Research Review
SPEAKER SERIES
Asthma Management in the 21st Century
Making Education Easy
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REGRESSION TO CRISIS-ORIENTED CARE

This publication summarizes a recent presentation by Professor Ken Chapman, Director of the Asthma & Airway Centre, University Health Network, Toronto. He spoke about optimum strategies for asthma control to panels of respiratory specialists and health professionals in Auckland, Tauranga, Wellington and Christchurch in February 2012.

Clinical monitoring of asthma

A typical patient who presents to the Asthma & Airway Centre is under the care of a family physician who may notice that the patient often requests repeat prescriptions for reliever despite a standing prescription for an asthma controller, typically an inhaled corticosteroid (ICS). This pattern of dependence on bronchodilators may prompt the attentive practitioner to seek the assistance of a specialized centre. Such a patient will often report other features of sub-optimal control: night-time awakening with occasional symptoms of cough or wheeze or episodes of 'bronchitis' treated at a walk-in clinic with prednisone but resulting in one or two workdays missed. Despite these frequent day-to-day symptoms the patient's asthma has not resulted in her receiving emergency room care or being hospitalized.

Several years ago, the only standard for asthma care was whether or not the patient needed hospital treatment; the focus was on crisis management. Importantly, while the patient in this case study has not been admitted to the emergency room or hospital, she nonetheless has poor asthma control.

As early as 1995, the Canadian guidelines[1] contended that good control of asthma was defined by absence of daytime and night-time symptoms, no compromise of physical activity, no flare-ups, no absences from school or work, and not needing a quick-relief beta$_2$ agonist. At that time, the guidelines suggested that rare symptoms of asthma in the daytime or night-time were acceptable, as long as they did not compromise physical activity; any exacerbations that occurred had to be mild and so infrequent as to not result in time off school or work, and beta agonist use was at a minimum.

This symptom list has since been transformed into the 5-question Asthma Control Test (ACT) questionnaire that all patients are required to complete when they attend the Asthma & Airway Centre. The ACT covers the previous 4 weeks and scores each question from 1–5. A score of 20–25 indicates good control of asthma, whereas a score of 19 or less indicates poor asthma control.

The ACT score has been validated in a number of studies, one of which evaluated ACT scores at baseline and risk of subsequent exacerbation over 12 months.[2] In that study, an ACT score of 15 at baseline suggested a much higher risk of asthma exacerbations than a score of 20 (OR, 1.60; 95% CI 1.58 to 1.62), while an ACT score of 19 was minimally associated with future asthma exacerbations (OR, 1.09; 95% CI 1.07 to 1.11).

Worldwide, surveys have revealed that despite suboptimal control of asthma as defined by guideline targets, patients are nevertheless reportedly satisfied with their disease control; a Canadian survey by Chapman and colleagues in 2001 assessed the degree of asthma control achieved by patients.[3] Only 24% of patients had controlled disease according to the guideline criteria, while 57% were considered poorly controlled. Nevertheless, 54% of patients with poorly controlled asthma thought that their asthma was adequately controlled and 30% reported it was very well controlled; the overwhelming majority (84%) were satisfied with the control of their asthma. Similar outcomes have been reported with New Zealand research.[4,5]

It is unclear why patients appear to have low expectations for their disease control. Professor Chapman believes it may be the way physicians approach asthma management with their patients. Physicians understand that the intensity of their therapy should be roughly proportional to underlying disease. This often leads physicians to prescribe treatment incrementally, beginning with minimal therapy and moving to more treatment only in response to patient perceptions of continuing problems. Many patients will accept inadequate treatment and residual asthma disability – settling for second best. Professor Chapman believes that this approach results in under-treatment with too much reliance on beta agonists, with adequate controller therapy prescribed only for the uncommon patients who seek complete freedom from symptoms. Professor Chapman stressed the inappropriateness of this approach for asthma management.

How can we best achieve then maintain asthma control?

The optimal approach is to start with more aggressive treatment at the outset. Twice-daily controller therapy, particularly with ICS and long-acting beta$_2$ agonists (LABAs) in combination, leading to the rapid abolition of symptoms establishes the patient's faith in the therapy or strategy and is likely to encourage compliance. After successfully establishing control for a period of time, therapy may be stepped-down to the lowest level needed to maintain disease control.

