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Early Childhood's Antibiotic Use and Risk of Allergic Diseases

Mohammad Ehlayel[1, 2*]

1 Weill-Cornell Medical College, State of Qatar.

2 Section of Pediatric Allergy-Immunology, Department of Pediatrics, Hamad Medical Corporation, Doha, Qatar.

*** Correspondence:**

mehlayel@hmc.org.qa
mehlayel@gmail.com

Mohammad S. Ehlayel, MD, FACAAI, FAAAAI, FAAP.
Assoc. Prof., Weill-Cornell Medical College-Qatar.
Senior Consultant, Section of Allergy-Immunology.
Department of Pediatrics, Hamad Medical Corporation.

PO Box 3050.
Doha – State of Qatar.
Office Tel: 974- 4439 2834.
Office Tel: 974- 4439 2321.
Fax Office: 974-4443 9571.

Abstract

This review considers the knowledge on the colonization of the infant's gut with beneficial bacteria starting from early days of life. This colonization drives the developing, but immature, immune system of the infant through the local, intestinal, well-regulated, immune mechanisms, to tolerogenic immune response and "no-disease" state. This response is characterized by TH1 predominance. Any perturbation of this homeostasis by environmental factors such as antibiotics, "swings back" the immune response towards TH2 response, increasing the propensity to develop allergic inflammation, and clinical allergic diseases. There is emerging evidence to support the role of intestinal microbiota in developing allergic disease.

At clinical level, there is vivid research to determine role of antibiotics exposure in developing allergic diseases such as asthma, allergic rhinitis, eczema, and food allergy. The results of studies appear as if they are inconsistent or even conflicting. However, this inconsistency seems to be related to some methodological factors in evaluating the host, exposure, outcome and confounders. Still, there is clear evidence that antibiotic exposure during prenatal period, infancy, or early childhood is associated with high risk of allergic diseases and asthma during infancy, childhood or early adolescence. This risk is governed by individual's genetic background & place of residence, type and dose of antibiotics. It is quite important to remember, that antibiotics exposure or use is only one of the risk factors of increased risk of allergy among children and does not exclusively account for this rise.

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Introduction

Allergic diseases are chronic, non-infectious, immune-mediated diseases [1]. Among them, of major concern, are asthma, allergic rhinitis and atopic dermatitis. They are more common among children than adults. It is estimated that respiratory allergic diseases (asthma, allergic rhinitis) alone affect 700 million individuals in the world [2]. It is noticeable that their prevalence during the last decades had been increasing, but at different rates, in various regions of the world [2-3]. Currently, asthma is the most common chronic childhood condition [3]. In some developed countries the prevalence of asthma reached 35-40 %, whereas it is less

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than 5% in many developing countries [4]; and asthma is still increasing in many low- and middle-income countries [3, 5].

Allergic diseases exert a tremendous impact on affected individuals, their families, and societies. They affect the quality of life, increase risk of comorbid conditions, and risk of death, as in asthma [2, 6]. In addition, the economic burden of these diseases is substantial. It is related to considerable direct medical cost (physician's visits, emergency department visits, hospital admissions, laboratory and radiological workup, therapy… etc.) and indirect medical cost (frequent absences from work or school, reduced productivity, impaired school performance ... etc.) [2, 6, 7]. The fact that these diseases are of high prevalence and chronic, the annual economic impact considerable. For example, makes the total cost of asthma had been estimated to be about £2.5 billion in UK [2]. In USA, between 2002 to 2007, the annual economic cost of asthma was $56.0 billion; direct medical costs were $50.1 billion and indirect costs were $5.9 billion [8].

This prompted extensive research to identify the risk factors and "origin "of asthma. Allergic diseases, including asthma, do not follow simple Mendelian inheritance but they result from the interplay of multiple genetic and interacting environmental factors [9]. Risk factors for development of asthma are numerous, including infectious agents (respiratory syncytial virus, human rhinoviruses, chlamydophila, and mycoplasma), allergen exposure (pollens, house dust mites, indoor pets, and molds), exposure to pollutants (tobacco smoke exposure, diesel exhaust, gases,) and medication exposure [10-12]. These factors work, singly or in combination, at critical "window-time" while infant's immune system is still developing.

