CONCLUSIONS. Children developing asthma by 7 years of age had a lung function deficit and increased bronchial responsiveness as neonates. This lung function deficit progressed to age 7 years.

REVIEWER COMMENTS. Our interventions to try to prevent or to treat asthma may have to begin even before birth because it seems that children who go on to have asthma are born with decreased lung function. Furthermore, we will need more effective treatments because the loss of lung function progressed throughout childhood despite treatment with inhaled corticosteroids.

Influence of β2-Adrenergic Receptor Polymorphisms on Asthma Exacerbations in Children With Severe Asthma Regularly Receiving Salmeterol

PURPOSE OF THE STUDY. Polymorphisms of the β2-adrenergic receptor (AR) gene have been associated with response to both long-acting and short-acting β agonists. Studies have suggested that patients with homozygous arginine at position 16 are more likely to have reduced bronchodilator effects, increased asthma exacerbations, or decreased pulmonary function compared with those with homozygous glycine or heterozygous glycine/arginine at the same position. Studies are contradictory, however, on the relationship between these polymorphisms and asthma exacerbations, which could be related to the severity of asthma being studied. The purpose of this study was to determine if these polymorphisms had any effect on asthma exacerbations in children with severe asthma taking higher-dose inhaled corticosteroids who are regularly receiving salmeterol.

STUDY POPULATION. The study population consisted of Argentinian children (N = 97) with a diagnosis of severe asthma who were genotyped for β2AR variants. All children had stable asthma and were taking medium- to high-dose inhaled corticosteroids and were placed on twice-daily albuterol during the study.

METHODS. Information on asthma exacerbations, need for albuterol, courses of oral steroids, and hospital admissions was collected at monthly clinic visits over the 12-month study. The severity of asthma exacerbations was defined according to a consensus statement recently published. Pulmonary function was performed at each clinic visit. Patients were treated according to their personalized action plans.

RESULTS. There was no difference among genotypes in the proportion of participants with severe asthma exacerbations, the rate of asthma exacerbations, hospitalizations, or the time to first asthma exacerbation. In addition, no differences were noted in the use of albuterol or symptom-free days.

CONCLUSIONS. Genotypic effects on asthma control were not present among children using medium- to high-dose inhaled corticosteroids plus a long-acting bronchodilator.

REVIEWER COMMENTS. This study reveals that children with severe asthma who are taking medium- to high-dose inhaled corticosteroids do not demonstrate increased asthma exacerbations or loss of asthma control on the basis of their β2AR genotype. It is possible that any effects due to a difference in genotype may have been overcome by the dose of inhaled corticosteroids.

Apopotic Cell Clearance by Bronchial Epithelial Cells Critically Influences Airway Inflammation

PURPOSE OF THE STUDY. Airway epithelial cells naturally undergo programmed cell death, or apoptosis, after encounter with airborne allergens and pollutants. The authors investigated how these apoptotic cells are cleared by the lungs, and whether this process was important in preventing airway inflammation.

STUDY POPULATION. Studies were performed in mice and by using human cells.

METHODS. Flow cytometric and histologic assays were used to examine the phagocytic capacity of airway epithelial cells in vitro. For in vivo studies, the authors used genetically modified mice in which proteins were deleted from airway epithelial cells only.

RESULTS. The authors found that airway epithelial cells from humans and mice were able to engulf apoptotic cells, resulting in the secretion of antiinflammatory cytokines, such as interleukin (IL)-10. Uptake of apoptotic cells was dependent on the intracellular protein Rac1, a GTPase important for cytoskeletal rearrangement during phagocytosis. Mice that lacked Rac1 expression specifically in airway epithelial cells were unable to effectively clear apoptotic cells from the lungs. This defect in phagocytosis resulted in decreased secretion of antiinflammatory cytokines, exaggerated airway inflammation after challenge with house dust mite allergens, and failure to develop tolerance to inhaled
aggregates. The inflammatory cytokine IL-33 was elevated in Rac1-deficient lungs, which was associated with expansion of proallergic innate lymphoid cells. Furthermore, suppression of Rac1 in human nasal epithelial cells resulted in enhanced production of IL-33, suggesting that Rac1 negatively regulates inflammatory signaling pathways. Finally, treatment with IL-10 was shown to mitigate the allergic inflammation seen in Rac1-deficient airways.

