

What Color is Your Yellow Zone? Is There a Role for Escalation of Anti-inflammatory Therapy Short of an Oral Corticosteroid Burst?

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ABSTRACT

Current asthma management guidelines advise management of mild asthma exacerbations with short-acting beta agonists, followed by consideration of a short course of systemic corticosteroids. Problems with this approach include lack of effect of beta agonists on flareup progression, and the toxicity of systemic corticosteroids. There is a need for a management strategy for mild exacerbations intermediate between beta agonist only and addition of systemic corticosteroids. Randomized controlled clinical trials on doubling doses of inhaled corticosteroid AFTER an asthma exacerbation is established have shown no benefit; however, this strategy may be too little, too late. Other randomized controlled clinical trials have examined either escalation from low- to high-dose inhaled corticosteroid (quadrupling dose) or escalation of the inhaled corticosteroid concurrently with the beta agonist in an inhaler that combines both medications (i.e., one combination inhaled steroid + rapid acting beta agonist inhaler for both “maintenance” and “quick relief”). These studies have demonstrated significant benefit from the early and aggressive escalation of the inhaled corticosteroid component. Another randomized controlled clinical trial has demonstrated benefit from the intermittent use of montelukast with asthma flares in children who are well between flares. In contrast to the recommendations of current asthma guidelines, these recently published studies demonstrate that sufficient escalation of asthma controller therapy sufficiently early in an asthma exacerbation can reduce the progression of a mild exacerbation, and should be considered as a treatment option for the management of mild exacerbations of asthma. (Pediatr Asthma Allergy Immunol 2008; XX(X):XX–XX.)

INTRODUCTION

ASTHMA IS A CHRONIC INFLAMMATORY DISORDER of the airways that causes recurrent episodes of coughing, wheezing, breathlessness, and chest tightness.¹ Regular use of inhaled corticosteroid medication to control the inflammation reduces asthma morbidity and mortality. Frequent use of beta agonist bronchodilator medication—particularly in the absence of an inhaled corticosteroid—is associated with increased

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asthma morbidity and mortality. The use of a short burst of systemic corticosteroids for acute asthma exacerbations has been shown to reduce the duration and severity of the exacerbation.²

Although the benefit of oral corticosteroid medication for the treatment of moderate to severe asthma flareups is documented and well accepted, the therapy for mild asthma exacerbations is less well defined. Some mild flareups will resolve on their own with only symptomatic care. Others will progress to moderate or severe flareups. Ideally, one would like to have an effective and nontoxic intervention that when instituted in a mild flare would attenuate progression and speed resolution.

The literature review for the National Asthma Education and Prevention Program Expert Panel Report-3 was completed in March 2006; studies published subsequent to that date may not be reflected in the guideline recommendations. These guidelines suggest that for mild to moderate asthma exacerbations, treat with inhaled short acting beta agonists, and if response is incomplete, add an oral corticosteroid.¹ There are two major problems with this approach. The first is that short-acting beta agonist administration will not prevent a mild exacerbation from progressing; it only provides temporary symptom relief. The second is that oral corticosteroids, although effective, have significant toxicity even in short bursts. An effective strategy is needed to attenuate the progression of a mild to moderate exacerbation that involves more than short acting beta agonists but less than oral corticosteroids.

Current guidelines advise initiation or escalation of daily asthma controller therapy if there are two or more exacerbations requiring oral corticosteroids per year.¹ It has been shown that the regular use of inhaled corticosteroid medication reduces exacerbations needing oral corticosteroid “bursts,” reduces urgent care, and hospitalization rates.^{3,4} The problems with this recommendation include (1) The need to wait for two moderate to severe exacerbations before escalating therapy, and (2) nonadherence to the regular use of asthma controller medication is common.^{5,6}

Although effective, oral corticosteroids are not benign

In short bursts oral corticosteroids affect a child’s mood and behavior, causing anxiety, mania, irritability, and/or aggressive behavior.^{7,8} Systemic corticosteroid therapy can increase the risk for developing tuberculosis disease⁹ and severe varicella infection,¹⁰ a concern in communities where these diseases are endemic. Long-term oral corticosteroid therapy leads to severe adverse effects, including suppression of growth, osteopenia, cataracts, adrenal suppression, hypertension, “cushingoid” body habitus, easy bruising, acne, and myopathy.¹¹

