The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma

Kecia N. Carroll, MD, MPH,[a,e] Pingsheng Wu, PhD,[b,c] Tebeb Gebretsadik, MPH,[c] Marie R. Griffin, MD, MPH,[b,d,f,h,j] William D. Dupont, PhD,[c,d] Edward F. Mitchel, MS,[d] and Tina V. Hartert, MD, MPH[b,g,i] *Nashville, Tenn*

Background: Infants hospitalized for bronchiolitis have a high rate of early childhood asthma. It is not known whether bronchiolitis severity correlates with the risk of early childhood asthma or with asthma-specific morbidity.

Objectives: We sought to determine whether a dose-response relationship exists between severity of infant bronchiolitis and both the odds of early childhood asthma and asthma-specific morbidity.

Methods: We conducted a population-based retrospective birth cohort study of term healthy infants born from 1995-2000 and enrolled in a statewide Medicaid program. We defined bronchiolitis severity by categorizing infants into mutually exclusive groups based on the most advanced level of health care for bronchiolitis. Health care visits, asthma-specific medications, and demographics were identified entirely from Medicaid and linked vital records files. Asthma was ascertained at between 4 and 5.5 years of age, and 1-year asthma morbidity (hospitalization, emergency department visit, or oral corticosteroid course) was determined between 4.5 and 5.5 years among children with prevalent asthma.

Results: Among 90,341 children, 18% had an infant bronchiolitis visit, and these infants contributed to 31% of early childhood asthma diagnoses. Relative to children with no infant bronchiolitis visit, the adjusted odds ratios for asthma were 1.86 (95% CI, 1.74-1.99), 2.41 (95% CI, 2.21-2.62), and 2.82 (95% CI, 2.61-3.03) in the outpatient, emergency department, and hospitalization groups, respectively. Children hospitalized with bronchiolitis during infancy had increased early childhood asthma morbidity compared with that seen in children with no bronchiolitis visit.

Conclusion: To our knowledge, this is the first study to demonstrate the dose-response relationship between the severity of infant bronchiolitis and the increased odds of both early childhood asthma and asthma-specific morbidity. (J Allergy Clin Immunol 2009;123:1055-61.)

Key words: *Bronchiolitis, asthma*

Asthma is one of the most common chronic conditions of childhood and accounts for significant morbidity.[1] The cause and morbidity of asthma are thought to be due to a number of modifiable and nonmodifiable factors, including family history, genetic predisposition, and environmental exposures, such as viral infections.[2-4] Viral bronchiolitis results in significant morbidity, affecting 20% of infants annually.[5,6] Furthermore, up to 3% of healthy infants in the United States are hospitalized for bronchiolitis, resulting in an estimated 120,000 hospitalizations annually, and bronchiolitis rates are increasing.[7] Not only is morbidity high related to the infant bronchiolitis episode, but also a high rate of asthma within the first decade of life has been observed after severe bronchiolitis during infancy.[8-10] Although observational studies have reported that more than 30% of infants hospitalized with bronchiolitis subsequently have asthma, the relationship between the infant bronchiolitis episode and later asthma is not completely understood because the majority of infants with bronchiolitis do not have asthma.[11]

Several seminal observational studies have tracked childhood asthma outcomes among children with a history of a bronchiolitis hospitalization during infancy and a nonhospitalized comparison group.[8,9,11-17] However, asthma outcomes for outpatient infant bronchiolitis-related events in the nonhospitalized groups were not reported, and thus the relationship between infant bronchiolitis severity and subsequent risk or morbidity of asthma is not known from these investigations. A limited number of prospective birth cohorts, including 2 with children at high risk for asthma, have also contributed to our understanding of asthma risk among children with a history of bronchiolitis or wheezing lower respiratory tract illness in the first years of life.[6,10,18-21] However, the wheezing illnesses identified within these cohorts were primarily outpatient events, and the risk and morbidity of asthma associated with infant bronchiolitis requiring emergency department (ED) visits or hospitalizations were both infrequent and not reported. Therefore despite several longitudinal investigations focused on the role of viral infections in asthma inception, it is not known whether there is a severity-dependent relationship between the severity of infant bronchiolitis and both the risk and morbidity of early childhood asthma. Nor is it known, at a

From the Departments of [a]Pediatrics, [b]Medicine, [c]Biostatistics, and [d]Preventive Medicine; the Divisions of [e]General Pediatrics, [f]General Internal Medicine, and [g]Allergy, Pulmonary and Critical Care Medicine; [h]the Center for Education and Research on Therapeutics; and [i]the Center for Health Services Research, Vanderbilt University School of Medicine, and [j]the Mid-South Geriatric Research Education and Clinical Center and the Clinical Research Center of Excellence, Veterans Affairs, Tennessee Valley HealthCare System, Nashville.

