

Antibiotic Use and Symptoms of Asthma, Allergic Rhinitis and Eczema in Children

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Abstract

Objective: Allergic diseases are frequent in children and their prevalence and severity differ in different regions of the world. It has been hypothesized that antibiotic use, early in life, may increase the subsequent risk of asthma and other allergic disorders. The aim of this study was to investigate the association between the use of antibiotics in the first year of life and the subsequent development of asthma and other allergic symptoms.

Methods: In our survey using standardized methods (International Study of Asthma and Allergies in Childhood), parents of 6-7 year-old children were questioned regarding asthma, allergic rhinitis and eczema symptoms in their children.

Findings: The prevalence of ever wheezing, wheezing during past 12 months and exercise-induced asthma in the children who took antibiotics in the first year of life were not different statistically but the prevalence of asthma ever was significantly higher. No significant relationship was found between the use of antibiotics and hay fever or eczema.

Conclusion: We found that the use of antibiotics in early childhood was not associated with an increased risk of developing allergic symptoms in children.

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Key Words: Allergy; Antibiotics; Asthma; Rhinitis; Eczema; ISAAC

Introduction

Antibiotics are commonly used to treat infections during early childhood. Over the

past four decades, there has been a significant increase in allergy and asthma in some countries, which correlates with widespread use of antibiotics^[1]. The sales of systemic anti-

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infective agents in general, particularly antibacterials and tuberculostatics, were greater in Iran than in three European countries. Broad-spectrum antibacterial agents accounted for a larger proportion of total sales in Iran [2].

The increase in pediatric allergy and asthma parallels the increase in the use of antibiotics. There is also some evidence that antibiotic and/or paracetamol use may increase the risk of asthma. Antibiotics disturb the flora of the gastrointestinal tract, possibly perturbing the developing immune system [3]. Many lifestyle and medical care characteristics, including the use of antibiotics, have changed the patterns of infectious diseases and bacterial exposure in infancy in the past three decades. Antibiotic use, in addition to affecting the natural history of infection, is well-known to alter gut flora [3]. In industrialized countries, the prevalence of asthma has increased significantly over the last 30 years and is a major public health concern. Although the reasons for asthma epidemic are not clearly understood, one hypothesis is that it is related to the exposure of infants to antibiotics. This is consistent with the "hygiene hypothesis," which suggests that growing up in a more hygienic environment with less microbial exposure may increase atopic (T-helper type 2) immune responses, thus causing the development of asthma.

We studied the relationship between the use of oral antibiotics in the first year of life and asthma, allergic rhinitis, and eczema symptoms at the age 6-7 years in children.

Subjects and Methods

The study was fulfilled by analytic cross-sectional method in 6-7 year-old Yazdi students. Cluster sampling was applied and each school was used as a cluster. Sample size calculated by $P=4\%$ (prevalence of asthma), $\alpha=0.05$ and $d=0.01$ came to 1476 and regarding coefficient clustering and missing data, required sample size was set to 3000.

The questionnaire was designed based on the questions from the International Study of Asthma and Allergies in Childhood (ISAAC); then the validity and reliability of the translated questionnaire were tested. Questionnaires were completed by parents who had children aged 6-7 years. The key asthma questions used were those on 'wheeze ever', 'wheeze in the last 12 months', and 'asthma ever'. The key rhinitis questions used were those on 'nose problems ever (sneezing or runny/blocked nose)', 'nose problems in the past 12 months', and 'nose problems with itchy-watery eyes in the past 12 months'. The key eczema questions used were those on 'eczema ever', 'itchy rash ever' (coming and going for ≥ 6 months), and 'rash in the last 12 months'. The data was first analyzed by Epi6 software and after being controlled, it was translated into SPSS 11.5 software. The results were then analyzed by using Chi-Square, Fisher-Exact, and ANOVA tests.

Findings

There was no significant relationship between early antibiotic use and ever wheezing (OR: 1.13, 95% CI: 0.77-1.67), wheezing during past 12 months (OR: 0.89, 95% CI: 0.41-1.95) and exercise-induced asthma (OR: 1.42, 95% CI: 0.82-2.47) but was associated with asthma ever (OR: 2.21, 95% CI: 1.05- 4.8). No significant relationship was found between the use of antibiotics with hay fever and eczema symptoms (table 1). Antibiotic use during the first year of life was not significantly associated with 'ever hay fever' (OR: 1.22, 95% CI: 0.87-1.72) and eczema (OR: 1.3, 95% CI: 0.79-2.13) symptoms.

