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REVIEW

# Pharmacological strategies for self-management of asthma exacerbations

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**ABSTRACT: Written action plans are effective within asthma self-management, but there are few guidelines about the specific medication adjustments which can be recommended for self-treatment of exacerbations.**

**This review examines pharmacological strategies for self-management of asthma exacerbations in adults, including those for inhaled corticosteroid/long-acting $\beta_2$-agonist (ICS/LABA) users.**

**Oral corticosteroids are well-established in clinical practice and clinical trials for the treatment of severe exacerbations, including during combination therapy. Evidence supports 7–10 days treatment, with no need to taper except to reduce side-effects. Doubling the dose of ICS is not effective. Several studies have shown benefit from high-dose ICS (2,400–4,000 μg beclomethasone equivalent) for 1–2 weeks. This may be achieved by adding a high-dose ICS inhaler to maintenance ICS or ICS/LABA therapy. There is inconclusive evidence about acutely increasing the dose of maintenance budesonide/formoterol for exacerbations, and no studies of this approach with fluticasone/salmeterol. For patients taking maintenance budesonide/formoterol, use of the same medication as-needed reduces exacerbations. Short-acting $\beta_2$-agonists are still effective in producing bronchodilation during combination therapy; however, a higher dose may be required.**

**There is a need for further studies to clarify remaining issues about self-management of asthma exacerbations, particularly with regard to side-effects of treatment and patient acceptability.**

**KEYWORDS: Asthma exacerbations, asthma management, asthma pharmacotherapy, combined modality therapy, self-management**

There is an increasing focus in medical literature and international guidelines on the importance of early identification and treatment of asthma exacerbations. Although frequent exacerbations are a feature of severe persistent asthma, severe exacerbations can occur even in patients with very mild [1] or well-controlled [2] disease. Delayed initiation of treatment [3] is an important risk factor for mortality and morbidity from asthma exacerbations [4]. This has led to an increased awareness of the potential benefits of written asthma action plans, which provide advice for patients about how to recognise and manage worsening asthma. A Cochrane review demonstrated that written action plans, when part of self-management education and regular review, were associated with substantially improved health outcomes, such as hospitalisation rates [5]. The studies that were included in this meta-analysis each compared usual care against a ''package'' of interventions, including self-management education and regular practitioner review, as well as two or more specific action points and pharmacological intervention(s) for exacerbations [6]. Despite the strength of the evidence for benefit from integrated programmes, which included action plans, the diversity of the action points and treatment instructions which were used in these studies makes it difficult to know what therapeutic interventions should currently be recommended for incorporation into action plans.

The initiative for carrying out the present review was the day-to-day decision process faced by clinicians in determining the specific therapeutic instructions that should be included in written asthma action plans. In recent years there has been an increase in the proportion of patients being prescribed combination inhaled

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corticosteroid/long-acting $\beta_2$-agonist (ICS/LABA) therapy in one inhaler device for the management of persistent asthma. Although, in clinical trials, combination therapy results in a reduction in exacerbation rates compared with ICSs alone, exacerbations still occur. However, most of the advice in current international guidelines about how to manage exacerbations was published prior to the introduction of combination therapy. This has raised the question of how exacerbations should be managed in patients taking combination therapy and, particularly, how to write an asthma action plan for initial self-management of exacerbations by such patients.

This review was performed in an attempt to answer these questions, and to develop recommendations for the treatment of exacerbations, including those in patients taking combination ICS/LABA products.

## PRIMARY AIMS AND OBSERVATIONS

The primary aims that defined the scope of the review were as follows: 1) To determine the efficacy of using oral corticosteroids (OCS) in adults experiencing an exacerbation, both in general, and in particular, while receiving combination therapy. 2) To determine the efficacy of increasing ICS dose during an exacerbation, both in general, and in particular, while receiving combination therapy. 3) To determine the efficacy of increasing the dose of combination therapy during an exacerbation in adults currently receiving combination therapy. 4) To determine the efficacy of using short-acting β-agonists (SABAs) during an exacerbation, both in general, and in particular, while receiving combination therapy.

Literature regarding anticholinergic agents and antibiotics in the management of exacerbations was also reviewed.

A Medline search was performed covering the period 1990–2004, and any articles relevant to the above points were reviewed. The bibliographies of these publications and the personal reference libraries of the present authors were also searched. The search was limited to English-language publications relating to adults ($\geqslant$19 yrs of age). All publication types and fields were searched; however, in some cases search terms were limited to the title in order to refine the searches. The major international asthma guidelines were also examined to identify the recommendations about management of exacerbations, including those in patients taking combination therapy.

One notable observation during the review process related to the titles of publications which were identified by the search. Two examples of well-known studies are by HARRISON *et al.* [7] and PAUWELS *et al.* [8]. Both studies looked at ''prevention'' of exacerbations, the former by short-term treatment of each individual episode of worsening asthma to avoid progression to severe exacerbation, and the latter by long-term medication regimens, using exacerbation rates as a marker of overall asthma control. These two quite different therapeutic questions, the first of which was the subject of the present review, could often not be distinguished simply from the title of a publication. Given that many clinicians browse the tables of contents of medical journals by looking at publication titles, the present ambiguity between studies of acute treatment and of long-term prevention of exacerbations is confusing. Interestingly, the present authors found that studies of these two therapeutic questions could also only rarely be distinguished by Medline Subject Headings (MeSH), as there is no MeSH heading for ''exacerbations'', and the MeSH heading ''Acute Disease'' was only infrequently found in publications that were clearly relevant to the present review topic.

### *Definition of exacerbations*

In clinical practice, there is clear recognition of the concept of asthma exacerbations, particularly in their more severe forms, as episodes of acute or subacute deterioration from the patient's usual status. The current therapeutic algorithm for treatment of exacerbations is based upon the concept of commencing additional or different medications when symptoms and/or airway obstruction reach a predefined threshold. However, defining this threshold has been problematic in the past. Exacerbations are not defined from dichotomous variables. Instead, they are defined from a continuum of increased symptoms and airway obstruction. They may range in severity from mildly inconvenient to life-threatening, but are characterised by being outside the recent range of variation for that particular patient. They are also characterised as being clinically important, *i.e.* requiring treatment in order to provide relief or reduce risk to the patient.

It is immediately obvious from reading the publications included in the present review that a wide diversity of criteria (summarised in table 1) have been used to define exacerbations. These range from retrospective criteria, such as prescription of OCS, through different types of subjective symptom scores (symptom frequency, symptom intensity or symptom impact), to more objective criteria, such as changes in peak expiratory flow (PEF). Indirect criteria, such as healthcare utilisation (unscheduled doctor visit, Emergency Dept (ED) presentation, hospital admission), are commonly used to define more severe exacerbations. A range of terminology has been used in these studies, such as mild or severe exacerbations, worsening of asthma, and acute asthma, but these labels do not correlate reliably with specific diagnostic criteria. What is described as a worsening of asthma in one study may have the same characteristics as an exacerbation in another. What is termed a ''mild'' exacerbation in the ED may be regarded as a severe exacerbation in the context of self-management. For example, in one meta-analysis [41], the term ''mild acute asthma'' was used to refer to a subanalysis of patients with a forced expiratory volume in one second ($FEV_1$) of >30% predicted [42]. The results of studies carried out in EDs or in hospital are thus not necessarily directly applicable to self-management by patients using written action plans, who will usually be dealing with much less severe events. In addition, heterogeneity in the diagnosis of asthma contributes to heterogeneity in the diagnosis of exacerbations.

In some studies, exacerbations have been induced by the deliberate withdrawal of ICSs [28, 43]. While this model [38, 43, 44] allows treatment options to be investigated in a controlled fashion, the results of such studies cannot necessarily be extrapolated to spontaneous exacerbations in community patients, where the most common trigger in both adults and children is viral infection. The eosinophilic inflammation [44] and increased PEF variability seen with ICS reduction [44] and with poor asthma control [2] is very different from the reduced PEF variability and impaired $\beta_2$-agonist response seen during

