Results. One hundred three children remained in the study at the 4-year follow-up. Thirty-five percent had been diagnosed with asthma by pediatric allergists and 10.7% had episodes of wheezing, but were not diagnosed with asthma. Eighty-five percent of patients had specific IgE levels against at least 1 of the following 5 food allergens (egg white, milk, wheat, soybean, and rice). HDM-specific IgE increased from 11% at registration to 59% at the 1-year follow-up and 87% at the 4-year follow-up. Severity of asthma among children who developed BA showed early appearance of HDM-specific IgE and persistently high levels of food-specific IgE. Male sex, a positive family history of BA, and the appearance of HDM-specific IgE were identified as significant risk factors for the early development of BA, but the significance of these parameters decreased afterward. A positive family history of AD, the outcome of AD, and the keeping of furred pets were also identified as risk factors during part of the follow-up years. During the 4-year follow-up period, AD cleared in 33.8%, improved in 51.4%, was unchanged in 11.7% and worsened in 2.9% of the patients.

Conclusions. The early appearance of HDM-specific IgE antibodies in early childhood is a major risk factor for the subsequent development of BA in children with AD. However, the influence decreases after longer follow-up.

Reviewer’s Comments. This study supports the idea that early atopic sensitization to food is a risk factor for subsequent inhalant sensitization and, therefore, a risk factor for the development of asthma. Risk factors appeared to shift during the 4-year follow-up, but this may have been influenced by the loss of 39% if the original study population. Furred animals also appeared to be a risk factor in the development of asthma, contrary to some recent studies claiming that a pet in the home might have some protective effect. Unfortunately, the authors did not obtain animal-specific IgE levels. Studies in infants with AD where occlusive bedding is used as an intervention to reduce HDM sensitization and possibly, by extension, asthma, would prove interesting.

Helen Skolnick, MD
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SENSITISATION TO AIRBORNE MOULDS AND SEVERITY OF ASTHMA: CROSS-SECTIONAL STUDY FROM THE EUROPEAN COMMUNITY RESPIRATORY HEALTH SURVEY


Purpose of the Study. To assess whether the severity of asthma is associated with sensitization to airborne molds rather than to other seasonal or perennial allergens.

Study Population. One thousand one hundred thirty-two adults 20 to 44 years old with current asthma and with skin prick test results.

Methods. Participating centers of the European Community Respiratory Health Survey of over 30 centers (13 countries) randomly selected samples of 20– to 44-year-olds. They completed a short postal questionnaire about asthma symptoms. Twenty percent of random subsamples from this group were invited to come to a test center for skin prick and blood tests, spirometry, and methacholine challenge. Severity of asthma was determined according to score based on forced expiratory volume in 1 second, number of asthma attacks, hospital admission for breathing problems, and use of corticosteroids in the past 12 months.

Results. The frequency of sensitization to molds (Alternaria alternata or Cladosporium berarum, or both) increased significantly with increasing asthma severity (odds ratio: 2.34; 95% confidence interval: 1.56–3.52) for either severe or mild asthma). This association existed in all of the study areas (gathered into regions), although there were differences in the frequency of sensitization. There was no association between asthma severity and sensitization to pollens or cats. Sensitization to Dermatophagoides pteronyssinus was also positively associated with severity. In multivariable logistic regressions including sensitization to molds, pollens, D pteronyssinus, and cats simultaneously, the odds ratios for sensitization to molds were 1.48 (0.97 or 2.25) for moderate mild asthma and 2.16 (1.37–3.35) for severe mild asthma (P < .001).

Conclusions. Sensitization to molds is a powerful risk factor for severe asthma in adults. This should be taken into account in primary prevention, management, and patients’ education.