Recent Canadian data highlight the importance of patients achieving control of asthma symptoms.[6] Of 10,428 patients assessed in a large survey of asthma control in primary practice, the majority (59%) were uncontrolled. Importantly, when compared with controlled patients, the uncontrolled patients were over twice as likely to be hospitalized for their asthma, almost twice as likely to require specialist care, were over three times more likely to make emergency room

Professor Ken Chapman,

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Professor Chapman is an internationally respected researcher in the field of asthma, COPD and airway diseases. His publications have appeared in the New England Journal of Medicine and the Lancet. With more than 7,000 citations to his work, **Professor Chapman is in the top 1% of cited medical researchers.**

Professor Chapman is currently Director of the Asthma and Airway Centre of the University Health Network and Director of the Canadian Registry for Alpha-1 Antitrypsin Deficiency. His academic appointments are as Professor of Medicine in the Faculty of Medicine with a cross-appointment to the School of Graduate Studies (Institute of Medical Science, Toronto).

Professor Neil Barnes

Professor Neil Barnes has been a consultant in respiratory and general medicine at Barts and the London NHS Trust since 1988 and professor of respiratory medicine at Barts and the London School of Medicine and Dentistry since 2002.

Professor Barnes trained at Cambridge University and Westminster Medical School qualifying in 1979. He started specialising in respiratory medicine in 1982, training at King's College Hospital and the London Chest Hospital.

His main clinical and research interests are in asthma, in particular, **severe and difficult asthma, chronic obstructive pulmonary disease (COPD), pleural disease and cough.** His research focuses on the mechanisms and pharmacology of asthma and COPD and clinical trial design and interpretation.

He is currently co-chair of the Pharmacology section British Thorax Society/Scottish Intercollegiate Guidelines Network asthma guidelines. He has been an adviser for the National Institute of Health and Clinical Excellence. He is a member of the **Global Initiative for Asthma (GINA) Science Committee** and has acted as an advisor for the **Global Initiative for Chronic Obstructive Lung Disease (GOLD) and GINA Guidelines** on assembling evidence for guidelines.

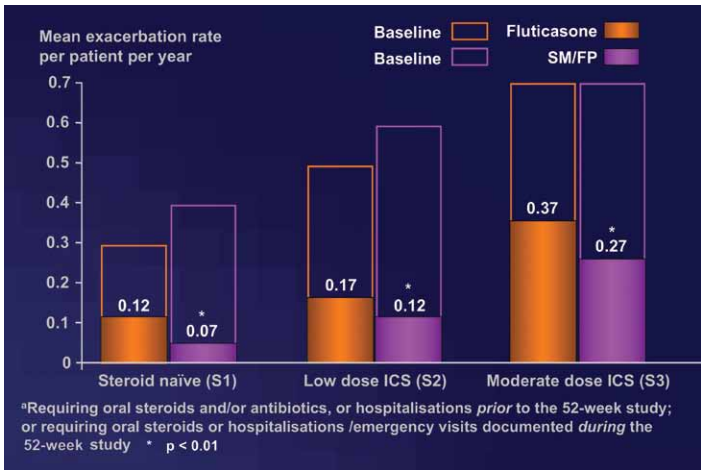
Professor Barnes has given invited lectures at most of the major respiratory meetings worldwide. He has served as Associate Editor for Thorax and has been on the Editorial Board of The American Journal of Respiratory and Critical Care Medicine, Primary Care Respiratory Journal and Treatments in Respiratory Medicine. He has been a reviewer for a wide range of general and respiratory journals and has published over 180 peer-review papers, book chapters, editorials and reviews.

visits, and almost six times as likely to require urgent asthma care from a doctor's office. In total, the risk of excess healthcare visits was almost six-fold higher among those with uncontrolled asthma. Thus, uncontrolled asthma is not only about occasional extra use of reliever therapy or occasional nocturnal awakening; it is associated with a future risk of considerable asthma instability.

Is asthma control achievable?

Worldwide, much evidence shows that the majority of patients with asthma fail to achieve guideline-defined asthma control. However, this does not have to be the reality. The landmark GOAL (Gaining Optimal Asthma ControL) study by Bateman and colleagues demonstrated that by avoiding the bronchodilator-driven crisis therapy characteristic of the 1980s and 1990s treatment paradigm, effective controller therapy abolishes symptoms.[7] This 1-year trial demonstrated that in patients with uncontrolled asthma, combination therapy with fluticasone propionate and salmeterol resulted in 80% being well-controlled; fewer achieved control with fluticasone alone. The treatment paradigm focussed on adjusting controller doses to abolish day-to-day symptoms of asthma. With this preventive strategy, rates of exacerbations requiring oral corticosteroids and/or hospitalisation or emergency visits were low in both treatment groups but significantly lower in the combination treatment group, and substantially lower than the participants had suffered during the year prior to study involvement (see Fig. 1). In particular, the GOAL strategy of aiming for total control significantly reduced severe exacerbations to extremely low rates (between 2–4%).

Figure 1. GOAL study: aiming for total control reduces all exacerbations[7]



Increasing ICS dose = better asthma control?

