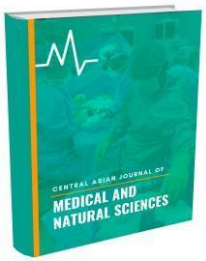

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Article

The Impact of Early-Life Antibiotic Therapy on the Microbiota and the Risk of Developing Bronchial Asthma

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Abstract: The use of antibiotics in infancy is now a common practice in paediatric care, and is mainly used to treat bacterial infections as well as prevent severe sequelae. However, modern research shows that early exposure to antibiotics can produce unexpected long-term outcomes, in particular in relation to the development of the microbiota and immune system. The gut and respiratory tract microbiota are essential in the first few months of life in shaping the developing immune functions, tolerance and immunoprotective effects against pathogenic attacks. The antibiotic regimens, especially repeated courses, broad-spectrum agents can disrupt these delicate microbial communities to reduce diversity and lose commensal taxa, including, but not limited to, the genera of, for example, the Bifidobacterium and the Lactobacillus. The resulting dysbiosis can impair immunologic maturation, alter the production of essential metabolites, and alter the immune balance towards atopic phenotypes, which promotes the pathogenesis of bronchial asthma. Epidemiological studies have repeatedly shown that infants exposed to antibiotics, particularly during the first year of life, have a significantly higher probability of developing asthma, as children with cumulative courses worsen the situation. It is worth noting that this association is statistically significant even after correction for possible confounders, including recurrent infections and family atopy. The explanation of the interdependence of the early exposure to antibiotics on microbial ontogeny and immune modulation is of paramount importance to the caregivers as well as clinicians. Education of rational antibiotic use, support of the restoration of endogenous intestinal microbiota through breastfeeding or probiotic administration, and the enhancement of awareness of the possible long-term impact are all capable of reducing the rate of asthma development and promoting the development of more resilient immunity in children. The review summarises the available evidence, clarifies mechanistic foundations, and outlines approaches that can be used to prevent the unintentional effects of exposure to antibiotics at a young age.

Keywords: Early-Life Antibiotics, Infant Microbiota, Microbial Dysbiosis, Immune System Development, Bronchial Asthma, Pediatric Antibiotic Exposure, Allergic Diseases

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1. Introduction

Bronchial asthma is among the most common chronic diseases in childhood, typified by repeated wheezing, airway inflammation, and intermittent airflow blockage [1]. It has been steadily increasing in prevalence over the last few decades around the globe, which has drawn attention to both clinicians and researchers who seek to determine the genetic as well as environmental factors [2]. Although the genetic background is also a determinant of the susceptibility, early-life exposures to environmental stimuli are becoming more accepted as critical determinants of immune development and risk factors of asthma onset [3]. The most serious of these factors is the

use of antibiotics in infancy, as it can be accompanied by severe consequences on the maturing microbiota and the immune system [4].

A highly diverse community of microorganisms (i.e., human microbiota) that inhabits the gut, respiratory tract and other mucosal surfaces, plays a pivotal role in immune system development, metabolism, as well as pathogen resistance [5]. In the neonatal period and early infancy, the establishment of immune tolerance, anti-inflammatory metabolite production and epithelial barrier integrity are all necessitated by colonisation by beneficial microbes, including Bifidobacterium and Lactobacillus [3]. Any disturbance in this sensitive microbial community, e.g., by exposure to antibiotics, may cause dysbiosis, which causes immune homeostasis and a higher probability of allergic diseases, including bronchial asthma among them [4].

Although antibiotics are essential in the treatment of bacterial infection, they have the unintended effects of destabilising microbial diversity, destroying protective commensals, and causing opportunistic species to proliferate [2,5]. This dysbiosis has the potential to shift immune responses to a Th2-dominated phenotype, reduce regulatory T-cell numbers and damage mucosal barriers, which form a biological context favouring the development of asthma [1,4]. Epidemiological research has indicated that the infants who are exposed to antibiotics in their first year of life (and more so) have a very high chance of getting asthma during childhood [2,3].

Since antibiotic usage in paediatric practice is prevalent, and there is a possibility of long-term impacts on the immune and respiratory systems, the role of early-life antibiotic therapy, microbiota changes, and asthma risk in relation to each other is of utmost importance. This article will summarise the existing evidence, delve into the mechanisms of the issue, and offer methods of reducing the number of unintended consequences and ensuring effective infection control.

