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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 of 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.

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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.

Previous studies have investigated the association of antibiotic exposure with childhood asthma with inconsistent results and with

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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)

^aData are number (percentage) of patients unless otherwise indicated.

Table 2
Risk of childhood asthma^a

Risk factor	Transient wheeze (n = 5,460)		Late-onset asthma (n = 6,418)		Persistent asthma (n = 5,946)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Antibiotic ^b	2.0 (1.9–2.2)	<.001	1.1 (1.0–1.1)	.10	1.6 (1.5–1.7)	<.001
LRI ^b	6.1 (5.8–6.5)	<.001	1.4 (1.3–1.5)	<.001	5.1 (4.8–5.5)	<.001
URI ^b	1.4 (1.3–1.5)	<.001	1.4 (1.3–1.5)	<.001	1.5 (1.4–1.6)	<.001
Male sex	1.3 (1.3–1.4)	<.001	1.3 (1.2–1.3)	<.001	1.6 (1.5–1.7)	<.001
Urban	1.1 (1.0–1.2)	.009	1.1 (1.0–1.1)	.048	1.3 (1.2–1.3)	<.001

Abbreviations: CI, confidence interval; LRI, lower respiratory tract infection; OR, odds ratio; URI, upper respiratory tract infection.

^aSeparate multivariate logistic regressions were performed to assess the risk of each of the 3 asthma phenotypes.^bExposure in the first year of life, expressed as a dichotomous value.

ICD-9 codes (eTable 1). Respiratory illnesses included bronchiolitis, bronchitis, pneumonia, influenza, and chronic airway obstruction. An additional analysis was performed to assess the effect of early-life LRI and URI on children unexposed to antibiotics in the first year of life. Analyses were performed using SPSS statistical software, version 21 (SPSS Inc, Chicago, Illinois). All statistical tests were 2-sided.

Results

Prevalence of Asthma

A total of 62,576 children were included in our study. Of these children, 18.5% developed wheezing or asthma between infancy and the age of 7 years (Table 1). The prevalence of asthma was equally distributed among the 3 asthma phenotypes: 5,460 cases (8.7%) were transient, 6,418 (10.3%) were late-onset asthma, and 5,946 (9.5%) were persistent asthma.

Frequencies of Antibiotic Exposure and Respiratory Infection

A total of 26,693 children (42.7%) in the study population were exposed to one or more courses of antibiotic in the first year of life, with a mean of 1.1 courses. A total of 12,131 (19.4%) and 27,537 (44.0%) had at least one episode of LRI and URI, respectively.

Association Between Antibiotic Exposure and Asthma

Antibiotic use in the first year of life was associated with the development of transient wheeze (OR, 2.0; 95% CI, 1.9–2.2; $P < .001$) and persistent asthma (OR, 1.6; 95% CI, 1.5–1.7; $P < .001$). There is no association between antibiotic exposure in infancy and late-onset asthma (Table 2).

After excluding children who experienced asthma or one or more episodes of LRI and URI in the first year of life, premature infants, and children with cystic fibrosis, the association between antibiotic use and the development of transient wheeze and persistent asthma remained (Table 3). A dose-response effect was observed, with each course of antibiotic exposure increasing the risk of developing asthma. When 5 or more antibiotic courses were received, the odds of transient wheeze and persistent asthma doubled; the odds of late-onset asthma remained insignificant.

The association between antibiotic exposure in the first year of life and persistent asthma appeared strongest at the age of 3 years

(OR, 2.5; 95% CI, 2.3–2.6; $P < .001$) and diminished with increasing age (Fig 1). The significance of the association remained at each age and persisted through 7 years of age (OR, 1.3; 95% CI, 1.1–1.5; $P < .001$).

Association Between Respiratory Infections and Asthma

Across all 3 asthma phenotypes, the risk of asthma was heightened in children who experienced LRI or URI in the first year of life (Table 2). Children who experienced LRI in infancy were especially susceptible to developing transient wheeze (OR, 6.1; 95% CI, 5.8–6.5; $P < .001$) and persistent asthma (OR, 5.1; 95% CI, 4.8–5.5; $P < .001$). The risk of developing late-onset asthma was much lower (OR, 1.4; 95% CI, 1.3–1.5; $P < .001$). There is a significant but modest association between early-life URI and all 3 asthma phenotypes.

After excluding children exposed to antibiotics in the first year of life, the association between early-life LRI and asthma diminished but the association for transient wheeze and persistent asthma remained significant (Table 4). However, the effect of LRI on late-onset asthma became insignificant (OR, 0.9; 95% CI, 0.8–1.0; $P = .26$). The association between URI and the 3 phenotypes remained modest but significant.

Discussion

In a large population-level data set, we demonstrate an association between antibiotic exposure in the first year of life and the development of childhood asthma. This association appears to be restricted to children who developed asthma in the first 3 years of life. In half of these children, early asthma was transient and resolved by the age of 3 years. In the remaining children, early asthma persisted after the age of 3 years through to at least 7 years of age. Exposure to antibiotics in infancy doubled the risk of transient wheeze and persistent asthma. This association was not observed in late-onset asthma that precipitated after the age of 3 years.

