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Adverse effects due to changes in the composition of the intestinal microbiota as result of the administration of antibiotics during the perinatal period

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Abstract

Antibiotic administration commonly induces allergic reactions, dysmicrobism and microbial resistance, but long-term effects due to changes in gut microbiota composition are difficult to assess. This paper aims to identify in the literature adverse effects induced by changes in gut microbiota composition after perinatal administration of antibiotics. Antibiotic administration during pregnancy is a predisposing factor for the development of bronchial asthma, eczema, or allergic rhinitis in children, but does not support the hypothesis as being a risk factor for childhood obesity/overweight. The effect on the newborn's microbiota of prophylactic administration of antibiotics during caesarean section is controversial. Postnatal treatments with antibiotics frequently causes intestinal dysmicrobism, the most severe form being necrotizing enterocolitis, especially among premature infants, but effects on the changes in body weight are controversial. Early administration of broad-spectrum antibiotics, particularly macrolides and cephalosporins, is strongly associated with the development of bronchial asthma at age 5 years. Recently, altered auditory processing and changes in recognition memory were described in newborn exposed to antibiotics in the absence of infection. More studies are needed to clarify the association between the type of antibiotic, the frequency, respectively period (both prenatal and intrapartum) of administration and long-term effects.

Keywords: antibiotics, adverse effects, intestinal microbiota, perinatal period

Individual microbial flora, called microbiota, is indispensable for maintaining the balance and proper functioning of the human body [1]. The mode of birth (natural or caesarean), gestational age and diet are the main defining elements for the composition of the gut flora [2]. Colonization of the gut is a process that takes place over many years, but the key period for establishing the composition of the gut microbiota is the first two years of life, which is decisive for the subsequent development of the microbiota throughout life [3]. The microbiota can be affected or destroyed much more easily in children and the elderly, which can sometimes explain a poor prognosis compared to the young adults, without associated diseases, in which the microbiota in most cases does not undergo any change or undergoes insensible ones.

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During antibiotic treatments, changes in the microbiota occur through the destruction of sensitive bacteria. In the long-term administration of antibiotics, changes can be "felt" in the form of serious negative effects, regardless of the patient's age and immunological capacity. Inadequate or excessive antibiotic administration impairs normal microbial flora and thus its function, causes the development of resistant bacteria or fungi, which can progress to severe forms of necrotizing enterocolitis or result in death [4,5]. Prophylactic administration of antibiotics to the mother, before and during giving birth, can influence the bacterial colonization of the newborn, so that changes in the microbiota composition occur in infants, even if the infant's diet provides the necessary nutrients for the development of different bacteria in the infant's gut [1].

Allergic reactions, dysmicrobism and microbial resistance to antibiotic administration are common and represent immediate adverse effects, but effects that occur late are more difficult to assess. The latter include eczema, obesity, or asthma, which may be due to changes in gut microbiota composition induced by antibiotic treatment. In this context, the paper aimed to identify in the literature adverse effects that are due to changes in gut microbiota composition induced by perinatal administration of antibiotics.

ADVERSE EFFECTS IN THE GUT AFTER PERINATAL ANTIBIOTIC ADMINISTRATION

A particular situation is the prophylactic administration of antibiotics to prevent infections during caesarean section. Drugs that are administered to the mother during labor may cause adverse effects in the newborn. Differences in gut microbiota composition have been observed in babies delivered via cesarean section compared to those born naturally, however there is controversy over the impact of antibiotic administration on the newborn's microbiota, including its subsequent effect on immune system potential, therefore studies are needed to understand the short- and long-term impact on microbiota in infants [6,7].

Group B Streptococci are harmless bacteria in adults, being part of the normal flora at vaginal and rectal level. During childbirth, these can be transmitted to newborns via vaginal secretions, which can cause severe bacterial infections. To prevent transmission to the newborn, antibiotic prophylaxis with a single dose of antibiotic is administered prior to natural childbirth in women who are positive for group B streptococci. Exposure of the infant to the administered antibiotic occurs due to the passage of the antibiotic through the umbilical cord and causes important effects on the gut microbiota of the infant's gut as it reduces beneficial commensal flora and increases potentially pathogenic bacteria [6,8].