Microbial colonization of infant's gut

Newborn's initial exposure to the microbes and gut colonization begin at time of birth and continue during infancy. The development of microbial flora is determined by the density or load (inoculum) of the first maternal microbiota, mode of delivery (vaginal delivery vs. caesarian section delivery), feeding practices (breast feeding vs. formula feeding), and antimicrobial use [13-15]. The type of maternal intestinal microbiota has its clear influence on the type of microbiota colonizing infant's intestine (16). This effect is not limited to the first month of life but it extends for the first few months of infant's life [16].

Infants delivered by caesarian section have been reported to harbor microbiota that is different from that seen in vaginally delivered infants, both in the timing of colonization and the composition of microbiota [14]. When compared to vaginally delivered infants, they take up to one month before similar numbers of bacteria are present, and higher numbers and prevalence of *Clostridium* species, *Klebsiella species*, *Enterobacteriaceae* [14, 17-18]. They are also colonized by *Bacteroides* species, *Bifidobacterium* and *E. coli* [17]. Interestingly, perturbation in the composition of intestinal flora of cesarean section infants last up to at least 6 months of age [19]. Risk of development of atopy, asthma, and allergic rhinitis is higher cesarean section infants [20] possibly due to deviations from in normal gut colonization with maternal flora.

In healthy breast-fed infants, Bifidobacterium constitute 60-70% of the gut microbiota (with predominance of *B. longum*, *B infantis*, and *B. breve* species) compared with formula-fed infants, where *Bacteroides*, *Clostridium and Enterobacteriaceae* predominate [14, 18]. Alterations in composition of intestinal microbial composition that leads to reduced bacterial load of Bifidobacterium species or predominance of more diverse non-beneficial microbiota have been associated with risk of allergies and infections [21] and other diseases [22].

Intestinal microbiota and atopic diseases

Although gut colonization is complete by age of one week, it takes few months for the bacterial species and numbers to become steadily consistent [14, 21]. This relative instability makes the gut colonization with intestinal flora liable to changes with negative impact on infant's health. The composition of intestinal microflora differs between atopic and healthy infants [17]. Atopic children have lower counts of lactobacillus, bifidobacteria and Bacteroides Species. In a large study on 957 Dutch infants, using real-time PCR on stool samples, the presence of *C. difficle* was associated with increased risk of recurrent wheeze, atopic dermatitis and atopic sensitization at age of 2 years [23]. Multiple clinical trials on oral administration of probiotic bacteria (Lactobacillus or Bifidobacteria) to the pregnant women or to the pregnant women and their infants indicate that they reduce risk of allergic diseases especially atopic dermatitis [24, 25]. Breast milk constitutes a major source of support to gut colonization by providing a large amount of galacto-oligosaccharides, which selectively accelerate the growth of bifidobacteria [26] and also it contains Bifidobacteria [27]. Multiple, recent, large, epidemiological studies confirmed the beneficial effects of breast feeding on reducing the risk of asthma, allergic rhinitis, and atopic eczema among children [28-30].

Infant's intestinal microbiota and immune response

In newborn, in addition to its important role in nutrition and metabolism, the gut microbiota functions in promoting and maintaining mucosal immune system, both in terms of its physical factors and function, and maintaining a very well-balanced immune response. Gut-associated mucosal lym-

