Research Review
SPEAKER SERIES

ADVANCES IN ASTHMA MANAGEMENT AND THE IMPACT ON PATIENTS February 2009

This publication is a summary of a recent presentation by Professor Paul O'Byrne, one of the world's leading asthma experts, who spoke to a panel of general practitioners in Auckland, Wellington and Christchurch in February 2009 about a global view of asthma: the global burden of asthma; how patients manage asthma and the goals of asthma management; the Global INitiative for Asthma (GINA) and new concepts in asthma control and severity. Professor O'Byrne also participated in a workshop with leading New Zealand asthma researchers in Auckland.

Paul O'Byrne MB, FRCPI, FRCP (Edin), FRCP(C)

Paul O'Byrne is the EJ Moran Campbell Professor of Medicine, the Executive Director of the Firestone Institute for Respiratory Health, and Chair of the Department of Medicine at McMaster University, Hamilton, Ontario, Canada.

He studied medicine at University College, Dublin and received his research training at McMaster University and at the University of California, San Francisco.

Professor O'Byrne's research interests have focused on the mechanisms involved in allergic asthma, including cell recruitment and activation, the inflammatory and bronchoconstrictor mediators released from inflammatory cells, including eicosanoids and cytokines, structural consequences of persisting inflammation in asthma, and the efficacy and mechanisms of action of anti-asthma drugs.

Professor O'Byrne has authored more than 270 peer-reviewed articles, 80 textbook chapters and editorials, edited 9 textbooks, and is a frequent lecturer at international meetings. He was Chairman of the Executive Committee of the Global Initiative on Asthma (GINA) until the end of 2007, but remains a member of the Executive Committee of GINA.

The global burden of asthma

Asthma is one of the most common chronic diseases worldwide and its prevalence is increasing, especially among children. Its impact is significant in New Zealand, disproportionately affecting Māori and Pacific Island people, as well as lower socio-economic groups. Notably, asthma is the leading cause for children's hospital admissions here and is associated with very high financial costs, including direct medical costs (such as hospital admissions and cost of pharmaceuticals) and indirect medical costs (such as time lost from work for adult patients or family members needing to take care of sick children, and loss of healthy life due to disability and premature death).

In 2004, the prevalence of clinical asthma was higher than 10% in many countries worldwide – for example, 15.1% in New Zealand, 14.7% in Australia, 14.1% in Canada and 10.9% in the USA.[1] Now, the prevalence of childhood asthma in Canada is 19.8% and exceeded only by New Zealand (1 in 3 children) (Asthma New Zealand, personal communication, February 23, 2009). Despite much high-quality, world-renowned research that has been produced in New Zealand over the years, the management of asthma remains imperfect. Recent patient surveys of asthma management practices in New Zealand[2,3] and worldwide (the Asthma Insights and Reality in Europe [AIRE] survey;[4] the Asthma Insights and Reality in Asia-Pacific [AIRIAP] survey;[5] and surveys conducted in Canada[6,7] and the US[8]) show that asthma is poorly controlled around the world, despite there being effective medications and several evidence-based recommendations.[9-12]

Poor asthma management

The GINA guidelines advise that one of the goals of asthma management is no or minimal need for emergency room visits or hospitalisation.[12] However, the worldwide surveys of asthma management revealed that high numbers of patients had been hospitalised overnight for asthma in the past year, had made emergency department visits for asthma in the past year, and unscheduled asthma-related emergency visits to a doctor's office, clinic or somewhere else (see Figure 1). Those surveys also revealed that as many as 54% of children and 30% of adults had missed at least 1 day of school or work in the past 12 months because of acute asthma. Some might argue that the reason these patients with asthma had so many visits and such a burden of disease was because their disease was very difficult to treat. However, that was not the case.

Revealingly, for each disease category, the rates of inhaled corticosteroid (ICS) uptake were low at the time of the surveys (ranging from 11% to 30% for mild asthma and from 9%–26% for both moderate and severe asthma).

We have a problem: lots of patients, lots of disease, a large burden. We need to communicate better to patients that asthma can be controlled and should be completely controlled with medications that are extremely safe and very cost-effective.

