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Impact of antibiotic-induced dysbiosis in childhood: Effects on immunological development and the risk of chronic diseases such as asthma, allergies, and obesity

Impacto de la disbiosis inducida por antibióticos en la infancia: Efectos sobre el desarrollo inmunológico y el riesgo de enfermedades crónicas como el asma, las alergias y la obesidad

Impacto da disbiose induzida por antibióticos na infância: Effects on immunological development and the risk of chronic diseases such asthma, allergies, and obesity

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ABSTRACT

Antibiotic-induced dysbiosis in childhood has significant consequences for immunological development and is associated with an increased risk of chronic diseases such as asthma, allergies, and obesity. Antibiotics alter the composition and diversity of the gut microbiome, which is crucial for the maturation of the immune system. This early alteration can affect local and systemic immunity, including the gut-lung axis. An exhaustive review of the scientific literature published in databases such as PubMed, Scopus, and Web of Science over the last 5 years was conducted. Search terms included combinations of keywords such as "dysbiosis," "antibiotics," "childhood," "immunological development," "asthma," "allergies," "obesity," and "chronic diseases." Observational studies, clinical trials, and systematic reviews that evaluated the association between antibiotic exposure in childhood, the resulting dysbiosis, and the risk of developing chronic diseases were included. Antibiotic-induced dysbiosis in childhood alters immunological development and increases the risk of asthma, allergies, and obesity. A healthy infant microbiome, crucial for immunity, is affected by antibiotics, reducing its diversity. This early dysbiosis is linked to chronic diseases. To mitigate this, rational antibiotic use, dietary modulation with prebiotics, the use of probiotics/symbiotics, and the investigation of antibiotic alternatives are recommended. An integrated approach is key for healthy immunological development and the prevention of chronic diseases.

Keywords: Dysbiosis, Antibiotics, Childhood, Immunological development, Asthma, Allergies, Obesity, Chronic diseases.

RESUMEN

La disbiosis inducida por antibióticos en la infancia tiene importantes consecuencias para el desarrollo inmunológico y se asocia a un mayor riesgo de enfermedades crónicas como el asma, las alergias y la obesidad. Los antibióticos alteran la composición y diversidad del microbioma intestinal, que es crucial para la maduración del sistema inmunitario. Esta alteración temprana puede afectar a la inmunidad local y sistémica, incluido el eje intestino-pulmón. Se realizó una revisión exhaustiva de la literatura científica publicada en bases de datos como PubMed, Scopus y Web of Science en los últimos 5 años. Los términos de búsqueda incluyeron combinaciones de palabras clave como «disbiosis», «antibióticos», «infancia», «desarrollo inmunológico», «asma», «alergias», «obesidad» y «enfermedades crónicas». Se incluyeron estudios observacionales, ensayos clínicos y revisiones sistemáticas que evaluaron la asociación entre la exposición a antibióticos en la infancia, la disbiosis resultante y el riesgo de desarrollar enfermedades crónicas. La disbiosis inducida por antibióticos en la infancia altera el desarrollo inmunológico y aumenta el riesgo de asma, alergias y obesidad. El microbioma infantil sano, crucial para la inmunidad, se ve afectado por los antibióticos, reduciendo su diversidad. Esta disbiosis precoz está relacionada con enfermedades crónicas. Para mitigarla, se recomienda el uso racional de antibióticos, la modulación de la dieta con prebióticos, el uso de probióticos/simbióticos y la investigación de alternativas a los antibióticos. Un enfoque integrado es clave para un desarrollo inmunológico saludable y la prevención de enfermedades crónicas.

Palabras clave: Disbiosis, Antibióticos, Infancia, Desarrollo inmunológico, Asma, Alergias, Obesidad, Enfermedades crónicas.

RESUMO

A disbiose induzida por antibióticos na infância tem consequências significativas para o desenvolvimento imunológico e está associada a um risco acrescido de doenças crónicas como a asma, as alergias e a obesidade. Os antibióticos alteram a composição e a diversidade do microbioma intestinal, que é crucial para a maturação do sistema imunitário. Esta alteração precoce pode afetar a imunidade local e sistémica, incluindo o eixo intestino-pulmão. Foi efectuada uma revisão exaustiva da literatura científica publicada em bases de dados como PubMed, Scopus e Web of Science nos últimos 5 anos. Os termos de pesquisa incluíram combinações de palavras-chave como “disbiose”, “antibióticos”, “infância”, “desenvolvimento imunológico”, “asma”, “alergias”, “obesidade” e “doenças crónicas”. Foram incluídos estudos observacionais, ensaios clínicos e revisões sistemáticas que avaliaram a associação entre a exposição a antibióticos na infância, a disbiose resultante e o risco de desenvolvimento de doenças crónicas. A disbiose induzida por antibióticos na infância altera o desenvolvimento imunológico e aumenta o risco de asma, alergias e obesidade. Um microbioma infantil saudável, crucial para a imunidade, é afetado pelos antibióticos, reduzindo a sua diversidade. Esta disbiose precoce está associada a doenças crónicas. Para atenuar esta situação, recomenda-se a utilização racional de antibióticos, a modulação da dieta com prebióticos, a utilização de probióticos/simbióticos e a investigação de alternativas aos antibióticos. Uma abordagem integrada é fundamental para um desenvolvimento imunológico saudável e para a prevenção de doenças crónicas.