Reviewer’s Comments. This is an interesting study of adults living in multiple countries and environments showing that sensitization to Alternaria and Cladosporium were actually associated with more severe asthma while sensitization to pollens and pets were not. Dust mite sensitization was also associated with more severe asthma as has been observed in previous studies. Previous studies have shown that exposure and sensitization to molds is associated with death from asthma and life-threatening exacerbations. However, this is the first population-based study that used criteria other than just health care attendance alone, and included spirometry, steroid use, and frequency of asthma attacks. It is also interesting to see that mold was important in various areas of the world and different environments.

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β-ADRENERGIC AGONIST THERAPY

LOW-DOSE LEVALBUTEROL IN CHILDREN WITH ASTHMA: SAFETY AND EFFICACY IN COMPARISON WITH PLACEBO AND RACEMIC ALBUTEROL


Purpose of the Study. Racemic albuterol (RAC) consists of equal parts of (R-) and (S)-albuterol, with all the therapeutic activity being found in levalbuterol (LEV), the (R)-isomer. In addition to lacking bronchodilating activity, (S)-albuterol might have properties, suggested by in vitro studies, that might exacerbate airway reactivity and impair asthma control. The authors sought to determine if LEV results in improved safety and efficacy in children.

Study Population. Children 4 to 11 years old with asthma severity ranging from mild intermittent to moderate persistent were included if baseline forced expiratory volume in 1 second (FEV1) was between 40% and 85% of predicted with at least 15% reversibility to RAC at screening.

Methods. Children in this multicenter, randomized, double-blind study received 21 days of LEV (0.31 or 0.63 mg), RAC (1.25 or 2.5 mg), or placebo 3 times daily. Ventolin (GlaxoSmithKline, Research Triangle Park, NC) metered-dose inhalers (MDI) and Nebules (GlaxoSmithKline, Research Triangle Park, NC) were available as rescue medications. The primary endpoint was peak percent change in FEV1 after receiving study medication on day 21. Diary cards were kept, and the Pediatric Asthma Caregiver’s Quality of Life (QOL) Questionnaire was administered at
days 0 and 21. Adverse events (AEs), serum potassium and glucose, vital signs, and electrocardiograms were monitored.

**Results.** All 4 active treatments significantly improved the primary endpoint versus placebo (P < .001), with FEV\textsubscript{1} immediately after nebulization as follows: placebo, 2.0%; LEV 0.31 mg, 19%; LEV 0.63 mg, 18.1%; RAC 1.25 mg, 12.4%; and RAC 2.5 mg, 15.6%. Both LEV doses led to significantly greater improvement in FEV\textsubscript{1} versus RAC 1.25 mg (P < .05). LEV 0.51 mg was the only treatment not significantly different from placebo for changes in heart rate, QTc interval, and glucose. All active treatments decreased serum potassium. There was no evidence of desensitization to either LEV or RAC as measured by FEV\textsubscript{1} at day 21 vs day 0. No significant differences were observed among the treatment groups for diary card parameters or QOL. (S)-albuterol did not appear to affect the clearance of (R)-albuterol. In a subset of patients with severe asthma, a dose-response relationship was observed for LEV, indicating that higher doses were more effective.

**Conclusions.** LEV had bronchodilator activity comparable to 4- to 8-fold higher doses of RAC and also demonstrated a slightly better safety profile. LEV should be used as the starting dose in 4- to 11-year-old children with asthma. Patients with more severe asthma might benefit from higher doses.

**Reviewer’s Comments.** The more favorable therapeutic index for LEV is certainly a valuable feature in children with overtly poor tolerance of RAC and deserves a trial in any child with more severe disease, where response to RAC is suboptimal. There is some suggestion that LEV would be more cost-effective in the hospital setting if it allows for less frequent dosing, as has been claimed. Factors mitigating against the empiric use of LEV first-line, especially at home, include the following: most children overtly tolerate RAC well; AEs noted are generally benign; no MDI form of LEV currently exists; there is a short storage time once a package is opened; and LEV costs much more.

