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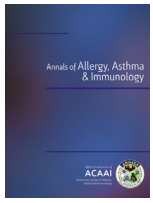

Consequences of antibiotics and infections in infancy: bugs, drugs, and wheezing

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ABSTRACT

Background: The prevalence of asthma has increased alarmingly in the past 2 to 3 decades. Increased antibiotic use in infancy has been suggested to limit exposure to gastrointestinal microbes and to predispose to asthma in later life.

Objective: To evaluate the association between antibiotic exposure during the first year of life and the development of asthma up to the age of 7 years.

Methods: A retrospective population-based study of a cohort of children enrolled in a nationwide employer-provided health insurance plan from January 1, 1999, through December 31, 2006, in the United States (n = 62,576). We evaluated the association between antibiotic exposure during the first year of life and subsequent development of 3 asthma phenotypes: transient wheezing (began and resolved before 3 years of age), late-onset asthma (began after 3 years of age), and persistent asthma (began before 3 years of age and persisted through 4-7 years of age).

Results: Antibiotic use in the first year of life was associated with the development of transient wheezing (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.9-2.2; $P < .001$) and persistent asthma (OR, 1.6; 95% CI, 1.5-1.7; $P < .001$). A dose-response effect was observed. When 5 or more antibiotic courses were received, the odds of persistent asthma doubled (OR, 1.9; 95% CI, 1.5-2.6; $P < .001$). There is no association between antibiotic use and late-onset asthma.

Conclusion: Antibiotic use in the first year life is associated with an increased risk of early-onset childhood asthma that began before 3 years of age. The apparent effect has a clear dose response. Heightened caution about avoiding unnecessary use of antibiotics in infants is warranted.

Introduction

The prevalence of childhood asthma has increased globally during the past few decades and appears to have increased in parallel with increased urbanization.[1] This has led to the hygiene hypothesis, which suggests that reduced microbial exposure during childhood may have contributed to the increase in atopic disorders, such as asthma.[2] An alternative interpretation of the evidence supporting the hygiene hypothesis gave rise to the microbiota hypothesis, which suggests that perturbations in the gastrointestinal microbiota due to aspects of the modern lifestyle have disrupted the mechanisms of mucosal immunologic tolerance.[3,4] This has, in turn, resulted in increased susceptibility to T_H2 cytokine-dependent allergic inflammation. In support of this hypothesis, accumulating evidence demonstrates the differences in the composition of intestinal microbiota between allergic and nonallergic infants.[5,6]

On the basis of the same reasoning, it has been postulated that antibiotic use in early life increases the risk of atopic disorders by altering the diversity and composition of the intestinal microbiota.[7,8] Lending support to this hypothesis, animal studies found that microbiota disruption caused by antibiotic exposure altered the immune regulation in the airways of mice, which subsequently led to the up-regulation of T_H2 responses to allergen exposure, thus promoting allergic airway disease.[8,9] A mechanistic study provides insights into the potential pathway through which the microbiota influences the immune regulation of T_H2 cytokine responses.[10] In this study, deliberate alteration of microbiota in mice via oral antibiotic treatment resulted in elevated serum IgE concentrations, increased steady-state circulating basophil populations, and exaggerated basophil-mediated T_H2 cell responses and allergic inflammation.

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Previous studies have investigated the association of antibiotic exposure with childhood asthma with inconsistent results and with concern that the observed association was confounded by lower respiratory tract illness (LRI) in early childhood.[11–13] Several studies failed to find an association between early antibiotic use and asthma after adjustments for respiratory infections,[14,15] leading to the suggestion that the reported positive association was attributable to confounding by indication. A number of studies suggested that LRI in infancy can be an early indication of host susceptibility to asthma.[16–18] Given the inconsistencies of existing data, the risk of antibiotic use in infancy on childhood asthma remains inconclusive.

In this study, we examined the association between antibiotic use in the first year of life and subsequent development of childhood asthma from infancy through 7 years of age in a large cohort of children. Characterizing the risk factors of asthma is challenging because of the heterogeneity of the disease. Different asthma phenotypes vary in prognosis, immune responses, and susceptibility to environmental factors.[19,20] Accordingly, we assessed the potential association between antibiotic use and the development of several asthma phenotypes, including transient wheeze (asthma that did not persist beyond 3 years of age), late-onset asthma (asthma that began after the 3 years of age), and persistent asthma (asthma that began in the first 3 years of life and persisted through 4-7 years of age). This approach sets us apart from existing studies in the field and may help unravel the inconsistencies found in existing studies. As a secondary objective, we investigated the effect of early-life respiratory infections on the 3 asthma phenotypes. The association between early-life respiratory infections and childhood asthma remains controversial. There is substantial variability in previously published risk estimates of asthma in children with early-life respiratory infections, with most studies based on small population samples.[21] We examined the association in a large national cohort.