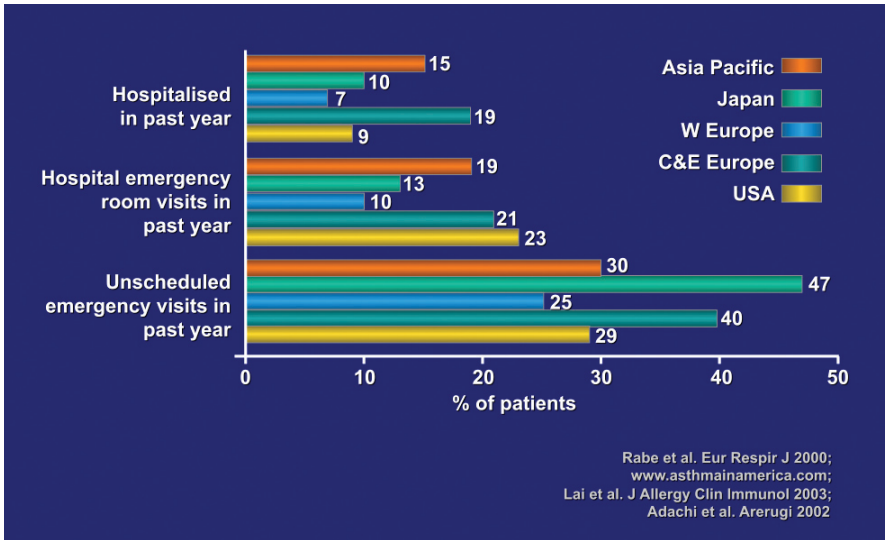

Figure 1: Emergency Room/Hospital Visits

GINA's global strategy

GINA was launched in 1995 as a collaborative effort between the USA's National Heart, Lung, and Blood Institute and the World Health Organisation, in an attempt to create global awareness of asthma and to improve prevention and management worldwide.[13] The Initiative prepares scientific reports on asthma, encourages dissemination and implementation of the recommendations, and promotes international collaboration on asthma research. Importantly, GINA offers a framework to achieve and maintain asthma control that can be adapted to local healthcare systems and resources. Overall asthma control is defined by GINA as:

- Current control: relief of symptoms, rescue or reliever use, maintaining activity and lung function,
- Reduction of future risk: preventing exacerbations, irritability/worsening, loss of lung function over time, and medication side effects.

We are failing to communicate to patients with asthma, and sometimes also to physicians who manage these patients, that asthma not only affects everyday life but is also associated with very real future risks that have to be managed and minimised. We should be constantly evaluating the level of asthma control in our patients, by asking five simple questions that monitor their status by symptoms and, if relevant, PEF or FEV_1:

When to increase treatment

Assess your level of Asthma Control

In the past week have you had:

Daytime asthma symptoms more than 2 times?	No	Yes
Activity or exercise limited by asthma?	No	Yes
Waking at night because of asthma?	No	Yes
The need to use your [rescue medication] more than 2 times?	No	Yes
If you are monitoring peak flow, peak flow less than _____?	No	Yes

If you answered YES to three or more of these questions, your asthma is uncontrolled and you may need to step up your treatment.

Individualising treatment means that clinicians and patients must communicate effectively. They should together prepare a medically appropriate and practical written personal asthma action plan, to reinforce the goal of asthma control. The Asthma and Respiratory Foundation of New Zealand provides adult and child self management plans that may be personalised for patients; these are available from the Foundation's website (www.asthmanz.co.nz).

5-step treatment guideline

As part of its asthma control strategy, the GINA guideline divides patients into five treatment categories, matching treatment with level of severity. Figure 2 details the treatments at each step for adults and children aged ≥5 years (preferred controller options are in darker green). This stepwise approach to pharmacological treatment has been designed to achieve and maintain control of asthma, taking into account the safety of treatment, the potential for adverse effects, and the cost of treatment required to achieve control. GINA advises that the available literature on treatment of asthma in children aged ≤5 years precludes detailed treatment recommendations.