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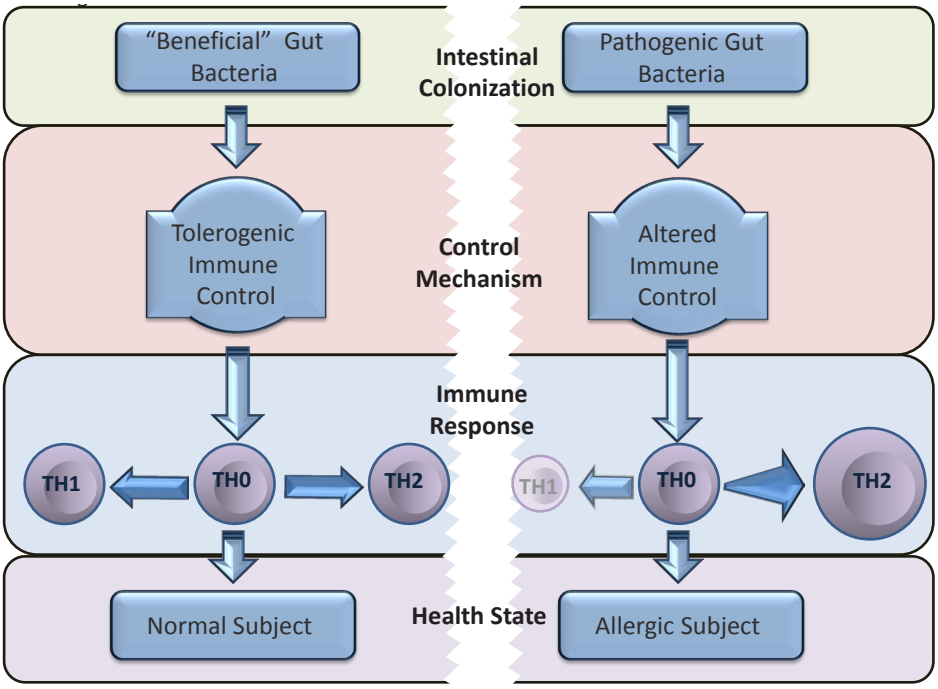

Fig. 1. In healthy subjects, beneficial gut flora stimulates the development of tolerance state (through intraintestinal epithelial cells and dendritic cells and their surface markers) leading to balanced TH1/TH2 response. Alterations (e.g. by antibiotics) disrupts this microbiota, immune tolerance, and induces allergic response.

phoid tissue (GALT) becomes reactive to pathogenic bacteria but tolerant to "beneficial" bacteria. Intestinal microbiota play an important role in development of tolerogenic DC from the mesenteric lymph nodes of the GALT and instrumental in production of secretory IgA.

Intestinal epithelium expresses various pathogen recognitions receptors (PRRs) including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) that activate immune response against pathogens. Since pathogenic bacteria and gut commensals express many of these pathogen-associated molecular patterns (PAMPs) there is a tight control on immune response mechanisms so that it will recognize and specifically respond to pathogens but remain, at same time, tolerant to commensals. These mechanisms involve intestinal epithelial cells (IECs), their TLRs, dendritic cells (DC), and Treg cells [31].

It is known that TH2 cells characterized by their production of IL-4, IL-5, IL-9 and IL-13 contribute to the development of and maintenance of allergic inflammatory process while TH1 cells by producing tumor necrosis-α (TNF-α) and interferon- γ (IFN-γ) modulate cell-mediated immunity. T-regulatory (Treg) cells with their immunomodulatory or immunosuppressive capability maintain immunological tolerance, and are key players in regulating immune response in non-disease states [31]. Deviations from this, in term of Treg numbers or functions, is associated with development of allergic disease (**Fig. 1**). At birth, the neonate's immature immune response is skewed towards TH2-like response. The microbial colonization of the gut stimulates the development of TH1 cells. The microbial strain (commensal or pathogenic) of the gut has an important role (through microbial PAMPs with gut cells-TLRs/NLR interactions) in modulating both intestinal innate and adaptive immune responses. Basic animal studies on germ-free (GF) mice revealed that in absence of microbial colonization, T-cells produced more TH2 cytokines. This TH2-cell predominance was corrected with colonization of GF mice with *B. fragilis* alone, promoted TH1 response, and restored the TH1/TH2 imbalance [32].

Evidence from clinical studies also demonstrated that probiotic bacteria reduced TH2 cytokine pattern while promoting TH1 response [33]. The intestinal microbiota has marked immunomodulatory effects that are essential in maintaining an immune tolerance. Dietary and environmental (e.g. antibiotics) factors can modulate the intestinal microbiota and thus capable of influencing immune response towards allergic diseases and asthma development.

