

**Methods.** START was a randomized, 3-year controlled trial of budesonide versus usual asthma therapy in early-onset asthma among 7165 subjects. Three age groups (5–10, 11–17, and  $\geq 18$  years) were studied separately and collectively. All patients were allowed to receive other asthma treatments including inhaled and oral corticosteroids, according to local practice. The cost-effectiveness evaluation of the START study was conducted primarily from the health care payer perspective (direct costs) and secondarily from the societal perspective (indirect costs). The primary outcome measure for effectiveness was the number of symptom-free days. This parameter was defined as a complete 24-hour period with no asthma symptoms and has been recognized as a clinical outcome with relevance to patients, providers, and other decision-makers. Unit costs in US dollars were based on reimbursed amounts for each of the health care–resource items such as hospital days, emergency department visits, physician and nurse visits, and telephone contacts. These costs were derived from a large medical- and pharmacy-claims database. The costs for school and work losses were estimated by using standard methods.

**Results.** Compared with usual therapy, patients receiving budesonide had 14.1 more symptom-free days per year, fewer hospital days and emergency department visits, and less school and work absence. Budesonide added \$0.41 per day to direct costs. After considering indirect cost offsets related to lower school and work absence, the net expense dropped to \$0.14 per day. Early intervention was most effective and cost saving in the youngest age group.

**Conclusion.** Long-term treatment with budesonide seems to be cost-effective in patients with mild persistent asthma of recent onset.

**Reviewers' Comments.** The health care system in the United States is only now beginning to experiment with methods that will raise awareness of direct health costs for patients/consumers. Although \$0.14 per day for better asthma control sounds like a great value, any comments that we currently make to patients or parents regarding cost-effectiveness of a given therapy usually fall on deaf ears. At the present time, we can better appeal to them by touting the improved quality of life associated with fewer days with symptoms, fewer asthma attacks, and lowered hospitalization risk and also by making it clear that the risks of disease far outweigh the risks of usual doses of ICS. This latter fact, so obvious to us, needs continued restating to parents of children with asthma.

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#### EFFECTS OF SHORT-TERM TREATMENT WITH INHALED CORTICOSTEROID ON AIRWAY WALL THICKENING IN ASTHMA

Niimi A, Matsumoto H, Amitami R, et al. *Am J Med.* 2004;116:725–731

**Purpose of the Study.** To examine the effect of inhaled corticosteroids (ICSs) on thickening of the asthmatic airway wall as measured by computed tomography (CT), pulmonary function, and serum levels of eosinophilic cationic protein (ECP).

**Study Population.** Fifty-one patients (mean age:  $54.4 \pm 13.8$  years) with persistent asthma and 28 healthy controls (mean age:  $48.1 \pm 15.9$  years).

**Methods.** Patients fulfilled American Thoracic Society criteria for asthma, and none had ever received systemic or inhaled steroids, cromones, or antileukotriene agents. Ex-

clusion criteria included asthma exacerbations or respiratory tract infections within 8 weeks before enrollment or a history of smoking. Cross-sectional, thin-section CT images of the right upper lobe apical bronchus were obtained before and after treatment. Using an enlarged image on a workstation, luminal and total airway areas (in millimeters squared) were calculated after manually tracing the internal and external perimeters of the airway. The airway wall area and airway wall area as a percentage of total wall area were used as indices of airway wall thickness. In asthmatic patients, CT, blood sampling for ECP, and pulmonary function tests were performed before and after treatment with beclomethasone dipropionate (400  $\mu\text{g}$ ) administered twice daily for 12 weeks.

**Results.** Before treatment, airway wall thickness was greater in asthma patients than controls ( $P < .0001$ ). After treatment, airway wall thickness decreased by 11% ( $P < .001$ ) but remained high ( $P < .0001$  vs control). Serum ECP levels decreased significantly after treatment ( $P < .001$ ). Forced expiratory volume in 1 second ( $\text{FEV}_1$ ), forced vital capacity (FVC), and  $\text{FEV}_1/\text{FVC}$  improved significantly after treatment, but the values remained lower than in controls. The decrease in wall thickness was associated with a decrease in the level of ECP ( $r = 0.39$ ;  $P = .009$ ) and an increase in the  $\text{FEV}_1$  ( $r = 0.45$ ;  $P = .003$ ) and was inversely related to disease duration at entry ( $r = -0.38$ ;  $P = .009$ ). Posttreatment wall thickness was related to disease duration ( $r = 0.45$ ;  $P = .003$ ) and remaining airflow obstruction.