Local guidelines on the diagnosis and management of asthma in children aged 1–15 years and those under 5 years are provided by the Paediatric Society of New Zealand (www.paediatrics.org.nz). The Society notes that few infants who wheeze have asthma. The guidelines advise that during acute episodes of recurrent or persistent wheeze, supportive treatment should be provided as described under management of acute wheeze. In individual cases a trial of bronchodilators may be considered. Regular daily ICS treatment may be indicated for the small group of infants considered to have asthma.

Patients in Step 1 of the GINA treatment categories only need a rescue inhaler occasionally, once or twice a week at the absolute most. In Professor O'Byrne's opinion, these patients are under-treated and have a burden of disease in relation to exacerbations. Be aware of how much reliever medication patients are using; regular or increased use of rescue inhalers indicates that asthma is not well controlled.

Patients in Step 2 only need low doses of ICS once or twice daily to achieve really good asthma control (preventing symptoms and attacks); these anti-inflammatory medications are currently the most effective available for asthma. The evidence for this simple, safe and inexpensive treatment is provided by data from the OPTIMA[14] and START[15] trials.

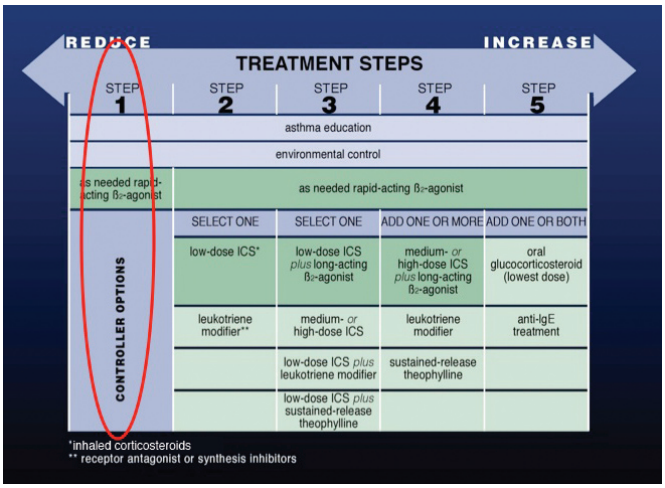

Figure 2: GINA Treatment Steps

OPTIMA trial

The OPTIMA (Oxis and Pulmicort Turbuhaler In the Management of patients with Asthma) trial was the first large study to examine the benefits of ICS in mild persistent asthma. OPTIMA involved two groups of patients: (Group A); ICS-naive patients with close to normal lung function (mean prebronchodilator baseline FEV_1 89.5%) and infrequent use of short-acting inhaled beta-agonists. Treatment comprised low-dose budesonide alone or in combination with eformoterol, or placebo, for 1 year. Budesonide monotherapy reduced the rate of severe exacerbations and poorly controlled asthma days by more than half. No further clinical benefit was obtained by adding eformoterol, although lung function was improved. In contrast, for patients in Group B (receiving corticosteroids at baseline), the addition of eformoterol to budesonide improved all outcome variables, and was significantly superior to doubling the ICS dose.

The START trial

The second large study to evaluate ICS in mild persistent asthma was the START (inhaled Steroid Treatment As Regular Therapy in early asthma) trial, in which over 7000 patients with new-onset persistent asthma were administered low-dose budesonide or placebo for 3 years.[15] In Year 1 of the study, 34% of placebo recipients versus 20% of budesonide recipients required additional corticosteroid treatment, and 4% of placebo recipients versus 2% of budesonide recipients had a severe asthma exacerbation. By Year 3 of the study, 50% of placebo-treated patients required additional corticosteroid treatment and 6% had a severe asthma exacerbation, compared with 30% requiring corticosteroid treatment and 3% with an exacerbation in the budesonide group. After 3 years, post-bronchodilator FEV_1 had declined significantly less in the budesonide group compared with those on placebo, but the difference between the groups was extremely small (mean difference 0.88% predicted).

The START data show that severe exacerbations are associated with a more rapid decline in lung function and inhaled budesonide reduces not only the risk for severe exacerbations, but also the associated decline in lung function. Avoiding exacerbations should be a primary outcome for patients and this future risk should be emphasised to both them and their physicians (see section on *Reducing the future risk of exacerbations* on Page 3).