Many physicians would advocate increasing the ICS dose for patients failing to achieve asthma control, which seems to make sense. Toogood and colleagues evaluated different dosages of beclomethasone and the percentages of patients who would achieve certain therapeutic asthma endpoints.[8] Outcomes are apparently improved upon increasing beclomethasone dose. However, most of the benefits from ICS therapy occur at low dosages; as the dosages are increased, the dividends lessen. Ind and colleagues investigated whether the benefit of adding salmeterol was superior to doubling the dose of fluticasone propionate over 6 months, compared to a control group who remained on a lower dose of fluticasone propionate (250 µg twice daily).[9] At 6 months, mean morning peak expiratory flow rates improved identically with either dose of fluticasone propionate alone; there was no additional benefit from doubling the dose, whereas adding a LABA to the lower dose of fluticasone propionate resulted in more than twice the improvement achieved with either dose of fluticasone propionate alone. Several other clinical studies have reported similar outcomes. Such evidence explains why national and international asthma guidelines recommend considering combination ICS/LABA therapy over medium- to high-dose ICS therapy.

Another reason for using combination therapy is the concern about ICS-related side effects, which may be dose-related. An investigation by Hanania and colleagues found dose-related reductions in bone density amongst asthma patients treated with ICS.[10] In another study, Australian researchers reported an association between the use of ICS and the development of cataracts.[11] High doses of beclomethasone (28 puffs/week) were associated with triple the risk of cataract formation when compared with patients using ≤14 puffs/week of beclomethasone.

The Canadian asthma guidelines recommend early supplementation of ICS with a LABA, stating that when adult asthma is not controlled with a low dose of ICS (250 µg/day of fluticasone or equivalent), then add-on LABA therapy should be introduced at this point, instead of increasing the dose of ICS monotherapy.[12]

When to step down?

Guidelines fail to give explicit guidance on stepping down of ICS therapy once asthma is controlled. Professor Chapman's thinking has been influenced clinically by the Lundback study, in which patients with asthma initially received 1 year of double-blind treatment with ICS and LABA, alone or in combination; over the following 2-year open-label follow-up period, the physician increased or decreased patients' medication to achieve and maintain asthma control.[13] Notably, airway hyperresponsiveness continued to improve throughout the study, with most of the improvement in peak flow, symptom-free and rescue-free days occurring during the first year; only slight improvements were observed over the next two years. The majority of patients achieved and maintained control of asthma over the 3-year study period with physician-driven medication changes. There was also evidence of a shift in the underlying asthma dialysis, results of methacholine challenge testing revealed that increasing doses to provoke a 20% fall in FEV_1 were required over the course of the study, particularly during the first year.

Professor Chapman suggests that attempting to step down asthma therapy within only 3 or 4 months of treatment initiation is premature; some patients deserve a longer period of disease control before stepping down can be considered. More research is required in this area.

How to step down?

Clinical evidence regarding maintenance of asthma control during step down supports the proposed strategy of starting with more aggressive treatment at the outset. A study that enrolled patients with asthma not being treated with controller therapy considered that only 1% were well-controlled at baseline.[14] All were immediately commenced on salmeterol/fluticasone propionate 50/250 µg twice daily. After 12 weeks, those patients who achieved well-controlled status during each of the last 4 weeks of this period were eligible to step down and were randomised to a further 3 months of treatment with twice-daily salmeterol/fluticasone propionate 50/100 µg or fluticasone propionate 250 µg monotherapy. At the end of the 3-month period, the majority of patients remained well-controlled.

Examining the results closely, Professor Chapman believes two messages can be taken from this study:

1. Following the strategy of controlling the disease by starting with higher treatment intensity and then stepping down, patients during the step-down tend to remain well-controlled – regardless of which step-down therapy they receive.

2. Asthma control was preserved in a significantly higher proportion of patients receiving the combination treatment despite receiving less than half the daily ICS dose that was administered in the monotherapy treatment group.

Interestingly, patients interpret their decreasing corticosteroid dose as progress – that they are able to achieve asthma control and they also appreciate being on a lower corticosteroid dose in regard to safety concerns.

Can we achieve good control with a symptom-reactive strategy?