Clinical experience and biologic plausibility suggest that frequent oral corticosteroid bursts can lead to adverse effects similar to those observed with long-term therapy; however, few studies have examined this issue. One “negative” study examined 83 children who presented to an emergency department with acute asthma, and evaluated their bone metabolism, bone density, and adrenal function. They found no difference in bone density Z-score after 12 months of follow-up in children who received repeated bursts of oral corticosteroids compared with unexposed children with asthma. There was a mean of four and a minimum of two systemic corticosteroid bursts in the preceding year in the exposed group. The comparison “unexposed” group was an average of 5 years older than the exposed group (11 years versus 6 years). Limitations of this study include small sample size and the substantial age discrepancy in the exposed versus unexposed groups.¹² In contrast, a study of 35 adults with asthma (mean age 60) found a significant decrease in bone mineral density over a 4-year period for those who received frequent short courses of oral corticosteroids (>2.5/year, mean of 26 courses over 4 years) compared to those who received only sporadic short courses (<2.5/year, mean of 2.3 courses over 4 years) of oral corticosteroids.¹³

Doubling dose of inhaled corticosteroids: Too little too late?

Studies evaluating the efficacy of doubling the inhaled corticosteroid dose in established asthma flareups have failed to show a benefit. The treatment approach of these studies could be considered *too little, too late*.

A clinical trial of 390 adults with current asthma on an inhaled corticosteroid randomized participants to doubling their inhaled corticosteroid dose versus placebo in case of a deterioration of asthma control, defined by a drop in peak flow of 15% from baseline or increase in symptom score by one point. There was

no difference in the need for prednisolone or symptom scores between placebo and active treatment groups.¹⁴ A clinical trial of 290 patients ≥ 13 years with current asthma on a stable inhaled corticosteroid dose converted participants to an equivalent dose of daily budesonide and randomly assigned participants to doubling dose budesonide versus placebo. The additional inhaler was started if two of the following criteria were met: peak flow fell to $\leq 80\%$ of the best on two consecutive readings, bronchodilator use ≥ 4 inhalations per day on 2 consecutive days, waking at night from asthma on 2 consecutive nights, asthma score increased by ≥ 3 on 2 consecutive days, unable to go to school or work due to asthma for 2 consecutive days, or unscheduled physician visit due to asthma. There were no between-group differences in the rate of treatment failures, symptom scores, or beta agonist use.¹⁵ A clinical trial of 22 adults with asthma who required daily inhaled corticosteroid medication compared short acting beta agonist + placebo, short-acting beta agonist + doubling dose-inhaled corticosteroid, and short-acting beta agonist + oral corticosteroid. Asthma exacerbations requiring use of study medication were defined as waking at night for 2 out of 3 nights due to asthma, requiring reliever medicine on four occasions more than baseline in a 24-hour period or on 2 out of 3 days. Participants served as their own controls in this randomized crossover design study. Treatment failure rates were similar between placebo and doubling dose of inhaled steroid (62% versus 58%, $p = 0.7$) and lower for oral corticosteroids (26%, $p = 0.02$ versus placebo).¹⁶ A study of 28 6- to 14-year-old children with asthma and on an inhaled corticosteroid converted subjects to beclomethasone MDI as daily therapy. A doubling dose of beclomethasone versus placebo was given if peak flow dropped below 80% of baseline for 24 hours or more, the child was woken at night with cough or wheeze, or bronchodilator requirement doubled. The study medicine was given for 3 days, following which the patient was examined by a pediatrician and given “definitive” treatment. There were no differences in peak flow or symptom scores between treatment and control groups.¹⁷ A study of infants at risk for developing asthma because of a first episode of wheezing and a history of maternal asthma were randomized to either budesonide 400 $\mu\text{g}/\text{day}$ or placebo for a 2-week period starting after 3 days of respiratory symptoms. Terbutaline was given for use as needed. There were no differences between groups in either respiratory symptoms or progression to persistent wheezing.¹⁸

It is important not to extrapolate the findings beyond the questions studied. Doubling of a low-dose inhaled corticosteroid can still leave one with a relatively low dose; perhaps to be effective a much higher dose is needed. Doubling of a high dose may have one already at or near the top of the dose-response curve and thus limit the benefit. Each of these studies waited to initiate treatment until after the episode was well established. Waiting until the peak flow has dropped by more than 15% to 20% or the presence of significant symptoms for 2 days or more prior to dose escalation may be waiting until the window of opportunity has passed. Perhaps if escalation of inhaled corticosteroid medication is to be effective, the dose increase needs to be substantial and initiated at the very first signs of an asthma exacerbation.

Quadrupling inhaled corticosteroid dose or inhaled corticosteroid/rapid acting beta agonist as maintenance and reliever: To be effective, start early and hit hard

There have recently been published several randomized, double-blind placebo-controlled clinical trials that suggest benefit from either inhaled corticosteroid dose quadrupling (i.e., from low to high dose) or dose escalation at the very onset of symptoms.

