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Review

Antibiotic administration and the development of obesity in children

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ABSTRACT

Antibiotics are the most common prescription drugs administered at the paediatric age, however their administration can cause unwanted problems. Among these issues, antibiotic-induced gut microbiota dysbiosis has appeared as an emerging issue and has been associated with obesity. This problem is particularly relevant in children because they are frequently treated with antibiotics. Early development of obesity increases the risk of adult obesity, which is associated with the emergence of very severe clinical problems. Dysbiosis induced in the first periods of life can have the most relevant practical consequences because a decrease in the number of microbes and their substitution with other microbes dramatically modifies the development of the immune system as well as glucose and lipid metabolism. Unfortunately, not all of the mechanisms that could explain the relationship between gut microbiota modification and the development of obesity have been defined. Consequently, no definitive therapeutic approach has been elucidated. Probiotics and prebiotics could play a role in treating microbial dysbiosis because the addition of specific bacterial strains has been associated with normal weight and has been demonstrated to be useful in clinical conditions other than obesity that are caused by microbiota disruption. Considering that antibiotics are commonly prescribed and that obesity is increasing in paediatric patients, further studies specifically designed to evaluate how to disrupt the relationship between antibiotics and dysbiosis are urgently needed. Presently, paediatricians have to consider dysbiosis to be a new and serious reason for the judicious use of antibiotics in clinical practice.

1. Introduction

Antibiotics are the most common prescription drugs administered in paediatric patients [1] and have modified the morbidity and mortality associated with a great number of bacterial infectious diseases, with enormous advantages from a medical, social and economic point of view. However, antibiotic administration can cause unwanted problems. Among these, the development of bacterial resistance and antibiotic-related adverse events were considered the most important problems until a few years ago [2–4]. Recently, however, a series of new problems related to antibiotic-induced gut microbiota dysbiosis have emerged [5]. Of these, obesity appears to be of particular relevance.

Obesity in children is increasing worldwide. Increased weight in the first years of life has been shown to be a significant risk factor for difficult-to-treat obesity at an adult age, with the early development of type 2 diabetes, cardiovascular diseases and a number of other serious co-morbidities [6,7]. Paediatricians must pay particular attention to the potential association between antibiotic use and obesity and consider this problem to be a new and serious reason for the judicious use of antibiotics in clinical practice. In this review, exposure of children to antibiotics will be summarised. The relationships between antibiotic administration, microbiota composition and the development of obesity will be discussed, together with potential therapeutic approaches.

2. Childhood exposure to antibiotics

Beginning in the uterus, children are exposed to antibiotics. An analysis of 987 973 pregnancies of Danish residents during the period 2000–2010 showed that 33.4% of women with a delivery had one or more systemic antibiotic treatments during pregnancy [8].

Moreover, exposure to antibiotics remains very high perinatally and in the first periods of life. A great number of mothers receive antibiotics for prophylaxis of vaginal group B streptococcus (GBS) and caesarean section (CS) delivery, although with differences based on patient characteristics and national recommendations [9,10]. In Canada, Persaud et al. reported that 45.0% of neonates were exposed to antibiotics during the perinatal period [11].

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Overweight women and women with hypertension were significantly more likely to receive intrapartum antibiotics than other women. Moreover, antibiotic treatment of neonates was highest following an emergency CS (12%) or unknown maternal GBS status (20%). Only slightly lower antibiotic prescription rates in the perinatal period were found in countries such as Norway, where maternal intrapartum antibiotic prophylaxis is not recommended in women who undergo elective CS [12], and Denmark, the UK and Australia, where a non-culture-based risk factor approach for GBS prophylaxis is followed [13,14]. For example, Stokholm et al. showed that in Denmark, the prevalence of intrapartum antibiotic use was 33% [13]. Antibiotics were prescribed to all of the women who gave birth by CS and to 13% of those who gave birth vaginally.

A number of neonates, particularly premature infants, receive antibiotics to prevent or treat bacterial infections, mainly early- or late-onset sepsis. A nationwide population-based study from the Norwegian Neonatal Network showed that during the period from 2009 to 2011, 3964 of 168 877 live-born term infants were administered intravenous antibiotics: 39% of all admissions and 2.3% of all live-born term infants [15]. Higher prescription rates were shown in preterm or term infants with relevant clinical problems. In a study involving neonates admitted to the neonatal intensive care unit, more than 88% of extremely low birth weight infants received antimicrobial drugs [16].