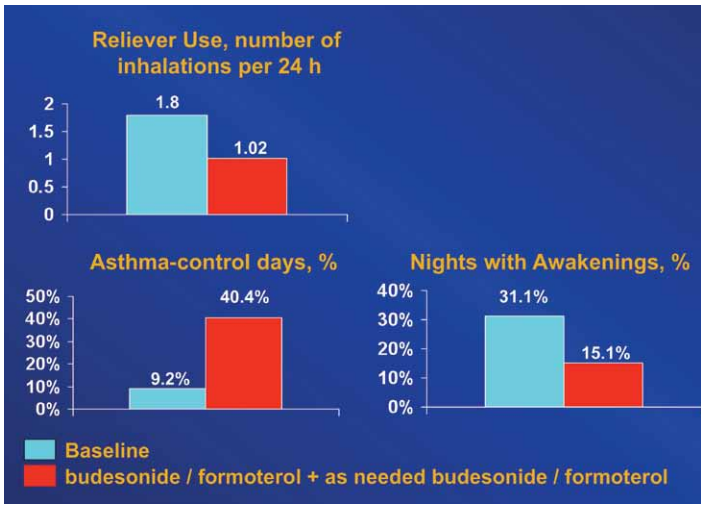
Professor Chapman considers a symptom-reactive, bronchodilator-driven strategy to be a return to crisis-oriented care. Symptom-reactive dosing is also known as single-inhaler therapy (SIT) with budesonide and formoterol, or Single Maintenance And Reliever Therapy (SMART), which has been variously described as "a preferred combination strategy", providing "medicine at just the right time", offering the associated advantages of "reducing ICS exposure" and as "a 'Trojan horse approach', whereby patients will always get ICS even using inhaler prn". Professor Chapman believes that this mode of thinking has allowed doctors to lower their standards of care, by failing to make their patients effective partners in disease management. Crucially, the lifelong nature of asthma makes it vital that patients understand how best to manage the disease, instead of simply being given a symptom-driven therapy.

The evidence on SMART therapy has been critically reviewed by Professor Chapman and colleagues.[15] Some aspects of the strategy are revealing by inspection of some of the larger trial results. The SMILE study was a randomized, double-blind, 12-month, parallel-group study, in which patients received budesonide/formoterol maintenance therapy (160/4.5 µg one inhalation twice daily) plus one of three alternative as-needed medications – terbutaline (0.4 µg), formoterol (4.5 µg), or additional budesonide/formoterol (160/4.5 µg), this last arm being "SMART" therapy.[16] The obvious implication of this design is that the patients in the as-needed SMART therapy arm improved by a greater extent compared with the other patient groups because they were receiving

more medication (50% higher doses of ICS), not because they were receiving the medication "at just the right time". Professor Chapman also noted that the study participants started the trial on an average daily dose of budesonide 800 µg; the strategy was to destabilise their uncontrolled asthma still further, by reducing the dose to 400 µg/day – not a realistic clinical strategy.

In all but one of the SMART studies, the primary endpoint is time to first severe exacerbation: a lowering of standards; a return to crisis-oriented care. In the SMILE study, while time to first severe exacerbation was longer with as-needed budesonide/formoterol versus either of the other study treatment arms, by the end of the year, the rate of severe exacerbations was 13% amongst SMART-treated patients – one in seven.[17] This is in stark contrast to the much lower rates of 2–4% severe exacerbation rates observed in the GOAL study, which followed a strategy of adjusting controller therapy to prevent symptoms. Patients on SMART therapy are driving their therapy in a crisis-oriented fashion. Importantly, the results from the SMILE study show that while SMART therapy improved asthma outcomes, it did not lead to controlled asthma (i.e., at 1 year, SMART therapy was associated with once-daily reliever use, two-thirds of days without asthma control, nocturnal awakenings once a week) (see Fig. 2).

Figure 2. SMART control outcomes in the SMILE study[17]



When outcome data are averaged from several SMART studies, their asthma control outcomes do not compare well against GINA guideline targets, as shown in the adjacent table.[15-22]

	SMART asthma control outcomes (weighted-average)	GINA guideline targets
% Symptom-free days	45%	Over 72%
Reliever need (uses per day)	0.92	0.2 (i.e., twice or less/week)
% Reliever-free days	55%	~70%
% Nights with awakenings	11%	zero
Severe exacerbation rate (events/year)	0.22 (i.e., 1 in 5 patients per year)	zero*
* Similarly, the GINA guideline target is zero for exacerbations.		

How many patients on SMART therapy achieve control?

In a detailed analysis of asthma control involving five studies including a total of over 5000 patients on SMART therapy, only 17% of SMART-treated patients achieved GINA-defined clinical asthma control (44% were categorized as uncontrolled and 38% were partly-controlled).[17-19,21-23]

The effect of symptom-reactive or variable dosing on airway inflammation has been investigated in a 1-year study where patients with asthma received either budesonide/formoterol 200/6 µg twice-daily maintenance and reliever therapy (SMART) or fixed-dose (regular dosing) budesonide/formoterol 800/12 µg twice daily.[24] While the between-treatment differences in most variables measured were non-specific, CD4+ lymphocytes and subepithelial eosinophils were significantly increased in the SMART group.