Methods

Study Population and Design

We performed a population-based retrospective cohort study of children enrolled in a nationwide employer-provided health insurance plan in the United States. The data source comprised medical insurance claims of 1,604,580 children distributed nationally from January 1, 1999, through December 31, 2006. Our study population consists of all children (n = 62,576) continuously enrolled from birth through at least 5 years of age. Claims data included dates of enrolment in the insurance program, outpatient and inpatient visits, and prescription drugs dispensed. Demographic data included sex, age, and zip code of residence. All health care encounters were coded with up to 4 diagnostic codes from the *International Classification of Diseases, Ninth Revision* (*ICD-9*). Prescription drugs were reported using the National Drug Code.

The study was approved by the institutional review board at Boston Children's Hospital. All data used in this study were deidentified. A waiver of consent was obtained from the review board.

Exposure Identification

Antibiotic exposure was defined as the receipt of at least one prescription of antibiotic in the first year of life. Antibiotic exposure was examined as a dichotomous variable (≥1 courses vs 0) and as a continuous variable (total number of treatment courses in the first year of life). One course of antibiotic prescription was defined as a single continuous prescription, typically lasting 7 to 10 days.

Outcome Identification

The primary outcome measure was asthma development in children between infancy and 7 years of age. We stratified our outcome based on 3 asthma phenotypes[20,22]: (1) transient wheeze: began and resolved before 3 years of age; (2) late-onset asthma: began after 3 years of age; and (3) persistent asthma: began before 3 years of age and persisted through to 4 to 7 years of age.

Children with asthma were identified using a revised definition of the Health Employers Data Information System (HEDIS) criteria for the National Committee on Quality Assurance definition. The 2012 HEDIS measure defines a child as having persistent asthma if at least one of the following criteria was met in the 2 years previous to the measurement year: (1) at least one emergency department (ED) visit with asthma as the principal diagnosis, (2) at least one acute care inpatient encounter with asthma as the principal diagnosis, (3) at least 4 outpatient asthma visits with asthma as one of the listed diagnoses and at least 2 asthma medication dispensing events, and (4) at least 4 asthma medication dispensing events. In our study, asthma was considered present if the HEDIS measure was met in the year of measurement.

Asthma diagnosis was identified using *ICD-9* codes (eTable 1). Type of visit (outpatient, acute care inpatient, or ED) was determined using *Current Procedural Terminology* codes (eTable 2). Dispensing events were calculated in accordance with the HEDIS measure: an oral medication dispensing event was defined as one prescription of an amount lasting 30 days or less; inhalers were counted as one dispensing event.

Statistical Analysis

Descriptive statistics were presented for antibiotic exposure frequencies and asthma prevalence. Associations between antibiotic prescriptions and asthma were estimated using logistic regression. Separate analyses were performed to assess the risk of transient, late-onset, and persistent asthma. The control population consists of children who were not diagnosed as having asthma since birth through 7 years of age. Risk was adjusted for sex, geographic region (urban/rural), and exposures to LRI and URI in infancy. The results were expressed as odds ratios (ORs), with 95% confidence intervals (CIs).

To address the potential for reverse causality and confounding by indication caused by preexisting asthma and respiratory illnesses in infancy, we performed a sensitivity analysis on a subset of children, excluding those who were diagnosed as having asthma, LRI, and URI in the first year of life, as well as premature infants and children with cystic fibrosis. All conditions were identified using

Table 1
Demographic characteristics of study participants

Characteristic	No. (%) of study participants[a] (N = 62,576)
Sex	
Female	30,261 (48.4)
Male	32,315 (51.6)
Geographic region	
Urban	49,897 (79.7)
Rural	12,679 (20.3)
Asthma prevalence	
Transient (began and resolved before 3 years of age)	5,460 (8.7)
Late onset (began after 3 years of age)	6,418 (10.3)
Persistent (began before 3 years of age and persisted to 4-7 years of age)	5,946 (9.5)
Never (no asthma from birth to 7 years of age)	44,752 (71.5)
Antibiotic use in the first year of life	
≥1 Course	26,693 (42.7)
Mean (SD)	1.1 (1.8)
Lower respiratory illness in the first year of life	
≥1 Episode	12,131 (19.4)
Mean (SD)	0.5 (1.6)
Upper respiratory illness in the first year of life	
≥1 Episode	27,537 (44.0)
Mean (SD)	1.0 (1.6)

[a]Data are number (percentage) of patients unless otherwise indicated.