

Original Article

Antibiotic Use in Early Life, Rural Residence, and Allergic Diseases in Argentinean Children

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What is already known about this topic? Antibiotic use in early life has been associated with allergic diseases in some studies but not in others, perhaps due to the effects of concurrent environmental exposures.

What does this article add to our knowledge? Antibiotic use in the first year of life is associated with current wheeze and allergic rhinoconjunctivitis among school-aged children who lived in an urban area of Córdoba (Argentina) early in their lives, but not among children who lived in a rural area early in their lives, suggesting that rural residence in early life may protect against detrimental effects of antibiotic use on allergic diseases.

How does this study impact current management guidelines? Because the link between antibiotic use and allergic diseases requires further investigation, clinicians should adhere to current guidelines for prescribing antibiotics, while educating patients about detrimental effects of inadequate antibiotic use in children, including treatment resistance and alterations of the gut microbiome.

BACKGROUND: Little is known about differential effects of antibiotic use on allergic diseases in rural versus urban environments.

OBJECTIVE: To examine whether area of residence in the first year of life modifies the relation between antibiotic use in early life and allergic diseases during childhood.

METHODS: Cross-sectional study of allergic diseases in 1517 children (ages 6-7 years) attending 101 schools in urban and rural areas of San Francisco (Córdoba, Argentina). Current asthma, wheeze, and allergic rhinoconjunctivitis were defined on the basis of responses to a validated questionnaire from the International Study of Asthma and Allergies in Childhood. Multivariate logistic regression was used for the analysis of antibiotic use and allergic diseases.

RESULTS: After adjustment for paracetamol use, bronchiolitis, and other covariates, antibiotic use in the first year of life was associated with increased odds of current wheeze (odds ratio

[OR], 1.8; 95% CI, 1.3-2.6) and allergic rhinoconjunctivitis (OR, 1.9; 95% CI, 1.3-2.7). After stratification by area of residence, antibiotic use was associated with current wheeze (OR, 2.4; 95% CI, 1.5-4.0) and allergic rhinoconjunctivitis (OR, 2.1; 95% CI, 1.3-3.4) among children who lived in an urban area in their first year of life, but not among those who lived in a rural area in their first year of life.

CONCLUSIONS: Early-life antibiotic use is associated with current wheeze and allergic rhinoconjunctivitis in Argentinean children who lived in urban areas during their first year of life. Exposure to a rural environment early in life may protect against the adverse effects of antibiotics on atopic diseases in children. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Antibiotics; Rural residence; Wheeze; Asthma; Hay fever; Children

Allergic diseases such as asthma and allergic rhinoconjunctivitis are an important public health issue worldwide.^{1,2} A previously noted upward trend in asthma prevalence may have reached a plateau in industrialized countries, but this rising trend continues in developing countries.² The causes of this “asthma epidemic” are unclear but most likely due to changes in environment or lifestyle.

Over the past decade, antibiotic use has substantially increased worldwide, especially in developing countries.³ This is concerning, because antibiotics can disturb the normal gut microbiome, which could alter immune programming and predispose to allergic diseases in children.^{4,5} To date, however, epidemiologic studies have provided inconclusive evidence of a causal link between antibiotic use in early life and asthma or allergic diseases in childhood.^{6,7} For example, a meta-analysis of data from more than 600,000 subjects in 22 studies showed that antibiotic use in the first year of life was significantly associated with 1.5-fold

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Abbreviations used
OR- Odds ratio

increased odds of childhood asthma (95% CI for odds ratio [OR], 1.30-1.77).⁷ However, this association became much weaker and nonstatistically significant when the analysis was restricted to data from longitudinal studies ($n = 9$) and adjusted for confounding by indication (OR, 1.12; 95% CI, 0.98-1.26).⁶

Conflicting results from meta-analyses of epidemiologic studies of antibiotic use and asthma or allergic diseases^{6,7} may be partly due to heterogeneity in population's demographic characteristics, geographic location, and environmental exposures across studies. Indeed, one study reported that antibiotic use in the first 6 months of life was more strongly and significantly associated with atopy (defined as skin test reactivity to at least 1 allergen) in school-aged children who had fewer than 2 pets (OR, 1.73; 95% CI, 1.07-2.80; $P = .02$) than in those with at least 2 pets (OR, 0.25; 95% CI, 0.05-1.20),⁸ a finding that may be explained by immune modulatory effects of bacterial products in mammalian feces or increased richness and diversity of the gut microbiome among children living with pets.⁹

