Pediatrics & Therapeutics

ISSN: 2161-0665

Azad and Ben, Pediatr Ther 2017, 7:2
DOI: 10.4172/2161-0665.1000320

Review Article OMICS International

The Development and Role of Micro Biome in Infant Gut: An Overview of Recent Literature

Sanjay Kumar Azad and Xiao-Ming Ben*

Department of Neonatology, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, P. R. China

***Corresponding author:** Xiao-Ming Ben, Department of Neonatology, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai 200040, P. R. China, Tel: 13162399158; E-mail: benxm@163.com

Received date: May 17, 2017; **Accepted date:** May 29, 2017; **Published date:** May 31, 2017

Abstract

More than 1 trillion microbes living inside and outside of our body environment throughout our life is microbiome, the interplay between microorganisms and the intestine of new born infant is associated with diverse functional and clinical outcomes that result from the specific interaction among microbial communities, their products and the unique characteristics of the gastrointestinal tract. The gut microbiome, the study of its origins and establishment of the neonatal gut microbiome beginning in utero and how it is affected by nutritional status (breast feeding versus formula feeding) and other by delivery mode (cesarean section versus vaginal delivery), environmental factors (inside and outside utero), gestational age (term versus preterm), use of antibiotics. This review is aimed at reporting the most recent knowledge of microbiota origin and development in the human newborn and on the multiple factors influencing development and maturation of microbiota including the use and misuse of antibiotics and use of probiotic.

Methods: To evaluate the evidence based overview of recent literature about the development and role of microbiome in infant gut, the following key search terms were used: Infant, microbiome and influencing factors.

Infant development and microbiome - microbiota effect and infant gut: The criteria for the search were limited to systematic reviews, meta-analysis, case studies, randomized control trials. A comprehensive literature search was performed in PubMed, web of science, from 1990 to 2015. Subjects, age and research in humans limited the search. Originally 596 references were obtained among them 47 were sent to trash and the rest systematic articles and reviews were used for the over view for recent literature.

Keywords: Gut microbiome; Infant; Development and function; Influencing factor

Introduction

The development and role of micro biome in newborn and infants

The microscopic organism more than 1 trillion living inside and outside of our body environment throughout our life is known as microbiome [1]. They carry out their actions by influencing immunological, endocrine and neural pathway, the gut microbiota has three essential roles as protective, metabolic and tropic [2]. The relationship of the microbiome with human is as the role of probiotics and the prebiotics as they support each other, simply as synbiotic [3]. Which is related with the digestion of the food, improving our immune system and metabolic system, creating a barrier for the defense of the other harmful pathogens, the infant has to face lot of challenges after they come out of the intra uterine life, as the infant intestine is sterile during birth, some microbial colonization take place during the development of the infant which is a complex dynamic process between the infant cell and the environment influences. Alter in the development and equilibrium of colonization of microbiota in the infant cell can lead to immune and metabolic dysfunction that leads to illness, which is also known as dysbiosis. Most frequently use of antibiotics has been blamed to the responsible of increasing prevalence of health condition, as aberrant metabolism and immune reorganization, microbiota compared to that of ancient time has been all transformed to modern by different factors consisting source of water, sewage system, refrigeration, immunizations, using pesticides, mode of delivery as cesarean section, changing the mode of agriculture, formula feeding, large grocery, preoperative antisepsis, haphazard use of antibiotics has been controlled and is used only for life saving and prophylaxis [4].

Influence of Microbiota

Human placenta contains low nonpathogenic species as anaerobic, gram-negative bacteria and other from different phylum as proterobacteria, bacteroidetes and tenericutes. These organism in the placenta are very similar to the organism of human mouth, these organism trigger the immunity system after delivery [5]. After delivery the newborn intestinal microbiome undergoes different continuous huge successive changes over time which depends upon the factor as place, use of antibiotics, maternal colonization, external environment, infant and maternal diet, mode of delivery, feeding including breast milk and donor milk, formula feeding, so it is important to understand the normal microbiota colonization to avoid dysbiosis and recovery of the deterioration [6]. The bacteria experienced by the infant with vaginal deliveries are like bifidobacterium, bacteroides, lactobacillus and prevotella. In the cesarean section they encounter by staphylococcus, corynebacterium, propionibacterium [7]. In case of

