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Increased risk of childhood asthma from antibiotic use in early life

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RUNNING HEAD: Antibiotic use in early life and asthma

ABSTRACT

Background: To address the major methodological issues of reverse causation and selection bias in epidemiologic studies of antibiotic use in early life and the development of asthma, we undertook a cohort study of this association in a complete population of children.

Methods: Using Manitoba, Canada's health care and prescription databases, this longitudinal study assessed the association between antibiotic prescription use during the first year of life and asthma at age 7 in a 1995 birth cohort of 13,116 children.

Results: Independent of well-known asthma risk factors, children receiving antibiotics in the first year of life were significantly more likely to develop asthma at age 7. The association with asthma was observed for antibiotic use in non-respiratory tract infections (adjusted OR=1.86, 95% CI: 1.02-3.37). The risk of asthma was highest in children receiving > 4 courses of antibiotics (adjusted OR=1.46, 95%CI: 1.14-1.88), especially among rural children, and in the absence of maternal asthma or a dog in the birth-year. Broad-spectrum cephalosporin use was more common in these subpopulations of children.

Conclusions: Antibiotic use in early life was associated with the development of childhood asthma, a risk which may be reduced by avoiding use of broad spectrum cephalosporins.

50 KEY WORDS: Anti-Bacterial Agents, Infant, Asthma, Child

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73 ABBREVIATIONS

74 MHSIP: Manitoba Health Services Insurance Program

75 BS: broader-spectrum

76 NS: narrow-spectrum

77 SAGE: Study of Asthma, Genes and the Environment

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196 INTRODUCTION

197 Asthma is one of the most common chronic diseases worldwide, significantly impacts quality of
 198 life and represents a significant cost to the health care system.(1-3) The increasing prevalence of
 199 asthma in the industrialized world over the last quarter century have produced several theories on
 200 its origins.(4) In particular, the “hygiene hypothesis” postulates that growing up in a more
 201 hygienic environment with less microbial exposure may promote the fetal immune response
 202 which is skewed in the atopic Th2 direction, whereas microbial pressure would drive the immune
 203 system towards a balanced Th1 and Th2 immunity. (5;6) Studies of farmer children suggest that
 204 early life exposure to endotoxin from gram negative bacteria may be the key element of less
 205 hygienic environments which results in a lower prevalence of allergy and asthma.(7) However,
 206 many argue that the regulation of the immune response is not likely dependent upon external
 207 microbial exposure and have proposed the “microflora hypothesis” of allergic disease.(8) This
 208 theory posits that maturation of the mucosal immune system during infancy, namely the
 209 development of immunologic tolerance via regulatory T cells, requires the presence of
 210 commensal microbial flora in the gastrointestinal tract. (9) Evidence for this thesis comes from
 211 epidemiologic studies which link variations in gastrointestinal microflora and probiotic
 212 administration with less allergy and asthma, (10-12) and from murine models which document
 213 that antibiotic administration causes altered intestinal flora, impaired barrier function, diminished
 214 Th1 immune responses and allergic airway disease.(13-15)

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 216 To date findings from epidemiologic studies have supported(16-22)} and refuted (23-25) an
 217 association between antibiotic use in early life and the development of asthma. Since oral
 218 antibiotics are frequently prescribed for upper and lower respiratory tract infections in children

(26;27), an understanding of the relation between antibiotic use and asthma is critical to clinicians and health care policymakers worldwide. Previous attempts to assess whether the relationship between antibiotic use in early life and asthma is causal have been hampered by cross-sectional or retrospective study design, in which it is difficult to discern whether the association is subsequent to antibiotic use for wheeze-related respiratory illnesses which precede asthma. A recent meta-analysis of antibiotic use in the first year of life has reported a two-fold increased risk of childhood asthma following antibiotic use, but no association among studies conducted prospectively. (28) Further, some studies have been limited to high risk cohorts (23;24) or to urban populations. (25) We examined the association between oral antibiotic use in the first year of life and asthma at age 7 years in a large cohort of children followed from birth, living in urban and rural environments with universal access to health care insurance. As a secondary objective, we tested this association in subgroups of antibiotics and subgroups of children. Preliminary findings from this research have been published in an abstract. (29)