Delaying ICS therapy is harmful

In 1994, Danish researchers were the first to suggest that early intervention with ICS may prevent the development of irreversible airway obstruction.[16] In their study, children with asthma received inhaled budesonide soon after diagnosis or other agents (theophylline, β2-agonists and/or sodium-cromoglycate) but not including ICS (controls). Children who did not receive budesonide experienced an annual decrease in percentage predicted FEV_1 of 1–3%, whereas FEV_1 improved significantly with time during budesonide treatment, both compared with the run-in period and with the control group. Moreover, FEV_1 after 3 years of budesonide was significantly lower in children who began treatment more than 5 years after the onset of asthma than in children who began treatment within the first two years after onset (see Figure 3 on page 3).

Uncontrolled asthma - Step 3

Clinical trial data have shown that low-dose corticosteroids alone may not provide enough asthma control.[17] In the GOAL (Gaining Optimal Asthma control) trial, patients with uncontrolled asthma across a wide range of severities were assigned to treatment with fluticasone propionate alone or in combination with salmeterol. Significantly more patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved comprehensive, guideline-defined control with combination inhaled therapy than those given increasing doses of fluticasone alone.

In line with this evidence, GINA recommends that patients in Step 3 (those with severely uncontrolled asthma) receive a low-dose ICS with an inhaled long-acting β2-agonist (LABA), either in a combination inhaler device or as separate components. However, in Professor O'Byrne's opinion, LABAs should only be prescribed in a combination inhaler; repeated dosing of bronchodilator monotherapy increases the risk for persistence of β-agonist-related adverse systemic side effects. For children, the guidelines recommend increasing the dose to a medium-dose inhaled glucocorticosteroid.

Reducing the future risk of exacerbations

The GINA panel recently considered the evidence for using a rapid-onset LABA (eformoterol) and an inhaled corticosteroid (budesonide) in a single inhaler both as maintenance and reliever therapy in maintaining a high level of asthma control and reducing exacerbations (refer below to Symbicort® SMART® therapy). The benefit appears to result from early intervention at a very early stage of a threatened exacerbation. Evidence from several asthma trials demonstrates that using budesonide and eformoterol as maintenance and reliever therapy (Symbicort® SMART®) effectively reduces the risk of subsequent exacerbations (see Figure 4).

The reason for this benefit is probably because asthma exacerbations develop over days, not over hours. In an analysis of about 400 exacerbations, asthma symptoms began some 7–10 days before the exacerbation was identified and treated with a β-agonist (see Figure 5).[18] The Symbicort® SMART® approach allows an increased dose of corticosteroid as an anti-inflammatory rescue therapy, rather than just the higher doses of rescue inhaler that most asthma action plans recommend [see boxed text]. This approach does have an advantage for patients with difficult asthma who require a combination device and who are at risk of exacerbations. For such patients, this is the only way we should be treating them, as opposed to two separate inhalers. Using a lower dose of corticosteroid does not result in more severe exacerbations.

Indeed, a recent analysis showed that the Symbicort® SMART® approach (ICS dose 748 µg/day) achieves similar or improved clinical control in persistent asthma compared with conventional best practice (ICS dose 1015 µg/day), while maintaining similar control of eosinophilic inflammation.[19]

SMART® therapy

The first combination inhaler containing both budesonide and eformoterol to be used for both regular maintenance treatment and relief of breakthrough symptoms, thereby delivering increased anti-inflammatory therapy at the first sign of increased symptoms, has become widely known as Symbicort® Maintenance And Reliever Therapy, or SMART®.

In New Zealand, budesonide/eformoterol combination delivery options include Symbicort® Turbuhaler, a multidose inspiratory flow-driven, dry powder inhaler containing budesonide 100 µg or 200 µg and eformoterol 6 µg per inhalation. Symbicort® Turbuhaler is indicated in the regular treatment of asthma where use of a combination (ICS and LABA) is appropriate. This includes:

- patients who are symptomatic on ICS therapy
- patients who are established on regular LABA and ICS therapy.

Symbicort® SMART® may be prescribed as 200/6 µg twice daily and as needed. Patients should take one additional inhalation in response to symptoms. If symptoms persist after a few minutes, an additional inhalation may be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations can be used temporarily.