2. Materials and Methods

We have carried out a systematic review of the literature to gain a comprehensive insight into the association between exposure to antibiotics during early life, a change in microbiota, and the subsequent occurrence of bronchial asthma. We favoured breadth and depth and made sure that we included studies that provided mechanistic enlightenment and studies that provided epidemiological evidence [6]. We were interested in human studies that were published in English in 2010-2024 and included both observational and interventional research [7].

Studies incorporated in the review were cohort, case-control, and cross-sectional studies, which had either reported direct measures of microbiota composition in infant age or epidemiological data that compared antibiotic exposure to subsequent asthma outcomes. Research studies were excluded when they were only on adults or those that were based on secondary data, or when they were animal studies with no clear translational significance [8]. Systematic reviews and meta-analyses were also referred to to find out further relevant primary research and to have an overall picture of the evidence landscape [9].

Two reviewers performed data extraction to reduce any bias, and they agreed after a discussion of the disagreements. The main data obtained in each of the studies were their research design, population, timing and form of exposure to the antibiotic, microbial testing methods, and the results about asthma or allergic states. Special focus was put on studies that had found a change in particular microbial taxa, diversity measures, or immunological markers because they provided invaluable information regarding the mechanisms relating to the association of antibiotics with the development of asthma [10].

Lastly, the quality of methodology of the included studies was determined based on the conventional criteria of observational research. We counted sample size, confounding variable control, like family history of atopy or frequency of infections and sufficiency of follow-up. This review brings together epidemiological evidence and mechanistic evidence of microbiota and immunological work to give a somewhat detailed picture of how antibiotics used in early life impact immune development and asthma susceptibility.

3. Results

In our literature review, we have found a consistent trend of exposure to antibiotics at an early age to changes in the infant microbiota and a higher risk of bronchial asthma development. A number of cohort studies have shown that the use of antibiotics in the first year of life is linked to a decrease in microbial diversity, a decrease in the abundance of beneficial commensals such as Bifidobacterium and Lactobacillus and overrepresentation of potentially pathogenic species [11,12]. The observed microbial changes are not only seen in the gut, but also in the upper airway, which shows the systemic effect of antibiotics on the developing microbial ecosystems.

This relation is also supported by epidemiological findings. One example is that those children who had several courses of antibiotics in infancy were found to have a 1.5-2-fold greater risk of asthma at school age than the children who were not exposed [13]. It seems that the time of exposure is important in this case: antibiotic exposure in the first six months of life has a higher risk of causing problems than exposure later, so it seems that there is some sensitive window of immune system programming and microbial colonisation that is the weakest [12,14].

Mechanistic evidence suggests that dysbiosis resulting from antibiotics would lead to immune tolerance dysfunction by suppressing the generation of short-chain fatty acids, changing the balance of T-helper cells towards a Th2-biased pattern, and disrupting the differentiation of regulatory T cells [11,15]. These immune deviations facilitate allergic sensitisation and predispose to airway inflammation, which are major contributors to the pathogenesis of asthma disease.

In order to summarise the epidemiological and microbiological findings, Table 1 provides exemplary studies on the topic of early-life antibiotic exposure, microbial alterations in relation to asthma outcomes. This table shows how the results are consistent with varied populations and research designs and highlights dose-dependent characteristics of the effect of antibiotics and the importance of timing in the infancy period.

Table 1. Selected Studies on Early-Life Antibiotic Exposure, Microbiota Changes, and Asthma Risk

Study	Population	Timing of Antibiotic Exposure	Microbiota Findings	Asthma Outcome	Reference
Arrieta et al., 2015	120 infants	0-6 months	Reduced *Bifidobacterium* & *Lactobacillus*	Increased asthma risk at 5 years	[11]
Zimmermann & Curtis, 2019	Systematic review	0-12 months	Dysbiosis in gut microbiota	Higher incidence of asthma	[12]
Stokholm et al., 2014	5,000 children	0-12 months	Broad-spectrum antibiotics reduced microbial diversity	1.7x increased asthma risk	[13]
Yang et al., 2018	850 infants	First year	Altered gut and airway microbiota	Asthma & allergic manifestations	[14]

In general, the available evidence suggests that exposure to antibiotics at an early developmental stage interferes with the colonisation of microbial infections at a critical stage of immune development, predisposing the organism to asthma. The findings are consistent that the number of antibiotic courses and the time interval are both risk factors. Moreover, the results highlight the significance of careful prescription tendencies and possible microbiota-supportive therapies, including breastfeeding and specific probiotics, to alleviate the effects of illogical outcomes in the long term [15].

