

episodes requiring oral steroid treatment (<6 courses), or 1 episode requiring urgent care and oral steroid treatment.

**METHODS.** The study design was a randomized, double-blind, placebo-controlled trial, with children assigned randomly to 1 of 3 treatment groups with instructions to treat for 7 days at the onset of each RTI-associated symptom set during a 12-month period: (1) budesonide suspension (1 mg twice daily) plus LTRA placebo, (2) montelukast (4 mg daily) plus ICS placebo, or (3) ICS placebo plus LTRA placebo. All groups received albuterol 4 times per day for the first 48 hours of illness plus as-needed dosing. Orally administered steroids were available if needed, but other asthma medications were prohibited. Symptom/treatment diaries were maintained, and clinic/telephone follow-up evaluations were conducted. The primary outcome was the proportion of episode-free days (EFDs). Secondary outcomes included severity of lower respiratory tract symptoms in the 14-day period after initiation of treatment, time to initiation and number of orally administered steroids, number of wheezing episodes, days missed from day care and work, caregiver quality of life, unscheduled visits because of acute wheezing, and linear growth.

**RESULTS.** Two hundred thirty-eight children were randomly assigned and were well matched with respect to baseline characteristics. Adherence to therapy was similar between the groups. EFDs did not differ among the 3 treatment groups (adjusted EFD mean: budesonide: 76%; montelukast: 73%; placebo: 74%). Relative to placebo, there were significant reductions in trouble breathing (budesonide: 37.5%; montelukast: 36.8%;  $P = .003$ ) and interference with activity (budesonide: 31.9%;  $P = .01$ ; montelukast: 39.6%;  $P = .001$ ). Wheezing scores were reduced with montelukast (33.5%;  $P = .02$ ) but not with budesonide (24.6%;  $P = .09$ ). Overall, total symptom scores were reduced with montelukast (29.6%;  $P = .006$ ) and budesonide (24.6%;  $P = .02$ ). Among participants with positive asthma predictive index status, both budesonide and montelukast significantly reduced scores for trouble breathing (budesonide: 48.0%;  $P = .001$ ; montelukast: 40.3%;  $P = .007$ ) and activity interference (budesonide: 43.6%; montelukast: 53.7%;  $P < .001$ ); only montelukast reduced wheezing ( $P = .049$ ). Similar findings were seen for children with previous oral steroid therapy use.

**CONCLUSIONS.** For preschool-aged children with moderate-to-severe intermittent wheezing, episodic use of either budesonide or montelukast early in RTIs did not increase the proportion of EFDs. However episodic use of an ICS or LTRA decreased symptom burden, particularly for those with risk factors for asthma or greater illness severity (use of oral corticosteroid therapy).

**REVIEWERS COMMENTS.** This study was conducted to address an important clinical question: is the episodic use of an ICS or LTRA effective in decreasing the morbidity associated with severe intermittent wheezing in preschool-aged children? Using a unique study design, the authors demonstrated benefit for children with symptoms and treatment predictive of asthma, indicating consideration for the early use of antiinflammatory medications. Additional study is needed to address this important question fully.

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### Daily Versus As-Needed Inhaled Corticosteroid for Mild Persistent Asthma (The Helsinki Early Intervention Childhood Asthma Study)

Turpeinen M, Nikander K, Pelkonen AS, et al. *Arch Dis Child*. 2008;93(8):654-659

**PURPOSE OF THE STUDY.** To compare the effect on mild persistent asthma of inhaled budesonide given daily or as needed.

**METHODS.** A total of 176 children 5 to 10 years of age with newly diagnosed asthma were randomly assigned to 3 treatment groups, (1) continuous budesonide dry powder inhaler, given at 400 mg twice daily for 1 month, 200 mg twice daily for months 2 to 6, and 100 mg twice daily for months 7 to 18; (2) budesonide treatment identical to group 1 for months 1 to 6 and then placebo for months 7 to 18; or (3) cromolyn metered dose inhaler at 10 mg 3 times daily for months 1 to 18 (control group). All patients were given rescue medication (terbutaline, 0.25 mg per dose) as needed. For all groups, during exacerbations of asthma, study medication was replaced by budesonide at 400 mg twice daily for 2 weeks. Outcome measures were lung function, number of exacerbations, number of asthma-free days, and growth.

