The Characteristics of Microbiome in Newborns and Children and the Effects of Antibiotic Use

DANA CLAUDIA THOMPSON[1#], MADALINA GABRIELA BARBU[1#], OANA DANIELA TOADER[2,3#], LUCIAN POP[2#], ANDREI DENNIS VOICHITOIU[2,3#], NICOLAE SUCIU[2,3#], IOAN SORIN TUDORACHE[4*], DRAGOS PREDESCU[5]

[1]Alessandrescu-Rusescu National Institute of Mother and Child Health, Fetal Medicine Excellence Research Center, 120 Lacul Tei Blvd., 20395,Bucharest, Romania

[2]Alessandrescu-Rusescu National Institute of Mother and Child Health, Polizu Clinical Hospital, Department of Obstetrics and Gynecology,38-52 Gheorghe Polizu Str.,022455, Bucharest, Romania

[3]Carol Davila University of Medicine and Pharmacy, Department of Obstetrics, Gynecology and Neonatology,37 Dionisie Lupu Str., 020021, Bucharest, Romania

[4]Titu Maiorescu University, Faculty of Medicine,67A Gheorghe Petrascu Str, 031593, Bucharest, Romania

[5]Sf. Maria General and Esophageal Surgery Clinic, Carol Davila University of Medicine and Pharmacy, 37-39 Gheorghe Mihalache Blvd., 011172, Bucharest, Romania

The acquisition of the infant's microbiota is a vastly researched subject and of high interest. As more information is gathered, scientists prove the link between an unbalanced microbiome and certain afflictions. Antibiotics are widely used drugs and one of the factors that can shape the composition of the infant's gut bacterial colonization. In this paper we aim to present the natural history of the child's microbiome and the way it can be influenced by the use of antibiotics.

Keywords: microbiota, microbiome, afflictions, antibiotics

It is well known that the microbiota plays an important part in the functioning of the human body. Not only because locally it synthesizes vitamin k, biotin and a number of short chain fatty acids[1], but it is also involved in the maturation of the immune system[2] and it is believed to have a protective role against colonization with pathogenic bacteria[3]. There are many factors that influence the composition of the neonatal microbiome, among which the most significant one is the mode of delivery [3,4]. It has been shown that vaginally delivered babies have a similar microbiome composition to their mother's vaginal bacterial spectrum and are known to be protected against bacterial infections, chronic inflammatory diseases and allergies in comparison to newborns delivered by C-section, who have a microbiota similar to that found on the skin and are more prone to developing the previously mentioned afflictions[3,5]. Furthermore, the use of antibiotics during pregnancy changes the mother's microbiome, and as a result the newborn's, as the microbial colonization primarily takes place during birth [6].

How the Maternal Microbiome Influences the Newborn

The maternal microbiome is not the same throughout pregnancy, as in the first trimester it has been discovered that the composition is dominated by butyrate-producing organisms, such as Faecallibacterium praustnitzii[7]. In the third trimester, the diversity of the microbiome decreases together with the abundance and evenness, the dominant strains being represented by Enterobacteriaceae, streptococci and enterococci, the same bacteria that can be found in the first days in the gut microbiome of newborns[8].

It has been proven that the composition of the microbiome is shaped by the delivery mode. Studies show that babies that are vaginally delivered have a microbiota similar to their mother's vaginal one. It is mainly comprised of Prevotella, Lactobacillus and Sneathia spp. Furthermore, research has also shown that the newborn's microbiome is more alike their mother's vaginal flora than it is to other babies born through the same method, supporting the idea that the early microbiome is transmitted vertically [3]. At the same time, C-section born babies tend to have comparable microbiome to the one found on the skin surface, comprising bacteria like Staphylococcus, Propionibacterium and Corynebacterium spp [9]. Because of the composition of their gut microbiome, C-section born babies are more susceptible to develop allergies and chronic inflammatory diseases [10].

Another interesting fact is that certain studies suggest that the acquisition of the microbiome begins in utero, although for many years it was believed that babies are born sterile and their microbiota is formed seconds after birth. Evidence of bacterial colonization has been found in the mother's placenta, umbilical cord and in the fetal meconium [11].

