METHODS. Pediatric office health care providers and personnel in 6 Connecticut communities were trained in an asthma-management program entitled "Easy Breathing," which was based on NAEPP guidelines. Quality parameters encompassed enrollment census, relevant use of anti-inflammatory medications, and provision of a written action plan. Utilization of medical services was confirmed for Medicaid-covered children and compared by using relative rates and 95% confidence intervals (CIs) before and after enrollment.

RESULTS. There were 51 practices and 297 health care providers who enrolled 32 680 children from 2002 to 2007; 10 467 of these children had asthma according to history, 4354 of whom were insured by Medicaid. Children with persistent asthma according to history had a decline in the number of hospitalizations (relative rate: 0.51 [95% CI: 0.39–0.65]) and emergency department encounters (relative rate: 0.70 [95% CI: 0.68–0.84]) but no decline in the number of outpatient visits (relative rate: 0.99 [95% CI: 0.9–1.10]). The use of inhaled corticosteroids doubled with an increment in relevant utilization of anti-inflammatory medications to 96%, and a written action plan was provided to 94% of enrolled children with asthma.

CONCLUSIONS. The authors concluded that general pediatricians can effectively institute an asthma-management program, using NAEPP guidelines, that enhances asthma care for a large population of children.

REVIEWER COMMENTS. The limitations of this study that affect its generalizability were (1) claims data were only available for Medicaid-insured children, (2) the intermittent character of state funding, and (3) the fact that both the number of outpatient visits and the filled-prescription rate were low. Therefore, the actual number of children who both filled prescriptions and received them is unknown. However, these results indicate that a disease-management program for pediatric asthma can be implemented successfully in a community pediatric setting with a subsequent significant decrease in the number of hospitalizations and emergency department visits in a large Medicaid-insured population of children.

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Genetic Variations in Nitric Oxide Synthase and Arginase Influence Exhaled Nitric Oxide Levels in Children

Salam MT, Bastain TM, Rappaport EB, et al. *Allergy*. 2011;66(3):412–419

PURPOSE OF THE STUDY. Elevated fractional exhaled nitric oxide (FeNO) has been shown to be a sensitive biomarker for airway inflammation in children with asthma. This study examined whether a relationship could be demonstrated between genetic variants in nitric-oxide synthase and arginase genes and FeNO in asthma.

STUDY POPULATION. Subjects aged 5 to 7 years were recruited from 13 Southern California communities for a Children's Health Study cohort established in 2003. Although FeNO data were available irrespective of race/ethnicity, genetic data were only available from Hispanic and non-Hispanic white children, and data from 2773 children were available for the combined analysis.

METHODS. FeNO measurements were made with breath-sample collections that followed American Thoracic Society guidelines and took place in 2 consecutive school years. Variations in 5 genetic loci were characterized by tag single-nucleotide polymorphisms. Repeated-measures analysis of variance was used to evaluate the association between these genetic variants and FeNO.

RESULTS. Sequence variations in the *NOS2A* and *ARG2* loci were globally associated with FeNO ($P = .0002$ and 0.001, respectively) but in opposite directions regarding FeNO levels. The *ARG2* association was tagged by intronic variant rs3742879 with stronger association with lower FeNO levels. The directional change noted between FeNO levels and the above-mentioned genetic variants was more pronounced in the children with asthma than in those without asthma.

CONCLUSIONS. Variants in the nitric-oxide synthesis pathway genes jointly contribute to the differences in FeNO concentrations. Some of these genetic influences were stronger in children with asthma. Further studies are required to confirm these findings.

REVIEWER COMMENTS. Exhaled nitric oxide has become a more widely used tool in asthma patient care and clinical research settings. This report points out that there are genetic variants that could influence the interpretation of FeNO results. More studies are needed to determine the potential role of these genetic variants in the pathogenesis of asthma.

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MEDICAL THERAPIES

Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy

Price D, Musgrave SD, Shepstone L, et al. *N Engl J Med*. 2011;364(18):1695–1707

PURPOSE OF THE STUDY. To evaluate the real-world efficacy of leukotriene-receptor antagonists (LTRAs) for the

treatment of asthma by comparing LTRAs with both inhaled glucocorticoids for first-line therapy and long-acting β_2 agonists (LABAs) for add-on therapy.

