Antibiotic treatment in infants:

effect on the gastro-intestinal microbiome and long-term consequences

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Abstract

The gastrointestinal microbiome is crucial for the development of a balanced immune system. Antibiotics are frequently administered to infants and cause intestinal dysbiosis. Dysbiosis, also called dysbacteriosis, is a term for a microbial imbalance or maladaptation on or inside the body, such as an impaired gastro-intestinal microbiota. The necessity of administration of antibiotics should be well thought through because of short-term adverse effects such as antibiotic associated-diarrhea. This narrative review highlights the long-term health consequences of antibiotic administration to infants and young children, including overweight, inflammatory bowel syndrome, and allergic disease.

Conclusion: The pros and cons of antibiotic administration to infants and young children should be carefully weighed.

What is known

Antibiotics can kill bacterial pathogens but also damage the healthy microbiome.

What is new

Dysbiosis during early infancy may have long term health consequences.

Keywords: antibiotic, immune system, microbiome, microbiota, probiotic, diabetes, overweight, allergy

Abbreviations

AAD antibiotic-associated diarrhea

BMI body mass index

Introduction

The human gut microbiota has been estimated to be up to 100 times more numerous than the cells composing the human body [1]. Microbial colonization of the human gut begins on a small scale in utero since bacteria have been detected in the umbilical cord, placenta, amniotic fluid and also in meconium [2]. After birth, the gastrointestinal tract is colonized by a rapidly diversifying microbiota. During the first years of life a stable gut microbiome is established, and will persist into adulthood. Microbial colonization of the infant gastrointestinal tract begins immediately after birth, and is determined by many factors such as the maternal microbiota, delivery mode, feeding mode and medication such as antibiotics and proton pump inhibitors [1]. Early colonization is crucial for a balanced development of the acquired immune system. In other words: early colonization is a major factor influencing later health.

It has been well established that antibiotics not only kill bacterial pathogens, but they will also profoundly disturb the equilibrium of the gastro-intestinal microbiome and are a well-known cause of dysbiosis. The use of antibiotics increased globally by 36% in the last decade [3]. Sixty-nine percent of children were reported to have been exposed to antibiotics before age 24 months, with a mean (SD) of 2.3 (1.5) episodes per child [4]. The long-term consequences of the intake of antibiotics during the first year of life, its effect of the gastro-intestinal microbiome composition, and the long-term consequences of the latter are the focus of this narrative review. There is a strong association between the microbiota composition and factors such as age, nutrition, stress, and many diseases and conditions such as allergy, diabetes, irritable bowel syndrome, overweight and inflammatory bowel disease. While much of the emerging literature has focused on the potential benefits of probiotic treatment, antibiotics used to treat pathogenic bacterial infections are known to disrupt the diversity and number of microbial organisms in the intestine.

Antibiotic-associated diarrhea

The most frequent and best studied consequence of intestinal dysbiosis as a consequence of antibiotic intake is antibiotic-associated diarrhea (AAD). AAD is an immediate or short-term adverse effect of antibiotic treatment, and occurs in about 20 % of all antibiotic courses, depending on the class of antibiotic, the presence of risk factors in patients (host factors, hospitalization, nosocomial outbreaks) and the definition of AAD. AAD is usually defined as a marked change in stool frequency with at least three liquid stools/day for two consecutive days, occurring from two (early onset) to six (late onset) weeks after antibiotic treatment, and if no other cause can be identified (intercurrent viral or bacterial infection, laxative use, other cause) [5]. The class of antibiotics (broad spectrum), the duration of administration and the age of the patient are risk factors

for the development of AAD. The administration of some probiotic strains such as *Lactobacillus rhamnosus* and *Saccharomyces boulardii* CNCM I-745 reduces the incidence and severity of AAD [6].