**TABLE 1** Summary details for included studies

| First author [ref.] | Patients n | Study design | Community or hospital | Criteria for intervention | Interventions | Primary outcome variable |
|---|---|---|---|---|---|---|
| **Duration of OCS therapy** | | | | | | |
| HASEGAWA [9] | 20 | Randomised, open-label | Hospital | Hospitalised for acute asthma | 1 or 2 weeks of prednisone 0.5 mg·kg$^{-1}$ after 3 days *i.v.* CS | Morning PEF |
| JONES [10] | 44 | Double-blind | Hospital | Hospitalised for acute asthma, PEF <65% pred | 5 or 10 days of prednisolone | Waking PEF and asthma exacerbations |
| **Tapering of OCS** | | | | | | |
| O'DRISCOLL [11] | 35 | Double-blind | Discharge from hospital | Hospitalised for acute asthma, PEF <65% pred | OCS 40 mg·day$^{-1}$ during admission, randomised to abrupt cessation or taperingover 1–2 weeks | Morning PEF |
| HATTON [12] | 35 | Double-blind | Discharge from hospital | Hospitalised for acute asthma; for discharge, PEF at least double *cf.* admission, variability <15% over 48 h | Prednisolone 40 mg·day$^{-1}$ during admission; post-discharge, 14-day reducing course starting at 40 mg·day$^{-1}$, or placebo | Not stated. PEF, $FEV_1$, FVC and TLC reported |
| CYDULKA [13] | 15 | Double-blind | Post-ED | ED presentation; well enough for discharge | 40 mg·day$^{-1}$ prednisone for 8 days, or tapered over 8 days | $FEV_1$ and symptoms on day 12 |
| KARAN [14] | 26 | Randomised open-label | Post-ED | ED presentation; well enough for discharge | 40 mg·day$^{-1}$ prednisone for 8 days, or tapered over 8 days | Symptoms of relapse <21 days; $FEV_1$ day 12 and 21; adrenal suppression |
| **Doubling ICS** | | | | | | |
| FITZGERALD [15] | 290 | Double-blind | Community | Composite criteria for 2 days (symptoms, PEF, healthcare utilisation) | Double ICS dose for 14 days or maintain previous dose | Failure to regain control (composite criteria) |
| HARRISON [7] | 390 | Double-blind | Community | PEF ↓ by 15% or symptom score ↑ by 1 point from baseline (both permissible during run-in) | Double ICS dose for 14 days or maintain previous dose | Need for OCS |
| RICE-MCDONALD [16] | 22 | Double-blind crossover | Community | Night waking, symptoms reliever use or PEF | Placebo or double ICS or dexamethasone 0.1 mg·kg·day$^{-1}$ for 7 days | Treatment failure (3 days) – symptoms, PEF, withdrawal due to asthma or adverse event |
| **Higher dose ICS** | | | | | | |
| FORESI [17] | 142# | Double-blind | Community | PEF ↓ by 30% for 2 days | Budesonide 200 μg·day$^{-1}$, plus 800 μg·day$^{-1}$ or placebo for 7 days | Exacerbations = PEF ↓ by 30% for 2 days |
| LEVY [18] | 413 | Double-blind | Community (primary care offices) | Clinician judgement that OCS needed; post-BD PEF 60–90% best or predicted | Fluticasone 1 mg *b.i.d.* or prednisone 40 mg reducing (16 days) | Treatment failure (symptoms, PEF) |
| NANA [19] | 81 | Double-blind | Post-ED | Discharged from ED | Budesonide 1600 μg *b.i.d.* or prednisolone reducing course (7 days) | $FEV_1$ after 7 days |
| FITZGERALD [20] | 175 | Double-blind | Post-ED | ED presentation; well enough for discharge ($FEV_1$ >50% pred) | Budesonide 600 mcg *q.i.d.* or prednisolone 40 mg·day$^{-1}$ (7–10 days) | Relapse rate (return to ED) |
| LEE-WONG [21] | 40 | Double-blind | Post-admission | Admitted for asthma, PEF ≤50% pred | Flunisolide 2000 μg *b.i.d.* or prednisone 40 mg·day$^{-1}$ for 7 days | Not stated. PEF, $FEV_1$, symptom scores reported. |
| DI FRANCO [22] | 37 | Double-blind | Asthma clinic | ≥5 days symptoms, $FEV_1$ ≤70% pred and ≤80% recent best | Fluticasone 1000 μg *b.i.d.* or prednisone reducing from 40 mg·day$^{-1}$; usual ICS ceased | Sputum eosinophil percentage at 2 weeks |

**TABLE 1** (Continued)

| First author [ref.] | Patients n | Study design | Community or hospital | Criteria for intervention | Interventions | Primary outcome variable |
|---|---|---|---|---|---|---|
| **Acute use of ICS in the ED** | | | | | | |
| GUTTMAN [23] | 60 | Double-blind | ED | ED presentation; $FEV_1$ <70% pred; ⩾1 criterion for receiving *i.v.* steroids | Two doses *i.v.* CS, plus inhaled beclomethasone 7000 μg or placebo, divided into five doses over 8 h | $FEV_1$ change over 12 h |
| AFILALO [24] | 54 | Double-blind | ED | ED presentation; $FEV_1$ 40–69% pred | Inhaled beclomethasone 5000 μg or placebo, over 4 h | $FEV_1$ (6-h study) |
| RODRIGO [25] | 94 | Double-blind | ED | ED presentation; PEF and $FEV_1$ <50% pred | Flunisolide 18000 μg or placebo (dosing every 10 min for 3 h) | $FEV_1$ (3-h study) |
| PANSEGROUW [26] | 40 | Double-blind | ED | ED presentation with ''acute resistant asthma'' = $FEV_1$ and FVC <70% pred; misuse of $\beta_2$-agonist in 2–4 h prior to presentation; lack of response to $\beta_2$-agonist | Single-dose BDP 200 μg or placebo | Not stated. Primary aim related to resensitisation of airways to $\beta_2$-agonist (fenoterol) |
| RODRIGO [27] | 106 | Double-blind | ED | ED presentation, PEF or $FEV_1$ <50% pred | Fluticasone 9000 μg (dosing every 10/60 for 3 h) or 500 mg *i.v.* hydrocortisone | $FEV_1$ or PEF over 3 h; admission rate |
| **Single high-dose ICS** | | | | | | |
| LEUPPI [28] | 19 | Double-blind | Exacerbations Induced by ICS reduction | Symptoms + PEF >3 SD below baseline mean | Double last pre-exacerbation dose, plus budesonide 3200 μg or placebo | Not stated |
| **Increased dose of budesonide/ formoterol – AMD** | | | | | | |
| CANONICA [29] | 2358 | Open-label | Community | Step up if 2 consecutive days of reliever ⩾3 times·day$^{-1}$ or night waking | Budesonide/formoterol 200/6 or 100/6 AMD or FMD; AMD included step-up to four puffs *b.i.d.* until symptoms resolved or 14 days | Exacerbations (asthma-related SAE, hospitalisation/ED, OCS ⩾5 days; asthma-related withdrawal) |
| IND [30] | 1539 | Open-label | Community | Step up if 2 consecutive days of reliever ⩾3 times·day$^{-1}$ or night waking | Budesonide/formoterol 200/6 or 100/6 AMD or FMD; AMD included step-up to four puffs *b.i.d.* until symptoms resolved or for 14 days | Treatment successes (NHLBI criteria for asthma severity) and treatment failures (serious asthma exacerbation, OCS ⩾5 days, hospitalisation, emergency treatment, asthma-related withdrawal) |
| LEUPPI [31] | 127 | Open-label | Community | Step up if 2 consecutive days of reliever ⩾3 times·day$^{-1}$ or night waking or PEF <80% baseline mean | Budesonide/formoterol 200/6 AMD or FMD; AMD included step-up to 2–4 puffs *b.i.d.* for 7–14 days | Treatment successes (NHLBI criteria for asthma severity) and treatment failures (serious asthma exacerbation, OCS ⩾5 days, hospitalisation, emergency treatment, asthma-related withdrawal) |
| BUHL [32] | 4025 | Open-label | Community | Step up if reliever ⩾3 times·day$^{-1}$ or night waking or PEF <80% baseline mean | Budesonide/formoterol 200/6 AMD or FMD; AMD included step-up to two puffs *b.i.d.* for 7 days, +/- step up to four puffs *b.i.d.* for further 7 days | Asthma-related quality of life over 12 weeks |

**TABLE 1** (Continued)

| First author [ref.] | Patients n | Study design | Community or hospital | Criteria for intervention | Interventions | Primary outcome variable |
|---|---|---|---|---|---|---|
| STALLBERG [33] | 1034 | Open-label | Community | 2 consecutive days of: reliever $\geq$3 times·day$^{-1}$, or night waking or PEF <85% baseline mean | Budesonide/formoterol 200/6 or 100/6 AMD or FMD; AMD included step-up to four puffs *b.i.d.* for 7–14 days | Exacerbations (OCS, medical care unit, asthma-related SAE, asthma-related withdrawal) |
| FITZGERALD [34] | 995 | Open-label | Community | 2 consecutive days of: reliever $\geq$3 times·day$^{-1}$, or night waking or PEF <85% baseline mean | Budesonide/formoterol 200/6 or 100/6 AMD or FMD; AMD included step-up to four puffs *b.i.d.* for 7–14 days | Exacerbations (OCS or extra ICS, ED visit, asthma-related SAE, asthma-related withdrawal) |
| **Acute use of budesonide/ formoterol** | | | | | | |
| BALANAG [35] | 103 | Double-blind | ED | ED presentation, $FEV_1$ 30–60% pred | Budesonide/formoterol 1600/ 48 μg in two doses or salbutamol 1600 μg MDI+spacer in two doses | Mean $FEV_1$ up to 3 h |
| **Use of LABA for exacerbations** | | | | | | |
| TURNER [36] | 34 | Double-blind | Community | Mild exacerbations of at least 2 weeks duration, post-BD $FEV_1$ $\geq$75% pred or personal best, sputum eosinophils >4% | Salmeterol 50 μg *b.i.d.* or beclomethasone 500 μg *b.i.d.* or placebo (3 weeks) | Sputum eosinophils |
| BOONSAWAT [37] | 88 | Double-blind | ED | ED presentation, $FEV_1$ 30–60% pred | Formoterol 54 μg by Turbuhaler® *cf.* with 2400 μg salbutamol MDI+spacer, as three doses over 1 h | $FEV_1$ at 75 min |
| **Studies not specifically of exacerbations, but relevant to self-management** | | | | | | |
| **Treatment of sputum eosinophilia** | | | | | | |
| GIBSON [38] | 26 | Double-blind crossover | Induced by ICS cessation for 4 days | No exacerbations required – sputum eosinophilia only | Single dose budesonide 2400 μg or placebo | Sputum eosinophils at 6 h |
| **SMART Symbicort® studies**[¶] | | | | | | |
| SCICCHITANO [39] | 1890 | Double-blind | Community | As-needed for symptoms including during early stages of exacerbations | (Budesonide 400 μg *b.i.d.* + terbutaline prn or Budesonide/ formoterol 200/6 2 od + Symbicort® 200/6 1 puff prn) | Time to first severe exacerbation (hospitalisation or ED, OCS or PEF ↓30% for 2 consecutive days) |
| O'BYRNE [40] | 2760 | Double-blind | Community | As-needed for symptoms including during early stages of exacerbations | (Budesonide 400 μg *b.i.d.* + terbutaline prn or Budesonide/ formoterol 100/6 2 puffs *b.i.d.* + terbutaline prn or Budesonide/ formoterol 100/6 *b.i.d.* + Budesonide/formoterol 100/6 prn) | Time to first severe exacerbation (hospitalisation or ED, OCS or PEF ↓ 30% for 2 consecutive days) |