METHODS

This was a longitudinal study (known as the Study of Asthma, Genes and the Environment) of a cohort of 13,980 children born in Manitoba in 1995 and continuously registered with the Manitoba Health Services Insurance Plan (MHSIP) until 2003. The likelihood of asthma at age 7 according to antibiotic prescription use during the first year of life was determined. Data sources were the complete health care administrative records for the cohort, including all physician visits, hospitalizations and prescription drugs collected by MHSIP in the provision of universal health insurance to Manitoba residents. MHSIP databases are reliable and valid data sources.(30;31) Database record linkages were achieved through anonymized personal

identifiers. A family registration number permitted linkage of maternal and child records. This study was approved by the Health Research Ethics Board at the University of Manitoba and the Health Information Privacy Committee.

Current asthma at age 7 was defined as at least two physician visits for asthma, one asthma hospitalization or two prescriptions for any asthma drug (beta-agonists, inhaled corticosteroids, cromones or leukotriene receptor antagonists) in the year following the 7th birthday. This definition was chosen from a validation study in a subset of 539 cohort children recruited for clinical assessment by an allergist, (34) on the basis of a high positive predictive value (94%, 95%CI: 82-99%) and high specificity (92%, 95%CI: 78-98%).

Antibiotic use during the first year of life was categorized by the number of oral antibiotic prescriptions (0, 1-2, 3-4 and 5 or more courses, as classified in other publications testing the association between antibiotic use and asthma development).(25) Pencillin, cloxacillin, cephalixin, cefadroxil and erythromycin were defined as narrow-spectrum (NS) antibiotics. The remaining antibiotics fell into the broad-spectrum (BS) category. Physician visits for childhood infections were classified by the number of lower respiratory tract [bronchitis, bronchiolitis, pneumonia], upper respiratory tract [otitis media, pharyngitis, sinusitis] and non-respiratory tract infections [genito-urinary infections, cellulitis and impetigo]. Risk and protective factors for asthma, derived from health care administrative records, included gender, urban (municipality population > 40,000) or rural location, neighbourhood income, total number of siblings at age 7, number of health care visits during the first year of life and maternal history of asthma (at least one physician visit or hospitalization for asthma or one prescription for an asthma drug).

In order to control for reverse causation, 864 children with asthma diagnoses during the first year of life were excluded. In a subset of 2,859 children, health care database records were linked to parent report of pets in the home during the birth-year of their child. This information was obtained from a mailout survey of the 1995 cohort on health and home environment exposures.

Multivariate logistic regression analysis was conducted with SAS software (SAS Institute, USA). Variables were retained in models at the 95% level of confidence. Separate multivariate models were tested by antibiotic type (NS and BS antibiotics) and for children living in urban and rural areas, for children with and without maternal history of asthma, and for children exposed and not exposed to dogs at birth. Although the stratified analyses were based on a priori questions, the interaction term for antibiotic use and the stratum was tested for statistical significance. Type of antibiotic and timing of administration were compared among these subpopulations of children.

RESULTS

In the study cohort of 13,116 children at age 7 years, 50% were males, 57% lived in urban areas, 24% were low income, 90% had siblings, 6% had current asthma at age 7 and 5% had a maternal history of asthma. 65% of children had received at least one antibiotic prescription during the first year of life. 3% of children received NS antibiotics and no BS antibiotics, 52% received BS antibiotics and no NS antibiotics and 10% received both types of antibiotics. The majority of children (55%) received at least one prescription for a BS penicillin, 9% received a BS cephalosporin and 1% received a BS macrolide (Figure 1). Linkage of a physician diagnosis with an antibiotic prescription dispensed within 7 days following the physician visit showed that 40%

of children received antibiotics for otitis media, 28% for other upper respiratory tract infections, 19% for lower respiratory tract infections and 7% for non-respiratory tract infections.