A clinical trial of 220 adults with persistent asthma were randomized to one of three groups, budesonide 400 μg b.i.d. + placebo in case of exacerbation, budesonide 100 μg b.i.d. + placebo in case of exacerbation, and budesonide 100 μg b.i.d. + budesonide 200 μg q.i.d. in case of exacerbation (quadrupling dose). An exacerbation was defined as a peak expiratory flow drop to $< 70\%$ of baseline. The number of exacerbations, number of days with exacerbations, and requirement for oral corticosteroids was lower in the high-dose Budesonide and low-dose daily dose + quadrupling dose as needed compared to the low-dose + placebo groups.¹⁹ These results suggest that low-dose inhaled corticosteroid with quadrupling dose as needed provides equivalent control compared to daily high-dose inhaled corticosteroid and superior control to continued low-dose inhaled corticosteroid.

A large clinical trial of 3,394 teenagers and adults with symptomatic asthma placed all participants on budesonide 160 $\mu\text{g}/\text{formoterol}$ 4.5 μg b.i.d. via turbuhaler. Participants' quick reliever medication was

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randomly assigned as budesonide 160 μg /formoterol 4.5 μg , formoterol 4.5 μg , or terbutaline 0.4 mg via identical appearing turbuhaler. The time to exacerbation, severe exacerbations (194 versus 296 and 377 events) and emergency room visits (70 versus 98 and 115 events) were all decreased in the group that received budesonide/formoterol for maintenance + reliever use compared to the other groups.²⁰ An analysis of the pediatric data from the Symbicort® Maintenance and Relief Therapy trial examined 341 children ages 4–11 with current asthma on a stable inhaled corticosteroid dose. Patients were randomized to a maintenance budesonide 320- μg daily plus terbutaline reliever as needed versus maintenance budesonide 80 μg /formoterol 4.5 μg combination daily plus terbutaline reliever as needed versus maintenance budesonide 80 μg /formoterol 4.5 μg combination daily with additional doses of the combination product as needed for symptom relief. When the budesonide/formoterol combination as maintenance plus reliever group was compared to the Budesonide/formoterol maintenance and the higher dose Budesonide maintenance groups, there were fewer exacerbations requiring medical intervention (8% vs 31% and 20%, respectively, $p < 0.02$) and fewer oral corticosteroid days (32 versus 230 and 141, respectively, $p < 0.0001$).²¹

A placebo-controlled clinical trial of adults with mild persistent asthma randomized 466 patients to one of four treatment groups, as needed beclomethasone 250 μg /albuterol 100 μg as a fixed dose combination inhaler, as needed albuterol 100 μg , 250 μg beclomethasone twice daily + albuterol 100 μg , and beclomethasone 250 μg /albuterol 100 μg as a fixed dose combination inhaler plus albuterol 100 μg as needed. Time to first asthma exacerbation and number of exacerbations per patient-year was improved for those on “as needed” combination therapy and regular beclomethasone therapy compared to those on regular combination therapy or albuterol as needed. The cumulative beclomethasone dose was lower in those on as needed combination therapy compared to those on regular beclomethasone therapy.²²

The results of these double-blind, placebo-controlled randomized clinical trials provide Level I evidence showing a benefit of escalation of inhaled corticosteroid dose concurrent with the long- or short-acting beta agonist dose, with the benefit attributable to the inhaled corticosteroid dose escalation and not the beta agonist dose escalation. In contrast to the “doubling dose” studies that showed no benefit, these studies incorporated early (with first perception of need for quick relief medicine) and substantial (from low to high dose or concurrent with escalation of beta agonist dose) inhaled corticosteroid dose escalation. Similar results were found in adults and school-age children.

Epidemiologic data supporting a role for the intermittent use of inhaled corticosteroids

Large population studies have used medication dispensing data from health plan claims databases to examine effect of medication dispensing patterns on risk for adverse asthma outcomes. A nested case-control study of asthma mortality using data from Saskatchewan Health found a significant reduction in asthma mortality risk associated with increasing levels of inhaled corticosteroid medication dispensing. Risk reductions were observed even at dispensing levels consistent with the intermittent use of the medication.²³ A study of Medicaid-insured children with asthma who required short-acting beta agonist dispensing four times a year or more found that hospital-based events (hospitalizations and emergency department visits) were reduced even at inhaled corticosteroid-dispensing levels that were not consistent with regular use of the medication.²⁴ Although both of these studies show greater reductions in adverse outcomes with increasing number of inhaled corticosteroid-dispensing events, at levels of dispensing consistent with intermittent medication use (i.e., two to four dispensing events per year), benefit is still seen.

Montelukast for intermittent use?