**RESULTS.** Compared with cromolyn (group 3), the initial regular budesonide treatment (groups 1 and 2) resulted in significantly improved lung function (increase in forced expiratory volume in 1 second of 9.6% vs 5.9%), fewer exacerbations per patient (0.32 vs 1.24 exacerbations), more asthma-free days (increase of 20.1% vs 4.1%), and a small but significant decrease in growth velocity. After 18 months, the lung function improvements did not differ between the groups. During months 7 to 18, patients receiving continuous budesonide treatment had fewer exacerbations per patient (0.97 exacerbations, compared with 1.69 exacerbations in group 2

and 1.58 exacerbations in group 3). Three patients in group 1 and 9 patients in group 2 were withdrawn because of asthma deterioration after 6 months of treatment. The number of asthma-free days did not differ between groups 1 and 2 but remained better than in group 3. Growth velocity was normalized in groups 1 and 2.

**CONCLUSIONS.** Regular use of budesonide afforded better asthma control but had a more systemic effect than did as-needed use of budesonide.

**REVIEWER COMMENTS.** It is not a surprise that the inhaled corticosteroids achieved better asthma control than did cromolyn and are the preferred medications. The question addressed by this study is whether inhaled corticosteroids can be used as needed versus continuously. Although these 2 approaches did not differ in lung function or number of asthma-free days, the continuous-treatment group had significantly fewer exacerbations. An accompanying editorial (Pedersen S. *Arch Dis Child*. 2008;93[8]:644–645) asks, “Do the benefits of daily inhaled steroid treatment of mild asthma outweigh the risks?” and answers in the affirmative, noting that regular use is safe (6 of 7 studies found no long-term effects on growth), as well as more effective and less expensive than any other treatment.

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### **Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children**

Ducharme FM, Lemire C, Noya FJD, et al.  
*N Engl J Med*. 2009;360(4):339–353

**PURPOSE OF THE STUDY.** To examine the efficacy and safety of preemptive, high-dose fluticasone treatment in reducing the severity of recurrent virus-induced wheezing in children.

**STUDY POPULATION.** Children between 1 and 6 years of age ( $N = 129$ ) with moderate-to-severe, virus-induced wheezing were included. The investigators tried to exclude subjects with sensitization to aeroallergens, but 7% of the randomly assigned children developed symptoms of persistent or atopic asthma during the study period.

**METHODS.** The subjects received 750  $\mu\text{g}$  of fluticasone propionate or placebo twice daily, beginning at the onset of an upper respiratory infection and continuing for a maximum of 10 days, over a period of 6 to 12 months. The primary outcome measured was the use of rescue oral

steroid treatment. Secondary outcomes included symptoms, use of  $\beta_2$ -adrenergic receptor agonists, acute care visits, hospitalizations, discontinuation of study drug administration, changes in growth and bone mineral density, basal cortisol level, and adverse events.

**RESULTS.** Over a median period of 40 weeks, 8% of upper respiratory infections in the fluticasone group led to systemic steroid treatment, compared with 18% in the placebo group (odds ratio: 0.49). However, children treated with fluticasone, compared with the placebo group, had smaller gains in height ( $6.23 \pm 2.62$  vs  $6.56 \pm 2.90$  cm) and weight ( $1.53 \pm 1.17$  vs  $2.17 \pm 1.79$  kg). There were no significant differences between the groups in basal cortisol levels, bone mineral density, or adverse events.

**CONCLUSIONS.** In preschool-aged children with moderate-to-severe, virus-induced wheezing, preemptive treatment with high-dose fluticasone, compared with placebo, reduced the use of rescue oral steroid treatment. High-dose fluticasone treatment, however, was associated with smaller gains in height and weight. Therefore, the authors concluded that this approach should not be adopted in clinical practice until long-term adverse effects are clarified.

**REVIEWER COMMENTS.** The investigators showed, on one hand, improvement in the need for oral steroid treatment for children treated with high-dose fluticasone but, on the other hand, smaller gains in height and weight for these patients. The question for the rest of us is how to incorporate these new data into clinical practice. For example, the dose of fluticasone that was used was quite substantial for small children. Was this dose on the flat part of the dose-response curve for corticosteroids? Would a smaller dose give the same benefit without the detriment? Also, how do these data apply to children with clinical allergy or risk factors for allergy?

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### **Effect of Long-term Corticosteroid Use on Bone Mineral Density in Children: A Prospective Longitudinal Assessment in the Childhood Asthma Management Program (CAMP) Study**

Kelly HW, Van Natta ML, Covar RA, et al.  
*Pediatrics*. 2008;122(1). Available at: [www.pediatrics.org/cgi/content/full/122/1/e53](http://www.pediatrics.org/cgi/content/full/122/1/e53)

**PURPOSE OF THE STUDY.** To evaluate the effects of multiple short courses of oral corticosteroid treatment and long-

**Daily Versus As-Needed Inhaled Corticosteroid for Mild Persistent Asthma (The Helsinki Early Intervention Childhood Asthma Study)**

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