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REVIEW ARTICLE

Gut Microbiome and Antibiotics

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Despite that the human gastrointestinal tract is the most populated ecological niche by bacteria in the human body, much is still unknown about its characteristics. This site is highly susceptible to the effects of many external factors that may affect in the quality and the quantity of the microbiome. Specific factors such as diet, personal hygiene, pharmacological drugs and the use of antibiotics can produce a significant impact on the gut microbiota. The effect of these factors is more relevant early in life, when the gut microbiota has not yet fully established. In this review, we discussed the effect of type and doses of the antibiotics on the gut microbiota and what the major consequences in the use and abuse of these antimicrobial agents.

Key Words: Antibiotic treatments, Autoimmune diseases, Microbiome, Obesity.

Introduction

More than 100 trillion microorganisms populate the human adult large intestine, with over 1000 species occupying this region and the majority of them are able to survive under anaerobic conditions (1,2). About 90% of microbes colonizing the gut are represented by only six phyla, *Firmicutes*, *Bacteroides*, *Actinobacteria*, *Fusobacteria*, *Proteobacteria,* and *Verrucomicrobia* (3,4). Although microbiota composition in the gut is influenced by diet, gender, geographic location, and ethnicity (5,6), delivery mode appears to be the most critical and influential factor when acquiring our primary microbiota. Babies are coated by the maternal vaginal and gut microbiota at birth which is mainly dominated by *Lactobacillus*, composing more than 50% of the total microbiota (7,8). After birth, babies acquire their secondary microbiome from their family members or the surrounding ecosystem. However, it is the initial microbiota that will influence the microbiome composition later in life, with long-lasting effects on the microbial community and host physiology (6). The period of microbiota acquisition coincides with development of a child's immune system, and both influence each other strongly, making this window in early life absolutely critical in conferring appropriate host immune responses (9,10). Vaginally delivered babies acquire a bacterial composition resembling their mother's vaginal microbiota, dominated by *Lactobacillus, Prevotella,* or *Sneathis* (7). In contrast, babies delivered by Cesarean section acquire bacteria that resembles those present on the skin, like *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* (7). These bacteria are not maternally derived but are delivered from hospital staff, with whom the babies have had contact (7). Several studies suggest a correlation between C section and the autoimmune system due to the essential role of the maternal microbiome on the development of the perinatal immune system (11−14). However, recent publications from Swedish and Irish cohorts reported that there was no significant influence of C section on the risk of type 1 diabetes (T1D) (15,16). Similar to T1D, as the incidence of asthma has also been increasing for the past 30−40 years in developed countries (17). The correlation between C section and the risk of asthma is a different story. Some results showed a negative correlation (18,19); on the other hand, there were also reports of positive data (13,14,20,21). Interestingly, it was critical to assess the correlation between whether C section was performed before membrane rupture or not (20). Although meta-analysis indicated that C section contributes to the risk of asthma, further studies are needed. When it comes to perturbation of microbiota in early life, C section is a good model to discuss the risk of auto-immune disease. However, T1D and asthma seem to have different correlations. This might suggest the possibility that other factors may be involved in

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both autoimmunity and microbiome perturbation in early life. Antibiotic treatment may be the missing link.

The Breakthrough of Sequencing Methods for the Study of Gut Microbiome

Many scientists have been interested in the small and large intestines for a long time, because the intestinal tract is one of the lesser known organs in terms of bacterial content, especially in regard to commensal resident bacteria. One of the major difficulties when surveying gut communities is the ability to culture the organisms. Nearly 70% of microbes colonizing the gut cannot be cultured even now (22), therefore the analysis of the microbiota has been a very difficult work for a long time. In order to assess and identify human gut microbiota, 16S rRNA sequencing has become a revolutionary and useful technique to detect diversity and abundance of the microbiome, taking advantage of curated 16S rRNA sequence databases (23−25). Purified DNA obtained from feces, rectal swabs, or other samples is amplified and barcoded for multiplex high-throughput sequencing using universal primers targeting the V (variable) regions of the bacterial 16S rRNA gene. After running PCR and adjusting the concentration, sequencing is performed using the Illumina MiSeq, HiSeq, Ion Torrent or another sequencing platform. Analysis of sequencing results using the QIIME software package is performed by clustering similar sequences (97% similarity) into operational taxonomic units (OTUs) and comparing the reference sequence against the Greengenes Core set. Finally, α-diversity (within-sample), β-diversity (between-sample), and relative abundance can be determined using this data.