Palavras-chave: Disbiose, Antibióticos, Infância, Desenvolvimento imunológico, Asma, Alergias, Obesidade, Doenças crónicas.

Introduction

Globally, antibiotics continue to save millions of lives, alleviate suffering, and prevent long-term illnesses. Large quantities of these medications are used: for example, in the U.S. alone, more than 250 million antibiotic prescriptions were issued in 2016. It can be reasonably hypothesized that, worldwide, the majority of people (especially children) are treated with an antibiotic at least once a year. Antibiotics are extremely effective and generally lead to the eradication of the targeted pathogenic bacteria. By definition, antibiotics create dysbiosis by killing significant components of the intestinal community. Generally speaking, the levels of drug-resistant *Enterobacteriaceae, Bacteroidaceae, enterococci*, and *Escherichia coli* increase after antibiotic treatment in adults, while the levels of bifidobacteria, lactobacilli, actinobacteria, and Lachnospiraceae decrease. Despite the emergence of antimicrobial resistance as a long-term public health risk, antibiotics remain irreplaceable in the treatment of bacterial infections (1).

Antibiotics should be prescribed to patients with some infectious bacterial pathology; inappropriate prescription can lead to the creation of bacterial resistance and alteration of the balance between humans and their microbiological environment. Nevertheless, high rates of bacterial resistance have already been recorded worldwide in recent years. Antibiotics alter the microbiota of our organism, which can modify the functioning of the immune, endocrine, and metabolic systems, with transient and, in some cases, permanent consequences for health (2).

Changes in lifestyle and environmental factors have been adopted by societies since the industrial revolution, progressing with the human genetic makeup. Consequently, the human microbiome has co-evolved with the genome of its eukaryotic host, colonizing the interfaces with the external world, including the gastrointestinal tract, skin, respiratory tract, and genitourinary tract. Changes in environmental conditions occur at a faster rate than that of the host genome, which is why in recent decades, multifactorial modern diseases such as autoimmune, inflammatory bowel and extraintestinal diseases, metabolic disorders, cancer, and neurological disorders may be associated with an increasing incidence, related to an abnormal microbial structure, called dysbiosis, that affects the taxonomic composition as well as the metagenomic function of the microbial community (3).

Dysbiosis has been associated with many disease states, including autoimmune diseases, metabolic diseases, malnutrition, and others. The microbiota has been shown to play roles in the modulation of the immune system, in hormone secretion and responses, and in metabolism. Therefore, alterations in the composition of the microbiota caused by antibiotics are likely to have additional health consequences, specifically associated with weight gain and metabolic imbalance, as well as susceptibility to diseases. In fact, exposure to antibiotics in early childhood is associated with an increased risk of excessive weight gain, asthma, allergies, and autoimmune diseases, such as inflammatory bowel disease (IBD). As has been demonstrated in germ-free animal models that the microbiota plays a role in the development of brain structure, and potentially function, concerns have also been raised about the possible effects of antibiotics on infant brain development (4).

Methods

A comprehensive review of the scientific literature published in databases such as PubMed, Scopus, and Web of Science from the last 5 years was conducted. The search terms included combinations of keywords such as "dysbiosis," "antibiotics," "childhood," "immunological development," "asthma," "allergies," "obesity," and "chronic diseases." Observational studies, clinical trials, and systematic reviews that evaluated the association between antibiotic exposure in child-

hood, the resulting dysbiosis, and the risk of developing chronic diseases were included. A qualitative analysis of the evidence was performed to synthesize the findings.

Results

Development of the Microbiome in Childhood and its Relationship with the Immune System

The development of the microbiome in childhood is a critical process for the maturation of the immune system, where the interaction between intestinal microbes and immune cells establishes the foundation for immunity and mucosal homeostasis. Dysbiosis, especially that induced by antibiotics, can disrupt this balance, affecting pulmonary immunity through the gut-lung axis and increasing the risk of chronic diseases such as asthma and allergies. Factors such as short-chain fatty acids (SCFAs) and secretory immunoglobulin A (sIgA) play key roles in this relationship, underscoring the importance of a healthy microbiome in early life for long-term health (5).