A fixed-dose 400/12 µg strength is also available, but is not indicated for use in the Symbicort® maintenance and reliever therapy regimen.

Another budesonide/eformoterol combination delivery option is the pressurised metered dose inhaler Vannair, containing either budesonide 100 µg or 200 µg and eformoterol 6 µg per inhalation. Vannair is registered for use as a fixed-dose therapy only, not as maintenance/reliever therapy.

For full prescribing details regarding these treatments, consult the corresponding New Zealand Medsafe data sheets (http://www.medsafe.govt.nz).

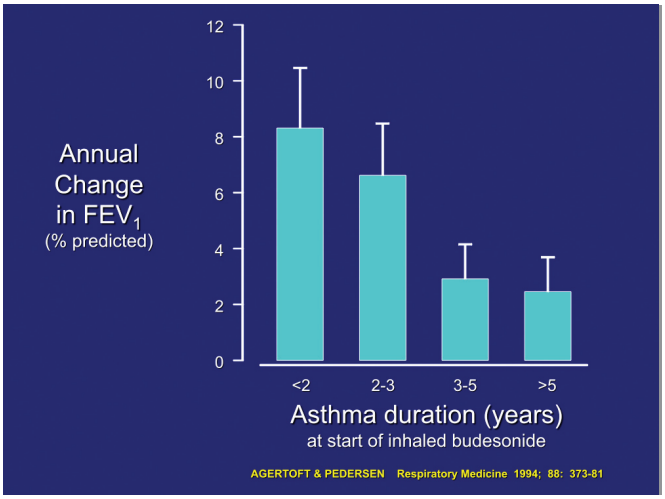

Figure 3: Agertoft & Pedersen data

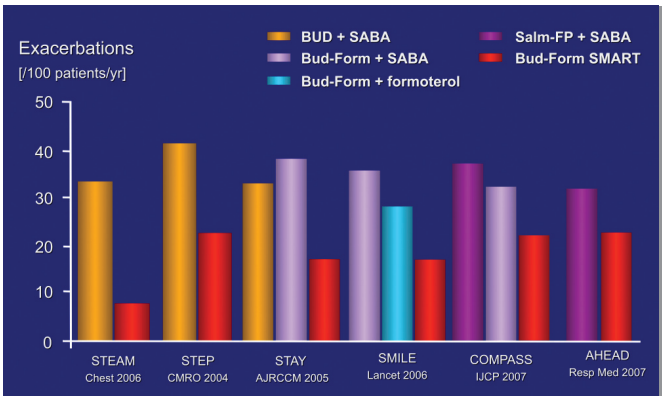

Figure 4: Reduction of Severe Exacerbations

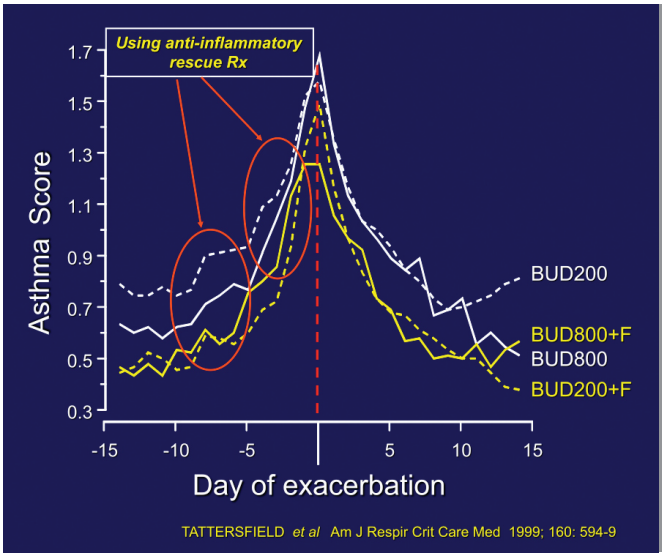

Figure 5: Development of Asthma Exacerbations

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Managing difficult asthma - Step 4

The most common reason for difficult-to-control asthma is that patients are not using their medications. Lack of adherence is a big problem in chronic asthma; many patients tend not to use their medications in the absence of symptoms.