Antibiotic Strengths and Weaknesses

After the discovery of antibiotics in the early 20th century, specifically the discovery of penicillin by Alexander Fleming in 1928, the use of antibiotic treatment have spread throughout the world, despite the fact that it took more than 10 years to purify and manufacture penicillin. The use of antimicrobial drugs to fight infectious disease in humans started when Gerhard Domak discovered sulfonamide chrysoidine in 1939. A particular event in human history, World War II, played an important role in the development and widespread use of antibiotic treatment. Since the discovery of sulfonamide chrysoidine, the last 75 years has seen a tremendous amount of people saved from previously lethal infectious diseases. Unmistakably, antibiotics are among the most important drugs used in human and animal medicine in the last 100 years. However, there are some negative aspects of antibiotic treatment that have been becoming more apparent in the last 20 years. a) Antibiotic abuse has selected for antibiotic resistance in many bacteria, and has made antibiotic treatments ineffective, claiming many lives, particularly those of compromised patients in hospital settings, like MRSA, VRE, or *Clostridium difficile* (26,27). The emergence of multi-drug resistant bacteria has risen due to antibiotic abuse, with a consequent increase in mortality due to infectious disease. b) It is getting more difficult to develop new antibiotics and there aren't any indications that new antibiotics will be available in the next 5−10 years. c) A strong correlation has been observed between early antibiotic use and the development of allergic and autoimmune diseases. For example, the number of children with asthma has been steadily increasing, especially in developed countries, where antibiotics have been used for the longest period of time. In a Danish study, 78% of mothers who received antibiotic drugs from 80 weeks before pregnancy to 80 weeks post-partum showed that maternal use of antibiotic drugs was associated with an increased risk of childhood asthma (28). There was a dose-related association for the risk of the offspring acquiring asthma. Moreover, many reports indicate that prenatal antibiotic exposure promotes both weight gain in babies and an increased risk of obesity (29,30).

Type 1 Diabetes (T1D)

T1D is an autoimmune disease that causes destruction of pancreatic beta cells and subsequent hypoinsulinemia. The incidence of T1D is increasing in developed countries (such as the Scandinavian nations, Canada, and Australia), more rapidly than in developing countries. In such developed countries, the onset of T1D is occurring earlier and earlier (31,32). Incidence has increased 3−5% annually worldwide (33−35). The assumption is that some environmental changes have occurred in early life that is associated with T1D incidence. Early life interactions between hosts and their gut microbiota are key for the immunological development of the infant (36) and perturbations of the microbiome such as early-life antibiotic use may have an effect in the development of allergies, asthmas and T1D. Some recent evidence supports the concept of an altered microbiota in T1D (37). As mentioned above, a strong correlation between Caesarean section and the incidence of asthma has been reported (28); thus, many researchers are now focusing on the association between perturbation of the microbiome in early life, particularly due by antibiotics and T1D.

In non-obese diabetic (NOD) mice there is spontaneously develop of T1D-like and there is some evidence that microbial exposure affects diabetes incidence. In particular, it is well known that increased microbial exposures (''dirty'' conditions) protect NOD mice from the development of T1D (38,39). We have demonstrated that using antibiotics in pregnancy and early life showed enhancement and acceleration of T1D (Figure 1).

Obesity

Obesity has been one of the biggest health problems for more than 20 years worldwide and it is still increasing. It is a critical situation, especially in United States. Although