Antibiotics early in life

Antibiotics may have a much broader impact, especially if given perinatally or to young infants. The administration of antibiotics intrapartum both during caesarean and vaginal delivery are associated with infant gut microbiota dysbiosis [7]. Maternal intrapartum antibiotic treatment is a key regulator of the initial neonatal oral microbiome [8]. Maternal intrapartum antibiotic prophylaxis will have a significant impact on the infant fecal microbial population, particularly among breastfed infants [9]. Intrapartum antibiotic administration results in a significant reduction in Bifidobacterium spp. strains [10]. The reduced abundance of these beneficial microorganisms, together with an increase in potentially pathogenic bacteria, may suggest these infants are more at risk of gastrointestinal or other health disorders later in age [10]. Dysbiosis acquired perinatally or during early life is likely to induce long term consequences. Maternal antibiotic treatment, administered during pregnancy and lactation results in profound alterations in the composition of the microbiota in mothers and infants [11]. Prenatal antibiotics are associated with a higher body mass index (BMI) at the age of two years [12]. Children experiencing a higher number of respiratory tract infections in the first year of life already demonstrate an aberrant microbial developmental trajectory from the first month of life on [13]. Independent drivers of these aberrant developmental trajectories of respiratory microbiota were mode of delivery, infant feeding, crowding, and recent antibiotic use [13]. Perinatal administration of antibiotics is often lifesaving and thus a medical need. However, special attention should be given to a balanced development of the gastrointestinal microbiome of infants born in these circumstances.

Antiobiotics and long-term health effects

Several types of potential long-term impacts of childhood antibiotic usage are summarized in Table 1. The data are divided into subgroups and estimated odds ratios (OR) are given for each.

Antibiotics and weight

Sub-therapeutic doses of antibiotics have been used as growth promoters in animal farming since the 1950s [14]. The effect is more pronounced for broad-spectrum antibiotics, and is attenuated when animals are raised in sanitary conditions. Burgeoning empirical evidence suggests that antibiotics also affect human growth. As early as 1955, a randomized controlled trial in Navy recruits showed that a 7-week course of antibiotics led to significantly greater weight gain in the treated group compared with placebo [14].

Antibiotic exposure before six months of age or repeatedly during infancy, was associated with increased BMI in healthy children [15]. Repeated exposure to antibiotics early in life, especially β-lactam agents, was shown to be associated with increased weight [16]. This adverse effect of antibiotics may play a role in the worldwide childhood obesity epidemic and highlight the importance of judicious use of antibiotics during infancy, favoring narrow-spectrum antibiotics [15]. Administration of three or more courses of antibiotics before children reach an age of two years is associated with an increased risk of early childhood obesity [17]. In a cohort study, 6.4% children were obese at four years of age and exposure to antibiotics was associated with increased risk [17]. The more antibiotic courses, the higher the risk [17]. Children receiving antibiotics in the first year of life are more likely to be overweight at 12 years of age compared with those who were unexposed (32.4 *vs* 18.2%, P=0.002) [18]. Repeated exposure to broad-spectrum antibiotics at ages 0 to 23 months is associated with early childhood obesity [16]. Sixty-nine percent of children were exposed to a mean of 2.3 antibiotic courses before the age of 24 months and it was shown that repeated exposure to broad-spectrum antibiotics was associated with early childhood obesity [19]. In a large international cross-sectional survey [20], exposure to antibiotics during the first 12 months of life was associated with a small increase in BMI in boys at 5-8 years of age, but not in girls. The intestinal microbiota of infants is thus somewhat predictive of later BMI and may serve as an early indicator of obesity risk. Bifidobacteria and streptococci, which are indicators of microbiota maturation in infants, are likely candidates for metabolic programming of infants, and their influence on BMI appears to depend on antibiotic use [21].

Administration early in life, cumulative exposure and broad-spectrum antibiotics were additional risk factors associated with later obesity. Because common childhood infections were the most frequent diagnoses co-occurring with broad-spectrum antibiotic prescription, narrowing antibiotic selection is a potentially a modifiable risk factor for childhood obesity [19]. In comparison to broad-spectrum antibiotics, narrow-spectrum antibiotics were not at any age or frequency associated with a risk for increased weight [19].