breast-feeding the intestinal microbiome flora consist of bifidobacterium, bacteroides, lactobacillus, clostridia. Similarly in case of formula milk there are bacteroides, clostridia, enterobacteriacea. In most of the countries the cesarean section is being more popular, different macrobiota depends upon the mode of delivery, as in the case of vaginal delivery on day 3 of life large number of bifidobacterium species are seen in comparison to cesarean section [8]. Vaginally delivered infant has seen to develop bacterial colonization of same profile of pre delivered vaginal bacterial content as (primarily Lactobacillus, Prevotella, Sneathia species) which can be demonstrated with in five minitue of age, which is vertically transmitted during delivery. *Bifidom longum* is seen in early infant delivered vaginally which is to identical to the mothers fecal microbiome, which is transmitted through fecal-oral route which regulates the immune system of the body, similarly in case of caesarian section delivery the species of the skin and oral microbes and the surrounding delivery environment microbes are to be seen. Exposure to the mother's vaginal flora is considered to explain a greater diversity in the gut micro- biota of vaginally born infants compared with those delivered by caesarean section [6]. Although the bacterial colonization in the vaginally delivered infants are with the microorganism as, Enterobacteriaceae, Staphylococci, Escherichia/Shigella and Streptococcus, but these organisms are replaced by anaerobes as Bifidobacterium, Lactobacillus, Clostridia and Bacteroides, as well there are different types of micro organishm in the different mode of delivery but they comes more or less similar after the first year of life.

Breast-feeding versus formal feeding

Breast milk is colonized with bacteroides and clostridia and are rich in non-digestible human milk oligosaccharides with maternal antibodies that inhibits in colonization with other pathogens, bifidobacterium colonization with nutritional substrate it generates lactate and fatty acids giving more acidic environment that prevents from invasion of harmful pathogens, the intestinal flora of the infant under breast feeding consist of bifidobacterium, bacteroides, lactobacillus, clostridia [9]. Among these bifidobacteria species remains predominant until weaning when clostridia and bacteroides become more prevalent, in the breast feeding lactobacillus colonization is seen to be predominant in around six months, in comparison to breast feeding infant the formula feeding infant has higher quantity of bacteroides, clostridia species and enterobacteriaceae and less colonization with bifidobacteria. *Actinomyces gerencseriae* and *S. australis* were detected more frequently in exclusively breast-fed compared with formula- fed infants [10]. The other factors that changes the composition of microbiota of infant similar to adult is mode of delivery, stopping breast feeding and weaning, in which the *lactobacilli*, bifidobacteria and enterobacteriaceae is changed to clostridium and bacteroides species [11]. Microbiota enhance many other microorganisms during first year of life which are capable in breaking down the complex sugars and starch by the second year they enrich the organisms that produce short chain fatty acids that is correlated with the increased body mass index, within three years microbiota composition is as similar to adult [12].

Antibiotic related dysbiosis

When the infant is treated with antibiotics there is decreased in the intestinal micribiota and species diversitiy for prolong period, can cause malfunctions in infants immunologic dysfunction, endocrine and metabolic disturbances, causing chronic disease related to endocrine and metabolic system, same time there is rapid increase in the competing bacterial species, specially *E. coli*, some enteric colonizers inhibits enterobacteriaceae species, *lactobacilli* secrete mucins that inhibit adhesion of enteropathogenic organisms, even recently we know that the antibiotic related dysbiosis is prolonged, even some of them use to return towards their baseline in some weeks, the recovery is delayed. Infant treated with antibiotics shows lower fecal bacterial diversity, having bifidobacterium colonization less and the enterococcus is more [13].