The development of the gut microbiome (GM) in the first years of life is a crucial process that significantly impacts the infant immune system. Although initially it was considered that bacterial colonization mainly came from the maternal vaginal microbiota, recent research suggests the possible existence of a uterine microbiota, although its influence is smaller. During the first few days, the infant's GM evolves from aerobic and facultative anaerobic bacteria to anaerobes such as Bifidobacterium and Clostridium, an essential process for immunological maturation that culminates around 1-3 years of age (6).

Various factors, such as gestational age, type of birth, antibiotic use, feeding, and environment, can alter this GM maturation process. Breastfeeding, rich in human milk oligosaccharides (HMOs) and IgA, plays a key protective role against diseases such as necrotizing enterocolitis (NEC). Gut dysbiosis, an imbalance in the GM, is associated with childhood diseases such as sepsis, obesity, and behavioral disorders, negatively affecting the immune response. A healthy GM, promoted by breastfeeding and an appropriate environment, is essential for the optimal immunological development of the child (6).

Antibiotics and their Impact on Microbiome Composition

Antibiotics exert a profound impact on the composition of the gut microbiome, especially in the context of inflammatory bowel diseases such as severe acute ulcerative colitis (SAUC). Their use tends to reduce bacterial diversity, altering the balance between microbial populations and, in some cases, favoring the growth of pathogens. This alteration can influence the response to treatment, as observed in patients with SAUC, where initial microbial diversity is negatively correlated with the response to steroids, an effect that is modified by the introduction of antibiotics. Furthermore, the risk of antibiotic resistance, although transient for many agents, underscores the need for prudent use of these drugs (7).

The impact of antibiotics on the composition of the infant microbiome is a topic of growing concern in medical research. Recent studies have shown that the administration of antibiotics, especially in the early years of life, can significantly alter the diversity and composition of the gut microbiome. This alteration not only manifests as a reduction in bacterial richness but also as specific changes in the abundance of certain bacterial phyla and genera. Specifically, a decrease in beneficial bacteria such as Bifidobacteria and Lactobacilli, which play a crucial role in the production of short-chain fatty acids and in the maintenance of gut health, has been observed. At the same time, an increase in the presence of Bacteroidetes and Proteobacteria, phyla that include potentially pathogenic species, has been detected. Furthermore, the loss of species such as

Akkermansia muciniphila, known for its anti-inflammatory properties, underscores the complexity of the effects of antibiotics on the microbiome (8).

It is important to note that the magnitude and duration of these changes vary depending on the type of antibiotic used, the duration of treatment, the age of the child, and other individual factors. Although some studies suggest that these changes may be transient, others indicate that they can persist in the long term, with potential implications for the child's health. Therefore, it is essential to carefully consider the use of antibiotics in the pediatric population and explore strategies to mitigate their impact on the microbiome (8).

Effects of Antibiotics on the Gut Microbiota

Antibiotics alter the gut microbiota, reducing its diversity, modifying the metabolome, and promoting bacterial resistance (9).

Reduced Diversity

The use of antibiotics decreases the diversity of species in the microbiota, an effect that can persist for months. This imbalance favors the growth of pathogens such as *C. difficile*. Although the diversity of species decreases, the total bacterial load may increase (9).

Altered Metabolome

Antibiotics modify the gut metabolome, an area less studied than microbial diversity. These changes, observed in studies with mice, include alterations in the metabolism of carbohydrates, lipids, and amino acids, and may influence susceptibility to infections (9).

Antibiotic Resistance

The excessive use of antibiotics drives bacterial resistance, a global threat. Bacteria develop mechanisms to resist antibiotics, including altering their membranes and producing neutralizing enzymes. The gut microbiota acts as a reservoir of resistance genes (9).

Relationship between Early Dysbiosis and Chronic Diseases, Specific Mechanisms through which Dysbiosis Contributes to these Diseases

Asthma and Allergic Diseases

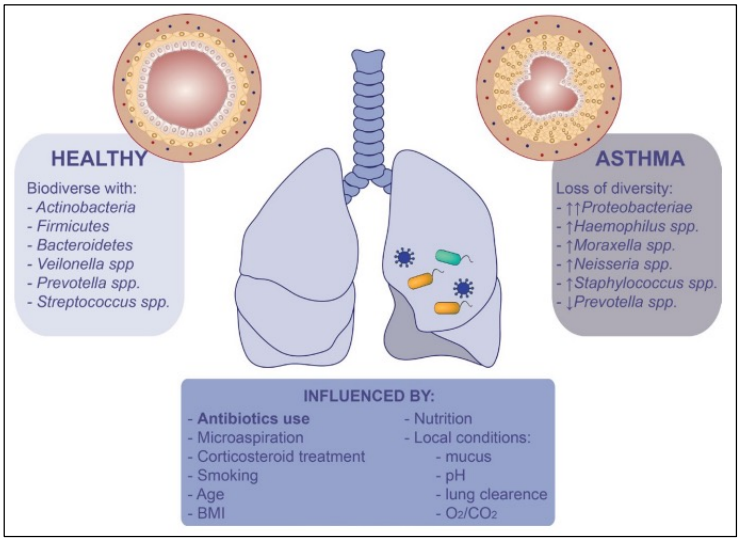

Figure 1. This figure summarizes the respiratory microbiome patterns found in healthy and asthmatic subjects. The composition of the microbiome is also influenced by other factors besides the disease condition

Fuente: Tramper-Stranders et al (10).