OCS: oral corticosteroids; ICS: inhaled corticosteroid; ED: Emergency Department; AMD: adjustable maintenance dosing (see text for explanation); LABA: long-acting $\beta_2$-agonist; SMART: (Symbicort® Maintenance And Reliever Therapy) Symbicort® studies; *i.v.*: intravenous; CS: corticosteroids; PEF: peak expiratory flow; % pred: % predicted; $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; BD: bronchodilator; BDP: beclomethasone dipropionate; FMD: fixed maintenance dosing (see text for explanation); SAE: serious adverse event; NHLBI: National Heart, Lung and Blood Institute; MDI: metered dose inhaler; od: one daily; prn: as needed. [#]: Groups 2 and 3 of the study by FORESI *et al.* [17]. [¶]: These studies did not specifically examine the management of exacerbations, but as-needed use of the study medication would have included periods of mild-to-moderate exacerbations.

viral infections [2], during which the inflammatory profile may be neutrophilic [45].

The specific diagnostic criteria used in any individual study will obviously have a substantial impact on the observed efficacy of treatment interventions. The most obvious example is limitation of exacerbations to those characterised by sputum eosinophilia, because of the observed association between neutrophilic inflammation and relative steroid resistance [46, 47]. Few of the reviewed studies examined treatment responses according to exacerbation aetiology or inflammatory profile. In terms of clinical diagnostic criteria, the application of too stringent criteria may result in late initiation of treatment, which is known to increase the risks of mortality and morbidity [4], whereas choice of too minor a threshold for diagnosis of exacerbations will increase the risk of over-treatment and reduce the chance of showing a significant effect of the intervention. The dilemma in designing exacerbation criteria for clinical trials is in waiting long enough to provide confirmation that the event is both outside the patient's usual range of variation and clinically important, without excessively delaying the commencement of treatment. Some specific problems arise in defining exacerbations on the basis of need for OCS, particularly in the assessment of therapies which might be considered as an alternative to OCS. There is an obvious need for utilisation of statistically appropriate methods for refining the diagnostic criteria for exacerbations, and for standardisation of exacerbation definitions in order to allow more ready comparison between studies. These issues form part of the scope of a joint European Respiratory Society/American Thoracic Society Task Force, which is currently in progress.

### Additional studies

Studies of interventions that were only relevant to in-hospital management of exacerbations, *e.g. i.v.* magnesium, were excluded.

Two studies which compared salmeterol/fluticasone propionate combination in a fixed dose with an adjustable maintenance dosing regimen of budesonide/formoterol combination [48, 49] were excluded from the present review because, in each case, it was not possible to separate out the effect of the two different maintenance medications from the effect of the two different strategies for treatment of worsening asthma. Maintenance asthma treatment is known to affect both the incidence of asthma exacerbations and the severity and duration of exacerbations [8, 50], so the impact of acute changes in budesonide/formoterol dose on the outcome of exacerbations in one arm of each of the above studies could not be assessed.

## OCS IN THE MANAGEMENT OF EXACERBATIONS

OCS have been accepted for many years as an effective way of treating asthma exacerbations. A meta-analysis by ROWE *et al.* [51], showed that corticosteroid therapy provides important benefits to patients presenting to the ED with acute exacerbations, particularly with regard to relapses and admission rates.

More recently, the benefits of systemic corticosteroids for the treatment of exacerbations in asthmatic patients were also presented in a Cochrane review by ROWE *et al.* [52]. This review of patients discharged from an acute setting after treatment of an acute asthmatic exacerbation showed that significantly fewer patients receiving corticosteroids relapsed to receive additional care in the first week post-discharge, with this favourable effect being maintained over the first 21 days. Patients receiving corticosteroids also had less need for $\beta_2$-agonists.

There are two main questions that continue to arise when it comes to treatment with OCSs. The questions relate to the most effective duration of OCS treatment, and whether OCS dose should be tapered.

### Duration of OCS therapy

In the aforementioned Cochrane review by ROWE *et al.* [52], OCS treatment for 7–10 days was found to be highly effective compared with placebo. Two placebo-controlled studies have examined duration of OCS treatment in patients discharged from hospital or ED. HASEGAWA *et al.* [9] found no difference between 1 and 2 weeks of oral prednisolone 0.5 mg·kg$^{-1}$, given after 3 days' *i.v.* corticosteroids, but JONES *et al.* [10] found that symptoms were higher in patients treated with prednisolone (40 mg) for 5 days compared with 10 days. There are no published studies that provide evidence for OCS to be continued for >10 days.

### Tapering of OCS dose

Historically, tapering has been used in the belief that this approach would avoid rebound exacerbations by maintaining treatment for a longer period without the side-effect risks of full dose, or that it would reduce the risk of adrenal suppression.

A number of small studies have been performed to address this question [11–14]. Two studies [11, 12] gave standard treatment of 40 mg·day$^{-1}$ during hospital admission followed by randomisation to abrupt cessation or tapering over 1–2 weeks. Two further studies randomised patients on discharge from the ED to 8 days of prednisolone 40 mg·day$^{-1}$ or tapering from 40 mg to 0 mg [13, 14]; both of these studies included adrenal stimulation tests at follow-up. The studies indicate that the theoretical concerns of rebound asthma severity resulting from the abrupt cessation of prednisolone therapy are not seen in practice. In all of these studies, similar results were obtained in relation to $FEV_1$, PEF and incidence of relapses in patients receiving either tapering or nontapering prednisolone treatment. It is important to note that patients were also discharged on ICS and inhaled $\beta_2$-agonists, which may have contributed to their recovery. What has not been considered, however, is the difference between tapering and abrupt cessation on the incidence of side-effects, particularly for patients with frequent exacerbations.

### OCSs in patients taking combination therapy

At the time of introduction of combination ICS/LABA therapy, the role of OCS in management of severe asthma exacerbations was already well established. As a result, there are no published placebo-controlled studies which have set out to determine efficacy and safety of OCS specifically in patients on combination therapy, and it would be difficult to justify setting up such a study. However, OCS have been used to treat severe exacerbations in all major studies of combination therapy, such

as the Gaining Optimal Asthma ControL (GOAL) study (fluticasone/salmeterol) [50], Formoterol And Corticosteroids Establishing Therapy (FACET) study (budesonide/formoterol) [8], and the recent studies of adjustable maintenance dosing and as-needed dosing of budesonide/formoterol [39, 40], showing that during all current combination therapy regimens, OCS are considered by clinical consensus to be the first line of treatment for severe exacerbations or those that cannot be controlled by increasing the dose of SABA or combination therapy.

## ICS IN THE MANAGEMENT OF EXACERBATIONS

### *Doubling ICS dose in self-management of exacerbations*

Over the past 10 yrs, clinical consensus has promoted doubling of ICS dose as the first step in written action plans for self-management of exacerbations, and this therapeutic strategy was utilised in many of the studies which demonstrated a benefit from programmes with written action plans [6]. Three recently published studies have now examined doubling of ICS dose in double-blind, randomised, placebo-controlled studies.