Immunes system

Hygiene hypothesis given by Strachan is that the developing immune system is not inadequately stimulated if we are not exposed to the infectious agents and another is the microfloara hypothesis due to use of antibiotics or the environmental exposure causing dysbiosis and stimulating immune system. According to the experiment of hesselmar et al. [14], children with family history of allergy, those whose parents sucked their pacifiers to clean them had less likely to have asthma, eczema, or allergic sensitization, the other experiment given by Hesselmar et al. [15] in comparison to the family using hand to wash dishes and using dishwasher, the family who washed dishes by hand had less chance of developing allergy in comparison to other. Immune system is regulated by gut microbiota, as the bacterial colonization takes place immune system is stimulated, at the early beginning they block the gut epithelial cell producing antibacterial substance, creating tight junction and stimulating IgA, second is to identification between the symbiotic and pathogenic bacteria by immune system at gut mucosal surface, the intestinal micribiota can regulate interleukin (IL)-1 and toll like receptors, even directly influence dendritic cell, T-cell, B lymphocytes and epithelial and stromal cell, dysbiosis causes chronic inflammation resulting in metabolic dysfunction and immune regulated disease by interfering immune regulatory system. Such as environmentally allergy, eczema, asthma, celiac disease, type 1 diabetes mellitus, Vebo et al. [16] showed that for the children in the risk for allergic disease enterococcus was seen in sufficient amount in bowel microflora at 4 months, of age and bifidobacteria at 1 yr of age, Yap et al. [17], found enterobacteriaceae and clostridium perfrigens in large quantity in children who developed eczema before 2 yrs and low abundance of bifidobacterium in at age 5 in the same case. Johansson et al. [18], according to the study, gut colonization in 2 months of age in relation to mononuclear cell cytokine, high number of cells of staphylococcus aureus colonization was seen, producing interleukine IL-4 and IL-10 and also interferon (IFN) in co-colonization with *S. aureus* and *Lactobacilli*. Benn et al. [19] found that maternal vaginal colonization with ureaplasm urealyticum and antibiotic treatment were associated with infant hospitalization for wheezing in the age of 0-3 yrs and mother receiving antibiotic treatment during pregnancy the infant has risk of asthma at 4-5 yrs, also mode and place are related with the risk of allergic disease, infant born by C-section is at high risk of eczema, food allergy and asthma in comparison to the infant delivered vaginally and at home, even the infant who received antibiotics and had low intestinal microbial diversity in the period of first month of life had chance to develop atopic eczema later and the allergic rash during school age and the use of antibiotic against anaerobic microbial organisms have more chance to develop inflammatory bowel disease an and even they have low level of Th-1 in the blood causing imbalance in the development of T-cell, that implies different immune related disease. C-section with use of antibiotic even has chance to develop type 1 diabetes mellitus.

The microbiome gut brain axis and implications for infant development

The early lifetime of infant around the first one year is the time of rapid change in between the gut and the microbiome and the developing infant Central Nervous System [20]. Microbiome is one of the important clinical and nonclinical factors that help for the study in neurocognitive and emotional status. Research based on rodents shows that the the gut microbiome modulates brain development, synaptic related proteins and behavior depends upon the three psychoneuroimmune pathways i.e., immune, hypothalamic pituitary adrenal axis and vagus nerve. Which results in the as the result the growing gut microbiome influence over a range of developmental indices, mood, sociability [21]. Notably it has seen that postweaning microbial colonization of the gut result in the previous social deficits, which suggest that microbiome associated developmental delays, can be changed by treatment. Similarly as rodent in human studies have linked that the abnormal gut microbiome composition results in the neurodevelopmental disorder. According to the study done previously proved that the use of antibiotic and the diet impacted the microbiome. The study on both animal and human shows that the emotional development and the congnitive relevant area of brain are negatively impacted anatomically and physiologically due to high level of glucocorticoids [22]. Microbiome is important for the regulation of the HPA axis; potentially important factor on the HPA axis and infant microbiome is maternal prenatal stress. The studies has shown that there is a positive relationship between the maternal stress level and pathogenic strains of Escherichia and enterobacter and inverse association with level of beneficial bacteria as lactobacillus or bifidobacteria in the infant gut microbiome. The production of the increased proinflammatory cytokines like IL-6 depends upon the stress induced change in microbial composition, which causes damage to the brain development interfering white matter and brain plasticity. Thus a major key role in the brain functioning is the gut microbiome, which has capacity to influence CNS development ranging from cognition to anxiety, mood and sociability, therefore, the way of microbiome gut brain axis operated during infancy shows the early life neurocognitive and social emotional development. And even the modification and influence of the microbiome depends upon the way of the care given to the mother and the infants during the first 1000 days of life by the midwives and neonatal nurse who takes care of the infant and the women [23].