Following adjustment for gender, maternal history of asthma, number of siblings, urban/rural location and number of health care visits (Model 1 in Table 1), antibiotic use in the first year of life (versus no use) was significantly associated with a greater odds of asthma at age 7. This likelihood increased with the number of antibiotic courses, as confirmed by analyses which treated antibiotic use as a continuous variable (OR=1.09, 95%CI:1.06-1.12). Children receiving more than 4 courses of antibiotics were almost twice as likely to have asthma. Separate adjustments for the number of infections of the lower respiratory and non-respiratory tract reduced, but did not eliminate the association with asthma.

In a model which adjusted for all risk factors for asthma (Table 2), children receiving antibiotics were significantly more likely to develop asthma in a dose-dependent manner. The multivariate model included all of the factors tested with the exception of neighbourhood income and number of upper respiratory tract infections, which were not significantly associated with asthma at age 7. The highest risk of asthma was among children receiving more than 4 courses of antibiotics (OR=1.46, 95%CI: 1.14-1.88). The association between asthma and use of BS antibiotics was statistically significant (OR=1.50, 95%CI: 1.16-1.93), but this was not the case for NS antibiotics (OR=1.35, 95%CI: 0.29-6.23), although the odds ratios were not appreciably different from each other.

Asthma at age 7 was almost twice as likely (OR=1.86, 95% CI: 1.02-3.37) in children receiving one or more antibiotic prescriptions for non respiratory tract infections in comparison to children who had not received antibiotics. These analyses were adjusted for maternal history of asthma, number of health care visits, number of siblings, household income, urban/rural location and gender. A total of 148 children had received antibiotics for non respiratory tract infections only (33 children had urinary tract infections and the remainder had skin infections), as determined from linkage of the antibiotic prescription to the preceding physician visit. This risk for asthma following antibiotic use in non-respiratory tract infections was greater than that for non-respiratory tract infections alone (OR=1.15, see Table 2).

The interaction term for antibiotic use and presence/absence of maternal asthma was statistically significant ($p=0.03$), as was the interaction term for antibiotic use and urban/rural location ($p=0.04$). Limiting the analysis to 7517 children living in urban areas reduced the association with antibiotic use to non-significance (Table 3). However in 5599 rural children the association remained among children receiving more than 4 courses of antibiotics (OR=1.88). Antibiotic use was associated with asthma in children with no history of maternal asthma, especially in children receiving multiple courses of antibiotics (OR=1.57). The interaction term for antibiotic use and presence/absence of a dog during the birth-year was also statistically significant ($p=0.03$). The absence of a dog in the home at birth increased the strength of the association between more than 4 courses of antibiotics and asthma (OR=2.02).

Time to receipt of first antibiotic was shorter in rural than urban children (Table 4, $p=0.06$).

While 100% of children in each subpopulation received BS antibiotics, there were differences in

the use of BS cephalosporins (eg. cefixme, cefprozil, cefuroxime). In comparison to urban children, a significantly higher proportion of rural children received BS cephalosporins. Percentage use of BS cephalosporins was higher, but not statistically significant, in children with no maternal asthma or no dog exposure versus their counterparts. No other group differences in antibiotic type were observed.

DISCUSSION

In a cohort of 13,116 children born in Manitoba in 1995, we found an association between antibiotic use in the first year of life and asthma at age 7. Children receiving more than 4 courses of antibiotics were at one and half times the risk of developing asthma than children not receiving antibiotics. Our analysis adjusted for reverse causation, health care utilization bias and many well-known risk factors for asthma, and used a health care database definition of asthma with a high positive predictive value for allergist diagnosed asthma.(33;34) Moreover, the association was observed for antibiotic use in non-respiratory tract infections, for which the risk of asthma was doubled.