Finally, despite a recent reduction after implementing antimicrobial stewardship programmes [17,18], widespread antibiotic use in infants and children remains a relevant health problem in the entire industrialised world, regardless of differences between countries and within the same country. In the USA, it was calculated that in 2010, by the age of 2 years on average a child had received nearly three antibiotic courses, about ten courses by the age of 10 years, and ca. 17 courses by 20 years of age [19]. Most prescriptions were written in an ambulatory setting and were frequently inappropriate, as shown by Hersh et al. [20]. These authors used National Ambulatory and National Hospital Ambulatory Medical Care surveys from 2006 to 2008, which are nationally representative samples of ambulatory care visits in the USA. They reported that antibiotics were prescribed during 21% of paediatric ambulatory visits, and 50% of those prescribed were broad-spectrum. Respiratory conditions accounted for >70% of visits, in which both antibiotics and broad-spectrum antibiotics were prescribed. Twenty-three percent of the visits in which antibiotics were prescribed were for respiratory conditions for which antibiotics are not clearly indicated, accounting for >10 million visits annually.

However, even in countries in which the prescribing pattern usually adheres to national guidelines with respect to the choice of antibiotics, antibiotics are still largely prescribed to children, particularly very young children. Pottegård et al. analysed 5 884 301 prescriptions for systemic antibiotics issued to 1 206 107 children aged 0–11 years from 1 January 2000 to 31 December 2012 in Denmark. They found that prescriptions were written for ca. 800–900 per 1000 children in subjects <2 years, compared with ca. 600 and 300 per 1000 children from 2 to 4 years old and 5–11 years old, respectively [21]. These values were comparable with those reported in Germany [22], Norway [23] and the UK [24], although they are somewhat lower than those previously collected in Sweden [25]. They were significantly higher than those evidenced in The Netherlands [26].

In addition to antibiotic exposure for infection prevention and therapy, children could potentially be substantially exposed to antibiotics through the food supply chain or, more rarely, drinking water. Despite stringent regulations in most countries that limit this type of exposure [27], contamination with traces of these drugs is possible in meats, seafood, milk and municipal water of some villages [28].

Table 1
Conditions associated with exposure to antibiotics through childhood.

Systemic antibiotic treatment during pregnancy
Antibiotic prophylaxis of vaginal group B streptococcus and caesarean delivery
Treatment of early- or late-onset sepsis
Treatment of common paediatric infectious diseases
Food supply chain and drinking water

Table 1 summarises conditions associated with exposure to antibiotics through childhood.

3. Antibiotic use and the development of obesity in children: epidemiological evidence

The antibiotic-mediated promotion of growth in animals was shown several years ago [29] and is widely practiced by farmers to improve the growth of mammalian livestock and poultry [30]. Moreover, the association between antibiotic use and an increase in fat mass has been confirmed in experimental animals [31]. Emerging epidemiological studies have shown that this phenomenon can also occur in humans starting in the foetal stage of life. In the USA, Mueller et al. performed a cohort study of 436 mother–child dyads followed from birth and found that children born to mothers treated with antibiotics in the second or third trimester of pregnancy had an 84% higher risk of obesity at 7 years of age compared with children born to mothers without antibiotic exposure during this time [32]. Similar results were obtained by Mor et al. in a study carried out in Denmark of 9886 school children, 3280 (33%) of whom were prenatally exposed to antibiotics [33]. Adjusted prevalence ratios (aPRs) associated with the exposure were 1.26 [95% confidence interval (CI) 1.10–1.45] for overweight and 1.29 (95% CI 1.03–1.62) for obesity.

An association between early antibiotic exposure and the development of obesity in later paediatric life has also been shown in children who received antibiotics perinatally or in the first months of life. Unfortunately, most of these studies were limited by several factors, such as a small sample size, evaluation of exposure only in infants, analysis of only one antibiotic class, and the inclusion of individuals with serious infections or chronic disease, with the possibility that weight gain might reflect the resolution of the infection or an improvement in the chronic disease [34,35]. However, available data suggest that early antibiotic administration is strongly associated with later overweight or obesity. In particular, a significant risk of increased body mass index (BMI) was shown in a large number of children who were prescribed antibiotics in the first 6 months of life or were given these drugs repeatedly during the first 2 years of life [34,36,37]. Moreover, birth by CS was identified as a risk factor for an increased BMI later in life [38]. Studies carried out in children exposed to antibiotics during foetal life suggested that overweight and obesity related to early antibiotic administration tended to persist until school age and adolescence, even if antibiotics were no longer prescribed. These studies were eventually confirmed. In a study carried out in Canada, antibiotic use in the first year of life was associated with an increased risk of overweight at 9 years and 12 years of age and, in most cases, elevated central adiposity, a well known marker of metabolic syndrome [39]. Moreover, it was found that boys were at greater risk than females.

The data collected by Saari et al. examined 6114 healthy boys and 5948 healthy girls using primary care weight and height measurements and drug purchase data from birth to 24 months [40]. These authors found that all of the children who had received systemic antibiotics during infancy were, on average, heavier than the unexposed children and that the boys were more overweight than the girls [adjusted BMI-for-age z-score difference in boys 0.13 standard deviation (S.D.), 95% CI 0.07–0.19, $P < 0.001$, and in girls