The pulmonary microbiome has revealed its importance in the pathogenesis of asthma since the first study on this topic was published in 2010. Despite the previous belief that the lower respiratory tract was sterile, research has documented the presence of distinct bacteria and oral flora in this region, suggesting that certain microbiome profiles may influence the onset and exacerbations of asthma. In infants, the composition of the respiratory microbiome has been linked to the development of wheezing and asthma. Specifically, associations of childhood asthma with the colonization of the upper respiratory tract by bacteria such as *Haemophilus influenzae* and *Moraxella catarrhalis* have been found. Studies prior to 16S sequencing methods identified Mycoplasma *pneumoniae* and *Chlamydophila pneumoniae* with severe asthma, while an increase in microbiota diversity correlated with better asthma control in some cases, and with more symptoms in others, depending on colonization factors (10).

The interaction between the host and organisms such as M. pneumoniae has been observed, as allergy and asthma can hinder their elimination, triggering inflammatory responses that contribute to asthmatic pathology. Although colonization by certain microorganisms is related to inflammation, their role in the direct exacerbation of asthma remains unclear. On the other hand, asthmatics are more prone to a higher abundance of Proteobacteria, associated with poorer asthma control, while non-asthmatics predominantly have beneficial phyla such as Firmicutes and Actinobacteria. The differences in the composition of the respiratory microbiome between these groups suggest that promoting microbial diversity in the airways could be an important preventive strategy, while limiting the use of antibiotics to avoid adverse consequences (10).

Atopic Dermatitis

The skin microbiota is crucial for immunological tolerance. Its alteration, especially in childhood, predisposes to atopic dermatitis. Colonization by S. aureus and the reduction of commensal staphylococci are key factors. Antibiotics and type 2 cytokines influence this process (10).

Food Allergy

The gut microbiota in infancy determines the risk of food allergies. A diverse microbiota prevents allergic sensitization. Broad-spectrum antibiotics alter this balance, increasing the risk of allergies (10).

Antibiotics, the Development and Treatment of Allergic Diseases

The use of antibiotics during pregnancy and infancy alters the microbiota, increasing the risk of atopy, asthma, and allergies. The resulting dysbiosis interferes with immune development. Prudent use of antibiotics, especially in pregnant women, is crucial to minimize the risk of allergic diseases in children (10).

Childhood Obesity and Metabolic Disorders

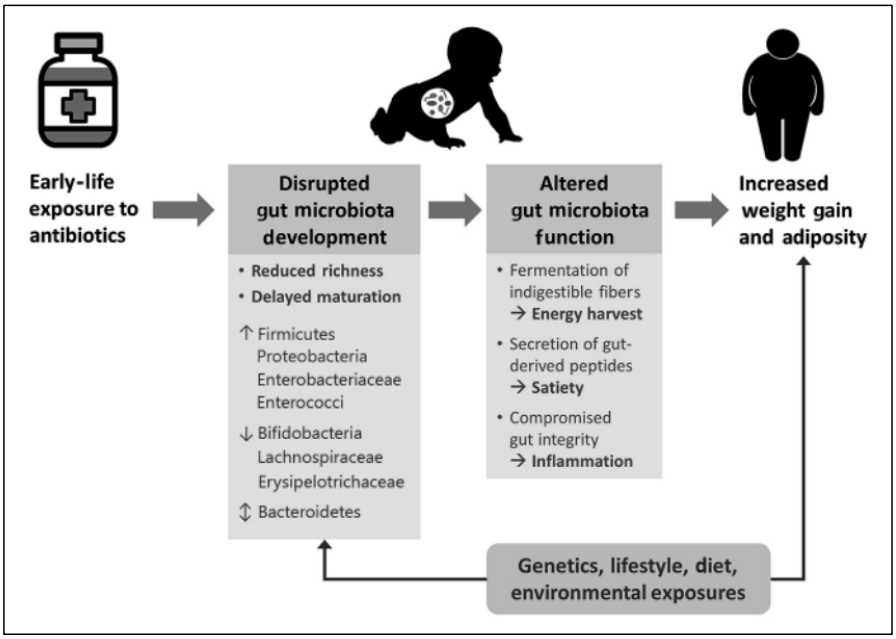

Figure 2. Early exposure to antibiotics, gut microbiota, and development of obesity. Schematic summary of associations observed in human and rodent studies.