While our findings are consistent with many retrospective surveys and some prospective health care database studies, they do not agree with a similar database study conducted by Celedon.(25) These authors reported no association for asthma until age 5 in children receiving multiple course of antibiotics. We speculate that the discrepant findings are related to differences in populations studied. Almost half of our cohort children lived in rural areas, while the Celedon study drew its data from an urban population. We also did not find an association with antibiotic

use in urban Manitoba children, but the risk was two-fold in rural children receiving multiple courses of antibiotics.

Similar to its distribution worldwide, asthma prevalence was lowest in our rural children, (35) which may be attributed to the protective effect of endotoxin exposure in Manitoba's farming communities. (7;36;37) Urban-rural differences in allergy and asthma are also supported by the "microflora hypothesis." The gut microbiota of infants in more rural countries has higher levels of anaerobic bacteria, such as lactobacilli or bifidobacteria, and lower levels of *Clostridium difficile*.(11;38) These same patterns of gut colonization are more common in non-allergic than allergic infants.(39;40) Antibiotics may alter the protective effect of gut flora in rural children, but have little effect on the gut flora of urban children, which is already predisposed to atopic disease. Of interest, Voor et al also reported an association between antibiotic use and atopy in Estonian children and not in the more urbanized Swedish infants.(41)

An alternate explanation for the increased risk of asthma from antibiotic use in rural children may be related to type of antibiotic, which has not been investigated in intestinal microflora studies of infants. (38-40) All antibiotics decrease anaerobic microflora in infants, but the BS cephalosporins lead to significant suppression of lactobacilli and bifidobacteria, and overgrowth of *Clostridium difficile*. (42-44) The microflora of rural Manitoba children may be subject to the more potent effect of BS cephalosporins. Voor and colleagues have offered a similar account for their findings of increased atopy following antibiotic use in Estonian, but not Swedish children; the former children were more likely to receive broad-spectrum antibiotics.(41) Still another

explanation for the increased risk of asthma among our rural children may be related to the earlier administration of antibiotics following birth. (45)

Children with multiple antibiotics born to women without a history of asthma were at greater risk of developing asthma than those not receiving antibiotics. No antibiotic effect was observed in the presence of maternal asthma, consistent with findings from high risk cohort studies. (24) An increased sensitivity to antibiotics in the absence of maternal asthma may be analogous to the protective effects of dog ownership in children with no parental history of asthma.(46) Postnatal maturation of Th1 immunity is faster in genetically low risk versus high risk children, so low risk children are potentially more susceptible to the effects of early life antibiotic administration on intestinal microflora than high risk children, (47) in whom changes in microflora have already occurred. (48) Alternatively, as with our rural children, increased use of BS cephalosporins may explain the increased asthma among children with no maternal history of asthma.

Lack of dog exposure during the birth-year also increased the antibiotic association with asthma among children taking multiple courses of antibiotics. This concentration of risk for atopy with antibiotic use in children exposed to fewer pets in the first year of year has been reported by others.(45) We hypothesize that lesser contact with dogs during infancy results in a lower microbial load and makes infants more vulnerable to the effects of antibiotics, especially if they are BS cephalosporins.

The strongest evidence against reverse causation in our study is the finding of an association between asthma and antibiotic use for non-respiratory tract infections. The majority of non-

respiratory infections were skin infections, which may represent misdiagnosed atopic dermatitis. Atopic dermatitis in early life is a major risk factor for asthma, as between 50 to 80% of children with atopic dermatitis will develop asthma in childhood.(49) It is the earliest disease manifestation of future allergic asthma. However, recent findings on the immunogenetics of asthma and atopic dermatitis have identified the epithelium as a common pathway for the development of both of these diseases.(50) It is plausible that early life skin infections are manifestations of impaired barrier function of the epithelium, including the gastrointestinal epithelium, which leads to allergen penetration and subsequent inflammation. Antibiotic disruption of intestinal microflora may further increase this inflammation by preventing immunologic tolerance via regulatory T cells.(8) This is suggested in our findings of a greater risk of asthma following antibiotic use in non-respiratory tract infections than for non-respiratory tract infections alone.

