Ann Allergy Asthma Immunol 121 (2018) 18–21

Contents lists available at ScienceDirect

Oral corticosteroids should be available on-hand at home for the next asthma exacerbation!

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ARTICLE INFO

Article history:
Received for publication March 3, 2018.
Received in revised form March 30, 2018.
Accepted for publication April 2, 2018.

Introduction

Asthma is characterized in many patients by recurrent exacerbations. For such patients, it is generally not a question of whether an exacerbation will recur but rather *when* the next one will occur. Unfortunately, this is not readily predictable. Patients with asthma exacerbations fill emergency rooms and represent a major cause of hospitalizations. Children with asthma are particularly prone to recurrent exacerbations, and asthma is the most frequent medical indication for hospitalization of children.[1] Treatment of asthma in emergency rooms and hospitals consists primarily of bronchodilators and systemic corticosteroids. Although bronchodilators are readily provided for use at home, provision of oral corticosteroids to be on hand for early treatment of an exacerbation is associated with controversy and has not been routinely practiced. However, because parents can generally identify early signs of an exacerbation, these medications, if available on hand at home, could be given before the need for urgent medical care.

The following discussion does not address the issue of measures to control persistent asthma or prevent exacerbations. The reality is that exacerbations occur for many patients regardless of treatment efforts to avoid them. The focus of this Perspective is instead to address effective and early treatment of these exacerbations to prevent acute care visits and hospitalizations.

What is an Asthma Exacerbation?

There is general agreement that acute asthma is an exacerbation when the asthma symptoms become more frequent or severe and do not improve sufficiently with usual bronchodilator treatment. The consequence can be prolonged respiratory symptoms that interfere with sleep and activity, or progression of respiratory distress such that urgent medical care and hospitalization are needed. This occurs because of airway mucosal edema and mucous secretions, which is the inflammatory component of asthma that narrows the bronchial lumen. That component of airway obstruction is not prevented or eliminated by bronchial smooth muscle relaxation, the primary effect of bronchodilators.

What is the Evidence That Oral Corticosteroids Can Alter the Course of an Exacerbation?

Some may consider the answer to this question self-evident, but controlled evaluations of corticosteroids have not consistently demonstrated clinical benefit, even with severe exacerbations.[2] The controversy has been particularly apparent when the effect of parent-initiated corticosteroids was examined in the preschool-age group with the common pattern of viral respiratory infection–induced episodes of wheezing and respiratory distress.[3] Although that study showed no benefit from administration of corticosteroids, treatment of preschool-age children with high-dose systemic corticosteroid in the emergency room substantially and significantly decreased the frequency of hospital admission as early as 3 hours after the treatment.[4] Moreover, a more recent randomized, placebo-controlled clinical trial in the same age group demonstrated significant clinical efficacy of corticosteroids.[5]

Because both absence of benefit and significant therapeutic effect have been reported for systemic corticosteroids, we need to examine variables in patient selection and details of corticosteroid treatment that could have influenced outcomes of those studies. This is a critical issue; if corticosteroids are effective in the emergency department setting, then it would be reasonable to expect them to be effective if administered earlier at home during an exacerbation.

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Disclosures: Authors have nothing to disclose.

https://doi.org/10.1016/j.anai.2018.04.004

What About High-Dose Inhaled Corticosteroids at Onset of an Exacerbation?

Administration of high-dose inhaled corticosteroids at onset of exacerbation is a strategy used by some physicians with clinical impressions of benefit. However, a double-blind, placebo-controlled trial of 254 children, 5–11 years of age and receiving maintenance inhaled corticosteroids, had their dose either increased to 5 times maintenance or continued unchanged. The conclusion was that quintupling the dose of inhaled corticosteroids at the first signs of an exacerbation did not reduce the rate of severe exacerbations or improve other asthma outcomes.[6] Multiple studies of high-dose inhaled corticosteroids for exacerbations done more than 30 years ago also found little or no difference from placebo in preschool-age children.