FITZGERALD *et al.* [15] assessed whether doubling the dose of maintenance inhaled budesonide for 14 days from early in the course of an asthma exacerbation prevents worsening and the need for systemic corticosteroids. In this 6-month double-blind study, 290 patients using a maintenance dose (MD) of $\leqslant$1,200 μg·day$^{-1}$ of beclomethasone or equivalent were randomised to a MD group or a double dose (DD) group. The MD group received a maintenance budesonide inhaler, plus an additional placebo inhaler for twice daily use for 14 days during exacerbations. The DD group received a maintenance budesonide inhaler, with the additional inhaler dispensing the same dose of budesonide as the maintenance inhaler. Thus, the DD group received double their maintenance ICS dose during exacerbations, whereas the MD group continued on their usual dose. Exacerbations were defined by composite criteria incorporating symptoms, healthcare utilisation and/or PEF, with a minimum of two consecutive affected days. The primary outcome variable was the proportion of patients who, after introducing the additional inhaler for an exacerbation, failed to regain control. Such treatment failures were defined as need for OCS, unscheduled visit to physician/ED, or unstable asthma after 14 days of treatment. Stability of asthma was assessed by composite criteria incorporating PEF, reliever use, night waking and symptom score, over 2 consecutive days. During the study, exacerbations were experienced by 35% of MD patients and 32% of DD patients. After the additional inhaler was commenced for an exacerbation, 40% of MD exacerbations and 41% of DD exacerbations were regarded as treatment failures ($p=0.94$), with the most common reason being asthma instability after 14 days. A total of 17% of MD exacerbations and 26% of DD exacerbations (nonsignificant) were treated with OCS, with the median time from exacerbation onset to start of OCS being 3 days for each group. There were also no significant differences between treatment groups in the pattern of $\beta_2$-agonist use or nocturnal awakenings. The authors concluded that doubling the dose of ICS within 48 h of the onset of exacerbation did not change the outcome or the need for further intervention compared with continuing patients on their usual MD. Electronically recorded diary data indicated that, at a group level, symptoms and reliever use had begun to worsen ~5 days before the diagnostic criteria were satisfied. PEF data were unfortunately not available for analysis. Overall, the background occurrence of severe exacerbations in this study population was less frequent than expected, as indicated by the fact that only 6% of the total MD group used prednisolone in the 6-month study period, compared with a pre-study estimate of 12.5%.

Similar results were seen in a study by HARRISON *et al.* [7] who investigated whether doubling the dose of ICS when asthma control deteriorates reduces the number of patients needing prednisolone, or has any effect on the severity and duration of the subsequent exacerbation. In this study, 390 patients with stable asthma were randomised to MD or DD treatment when asthma worsened, receiving a study inhaler which was either a placebo or matched their usual ICS dose. Patients were instructed to add the study inhaler for 14 days if their morning peak flow fell by 15% from run-in mean or if their daytime symptom score increased by one point from run-in median score. These criteria defined mild worsening of asthma, as seen by the fact that both criteria were permitted to be exceeded during the 2-week run-in period. During the 12-month study, 57% of patients in the active group and 45% of those in the placebo group commenced their extra inhaler. No significant differences were observed between the treatment groups in relation to the need for prednisolone (risk ratio 0.8; 95% confidence interval (CI) 0.45–1.4; $p=0.53$). The authors concluded that the findings provide little support for the recommendation that patients taking ICS should double the dose when asthma control is deteriorating. Once again, severe exacerbations were infrequent, with only 12% of the control group commencing prednisolone during the study.

A recent study by RICE-MCDONALD *et al.* [16] also compared the effectiveness of doubling ICS dose with maintaining usual ICS dose. This study was a three-way randomised, double-blind, double-dummy crossover comparison of placebo, 7 days of doubled inhaled fluticasone dose, and 7 days of oral dexamethasone (0.1 mg·kg$^{-1}$·day$^{-1}$), given in addition to usual inhaled fluticasone dose for successive exacerbations defined from symptoms or PEF. Altogether, 35 patients were randomised, and 22 contributed exacerbation data. Due to the placebo arm, the investigators specified early treatment failure criteria (3 days); these were met by 13 out of 21 (62%) patients receiving placebo, 11 out of 19 (58%) patients receiving doubled ICS, and five out of 19 (26%) receiving OCS. Only treatment with OCS improved PEF by a statistically significant ($p=0.006$) and clinically relevant amount, and achieved a PEF >80% predicted for the group as a whole. Prospective recording of side-effects identified a high rate of mood change, insomnia and change in appetite during OCS therapy. Although the numbers in this study were small, dose of maintenance ICS at exacerbation, and hence the ICS dose which was achieved by doubling, appeared to be a predictor of response to doubled ICS dose ($p=0.04$), as treatment success was more common if fluticasone dose taken during exacerbations was $\geqslant$2,000 μg (five out of eight, 63%) compared with <2,000 μg (three out of 11, 27%). This suggests that, although the strategy of doubling ICS dose is generally ineffective for treatment of exacerbations, success may partly depend on the total daily ICS dose taken during the exacerbation. However, no such association was seen by FITZGERALD *et al.* [15], in an

analysis of patients receiving MDs of $\leqslant$400 μg and >400 μg budesonide at entry.

These three randomised, placebo-controlled studies have failed to show benefit from doubling the dose of ICS to treat exacerbations. No specific data are available from these studies about patients taking combination therapy. LABA therapy was prohibited in the study by FITZGERALD *et al.* [15]. In the study by HARRISON *et al.* [7], 35–40% of subjects were using LABA at entry, but subgroup analysis was not performed. In the study by RICE-MCDONALD *et al.* [16], 68% of subjects were using LABA, and no effect was seen on outcome.

### *Increasing ICS to high doses to treat exacerbations*

Several studies have examined the effect on outcome of exacerbations of using high doses of ICSs, either over 1–2 weeks in community patients or patients discharged from hospital, or in ED studies over a period of several hours.

#### Constant low ICS dose *versus* five-fold increase in ICS dose

The efficacy of a five-fold increase in budesonide dose for management of exacerbations was examined as part of a study by FORESI *et al.* [17]. In this study, subjects were initially treated for 1 month with budesonide 800 μg *b.i.d.*, then randomised to 6 months treatment as follows. Group 1: budesonide 400 μg *b.i.d.* plus placebo *q.i.d.* for exacerbations. Group 2: budesonide 100 μg *b.i.d.* plus budesonide 200 μg *q.i.d.* for exacerbations. Group 3: budesonide 100 μg *b.i.d.* plus placebo *q.i.d.* for exacerbations. Additional treatment for exacerbations was given for 7 days. Significant differences in the number of exacerbations were seen between groups 1 and 3 ($p<0.04$) and between groups 2 and 3 ($p<0.025$). In treated patients (n=209), the number of patients who experienced at least one exacerbation in group 3 (n=24, 32%) was significantly higher than in group 1 (n=11, 16.4%; $p<0.04$) and group 2 (n=12, 17.9%; $p<0.05$). In addition, the number of days during which patients in group 3 received OCS (116 days) was significantly higher than in group 1 (37 days, $p<0.001$) and group 2 (47 days, $p<0.001$). These results suggest that increasing budesonide dose from 200 μg·day$^{-1}$ to 1,000 μg·day$^{-1}$ for short periods during exacerbations is as effective as a standard maintenance budesonide dose (800 μg·day$^{-1}$), and may lead to a reduction in the number of exacerbations compared with low-dose treatment alone. However, the fact that exacerbations were defined by the same criterion for commencing the additional inhaler, namely a fall in PEF on $\geqslant$2 consecutive days to <70% baseline mean, and the fact that the majority of exacerbations were single exacerbations, suggests the possibility that the difference in exacerbations between groups 2 and 3 may have occurred by chance, as the randomised step-up treatment was only commenced in each case after an exacerbation (the primary outcome variable) had been registered.

#### Increased ICS dose for 1–2 weeks *versus* OCS

In a double-blind, double-dummy study of 413 adults with acute exacerbations in primary care, LEVY *et al.* [18] compared inhaled high-dose fluticasone 1 mg *b.i.d. via* a volumatic spacer with a short reducing course of oral prednisolone (starting at 40 mg and reducing by 5 mg every 2 days) for 16 days. There was no significant difference in the number of treatment failures between the two treatment groups (27% for ICS, 22.7% for OCS), with the reasons for treatment failure also being similar in the two groups (mainly being a reduction in PEF or failure to improve symptoms). Due to under-recruitment, the study was underpowered for the pre-determined 10% difference in failure rate between the treatments. Improvements in PEF, of the order of 12% pred, were very similar for the two treatments.

Two further double-blind, double-dummy studies have examined the use of high-dose ICS compared with OCS after discharge from the ED. In these two studies, treatment during the ED presentation included a single dose of systemic corticosteroids. NANA *et al.* [19] investigated whether high-dose inhaled budesonide may substitute for OCS after an acute asthma exacerbation. Eighty-one patients discharged from the ED were randomised to receive either budesonide Turbuhaler 1,600 μg *b.i.d.* or prednisolone reducing from 40 to 5 mg over 7 days, and were followed up at 7 days. The mean increase in $FEV_1$ at follow-up was similar in both groups, with no statistically significant difference between the groups. There was no significant difference in PEF increase between the two groups. The mean clinical symptom scores were numerically higher in the budesonide group, but the difference was not statistically significant.

FITZGERALD *et al.* [20] compared the incidence of asthma relapse in 175 patients discharged from the ED, randomised to 7–10 days of inhaled budesonide 2,400 μg·day$^{-1}$ (given in divided doses *q.i.d.*) or prednisolone 40 mg daily. All patients received one dose of systemic corticosteroid (either 125 mg methylprednisolone or oral prednisolone 40–60 mg) before randomisation. Relapse rates were comparable between the budesonide and prednisolone treatment groups, and there were no significant differences in improvements in $FEV_1$, PEF or symptoms between the groups.

EDMONDS *et al.* [53] reviewed the above three studies, together with four paediatric studies which also examined use of ICS instead of OCS after discharge from the ED. There was considerable variation in the choice of outcome measures in these studies, leading to difficulties in pooling data. EDMONDS *et al.* [53] considered relapse rate to be the most important outcome, although they noted that relapse to the point of needing additional medical care was infrequent after mild-to-moderate exacerbations. From the meta-analysis, the authors concluded that ICS alone did not appear to be less effective than standard corticosteroid therapy for acute asthma, but that there was insufficient evidence to state that they were of equivalent efficacy. The latter concern was based on the width of the 95% CI around the odds ratios (OR) for relapse rate (1.0 (0.66–1.52)). The authors concluded that there was some support for the use of ICS alone in mild asthmatics, but no evidence to support this practice in moderate or severe acute asthma. Data for adult and paediatric studies were not analysed separately.

