

Asthma exacerbations: prevention is better than cure

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Abstract: Poorly controlled asthma is currently treated by adding or removing asthma medication in a stepwise fashion to try and improve symptoms and maintain lung function. It is becoming apparent that asthma exacerbations are independent of asthma control and severity, and that the simple method of using rescue courses of corticosteroids to treat an asthma exacerbation can be bettered by aiming to prevent its occurrence. New tools that can predict and prevent exacerbations are now becoming available. This article discusses these tools and takes a more detailed look at new treatment regimes being used.

Keywords: asthma exacerbation, corticosteroids, asthma treatment regimes

Introduction

The medical, social, and financial costs of poorly controlled asthma are huge. A survey by Asthma UK found that 5.2 million people in the UK have asthma, which led to over 1400 deaths in 2002. The financial cost of asthma to the UK is over £2.3 billion per year. Studies have consistently shown that poorly controlled asthma costs a great deal more than well controlled asthma. For example, Hoskins et al (2000) found the average cost per patient was 3.5 times higher for a patient having an asthma attack, compared with a patient who did not. Similar figures have been presented by Van Ganse et al (2002). Barnes et al (1996) suggested there was significant scope for cost reduction by improving disease control, and that a third of the direct cost of asthma is related to emergency room use, hospitalization, and death.

Severity versus control

Asthma treatment guidelines aim to improve asthma symptoms and prevent exacerbations (ATS 2000; Bousquet 2000; BTS and SIGN 2003), but the definitions differ for asthma deteriorations, severity, and control. One of the best definitions of asthma severity and control was published by Cockcroft and Swystun (1996), who defined asthma severity as the minimum medication (inhaled or oral corticosteroids) required to achieve asthma control. Control was defined as lack of symptoms, normal lifestyle, near normal lung function, and lack of morbidity; the implication being that once a patient has good asthma control there should be little resting bronchoconstriction and little response to bronchodilator. This definition separates severity from control and allows the proper categorization of patients in clinical trials. A patient may have mild but poorly controlled asthma; having symptoms that are easily preventable by administration or increase in their corticosteroid dose. Conversely, a patient may have severe but well controlled asthma, requiring continuous high dose inhaled or oral corticosteroids to remain asymptomatic (Cockcroft and Swystun 1996).

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Asthma exacerbations

Defining asthma exacerbations is problematic and should be separate from control and severity. Reddel et al (1999) compared peak flow patterns during asthma exacerbations with periods of poor asthma control. Peak flow variation was strikingly different during an asthma exacerbation when compared with episodes of poor asthma control, falling, and improving linearly over several days, whereas episodes of poor asthma control were characterised by morning dipping, wide diurnal variability, and by an impressive bronchodilator response. However, there was no difference in peak flow diurnal variability during asthma exacerbations compared with episodes of poor asthma control, which suggests this commonly measured parameter may fail to detect important changes in lung function. During asthma exacerbations there was also an impaired response to inhaled β_2 agonist. This failure of response to a β_2 agonist therefore appears to delineate poor asthma control from an asthma exacerbation. The study also demonstrated that patients with well controlled asthma were still prone to asthma exacerbations (Reddel et al 1999). Criteria used in studies to define an exacerbation include: peak flow dropping from a pre-determined baseline; need for rescue oral corticosteroids; an increase in the use of rescue β_2 agonist; night time awakening; or increased symptom scores.

The incidence of asthma exacerbations in studies varies with the definition used and the baseline severity and control of the population being studied. In the Formoterol and Corticosteroids Establishing Therapy International Study Group (FACET) study designed to evaluate the benefits of adding a long acting β_2 agonist to different doses of inhaled corticosteroid, a severe exacerbation was defined as an episode requiring treatment with oral corticosteroids, as judged by the investigator, or a decrease in the morning peak flow to more than 30% below the baseline value (established during the run-in period) on 2 consecutive days (Pauwels et al 1997). Mild exacerbations were defined as at least 2 consecutive days with a peak flow 20% less than baseline, or nocturnal awakening, or 3 additional inhalations of terbutaline, when compared with the run-in period. Approximately 850 patients entered the study and were randomized into one of four groups. The total number of severe exacerbations was 425 over a 12-month period, giving an overall exacerbation rate of 0.5 exacerbations/patient/year. The total number of mild exacerbations was a massive 16463. In the Gaining Optimal Asthma Control study, a combination of salmeterol/fluticasone (as Seretide[®]) was compared with fluticasone alone in 3 different groups of