Consequences of Antibiotic Use During Pregnancy

A lot of women are known to recieve antibiotic treatment during pregnancy, some of which have the ability to pass the placenta and are transfered to the fetus[12]. Also, during labor doctors prescribe antibiotics in order to prevent a possible colonization with group B streptococcus and chorioamnionitis[6]. As we mentioned before, it is now believed that the baby acquires the microbiome before birth and as a result antibiotic treatments should be administered with caution. Prior studies have shown that antibiotic use during pregnancy can lead to a decrease in protective bacteria species, such as Bifidobacteria and Lactobacillus in the baby's gut microbiome. Although intrapartum administered antibiotics have lowered the risk of complications related to pathogen exposure, the posibility of drug-resistant infections with methicillin-resistant Staphylococcus aureus and Clostridium difficile should be considered for both the mother and the baby, especially for those born preterm[13].

* email: soryntudorache@yahoo.com # Authors have equal contribution

The Evolution of the Gut Microbiome in Children

Different studies have shown that the gut microbiome goes through a very dynamic phase in the first 3 years of life [4,14,15]. While some claim that its development ends at the age of 3 [4, 14, 16], others support the idea that the process continues, on a smaller scale, until the age of 18 [17-19]. In all cases however, the formation and evolution of the gut microbiome are directly influenced by: birth mode (vaginal delivery or cesarean section influence the composition and development of the microbiome in the first 6 months of life [3,20,21]), gestational age (preterm babies require hospitalization in the neonatal intensive care unit, the use of antibiotics and formula feeding [20]), environment determinants (the presence of siblings or household pets is associated with a more diverse microbiome [22-24]), feeding and diet (formula fed babies have more bacteria associated with inflammation compared to ones that were breast fed and also acquire the adult microbiome faster [4,20,25]) and the use of antibiotics[26].

During the first year of life, the infant's microbiome is turning from a simple one, which is mainly specialized in the digestion of human milk oligosaccharides (the majority of which is formed by *Lactobacillus, Staphylococcus,* and *Bifidobacterium* in the case of breast fed babies and *Roseburia, Clostridium,* and *Anaerostipes* in the case of the formula fed ones [4]), to a more developed one, coming one step closer to the adult state. Now the population of bacteria becomes richer in *Firmicutes* and *Bacteroides* [4,27], thus turning more specialized towards the digestion of plant polysaccharides, even before they are introduced into the child's diet, followed by the expression of genes required for the metabolism of carbohydrates, the vitamin biosynthesis, and the xenobiotic degradation [28]. Further on, in the next 2 years, the microbiome continues to develop, until the age of 3, when many authors consider that it reaches the final stage [4,14,15]. However, multiple studies have shown, that even though there aren't significant differences at the phylum level, when it comes to the genum level, the adult microbiome is significantly richer in abundance and variety than that of young children[18].

Impact of Antibiotic Treatment on the Infant Gut Microbiome

The current understanding of the evolution of the infant gut microbiome shows that its balance and diversity are crucial for an appropriate development during the first years and also for a healthy adult life. Whenever this balance is disrupted, it can lead to a wide array of diseases including allergies, recurrent *C difficile* infection [29], inflammatory bowel disease[30,31], obesity[32] and neurological disorders like autism[33]. Antibiotics represent one of the factors that can lead to such a disruption. Recent studies show that children who receive antibiotic treatment during the first 3 years of life have a less diverse gut microbiome, particularly at the strain level and also less stable communities [14]. This can lead to limitations in terms of the immune system education including its capabilities to identify commensal microbes[2]. Furthermore, antibiotic treatment promotes the development of antibiotic resistance genes which is a very important public health issue currently [14].

In newborn babies, postnatal exposure to antibiotics in the first 48 hours (gentamicin and ampicillin) lead to decreased levels of *Lactobacillus* and *Bifidobacterium* compared to untreated children, 4 weeks after stopping the treatment[34]. In the case of premature babies, the use of antibiotics has been associated with a high incidence of necrotizing enterocolitis (NEC)[35]. At the same time, some papers suggest that preterm babies' microbiome is not significantly influenced by the use of antibiotics, but a more important role is played by the amount of time spent in the neonatal intensive care unit, which can lead to the colonization of their microbiota by antibiotic-resistant bacteria, therefore posing a threat to their survival[35].

Conclusions

In this review, we summarized the evolution of the microbiome beginning in utero, the importance of the microbiome for the developing infant and also the effects of antibiotic use over the commensal bacteria. Antibiotic usage is a very common practice and because of the wide exposure of infants to these types of drugs, bacteria have become more resistant to the treatment and even more aggressive, leading to various pathologies. The technological development helps us understand more about the microbiome and at the same time, it helps us reevaluate our current therapeutic approaches and develop new ways to treat certain diseases.

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