A further study by LEE-WONG *et al.* [21], described by its authors as underpowered, compared inhaled flunisolide 2,000 μg *b.i.d.* with prednisone 40 mg·day$^{-1}$ for 7 days after admission to hospital, with all subjects initially receiving eight doses of *i.v.* corticosteroids. Similar improvements in PEF, $FEV_1$ and symptom scores were seen in both groups at 7 days.

A recent study by DI FRANCO *et al.* [22] compared 2 weeks of treatment with high-dose fluticasone (1,000 μg *b.i.d.*) or oral prednisone (40 mg·day$^{-1}$ reducing to 10 mg·day$^{-1}$) in 37 adults presenting to an asthma clinic with at least 5 days' of symptoms, with FEV1 ⩽70% pred and ⩽80% recent best but not requiring hospitalisation. Baseline FEV1 was ~50% pred. The study included sputum examination (spontaneous or induced), and the majority of the exacerbations were found to be eosinophilic. High-dose fluticasone, compared with prednisone, produced similar improvements after 2 weeks in lung function, symptom score and bronchodilator use, but greater improvements in sputum eosinophilia. In the study, the randomised treatment was given in place of the patients' usual ICS treatment.

### Repeated high ICS dose in the ED

Four randomised, placebo-controlled studies have examined the early use of high-dose ICS by metered-dose inhaler and spacer, repeated over a period of several hours, in adults presenting to the ED with acute severe asthma. In these studies, the study treatments were given in addition to usual bronchodilator therapy.

GUTTMAN *et al.* [23] compared inhaled beclomethasone 7000 μg (n=30) or placebo (n=30), given double-blind in addition to two doses of *i.v.* methylprednisone, with the study medication divided into five doses over 8 h. Baseline FEV1 was ~30% pred in both groups. This study showed no significant difference over 12 h between *i.v.* steroid and *i.v.* steroid + high-dose ICS in lung function, dyspnoea or vital signs. There was a trend toward reduced admissions in the ICS group (27% *cf.* 40%, OR 0.55 (95% CI 0.18–1.62)).

AFILALO *et al.* [24] compared beclomethasone 5,000 μg (n=28) and placebo (n=26), given double-blind in five divided doses over 4 h, in ED patients with baseline FEV1 ~50% pred. Systemic corticosteroids were not given within the study period. This study showed no significant difference in lung function up to 6 h, but a trend to reduced admissions with ICS (7% *cf.* 19%, OR 0.32 (95% CI 0.06–1.84)).

RODRIGO and RODRIGO [25] compared very high doses of inhaled flunisolide (1,000 μg every 10 min for 3 h, total 18 mg, n=47) and placebo (n=47) in a double-blind, randomised study of patients with acute asthma in the ED. At baseline, mean FEV1 was 26–28% pred. In the study, PEF was significantly higher in the flunisolide group at all time points after commencement of treatment (p=0.01), and the difference in PEF between groups increased with time (p=0.0001). The same pattern held for changes in FEV1 with a significant difference existing between groups in favour of flunisolide (p=0.04). There was a significant reduction in admissions with high-dose ICS (8.5% *cf.* 26%, OR 0.27 (0.08–0.92)).

The previously mentioned three ED studies of high-dose ICS, together with three similar studies in children, and an additional placebo-controlled study which examined a single low dose (200 μg) of beclomethasone in adults [26], were examined in a Cochrane review by EDMONDS *et al.* [54]. The overall conclusion was that early ICS treatment in the ED resulted in reduced admission rates and improved lung function. For adults, the OR for admission to hospital (=treatment failure) was 0.38 (95% CI 0.18–0.79). There were few reported side-effects with high-dose ICS treatment.

More recently, RODRIGO [27] compared the effect of repeated doses of inhaled high-dose fluticasone (500 μg every 10 min for 3 h, total 9,000 μg) with 500 mg *i.v.* hydrocortisone, in 106 adult patients with severe acute asthma (PEF or FEV1 <50% pred) in the ED. The study medications were administered in double-blind, double-dummy fashion, and all subjects also received salbutamol and ipratropium bromide. Mean baseline FEV1 was 30% pred. In this study, the improvements in PEF and FEV1 were significantly greater in patients receiving fluticasone ($p<0.05$ and p=0.04, respectively). The difference in PEF and FEV1 between groups also increased significantly with time (p=0.001 for both). A significantly greater number of patients in the fluticasone group reached discharge threshold during the 3 h of treatment. A subgroup analysis showed that patients with more severe obstruction (FEV1<1.0 L) showed a significantly greater increase in pulmonary function (p=0.001) and decrease in hospitalisation rate (p=0.05) with fluticasone compared with hydrocortisone.

### Single high ICS dose

LEUPPI *et al.* [28] investigated whether a single dose of 3,200 μg budesonide increased the rate of recovery from asthma exacerbations, which had been induced by reduction in ICS dose. Exacerbations were defined as PEF >3 SD below baseline mean, and increased symptoms. All subjects (n=19) were given double their last pre-exacerbation dose of ICS, and were randomised to also receive eight puffs of placebo or eight puffs of 400 μg budesonide as a single dose. The mean PEF 1 week post-exacerbation was significantly higher in the budesonide group (p=0.006). All patients in the budesonide group also experienced a symptom-free day within 5 days post-exacerbation compared with only two patients experiencing a symptom-free day in the placebo group. This difference was significant (p=0.0012). Interpretation of the results of this study is limited by the fact that, by chance, there were significant differences in severity of exacerbations between the two treatment groups, with FEV1 being significantly greater in the budesonide group compared with the placebo group at the time of exacerbation (99.7 and 79.5% predicted, p=0.04).

A study by GIBSON *et al.* [38] investigated the effect of a single dose of inhaled budesonide 2,400 μg in 26 adults with asthma who demonstrated significant sputum eosinophilia 4 days after cessation of ICSs. In this double-blind, crossover study, budesonide treatment resulted in a significantly lower sputum eosinophil count than placebo 6 h after treatment. Budesonide treatment also resulted in a 2.2-fold improvement in airway responsiveness to hypertonic saline (p=0.002) over the same period. There was no significant difference in symptom score between treatments, but subjects had been selected by their sputum profile after ICS withdrawal, without any requirement for clinical deterioration. Although this study did not examine exacerbations *per se*, the results provide support for the feasibility of high-dose ICS treatment for eosinophilic exacerbations by indicating that the anti-eosinophilic effect of high-dose ICS occurs far more rapidly than previously supposed.

Thus, several studies have shown that use of high-dose ICSs can improve symptoms and lung function during an

exacerbation to the same extent as a standard course of OCS, which, in turn, has been well-established by meta-analysis of good quality placebo-controlled studies to be effective in the management of exacerbations [51, 52]. Single high ICS doses, as well as high doses delivered in the ED over a 3–8-h period also produced improvements in symptoms and/or lung function similar, although not necessarily additive, to those which could be achieved by intravenous or OCS. It is not clear whether the final ICS dose achieved, and/or its frequency of administration, was the most important predictor of success. No specific data were available for patients on ICS/LABA combination therapy, but there is no *a priori* reason to suppose that the response to the addition of high-dose ICS during exacerbations would be different in this context.

## COMBINATION ICS/LABA IN THE MANAGEMENT OF EXACERBATIONS

### *Increased dose of budesonide/formoterol*

Several studies have assessed the efficacy and safety of acutely increasing the dose of combination ICS/LABA products for worsening asthma compared with maintaining a higher dose of ICS/LABA [29–34], and all have involved budesonide/formoterol. The criteria for ''worsening of asthma'' in these studies were similar to the criteria used in some other included studies for ''exacerbations''.

In the six budesonide/formoterol studies, patients underwent a run-in period where they received two inhalations *b.i.d.* of budesonide/formoterol (either 160/4.5 μg or 80/4.5 μg) in a single inhaler, followed by a randomised treatment period. Patients randomised to the adjustable maintenance dose (AMD) treatment arm were allowed to adjust dosing of budesonide/formoterol up to two or four inhalations *b.i.d.* for 1 or 2 weeks, or down to one inhalation *b.i.d.* for chronic dosing, depending on asthma control. Patients randomised to the fixed maintenance dosing (FMD) arm remained on two inhalations twice daily. The studies were all open-label in design.

CANONICA *et al.* [29] compared the efficacy and safety of AMD and FMD over 12 weeks. There was no significant difference in the number of exacerbations between the two treatment groups. AMD and FMD treatments also provided similar improvements in lung function in both groups. However, patients in the AMD treatment groups required significantly fewer daily inhalations of the study drug (and hence budesonide dose and total costs) compared with patients in the FMD groups ($p<0.0001$). Both treatment therapies were well tolerated with a similar frequency of adverse events in both groups.