Factors that influence the microbiota

A healthy individual can have different microbial combination, so it is not possible to define the normal microbiome, although it is being more important factor for knowing about the human microflora since long time [1]. So it is important to know about the role of the microflora in human health and the functional capacity and genetic potential of the microbiome, initially it was thought that the intestine of the fetal life was sterile, after the detection of the microbial DNA in the meconium of term and preterm infants the further exploration was done in the intra amniotic microbial environment. On the study of the uterine microbiome specially present in the amniotic fluid, fetal membrane and placenta, while in the uterine compartment, bacteria as Ureaplasma spp. and Fusobacterium spp. are mostly seen in the pre-term infants, during child birth the neonates are introduced by different microbes through different mode as maternal vaginal, fecal and skin medium. Anaerobes as Streptococci and entrobacteriaceae are the instant microorganism that colonizes the infant gut initially which comes in contact through the mother vagina and fecal route [24]. Further bacterial development takes place while initiating the infant oral feeding, beyond 48 hr, the number of bacteria is about 104-106 colony units per ml of intestinal contents. There are many factors as pre term birth or full term birth, vaginal delivery or cesarean section and based on diet as breastfeeding and formula feeding, environmental factor surrounding during delivery, use of antibiotics and proton pump inhibitors that interfair the bacterial colonization. Infant delivered vaginally has higher number of bacteria as bifidobacteria in comparison to cesarean section in which it delays for up to 6 months, the microbiota of vaginally delivered infant is similar to the microbiota of the mother's vagina and intestine, they are mainly composed of bacteria as lactobacillus, prevotella, bacterioides, Escherichia and bifidobacterium, biasucci, but in the cesarean section there is absence of bifidobacteria, vaginally delivered neonates were characterized by predominant bifidobacterim catenulatum, to recognize the bacterial communities between mothers and their newborn 16S rRNA gene pyrosequencing is done [25]. According to Dominguez-Bello [6] was that the bacterial communities between the mother and the newborns was directly contrast to the mode of delivery and the result showed was vaginally delivered newborns had similar bacterial communities as their own mother's vaginal microbiota, dominated by lactobacillus, prebotella and sneathia spp.; similary for the mode of delivery as cesarean section is dominated by the bacteria found in the own mother's skin surface as staphylococcus, corynebacterium and propionibacterium spp. there is difference in the colonization pattern between the preterm and term neonate gut, difference between them arises for the use of formula feeding and antibiotics in neonatal intensive care units, which can cause feeding intolerance and can develop neonatal necrotizing enterocolitis which can even cause short bowel syndrome and even death, the composition of the infant's gut microbiota depends upon the nature of the feeding as newborn on breast feeding or on formula feeding, the human milk contains human milk oligosaccharides (HMOs) which is very beneficial to intestinal microbiota of the neonate, which stimulate the growth of bifidobacterium and lactobacillus spp. and acts as prebiotics which alters the microbial composition of the the intestine, *Bifidobacterium infantis* with combination of multiple enzymes goes under deconstruction of the human milk glycans, as a result it can defense with other pathogens and other bifidobacteria in the gut lumen of healthy breast feeding infants, whereas in case of formula feeding infants the predominant bacteria are enterococci, bacteroides spp. and clostridia. There is direct link between the level of secretory immunoglobulin -A (IGA) [26] and the number of bifidobacteria in gut of the breastfeeding infant age around 1 month, during the same age the level of inflammatory cytokine interleukin-6 (IL-6) is inversely related to the number of bacteroides fragilis organisms, age related gastroenteritis can be caused due to excessive inflammation in infancy, human milk oligosaccharides not only stimulate bifidobacterium, *B. infantis* proliferation but also activate genes that take part in the pro- and anti-inflammatory balance with in the intestinal mucosa, these are the beneficial effect for the breastfeeding newborn infants. Human milk contains human milk oligosaccharides (HMOs) along with glycan's, which acts as the antimicrobial and prebiotic in behalf of the infants benefit [27]. According to some evidence that human milk is not sterile containing maternal derived bacterial molecular motifs, which stimulate the development of the immune system, which is known as "bacterial imprinting" there is symbiotic relationship between the colonization of bacteria and the host and immune system, which protect the infant from disease. There is another evidence that until 2-3 yrs of age the micorbiome does not reach its adult