patients over the course of one year. The baseline characteristics revealed that there were 3416 patients who experienced 1832 exacerbations, defined as hospitalization or requiring a course of antibiotics or oral corticosteroids, giving an overall exacerbation rate of 0.54 exacerbations/patient/year before entry into the study proper (Bateman et al 2004). These rough figures demonstrate that severe asthma exacerbations are common and that adding in a long-acting β_2 agonist reduces asthma exacerbations. The FACET study also revealed that higher dose inhaled corticosteroids have a marked beneficial effect on exacerbation frequency but relatively less effect on symptoms and peak expiratory flow, whereas with the addition of long-acting β_2 -agonists, the opposite was true (Pauwels et al 1997; Tattersfield et al 1999).

This indicates that exacerbation frequency does not closely relate to symptoms and measures of disordered airway function, suggesting that the mechanisms responsible for these features of asthma are different. Rosi et al (1999) also found that asthma exacerbation frequency does not relate closely to symptoms and measures of disordered airway function. This demonstrates that different strategies are needed to reduce asthma exacerbations, as well as optimise asthma control.

Treatment strategies

The current strategy recommended by the British Thoracic Society (BTS) suggests a stepwise approach to asthma control and exacerbations (BTS and SIGN 2003). However, patients who appear clinically well controlled on inhaled corticosteroids can still have evidence of airway inflammation and airway hyperresponsiveness (Boulet et al 1994; Sont et al 1996) and be vulnerable to exacerbations, airway remodeling, and possibly fixed airways obstruction (Lange et al 1998; Beckett and Howarth 2003). Self management plans advocate doubling the dose of inhaled corticosteroid if the peak flow drops. This approach has recently been questioned. Harrison et al (2004) found that doubling the dose of inhaled corticosteroid, based on a fall in peak flow of > 15% from baseline or an increase in the symptom score from baseline, did not prevent the need for oral corticosteroids. The authors surmised that a higher dose of inhaled corticosteroid may be needed to prevent an asthma exacerbation. Indeed, Foresi et al (2000) demonstrated that increasing (quadrupling) the inhaled corticosteroid dose at the onset of an asthma exacerbation had a beneficial clinical effect and reduced the requirement for oral corticosteroids compared with placebo. This suggests that it is not too late

for an exacerbation to be attenuated while peak flow or symptoms are deteriorating.

Other strategies that focus on the pathophysiological features of asthma have been tried with some success. Sont et al (1999) investigated a treatment strategy focused on reducing airway hyperresponsiveness in mild and moderate asthma in addition to the recommendations of the asthma guidelines at the time. Seventy-five adults with mild to moderate asthma were studied in a randomized prospective parallel trial. One group had their treatment adjusted according to the normal reference strategy. The other group had their treatment adjusted according to their degree of airway hyperresponsiveness. The treatment strategy based on attempting to return airway responsiveness towards normal reduced both exacerbations and subepithelial reticular basement membrane thickening. Patients treated by the airway hyperresponsiveness protocol had a 1.8-fold decrease in *mild* exacerbations when compared with the reference group. The authors concluded that monitoring airway hyperresponsiveness or other surrogate markers of airway inflammation may help in the long-term management of asthma.

Green et al (2002) directly tested this hypothesis with a management approach that both measured and attempted to normalize eosinophilic airway inflammation, as well as minimize symptoms and maximize lung function. Seventy-four subjects attending outpatients with moderate to severe asthma were randomized to treatment either according to the BTS guidelines or to a management strategy where treatment was adjusted according to the sputum eosinophil counts. In the sputum management group, decisions about antiinflammatory treatment were made in accordance with an algorithm based on control of symptoms and maintenance of the sputum eosinophil count at or below 3% with a minimum dose of antiinflammatory treatment. The 3% cut-off was chosen because this was previously shown to identify individuals with corticosteroid-responsive asthma (Pavord et al 1999). If the sputum eosinophil count was less than 1%, antiinflammatory treatment was reduced irrespective of asthma control. If the eosinophil count was 1%–3%, no changes to antiinflammatory treatment were made, and if the eosinophil count was greater than 3%, antiinflammatory treatment was increased. Decisions about changes in bronchodilator treatment were based on individual patients' symptoms, peak expiratory flow readings, and use of rescue β_2 agonists compared with baseline using the same criteria as in the BTS management group. Management decisions were made by an independent individual who was unaware