Antibiotics use and allergy risk: any evidence?

Worldwide, antibiotic prescriptions for outpatient use especially in children are usually high. This varies from one country to another [34], and even across the same country it is not uniform [35]. Antibiotics are frequently and commonly inap-

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	Subject (host) factors:
a.	Age of subject at antibiotic exposure: prenatal, perinatal, neonatal, first 6 month, etc.
b.	Genetic background: e.g. presence or absence of family history of allergies.
c.	Place of residence: e.g. urban vs. rural.
	Disease (outcome) factors:
a.	Heterogeneity of allergic diseases: e.g. asthma, eczema, food allergy, or wheeze.
b.	Disease phenotypes: some allergic disease have several phenotypes: e.g. early wheeze, late wheeze, or persistent wheeze.
c.	Validation of allergy diagnosis: e.g. physician-diagnosed allergy, questionnaire-based diagnosis, or laboratory–confirmed diagnosis.
d.	Variation of etio-pathology of allergies: presence of major non-immune mediated mechanisms: e.g. filaggrin in atopic dermatitis, matrix metalloproteinase in asthma, "leaky gut" in food allergy.
e.	Timing of development of the allergic disease: e.g. age of 2, 4, 6, 13 years, or even adulthood.
	Factors related to antibiotics (exposure):
a.	Spectrum of coverage: broad- vs. narrow-spectrum antibiotics.
b.	Classes or combinations of antibiotics; e.g. penicillins, or cephalosporins.
	Study design-related factors:
a.	Study type: e.g. Prospective, retrospective, case control.
b.	Sample size: e.g. large, medium or small.
	Other factors:
a.	Co-existent dietary factors: e.g. vitamin D
b.	Medications: e.g. Paracetmol.

propriately prescribed in the treatment of upper respiratory tract infections in children [36]. It was noticed that there was a correlation between high antibiotics use and development of microbial resistance [37]. It is logical that the observed parallel increase in antibiotic use and the rise in asthma prevalence would prompt research to test any causal relationship [38].

Sources of inconsistent clinical evidence

Numerous epidemiological studies have addressed the possible association between antibiotics during early infancy and development of allergic diseases. The reported results of these studies seem to be inconsistent or even conflicting. The reasons for discrepancies in the results could be attributed to the following methodological differences in evaluating the outcome, exposure and the host (**Table 1**):

1) Factors related to the subjects (hosts) under study. These include:

a. Age of individuals at time of exposure: the chronological time of an antibiotic exposure in a particular study is different from another study. One finds that in various studies there is a broad-spectrum of exposure time including exposures at some perinatal or neonatal period, while in others during the first 1, 3, 6 months, first year or even later.
b. Genetic background of individuals: some studies recruited only high-risk (positive family of allergic diseases in at least one parent or one sibling children). Generally, these studies showed weak or even no association between antibiotic use and allergy development. In studies that were conducted on children with no risk of allergy, the association was more evident.
c. Place of residence: studies conducted on children living in urban areas showed weak or no association compared to those done on children living in rural areas.

2) Factors related to allergic diseases (outcome):

a. Heterogeneity of allergic diseases where these include asthma, recurrent wheeze, atopic dermatitis (eczema), allergic rhinitis, cow's milk allergy.

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b. Some allergic diseases have several phenotypes as the case in wheeze or asthma. It is now known that ''asthma'' is an all-encompassing term for several disease phenotypes each triggered by different etiologic factor [39]. For example, wheeze phenotypes in preschool children include never/infrequent, transient early, prolonged early, intermediate onset, late onset and persistent wheeze [40]. Studies taking "asthma" as an outcome measure without taking in consideration these phenotypes may fail to show association between antibiotics and use this allergic disease.
c. Validation of diagnosis: in various studies the outcome measure was reached differently. For example, in some studies diagnosis of asthma was made by physician, while in others by questionnaire, or confirmed by laboratory tests. In others, the outcome was allergic sensitization (only lab diagnosis of tendency to allergy not necessarily associated with clinical manifestations [41]), which is different from allergy disease (clinical diagnosis).
d. Variation of etio-pathology of allergic diseases. Although these diseases share that they are immune-mediated, there are other non-immunological defects involved of pivotal role in disease etiology. For example, there is increasing evidence on the role of epithelial-barrier disturbance due to filaggrin defects [42] or lipid metabolism abnormalities in atopic dermatitis [43]; or matrix metalloproteinase/extracellular matrix in asthma [44]. These are not immune-mediated mechanisms and unlikely to be related to intestinal microbiota or modified by antibiotics.
e. Timing of the allergic disease: in some studies the occurrence of allergic diseases was evaluated at age of 2-3 years, while in other at 5-6 years or even later at adulthood.