Fuente: Azad et al (11).

Researchers have demonstrated complex interactions between diet, the gut microbiota, inflammation, and obesity. Mechanistically, the pathways involve the microbial production of energy substrates, inflammatory effects on metabolism, and even an impact on satiety through the gut-brain axis. There appears to be a characteristic microbiota profile for obesity: obese individuals have higher abundances of *E. coli, Lactobacillaceae, Escherichia, Shigella*, and *Negativicutes*. A large number of population-based studies have linked the administration of antibiotics to mothers during pregnancy and/or to infants in the first months of life with an elevated risk of being overweight later in childhood (1).

The colonization of the gastrointestinal tract in the early years of life is crucial for development and long-term health. The gut microbiota, which evolves from a dominance of Bifidobacteria in newborns towards a more complex composition, contributes to weight gain through the fermentation of carbohydrates into short-chain fatty acids (SCFAs), the regulation of appetite and energy homeostasis, and the modulation of inflammation. Studies have observed differences in the microbiota composition between obese and lean individuals, with a higher proportion of Firmicutes and a lower proportion of Bacteroidetes in obesity. Furthermore, alterations in the gut microbiota in the first months of life can predict a higher risk of later obesity. The transfer of an "obesogenic" microbiota from obese mothers to their children has also been suggested as a contributing factor. Given the influence of the microbiota on weight, there is a growing interest in probiotic therapies and in mitigating the impact of antibiotics on microbiota development to prevent or treat obesity (11).

Antibiotic Use and the Development of Obesity in Children: Epidemiological Evidence

The growth promotion observed in animals through antibiotics, a common practice in livestock farming, has led to studies on its effect in humans. Epidemiological investigations show an association between exposu-

re to antibiotics, both prenatal and in early childhood, and an increased risk of obesity in children. Studies in the U.S. and Denmark found that prenatal antibiotic exposure significantly increases the risk of overweight and obesity. Similarly, the administration of antibiotics in the first months of life is associated with a higher body mass index (BMI). Although some initial studies had limitations, larger investigations confirm that early exposure to antibiotics, especially macrolides and broad-spectrum antibiotics, and birth by cesarean section are related to a persistent increase in BMI up to adolescence. Male children have been observed to be more susceptible to this effect (12).

Recent studies indicate that the impact of antibiotics on BMI is not limited to early childhood but also occurs with later administration. A study with over 140,000 children aged 3 to 18 years showed an association between cumulative antibiotic use and progressive weight gain. Children with multiple antibiotic prescriptions experienced significant weight gain, especially by age 15. A meta-analysis of randomized controlled trials in low- and middle-income countries also found that antibiotic use increased height and weight in children aged 1 month to 12 years, with more pronounced effects in younger populations and African studies (12).

Research in animal models demonstrates that early antibiotic exposure can alter the gut microbiota and have long-term effects on metabolism, weight gain, and adiposity. Studies in rodents show that subtherapeutic antibiotic treatment (STAT) at weaning increases body fat and modifies microbiota composition. Antibiotic exposure from birth has more pronounced effects on growth and adiposity, especially in males, and these effects are exacerbated by a high-fat diet in adulthood. Although microbiota changes induced by STAT may resolve after treatment cessation, metabolic effects persist. Microbiota transplants from STAT-treated mice to germ-free mice cause increased weight gain and fat mass, confirming the causal role of the microbiota. Other studies mimicking pediatric antibiotic use with therapeutic doses of amoxicillin or tylosin also show microbiota alterations and, in some cases, long-term weight gain. Perinatal antibiotic exposure also alters the gut microbiota of offspring, although effects on weight are not always examined. Overall, experimental evidence suggests that early antibiotic exposure can have lasting consequences on the microbiota, metabolism, and susceptibility to obesity, influenced by factors such as the timing, type, dose, and duration of exposure, and potentially exacerbated by diet (11).

Antibiotic Administration, Microbiota Modification, and Obesity Development: Possible Relationships

Although it was initially thought that prophylactic antibiotics might influence growth, studies in germ-free (GF) animals showed that the gut microbiota regulates body weight and glucose and lipid metabolism. GF animals require more calories to maintain their weight and are protected from obesity induced by high-fat and high-sugar diets. Colonization of GF mice with microbiota from conventional mice increased body fat and caused metabolic modifications similar to those observed in human obesity. Bacterial fermentation, which increases available energy sources and regulates appetite, is considered the main mechanism. Short-chain fatty acids (SCFAs), produced by the microbiota, influence energy intake and metabolism. The microbiota is studied using 16S rRNA gene sequencing, with techniques such as qPCR and pyrosequencing. Experimental studies confirm that microbiota modification by antibiotics causes obesity. Antibiotic administration to GF animals does not induce weight gain, but colonization with microbiota from penicillin-treated animals does. Antibiotic-induced microbiota alteration persists even after treatment is discontinued. Obesity is associated with changes in microbiota composition, such as a decrease in Bacteroidetes and an increase in Firmicutes (12).