However, some studies do report contradictory results. Exposure to antibiotics within the first six months of life compared with no exposure was also shown not to be associated with a statistically significant difference in weight gain through age seven years [22]. According to a secondary analysis of data from a large clinical trial of trimethoprim-sulfamethoxazole prophylaxis for urinary tract infection, there was no evidence that prolonged exposure to this antibiotic had a concurrent effect on weight gain or the prevalence of overweight or obesity later in healthy infants and young children [23]. Weight gain in the trimethoprim-sulfamethoxazole group and the placebo group was similar (mean (SD) change in weight-for-age z score: +0.14 (0.83) and +0.18 (0.85), respectively; difference, -0.04 (95% CI, -0.19 to 0.12); P = .65). There was no significant difference in weight gain at 6, 12, or 18 months or in the prevalence of overweight or obesity at 24 months (24.8% vs 25.7%; P = .82) [23]. Subgroup analyses showed no significant interaction between weight gain effect and

age, sex, history of breastfeeding, prior antibiotic use, adherence to study medication, or development of urinary tract infection during the study [23].

In summary: although the literature is contradictory and thus the evidence is weak, the administration of broad spectrum antibiotics may be associated with a higher BMI during infancy and childhood.

Antibiotics and immunity and allergy

Symbiotic host and microbe interactions are critical for host metabolic and immune development. Early microbiota colonization may influence the occurrence of metabolic and immune diseases [1].

Maternal use of antibiotics before and during pregnancy was associated with an increased risk of cow's milk allergy in the offspring, and persisted after adjusting for putative confounders [24]. A clear association was found between three or more courses of antibiotics during early life and cow's milk allergy, non-milk food allergy and other allergies in a longitudinal analysis of 30,060 children [24]. The associations were stronger for younger age and differed by antibiotic class [24]. The risk of cow's milk allergy was higher with increasing number of child's antibiotics used from birth to diagnosis of the allergy (test for trend $P < 0.001$) [25]. The association between infant antibiotic exposure and increased atopy, (a genetic disposition to develop an allergic reaction such as allergic rhinitis or asthma), was noted in the multivariate analysis. Prenatal maternal exposure to dogs (OR: 0.60, 95% CI: 0.42-0.84) or acetaminophen (OR: 0.68, 95% CI: 0.51-0.92) was associated with decreased atopy [26].

Antibiotics and the respiratory tract

Delaying the introduction of solid foods to around the age of six months and environmental factors such as living on a farm are protective factors for the development of later allergic disease. But administration of antibiotics during early life are a risk factor for allergic rhinitis and wheezing. Antibiotics during the first year of life are associated with an increased risk for wheezing and asthma up to the age of three and six years, independent of lower respiratory tract infections during the first year of life [27-31]. The strength of the association differs with the class of antibiotics, probably correlating with their effect on the gastrointestinal microbiome [27]. A dose-response effect was observed: when five or more antibiotic courses were administered, the risk of developing asthma increased significantly ($p<001$). Compared with infants with the lowest number of exposures, infants with the highest number of exposures had a 7.77-fold increased odds of developing asthma (AOR: 7.77, 95%CI: 6.25, 9.65) [4]. There is no association between antibiotic use during childhood and late-onset asthma [29]. The increased risk to develop asthma was particularly strong in children

without a family history of asthma (P = 0.03) [28]. Antibiotic use within the first two years of life is a risk factor at the age of five years for current asthma, current atopic dermatitis and current allergic rhinitis [38]. Analysis of the associations by type of antibiotics showed that cephem was associated with current asthma (aOR 1.97, 95% CI 1.23-3.16) and current rhinitis (aOR 1.82, 95% CI 1.12-2.93), and macrolide was associated with current atopic dermatitis (aOR 1.58, 95% CI 1.07-2.33) [38].

Antibiotics and Irritable Bowel Syndrome

A statistically significant link between early life infections and irritable bowel syndrome (IBS) in adults aside from bronchitis could not be demonstrated [33]. These data confirm an early report concluding that antibiotic treatment does not seem to be a major risk factor for recurrent abdominal pain at 12 years of age [34]. However, antibiotic use during the neonatal period was reported to be associated with infantile colic [35].