composition, finally breast milk can help in the maturation of the immune system to develop and respond highly variable bacterial colonization and food antigen loads, later in the life the intestinal microbiota profile is developed according to the food consumed by the infant, short chain fatty acids (SCFAs) plays main role for the above process, SCFAs are organic fatty acids which is produced in the distal gut by bacterial fermentation of carbohydrates and proteins ,the rate and amount of SCFA production depends on the amount of microflora present in the colon. Most of the SCFAs present in the colon (90%-95%) consist of acetate (60%), propionate (25%) and butyrate (15%). Butyrate is the major energy source for colonocytes. Propionate is largely taken up by the liver. Acetate enters the peripheral circulation to be metabolized by peripheral tissues [28]. SCFAs has a role in improvement of metabolic function as controlling the blood glucose levels, as in type 2 diabetes mellitus, insulin resistant and glucagon like peptide secretion.

The use of antibiotics changes the pattern of the gut microbiota [29]. As administration of broad-spectrum antibiotic reduce the beneficial effect of Bacteroidetes, in respective to increase in Firmicutes, after ingestion of antibiotics in the early age <1 year the microbial diversity is often seen, without the complete recovery of the initial stage of the pattern of the microbiota, there is functional change in the microbiota due to the antibiotics treatment, during the treatment the response of the antibiotics on microbiota depends more or less on the type of antibiotics, length of dosing and baseline microbiome, the result of the use of antibiotics that targeted for the use of specific pathogen and disease will change the pattern of the microbial sequence and the host metabolic activity in great variation [30]. Prolonged use of antibiotics for the meconium in very low birth weight infant and for developing late onset sepsis will decrease the microbial diversity and help in the growth of predominant pathogens as clostridium, lebssiella and veillonella spp., that causes neonatal sepsis, extremely premature neonates are at high risk of sepsis, even the use of low dose of penicillin use in early life can change in microbiota and modify body composition which causes long term change in host metabolic effects [31].

Effect of gut microflora on functional development

The role of the enteric microbioata is important factor for the infant health and has important role in the infant later life. Several bacteria living in the colonic lumen affect host homeostasis, some bacteria are pathogens and can be source of infection and inflammation and where as the other may be beneficial to the host health. Some pathogenic bacteria are staphylococci, clostridia, enterobacteria, enterococci, streptococci and bacteroides [32]. Whereas the species which is beneficial to GIT are as lactobacillus and bifidobacterium, Enteric microbiota plays several benificial role for the intestinal physiology including structural protective and metabolic function, molecular mechanism that can explain the changes of the pattern of microbiota comes from the study of bacteroides thetaiotaomicron, prominent number of the intestinal microbiota of humans that modulate number of essential host functions. The epithelium, enteric bacteria provides the natural defense barrier against exogenous microbes, preventing invasion of pathogens by several mechanisms as displacement, competition for nutrients and epithelial binding sites, production of antimicrobial factors such as lactic acid and bacteriocins, the microbiota has a metabolic activity akin to that of virtual or hidden, inner organ. Difference in the gene in this microbial community provides different enzymes and biochemical pathways that are different from the constitutive resources of the host, as short chain fatty acid as acetate, butyrate and propionate are produced following fermentation of non-digestible prebiotic substances by few anaerobic bacteria [33]. SCFA enhance the growth of *lactobacilli* and bifidobacteria and play role in the physiology and metabolism of the colon and reduce the risk of developing disease as colon cancer and inflammatory bowel disease. Resident bacteria can also metabolize dietary carcinogens, synthesize vitamins as biotin, folate and vitamin k and absorption of calcium, magnesium and iron, benefit of the metabolic activity are recovery of metabolic energy and absorbable substrates for the host and supply of energy and nutritive compounds for bacterial growth and proliferation, gut microbiota has its specific metabolic activity individually and microbial composition which regulate energy storage and predispose to obesity between different individuals, as much the microbiota is metabolically active in host more it influences the normal structural and functional development of mucosal immune system [34]. Normal microbiota provides host substantial antigen challenge by strong stimulation to mature the gut associated lymphoid tissue and mucosal immunity, in fact most of the immunologically active cells of the body are located in the gut associated lymphoid tissue which is important in the immune system interactions. The ability of immunosensory cells as enterocytes, M cells and dendritic cells to discriminate pathogenic bacteria from commensal bacteria is mediated in two major host pattern recognition receptor systems, the family of toll like receptors and the nucleotide binding oligomerization domain, which has fundamental role in immune cell activation in response to specific microbial associated molecular patterns such as lipopolysaccharide, lipotechoic acid, peptidoglycan and flagellin [35]. Many pattern recognition receptor system are expressed by commensal bacteria, but the healthy gut do not evoke inflammatory response to these bacteria as bifidobacteri and *lactobacilli* providing protective effects by attenuating proinflammatory response created by different pathogens, even certain enteric bacterial components can ameliorate radiation induced mucosal injury.so it is possible that the composition of the enteric microbiota influences individual variations in immunity.

