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The impact of the microbes on puppies and kittens microbiota: a review

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ABSTRACT

Recently it was discovered that canine and feline neonates are not born in a sterile environment as was stated previously. The acquisition, colonization, and maintenance of early life microbiota is a rapidly developing area of research. In humans it has been seen that the infant microbiome plays an essential role in human health and its composition is determined by maternal–offspring exchanges of microbiota. Even though this topic is becoming more and more important in dogs and cats, the exact role of the neonatal microbiome is not yet known. In this review, the current knowledge about the neonatal microbiome in puppies and kittens is summarized.

Key words: Neonatology; birth; puppies; kittens; microbiome

Introduction

Limited information is available describing the development of the neonatal fecal microbiome in dogs and cats. During pregnancy, several healthy developmental changes occur in many physiological systems, to support fetal growth. The last decade of research has made it clear that dramatic changes in the composition of the microbiome also occur. However, their role is not yet fully understood (NURIEL-OHAYON et al., 2016).

For more than a century, it was assumed that the eutherian fetus inhabits a largely sterile environment in utero during pregnancy, and is protected from bacterial invasion by maternal and fetal vascular separation, the immune-privileged status of the placental trophoblast, and gestational maternal tolerance mechanisms (GOMEZ DE AGÜERO et al., 2016). However, recent studies in humans and animals have shown that bacterial communities can be found in the uterus, amniotic fluid, placenta and meconium of healthy pregnancies (AAGAARD et al., 2014; JIMÉNEZ et al., 2005; JIMÉNEZ et al., 2008; BEARFIELD et al., 2002; COLLADO et al., 2016; STEEL et al., 2005; RAUTAVA et al., 2012; ZHU et al., 2018; HANSEN et al., 2015; PARNELL et al., 2017; STINSON et al., 2019; ZAKOŠEK PIPAN et al., 2020). We now know that acquisition of the gut microbiome begins in utero and it continues to change after birth (SINGH and MITTAL., 2020). It also has a major impact on the health of the developing offspring. The gut microbiota is involved in the programming and maturation of the immune system (DZIDIC et al.,

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2018), the utilization and modification of nutrients from the diet, the shaping of the gut environment through the production of metabolites as byproducts of its metabolism (HENRICK et al., 2018), and the prevention of colonization of the gut by pathogens (DALBY and HALL, 2020). In mice, maternal colonization has been found to reprogram the intestinal transcriptional profiles of the offspring, including increased expression of genes encoding epithelial antibacterial peptides, and metabolism of microbial molecules. Some of these effects are dependent on maternal antibodies that can retain microbial molecules and pass them on to offspring during pregnancy. Puppies colonized during pregnancy were better able to avoid inflammatory responses and gut microbiota invasion, compared to puppies born without microbiota at birth (GOMEZ DE AGÜERO et al., 2016).

The purpose of this review is to provide an overview of the composition of the microbiota in neonatal puppies and kittens, to summarize the latest research in this field, and to gather knowledge about the health and development of puppies and kittens on the basis of their microbiome at birth.

Microbiota at birth

Acquisition of the gut microbiome is now thought to begin in utero and to continue to change after birth (SINGH and MITTAL, 2020). At birth, the microbiome of dogs and cats consists of a community of microbes likely acquired from the infant's mother through vertical transmission. Later, the microbiome develops and changes during the first month of life. These changes occur primarily in response to the changing nutritional environment, although other external factors, such as antibiotics, also significantly influence the community's composition. Several studies in humans have found significant effects of the mode of delivery on the neonatal gut microbiota composition (DZIDIC et al., 2018; HENRICK et al. 2018; DALBY and HALL, 2020; DOMINGUEZ-BELLO et al., 2010; BÄCKHED et al., 2015; MACINTYRE et al., 2015; RUTAYISIRE et al., 2016). The same was found in our study on puppies, where the delivery mode influenced the diversity and type of bacterial communities in the gut of newborn puppies (ZAKOŠEK PIPAN et al., 2020). Recently, a larger cohort study that examined the delivery method - either vaginal or caesarean delivery - and its influence on the infant's microbiota, found different compositions of the gut microbiome. They concluded the major importance of the initial microbiota to which an infant is exposed for the health of the child later in life (DOMINGUEZ-BELLO et al., 2010; STEWART et al., 2018; KERO et al., 2002). Infants delivered by C- section appear to have increased colonization by opportunistic pathogens from the environment, such as *Enterococcus, Enterobacter*, and *Klebsiella* species, due to impaired transmission of *Bacteroides* and *Bifidobacterium* from the mother (STEWART et al., 2018). It has been suggested that the interruption of bacterial transmission from the vagina to the newborn due to C – section delivery may have long-term health effects and lead to a higher incidence of asthma (KERO et al., 2002) and celiac disease (MÅRILD et al., 2012) in babies delivered by C - section. It has also been found that the gut microbiota of vaginally born infants is composed of bacteria present in the mother's vagina, and includes bacteria present in the mother's gut (MACKIE et al., 1999). In contrast, the gut microbiota of infants born by C - section is similar to the maternal skin and oral microbiota in humans (BÄCKHED et al., 2015). Similar observations were also made in dogs, where puppies born by C - section had meconium microbiota composed of the bacteria present in their mothers' oral cavity, whereas puppies born vaginally had mainly bacteria present in their mothers' vagina. In addition, it was found that the total microbial diversity was significantly higher in vaginally born puppies compared to puppies born by C - section (ZAKOŠEK PIPAN et al., 2020).