Firmicutes might have a protective effect against obesity by maintaining the integrity of ileal immunity. The microbiota influences the development of gut-associated lymphoid tissue and the maturation of the immune system. Antibiotics can delay the maturation of dendritic cells and alter cytokine production. Postnatal microbiota is crucial for establishing immune tolerance. Alteration of the microbiota can cause dysregulation of the immune system and promote low-grade inflammation and metabolic alterations related to obesity (12).

Autoimmune Diseases

The gut microbiome plays a fundamental role in the development and regulation of the human immune system. Dysbiosis, or an imbalance in the composition of the microbiota, has been associated with various autoimmune diseases. The interaction between the host and its gut microbiota influences immunological tolerance and the response to pathogens and self-antigens. Microbial metabolites such as SCFAs modulate the immune response. Increased intestinal permeability and translocation of intestinal pathobionts can trigger autoimmune responses in genetically susceptible individuals. The use of antibiotics and strategies to modulate the gut microbiota have potential therapeutic implications for autoimmune diseases (13).

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Although the multifactorial etiology (genetic and environmental) of JIA is poorly understood, early childhood antibiotic exposure has been linked to JIA onset. For example, Hestetun et al. studied 535,294 children born in Norway between 2004 and 2012. Of these, 149,534 (27.9%) were exposed to systemic antibiotics prenatally, and 236,340 (44.2%) were exposed during the first 24 months postpartum. JIA onset was associated with postpartum antibiotic exposure but not with prenatal antibiotic exposure. Interestingly, the association was stronger in children who had received sulfonamides, trimethoprim, and broad-spectrum antibiotics. However, reverse causality cannot be ruled out because inflammatory joint symptoms (especially in children) can be misconstrued as resulting from a bacterial infection (1).

Inflammatory Bowel Disease (IBD)

IBD, comprising Crohn's disease (CD) and ulcerative colitis (UC), is characterized by a dysregulated immune response to the gut microbiota in genetically susceptible individuals. Dysbiosis, with a decrease in bacterial diversity and specific changes in microbial composition, plays a crucial role in the pathogenesis of IBD. Bacterial species such as *Lactobacillus, Bifidobacterium*, and *Faecalibacterium* exert protective effects, while *Helicobacter pylori* infection shows a beneficial immunomodulatory effect. Altered intestinal permeability and the influence of antibiotics on the early microbiota are also considered relevant factors in the development of IBD (13).

Type 1 Diabetes (T1D)

T1D, an autoimmune disease that destroys pancreatic β-cells, also presents alterations in the composition of the gut microbiota. Genetically predisposed infants show reduced microbial diversity and an increased abundance of certain bacterial genera. The relationship between antibiotic use in infancy and the development of T1D is complex and still debated, with studies showing contradictory results. Increased intestinal permeability and translocation of pathogenic bacteria have been implicated in the pathogenesis of T1D, suggesting a link between the gut microbiota and pancreatic autoimmunity (13).

Strategies to Prevent or Reverse the Impact of Antibiotic-Induced Dysbiosis

Rational Use of Antibiotics in Pediatrics

The rational use of antibiotics in pediatrics is based on an accurate diagnosis that allows differentiation between bacterial and viral

infections, the latter being the most common in childhood, especially in the respiratory tract. Healthcare professionals should prescribe antibiotics selectively, reserving them solely for confirmed or highly suspected bacterial infections, avoiding empirical prescription in the face of uncertainty or parental pressure. The choice of antibiotic should be the most specific for the identified or suspected pathogen, prioritizing those with a narrower spectrum to minimize the impact on the child's microbiota and the selection of resistance (14).

Furthermore, the prescription should include the correct dose according to the patient's weight and condition, as well as an optimal duration of treatment, favoring short courses when scientific evidence supports it. It is crucial for physicians to develop skills to manage diagnostic uncertainty without automatically resorting to antibiotics, using strategies such as clinical follow-up or diagnostic tests when appropriate. Effective communication with parents or guardians is essential, establishing a relationship of trust where the diagnosis, treatment plan (including the reasons for not prescribing antibiotics if they are not necessary), alternatives for symptomatic relief, and a follow-up plan in case of worsening are clearly explained (14).