Adjusting for sex and geographic region did not alter the observed associations. Increased susceptibility to persistent asthma also remained after excluding children with asthma and respiratory illnesses (both upper and lower) in the first year of life, indicating that antibiotic exposure is associated with persistent asthma independent of early respiratory illnesses. A dose-response effect was consistently observed; the risk of childhood persistent asthma increased with increasing antibiotic courses during the first year of

Table 3
Risk of asthma after excluding children with asthma or any respiratory tract illnesses in the first year of life in 29,587 preterm infants and children with cystic fibrosis

Antibiotic exposure	Transient wheeze (n = 1,068)		Late-onset asthma (n = 2,842)		Persistent asthma (n = 1,402)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Any	1.8 (1.6–2.1)	<.001	1.0 (0.9–1.1)	.45	1.3 (1.1–1.4)	<.001
Per course	1.2 (1.2–1.2)	<.001	1.0 (1.0–1.1)	.16	1.1 (1.05–1.1)	<.001
≥5 Courses	2.4 (1.8–3.2)	<.001	1.1 (0.9–1.5)	.68	1.8 (1.3–2.4)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

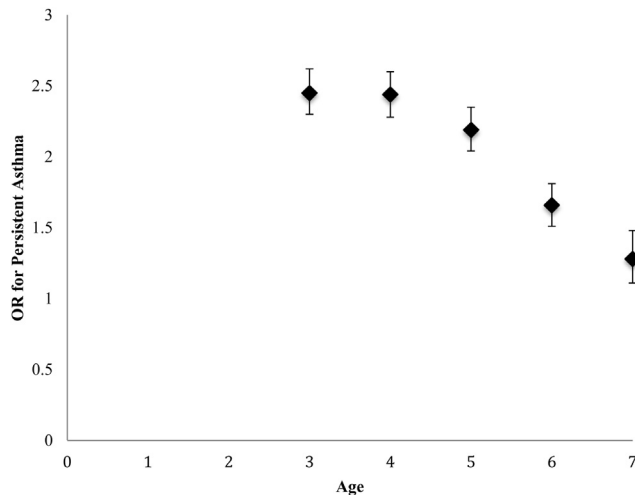


Figure 1. Association between antibiotic exposure in infancy and persistent asthma at 3 to 7 years of age. The odds ratios achieved statistical significance at all ages ($P < .001$).

life. The exclusion of respiratory tract illnesses in the first year of life distinguishes our study from other studies. Our exclusion criteria were stringent, requiring only one physician-diagnosed LRI or URI. This greatly reduces the possibility that residual confounding by LRI or URI during the first year of life drives our finding.

Several studies found an association between antibiotic exposure and asthma development at 2 years and younger but not at ages older than 4 to 5 years.^{23,24} This led to the suggestion that antibiotic exposure was not associated with asthma development but rather that frequent antibiotic use in early life was more common among asthmatic children. Research to date has yielded conflicting findings, with many reporting a lack of association.^{14–18,25} Our results appear to confirm findings in several studies that reported an association beyond the age of 2 years and also demonstrated a dose-response effect.^{26–28}

Unique to our study, stratification of childhood asthma by phenotypes may explain the inconsistencies found in existing studies. Our data revealed that the age at asthma onset is an important determinant, suggesting that any effects antibiotic may have on the development of asthma are likely to manifest in early life. Previous studies have reported that late-onset asthma tend to be nonatopic.^{29,30} These studies, along with our data, suggest that antibiotic exposure may be associated with allergic asthma and not nonallergic asthma. We were unable to confirm this association because claims database does not capture allergen sensitization data. Future studies should explore the differential effect of early-life antibiotic exposure on atopic and nonatopic asthma.

Our analysis examined 3 asthma phenotypes. However, the concept of asthma phenotypes is still evolving, and our knowledge remains incomplete. Although there is strong evidence supporting the existence of an early-onset, mostly atopic and allergic asthma

phenotype, the specific age cutoff for early-onset asthma has yet to be agreed on.³⁰ Other asthma phenotypes have also been proposed, including a study that identified 5 childhood asthma phenotypes based on age at onset, lung functions, atopic functions, treatment response, and environmental and genetic risk factors.³¹ Further studies are needed to assess the consistency of the identified phenotypes.