Interesting results were obtained in our previous study when we investigated the microbiota of puppies and their weight gain in the first days of life, where puppies with bacterial microbiome in the meconium or placenta gained more weight than puppies born with sterile meconium or placenta. The difference in weight gain became significant on days 3 and 4. Although the difference was not significant on the first day, from a clinical point of

view, puppies with a sterile placenta lost an average of 1.9% of body weight, while those with placental microbiota gained an average of 0.06% of their body weight (ZAKOŠEK PIPAN et al., 2020). This is extremely important for the better survival of puppies in the first week of life, when mortality is known to be relatively high (TØNNESSEN et al., 2012). The higher relative weight gains in puppies born vaginally compared to puppies born by C - section could be due to the greater diversity of the meconium microbiota in puppies delivered vaginally and, consequently, the better food intake from the intestine (ZAKOŠEK PIPAN et al., 2020).

During pregnancy, the female body undergoes physiological changes to support fetal growth and development (VAN DER WEYDEN et al., 1989; ALMEIDA et al., 2018). Changes in metabolism, hormones, the cardiovascular system, and immune modulations are observed. Along with the immune changes, there are striking changes in the gut microbiota of dams during pregnancy (VILSON et al., 2018). While *Fusobacterium, Bacteroidetes* and *Firmicutes* are co-dominant in the fecal microbiome of healthy dogs (PILLA and SUCHODOLSKI, 2020), *Firmicutes, Proteobacteria* and *Lactobacillus Phyla* predominate at the end of gestation. Similar observations have been made in humans, where the gut microbiota changes dramatically from the first to the third trimester, with a dominance of phyla *Actinobacteria* and *Proteobacteria*, and a decrease in individual richness (KOREN et al., 2012). A change in the relative abundance of different bacteria during lactation, and an increase in diversity from pregnancy to the end of lactation have also been observed in the gut of pregnant and lactating dams (VILSON et al., 2018).

How microorganisms enter the fetal compartment of the placenta remains unclear. Since bacterial translocation via the bloodstream is known to be increased during pregnancy (AAGAARD et al., 2014), this could result in microorganisms entering the circulation and colonizing the placenta (ROMERO et al., 2015). Another possibility is that bacteria ascend from the vagina to the placenta and/or they are transported from the intestinal lumen to the placenta via maternal dendritic cells (ROMERO et al., 2015; ZHENG et al., 2015). Transmission of microbes from the mother to offspring is known in animals, including marine sponges, mollusks, insects, domestic chicken, fish, turtles and mice. This suggests that this is an ancient and advantageous evolutionary mechanism enabling the first beneficial microbe inoculation before birth (FUNKHOUSER and BORDENSTEIN, 2013).