Similar results were seen in a study by IND *et al.* [30]. This study also compared AMD with FMD over 12 weeks with the primary efficacy variables being the number of treatment successes and treatment failures. No significant difference in the proportion of patients experiencing treatment failures was seen within each group. There was a statistically significant but small difference in change in morning and evening PEF, favouring the FMD arm. Once again, a significant difference was seen for the number of inhalations of study medication ($p<0.05$) and for mean daily ICS dose, favouring the AMD arm. Use of reliever medication was lower in the AMD groups ($p<0.001$).

LEUPPI *et al.* [31] also compared AMD with FMD over 12 weeks, with the primary efficacy variables being the number of treatment successes and failures. No significant difference was seen in the number of exacerbations or in symptom severity grade between the two groups. Like the other studies, patients in the AMD group used significantly less study medication ($p<0.0001$). There was also a significant shift to a lower symptom severity status ($p=0.004$) and a lower frequency of nocturnal awakenings ($p=0.006$) in patients in the AMD group. Although reliever use was infrequent, it was significantly higher in the FMD group ($p<0.0001$).

In a study by BUHL *et al.* [32], the effect of AMD on health-related quality of life and asthma control was compared with FMD. The primary efficacy variable was the change in overall Asthma Quality of Life Questionnaire (AQLQ) score over 12 weeks. The AMD regimen was one inhalation *b.i.d.* of budesonide/formoterol, increasing to two or four inhalations *b.i.d.* when required for worsening asthma; the FMD comparator was two inhalations *b.i.d.*. During the randomisation period, there were small nonsignificant improvements in both groups in AQLQ, PEF, symptom severity score and nocturnal awakenings. The number of treatment failures/exacerbations did not differ between treatment groups. Similar to other studies, patients on AMD in this study used significantly fewer inhalations of budesonide/formoterol overall than patients on fixed dosing ($p<0.001$).

In an earlier study by STALLBERG *et al.* [33], the efficacy of AMD and FMD was reviewed over a 6-month treatment period. Unlike the above studies, this study showed that a lower proportion of patients in the AMD group experienced one or more exacerbations compared with the FMD group ($p=0.049$), and the time to first exacerbation was longer with AMD ($p=0.05$). Most of the exacerbations were identified by the use of OCS or treatment at a medical care unit. There was no significant difference in the proportion of patients experiencing exacerbation between the 80/4.5 μg and 160/4.5 μg strengths of budesonide/formoterol ($p=0.46$). As in the other studies, AMD patients used fewer inhalations per day of budesonide/formoterol than patients in the FMD group ($p<0.001$). However patients in the AMD group had a slightly greater use of reliever medication compared with the FMD group ($p=0.0011$). Nocturnal awakenings were rare in both groups, but more frequent in the AMD group ($p=0.011$).

Likewise, the study by FITZGERALD *et al.* [34] also showed that AMD reduced asthma exacerbations compared with traditional FMD. In this study, the primary efficacy variable was the proportion of patients experiencing asthma exacerbations. With AMD compared with FMD, the relative risk reduction of exacerbations was 55% ($p=0.002$), and the time to first exacerbation was longer ($p=0.001$), with a 47% reduction in mean number of severe exacerbations ($p=0.02$). As in the other studies, patients in the AMD groups used significantly fewer inhalations of budesonide/formoterol than patients on FMD ($p<0.001$). In this study, the use of OCS was also higher in the FMD group.

In summary, while two of these six studies showed that using AMD for management of worsening asthma resulted in a significant reduction in the number of episodes which

progressed to exacerbations, compared with continuing a higher MD, the other four studies showed no significant differences in asthma outcomes between treatment groups. Although these studies could potentially be evaluated by meta-analysis, the combination of an open label design and the inclusion of OCS treatment as a diagnostic criterion for exacerbations would still preclude any definitive conclusions about the efficacy of this approach in the management of worsening asthma. If a patient presented with worsening asthma, and the clinician knew that his/her budesonide/formoterol dose could be increased four-fold (AMD group), the clinician would be less likely to prescribe OCS immediately, for the same current level of severity, than if the maintenance medication could not be adjusted (FMD group). As many asthma exacerbations resolve spontaneously, any such systematic delay in prescribing OCS would increase the probability of a reduction in the frequency of their prescription, hence favouring the AMD arm in exacerbation rate. However, the AMD studies showed that at least equivalent outcomes with regard to exacerbations could be achieved with significantly lower doses of maintenance budesonide/formoterol than with fixed higher-level dosing.

#### *Use of budesonide/formoterol for maintenance and relief*

The above studies have essentially been superseded by studies in which budesonide/formoterol has been used both for maintenance and relief (called ''Single-Inhaler Therapy'' or ''Symbicort® for Maintenance and Relief'' (SMART)) [39]. In the context of the present review, these studies constitute a special case. This approach is obviously relevant to the management of worsening asthma in patients already taking Symbicort®, but their design merges the previously distinct concepts of long-term maintenance treatment to prevent exacerbations, and short-term treatment of worsening asthma. The large double-blind study by O'BYRNE *et al.* [40] compared three different maintenance regimens, namely moderate-dose budesonide with as-needed terbutaline for symptoms, low-dose budesonide/formoterol with as-needed terbutaline, and low-dose budesonide/formoterol with as-needed budesonide/formoterol, over 12 months of treatment. Severe asthma exacerbations (the primary outcome variable) were defined, as in the FACET study [8], by healthcare utilisation, OCS treatment, and/or PEF $\leqslant$70% baseline on two consecutive days. Subjects using budesonide/formoterol as maintenance and relief had a significantly longer time to first exacerbation and reduction in number of exacerbations than subjects in the other two arms. Symptoms, reliever use and PEF were significantly better for this group than with either the same dose of budesonide/formoterol as fixed maintenance treatment or a higher dose of maintenance budesonide. The choice of treatment arms for this study clarified issues raised by the earlier study by SCICCHITANO *et al.* [39], which compared low-dose maintenance budesonide with terbutaline as needed, and low-dose maintenance budesonide/formoterol with budesonide/formoterol as needed. The latter study also showed significantly better outcomes for the group receiving budesonide/formoterol as maintenance and relief. These studies used a double-blind study design so, unlike the previously-mentioned open-label AMD studies, it is appropriate to attribute the observed difference in exacerbation rates to the use of as-needed budesonide/formoterol in place of as-needed terbutaline. With the SMART Symbicort® approach, outcomes were better than with a higher dose of budesonide for maintenance treatment, but current interest lies in the question of whether the differences between the other two groups were attributable to as-needed budesonide or formoterol or whether both were important.

As indicated above, the SMART Symbicort® studies constitute a special case in the context of discussions about exacerbation management. The observed lengthening of time to first exacerbation with budesonide/formoterol as maintenance and relief could have been due to the effect of the long-term management regimen, *i.e.* by improved asthma control leading to secondary prevention of exacerbations, and/or it could have been due to the further increase in as-needed budesonide/formoterol dosing, which would have occurred in response to increased symptoms during the early stages of an exacerbation, *i.e.* prevention by early treatment of exacerbations. This distinction cannot be drawn from the currently published studies, but is of great interest in terms of the pathogenesis of exacerbations. Despite the lack of certainty about its theoretical mechanism of action, this treatment approach appears to result in substantial reductions in need for OCS use or healthcare utilisation, with lower ICS doses, and may circumvent the need for specific definitions for mild-to-moderate exacerbations for patients using Symbicort® therapy. Further studies are needed to examine the use of this approach in patients with poor perception of airway obstruction.

#### *Acute use of budesonide/formoterol during exacerbations*

A study by BALANAG *et al.* [35] examined the efficacy and safety of budesonide/formoterol (1,600/48 μg in two doses) by Turbuhaler® (AstraZeneca Liquid Production, Södertälje, Sweden) compared with salbutamol (1,600 μg in two doses) by metered-dose inhaler and spacer, in the treatment of 103 patients with acute asthma in the ED. The improvements in $FEV_1$ with budesonide/formoterol were similar to those with salbutamol at all time points to 3 h, with a lower pulse rate in those treated with budesonide/formoterol. Only a small proportion of subjects (10%) had been taking LABA prior to entry, and no separate data are available for these subjects.

#### *Increased dose of salmeterol/fluticasone for exacerbations*

No studies have examined the efficacy or safety of increasing the dose of salmeterol/fluticasone combination therapy for treatment of asthma exacerbations. One randomised double-blind study examined the safety of doubling salmeterol/fluticasone for a period of 2 weeks in adults with stable asthma [55]. This study showed no difference in side-effects, including Holter monitoring, serum glucose and serum potassium, between subjects receiving single dose and DD Seretide Accuhaler® (GlaxoSmithKline, Middlesex, UK).

## $\beta_2$-AGONISTS IN THE MANAGEMENT OF EXACERBATIONS

The general role of SABAs in the self-management of asthma exacerbations is well-established, with the main interest in recent years relating to the ED management of acute severe asthma, such as the supplementary role of other medications including *i.v.* aminophylline [56] or *i.v.* or nebulised magnesium [57, 58], or the mode of delivery of $\beta_2$-agonist (intravenous, metered-dose inhaler and spacer, and nebuliser) [59,

60]. The finding that, in exacerbations severe enough to warrant ED treatment, metered-dose inhaler plus spacer is as effective as a nebuliser for delivery of $\beta_2$-agonist [60] is also relevant to self-management of exacerbations, suggesting that patients do not need to go to the expense of purchasing a nebuliser for home use.