What Has Already Been Published Related to Use of Corticosteroids by the Patient or Family at the Onset of a Self-Recognized Exacerbation?

The first randomized, double-blind, placebo-controlled trial of prednisone for treating an asthma exacerbation at home was reported in 1987.[7] Parents of 41 school-age children whose asthma had been associated with previous exacerbations were provided with a week's prednisone sufficient for 30 mg twice daily (under age 13 years) or 40 mg twice daily (13-year-olds or older) or placebo to be on hand at home for the next exacerbation. Parents were instructed to begin the study medication at onset of symptoms that were incompletely responsive to bronchodilators. Worsening of symptoms was treated by a protocol-directed rescue. Although none of the prednisone-treated patients required the rescue treatment, 42% of the placebo-treated patients required rescue. However, 58% of the placebo-treated patients improved at a rate similar to that of the prednisone-treated patients. Although the difference in the frequency of rescue between prednisone- and placebo-treated patients was statistically significant, those patients who spontaneously improved were not initially distinguishable from those whose symptoms increased and were rescued. If sufficient numbers of children in a study improve spontaneously, treatment effect in the sample studied may not be apparent.

Examining other studies provides additional examples of conflicting results and interpretations. No clinical benefit could be identified in a placebo-controlled trial of 78 children addressing the effect of a single dose of oral prednisone available to parents at home to be given at the onset of an acute asthma exacerbation.[8] That study demonstrated the ineffectiveness of a single dose of corticosteroid for an asthma exacerbation. Another placebo-controlled study of at-home-initiated oral corticosteroid involved 131 children provided a 1-mg/kg, once-daily dose of prednisone given for 3–5 days (duration based on parents' observations) at the onset of a perceived exacerbation.[9] That study showed reductions in asthma symptoms, health resource use, and school absenteeism, but the authors expressed concern for recommending routine use of parent-initiated corticosteroid because of the very modest magnitude of benefit. Examination of the data suggests that the rather modest degree of benefit seen in those children could be from spontaneous improvement in many that matched any corticosteroid effect. Alternatively, a suboptimal dose or dose frequency may have minimized the detection of clinical benefit.

In a study of 23 children who had a previous year's history of frequent hospitalizations due to viral respiratory infection, prednisone was begun at the onset of a viral respiratory infection in half of the children.[10] During the subsequent year, 90% fewer hospitalizations occurred in the treated group, whereas the control group showed no decrease. In a retrospective study of 119 children with a history of episodic viral respiratory infection–induced asthma

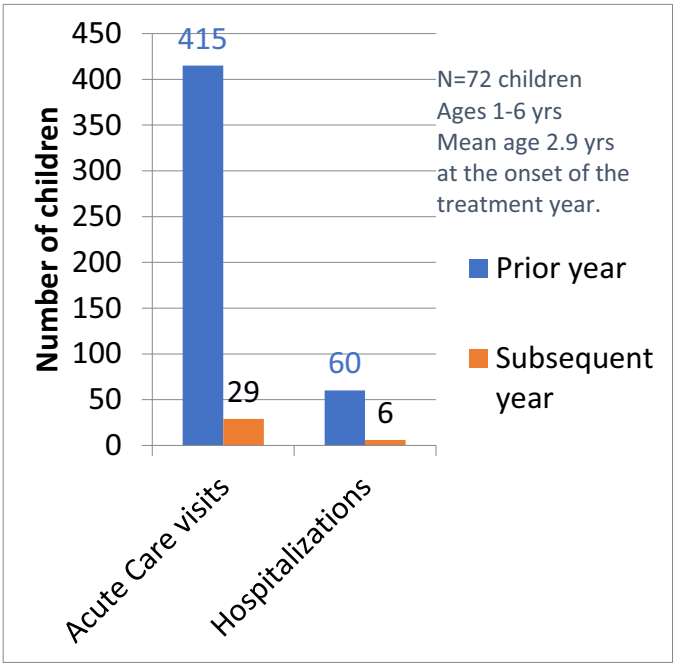

Figure 1. Number of acute care visits and hospitalizations among preschool-age children in the year before having oral corticosteroids at home and in the subsequent year when corticosteroids were provided to parents to begin at the onset of an exacerbation.[11]