**Conclusions.** In patients with persistent asthma, treatment with inhaled beclomethasone for 12 weeks significantly reduced airway wall thickness as assessed by CT. Airway wall thickness remained significantly greater than in controls. ICSs had less of an effect on airway wall thickening in patients with long-standing asthma.

**Reviewer's Comments.** This study raises questions. Is the reduction in airway wall thickness indicative of reductions in airway inflammation? Additional studies (eg, with airway biopsy specimens) are needed to confirm this. Would earlier intervention with ICSs result in normalization of airway wall thickness? This is a particularly important question for those who treat children with asthma.

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#### EFFECTS OF INHALED FLUTICASONE PROPIONATE IN CHILDREN LESS THAN 2 YEARS OLD WITH RECURRENT WHEEZING

Teper AM, Colom AJ, Kofman CD, Maffey AF, Vidaureta SM, Bergada I. *Pediatr Pulmonol.* 2004;37:111–115

**Purpose of the Study.** To evaluate the efficacy and safety of inhaled fluticasone propionate in children  $< 2$  years old with a history of recurrent wheezing and risk factors for asthma persisting into late childhood.

**Study Population.** Subjects were 30 children, aged 7 to 24 months, with  $\geq 3$  episodes of wheeze responsive to bronchodilators and a family history of asthma, allergic rhinitis, or eczema.

**Methods.** In this double-blind study, subjects were randomized to receive either inhaled 50  $\mu\text{g}$  of fluticasone twice daily, 125  $\mu\text{g}$  of fluticasone twice daily, or placebo for 6 months. Medication was administered with a metered-dose inhaler using an Aerochamber and mask. Efficacy end points included number of wheezing episodes and number of days on which albuterol was required. Parents were trained to record these clinical symptoms and medication use on a chart. Subjects were seen monthly to assess proper use of the medication device and evaluate daily symptom

records. Safety end points included measurement of growth, serum insulin-like growth factor-binding protein 3, cortisol, osteocalcin, and alkaline phosphatase. Clinical and safety outcomes were assessed before and after 6 months of treatment in both treatment and placebo groups.

**Results.** Mean wheezing episodes were  $6.0 \pm 1.9$ ,  $1.9 \pm 1.9$ , and  $2.8 \pm 1.2$  per patient for placebo, 100- $\mu\text{g}$  fluticasone, and 250- $\mu\text{g}$  fluticasone groups, respectively. Mean days of albuterol use were  $24.3 \pm 1.3$ ,  $6.5 \pm 0.8$ , and  $9.1 \pm 0.8$  for placebo, 100- $\mu\text{g}$  fluticasone, and 250- $\mu\text{g}$  fluticasone groups, respectively. There was a significant reduction in wheezing episodes and albuterol use in the 2 fluticasone groups compared with placebo ( $P < .01$ ), but there were no significant differences between the 2 fluticasone groups. After treatment, there were no significant differences observed in serum cortisol, bone metabolism markers (insulin-like growth factor-binding protein 3, alkaline phosphatase, and osteocalcin), or growth among the groups.

**Conclusions.** The authors concluded that inhaled fluticasone (50 or 125  $\mu\text{g}$ ) given twice daily over a 6-month period improved asthmatic symptoms and had no significant adverse effects on growth, bone metabolism, or serum cortisol in children aged 7 to 24 months.

**Reviewers' Comments.** This study suggests that the use of inhaled fluticasone in young children with recurrent wheezing and a positive family history is both safe and effective. In addition, the study is one of the few pieces of evidence that off-label use of inhaled steroid administered with a metered-dose inhaler with a holding chamber and mask is effective in chronic asthma in the very young (with the caveat of monthly review of technique). The safety findings of the study are limited, unfortunately, by its very small size. It is encouraging that the children studied, who would be predicted by the Tucson Children's Respiratory Study data to be likely to develop persisting asthma, clearly respond to the therapy. The study does not address whether wheezy infants without risk factors for persisting asthma would respond to similar therapy. Larger studies including other subgroups of wheezy infants are needed to support these results.