Summary

- Achieving controlling rapidly and completely can encourage patient compliance and establish for both patient and physician the long-term treatment targets.
- When stepping down, stepping down within the ICS/LABA combination formulations is more likely to maintain control than stepping across to ICS without LABA.
- Variable, symptom-driven dosing (SMART) is associated with poor control and increasing airways inflammation.
- The best long-term outcomes have been demonstrated with symptom-preventive rather than symptom-reactive dosing.

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IS COMPLIANCE ABOUT THE PHARMACOLOGY, THE PHYSICIAN OR THE PATIENT?

This publication summarises a recent presentation by Professor Neil Barnes, Consultant Respiratory Physician at the London Chest Hospital, Bart's and the London Trust and School of Medicine and Dentistry. His thought-provoking case studies and research provided insight into the question as to whether therapeutic compliance is about the pharmacology, the physician or the patient. He shared his expertise and experience with respiratory health professionals in Auckland, March 2012.

An important aspect of the earliest asthma guidelines was their determination that asthma treatment should aim for long-term control of the disease.[1-3] Good asthma control is defined by the Global Initiative for Asthma (GINA) as no (or minimal) daytime symptoms, no nocturnal symptoms or awakenings, no (or minimal) need for rescue medication, no limitations on activity including exercise, (near) normal lung function and no exacerbations.[4] Levels of asthma control are variously described by national and international guidelines; GINA describes asthma control as controlled, partly controlled or uncontrolled asthma.[4]

Asthma control: patient perspective

Asthma management guidelines have increasingly recognised the importance of patient-defined treatment success. Patient surveys have provided a good insight into what is important to them in terms of their asthma management; in a UK survey, patient goals matched those of the asthma guidelines - 'be free of exacerbations' and 'not having to use rescue medications'.[5] The same survey identified that the most important aspect to patients was the prevention of asthma exacerbations, whereas approximately only 10% of patients wanted their asthma to be controlled to prevent it interfering with their working lives.

Criteria for predicting corticosteroid-treated exacerbations were investigated in an analysis of a database consisting of almost 1000 patients with asthma who were followed for one year in the TRUST (The Regular Use of Salbutamol Trial) study, which was a comparison of regular and as-required β_2-agonists.[6] All study participants were recruited from general practice. They maintained daily diary cards, peak flow monitoring and symptom scores. The main outcome measure was the number of exacerbations requiring a course of oral corticosteroids. The best predictor of an exacerbation was found to be an increase in daytime symptoms. Similar findings were revealed in a secondary analysis of the FACET (the Formoterol and Corticosteroids Establishing Therapy study) database.[7]

Probably the best short, self-administered questionnaire for assessing asthma control is the Asthma Control Test (ACT™), which determines the effects of daily symptoms on the odds of starting a course of oral corticosteroids.[8] Five of the 22 survey items were found to have the greatest validity in discriminating between patients who differed in the specialist's rating of asthma control, and were selected in the following order:

- Shortness of breath
- Patient rating of control
- Use of rescue medication
- Activity limitation due to asthma
- Nocturnal asthma symptoms.

Notably, data from the GOAL (Gaining Optimal Asthma ControL) study demonstrated that those patients who had good control of asthma had a quality of life within the normal range and it was significantly better than for those whose asthma was not controlled.[9]

Thus, when considering asthma control from the patient's perspective, it is what they want and if they have good control, they have few symptoms, are at little risk of asthma exacerbation and have a better quality of life.

Asthma control: clinician's perspective

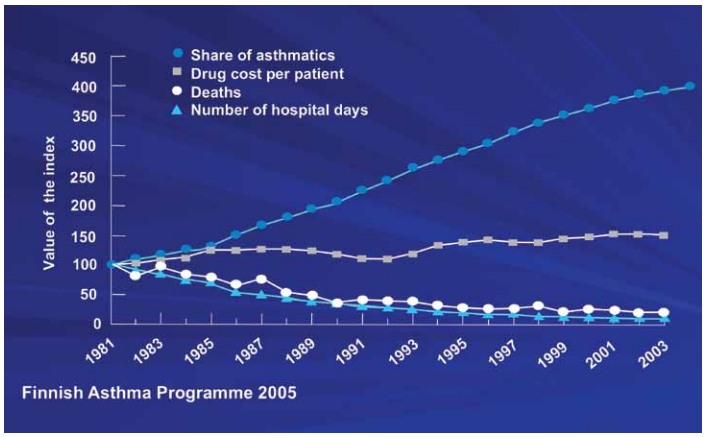
Asthma is an inflammatory disease that clinicians wish to control, but the evidence shows that this takes time. In a study involving 35 asthmatic patients administered inhaled fluticasone propionate, FEV_1 was improved after 3 months of treatment with no further improvements at 12 months.[10] Despite this plateau in lung function, an improvement in airway hyper-responsiveness (AHR) was observed. This indirect measure of underlying inflammation continued to improve throughout the year-long study. Further clinical evidence reveals even longer periods of improvement – 18 months to 2 years. Importantly, particularly in the moderate or more severe asthma cases, clinicians need to accept that prolonged treatment is necessary for maximum benefit of the underlying disease: changes in physiology (lung function), inflammation and remodelling are not temporally concordant.