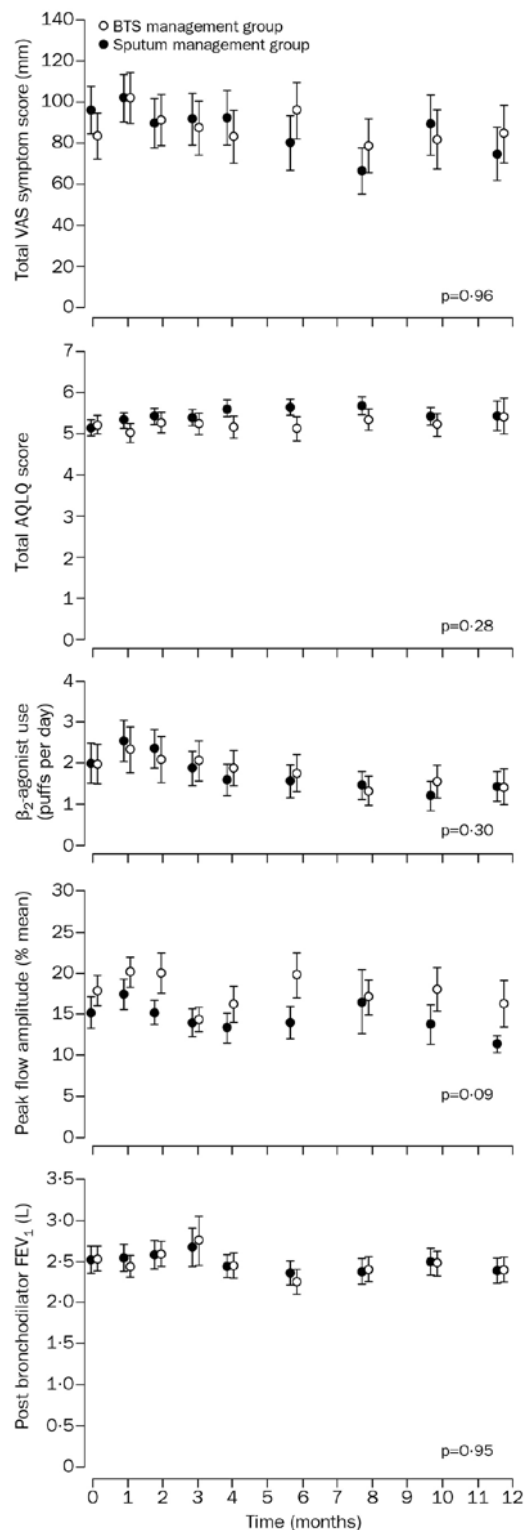


Figure 1 Comparison of effects of two treatment strategies on symptoms score (assessed by visual analogue score [VAS]). Asthma quality of life questionnaire (AQLQ), β_2 agonist use to relieve asthma symptoms, peak expiratory flow, and post-bronchodilator forced expiratory volume in 1 second (FEV₁). One strategy (British Thoracic Society [BTS] management group) utilized standard BTS guidelines and the other (sputum management group) adjusted the antiinflammatory treatment with corticosteroids based on the eosinophil counts. Source: Green RH, Brightling CE, McKenna S, et al. 2002. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet*, 360:1715–21. Copyright © 2004. Reprinted with permission from Elsevier.

of the clinical characteristics of the patient, and who recorded separate treatment plans to be followed depending on whether the patients' asthma was poorly or well controlled. The strategy based on sputum eosinophil counts achieved significantly better control of eosinophilic related airway inflammation over the twelve-months of the trial. There was also an improvement in methacholine PC₂₀ (Figure 1). Both management strategies achieved equivalent control of symptoms, quality of life, and disordered airway function. Importantly, in the sputum management group there was a marked reduction in severe asthma exacerbations and significantly fewer hospital admissions with asthma exacerbations. There were 109 severe exacerbations in the BTS group, compared with 35 in the sputum group and 6 asthma admissions in the BTS group, with 1 in the sputum group (Figure 2).