Our population-based study of a 1995 cohort of children identified antibiotic use as a risk factor for developing asthma at age 7. While we have constructed our study to diminish the likelihood of reverse causation and confounding bias, and have implemented a validated definition of childhood asthma, we cannot confirm nor refute the causative role of antibiotics in the development of asthma. However, our study has yielded some interesting findings in subpopulations of children, which we postulate are due to use of broad-spectrum cephalosporins or to increased sensitivity to the antibiotic effect among children with genetic predisposition to impaired barrier function of the epithelium. Further large-scale studies are required to determine the longitudinal association between the composition of intestinal microflora, antibiotic use, and atopic dermatitis during infancy, and the development of asthma in low and high risk children. In

the interim, it would be prudent to avoid unnecessary use broad-spectrum antibiotics in the first year of life when other antibiotics are available.

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Insert Figure 1

Table 1. Risk of asthma at age 7 following antibiotic use in the first year of life, adjusted for respiratory and non-respiratory infection episodes

Variable (reference group)	Odds Ratio (95% CI) *			
	Model 1	Model 2	Model 3	Model 4
Courses of antibiotics (none)				
1-2	1.27 (1.06 - 1.53)	1.25 (1.04 - 1.51)	1.27 (1.05 - 1.53)	1.23 (1.02 - 1.48)
3-4	1.41 (1.12 - 1.76)	1.36 (1.08 - 1.70)	1.40 (1.10 - 1.78)	1.35 (1.07 - 1.69)
>4	1.74 (1.37 - 2.22)	1.64 (1.29 - 2.10)	1.72 (1.27 - 2.34)	1.56 (1.22 - 2.00)
Each infection of the lower respiratory tract (e.g. 0 vs. 1, 1 vs. 2, 2 vs. 3 etc)		1.05 (1.02 - 1.09)		
Each infection of the upper respiratory tract (e.g. 0 vs. 1, 1 vs. 2, 2 vs. 3 etc)			1.00 (0.98 - 1.03)	
Each infection of the non-respiratory tract (e.g. skin, urinary tract)				1.15 (1.11 - 1.19)

* All models were adjusted for gender, urban/rural location, maternal history of asthma, number of health care visits and number of siblings

Table 2. Risk of asthma at age 7 following antibiotic use in the first year of life, final model

Variable (reference group)	Odds Ratio (95% CI) * All Children (n=13116)
Courses of antibiotics (none)	
1-2	1.21 (1.01 - 1.46)
3-4	1.30 (1.04 - 1.63)
>4	1.46 (1.14 - 1.88)
Each infection of the lower respiratory tract (e.g. 0 vs. 1, 1 vs. 2, 2 vs. 3 etc)	1.06 (1.02 - 1.09)
Each infection of the non-respiratory tract (e.g. skin, urinary tract)	1.15 (1.12 - 1.19)
Maternal history of asthma	2.21 (1.73 - 2.81)
Number of health care visits during first year	1.01 (1.00 - 1.02)
Number of siblings	0.82 (0.76 - 0.87)
Urban location	1.65 (1.40 - 1.94)
Male gender	1.75 (1.50 - 2.04)

*adjusted for all variables in model

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Table 3. Risk of asthma at age 7 following antibiotic use in the first year of life in specific childhood environments