Therapeutic antibiotic administration frequently causes intestinal dysmycobacteria, the most severe form being necrotizing enterocolitis. There are two relatively recently published retrospective randomized clinical trials [4,9] that assessed the association between antibiotic exposure and the occurrence of necrotizing enterocolitis among premature infants hospitalized for very low birth weight who were given at least one full antibiotic treatment (Table I). These studies assessed the association between frequency of antibiotic use and mortality and morbidity compared with infants without sepsis.

TABLE 1. Comparison of exposure to at least one full antibiotic treatment and the occurrence of necrotizing enterocolitis in two retrospective randomized clinical trials

	Ting et al., 2016	**Raba et al., 2019**
Time period	2010-2014	2012-2014
Country	Canada	Ireland and Czech Republic
Number of premature infants	13,378 premature infants (of which 11,669 treated with antibiotics)	371 premature infants
Necrotizing enterocolitis	810 (7%)	33 (9%)
Causal relationship	No causal relationship could be identified	Causal relationship between gentamicin or meropenem and intestinal flora

The studies were conducted at approximately the same time, one in Canada [4], the other in two European countries, Ireland and the Czech Republic [9]. The results of the two studies seem contradictory, although the incidence of necrotizing enterocolitis in each of the two studies is very close in value, although one group of premature patients taken in the study [4] was 30 times larger than the group in the second study [9].

In the first study [4], a causal effect of the use of broad-spectrum antibiotics, especially due to cephalosporin or carbapenem groups, and neonatal complications, identified as related to adverse events

and infectious diseases, could not be identified. In the second study [9], infants exposed to gentamicin or meropenem for a long time had a higher risk of necrotizing enterocolitis compared with administration of other antibiotics. Both gentamicin and meropenem are broad-spectrum antibiotics, therefore their antibacterial effect on the intestinal flora explains the reduction of bacteria of species beneficial to the body, which plays a key role in preventing the development of necrotizing enterocolitis.

Although antibiotic administration is essential for the treatment of bacterial infections, prolonged administration of empiric antibiotics to premature infants with sterile cultures in the first week of life is associated with subsequent severe outcome [4].

CONTROVERSY REGARDING THE ASSOCIATION BETWEEN BODY WEIGHT CHANGES AND REPEATED ANTIBIOTIC ADMINISTRATION IN THE PERINATAL PERIOD

The association between ***postnatal antibiotic administration*** and changes in body mass index (BMI), has been evaluated in retrospective cohort studies, with controversial results.

- Trasande et al. analyzed a cohort of 11,532 children in the United States and observed that antibiotic administration in the first 6 months of life is associated with late BMI increase in the 10-38 months range, but antibiotic administration in the 6-12 months period is not correlated with BMI change. Furthermore, the study observed that taking antibacterial drugs in the first 6 months of life is not correlated with being overweight or obese at 7 years of age [10].

- A subsequent study by Bailey et al. on a larger cohort than previously reported, of 65,480 children in the United States, observed a strong association of antimicrobial administration and the occurrence of obesity, especially in children given more than 4 full antibiotic treatments, as well as the association of broad-spectrum antibiotics and increased BMI [11].

- A confirmation of the former observations was performed in another study, coordinated by Saari et al., on a cohort of 12,062 children in Finland. It was observed that repeated administration (more than 4 full antibiotic treatments) of antibiotics before the age of 6 months is a cause of overweight and obesity even before the age of 2 years. Gender analysis showed that boys received more full antibiotic treatments than girls, and 1 in 5 boys who received antibiotic treatments were overweight or obese, compared to 1 in 10 girls. In boys, an inversely proportional relationship was established between age, number of exposures and increased BMI: the earlier antibiotic administration and the greater the number of full antibiotic treatments, the greater the risk of obesity. Moreover, boys who received more than 4 antibiotic treatments were, on average, taller compared to boys who did not receive antibiotic treatments, and for girls, administration of more than 2 cephalosporin treatments resulted in increased height [12].

- In contrast to previous results, the study published by Uzan-Yulzari et al. on a cohort of 14,969 children, observed a reduction in childhood weight and increase in height in boys treated with antibiotics in the first days of life, although previous studies have noted increased risk of overweight and obesity [13].