For those patients who really are using their maintenance medications, the preferred treatment as stated by GINA for patients at Step 4 is to combine a medium or high dose of inhaled corticosteroid with a LABA. However, in most patients, increasing from a medium dose to a high dose of inhaled corticosteroid long-term provides relatively little additional benefit. A higher dose is recommended only on a trial basis for 3 to 6 months in cases where asthma cannot be controlled with a medium-dose inhaled corticosteroid combined with a LABA. Adding oral corticosteroids to other controller medications may be effective but can cause severe side effects and should be considered only if the asthma remains severely uncontrolled on Step 4 medications.

For patients with allergic asthma (at Step 5), subcutaneous injections of a monoclonal anti-immunoglobulin (IgE) antibody every 2 to 4 weeks has been shown to improve control of allergic asthma when other options have failed. This has proven to be an effective option, but is also very expensive ($CAN1500/month).

Take home messages

- Asthma control can be achieved in most patients.
- ICS are the mainstay of therapy and can be used as monotherapy in most patients.
- Combination therapy with ICS and LABA improves asthma control and reduces exacerbations, in patients not controlled on ICS alone.
- The combination of budesonide and eformoterol used as maintenance and reliever therapy (Symbicort® SMART®) further reduces severe exacerbation risks.

Concerns about steroid therapy and growth

Currently available ICS treatments may slow the rate of growth in children, but this effect is relatively short lived, after which growth reverts to pretreatment levels.[20] Younger, prepubertal children seem to be more sensitive to the growth suppressive effects of ICS. It is important to emphasise to parents that untreated moderate asthma delays puberty by about 1 year 4 months and that severe asthma might decrease adult height, but by no more than 1.25 cm.[20]

However, recent longitudinal data provide reassurance that long-term use of budesonide in children with chronic asthma allows them to reach their predicted adult height, even after 13 years of treatment.[21] Key findings of the trial data are that, regardless of the duration of budesonide treatment and dose used, there was no significant difference between predicted and final height, and also the overall total dose of budesonide was unrelated to the height achieved for each child.

Local adverse effects of ICS therapy (including fluticasone, beclomethasone and budesonide) include hoarseness and dysphonia, occurring in approximately 5–7% of treated adults but very infrequently in children; higher dosages and frequency of use exacerbate the problem. It is therefore important to find the lowest effective dose of an ICS. Gargling and rinsing the mouth with water and spitting it out after each inhalation may reduce such effects. The best treatment is avoidance or cessation, which of course is not possible because of the need for this drug.

It is important for patients to know that the long-term benefits of using inhaled steroids to control asthma appear to significantly outweigh the long-term side effects.

Oral corticosteroid therapy is sometimes advised for severe asthma attacks in children, but it should only be prescribed when really necessary. The equivalent of budesonide 400 µg/day is <1 mg/day of oral prednisone; higher doses of prednisone (2 or 3 mg/day) are inadvisable, as such treatment suppresses adrenal gland hormone production. Some evidence indicates that using intermittent oral steroids stunts growth in young children. In addition, a single course of prednisone is associated with an increased risk of fractures in children. Recent evidence indicates that multiple oral corticosteroid bursts over a period of years can produce a dosage-dependent reduction in bone mineral accretion and increased risk for osteopenia in children with asthma.[22]

Conclusion

Compelling evidence exists showing that combination ICS and LABA therapy inhalers give better control in terms of reduced symptoms, improved lung function and reduced exacerbations in patients with mild, moderate or severe persistent asthma, as opposed to increasing the dose of corticosteroids in patients not well controlled on lower doses, and ensure that the corticosteroid is not discontinued when the LABA is added and are consistently cost-effective.

In particular, combination therapy inhalers are more convenient to use than separate inhalers, which may mean that higher numbers of patients comply with long-term treatment. Treatment compliance may be further enhanced by the fact that patients directly attribute their short-term improvement in symptoms and lung function to these combination inhalers. With increased compliance, asthma outcomes are improved as the patient takes regular ICS, thereby reducing the airways inflammation that characterises asthma.

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Treatment decisions based on these data are the full responsibility of the prescribing physician.