients with asthma, but has significant systemic adverse drug reaction effects that preclude its clinical development.

Oral therapies may become more prevalent in the future for managing asthma. However, oral therapy is associated with a much greater risk of systemic adverse effects compared with inhalation therapy, and therefore needs to be specific for asthma. Currently, there is a search for small molecule inhibitors of TNF-α, of which the most promising are inhibitors of TNF-α converting enzyme. Other oral anti-inflammatory treatments which are currently under development include inhibitors of phosphodiesterase (PDE) 4, p38 mitogen activated protein (MAP) kinase, chemokine receptors, and transcription factors. PDE4 and p38 MAP kinase inhibitors inhibit TNF-α release from inflammatory cells. Several small molecule inhibitors of the chemokine receptor CCR3, including UCB35625, SB-297006 and SB-328437, have been shown to inhibit eosinophil recruitment in allergen models of asthma. Many of the inflammatory genes that are expressed in asthma are regulated by NF-κB which has prompted a search for specific blockers of this transcription factor. However, there are concerns that inhibition of NF-κB may cause adverse effects, such as increased susceptibility to infections, which has been observed in gene disruption studies when components of NF-κB were inhibited.

In the absence of ground breaking new discoveries in asthma treatment, it is likely that β2-agonists and ICSs will remain the mainstay of asthma management strategies for the next 15 years. The use of drug combination inhalers will be prescribed for patients, who need β2-agonists and ICS on the daily treatment basis. Further developments of existing treatments are likely, such as once daily β2-agonists and ICSs which have a better safety profile. Inhalation therapy will remain the optimum method of drug delivery.

Conclusions

Current asthma treatments are highly effective. Management guidelines have been important in improving the management of asthma worldwide but they do have some limitations. For example, they are based on the best available scientific evidence, but randomised controlled studies are highly selective and may not represent patients in the 'real world'. Additionally, systematic reviews and meta-analyses are frequently biased and do not always provide the right answer. Poor compliance with treatment is also a major barrier to asthma management, particularly in the use of ICSs. The guidelines recommend pharmacological treatments available for the treatment of asthma but do not detail the best type of delivery device to deliver these drugs to the lungs. The choice of inhaler device is extremely important, as inhalation therapy is likely to persist for many years to come. The 'ideal' inhaler should be easy to use and efficient and therefore, cost-effective as well as being capable of delivering medication to all sites of inflammation in the lungs, including the small airways. Finally, it is highly unlikely that ICSs and LABAs will be replaced in the next 15 years by any...
new treatment which will be more effective. Therefore, in the future, inhaler devices are likely to become more important than development of new drugs, so the most effective inhalers should be sought.

References