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 ± 1.9, 1.9 ± 1.9, and 2.8 ± 1.2 per patient for placebo, 100-μg fluticasone, and 250-μg fluticasone groups, respectively. Mean days of albuterol use were 24.3 ± 1.3, 6.5 ± 0.8, and 9.1 ± 0.8 for placebo, 100-μg fluticasone, and 250-μg 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 μg) 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


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 (β2-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.

Reviewers’ 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 persist 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


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 ± SD duration of ICS treatment was 10.3 ± 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
LONG-TERM EFFECT OF BUDESONIDE ON HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTION IN CHILDREN WITH MILD TO MODERATE ASTHMA


**Purpose of the Study.** To determine the safety of 36 months of inhaled budesonide administration on hypothalamic-pituitary-adrenal (HPA) axis function in children with mild to moderate asthma.

**Study Population.** Sixty-three children enrolled in the previously published Childhood Asthma Management Program (CAMP) study with mild to moderate asthma (mean age: 9.5 ± 1.9 years). CAMP participants were between 5 and 12 years of age.

**Methods.** Children received placebo, nedocromil (16 mg/day by metered-dose inhaler), or budesonide (400 µg/day by Turbuhaler). HPA axis function was assessed at baseline and after 12 and 36 months of continuous treatment using serum cortisol levels at 0, 30, and 60 minutes after administration of 0.25 mg of adrenocorticotropic hormone (ACTH) and 24-hour urinary free-cortisol (UFC) excretion. Data for children treated with placebo and nedocromil were combined and compared with those treated with budesonide.

**Results.** Serum cortisol measurements were obtained for 54 children at 12 months (5 missed the study visit, and 4 had declines in cortisol after ACTH) and 56 children at 36 months (5 missed the visit, and 2 declined participation). After adjusting for age at randomization, race, gender, clinic, body surface area, and baseline serum cortisol level, there were no differences in serum cortisol levels during ACTH simulation testing between treatment groups. During the study, the serum cortisol levels at successive time points tended to decrease in both treatment groups. Additionally, cortisol levels of children who did and did not receive supplemental ICSs during the study were similar. Oral corticosteroids were prescribed to 6 participants before randomization (3 budesonide and 3 placebo/nedocromil), and additional courses were used during the study for exacerbations. When all groups were combined, oral corticosteroid use 4 months preceding the 12- and 36-month visits did not affect cortisol levels after ACTH stimulation. Subgroup analyses confirmed these findings, adjusting for any supplemental corticosteroid use. Technical problems allowed UFC measurement at only the 36-month visit for 56 patients. Although UFC levels were similar in both treatment groups, ICS use within the 4 months before the 36-month visit was borderline significantly lower (22 vs 34 µg/m² per 24 hours; \( P = 0.05 \)), however, oral prednisone did not show any effect. Finally, there was no difference in serum cortisol or UFC between treatment groups based on cumulative ICS dose.

**Conclusions.** There was no increased fracture risk associated with current exposure to ICSs when compared with nonusers even in individuals with current longer-term exposure, ie, ≥20 prescriptions (adjusted odds ratio: 1.15; 95% confidence interval: 0.89, 1.48). For individuals with current or previous exposure to oral steroids, the adjusted odds ratio for current long-term inhaled steroid use compared with nonuse was 1.21 (95% confidence interval: 0.99, 1.49).

**Conclusions.** The conclusions of the authors were that exposure to ICSs for asthma control. There is little information available concerning how often inhaled steroids are used during the first 2 years of life in the treatment of obstructive airway disease and limited information on the modifying effects of ICSs on the development of lung function in early life. As expected, infants with recurrent bronchial obstruction and lower lung function were treated more often with ICS compared with matched controls. Improvement in lung function in these children increased with increasing duration of treatment. This study suggests that the choice of medical therapy is often determined by the clinical state of the child, and once started, it may be a factor that can influence later outcome. More studies such as this are desirable to fully understand the role of ICSs in early life.

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Effect of Inhaled Steroids on Lung Function in Young Children: A Cohort Study
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