STUDY POPULATION. Patients aged 12 to 80 years were considered eligible if they had a Mini Asthma Quality of Life Questionnaire (MiniAQLQ) score of ≤6 or an Asthma Control Questionnaire (ACQ) score of ≥1. Trials were conducted at 53 primary care sites in the United Kingdom.

METHODS. Patients were randomly assigned to an LTRA (n = 148) or inhaled glucocorticoid (n = 158) in the first-line therapy trial and an LTRA (n = 170) or an LABA (n = 182) in the step-up therapy trial. Patients were managed by their primary care provider during the 2-year trial period, and treatments were given in an open-label fashion. After the initial visit, patients were followed either by telephone or in the clinic at months 2, 6, 12, 18, and 24. Patients' MiniAQLQ score was the primary outcome measure. Secondary outcome measures included the ACQ score, the Royal College of Physicians 3-item asthma questionnaire score, the Mini Rhinoconjunctivitis Quality of Life Questionnaire score, and the frequency of asthma exacerbations that required oral glucocorticoids or hospitalization.

RESULTS. Over the 2-year treatment period, the mean MiniAQLQ score increased by 0.8 to 1.0 in both trials. Assessment of data at 2 months revealed noninferiority between LTRAs and inhaled glucocorticoids for first-line therapy on the basis of the primary outcome of MiniAQLQ score. At 2 years, results approached equivalence between the treatment groups in both trials; however, the data could not prove noninferiority. There were no significant differences between treatment groups regarding all other secondary outcome measures at both 2 months and 2 years. There was no significant difference in adherence rates in either trial.

CONCLUSIONS. Results at 2 months suggest comparable efficacy between LTRAs and inhaled glucocorticoids as first-line controller therapy and equivalence to LABAs as add-on therapy. Equivalence at 2 years was not proved for either trial.

REVIEWER COMMENTS. Although LTRAs are a comparable option for both first-line and step-up therapy in asthma, true long-term equivalence has not been demonstrated. Results of previous randomized trials that examined LTRA use tend to support inhaled glucocorticoids as the preferred choice for first-line therapy and LABAs as the preferred choice for step-up therapy. The authors of a Cochrane review of 27 randomized controlled trials, mainly in adults with mild-to-moderate asthma, concluded that inhaled corticosteroid was more effective than LTRAs. A meta-analysis of 18 randomized controlled trials in children younger than 18 years with similar asthma found that inhaled corticosteroid was more effective than montelukast for preventing severe asthma exacerbations. The absence of a placebo group makes it difficult to judge whether the changes observed in MiniAQLQ score in either group from baseline are truly clinically meaningful. However, this study does provide a better, although not perfect, real-world perspective, with data approaching equivalence for LTRA use as both first-line and step-up therapy for asthma. Results from previous randomized controlled trials combined with data from this pragmatic study might not change how we currently practice but can guide us in our decision-making process more effectively in the real-world clinic setting.

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Effect of Addition of Single Dose of Oral Montelukast to Standard Treatment in Acute Moderate to Severe Asthma in Children Between 5 and 15 Years of Age: A Randomised, Double-Blind, Placebo Controlled Trial

Todi VK, Lodha R, Kabra SK. *Arch Dis Child.* 2010;95(7):540–543

PURPOSE OF THE STUDY. Montelukast has both anti-inflammatory and bronchodilator properties. Does giving a single dose at the time of an emergency department (ED) visit for an asthma exacerbation improve outcomes compared with standard therapy alone?

METHODS. One hundred seventeen children who presented to an ED with moderate-to-severe asthma exacerbations defined as a Modified Pulmonary Index Score of ≥9 were randomly assigned to receive either montelukast (n = 60) or placebo (n = 57) in addition to standard therapy, which included nebulized albuterol and ipratropium and oral corticosteroids.

RESULTS. The percentage of children whose Modified Pulmonary Index Score decreased to <9 within 4 hours was no different in the montelukast (55%) and placebo (63%) groups (P = .37). There were no differences in the improvement in lung function or hospitalization rates.

CONCLUSIONS. Single-dose oral montelukast added to standard therapy of inhaled bronchodilators and systemic glucocorticoids did not provide additional clinical benefit for children with acute moderate-to-severe asthma.

REVIEWER COMMENTS. Because montelukast can act quickly and works in a different way than other bronchodilators,

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