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Development of the Microbiota in Infants and its Role in Maturation of the Gut Mucosa and the Immune System

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Dysbiosis of the gut microbiota has been associated with increasing numbers of diseases, including obesity, diabetes, inflammatory bowel disease, asthma, allergy, cancer and even neurologic or behavioral disorders. The other side of the coin is that a healthy microbiota leads to a healthy human development, to a mature and well trained immune system and to an efficient metabolic machinery. What we have learned in adults is in the end the result of a good start, a programmed, healthy development of the microbiota that must occur in the early years of life, probably even starting during the fetal stage. This review aims to present and discuss reports that helps us understand what we have learned of the development of microbiota during the early times of life, from pregnancy to delivery to the early years after birth. The impact of the establishment of ''healthy'' bacterial communities on human surfaces in the maturation of epithelia, immune system and metabolism will also be discussed. The right process of maturation of the bacterial communities that establish a symbiosis with human surfaces depends on a number of environmental, genetic and temporal factors that need to be understand in order to have tools to monitor a healthy development and eventually intervene to correct undesired courses. © 2017 IMSS. Published by Elsevier Inc.

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Factors Influencing the Development of Infant Microbiota

Effect of delivery mode. Studies in different human groups have consistently reported that gut microbial diversity is higher in infants vaginally delivered and that diversity remains higher than C-section infants during the first months of life, after which time these differences tend to disappear. After the ''unnatural'' cesarean section (C-section) delivery, intestinal microbiota in the newborn has been found more similar to that found in mother's skin, dominated by *Staphylococcus*, *Corynebacterium* and *Propionibacterium*, and characterized by a delayed in colonization by *Bacteroides* and *Bifidobacterium* that may persist throughout the first year of life (1,2). Although results may vary from population to population and in some studies *Bifidobacterium,* Clostridiales and Enterobacteriaceae have been reported more abundant during this first year of life (3). In most studies the presence of *Bacteroides* can be detected until up to 6−18 months, which is relevant since *Bacteroides sp*. has an important role in the maturation of the immune response. Its long-lasting reduction during the first year may be responsible for the reported increased risk for asthma, allergies and obesity in C-section delivered infants. In some instances, C-section may initially result in a higher diversity in gut microbiota, although this diversity subsequently decrease and remains lower for up to two years, suggesting a long-lasting effect of C-section in the infant microbial composition (3).

In contrast, after vaginal delivery microbial composition in the newborn resembles vaginal flora, with *Lactobacillus*, *Prevotella* or *Sneathia* among the most abundant genus during the early days after delivery (4); although as noted

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before, the differences with C-section infants tend to disappear after six weeks of age (5). Similar observations were reported in a study in an Ireland infant cohort that compared microbiota composition in full term and preterm infants, delivered vaginally or by C-section (6). Main differences between groups were observed during the first four weeks of age, where *Bacteroides* and *Bifidobacterium* were significantly more abundant in full-term vaginally derived infants, whereas Proteobacteria was significantly higher in preterm neonates. It was also noted that diversity was higher in full-term vaginally derived infants. However, the discrepancies between groups gradually disappear and by six months of age no significant differences in microbiota composition were observed between groups. Thus, the early perturbations in the developing microbiota of full term C-section and preterm infants caused by antibiotics to the mother and infant, hospitalization or by birth mode itself were recovered within weeks, and no major differences were observed after six months of age.

In another study in Swedish newborns sampled within the first five days of life, for the 178 OTUs present in vaginally delivered infants, 135 were also found in their mothers, including *Escherichia*, *Bifidobacterium*, *Enterococcus* and *Bacteroides*. In contrast, for the 135 OTUs present in C-section newborns, only 55 were also present in their mothers (7). The study confirms that in vaginally delivered infants most of the early colonizers of the neonate gut originate from their mother, either from gut or vagina; whereas in C-section newborns most bacteria comes from mother's skin. As in previous studies, these differences faded with age of the infant and by 12 months most of them disappeared. Other relevant findings of this study were that genes for antibiotic resistance were more frequent in C-section babies. It should be noted that in neonates delivered by a labored cesarean procedure microbiota resembled vaginal and skin maternal flora; whereas neonates delivered by unlabored C-section were colonized by microbiota found in the maternal skin (5).

The reduced microbial diversity and low colonization by *Bacteroides* and *Bifidobacterium* observed in C-section infants may eventually results in an inappropriate stimulation of the immune system, and in predisposition to Th2-mediated allergy. A study suggested that reduced microbial diversity in CS infants is due in part to a delayed colonization by Bacteroidetes, particularly during the first year of life, which was also associated to reduced circulating levels of Th1 chemokines (8). Another study in mestizo and Amerind infant population in Venezuela found that C-section newborns presented altered microbiota in samples taken during the first 24 h of life, and authors suggested that this altered composition was the result of a lack of exposure to vaginal flora (4). However, it has been questioned that sampling during the very first hours of life, as done in this study, does represent the microbes transmitted during delivery; and not that they rather represent early colonizers from the environment (9). It has also been questioned that altered bacterial composition might be the result of the underlying pathological conditions that lead to cesarean delivery in the first place, and not really to the procedure itself. It is argued that C-section studies should considered other confounding factors that may also affect bacterial colonization, such as maternal intrapartum and neonatal exposure to antibiotics, gestational age, diet, host genetics, among others (9). Maternal high-fat diet, which may be an indication for C-section, has also been associated with disturbance of bacterial communities at birth, an effect that may last for up to six weeks in the neonate (10).

Effect of antibiotics. Exposure to antibiotics early in life diminishes α-diversity that last for months, although this diversity is recovered within the first year. Antibiotics also cause a delay in the maturation of microbiota, due to depletion of Lachnospiraceae and Erysipelotrichaceae. Lachnospiraceae and Clostridiales have been found particularly sensitive to antibiotic exposure in infants, which is relevant since Lachnospiraceae may produce butyrate and other short-chain fatty acids, important in the maturation of the infant immunity by signaling epithelial cell, colonic T regulatory cells and macrophages (3). In fact, Lachnospiraceae has been suggested as a marker for intestinal microbiota maturation in Bangladeshi infants, highlighting the important role of this family in microbiota development across countries. Repeated exposure to antibiotics during the first year of life caused a less stable microbial community and a decreased diversity which lasted till the three years of life (3) (Perez-Perez G, et al. in press). It also resulted in an increased abundance of antimicrobial resistance genes, which interestingly was observed as a sharp increase and then a decrease when genes were chromosomal, but lasted much longer when genes were present on mobile elements (3). The administration of antibiotics is common in preterm neonates, where WGS studies have shown that whereas meropenem, cefotaxime and ticarcillin-clavulanate significantly reduce species richness, vancomycin and gentamicin had a non-uniform and less marked effect (11). The study also demonstrated that preterm infant microbiota was dominated by multi-drug resistant *Escherichia*, *Klebsiella* and *Enterobacter*. Results of this study showed that preterm infant ''resistome'' is established early in life, which is probably not the result of direct antibiotic selection, but because of exposure to resistance genes in other habitats.

Exposure to antibiotics in school children (2−7 years old) also caused long lasting changes in the microbiome and in health. Particularly, children exposed to macrolides had significant changes in microbiota composition, reduced richness, with reduction in Actinobacteria (specially *Bifidobacterium*) and increased in Proteobacteria (particularly Enterobacteriaceae) and Bacteroidetes (12); changes that remained up to two years after macrolide treatment.

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