There has been considerable interest in recent years about the potential advantages of using levalbuterol, the (*R*)-isomer of albuterol, although it is more costly than racemic albuterol. For regular administration in chronic stable asthma, the evidence from randomised double-blind studies is mixed, with one study supporting [61] and one not supporting [62] a therapeutic advantage for levalbuterol. There do not appear to have been any double-blind studies comparing levalbuterol and racemic albuterol in the management of asthma exacerbations in adults, and several recent double-blind studies in acute asthma in children have failed to find a therapeutic advantage for levalbuterol [63–65]. The observed development of bronchodilator tolerance with regular administration of SABA [66] is obviously of concern in the context of increasing $\beta_2$-agonist usage during asthma exacerbations, but the initial suggestion that such tachyphylaxis may be due to (*S*)-albuterol [61] appears not to be supported by evidence [67, 68].

#### *Efficacy of SABAs in ICS/LABA treated patients*

The issue of bronchodilator and bronchoprotective subsensitivity to $\beta_2$-agonist is also highly relevant in the context of regular use of LABA [69–75]. Some studies investigated the impact of such subsensitivity on the acute effectiveness of salbutamol [69, 72–75], and some on the acute effectiveness of the LABA itself [70, 71, 76], but all showed a reduced acute response to $\beta_2$-agonist in patients treated with regular LABA. Some of these studies showed that bronchodilator subsensitivity produced by $\beta_2$-agonists could be partially reversed by the administration of corticosteroids [70, 71, 74], while others did not [76–78]. These studies were all performed in patients with stable asthma in a controlled laboratory setting, with FEV1 reduction achieved by challenging patients with methacholine [72, 73, 75], adenosine monophosphate [71] or histamine [69].

Only one study, by KOROSEC *et al.* [79], evaluated the effectiveness of albuterol in a clinical emergency setting in patients who had been using regular salmeterol. In this study, 114 acutely ill asthmatic patients (57 who took regular salmeterol and 57 who did not) with mean PEF 40–45% predicted were treated with nebulised albuterol, either three doses of 2.5 mg at 20-min intervals (n=33 in each group) or two doses of 5.0 mg 20 min apart (n=24 in each group). Both albuterol regimens improved peak flow. There were no significant differences in percentage improvements in peak flow between the salmeterol group and the control group (low-dose albuterol group/salmeterol 64% *versus* control 52%, p=0.13; high-dose albuterol group/salmeterol 47% *versus* control 44%, p=0.78). There were also no significant differences between the control group and the salmeterol group in the mean length of stay, proportion of subjects admitted to hospital or the number of return visits. Without random allocation, this study does not exclude a reduction in efficacy of SABA in patients using LABA at the time of an exacerbation, but suggests that such patients will respond to standard ED doses of SABA.

However, outside the context of the very high doses of salbutamol that are routinely given in the ED, it is still possible that patients taking LABA may need to use more actuations of SABA at home to relieve bronchoconstriction than patients not using LABA.

#### *LABAs in the management of exacerbations*

TURNER *et al.* [36] studied the effect of 3 weeks of treatment with salmeterol 50 μg *b.i.d.* in patients with mild eosinophilic asthma exacerbations with post-bronchodilator FEV1 $\geqslant$75% pred or personal best, in a randomised double-blind comparison with beclomethasone 500 μg *b.i.d.* and placebo. Salmeterol and beclomethasone led to a similar improvement in clinical measures, with the difference from placebo only significant for salmeterol; however, importantly, a reduction in sputum eosinophils was seen only with beclomethasone. This study was restricted to subjects with exacerbations of at least 2-weeks' duration, with sputum eosinophils $\geqslant$4%, and, thus, may have included patients with progressive loss of asthma control rather than acute exacerbation, two conditions which may have different pathophysiology [2]. Nevertheless, the study highlights the limitations of conventional clinical measures in assessing response to treatment of exacerbations.

A double-blind, double-dummy study by BOONSAWAT *et al.* [37] examined the acute efficacy of 54 μg formoterol by Turbuhaler® (AstraZeneca Liquid production) compared with 2,400 μg salbutamol by metered-dose inhaler and spacer, each given in three divided doses over 1 h, in 88 patients presenting to the ED with acute asthma. This study showed similar bronchodilatation at 75 min (37% *versus* 28%, p=0.18) and greater bronchodilatation at 4 h (51% *versus* 36%, p<0.05) with formoterol compared with salbutamol. Only four subjects (5%) had been using LABA prior to entry, two in combination with ICS.

## ANTICHOLINERGICS IN THE SELF-MANAGEMENT OF EXACERBATIONS

A meta-analysis of ED studies concluded that nebulised anticholinergic agents, given with $\beta_2$-agonist, are associated with a reduction in hospitalisations and an increase in lung function compared with $\beta_2$-agonist alone [41]. In an analysis of subgroups [41], no evidence was found for efficacy of anticholinergics in patients with ''mild acute asthma'', a category which included all patients with pre-treatment PEF >200 $L \cdot min^{-1}$ [80] or pre-treatment FEV1 >30% pred [42], *i.e.* well below the range that would usually be managed at home. Thus, although some patients may benefit from commencing an anticholinergic agent at home during exacerbations, there is no evidence at present to support their general use in exacerbation self-management. No specific information is available about efficacy of anticholinergics in patients taking LABAs.

## OTHER PHARMACOLOGICAL INTERVENTIONS

GRAHAM *et al.* [81] reviewed the evidence for use of antibiotics for acute asthma, but found only one relevant study in adults. The study by GRAHAM *et al.* [82], published in 1982, found that lung function was significantly higher in subjects treated with

placebo compared with amoxicillin. Despite the lack of evidence, antibiotics appear to be widely used in the management of asthma exacerbations, with surveys of general practitioners in France [83] and of charts of hospitalised patients in Chicago [84] each showing that approximately two-thirds of patients with acute asthma were given antibiotics. Recent research interest has focussed on the use of macrolides in the management of acute asthma exacerbations [85]. Novel pharmacological options for the treatment of virus-induced asthma exacerbations have recently been reviewed by EDWARDS *et al.* [86].

## INFLAMMATORY PROFILE OF EXACERBATIONS

The examination of sputum cellular profile or exhaled nitric oxide level (eNO) at the time of exacerbation, currently available only in a few centres, may provide further insight into the treatment of exacerbations, particularly where heterogeneity in response is observed either within or between studies. When the sputum profile has been examined during spontaneous acute exacerbations, some investigators have found primarily eosinophilic exacerbations [39, 87] and others, primarily neutrophilic exacerbations [43, 45, 88], particularly in those of viral origin [45, 89]. Such differences in the inflammatory profile during exacerbations may be due to factors such as differences in the aetiology of the exacerbations, and differences in the maintenance treatment used by the study populations. The inflammatory profile may affect the outcome of treatment of exacerbations, as there is evidence from stable asthma that a neutrophilic profile may be associated with a reduced response to corticosteroids [47]. DI FRANCO *et al.* [22] found high levels of sputum eosinophils (geometric mean levels of 38–52%) during spontaneous exacerbations, with no association between change in sputum eosinophils and change in FEV1. WARK *et al.* [45] found mean eosinophil percentages of 1.5% in viral exacerbations and 7% in nonviral exacerbations, with a significant difference between these groups in lung function both during exacerbation and 4–5 weeks later after corticosteroid treatment.

Levels of eNO are increased both in ICS-reduction exacerbations [90] and during rhinovirus infections [91], but the relationship of eNO levels with treatment response is likely to be complex, as higher eNO levels appear to be protective during viral infection [91].

## SAFETY DATA

This review originally intended to identify published data about the safety of exacerbation treatment as well as its efficacy. Although some safety data were presented in most of the reviewed papers, the information provided was often quite brief, making it difficult to draw general conclusions about the safety of the various treatments trialled. For general conclusions about safety to be drawn, a more comprehensive safety review would be required. One problem with existing publications is that side-effects of OCS, such as mood changes and insomnia, are often not considered by patients to be ''health problems'', and hence they may be under-represented with routine collection of clinical trial adverse events. A high rate of such side-effects was observed in the study by RICE-MCDONALD *et al.* [16] when specific questionnaires were administered. The same situation applies to some side-effects of inhaled medications, such as hoarseness or anxiety.

The potential side-effects of treatment options for management of exacerbations may affect patients' adherence with their action plan. For example, patients may be unwilling to comply with an action plan which goes straight from usual maintenance treatment to OCS, because of the real or perceived side-effects of the latter. JANSON *et al.* [3] found that 31% of patients would delay seeking medical attention for acute asthma because of fear of being given systemic corticosteroids.

## CURRENT CLINICAL PRACTICE GUIDELINES FOR SELF-MANAGEMENT

The bulk of information provided in current clinical practice guidelines for management of asthma exacerbations relates to the context of healthcare settings, either the primary care office or the ED. Given that presentation to a healthcare facility is usually a *de facto* indication of a severe exacerbation, it is only appropriate that considerable attention should be paid by guideline documents to the management of exacerbations in this context.

All of the current major guidelines also provide strong evidence-based recommendations [5] for the use of written action plans for self-management of exacerbations. Emphasis is placed on tailoring the content of the action plan to the individual patient. Most of the guidelines provide clear and detailed instructions for use of SABA, which will not be further itemised here, and give specific instructions about dose and duration of OCS therapy. However, much less information is provided about adjustments to inhaled therapy.