Discussion

In our previous study in Yazd city (central Iran) the prevalence of asthma, allergic

Table 1: Antibiotic use during the first year of life and the symptoms of asthma, rhinitis and eczema in 6-7 year-old children

Records	Antibiotic usage in the first year of life				
	Yes N (%)	No N (%)	P Value	95% CI	OR
Ever wheezing	95 (9.9)	46 (8.9)	0.5	0.77 - 1.67	1.13
Wheezing in the past 12 months	52 (55.9)	27 (58.7)	0.7	0.41 - 1.95	0.89
More than 3 attacks of wheezing in the past 12 months	11 (21.6)	5 (18.5)	0.7	0.21-3.08	0.83
One or more nights per week disturbed sleep due to wheezing in the past 12 months	28 (57.1)	9 (33.3)	0.04	0.12-1.12	0.38
Speak limitation due to severe wheezing in the past 12 months	11 (22.4)	3 (12.5)	0.3	0.44-10.5	2.03
Positive history of asthma	39 (4.2)	10 (1.9)	0.02	1.05 - 4.80	2.21
Wheezing during/after exercise in the past 12 months	54 (5.8)	21 (4.2)	0.1	0.82 - 2.47	1.42
Dry night coughs in the past 12 months	166 (17.5)	72 (14)	0.08	0.95 - 1.78	1.3
Ever sneezing, runny or blocked nose	134 (14)	61 (11.8)	0.2	0.87 - 1.72	1.22
Sneezing, runny/blocked nose in the past 12 months	96 (72.2)	45 (73.8)	0.8	0.44 - 1.94	0.92
Sneezing, runny or blocked nose and itchy-watery eyes during the past 12 months	34 (35.8)	12 (27.3)	0.3	0.63 - 3.54	1.49
Daily activity disturbance because of sneezing, runny or blocked nose in the past 12 months	23 (24)	10 (22.2)	0.8	0.35-2.29	0.91
Ever itchy rash	63 (6.6)	27 (5.2)	0.2	0.79 - 2.13	1.3
Itchy rash during the past 12 months	41 (65.1)	19 (70.4)	0.6	0.26 - 2.32	0.78
Severe sleep disturbance because of itchy rash during the past 12 months	15 (37.5)	5 (27.8)	0.4	0.16-2.51	0.64

rhinitis and eczema symptoms in children aged 6-7 years was 10.9%, 15.5% and 7.3% respectively^[4]. Also we showed the association of asthma with acetaminophen usage in the first year of life and indicated that using some drugs in infancy may be an important risk factor for the subsequent development of atopy and asthma^[5].

Research on antibiotic exposure early in life and subsequent risk of asthma and other allergic symptoms has yielded conflicting results. Many studies show that early antibiotic use is associated with the subsequent development of wheezing and other allergic symptoms^[3,6,7,8]. Wjst and colleagues examined a possible association of asthma epidemic and antibiotic use in a population-based study of 2,512 children aged 5-14 years in East Germany. They found that wheezing was associated with an increasing number of antibiotic courses (never versus one time OR 1.9, $P=0.012$, 2 to 5 times OR 3.0, $P<0.001$ and more than 5 times OR 6.9, $P<0.001$) which was also seen for asthma diagnosis. The risk increased with earlier administration (never versus second year OR 4.6, month 7-12 OR 5.4 and birth until month 6 OR 7.9, all $P<0.001$)^[9].

Kozyrskyj and colleagues found that independent from well-known asthma risk factors, asthma was significantly more likely to develop in children who had received antibiotics in the first year of life at age 7 years^[10]. The association with asthma was observed for antibiotic use in non-respiratory tract infections (adjusted OR 1.86; 95% CI 1.02 to 3.37). The risk of asthma was highest in children receiving more than four courses of antibiotics (adjusted OR, 1.46; 95% CI, 1.14 to 1.88), especially among rural children, and in the absence of maternal asthma or a dog in the birth year. Broad-spectrum (BS) cephalosporin use was more common in these subpopulations of children^[10].

Administration of broad-spectrum antibiotics, frequent practice in pediatric offices, impairs intestinal bacterial colonization during infancy^[11]. Noverr et al showed that antibiotic treatment in mice combined with fungal colonization led to

increased sensitization to an airway antigen and to pulmonary allergic responses^[1]. In humans, the immune response of newborns is associated predominantly with the helper T cell type 2 (Th2) cytokine phenotype, whereas rapid suppression of Th2 immune responses during the first year of life occurs in nonatopic children. Atopic individuals exhibit a continuation of fetal allergen-specific Th2 responses during infancy^[12]. Because antibiotic use in infant mice leads to alterations of the intestinal flora and impaired Th1 immune responses, it has been hypothesized that the previously observed association between antibiotic use in early life and asthma in humans is due to antibiotic-induced changes in intestinal flora leading to a Th2-polarized immune deviation^[13]. Nutten and colleagues found that antibiotic administration early in life negatively affects the specific immune response to a luminal antigen when it is first introduced during antibiotic administration. The increased mast cell numbers and mediator concentrations in the intestinal mucosa of the antibiotic-treated animals may testify the early stages of an altered immune system homeostasis^[14].