For their part, parents and guardians should seek appropriate medical care for their children's illness, avoiding self-medication with leftover antibiotics. It is important for them to understand the difference between viral and bacterial infections and trust the clinical judgment of healthcare professionals, without exerting pressure to obtain an unnecessary antibiotic prescription. They should strictly follow medical instructions regarding the administration of prescribed antibiotics, completing the full course, even if the child shows improvement. At the social and health policy level, effective awareness campaigns aimed at the population and professionals are required, facilitating access to rapid diagnostic tools in primary care, implementing clinical guidelines and prescription protocols, promoting research into new therapeutic alternatives, and adopting a comprehensive "One Health" approach to address the problem of antimicrobial resistance. Ultimately, the rational use of antibiotics in pediatrics is a shared responsibility that seeks to preserve the effectiveness of these vital drugs for present and future generations (14).

Probiotics and Prebiotics

The effectiveness of probiotics and prebiotics in restoring the microbiome has been supported by various studies. For example, butyrate, a short-chain fatty acid produced by the fermentation of prebiotics, has been shown to have beneficial effects on intestinal health, highlighting species such as *Faecalibacterium prausnitzii* and *Eubacterium rectale* as potential probiotics. In addition, galacto-oligosaccharide (GOS) has stimulated the growth of bifidobacteria in mice, modulating receptor expressions associated with anxiety and improving the function of the blood-brain barrier. Oligofructose has been shown to reduce diet-linked obesity and inflammation through changes in microbial composition and metabolic functions. Likewise, prebiotics have been suggested to influence the immune system, as observed in the reduction of atopic dermatitis in children, and the alteration of the bile acid profile may serve as a biomarker of their intake and effects on intestinal and systemic health. These findings underscore the importance of probiotics and prebiotics in the restoration and balance of the microbiome, positively impacting overall health (15).

Diet Modulation in Children with a History of Antibiotic Use

In children with a history of antibiotic use, diet modulation would primarily focus on the incorporation of prebiotics. Given that antibiotics can disrupt the balance of the gut microbiota, the dietary strategy would seek to selectively favor the growth of beneficial bacteria. Fructooligosaccharides (FOS) and galactooligosaccharides (GOS) are prebiotics highlighted in the text for their ability

to stimulate the growth of Bifidobacteria, a bacterial genus often considered beneficial. By including foods rich in natural prebiotics or considering supplementation with FOS or GOS (always under professional supervision), the aim would be to provide substrates that beneficial bacteria can use to proliferate and thus help restore the balance of the gut microbiota that may have been affected by previous antibiotic use (15).

Alternatives to Antibiotics in Common Infections

Glycopeptides, such as vancomycin, remain an initial option for treating staphylococcal infections, although an increase in vancomycin MIC in methicillin-resistant *S. aureus* is observed in neonates. For non-responsive Gram-positive infections, linezolid and daptomycin are valuable alternatives. On the horizon, new antibiotics such as ceftaroline and ceftobiprole show activity against multidrug-resistant staphylococci, with promising pharmacokinetic and safety profiles in neonates. Likewise, lipoglycopeptides such as oritavancin, dalbavancin, and telavancin offer activity against MDR Gram-positive pathogens, with preliminary studies suggesting a single dose of dalbavancin could be adequate in young children.

In the treatment of Gram-negative sepsis with highly resistant pathogens, carbapenems such as meropenem and the more recent doripenem are fundamental pillars, with monotherapy being recommended. However, the increasing resistance to these drugs has led to a reconsideration of older agents such as colistin, fosfomycin, and tigecycline, although their use in neonates has limitations and requires caution. Finally, newer antibiotics specifically targeting carbapenem-resistant organisms (CROs) such as aztreonam/avibactam, vaborbactam/meropenem, and plazomicin still have limited evidence in the neonatal population (16).

Research has also increased towards developing novel approaches to treat infections without the use of antibiotics. One promising area is the use of bacteriophages to target bacterial infections. Although rigorous studies are required to validate this therapy, published case reports indicate that phage therapy holds promise. Demonstrations of safety, efficacy, generalizability, and cost-effectiveness are required before phage therapy becomes mainstream. However, it is an attractive approach to infection due to its demonstrated potential to treat extremely drug-resistant bacteria (albeit case reports) and because it is a uniquely targeted therapy that theoretically would not broadly alter the host microbiome. Bacteriocins and antimicrobial peptides have also been proposed as possible alternatives to antibiotic therapy. Antimicrobial peptides have been further refined with the development of specifically targeted antimicrobial peptides (STAMPs), which consist of an antimicrobial peptide fused to a targeting domain. One example is STAMP C16G2, which was shown to selectively kill *Streptococcus* mutans in a polymicrobial biofilm, suggesting a high degree of specificity that would preserve the host microbiota. Indeed, in a small clinical trial, this engineered peptide selectively cleared *S. mutans* from dental plaque without altering the overall oral microbiota. More work is needed to validate, test the safety, and determine the cost-effectiveness of these novel therapies for wider clinical use (17).