Asthma control: payer's perspective

Prof. Barnes considers that the report of the Finnish Asthma Programme is one of the most important studies to be published on asthma in the last 10 years.[11] From 1994 to 2004, Finland undertook a national programme to improve asthma care, signed up to by the government and health professionals. The programme has resulted in an 85% reduction in asthma deaths and a 90% fall in asthma admissions, statistics that remain unmatched worldwide (see Figure 1).

Finland does not have access to novel drugs that are unavailable elsewhere and healthcare spending is similar to the level spent in the UK. Instead, the programme outcomes are explained by better delivery of asthma care. The programme has lessened the burden of asthma to society, with a reduction in costs per patient per year of 36% (from €1611 to €1031), due to less expenditure on hospital admissions and disability pensions. Patients are being treated effectively outside the hospital. The challenge to the rest of the world is to do as well as Finland, according to Prof. Barnes.

Figure 1. Asthma in Finland 1981–2003[11]



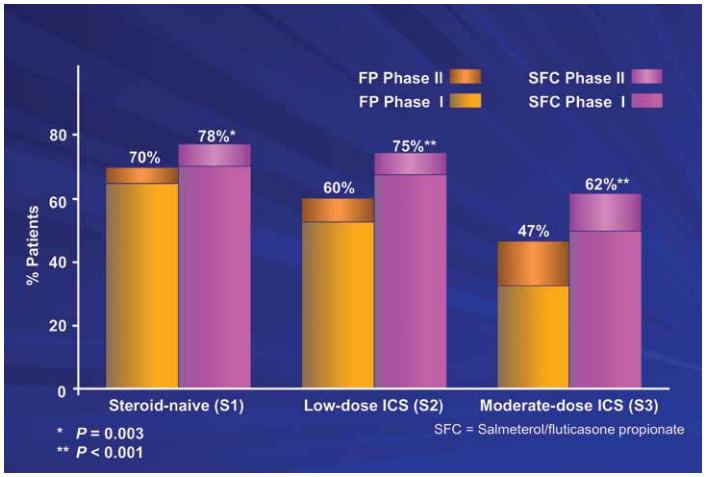
Management approach based on control

A stepwise (step-up if necessary and step-down when possible) approach to asthma management is used in the current guidelines.[12] In the late 1990s, there was a need to establish the proportion of asthmatics at each step of the recommended asthma management guidelines. Evidence from a sample of general practices in the UK indicates that the majority of patients were not well-controlled at Steps 1–3.[13]

The GOAL study was set up by the GINA Science Committee to answer the question as to how well patients can do if they follow the guidelines on asthma control.[9] Two features in this study were designed to reproduce routine clinical practice: firstly, patients commenced the treatment appropriate to the level of asthma severity (i.e. mild asthmatics were started on fluticasone propionate (FP) 100 µg alone or in combination with salmeterol (Seretide®) 100 µg twice daily, while more severe asthmatics already receiving ICS therapy commenced on FP 250 µg or Seretide 250 µg twice daily. Secondly, patients with uncontrolled asthma were allowed to step up their treatment. Treatment was stepped-up until total control was achieved (or maximum 500 µg corticosteroid twice a day).

Results from the GOAL study support the goal of guideline-derived asthma control. Significantly more patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved control with salmeterol/fluticasone than fluticasone (see Figure 2).

Figure 2. Composite measure of asthma control: well-controlled asthma over 8-week periods (GOAL)[9]



Well-controlled asthma

The GOAL study data also support the idea that treatment needs to be sustained in some asthmatics who continue to improve over time. In this study, drug dosage escalation up to week 24 was associated with rapid improvement of symptoms. Thereafter, despite no further increases in drug dosage there was a gradual improvement in percentage of control. By week 52, almost 80% of patients had well-controlled asthma (i.e., no exacerbations, no nocturnal awakening, not requiring a β_2-agonist more than twice weekly).

In all three Stratum, very few patients experienced severe exacerbations (defined as those requiring hospitalisation or emergency room visits). In terms of reducing the risk of exacerbations, the effect was significantly greater in Strata 1 and 3 with Seretide than with ICS monotherapy with FP alone.

The GOAL study showed that by adhering to the guidelines, patients can do very well. Moreover, there were no significant differences in adverse events between the two groups and the range of side effects was benign.

