Neonatal Bronchial Hyperresponsiveness Precedes Acute Severe Viral Bronchiolitis in Infants


PURPOSE OF THE STUDY. To determine if host factors in neonates expressed as bronchial hyperresponsiveness precede later development of acute severe bronchiolitis. Previous studies showed that abnormal neonatal pulmonary function was associated with asthma by age 7 years.

STUDY POPULATION. This study was nested in the Copenhagen Prospective Studies on Asthma in Childhood, a prospective study of a birth cohort of 411 neonates born to mothers with a history of asthma. Infants were enrolled at 1 month of age. Exclusion criteria included symptoms of lower airway infection, mechanical ventilation before inclusion, gestational age of <36 weeks, and any congenital abnormality or systemic illness.

METHODS. Infant lung function was measured in 402 subjects and bronchial responsiveness to methacholine was determined in 363 subjects by using the raised-volume rapid thoracoabdominal compression technique. These tests were conducted in 1-month-old neonates before they had developed any respiratory symptoms. The cohort was prospectively monitored for respiratory symptoms with daily diary cards and clinical examination at the research clinic every 6 months. Infants were also evaluated for acute respiratory symptoms and given a diagnosis of acute severe bronchiolitis according to a fixed algorithm.

RESULTS. Thirty-four (8.5%) of the infants had acute severe bronchiolitis before age 2 years. Twenty-one (62%) were hospitalized and 23 (67%) were diagnosed with respiratory syncytial virus. Children who later had severe bronchiolitis had a 2.5-fold increased responsiveness to methacholine as determined by a PD15 (provocation dose of methacholine producing a 15% decrease in transcutaneous oxygen pressure) at 1 month compared with control subjects (median PD15 in cases versus control subjects: 0.13 vs 0.33 μmol; $P = .01$). Differences in baseline airflow were not significant for forced expiratory volume at 0.5 seconds (mean $z$ score for cases versus control subjects: $-0.18$ vs $-0.01$; $P = .36$) and forced expiratory flow at 50% of forced vital capacity (mean $z$ score for cases versus control subjects: $-0.37$ vs $-0.09$; $P = .13$).

CONCLUSIONS. Bronchial hyperresponsiveness in an at-risk population of asymptomatic neonates precedes the later development of acute severe bronchiolitis. This finding suggests a preexisting host factor that would indicate an increased risk of an adverse reaction to common respiratory tract viruses.

Interaction Between Asthma and Lung Function Growth in Early Life


PURPOSE OF THE STUDY. Children with asthma have reduced lung function. This study addresses the question: Are they born that way?

STUDY POPULATION. Prospective birth cohort of 411 children from Denmark whose mothers had a physician’s diagnosis of asthma.

METHODS. At age 1 month, subjects’ spiometric and bronchial responsiveness to methacholine was obtained by thoracic compression technique. At age 7 years, subjects’ lung function was measured by using spirometry. Asthma was diagnosed prospectively, from daily diary cards and clinic visits every 6 months, if the following were noted: recurrent episodes of troublesome lung symptoms typical of asthma, need for rescue use of inhaled $\beta_2$-agonist, and response to inhaled corticosteroids.

RESULTS. Children with asthma by age 7 years (14%) already had a significant airflow deficit as neonates (forced expiratory flow at 50% reduced by 0.34, $z$ score, $P = .03$), which progressed (0.82 $z$ score, $P < .0001$) by age 7 years, suggesting that ~40% of the airflow deficit associated with asthma is present at birth, whereas 60% develops with clinical disease. Bronchial responsiveness to methacholine in neonates was associated with the development of asthma ($P = .01$).
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 \( \beta_2 \)-Adrenergic Receptor Polymorphisms on Asthma Exacerbations in Children With Severe Asthma Regularly Receiving Salmeterol


PURPOSE OF THE STUDY. Polymorphisms of the \( \beta_2 \)-adrenergic receptor (\( \beta_2 \)-AR) gene have been associated with response to both long-acting and short-acting \( \beta \) 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 \( \beta_2 \)-AR 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.

Apoptotic 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
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*Pediatrics* 2013;132;S36
DOI: 10.1542/peds.2013-2294HHH

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