Conclusion

It is well known that intestinal microbiota play a major role in immediately after birth by promoting intestinal function and by developing the gut immune system and development of the brain axis for infant. Numerous factors may influence early intestinal colonization as prematurity, cesarean section, breastfeeding, formula feeding and antibiotics. Enteric microbiota plays several beneficial roles for intestinal physiology including structural protective and metabolic function, molecular mechanism that can explain the change of pattern of microbiota related to the effect of gut microflora on functional development. Some of the literature says that may preterm infants are exposed to microbes in utero via the amniotic fluid even those without a history of rupture of membrane or culture positive chorioamniotics, as it is the hot topic there should be more research needed for the appropriate outcome.

References

1. Pfeiffer JK, Sonnenburg JL (2011) The intestinal microbiota and viral susceptibility. Front Microbiol 2: 92.
2. Neu J (2007) Perinatal and neonatal manipulation of the intestinal microbiome: A note of caution. Nutr Rev 65: 282-285.
3. Dishaw LJ, Cannon JP, Litman GW, Parker W (2014) Immune-directed support of rich microbial communities in the gut has ancient roots. Dev Comp Immunol 47: 36-51.

4. Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, et al. (2014) Prenatal exposure to antibiotics, Cesarean section and risk of childhood obesity. Int J Obes 39: 665-670.
5. Stout MJ, Conlon B, Landeau M, Lee I, Bower C, et al. (2013) Identification of intracellular bacteria in the basal plate of the human placenta in term and preterm gestations. Am J Obstet Gynecol 208: 226.
6. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, et al. (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 107: 11971- 11975.
7. Biasucci G, Rubini M, Riboni S, Morelli L, Bessi E, et al. (2010) Mode of delivery affects the bacterial community in the newborn gut. Early Hum Dev 86: 13-15.
8. Collado MC, Delgado S, Maldonado A, Rodríguez JM (2009) Assessment of the bacterial diversity of breast milk of healthy women by quantitative real-time PCR. Lett Appl Microbiol 48: 523-528.
9. Jeurink PV, van Bergenhenegouwen J, Jiménez E, Knippels LM, Fernández L, et al. (2013) Human milk: A source of more life than we imagine. Benef Microbes 4: 17-30.
10. Solís G, de Los Reyes-Gavilan CG, Fernández N, Margolles A, Gueimonde M (2010) Establishment and development of lactic acid bacteria and bifidobacteria microbiota in breast-milk and the infant gut. Anaerobe 16: 307-310.
11. Bode L (2009) Human milk oligosaccharides: Prebiotics and beyond. Nutr Rev 67: S183-S191.
12. Guaraldi F, Salvatori G (2012) Effect of breast and formula feeding on gut microbiota shaping in newborns. Front Cell Infect Microbiol 2: 94.
13. Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, et al. (1997) The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. J Immunol 159: 1739-1745.
14. Hesselmar B, Sjoberg F, Saalman R, Åberg N, Adlerberth I, et al. (2013) Pacifier cleaning prac- tices and risk of allergy development. Pediatrics 131: e1829-e1837.
15. Hesselmar B, Hicke-Roberts A, Wennergren G (2015) Allergy in children in hand versus machine dishwashing. Pediatrics 135: e590-e597.