3) Factors related to antibiotics:

a. Factors related to antibiotics: the antibiotic spectrum is dictated by type of infection in these children (e.g. neonatal sepsis versus upper respiratory tract infection). It also is governed by the timing of exposure, i.e. prenatal (e.g. maternal urinary tract infection), natal neonatal (e.g. neonatal sepsis), or first few months of infants life. Based on this, some studies evaluated broad-spectrum antibiotics, while others narrow-spectrum antibiotics, and their relationship to risk of allergies.
b. Different studies evaluated the association with different combinations of classes of antibiotics: e.g. macrolides, penicillins, cephalosporins, etc.

4) Factors related to study designs:

a. Study types: some studies were retrospective while others were prospective, case-controls, or cross-sectional. There are strengths and limitations inherent with each study design. The strength of association varied by the type of the study [45-47].
b. Sample size of children enrolled in these studies varied. It has its detrimental effect on the presence of absence or the strength of association between antibiotic exposure and development of allergies.

5) Other confounders:

In these studies, the possibility of other co-existing confounding factors was not explored apart from simultaneous use of paracetamol with antibiotics [48-49]. There is emerging evidence that vitamin D deficiency during prenatal period [50], or during childhood is associated with asthma [51].

Clinical studies on the association

Since prenatal exposure to environmental factors such as tobacco smoke exposure [52], Mediterranean diet [53], maternal stress [54], or pets [55] have been shown to increase risk of childhood allergies, research tried to determine if antibiotic has similar effect. Basic research on murine models treated prenatally (during 21 days of uterine life) with antibiotics affected mice intestinal microbiota, immune response and risk of asthma [56]. Mouse models exposed during neonatal period to vancomycin or streptomycin (including in utero period) developed experimental allergic asthma while animals exposed during adulthood did not [57]. Bronchoalveolar lavage showed increase of inflammatory cells, eosinophils counts and IgE. This asthma induction in vancomycin treated neonatal mice was associated with reduction in total bacteria in stool pellets, marked shift and reduced diversity of gut microbiota. In addition, there was reduction in Treg cells in the colon, but not in the lungs, of these newborn animals [57].

Prenatal exposure

Clinical studies on the association between indirect antibiotic exposure (during uterine life or lactation period) and allergic diseases showed increased risk for allergic diseases among children. In a large prospective birth cohort, a significantly positive association was demonstrated between prenatal antibiotic exposure and eczema up to age of 4 years, and also a positive but non-significant association with exposure during lactation period and recurrent wheeze [58]. Children recruited from the Copenhagen Prospective Study on Asthma in Childhood cohort had an increased risk of physician-diagnosed asthma and asthma exacerbations associated with material use of antibiotics [59]. The most commonly prescribed antibiotic class was B-lactam penicillins, followed by sulfamethoxazole and trimethoprim, macrolides and others. There was no evidence that a particular antibiotic had higher risk of asthma. The risk of asthma at age of 5 years was independent

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of the timing of maternal exposure to antibiotics for non-respiratory infections. This confirmed that antibiotic use was not confounded by the maternal asthma phenotype or risk. The association of maternal antibiotic use and higher risk of cow's milk allergy in infancy was demonstrated in a large, case-control study [60]. The prenatal use of cephalosporins, macrolides, tetracyclines, and broad-spectrum penicillins was associated with high risk of cow's milk allergy and the highest association was noticed with cephalosporins. In addition, child's use of antibiotics during the first month of life was also associated with an increased risk of cow's milk allergy. This association seems to be contradicting with the case-control, population study of early allergic sensitization in Lithuanian children [61] which showed that among multiple factors, maternal use of antibiotics had no significant impact on early atopic sensitization. A possible explanation for this contradiction that this latter study enrolled high percentage of children with high risk of allergy. In addition, other confounders such as socioeconomic factors, national habits and food were not considered.