referred to a pediatric pulmonary center, oral prednisone or prednisolone (prednisone and prednisolone are equivalent for dose) was provided for parents to administer at the onset of an exacerbation.[11] The frequency of urgent care visits and hospitalizations in the year after referral was substantially reduced compared with the previous year. This reduction also occurred in the preschool-age children included in that study (Fig 1). In another study of home corticosteroid use during asthma exacerbation in 132 children at a tertiary care center, there was a significant decline in emergency department visits per person per year when compared with a prior period when oral corticosteroids were not on hand for home use.[12] The 3 studies[10-12] described in this paragraph were conducted in children with a history of exacerbations severe enough to require acute care visits and hospitalizations. Thus, they were more likely to demonstrate significant beneficial effects from early corticosteroid administration.

Can We Identify the Variables That Influence the Differing Outcomes of the Various Studies?

Examination of earlier studies provides clinically relevant insights. Patient selection appears to be one factor. Asthma is a highly variable clinical problem and patients with mild self-limited acute symptoms are probably much more common than those with more severe or prolonged exacerbations. Spontaneous improvement was apparent in many of the studies. The inclusion of many patients with a rate of spontaneous improvement that matches or exceeds the rate of benefit from corticosteroids may result in apparent absence of significant effect.

Variation in doses used in the studies is another factor that can influence outcome. Guidelines from the 3 Expert Panel Reports from 1991 to 2007 of the National Asthma Education and Prevention Program included recommendations of 1–2 mg/kg/d for both preschool-age and older children with an upper limit of 60 mg/d. Dose frequency recommendations varied and were not included in some of the recommendations. An evidence base for the EPR

recommendations was not provided. To our knowledge, dose recommendations appear to be based more on custom or tradition, and may have been arrived at primarily by BOGSAT (ie, a "bunch of guys sitting around a table").

Is there more evidence-based information regarding dose that may influence study outcomes? This may be especially true for preschool-age children where studies have suggested an absence of benefit from recommended doses of corticosteroids during viral respiratory infection–induced exacerbations. Studies of preschool-age children with nephrotic syndrome demonstrated that a mg/kg dose appropriate for older children underdoses the preschool-age child with nephrotic syndrome in contrast to the larger dose determined by body surface area.[13] That is likely also true for asthma.

What is the optimal dose of corticosteroid for acute asthma? The dose–response effect of corticosteroids in adults admitted to intensive care with an asthma exacerbation was examined at 15, 40, and 120 mg every 6 hours. Earlier onset and greater improvement in forced expiratory volume in 1 second occurred at each progressively higher dose.[14] The top of the dose–response curve will, of course, vary with individual disease severity. Patients with less severe airway inflammation may attain maximal effect at a lower dose than severely obstructed patients, but a higher dose is likely to provide greater effect and thereby benefit more patients.

What about dosing interval? The studies examining home administration of corticosteroids included both once- and twice-daily administration. There are no controlled data in children providing guidance for once- or twice-daily dosing, but a study involving stable adults demonstrated peak flow decreasing 9 hours after a dose and not different from placebo at 12 hours.[15] This finding provides a rationale for 12-hour rather than once-daily dosing of prednisone.

Is earlier administration of an oral corticosteroid clinically advantageous?