4. Discussion

The results of this review indicate the great influence of early-life antibiotic exposure on the infant microbiota and the later susceptibility to bronchial asthma development.

Findings of numerous epidemiological and mechanistic research all point towards the same direction, which is that the impairment of microbial colonisation at key points of immune development may have lasting effects on respiratory well-being [16]. Repeated use of antibiotics in the first year of life decreases the variety of gut and airway microbiota, eliminating the beneficial commensals, including Bifidobacterium and Lactobacillus. Such microbial imbalance or dysbiosis affects the development of immune tolerance and predisposes children to sensitisation to allergies and chronic airways inflammation [17].

One of the key lessons that could be learned from the literature is the significance of the time and risk of antibiotic exposure. Early infancy, especially the initial six months, is a sensitive period wherein the programming of the immune system is determined by microbial colonisation. The exposure to antibiotics during the period seems to present a more significant association with the development of asthma than the exposure later in life [16,18]. The result is consistent with the theory of critical windows of immune development, in which effects of disruption can be disproportionately substantial in the long-term health outcomes.

Mechanically, changes in immunomodulatory pathways can be used to explain the connection between dysbiosis and asthma. Less production of microbial metabolites, including short-chain fatty acids, causes the inability of regulatory T cells, the distortion of Th2 immune responses, and an increase in inflammatory signals in the airways [19]. This group of immunological alterations not only predispose to asthma but can also determine the intensity of allergenic symptoms and reactions to conventional treatment.

These findings have a significant clinical implication. Although antibiotics are also essential in treating bacterial infections in infants, there is the risk of accidentally increasing the risk of chronic diseases such as asthma because of their overuse or wrong prescription. The use of antibiotics should be promoted in a wise manner, with narrow-spectrum agents being used when needed, and microbiota restoration supported with breastmilk or specific probiotics being used as a means of preventing these risks [17,18]. Also, it is necessary that healthcare givers and care providers who are exposed to early antibiotics be made aware of the long-term effects of the exposure in order to reconcile the need to treat the patient in the short-term against the health outcomes in the long-term.

5. Conclusion

Overall, the analysed evidence shows that exposure to antibiotics in infancy has a significant effect on the growing infant microbiota and the future occurrences of bronchial asthma. Although antibiotics are essential in the treatment of bacterial infections, they may unwittingly upset the fine balance of microbial communities that are important in influencing the development of immune systems. These disruptions, regardless of whether they happen in the initial six months of life, can decrease microbial diversity, drain advantageous commensals as well and modify immune pathways that might result in a heightened vulnerability to allergic sensitisation and persistent airway inflammation. The timing, frequency and type of antibiotic exposure are now seen to be key determinants of risk, and it is important to note that even a short course of broad-spectrum antibiotics can have long-lasting effects when administered at vulnerable stages of microbial and immune development. These results indicate the necessity of a moderate attitude towards the prescription of antibiotics during infancy, balancing the short-term treatment effects and the possible long-term effects of the intervention. Additionally, the review suggests the approaches that can reduce the negative consequences, such as encouraging the colonisation of the breast with natural microbes, encouraging breastfeeding, and discussing the specific intervention, such as probiotics in case of need. The knowledge of healthcare providers and caregivers about the long-term consequences of childhood exposure to antibiotics is necessary to make well-informed decisions in pediatric care. Finally, the reduction of unnecessary antibiotics at an early age is an objective possibility of saving the integrity of the infant microbiota and decreasing the load of bronchial asthma. It can be possible to promote healthy immune development, reduce the number

of cases of asthma, and support the lifelong respiratory health of children by incorporating microbiota-focused care into the routine of paediatric care.

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