Supported in part by NIH U01 HL 072471 (T.V.H.), the Thrasher Research Fund (T.V.H.), NIH KO1 AI070808 (K.N.C.), NIH K24 AI 077930 (T.V.H.), NIH F32 HL 086048 (P.W., T.V.H.), and the Parker B. Francis Research Foundation (K.N.C.).

Disclosure of potential conflict of interest: K. N. Carroll has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases and the Parker B. Francis Foundation. P. Wu has received research support from the National Institutes of Health and the Thrasher Research Fund. T. Gebretsadik has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases. M. R. Griffin has received research support from MedImmune, Pfizer, the Center for Disease Control and Prevention, and the Agency for Healthcare Research and Quality. T. V. Hartert has served as a speaker for and on the Advisory Board for Merck and has received research support from the National Institutes of Health and the Thrasher Research Fund. The rest of the authors have declared that they have no conflict of interest.

Received for publication October 10, 2008; revised January 28, 2009; accepted for publication February 17, 2009.

Available online April 13, 2009.

Reprint requests: Tina V. Hartert, MD, MPH, Division of Allergy, Pulmonary and Critical Care Medicine, Center for Health Services Research, 6107 MCE, Vanderbilt University School of Medicine, Nashville, TN 37232-8300. E-mail: tina.hartert@vanderbilt.edu.

0091-6749

doi:10.1016/j.jaci.2009.02.021

Abbreviations used
ED: Emergency department
EGA: Estimated gestational age
ICD-9: International Classification of Diseases, Ninth Revision
OR: Odds ratio
RSV: Respiratory syncytial virus
TABS: Tennessee Asthma Bronchiolitis Study

population-based level, what proportion of children with asthma had clinically significant bronchiolitis as infants or whether a familial predisposition to asthma modifies the risk of asthma after infant bronchiolitis.

To answer these questions, we used our population-based retrospective birth cohort of more than 90,000 term, non–low birth weight, otherwise healthy children in the Tennessee Asthma Bronchiolitis Study (TABS) constructed from health care visits, asthma-specific medications, and demographics identified from Medicaid claims, pharmacy data, and linked vital records files. We hypothesized that the severity of clinically significant bronchiolitis, including both outpatient and inpatient health care, would be positively correlated with both an increased odds of early childhood asthma and increased asthma-specific morbidity among children with prevalent disease. Lastly, in a subset of mother-infant dyads in whom maternal history could be determined, we investigated how maternal asthma modified the association between bronchiolitis and early childhood asthma inception.

METHODS

Study design and population

To estimate the association of bronchiolitis during infancy with the development of early childhood asthma, we conducted a population-based retrospective birth cohort study of more than 90,000 term, non–low birth weight infants enrolled in TennCare within the first month of life (1995-2000, the TABS). Only children born between 1995 and 2000 were included because all children were followed to 5.5 years by using the years for which data were available. In 1994, TennCare replaced the federal Medicaid program as a state-based managed health care program that covered Medicaid-eligible individuals and the uninsured.[22] TennCare provides health insurance for approximately 50% of infants born in Tennessee. Data were obtained from linked TennCare administrative data files and Tennessee State vital records files using previously described methods at our study institution.[23,24] Analysis files contained no personal identifiers, and study results are reported in aggregate and cannot be linked to individuals. The protocol was approved by the Institutional Review Board of Vanderbilt University and reviewed and approved by representatives of the Tennessee Department of Health and the Bureau of TennCare.