Variable (reference group)	Odds Ratio (95% CI)	
	Urban (n=7517) ^a	Rural (n=5599)
Courses of antibiotics (none)		
1-2	1.17 (0.94 - 1.45)	1.30 (0.91 - 1.85)
3-4	1.29 (0.99 - 1.68)	1.21 (0.78 - 1.89)
>4	1.22 (0.89 - 1.69)	1.88 (1.23 - 2.88)
	Maternal Asthma ^b (n=672)	No Maternal Asthma (n=12440)
Courses of antibiotics (none)		
1-2	1.11 (0.60 - 2.07)	1.21 (1.00 - 1.48)
3-4	1.34 (0.67 - 2.67)	1.28 (1.00 - 1.63)
>4	0.95 (0.42 - 2.13)	1.57 (1.20 - 2.04)
	Dog Exposure ^c (n=787)	No Dog Exposure (n=2072)
Courses of antibiotics (none)		
1-2	1.67 (0.82 - 3.37)	1.04 (0.69 - 1.55)
3-4	1.68 (0.69 - 4.07)	1.01 (0.60 - 1.72)
>4	0.72 (0.20 - 2.53)	2.02 (1.20 - 3.38)

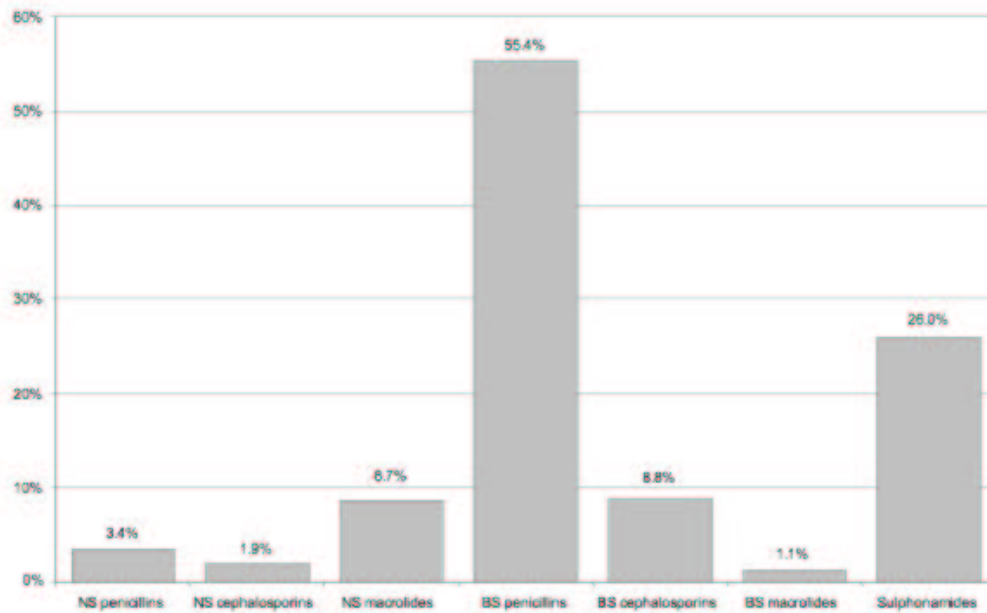
^a adjusted for respiratory/nonrespiratory infections, maternal asthma, number of health care visits, number of siblings and gender

^b adjusted for respiratory/nonrespiratory infections, urban/rural location, number of health care visits, number of siblings and gender

^c adjusted for respiratory/nonrespiratory infections, maternal asthma, urban/rural location, number of siblings and gender

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Figure 1. Frequency of children receiving antibiotics in the first year of life by drug class



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Table 4. Antibiotic characteristics in children with >4 prescriptions in the first year of life by urban/rural status, maternal asthma status and presence of dog

	Number of children	Time to 1st antibiotic Days	p value	BS cephalosporins %	p value
Rural residence	728	119	0.06	47.0	0.0001
Urban residence	773	126		32.1	
No maternal asthma	1381	123	NS	39.8	NS
Maternal asthma	120	122		33.3	
No dog in birthyear	208	134	NS	37.5	NS
Dog in birthyear	72	124		33.3	

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Increased risk of childhood asthma from antibiotic use in early life

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