A study of intermittent montelukast use enrolled 220 children 2–14 years (mean age, 4.4 years) with asthma that was asymptomatic between episodes but who had at least three and less than six asthma flares in the prior 12 months of sufficient severity to require either three urgent care visits or one hospitalization. Subjects received either montelukast or placebo at the onset of asthma or upper respiratory tract infection symptoms, and continued the medication for a minimum of 7 days or until symptoms had resolved for 48 hours up to a maximum of 20 days. Two hundred two (92%) children received at least one dose of study medication. The study found fewer acute care visits for asthma in the active treatment group compared to

placebo (163 versus 228 visits, $p < 0.01$) as well as decreased symptom score (14%, $p < 0.05$), decreased interruption of the child's school/child care (37%, $p < 0.0001$), and decreased interference with parent's work (33%, $p < 0.0001$).²⁵

Very high-dose inhaled corticosteroids for asthma exacerbations

Several studies have looked into the use of inhaled corticosteroids at very high doses for the treatment of moderately severe asthma exacerbations in the emergency department or urgent care setting. These studies used inhaled corticosteroid doses much higher than the maximum recommended doses, leading to an increased potential for steroid related side effects.

A clinical trial of 106 adults presenting to the emergency department with acute asthma, in addition to treatment with albuterol and ipratropium, were randomized to received either 500 μg of fluticasone via MDI/spacer every 10 minutes for 3 hours (i.e., 9 mg of inhaled fluticasone) or 500 mg of intravenous hydrocortisone as a single dose. There was no difference in need for hospitalizations (four in fluticasone, six in hydrocortisone, $p = 0.7$). Peak flow and FEV₁ % predicted was greater in the fluticasone group than the hydrocortisone group starting at 90 minutes and continuing until the end of the 3-hour treatment period.²⁶ In contrast, a randomized clinical trial of 2 mg (2,000 μg) of fluticasone versus 2 mg/kg prednisolone (60 mg maximum) among 69 children who presented to the emergency department with acute asthma found more rapid and greater improvement in the FEV₁ in the prednisolone group than the fluticasone group.²⁷

A recent Cochrane review of inhaled corticosteroids in the emergency department treatment of asthma concluded that very high-dose inhaled corticosteroid decreases admissions rates compared to placebo; however, there is insufficient evidence that inhaled corticosteroid therapy alone can be used to replace systemic corticosteroid therapy.²⁸ Furthermore, very high-dose inhaled corticosteroids are more likely to lead to steroid side effects, are less convenient to administer, and are more expensive than most oral corticosteroids.

What these studies don't address

The studies of inhaled corticosteroid dose escalation that have shown benefits did not address the issue of individuals already using high daily doses of inhaled corticosteroid. Escalation of inhaled corticosteroids from high dose to very high dose may yield side effects similar to oral corticosteroids, hence limiting its benefit relative to a short oral corticosteroid burst. Individuals at high risk for asthma mortality (prior ICU admission or intubation, multiple recent hospitalizations or emergency department visits, using more than two albuterol canisters per month, etc.¹) have not been specifically addressed in these studies. In the high-risk situation, it would be prudent to have a lower threshold to escalate to systemic corticosteroids.

CONCLUSION

Reliance on rapid-acting beta agonists and oral corticosteroids for the treatment of mild asthma exacerbations is not ideal. Beta agonists do not prevent progression of a flareup. Oral corticosteroids, although effective, have significant toxicity. Although a "doubling dose" of inhaled corticosteroid initiated after a flareup has become established has been shown to be ineffective, there is now good evidence from randomized, controlled clinical trials demonstrating that inhaled corticosteroids and montelukast can provide substantial benefit when the dose is escalated or initiated sufficiently early in an asthma flareup—at the very onset of symptoms.

Although there is evidence suggesting a benefit of very high-dose inhaled corticosteroids in the treatment of asthma exacerbations in the emergency department, the inconvenience, cost, and dose level required make this a less attractive option compared to oral corticosteroids.

Taken together, these studies demonstrate that for escalation of inhaled corticosteroid medication to be effective, the escalation needs to be substantial and early. Waiting for the exacerbation to become established may allow an important window of opportunity to pass. Escalation of inhaled corticosteroid dose in parallel with the rapid acting beta agonist dose, as in a combination inhaler, is an elegant and simple way

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to achieve this goal. Although giving the same medication in separate inhalers should yield similar results, it is likely that use of the combination product would improve adherence to escalation of the inhaled corticosteroid component.

ACKNOWLEDGMENTS

Edward G. Brooks, M.D., reviewed the manuscript and provided helpful suggestions.

AUTHOR DISCLOSURE STATEMENT

The author states that no competing financial interests exist.

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