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## INHALED CORTICOSTEROIDS AND GROWTH OF AIRWAY FUNCTION IN ASTHMATIC CHILDREN

Merkus PJFM, van Pelt W, van Houwelingen JC, et al. *Eur Respir J.* 2004;23:861-868

**Purpose of the Study.** To investigate the growth of airways and airspaces in children with moderate asthma who were treated at random with inhaled placebo or corticosteroids in a fixed dose irrespective of symptoms.

**Study Population.** Patients with moderate to severe persistent asthma who participated in a clinical trial recruited between 1988 and 1992 from outpatient clinics for respiratory medicine of Juliana Children's Hospital (The Hague, Netherlands) and Rotterdam University Hospital/Sophia Children's Hospital (Rotterdam, Netherlands).

**Methods.** Every 4 months for up to 3 years, lung function was assessed in 54 asthmatic children (initial age: 7-16 years) who inhaled 0.2 mg of salbutamol three times daily and 0.25 mg of budesonide three times daily ( $\beta_2$ -agonist [BA] + inhaled corticosteroid [ICS]) or placebo (PL) three times daily (BA + PL) in a randomized, double-blind design. Measurements were conducted before and after maximal bronchodilation. Airway growth was assessed

from the change of forced expiratory volume in 1 second and of maximal expiratory flows at 60% and 40% of total lung capacity (TLC) relative to TLC as measures of central, intermediate, and more peripheral airways. Growth patterns were compared with the longitudinal findings in 376 healthy children.

**Results.** Airway patency after maximal bronchodilation in patients on BA + PL remained reduced compared with healthy subjects, whereas in patients on BA + ICS a marked improvement was observed. No differences between patients and controls could be demonstrated for growth patterns of central and intermediate airway function. Compliance with BA + ICS was 75% of the prescribed dose, resulting in significant, sustained improvement of symptoms and postbronchodilator caliber of central and intermediate airways to subnormal within 2 months, but postbronchodilator small-airway patency remained reduced but improved compared with patients on BA + PL.

**Conclusions.** Anti-inflammatory treatment of asthmatic children is associated with normal functional development of central and intermediate airways. The reduced postbronchodilator patency of peripheral airways may reflect remodeling or insufficient anti-inflammatory treatment.

**Reviewer's Comments.** This study shows that treatment with ICS can improve several measures of lung function and promote normal lung growth in asthma but also demonstrates that residual functional abnormalities may present in asymptomatic children with asthma even with daily doses of ICSs. This suggests that anti-inflammatory treatment of children with asthma based on symptoms alone may not be enough to result in normalization of postbronchodilator airway function. There may be some ethical and practical considerations in treatment of asthmatic children in the absence of respiratory symptoms, and additional study is required to determine what is best for long-term optimal prognosis.

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## EFFECT OF INHALED STEROIDS ON LUNG FUNCTION IN YOUNG CHILDREN: A COHORT STUDY

Devulapalli CS, Haaland G, Pettersen M, Carlsen KH, Lodrup Carlsen KC. *Eur Respir J.* 2004;23:869-875

**Purpose of the Study.** To determine the use of inhaled corticosteroids (ICSs) for treating recurrent bronchial obstruction in young children up to 2 years of age and to assess possible modifying effects of ICSs on lung function in young children with recurrent bronchial obstruction.

**Study Population.** Observational, noninterventional birth cohort of 3754 newborn children (3697 with complete questionnaire data by 2 years of age); 306 children with documented recurrent bronchial obstruction by 2 years old were identified along with 306 matched controls.

**Methods.** Two tidal-flow/volume measurements were taken (1 at presentation of disease [children were steroid naive] and 1 at 2 years of age [mean ages: 11.2 and 25.6 months, respectively]) from 21 subjects who subsequently received ICS (ICS+), 33 who did not receive ICS (ICS-), and 15 controls. The mean  $\pm$  SD duration of ICS treatment was  $10.3 \pm 6.5$  months. The main outcomes were treatment with ICS and baseline ratio of time to peak expiratory flow/total expiratory time ( $tPTEF/tE$ ).

**Results.** From the entire cohort, 77 children (2.1%) and 64 of 306 children (21%) with recurrent bronchial obstruction had received ICS by 2 years of age. Baseline  $tPTEF/tE$  was significantly lower at the first visit in ICS+ subjects, as