Antibiotics and Inflammatory Bowel Disease

Exposure to antibiotics throughout childhood is associated with inflammatory bowel disease (IBD), a relationship which decreases with increasing age of exposure to antibiotics. Exposure before one year of age had the highest risk, decreasing at five and 15 years, although even antibiotics at the age of 15 still indicated a significant risk factor to develop IBD [36]. Each antibiotic course increased the risk to develop IBD by 6% (4%-8%) [36]. Antibiotic use is common in childhood, so its potential as an environmental risk factor for IBD warrants scrutiny [37]. Antibiotic exposure was significantly associated with Crohn's disease, being stronger in children, but was not significant for ulcerative colitis [38]. However, causality cannot be confirmed because the antibiotic courses may also be the consequence of unrecognized and undiagnosed symptoms of IBD. [37].

Antibiotics and diabetes

Exposure to a single antibiotic prescription was not associated with higher adjusted diabetes risk, whereas treatment during early life with two to five courses of penicillin, cephalosporins, macrolides or quinolones was associated with an increase in risk for type 2 diabetes but not type 1 [39,40, 41]. The risk increased with the number of antibiotic courses. There was no association with exposure to anti-virals and anti-fungals [39]. However, the findings may also represent an increased demand for antibiotics from an increased rate of infections in patients with yet undiagnosed diabetes [36].

Antibiotics and behavior

Antibiotic use in the first year of life was reported in 70% of 526 children with antibiotic data assessed at age three-and-a-half years. Those who had received antibiotics had more behavioral difficulties and more symptoms of depression at follow-up [1].

Antibiotic resistance

The most prevalent childhood bacterial infections in primary healthcare are respiratory, gastrointestinal and urogenital infections. Antibiotics are often unavoidable and sometimes life-saving. In many developing countries, antibiotic dispensing and its use in medicine, cattle breeding and agriculture are inadequately regulated, or existing laws are not being appropriately enforced. In addition, human travel contributes to antimicrobial drug resistance around the world. Increased travel from Australian citizens to countries where infections with multi-resistant Salmonella enterica subspecies is endemic in countries such as India and Indonesia, has been identified as a cause for the rise of this disease in Australia. All of these factors have led to a very high level of bacterial resistance [41].

Conclusions

Antibiotics can cause intestinal dysbiosis, which in turn is associated with an increased risk for adverse outcomes such as AAD, IBS, IBD, allergy, overweight, etc. Prudent use of antibiotics is important not only to reduce the propagation of antibiotic-resistant organisms but also to minimize the potentially detrimental long-term metabolic consequences of early antibiotic exposure.

The risk for long-term adverse effects of broad spectrum antibiotics should be considered before these drugs are administered to young infants. Wherever possible narrow spectrum antibiotics should be prescribed instead. The administration of some specific probiotics strains such as *Saccharomyces boulardii* have been shown to reduce the risk of short-term adverse effects of antibiotics such as the risk to develop AAD. Future studies should focus on the possible benefit of a rapid restoration of the dysbiosis caused by broad spectrum antibiotics. Whether probiotics might reduce the risk to develop long-term adverse effects of intestinal dysbiosis associated with repetitive antibiotic administration has not been determined and should be a focus of future research.

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Table 1. Antibiotics during early life and health effect.