Neonatal Exposure

One of the common indications of broad-spectrum antibiotics in the first month of life is neonatal sepsis. A large questionnaire–based (ISAAC) population cohort on children (median age 12 years) showed an association between use and late childhood asthma and also higher risk of eczema [62]. Another, but small, case control retrospective study did not show any association between perinatal antibiotic exposure and food allergy development [63]. The retrospective nature of the study, sample size, the urban based population and deficiency of data on genetic background of children and duration of breast feeding might have influenced the result.

Exposure by age of 6 months

Allergic disease such are quite common during infancy and early childhood. Research supports the association between antibiotic exposure by the age of 3 months and asthma and atopic sensitization [64]. Compared to no-antibiotic children, children who used antibiotics during the first 6 months of life did not show only high association of allergic diseases, they also demonstrated increased atopic sensitization as evidenced by skin prick tests and specific IgE [65]. Furthermore, strong association of antibiotic before 6 months and asthma and allergy (positive skin tests and IgE) was further confirmed and clearly shown that protopathic bias (antibiotic use was for respiratory non-asthma symptoms) had no role account for the main results (66).

Exposure by age of 1 year

Several previous studies reported the association of antibiotic use during the first year of life and allergies. In UK, a large birth control (n=29,238 children) showed association of exposure by age of 1 year and dose-related development of asthma, eczema, and hay fever [67]. A large, longitudinal birth cohort (n=13,116 children) showed antibiotic use by age of 1 year was significantly associated with asthma at age of 7 years [45]. This association was for non-respiratory tract infections and maximum in children who received more than 4 courses of antibiotics living in rural areas, with no maternal risk of asthma, and were not exposed to pets at time of birth. The last factors were also observed in other studies, make children most susceptible to antibiotic effects to develop asthma. This study confirmed the previous study on antibiotic use by age of 1 year and asthma, hay fever and eczema at age of 7-8 years [68]. In the same line, the simultaneous administration of paracetmol during the first year of life was associated with early wheeze (wheeze during the first 2 years of life) and persistent wheeze but weak with late wheeze [69]. This demonstrates the importance of taking in consideration the different phenotypes of asthma or wheeze when evaluating this association. In studies that showed there was no association of antibiotic exposure and childhood asthma, one of the possible reasons for these results that the study did not take in account type of wheeze. This antibiotic use during infancy may not have an increase of risk of asthma or allergies during late childhood [70] (or adulthood [71]).

Meanwhile, some studies reported that antibiotics exposure at age of 1 year is not association with asthma or atopic diseases such as the study on non-randomly selected children living only in metropolitan area and had parental history of asthma or allergies [72]. In addition, asthma diagnosis is difficult before age of 5 years, and eczema diagnosis was uncertain (in this study), and statistical power of the study was limited [72].

Exposure between 2-15 Years

The use of broad spectrum antibiotics during the first 5 years of life is associated with high risk of allergies 2011 [73]. An elegant research on elementary school children indicated that there is interaction between IL-13 genotype (IL-13 characteristically secreted by TH2 cells) and environmental factors, including antibiotic use during infancy for more than 3 days leading to risk of allergic rhinitis [74].