To assess the value of earlier administration of corticosteroids in the emergency room, outcomes of 644 children with an asthma exacerbation compared triage nurse initiation of oral corticosteroid treatment with administration after physician evaluation.[16] Nurse initiation was associated with reduced times to clinical improvement, earlier discharge, and reduced admission rates. In another study of 406 children (mean age, 4 years) in an emergency room, 50% of patients received systemic corticosteroids within 75 minutes, whereas it was delayed in 33% of the patients.[17] The authors observed that administration of systemic corticosteroids within 75 minutes of triage decreased hospital admission rate and length of active treatment. These studies support early administration of systemic corticosteroids during an exacerbation. Even earlier administration would occur if corticosteroid was given at home at the onset of a perceived exacerbation.

What are the Risks of Administration of Oral Corticosteroids at Onset of a Perceived Exacerbation?

Prolonged use of daily oral corticosteroids is associated with well-recognized risks of serious adverse effects, including growth suppression, change in body habitus, and bone demineralization. However, the risk of a short course of oral corticosteroid is not apparent, even if repeated several times over the course of a year.[18] Concern regarding potential misuse of corticosteroids by parents when available at home can be managed by the prescribing physician providing written and oral instructions (Table 1), reinforced by regular follow up.

Providing no refills for the corticosteroid without prescribing physician contact minimizes misuse and provides an opportunity for the prescribing physician to review instructions. With those precautions, the benefits from oral corticosteroids available at home for the next exacerbation far outweigh the risks. Preventing prolonged morbidity, need for urgent medical care, and hospitalization are the likely benefits, In the authors' experience, it is rare that parents misuse the corticosteroids. Any deviation from instructions by parents can be addressed before the next corticosteroid refill.

Table 1
Measures to Maximize Benefit and Minimize Risk for Home Use of Oral Corticosteroid to Treat an Asthma Exacerbation

- Instruct the patient and family regarding how to recognize an impending exacerbation—questioning them regarding previous experience can provide useful guidance.
- Provide an adequate dose, usual milligram-per-kilogram dose tends to underdose smaller preschool-age children; the absence of reliable dose–response data for children suggests that erring high may be more likely to prevent urgent care.
- Instruct the patient/family to notify the prescribing physician, once the oral corticosteroid has been started.
- The oral corticosteroid should be continued until the increase in symptoms stop, whether 3, 5, or 7 days, so long as progressive improvement is occurring; tapering is not indicated.
- Patient/family should contact prescribing physician if symptoms not beginning to improve within first 2–3 days or gone by 7 days.
- Adjust dose if unacceptable minor side effects of the corticosteroid dose used.
- Provide verbal and written instructions regarding appropriate use of oral corticosteroid—repeat verbal instructions at scheduled follow up.
- Review appropriateness and effect of corticosteroids after each use through communication before refill—no refills without contact.
- Prescribing physician responsible for adequate follow-up to review patient/family understanding and management of exacerbations. We all learn from repetition.

Providing an Oral Corticosteroid to be on Hand at Home is Rational, Humane, and Good Medicine!

There are 2 medication groups routinely given if a patient seeks urgent care for acute asthma: β-agonist bronchodilators and systemic corticosteroids. Providing a bronchodilator such as albuterol to have on hand for acute symptoms of asthma is routine and generally accepted as the standard of care. However, the continued transient effect of a bronchodilator, even while airway inflammation progresses, can delay seeking care and has been associated with fatalities from progression of airway obstruction.[19] In contrast to the risks of using only bronchodilators during an exacerbation, early addition of a corticosteroid has not been associated with increased risk of fatality.

Thus, providing corticosteroids to have at home for early use during an exacerbation is rational and evidence-based. Not beginning an oral corticosteroid in a timely manner increases the likelihood of prolonged morbidity, urgent care, hospitalization, and occasionally death. Consequently, that is not a humane practice. The World Health Organization and the US National Quality Forum have increasingly emphasized patient and family engagement in medical care as a means of improving medication safety.[20] Providing a corticosteroid to have at home for early use during an exacerbation is rational and humane and provides patient and family engagement in improving management of a chronic disease. Because of the importance of being able to treat an exacerbation of asthma early with an oral corticosteroid, we routinely emphasize "Don't leave home without it."

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