Our data confirmed existing evidence on the heightened risk of asthma in children with early-life LRI. Strikingly, the association between LRI and childhood asthma was also most evident in children who developed asthma in the first 3 years of life, with a 6- and 5-fold increase in the risk of transient wheeze and persistent asthma, respectively. The strength of the association diminished markedly in late-onset asthma (OR, 1.4). The effect of LRI was attenuated in children unexposed to antibiotics in infancy, with a 5-fold risk of developing transient wheeze and a 4-fold risk of developing persistent asthma. There was no association between early-life LRI and late-onset asthma in children unexposed to antibiotics in infancy. These findings are comparable to those of Kusel et al,¹⁷ who observed that LRI during infancy was significantly associated with subsequent development of persistent asthma that began before the age of 3 years but not with late-onset asthma that precipitated after 3 years of age. The authors hypothesized that resistance to viral infection and childhood asthma may be dependent on an overlapping series of immune mechanisms that are both strongly developmentally regulated and are therefore attenuated in early life. Thus, the age and stage of development of innate and adaptive immune mechanisms at the time of infection greatly influence the outcome.

Our findings are open to 2 broad interpretations. First, antibiotic exposure in the first year of life increases the risk of childhood asthma. This effect is likely to be mediated by intestinal microbial disruption in early life, which translates to heightened susceptibility to asthma, persisting in some children through to early childhood. A second interpretation is that antibiotic exposure in infancy is an indirect marker of asthma risk, without playing direct causal roles. Our studies have addressed the potential confounding caused by exposure to respiratory illnesses in infancy. However, there may be unmeasured confounders, such as immunodeficiency, that both cause the need for antibiotics and heighten the risk of asthma.

Our study has several limitations. First, claims data do not capture some important risk factors of asthma, including mode of delivery in childbirth, ethnicity, family history of asthma, family size (number of siblings), and smoking habit of either parent. Second, an inherent limitation of studies that involve administrative data is the possibility of misclassification. To minimize misclassification errors, we have used a stringent case definition to establish a diagnosis of asthma. Our study may not have identified milder cases that did not seek medical attention. It is also possible that respiratory conditions were not appropriately classified using the ICD-9 diagnosis code. Further, LRIs that did not result in health care visits would not be captured. As such, our study may still be confounded by early LRI. Third, our study participants were children who were insured by

Table 4
Risk of asthma in 35,883 individuals unexposed to antibiotics in the first year of life

Risk factor	Transient wheeze (n=1,877)		Late-onset asthma (n=3,711)		Persistent asthma (n=2,362)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
LRI ^a	5.3 (4.8-5.9)	<.001	0.9 (0.8-1.0)	.26	3.7 (3.3-4.1)	<.001
URI ^a	1.4 (1.2-1.5)	<.001	1.3 (1.2-1.4)	<.001	1.4 (1.3-1.6)	<.001
Male sex	1.2 (1.1-1.3)	.002	1.2 (1.1-1.3)	<.001	1.5 (1.4-1.6)	<.001
Urban	1.1 (1.0-1.3)	.06	1.0 (1.0-1.1)	.35	1.2 (1.1-1.3)	<.001

Abbreviations: CI, confidence interval; LRI, lower respiratory tract infection; OR, odds ratio; URI, upper respiratory tract infection.

^aExposure in the first year of life, expressed as a dichotomous value.

private insurance, most of whom were from urban areas; children who were uninsured or covered by government insurance were not studied. Therefore, findings from these data may not be generalizable to other populations, and the differences between rural and urban populations may not have been sufficiently captured.

An important strength of this study is the inclusion of large numbers of children enrolled continuously since birth through to 5 to 7 years of age. Therefore, our study was based on complete claims data for each participant. In addition, we assessed antibiotic exposures directly through insurance claims, and therefore our study was not subject to recall or other biases inherent in self-reporting. Further, we used a stringent case definition that required either multiple asthma-related health contacts or asthma-specific pharmaceutical claims to establish a diagnosis of asthma, reducing the potential for misclassification of asthma cases. Another strength of this study was the diversity of the study population with regard to geographic region and background. Therefore, the data presented are likely to be broadly generalizable to the commercially insured population of the United States. In contrast, many previous studies were limited by the small sample size with limited diversity.

In conclusion, our data demonstrate that antibiotic use in the first year of life is associated with an increased risk of childhood asthma that precipitates before the age of 3 years. The apparent effect has a clear dose response and provides evidence that supports the hygiene and microbiota hypotheses. Although the association observed does not prove causality, caution should be taken to avoid unnecessary use of antibiotics in infants.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.01.022>.

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eTable 1

International Classification of Diseases, Ninth Revision (ICD-9) codes to identify respiratory conditions

ICD-9 code	Respiratory conditions
277.0	Cystic fibrosis
466	Acute bronchitis, bronchiolitis
480-488	Pneumonia, bronchopneumonia, influenza
490-496	Bronchitis, emphysema, asthma, bronchiectasis, allergic alveolitis, chronic airway obstruction
764-765	Premature birth

eTable 2

Current Procedural Terminology (CPT) codes to identify visit type

Description	CPT code
Outpatient	99201-99205, 99211-99215, 99217-99220, 99241-99245, 99341-99345, 99347-99350, 99382-99386, 99392-99396, 99401-99404, 99411, 99412, 99420, 99429
Acute care inpatient	99221-99223, 99231-99233, 99238, 99239, 99251-99255, 99291
Emergency department	99281-99285