CONCLUSIONS. Clearance of apoptotic cells by airway epithelial cells is important for preventing allergen-induced airway inflammation.

REVIEWER COMMENTS. It is generally thought that traditional phagocytic cells in the lungs, such alveolar macrophages, are primarily responsible for keeping the airways clean through removal of cellular debris and inhaled particulates. However, this study reveals that airway epithelial cells, which are not typically known for their phagocytic function, play a critical role in the clearance of apoptotic cells and in maintaining an antiinflammatory environment in the lungs. This study, along with others evaluating innate immune activity of epithelial cells, emphasizes the importance of the respiratory mucosal barrier in maintaining lung homeostasis. Therapies aimed at enhancing the immunosuppressive activity of airway epithelial cells, or blocking their release of proinflammatory cytokines such as IL-33, may prove beneficial for the treatment of asthma and other immune-mediated respiratory diseases.

DIAGNOSIS AND MANAGEMENT

Outcomes of Stepping Down Asthma Medications in a Guideline-Based Pediatric Asthma Management Program

PURPOSE OF THE STUDY. Identifying strategies to adjust medications when managing chronic diseases poses a challenge to busy practitioners, and often the opportunity is lost to step down therapy. Clinical studies suggest that many patients currently treated with combination controller medications can be successfully stepped down. Use of a multidisciplinary care management team has also been a strategy associated with success in stepping down therapy. Nonadherence represents another method of step-down. This study was performed to identify predictive factors for success in stepping down therapy, the frequency of attempts to step down, and the relative success of guideline-eligible versus non-guideline-eligible step-down attempts.

STUDY POPULATION. The study included a retrospective, random sample of 477 participants in the Pediatric Asthma Management Program affiliated with the Mayo Clinic. The children were aged 5 to 8 years with asthma enrolled in a pediatric asthma management program in an integrated primary care practice. All children had persistent asthma, a history of emergency department or hospital visit for asthma during the past 12 months, or uncontrolled asthma symptoms.

METHODS. By using the National Asthma Education and Prevention Program Asthma Guidelines, participants were identified who were eligible, based on a defined control, to step down therapy. Other participants who did not meet the guidelines for step-down, but who attempted step-down anyway, were also analyzed. Age, gender, pulmonary function, smoking status, time of year, and type of step-down were analyzed for their predictive value.

RESULTS. Slightly more than 55% of the children in the study were eligible, based on the guidelines, to step down therapy, but only 33.7% did attempt to step down. A similar percentage of those who were not guideline eligible also attempted stepping down. Successful step-down occurred in 79.7% of guideline-eligible participants and in 61.7% of those who were non-guideline eligible. Time of year was the only predictive factor (success in any season except for fall), although guideline eligibility was significant in the univariate analysis.

CONCLUSIONS. Guideline-based stepping down of asthma medication is an option that should be frequently considered and will be frequently successful.

REVIEWER COMMENTS. The important finding in this study is that only a minority of children with asthma that is well controlled have attempted to step down therapy. Stepping down, regardless of whether guideline eligible or not, is often successful. It appears that stepping down in the fall is associated with less success. These findings underline the need for practitioners to regularly assess patients for eligibility to decrease asthma therapy.

Factors Associated With Elevated Exhaled Nitric Oxide Fraction in Infants With Recurrent Respiratory Symptoms

PURPOSE OF THE STUDY. To evaluate the relationship between exhaled nitric oxide fraction (FeNO) and increased airway responsiveness, and to clarify whether there are any
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