Interventions to Mitigate the Effects of Dysbiosis

One type of treatment is synbiotics, which combine probiotics (live beneficial bacteria) and prebiotics (foods that nourish these bacteria). In patients with T2DM and obesity, one study found that a multispecies synbiotic did not directly change how the body processed sugar (glucose metabolism). However, improvements were observed in some T2DM symptoms, certain blood markers related to the disease, and the patients' quality of life. Another similar study confirmed that, although synbiotics did not improve glucose metabolism in people with obesity and T2DM, they could have secon-

dary benefits, such as improving the intestinal barrier and the feeling of well-being. This suggests that synbiotics could be a useful tool to complement the treatment of these diseases (18).

Another promising approach is fecal microbiota transplantation (FMT), which involves transferring stool from a healthy donor to the recipient's intestine to restore a balanced microbiota. A study in patients with T2DM found that FMT, along with dietary changes, accelerated weight loss. During the study, an increase in bacteria considered beneficial, such as bifidobacteria, was observed, and this increase was related to improvements in blood sugar levels, blood pressure, blood fat levels, and body mass index (BMI). On the other hand, certain bacteria that could be harmful, such as sulfate-reducing bacteria, decreased, and this decrease was related to better blood sugar levels (18).

Conclusion

The development of the microbiome during infancy represents a foundational stage for the proper maturation of the immune system. The intricate interaction between the microorganisms that colonize the gut and immune cells establishes a delicate balance crucial for immunity and mucosal homeostasis. However, dysbiosis, an imbalance in this microbial community, especially when induced by the administration of antibiotics, can significantly disrupt this process. This alteration not only impacts local immunity in the gut but can also have distant effects, such as on pulmonary immunity through the gut-lung axis, increasing susceptibility to chronic diseases like asthma and allergies. Factors such as the production of short-chain fatty acids (SCFAs) by the microbiota and the secretion of immunoglobulin A (sIgA) in the intestinal mucosa are key mediators of this bidirectional relationship, underscoring the importance of a healthy microbiome from the early stages of life to ensure optimal long-term health.

The administration of antibiotics, while essential for the treatment of bacterial infections, exerts a profound and potentially lasting impact on the composition and diversity of the infant gut microbiome. This effect manifests as a reduction in bacterial richness and specific alterations in the abundance of certain microbial groups, such as the decrease of beneficial bacteria like Bifidobacteria and Lactobacilli, and the increase of potentially pathogenic species like Bacteroidetes and Proteobacteria. The loss of microorganisms with important functions, such as *Akkermansia muciniphila* with its anti-inflammatory properties, illustrates the complexity of the consequences of antibiotic exposure on the intestinal ecosystem. While some of these changes may be transient, there is growing evidence that others can persist in the long term, with significant implications for the child's health, including the development of the immune system and the risk of chronic diseases.

Early dysbiosis, resulting from factors such as antibiotic use, has been increasingly linked to the development of various chronic diseases in childhood. In the context of asthma, it has been observed that the composition of the respiratory microbiome in the first months of life can influence the risk of developing wheezing and asthma, with specific associations between certain bacteria and the disease. Similarly, skin dysbiosis and alteration of the gut microbiome have been implicated in the pathogenesis of atopic dermatitis and food allergies, respectively. Regarding childhood obesity and metabolic disorders, epidemiological and experimental evidence suggests that early antibiotic exposure can alter the gut microbiota and have long-term effects on metabolism, weight gain, and adiposity. Finally, in the realm of autoimmune diseases, dysbiosis has been associated with an increased risk of developing conditions such as juvenile idiopathic arthritis, inflammatory bowel disease, and type 1 diabetes, highlighting the crucial role of the microbiome in modulating the immune response and tolerance.

Given the significant impact of antibiotic-induced dysbiosis in childhood, it is imperative to implement strategies to prevent or mitigate its effects. The rational use of antibiotics in pediatrics, based on accurate diagnosis and the selective prescription of narrow-spectrum drugs for the necessary duration, constitutes the first line of defense. Additionally, diet modulation, especially through the incorporation of prebiotics that favor the growth of beneficial bacteria, and the strategic use of probiotics and synbiotics can contribute to the restoration of microbial balance. The active research into alternatives to antibiotics for common infections, such as bacteriophages and antimicrobial peptides, offers a promising perspective for reducing dependence on these drugs and minimizing their impact on the microbiome. Ultimately, a comprehensive approach that combines the prudent use of antibiotics with targeted interventions to modulate the microbiome represents a fundamental strategy for promoting healthy immunological development in childhood and reducing the risk of long-term chronic diseases.

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