New approaches

Unfortunately, given the resource implications and need for rapid sputum processing, a sputum management protocol is only really suitable for secondary care. According to Asthma UK, only approximately 18% of patients with asthma are seen in hospital outpatients; there is therefore a need for a simpler measure of airway inflammation that is applicable in a primary care setting.

An approach using measurements of nitric oxide in the exhaled breath may have clinical utility; although there are no published trials yet on the real world applicability of exhaled nitric oxide in reducing asthma exacerbations, several authors have noted that a rise in the fraction of

exhaled nitric oxide (FeNO) in the exhaled breath of patients with asthma seems to predict exacerbations. Harkins et al (2004) also monitored FeNO levels in a group of 22 patients with moderate and severe persistent asthma and found that those patients suffering an asthma exacerbation within 2 weeks of the initial visit had a higher mean FeNO at the initial visit. Jones et al (2001) withdrew inhaled corticosteroids aiming to induce loss of asthma control. They found that change in FeNO levels from baseline and FeNO levels at the prior visit were both good markers of impending loss of control, suggesting that FeNO may rise early enough for a therapeutic intervention to be of value. However, the study end point was loss of control, the definition of which was comparable to a mild exacerbation in the FACET study (Tattersfield et al 1999), rather than asthma exacerbation.

Recently, new treatment regimes have been suggested to improve asthma control and prevent asthma exacerbations. O'Byrne et al (2005) evaluated the use of budesonide and formoterol (combined as Symbicort®) as maintenance and reliever therapy (SMART), compared with budesonide/formoterol fixed dose therapy and high dose budesonide. SMART reduced the number of exacerbations when compared with fixed dose therapy. As noted in an excellent editorial by Gibson (2005), this approach might lead to over- or under-treatment of asthma so caution must be used when using SMART beyond the study entry criteria of moderate persistent asthma with poor symptom control despite inhaled corticosteroid therapy. Keeping this in mind, one other indication for SMART may be in the treatment of poorly concordant patients (Sovani et al 2004).

Conclusion

Asthma can differ in its severity, control, and exacerbation pattern. Categorizing asthma in this way is not just important for study outcomes, but also for patient care. Asthma exacerbations are common and costly and can be characterized as not responding to increased inhaled β_2 agonist use. Most importantly, they can be prevented by decreasing the airway inflammatory response with prompt and judicious use of corticosteroids. Identifying the precise time and proper dose of corticosteroid is becoming easier, using methods such as induced sputum and FeNO. Rather than be reactive to an asthma exacerbation, these tools allow proactive intervention which prevent exacerbations developing. Currently, FeNO looks to be the most practical method for predicting asthma exacerbations. Key questions remain: What factor in the lung is FeNO telling us most about? What is the "normal" level of FeNO for a patient

Results: Severe exacerbations

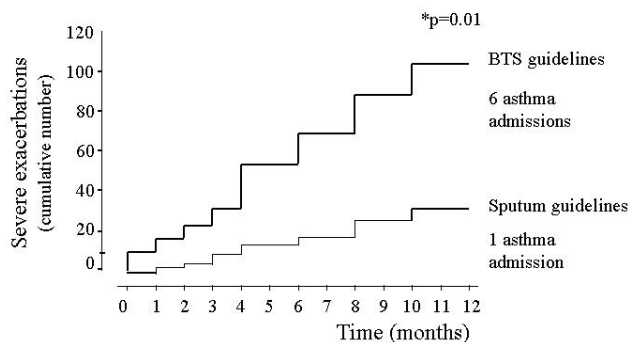


Figure 2 Comparison of effects of two treatment strategies on rates of severe exacerbations of asthma. One strategy (British Thoracic Society [BTS]) utilized standard BTS guidelines and the other (sputum management group) adjusted the antiinflammatory treatment with corticosteroids based on the eosinophil counts. Source: Green RH, Brightling CE, McKenna S, et al. 2002. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet*, 360:1715–21. Copyright © 2004. Reprinted with permission from Elsevier.

with asthma? As with most conditions in medicine, prevention may be better than cure.

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