These findings are further supported by a study involving β_2-agonist users aged ≥18 years enrolled in the UK General Practice Research Database (GPRD), which is linked to the national registry of hospitalisations.[14] The study included 507,966 patients with 5.5 million short-acting β_2-agonists (SABA), 4.0 million ICS and 1.3 million long-acting β_2-agonists (LABA) prescriptions (alone or in combination). The aim of the study was to determine the relative rate of mortality with these prescriptions and primarily to determine the risk for all-mortality associated with LABA exposure. The results of this study showed that the risk of dying was reduced at Step 2, reduced at Steps 3 and 4 (i.e. low- and high-dose combination treatment), whereas the death rate was increased in those patients on β_2-agonist therapy only. The results of this study did not indicate that LABA exposure was associated with an increased risk for all-cause mortality and they also showed that following the asthma guidelines was associated with a substantial reduction in risk of mortality.

At around the same time, the Medicines and Healthcare products Regulatory Agency concluded that LABA therapy is safe if used with ICS therapy and that the preferred way of using LABAs is as a combination therapy.[15]

The British guideline recommendations for stepwise management of asthma in children aged 5–12 years are similar to those for adults, except that paediatric drug dosages are lower.[16] In general, the evidence levels for pharmacological management of asthma are not as good for children as they are for adults. Thus, the results of the recently published BADGER study are particularly useful.[17] This US study involved 182 children (aged 6–17 years) who had uncontrolled asthma while receiving 100 µg of fluticasone twice daily. All were randomised to receive an increase in ICS dosage, added LABA therapy (LABA step-up), and added leukotriene-receptor antagonist (LTRA step-up), in a triple crossover design with 16 weeks per treatment. The primary endpoint was a composite of exacerbations, asthma-control days and FEV_1 to assess whether the frequency of a differential response to the step-up regimens exceeded 25%.

The results clearly showed that overall, adding a LABA was superior to increasing the ICS dose or adding an LTRA, although some individual children did better with increasing the ICS dose or adding the LTRA. The data demonstrate that the guidelines regarding paediatric asthma are also correct.

While clinical data attest to the fact that the available antiasthmatic medications are extremely effective, an enormous problem exists worldwide as to levels of adherence and compliance. Amongst the three forms of non-compliance – unintentional (forgetfulness), intentional, and rational – the first two are the most common. The commonest in asthma is intentional. Eliciting the rate of compliance is the first step for a clinician to take, in order to ascertain whether the patient is using the medication or not. Two good questions that will not elicit the answer are these:

- This is a very important treatment, are you taking it?
- The new inhaler I started you on last time, are you taking it?

Instead, clinicians need to ask questions that allow the patient to tell the truth, for example:

- You are on a lot of treatment do you ever forget to take them?
- If you are feeling good do you miss your treatment out?

This allows the start of dialogue about compliance. Taking objective measurements is even better. A UK study examined the prevalence of nonadherence to corticosteroid medication in a population with difficult asthma referred to a Specialist Clinic and examined the relationship of poor adherence to asthma outcome, using general practitioner refill records for the previous 6 months for ICS and SABA therapy compared with initial prescriptions.[18] Medication adherence was defined as taking ≥50% of inhaled medication prescriptions. Two-thirds were taking ≥50% of their inhalers and one-third was taking <50%. Those taking <50% were more likely to be admitted to hospital, to own a nebuliser and to be using a large quantity of nebules.

Due to the low rate of nebuliser use in New Zealand, it would be useful to examine the number of salbutamol inhalers to provide objective evidence of adherence. The clinic run by Prof. Barnes for difficult-to-control asthma performs objective measures of adherence as a routine part of a difficult asthma assessment. He advises that such objective data can then be used to challenge patients.

The key reason for patients not taking their medication involves healthcare beliefs. Research conducted by Prof. Barnes and Prof. Rob Horne, Professor of Behavioural Medicine, School of Pharmacy, University of London, reveals this central insight around patient beliefs:

- That inhaler is only for people with bad asthma
- If I take the inhaler now it will not help me when I am bad
- The effect of the treatment will wear off if I take it regularly
- I might get addicted

Unless a clinician elicits these erroneous beliefs from patients, they cannot be corrected. Prof. Barnes has found these insights very helpful when dealing with patients who will not take their treatment. When addressing compliance, the following physician/patient interaction factors are also important:

- Compliance is better if the treatment is perceived to address the patients concerns
- Compliance is improved if the patient feels the doctor has listened to their concerns
- Improved by written information
- Improved by repetition

In addition, different ways of delivering treatment result in different compliance rates. For instance, one study shows that simplifying treatment with the use of combination therapy versus separate inhalers improves compliance among children.[19]

The UK Asthma Guidelines offer practical tips to enable clinicians to uncover these patient beliefs:[16]