16. Vebo HC, Sekelja M, Nestestog R, Storro O, Johnsen R, et al. (2011) Temporal development of the infant gut microbiota in immunoglobulin E-sensitized and nonsensitized children determined by the GA-map infant array. Clin Vaccine Immunol 18: 1326-1335.
17. Yap GC, Loo EX, Aw M, Lu Q, Shek LP, et al. (2014) Molecular analysis of infant fecal microbiota in an Asian at-risk cohort-correlates with infant and childhood eczema. BMC Res Notes 7: 166.
18. Johnson CL, Versalovic J (2012) The human microbiome and its potential importance to pediatrics. Pediatrics 129: 950-960.
19. Benn CS, Thorsen P, Jensen JS, Kjaer BB, Bisgaard H, et al. (2002) Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. J Allergy Clin Immunol 110: 72-77.
20. Clouchoux C, Guizard N, Evans AC, du Plessis AJ, Limperopoulos C (2012) Normative fetal brain growth by quantitative in vivo magnetic resonance imaging. Am J Obstet Gynecol 206: 173.
21. Kerac M, Postels DG, Mallewa M, Alusine Jalloh A, Voskuijl WP, et al. (2014) The interaction of malnutrition and neurologic disability in Africa. Semin Pediatr Neurol 21: 42-49.
22. Isaacs EB, Gadian DG, Sabatini S, Chong WK, Quinn BT, et al. (2008) The effect of early human diet on caudate volumes and IQ. Pediatr Res 63: 308-314.
23. Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, et al. (2008) Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr 153: 170-175.
24. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, et al. (2011) Births: Final data for 2009. Natl Vital Stat Rep 60: 1-70.
25. Makino H, Kushiro A, Ishikawa E, Kubota H, Gawad A, et al. (2013) Mother-to-infant transmission of intestinal bifidobacterial strains has an impact on the early development of vaginally delivered infant's microbiota. PLoS One 8: e78331.
26. Grizard D, Barthomeuf C (1999) Non-digestible oligosaccharides used as prebiotic agents: mode of production and beneficial effects on animal and human health. Reprod Nutr Dev 39: 563-588.
27. Arrieta MC, Stiemsma LT, Amenyogbe N, Brown EM, Finlay B (2014) The intesti- nal microbiome in early life: health and disease. Front Immunol 5: 427.
28. Bergman EN (1990) Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol Rev 70: 567-590.
29. Jernberg C, Lofmark S, Edlund C, Jansson JK (2007) Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. ISME J 7: 456.
30. Jernberg C, Lofmark S, Edlund C, Jansson JK (2010) Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology 156: 3216-3223.
31. Schwartz S, Friedberg I, Ivanov IV, Davidson LA, Goldsby JS, et al. (2012) A metagenomic study of diet-dependent interaction between gut microbiota and host in infants reveals differences in immune response. Genome Biol 13: r32.
32. Likotrafiti E, Tuohy KM, Gibson GR, Rastall RA (2014) An in vitro study of the effect of probi- otics, prebiotics and synbiotics on the elderly faecal microbiota. Anaerobe 27: 50-55.
33. Sánchez de Medina F, Romero-Calvo I, Mascaraque C, Martínez-Augustin O (2014) Intestinal inflammation and mucosal barrier function. Inflamm Bowel Dis 20: 2394-2404.
34. Wallace TC, Guarner F, Madsen K, Cabana MD, Gibson G, et al. (2011) Human gut microbiota and its relationship to health and disease. Nutr Rev 69: 392-403.
35. Mondot S, de Wouters T, Doré J, Lepage P (2013) The human gut microbiome and its dysfunctions. Dig Dis 31: 278-285.