The 1997 USA guidelines [92] provide a flow chart for self-management of mild-to-moderate asthma exacerbations, defined as PEF 50–80% pred or personal best, symptoms of cough/breathlessness/wheeze/chest tightness or waking at night due to asthma, or decreased ability to perform usual activities. For adults who have a ''good response'', as assessed 1 h after initial SABA treatment (no symptoms, response to $\beta_2$-agonist sustained for 4 h [sic], PEF >80% pred or personal best), the guidelines recommend doubling of the ICS dose for 7–10 days. For patients with incomplete response, oral steroids are recommended at a dose of 40–60 mg for 3–10 days. As these guidelines were published in 1997, management of exacerbations in patients taking combination therapy is not discussed.

The British Thoracic Society guidelines (2003 update) [93] refer to the inclusion of doubling of ICS dose in previous guidelines and action plans, and state that this is of unproven value. Reference is made to the finding of a decrease in severity of exacerbations with a five-fold increase in low-dose ICS [33], but it is stated that this should not be extrapolated to higher doses of inhaled steroids. No other instructions are given about adjustments in ICS dose for self-management of exacerbations, but space is provided for adjustment of ICS dose in the action plan template which is provided (annex 8). The guidelines state that there is no evidence that ICS should be substituted for OCS in patients with acute severe or life-threatening asthma. The dosage of OCS which is recommended is 40–50 $mg \cdot day^{-1}$ for at least 5 days or until recovery, with no tapering provided the patient is on ICS therapy and has

received OCS for <3 weeks. Management of exacerbations in patients on combination therapy is not discussed.

In the section on home management of exacerbations, the Global Initiative for Asthma guidelines [94] describe limited support for the utility of increasing ICS early in an asthma exacerbation, citing the study by FORESI *et al.* [17]. The guidelines recommend use of OCS (0.5–1 $mg \cdot kg^{-1} \cdot day^{-1}$ prednisolone or equivalent) ''to speed resolution of all but the mildest exacerbations''. It is suggested that OCS are needed if the response to rapid-acting inhaled $\beta_2$-agonist alone is not prompt or sustained, such as if PEF is not >80% pred or personal best after 1 h. However, considerably more information about ICS studies is given in the subsequent section on hospital-based management of exacerbations, where the community-based studies of doubling ICS by HARRISON *et al.* [7] and FITZGERALD *et al.* [15] are cited. Several studies, described earlier in this review, which examined the use of high-dose ICS in the ED or post-discharge management of acute asthma, are also mentioned. The guidelines draw attention to the cost-effectiveness of a short course of oral prednisone, but note that if patients are intolerant of or not willing to take oral prednisone, similar results may be obtained with very high doses of ICS.

## CONCLUSIONS FOR SELF-MANAGEMENT OF EXACERBATIONS

The conclusions of this review article, and the extent of evidence available from randomised controlled trials, are summarised below. Many studies have been conducted in the ED, and the results are not necessarily generalisable to the less-severe exacerbations which may be managed by the patient at home. Some of the information presented in the review, although useful for the general management of exacerbations, may be difficult to extrapolate to the population of patients currently using single inhaler combination products. This is largely due to the fact that in many cases subset analyses of this patient group were not performed, or the information was either not provided or did not exist.

### *OCS to treat exacerbations*

OCS are an accepted and effective way of treating severe asthma exacerbations. The literature indicates that for severe exacerbations, OCS are effective when continued for 7–10 days after an exacerbation. There does not appear to be any significant benefit in extended therapy beyond this time. Upon the completion of therapy, OCS can be ceased abruptly. Tapering does not reduce the incidence of relapse and hence is not required, except for reduction of side-effects.

OCS have been used in clinical trials as the first line treatment of severe exacerbations in patients on combination therapy. Regarding duration of treatment and tapering, the advice given above for exacerbations in general is also presumed to be appropriate for patients taking combination therapy.

### *Doubling ICS dose to treat exacerbations*

The common practice of doubling ICS dose to treat exacerbations, although simple to implement, is not supported by published evidence. In three studies, doubling the ICS dose did not result in greater improvements in asthma outcomes or in the prevention of the need to use OCS. No separate data were available for patients on ICS/LABA combination therapy.

### *Increasing ICS to high doses as an alternative to OCS to treat exacerbations*

Increasing ICS to high doses as an alternative to OCS to treat exacerbations is supported by evidence in adults. Studies that used ICS doses equivalent to 2,400–4,000 μg beclomethasone for a period of 1–2 weeks during mild-to-moderate exacerbations demonstrated improved symptoms and lung function, with effects similar to those of conventional doses of OCS. The final ICS dose achieved and the frequency of administration may be important predictors of success. Single high ICS doses also produced improvements in symptoms, airway inflammation and airway hyperresponsiveness in the context of ICS withdrawal. No specific data were available for patients on ICS/LABA combination therapy.

When ICSs are chosen to treat an exacerbation, physicians should consider using daily doses of up to 2,000 μg of fluticasone or 3,200 μg of budesonide or equivalent for a period of 7–14 days. This may be achieved by adding a high-dose ICS inhaler to usual maintenance ICS or ICS/LABA therapy. For ease of administration, and potentially for better efficacy, the extra ICS should be divided through the day. OCS remain the treatment of choice for exacerbations which are severe or which fail to respond to high-dose ICS, but a recent study showed that very high ICS doses delivered over 3 h in the ED produced greater effects than *i.v.* corticosteroids during severe exacerbations.

### *Acutely increasing dose of inhaled ICS/LABA therapy to treat exacerbations*

A number of studies have compared the effectiveness of a two-to-four fold increase in budesonide/formoterol dose when asthma worsens *versus* fixed higher-level maintenance dosing, with the prevention of exacerbations as a primary outcome measure. Two studies showed reduced exacerbations, and four did not. No definitive recommendations can be made regarding acutely increasing the dose of maintenance budesonide/formoterol for the treatment of exacerbations, other than that this approach allows lower maintenance ICS/LABA doses and appears to be safe. There are no studies of increased fluticasone/salmeterol for management of worsening asthma or exacerbations.

### *Use of inhaled ICS/LABA for maintenance and relief*

The use of budesonide/formoterol for maintenance and relief is supported by evidence of reduced exacerbation rates in two studies. It is not clear whether this is attributable to long-term prevention of the initiation of exacerbations or to very early treatment of mild exacerbations preventing their progression to threshhold-defined severe exacerbations. There are no studies using fluticasone/salmeterol in this way.

### *SABAs in management of exacerbations*

There is strong evidence for the efficacy of SABAs in the management of exacerbations. There are no double-blind randomised controlled trials examining the use of levalbuterol (the *R*-isomer of albuterol) in exacerbations in adults, compared with racemic albuterol.

### *Efficacy of SABAs in ICS/LABA-treated patients*

The use of SABAs in ICS/LABA-treated patients is supported by evidence. Long-term therapy with a LABA is associated with some bronchodilator subsensitivity. Despite this, SABAs are still effective in producing bronchodilation; however, a higher dose may be required. SABAs should continue to play an important part of any asthma management programme, and should be used as rescue medication during exacerbations. It is important to advise patients on ICS/LABA therapy to have a SABA inhaler on hand and to use this during an exacerbation, as some patients mistakenly believe that they should not use SABA once they start combination therapy. Patients should also be advised that a larger dose of SABA may be required to produce bronchodilation and symptom relief than was required prior to beginning combination therapy. Patients should therefore be advised to use as much SABA as required to produce relief from symptoms, and to present for medical attention if they fail to obtain relief. Use of spacer devices should be encouraged for administration of SABA during exacerbations.

### *Addition of anticholinergic agents to SABA*

Although anticholinergic agents are effective in management of severe exacerbations in the ED, no additional benefit over SABA alone has been seen in subanalysis of patients with less severe exacerbations, such as would be managed in the community. Thus, the addition of anticholinergic agents to SABA is not supported by evidence for mild-to-moderate exacerbations.

### *Safety of interventions for treatment of exacerbations*

There is insufficient evidence from the present review to comment on the safety of interventions for the treatment of exacerbations.

## FURTHER STUDIES

There is a need for further community-based studies to clarify remaining issues about therapeutic interventions for self-management of asthma exacerbations, particularly with regard to cost-effectiveness, side-effects of treatment and patient acceptability. In view of the findings of this narrative review, particularly from more recent studies, several areas would be suitable for meta-analysis to quantify the magnitude of benefit. In view of differences between adults and children in aetiology of exacerbations, in maintenance treatment, and in reliability of lung function testing, it would be preferable to analyse adult and paediatric studies separately. It would also be preferable to separately analyse mild-to-moderate exacerbations and severe exacerbations, in order to provide more specific information for those writing asthma action plans for self-management of exacerbations.

Exacerbations are the cause of most of the morbidity and mortality due to asthma, and they contribute considerably to the burden of disease for patients. Although their incidence is reduced to low levels by current medication regimens, they are not eliminated completely. There is a continuing need to advise patients about how to manage exacerbations, once they occur, in order to reduce discomfort and risk. Written action plans have been shown to be effective within self-management education, but clinicians need more specific information about the treatment adjustments to record in these plans. The studies identified by the present review suggest that consideration should be given to changing some of the information in current guidelines in order to improve self-management of exacerbations in clinical practice.

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