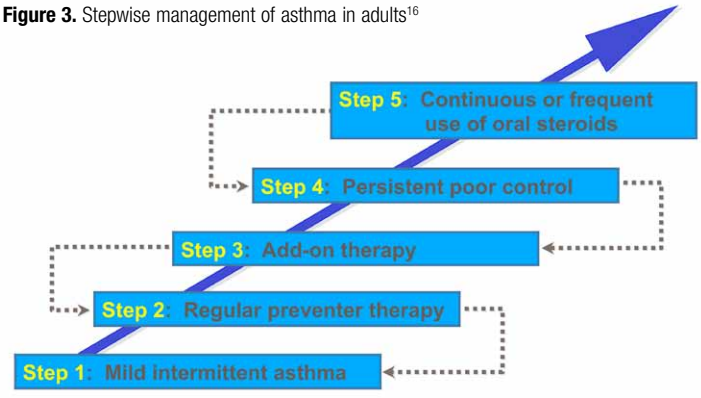
- Open-ended questions e.g. "If we could make one thing better about your asthma what would it be?"
- Make it clear you are listening to and responding to the patients concerns and goals
- Reinforce practical information and treatment plans with written information
- Reminder strategies
- Recall patients who miss appointments

The value of the self-administered ACT is that it can be used with or without lung function testing to assess control in patients with asthma and it also reflects the multidimensional nature of asthma control.[8] This 5-item, 5-response questionnaire yields a total score of between 5 (indicating very bad asthma) and 25 (excellent). The ACT correlates with a number of well-validated questionnaires, such as the Asthma Control Questionnaire (ACQ).[20] The ACT has also been shown to have value in predicting the likelihood of an exacerbation: an ACT score of 20–25 indicates good control, whereas a score of 15–19 is associated with inadequate control and a score of <15 indicates very poor asthma control.[8,20]

Since a lower ACT score is associated with a higher risk of exacerbations requiring oral corticosteroids, hospitalisations and emergency visits, this test can be used to assess asthma control and decide on level of treatment.

The British guidelines on asthma management also recommend stepping-down treatment in patients who are poorly controlled (see Figure 3).[16]

Figure 3. Stepwise management of asthma in adults[16]



Relatively few studies have explored the option of stepping-down. One good one is that by Bateman and colleagues, who randomised corticosteroid-naïve patients with moderate persistent asthma controlled on Seretide 250/50 µg twice daily to a 12-week step-down comparing FP 250 µg twice daily with Seretide 100/50 µg twice daily.[21] During the run-in open-label period, 68% of patients were well-controlled and entered the double-blind step-down period, which showed that stepping-down from Seretide 250 to 100 maintained the level of control, but some patients who stopped the β_2-agonist became poorly controlled. Thus, patients with asthma controlled on high- or moderate-dose combination therapy can have the ICS dose stepped-down. Those who are controlled on low-dose ICS/LABA therapy can discontinue the LABA component.

Recently, another method of using combination therapy has been suggested by the SMART® (Symbicort Maintenance and Reliever Therapy) management approach. Whereas the traditional approach has been to use the regular maintenance therapy with extra puffs of reliever therapy as needed, the SMART approach promotes use of a lower dose of combination therapy and using extra puffs of Symbicort if necessary.

A large retrospective analysis of data from five budesonide/formoterol maintenance and reliever therapy (Symbicort SMART Turbuhaler*) studies[22-26] (n=5246) assessed the relationship between the ACQ-5 and GINA-defined clinical asthma control and future risk of instability and exacerbations.[27] It shows that overall only 17% of patients using this strategy have good control of asthma. Furthermore, a recent Cochrane review of SMART concluded that this strategy provides no superior benefit over best clinical practice (i.e. guideline-based treatment).[28] Prof. Barnes and colleagues do not believe that SMART is a game-changing strategy that is superior to other management techniques. They prefer to endorse the traditional approach.

This viewpoint is supported by biopsy evidence from a study that examined the level of inflammation comparing regular dosing with the SMART strategy of variable dosing.[29] Worse inflammation was observed with the SMART approach: biopsy specimen subepithelial eosinophils doubled (from 6.2 to 12.3 cells/mm^2) in the SMART cohort whereas sputum and biopsy eosinophil counts decreased with high fixed-dose treatment.

In summary

- Asthma control is recommended in the guidelines and according to the evidence, this is what patients, clinicians and payers want
- With the use of ICS or ICS/LABA, the evidence from both trials and clinical practice shows that control can be achieved in the majority of patients
- Poor adherence is the main barrier to good asthma control
- Variable, symptom-driven dosing (SMART) is associated with poor control and increasing airways inflammation.

Take home message: Follow the asthma management guidelines and as long as patients use their medication, they will do very well.

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