Reference	**Topic**	**OR**	**95 % CI**
Metsälä [41]	CMPA (AB mother before pregnany)	1.26	1.20-1.33
	CMPA (AB mother during pregnancy)	1.21	1.14-1.28
Batool [26]	Atopy	2.04	1.42.88
Scott [16]	Obesity at 4 years	1.21	1.07-1.38
	Obesity at 4 years (< 3 AB courses)	1.07	0.91-1.23
	Obesity at 4 years (3-5 AB courses)	1.41	1.20-1.65
	Obesity at 4 years (> 6 AB courses)	1.47	1.19-1.82
Azad [17]	Obesity risk in boys	5.35	1.94-14.72
	Obesity risk in girls	1.13	0.46-2.81
	Obesity risk in boys (9 years)	2.19	1.06-4.54
	Obesity risk in girls (9 years)	1.20	0.53-2.70
	Obesity risk in boys (12 years)	2.85	1.24-6.51
	Obesity risk in girls (12 years)	1.59	0.68-3.68
Bailey [18]	Obesity (≥ 4 AB courses)	1.11	1.02-1.21
	Obesity (broad spectrum AB)	1.16	1.06-1.29
	Obesity (AB between 0-5 months)	1.11	1.03-1.19
	Obesity (AB between 6-11 months)	1.09	1.04-1.14
Hirsch [22]	Milk allergy	1.78	1.28-2.48
	Non-milk food allergy	1.65	1.27-2.14
	Other allergies	3.07	2.72-3.46
Risnes [25]	Asthma (>6 years)	1.52	1.07, 2.16

	Asthma (>3 years)	1.66	0.99, 2.79
	Asthma (no LRTI < 1 year)	1.66	1.12, 3.46
	Asthma (neg fam history)	1.89	1.00, 3.58
	Pos allergy test	1.59	1.10, 2.28
Ong [26]	Transient wheezing	2.0	1.9-2.2
	Asthma	1.6	1.5-1.7
	Asthma (>5 AB courses)	1.9.	1.5-2.6.
Alm [39]	Allergic rhinitis	1.75	1.03, 2.97
Yamamoto-Hanada K [38]	Allergic rhinitis	1.65	1.05, 2.58
Metsälä [40]	Asthma (AB mother)	1.31	1.21-1.42
	Asthma (AB infant)	1.60	1.48-1.73
Murk [28]	Asthma (review, all studies)	1.52	1.30-1.77
	Asthma (retrospective studies)	2.04	1.83-2.27
	Asthma (database, prospective studies)	1.25	1.08-1.45
	Asthma (adjusted for resp inf)	1.16	1.08-1.25
	Asthma (onset> 2 years)	1.16	1.06-1.25
	Asthma (AB during pregnancy)	1.24	1.02-1.50
Yamamoto-Hanada K [38]	Asthma	1.72	1.10, 2.70
Wu [4]	Asthma	1.16	1.15, 1.17
	Asthma (AB during pregnancy)	1.06	1.05, 1.08
Pedersen [42]	Otitis media (AB during pregnancy)	1.30	1.04-1.63
	Otitis media (n° of AB courses)	1.20	1.04-1.40
	Ventilation tubes (AB third trimester)	1.60	1.08-2.36
Yamamoto-Hanada K [38]	Atopic dermatitis	1.40	1.01, 1.94
Kronman [32]	IBD (AB < 1 year)	5.51	1.66-18.28
	IBD (AB < 5 years)	2.62	1.61-4.25
	IBD (AB < 15 years)	1.57	1.35-1.84
	IBD (1 or 2 AB courses)	3.33	1.69-6.58
	IBD (> 2 AB courses)	4.77	2.13-10.68
Hviid [33]	IBD	1.84	1.08 to 3.15
	Crohn's disease	3.41	1.45-8.02
	IBD (> 7 AB courses)	7.32	2.14-24.99
Ungaro [34]	Crohn’s disease	1.74	1.35-2.23
	Ulcerative colitis	1.08	0.91-1.27
	Crohn’s disease (in children)	2.75	1.72-4.38
	Crohn’s disease (metronidazole)	5.01	1.65-15.25
	Crohn’s disease (fluoroquinolones	1.79	1.03-3.12
Boursi [35]	Diabetes (> 1 AB course, penicillin)	1.08	1.05-1.11
	Diabetes (> 1 AB course, quinolones)	1.15	1.08-1.23
	Diabetes (> 5 AB course, quinolones)	1.37	1.19-1.58

Legend: OR: Odds ratio; 95% CI: 95% confidence interval; AB: antibiotic; IBD: inflammatory bowel disease; n°: number; pos: positive; resp inf: respiratory infection