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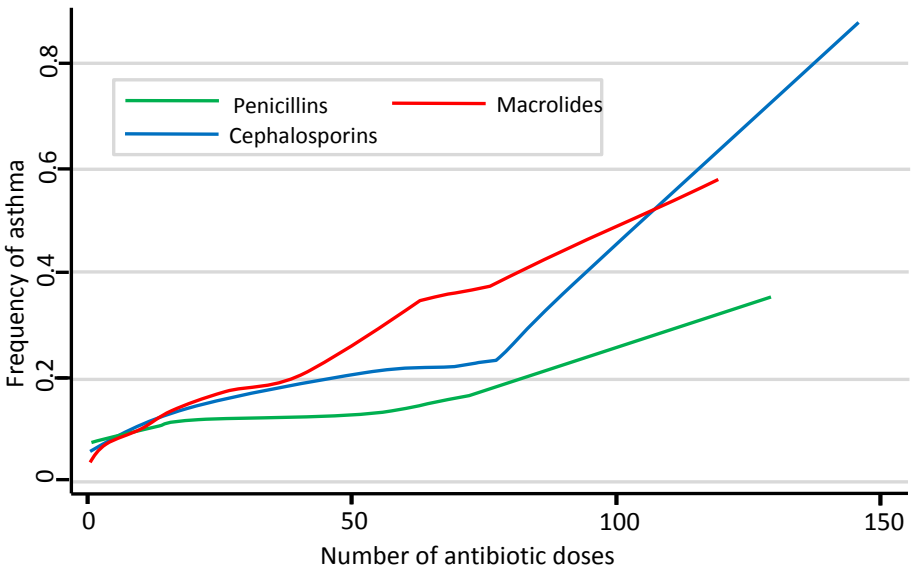

Fig. 2. Asthma frequency is positively associated with number of doses of classes of antibiotics used (Adapted from Jedrychowski et al. [73]).

Exposure during Adulthood

Recently, it has been reported that the total serum IgE, allergy symptoms, and diagnosis of allergic diseases (including TH2 predominance) were significantly higher in those who had antibiotics within 1 year of study compared to those who had antibiotics more than one year [75].

Amount of antibiotics and asthma risk

Studies on risk of asthma development and antibiotics also evaluated this risk in relation to number of antibiotic courses or total number of doses used during infancy. They compared no-courses versus 1-2, 3-4, and more than 4 courses of antibiotics [38, 67-78]. The odd ratio of asthma development related to the number of courses of antibiotics taken in the first year of life was 1.16 (95% CI, 1.05 to 1.28) for each additional course of antibiotics (above one) [79]. This was determined by few studies to be more than 4 courses [59, 67, 79]. The asthma risk was determined to be related to antibiotics doses in a dose-dependent manner (**Fig. 2**) [46].

Type of antibiotics and risk of asthma

Although some studies demonstrated that there was no association between asthma development and type of antibiotics used [80], several other studies demonstrated an association with specific type of antibiotics. However, the combinations of antibiotics varied in different studies. For example, Marra study [38] reported that penicillin, macrolides, cephalosporins and sulfonamide were associated with asthma development. It was also shown that amoxicillin, macrolides, cephalosporins and amoxicillin-clavulanic acid, but not penicillins were associated with asthma [67]. Other studies looked at risk of asthma and antibiotic coverage spectrum, that is narrow-spectrum antibiotics (penicillin, cloxacillin, cephalexin, cefadroxil, and erythromycin) versus broad-spectrum (other) antibiotics. Risk of asthma was higher with broad-spectrum antibiotics than narrow-spectrum antibiotics [45].

Conclusions

Early life exposure or use of antibiotics is associated with increased risk of allergic diseases particularly asthma. This effect is clearly evident during infancy and childhood, but becomes less evident in late childhood or adulthood. It seems that this risk is positively associated with total amount and type or spectrum of antibiotics used. There is increasing evidence that antibiotics, as environmental factors, exert their maximal disruptive effect on beneficial gut commensals in low-risk children living in rural areas. The resulting alteration of the gut commensals drives the immature immune system of the infant towards allergic inflammation, and later development of allergic diseases and asthma.

Taking in consideration the necessity to treat infections with appropriate antibiotics, the judicious use of antibiotics, particularly broad-spectrum antibiotics, in pregnant women and during early life exposure, might be of the cost-effective strategies that could be adopted to reduce the possible risk of childhood asthma and allergies.

Disclosures

No conflict of interest.

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