On the other hand, many studies found no significant association between antibiotic use in the first year of life and the subsequent risk of asthma, recurrent wheezing, allergic rhinitis, or eczema^[15,16].

A US birth cohort study of high-risk children in the Boston area did not implicate antibiotic use in the first year of life as a risk factor for the outcomes of asthma and atopy at the age 5 years, as reported by parents^[15]. Foliaki and colleagues have conducted an ecologic analysis of the relationship between antibiotics sale and the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in 99 centers from 28 countries. The result of this study showed a positive association between per capita antibiotics sale and the prevalence of symptoms for asthma, rhinitis, and eczema, but the associations generally became negative once the analyses had been adjusted for Gross National Product (GNP). Their findings are generally not consistent with the hypothesis that antibiotic use

increases the risk of asthma, rhinitis, or eczema^[17]. Taken together, we found significant association between treatment with oral antibiotics in the first year of life and subsequent ever asthma (OR: 2.21, 95% CI: 1.05–4.80) but not with ever wheezing, wheezing during past 12 months and exercise-induced asthma at the age 6-7 years. Our study could be influenced by recall bias, as parents of children with asthma may be more likely to report an exposure to antibiotics in infancy. Because of the limitations of our study, additional prospective studies are needed to investigate the association between antibiotic use in early life and allergic symptoms in childhood.

Conclusion

Although there are sufficient reasons to avoid unnecessary use of antibiotics, particularly broad-spectrum agents, the results of our study do not support the association between antibiotic use in early life and allergic symptoms in childhood.

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References

1. Noverr MC, Noggle RM, Toews GB, Huffnagle GB. Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. *Infect Immun*. 2004; 72(9):4996-5003.
2. Ansari F. Use of systemic anti-infective agents in Iran during 1997-1998: *Eur J Clin Pharmacol*. 2001;57(6-7):547-51.
3. Johnson CC, Ownby DR, Alford SH, et al. Antibiotic exposure in early infancy and risk for childhood atopy. *J Allergy Clin Immunol*. 2005;115(6):1218-24.
4. Karimi M, Mirzaei M, Ahmadi MH. Prevalence of asthma, allergic rhinitis and eczema symptoms in school aged (13-14 year old) children. *Yazd Scientific Med J*. 2007;6(3):270-5.
5. Karimi M, Mirzaei M. Acetaminophen use and the symptoms of asthma, allergic rhinitis and eczema in children. *Iran J Allergy Asthma Immunol*. 2006;5(2):63-7.
6. Droste JHJ, Wieringa MH, Weyler JJ, et al. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exper Allergy*. 2000;30(11):1547-53.
7. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder, *Thorax* 1998;53(11):927-32.
8. Cohet C, Cheng S, MacDonald C, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Commun Health*. 2004; 58(10):852-7.
9. Wjst M, Hoelscher B, Frye C, et al. Early antibiotic treatment and later asthma. *Eur J Med Res*. 2001;6(6):263-71.
10. Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. *Chest*. 2007; 131(6):1753-9.
11. Bennet R, Eriksson M, Nord CE. The fecal microflora of 1-3-month-old infants during treatment with eight oral antibiotics. *Infection*. 2002;30(3):158-60.
12. Prescott SL, Macaubas C, Smallacombe T, et al. Development of allergen-specific T-

- cell memory in atopic and normal children. *Lancet*. 1999; 353(9148):196-200.
13. Oyama N, Sudo N, Sogawa H, et al. Antibiotic use during infancy promotes a shift in the T(H)1/T(H)2 balance toward T(H)2-dominant immunity in mice. *J Allergy Clin Immunol*. 2001;107(1):153-9.
14. Nutten S, Schumann A, Donnicola D, et al. Antibiotic administration early in life impairs specific humoral responses to an oral antigen and increases intestinal mast cell numbers and mediator concentrations. *Clin Vaccine Immunol*. 2007; 14(2):190-7.
15. Celedón JC, Litonjua AA, Ryan L, et al. Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. *Am J Resp Critical Care Med*. 2002; 166(1):72-5.
16. Harris JM, Mills P, White C, Moffat S, et al. Recorded infections and antibiotics in early life: associations with allergy in UK children and their parents. *Thorax*. 2007; 62(7):631-7.
17. Foliaki S, Nielsen SK, Björkstén B, VonMutius E. Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema: *J Epidemiol*. 2004; 33(3):558-63.

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