Antibiotic exposure in the prenatal period and change in body mass index was recently evaluated in a meta-analysis that included 10 observational studies published up to 2019. Analysis of data from these studies does not support the hypothesis that prenatal antibiotic exposure is a risk factor for childhood obesity/overweight. On the other hand, the authors state the need for studies to clarify this hypothesis by assessing the association between antibiotic type and frequency, respectively period (both prenatal and intrapartum) of antibiotic administration [14].

OTHER LONG-TERM ADVERSE EFFECTS AFTER PERINATAL ANTIBIOTIC ADMINISTRATION

According to research conducted to date for the antibiotics most commonly used in practice during pregnancy, penicillin, cephalosporins or macrolides, are considered safe to administer [15].

Bronchial asthma and antibiotic administration in the perinatal period

A 2011 study by Jedrychowski et al. observed that ***early use of broad-spectrum antibiotics***, particularly macrolides and cephalosporins, is strongly associated with the development of bronchial asthma at age 5 years. However, administration of macrolides seems to increase the number of symptom-free days in asthmatic children, probably through their anti-inflammatory effect and less through disruption of the indigenous microbiota [16].

Antibiotic administration during pregnancy is a predisposing factor for the development of bronchial asthma, eczema, or allergic rhinitis in children.

- In this regard, a 2013 study by Stensballe et al. on a cohort of 30,675 children in Denmark found a link between antibiotic use during pregnancy and the development of bronchial asthma or eczema up to the age of 5 years. Mothers with bronchial asthma are more likely to have more episodes of respiratory infections and are at greater risk of passing on the predisposition to asthma to their children. This study observed a link between the number of antibiotic treatments and the occurrence of asthma, with the risk being significantly higher with increasing antibiotic prescriptions [17].

- Another study by Hoskin-Parr [18] looked at a cohort of 14,541 pregnant women in the United Kingdom to assess whether there was any link between the young age at which antibiotics were given and the onset of asthma. A robust and dose-dependent association was observed between antibiotic administration up to age 2 years and the frequency of bronchial asthma onset at age 7.5 years.

- A recent study conducted in 2021 by Şaşihüseyinoğlu et al. analyzed a group of 203 infants who suffered at least one wheezing attack in the first year of life, compared with a group of 223 healthy children selected from a cohort of 30,675 children in Turkey. The researchers observed a much higher prevalence of bronchial asthma in six-year-old children in the first group compared with healthy children and other studies, and identified antibiotic administration during pregnancy and the presence of atopy or allergic diseases in the mother and siblings as favoring factors [19].

Changes in brain function due to antibiotic administration in the perinatal period

A recent study by a group of researchers in the United States [20] observed that newborn exposure to antibiotics in the absence of infection causes changes in functional processes in the central nervous system. The researchers examined recognition memory at 1 month of age in healthy term infants, comparing a group of 15 antibiotic-exposed infants (with negative cultures) with a group of 57 unexposed infants. Infants exposed to antibiotics shortly after birth showed altered auditory processing and changes in recognition memory responses, supporting the possibility of a microbiota-gut-brain axis in humans during early life.

CONCLUSIONS

The administration of antibiotics, as a result of which the microbial flora is altered, is a factor that should not be ignored in the occurrence of adverse effects. The interaction between the antibiotic and the body is not only the result of two factors, but the way an antibiotic affects the body is much more complex. Microbial flora is one of the factors that are influenced by antibiotic administration, and its implications for human health are far beyond what has been previously suspected. Studies now show a clear link between antibiotic administration and intestinal dysmicrobism. Manifestations such as intestinal dyscyclobiasis that progress to severe manifestations such as necrotizing enterocolitis have been readily identified.

Changes in the intestinal flora as a result of antibiotic administration in the postnatal period or in the first years of life have consequences that are observed after a long period of time. Results are controversial in multifactorial diseases. Thus, there is controversy about the timing of antibiotic administration and the change in body mass index. On the other hand, there is clear evidence of a link with increased susceptibility to bronchial asthma and eczema. Recently, changes in the functional processes of the central nervous system in children receiving antibiotics in the first month of life have also been highlighted in other studies. Researchers emphasize that more studies are needed to clarify the effects of the association between the type of antibiotic and the frequency and timing of antibiotic administration.

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