Eligible children were continuously enrolled in TennCare during the first year of life, during which health care visits for bronchiolitis were captured, and between 3.5 and 5.5 years of age, during which early childhood asthma was defined. Continuous enrollment was considered no more than 21 days of nonenrollment during the first 12 months of life and no more than 60 days of nonenrollment between 3.5 and 5.5 years of life. This investigation included only term (estimated gestational age [EGA], >37 weeks), non–low birth weight (>2500 g), and otherwise healthy infants to investigate the association of bronchiolitis during infancy and subsequent asthma without the potential confounding of low birth weight or chronic disease. We determined EGA in weeks by date of last menstrual period on the birth certificate (87%) or imputed it based on median gestational period in weeks for the infant's race, birth weight, and birth year (13%).[25] We excluded infants with any of the following before 3.5 years of age (4.6%): Current Procedural Terminology code indicating surgery for congenital heart disease, receipt of respiratory syncytial virus (RSV) immunoprophylaxis, or International Classification of Diseases, Ninth Revision (ICD-9), code indicating congenital heart disease, chronic lung disease (bronchopulmonary dysplasia), congenital anomaly of the upper airway, upper alimentary tract atresia or stenosis, neurologic disorder, immunodeficiency, cystic fibrosis, diabetes mellitus, renal disease, or cancer.

Predictor variables

We identified health care visits for bronchiolitis during the first 12 months of life using ICD-9 codes for bronchiolitis (466.1), RSV-induced pneumonia (480.1), or both. ICD-9 diagnoses of bronchiolitis in infants have been validated by using models to correlate with RSV circulation.[26] Clinically significant bronchiolitis was defined as a health care visit for bronchiolitis. Bronchiolitis severity was defined by categorizing children into mutually exclusive groups based on their most advanced level of health care (hospitalization, 23-hour observation, ED visit, or clinic visit with ICD-9 codes for bronchiolitis). Hospitalizations and 23-hour observations were combined into the hospitalization group. Infants without any bronchiolitis visits were categorized into the no-visit group.

Other demographic and baseline characteristics were determined from birth certificate data and TennCare files. Infant race/ethnicity (mutually exclusive categories of white, black, Hispanic, or other/unknown) and region of residence (urban, suburban, or rural) were identified from TennCare enrollment files. Demographic variables determined from birth certificate data included birth weight, sex, siblings (none, 1, or $\geq$2 based on report of number of prior live births), maternal age at delivery, maternal education level, quantified maternal smoking during pregnancy, and marital status.

We used maternal asthma, one measure of familial predisposition to asthma, to evaluate whether maternal asthma modified the association between bronchiolitis during infancy and subsequent asthma development. Maternal asthma was ascertained in the nested subgroup of mother-infant dyads who met the following criteria: infants were term and otherwise healthy, and mothers were continuously enrolled in TennCare from 180 days before pregnancy through delivery. Maternal continuous enrollment included no more than 45 days of nonenrollment from 180 days before pregnancy through delivery. Maternal asthma was similarly determined by using health care encounter file claims, pharmacy file claims, or both using a previously validated method of identifying individuals with asthma.[25]

Outcome variables

The main outcome was diagnosis of early childhood asthma between 4 and 5.5 years of age among the population-based cohort of 90,341 children. We used a 1.5-year ascertainment period to capture children with milder disease who might seek treatment only as needed or during well-child visits. We studied asthma diagnoses after 4 years to exclude "transient early wheezers" who wheeze with viral infections during the first years of life.[4] Early childhood asthma was determined by using health care encounter file claims, pharmacy file claims, or both with similar algorithms used for both epidemiology and outcomes research.[27,28] Children with an ICD-9 diagnosis code of 493 (asthma) in any of the discharge diagnosis fields for inpatient, other hospital care (23-hour observation), or ED visit or 2 outpatient physician visit claims were considered to have asthma. In addition, children with 2 prescriptions for any short-acting β-agonist within a 12-month period or a prescription for other asthma medications (including inhaled corticosteroids and long-acting β-agonists) were considered to have early childhood asthma.

We also assessed the relationship between bronchiolitis severity during infancy and 1-year asthma morbidity among children with prevalent disease by 4.5 years of age. For this analysis, we required children to meet the definition of asthma between 3.5 and 4.5 years of age and have a full year of follow-up from 4.5 to 5.5 years of age during which the morbidity of their asthma was determined. One-year asthma morbidity was defined between ages 4.5 and 5.5 years as an asthma hospitalization, ED visit, and/or course of systemic corticosteroids among children with prevalent asthma diagnosed between 3.5 and 4.5 years of age.