JAMES R. BANKS, MD
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**β\textsubscript{-}2-AGONIST TOLERANCE AND EXERCISE-INDUCED BRONCHOSPASM**


**Purpose of the Study.** Tolerance to the bronchoprotective effects of β\textsubscript{-}2-agonists after regular use has been demonstrated by a number of groups. These authors asked whether patients receiving scheduled β\textsubscript{-}2-agonist had a decrease in response to rescue use of β\textsubscript{-}2-agonist when bronchospasm is induced by a “natural” stimulus, exercise. Thus, they were looking for loss of the bronchodilator response rather than loss of protection to bronchoconstriction.

**Study Population.** Adults aged 18 to 50 years with a history of exercise-induced wheezing and a drop of forced expiratory volume in 1 second (FEV\textsubscript{1}) by at least 15% after exercise. Subjects could have no interfering disease and could not be receiving >1500 µg/day beclomethasone or equivalent.

**Methods.** Subjects withheld β2-agonist s for 8 hours before testing (36 hours for long-acting β\textsubscript{-}2-agonists). The qualifying bicycle ergometer challenge used an incremental increase in workload till the subject could not continue. A 15% fall in FEV\textsubscript{1} was required for study entry. Before and after 1 week of study treatment, subjects performed dry-air exercise challenge at 80% of the demonstrated maximum workload for 7 minutes with an additional 1-minute dry air inhalation. Spirometry was repeated at 1, 3, and 5 minutes after exercise, then inhaled albuterol rescue was given and spirometry repeated at 10, 15, 20, and 25 minutes. The study treatments were albuterol via metered-dose inhaler (MDI) 2 puffs four times a day (QID) for 1 week. All 4 active treatments significantly improved FEV\textsubscript{1} at 5 minutes, although the baseline FEV\textsubscript{1} for the groups was similar. The final FEV\textsubscript{1} after albuterol rescue was significantly lower in the treated than placebo group, but the change in FEV\textsubscript{1} from its nadir was similar for the 2 groups, i.e., the response curves were parallel.

**Conclusions.** Scheduled short-acting bronchodilator use leads to increased bronchoconstriction after exercise and suboptimal response to rescue albuterol after exercise.

**Reviewer’s Comments.** Although the subjects are young adults, the results are probably applicable to children with asthma. The question of tachyphylaxis to β\textsubscript{-}2-agonists has been argued for 2 decades, at least. Large clinical trials generally have not suggested significant risk to frequent β\textsubscript{-}2-agonist use, but numerous studies show at least partial loss of bronchoprotective effects with routine use of β\textsubscript{-}2-agonists. Such studies have supported the recent tendency to reserve short-acting β\textsubscript{-}2-agonists for symptom relief. This study further justifies this restrictive approach to short-acting β\textsubscript{-}2-agonists. However, the mechanism by which the increased exercise response is generated is still unclear. The authors suggest that the effect is attributable to β\textsubscript{-}2-receptor downregulation, because the earlier onset of bronchoconstriction in the albuterol group would be consistent with lack of bronchoprotection from endogenous catecholamines. The alternative explanation of increased airway inflammation associated with routine β\textsubscript{-}2-agonist is not thought likely by the authors because the FEV\textsubscript{1} was similar at baseline. An interesting study to help tease out the mechanism would add levalbuterol as a study treatment, because studies suggest it, unlike racemic albuterol, is not associated with increased methacholine sensitivity after scheduled treatment.

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Durham, NC

**1-YEAR EFFICACY AND SAFETY OF INHALED FORMOTEROL DRY POWDER IN CHILDREN WITH PERSISTENT ASTHMA**


**Purpose of the Study.** Previous published studies in adults and children have shown the addition of long-acting β-agonists to low- to medium-dose inhaled corticosteroids provided symptom relief and pulmonary function improvement greater than doubling the dose of inhaled corticosteroids alone. This study investigated the 12-month efficacy and safety of 2 doses of formoterol dry powder capsules for inhalation in children receiving antiinflammatory therapy and still requiring daily administration of short-acting β-agonists for symptom relief.

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James R. Banks

Pediatrics 2003;112:480

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