In 2007, Argentina had the highest rate of antibiotic use of all countries in Latin America,¹⁰ a region of the world where both asthma and allergic rhinoconjunctivitis are common.¹¹⁻¹³ In a previous study, we reported that rural residence was associated with reduced odds of current wheeze and allergic rhinoconjunctivitis among adolescents (ages 13-14 years) living in the province of Córdoba (Argentina).¹⁴ Given that finding, as well as a previous report of potential effect modification of the effect of antibiotic use on atopy by presence of animals (pets) in the home,⁸ we hypothesized that antibiotic use would affect the risk of atopic diseases (current wheeze or allergic rhinoconjunctivitis) among children living in urban areas in early life, but not among those living in rural areas in early life (who are often exposed to farm animals and pets, and thus may be less susceptible to the detrimental effects of antibiotics by virtue of a richer and more robust gut microbiota). To test this hypothesis, we examined the relation between antibiotic use in early life and current asthma, current wheeze, and allergic rhinoconjunctivitis among children aged 6 to 7 years in Córdoba, first in all children, and then separately in children who lived in rural versus urban areas during their first year of life.

METHODS

Study population and design

From May to June 2007, all children aged 6 to 7 years who were enrolled in school and resided in the city of San Francisco and the surrounding rural areas (province of Córdoba, Argentina) were invited to participate in this study. Located in the center of Argentina, on a plain area with mild climate, San Francisco has about 60,000 inhabitants and is an industrial center with low levels of air pollution. The surrounding rural areas have a similar climate, and dairy farm activities and grain harvests (soya, corn, and wheat) are common.

The Education Ministry of the Province of Córdoba agreed to facilitate enrollment of all urban and rural students in public schools. A total of 101 public and private schools (22 urban and 79 rural) were contacted by the researchers and agreed to participate. A written questionnaire was then distributed to all children at their

school, for completion by their parents. Of the 2197 questionnaires distributed, 1887 (85.9%) were completed (1686 [89.3%] by the child's mother and 201 [10.7%] by the child's father or another caretaker), as follows: 1315 (83.8%) of 1569 from urban schools, and 572 (91.1%) of 628 from rural schools. Of the 1887 participants, 370 (19.6%) had missing data for at least 1 of the study outcomes (current asthma, wheeze, or allergic rhinoconjunctivitis), leaving 1517 (80.4%) with complete data in the current analysis.

Study protocol

The Spanish version of the International Study of Asthma and Allergies in Childhood phase III core questionnaire was completed for all participants.¹ This questionnaire, widely used in Argentina and other countries, has been shown to be a reliable tool to estimate the prevalence of allergic diseases. Information on any use of antibiotics in the first year of life, any use of paracetamol in the first year of life, and at least 1 hospitalization or visit to the emergency department for bronchiolitis in the first year of life was obtained from the core questionnaire, which was supplemented with questions on sociodemographic and household characteristics, history of allergic diseases, and the living environment. Height and weight were measured by trained personnel after each participant completed the study questionnaire, and approximated to the nearest centimeter and pound, respectively.

The study was approved by the Ethics Committee of the Regional Hospital and informed consent/assent was obtained from study participants.

Statistical analysis

Residence within the limits of San Francisco city was classified as urban, and residence in the area outside any city or population within the San Justo Department was classified as rural (the province of Córdoba is divided into departments, and San Francisco is the Head of the San Justo Department). *Current wheeze* was defined as parental report of any wheeze in the previous year. *Current asthma* was defined as parental report of physician-diagnosed asthma and current wheeze. *Current allergic rhinoconjunctivitis* was defined as parental report of naso-ocular symptoms apart from colds in the previous year.

Variables included in bivariate analyses were age, sex, body mass index, maternal education (completion of high school vs non-completion of high school), birth weight (<2500 g vs ≥ 2500 g), breast-feeding (never, <6 months, ≥ 6 months), number of older siblings (none, 1-2, 3 or more), maternal smoking, paternal smoking, any second-hand smoke at home, parental history of allergy, maternal exposure to farm animals during pregnancy, and current place of residence (rural vs urban). Reported environmental exposures in the first year of life included place of residence (rural vs urban), presence of a cat or dog in the home, consumption of unpasteurized milk (categorized as ever, and also as regular [at least once a week] or not), contact with farm animals (poultry, cows, lambs, horses, or pigs, categorized as ever, and also as regular [at least once a week] vs not), contact with silos of cereal, residence near a dairy farm, and day care attendance.

Wald chi-square tests and t tests were used for unadjusted analyses of binary and continuous variables, respectively. Logistic regression was used for the multivariable analysis of antibiotic use in the first year of life and current asthma, current wheeze, and allergic rhinoconjunctivitis. A stepwise approach was used to build the multivariable models. Variables associated with the outcome of interest at a P value of less than 0.25 were included in the initial models. All

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