In humans, mice and dogs, the healthy placental microbiome has been found to have more similarity to the oral microbiota than to the gut and vaginal microbiota (JIMÉNEZ et al., 2008; ZAKOŠEK PIPAN et al., 2020; PELZER et al., 2017). The transmission of oral bacteria was confirmed in a study conducted in mice, in which a group of pregnant mice were orally inoculated with a genetically labeled *E. fecium* strain. The labeled strain was isolated and detected by PCR from meconium of the vaccinated animals obtained by C-section one day before the expected term of delivery. In contrast, it was not detected in samples from a non-vaccinated control group (JIMÉNEZ et al., 2008). In dogs, the most common phyla isolated from the dams' placenta were *Staphylococcus spp, Streptococcus spp* and *Neisseria zoodegmatis* (ZAKOŠEK PIPAN et al., 2020). The similarity of bacteria in the placenta and oral cavity suggests the passage of bacteria from the oral cavity into the bloodstream and placenta (ROMERO et al., 2015). However, microbial density has been found to be very low in humans and dogs (ROMERO et al., 2015; ZAKOŠEK PIPAN et al., 2020). Therefore, careful sampling is of much greater importance, and scrutiny is necessary to avoid misinterpretation of results, which may be due to contamination. Samples collected after vaginal delivery have a high likelihood of contamination from the birth canal, unlike placental samples collected sterilely during a caesarean section.

While these studies have shed some light on the initial colonization of the infant gut and microbial succession dynamics, much remains to be discovered about the various pathways of microbes into the infant gut. Until now the research has focused mostly on bacteria, but there is an emerging world of viruses and fungi whose origins, transmission, and establishment in the gut and placenta are still unknown.

Shaping the microbiota

The health and well-being of companion animals, just as that of their owners, depends on the gut microbes. The gut microbiome contributes to the host metabolism, protects against pathogens, educates the immune system, and directly or indirectly affects most of the physiological functions of its host. A healthy and stable microbiome can simultaneously act pro- and anti-inflammatory, maintaining a balance to prevent excessive inflammation, while still being able to respond correctly to infections (WRIGGLESWORTH et al., 2020). The microbiome is dynamic and many changes occur during the life of the host in response to a variety of factors including diet, environment, medical interventions, and disease states. After maternal colonization of the infant gut, the composition of their microbiota is quickly changed and shaped by their diet and its components, i.e. breast milk or formula (or both). Breast milk is a complex biological fluid with many different nutritional and host components, such as enzymes and antibodies (DALBY and HALL, 2020). Recently, it was learned that the milk produced by domestic dogs and cats is unique in terms of its oligosaccharide profile. Oligosaccharides are important components of milk, serving as substrates for the intestinal microbiota, acting as antimicrobials that prevent pathogen colonization, and supporting the developing gastrointestinal immune system of neonates (WRIGGLESWORTH et al., 2020). In dogs, a 100- fold increase in Lactobacilli in the luminal contents of the distal colon by day 21 in neonate beagle puppies was detected. This increase can be explained since canine milk is a natural source of lactobacilli for sucklings (MARTÍN et al., 2010), and it has been proven in humans that breast milk is a source of lactic acid bacteria in the infant gut (MARTÍN et al., 2003). Lactobacilli are therefore the most dominant bacteria present in early neonatal life, and they commonly inhabit all parts of the dog intestine (SUCHODOLSKI, 2011), with *Lactobacillus acidophilus* being dominant (TANG et al., 2012). *Lactobacillus fermentum, Lactobacillus rhamnosus,* and *Lactobacillus salivarius* are reported as part of the healthy canine intestines (BEASLEY et al., 2006). Other canine lactobacilli are represented by *Lactobacillus murinus* and *Lactobacillus reuteri* (SUCHODOLSKI, 2011), *Lactobacillus animalis, Lactobacillus sanfranciscensis* and *Lactobacillus paraplantarum* (SILVA et al., 2013). Lactobacilli found in cats are typical intestinal lactobacilli, e.g. *Lactobacillus acidophilus, Lactobacillus salivarius, Lactobacillus johnsonii, Lactobacillus reuteri* and *Lactobacillus sakei*, which can be seen in other animals, including humans (RITCHIE et al., 2008).

Knowledge about the acquisition and later development of the intestinal microbiome in dogs and cats is limited to a handful of studies in kittens and puppies. In kittens, it was found, as in humans, that the early fecal microbiome is characterized by a high degree of interindividual variation, and that intraindividual diversity and composition change with age. Similar to humans, the relative abundance of *Lactobacillus* and *Bifidobacterium* decreases with age, whereas *Bacteriodes* and bacterial genes, associated with the ability to metabolize complex carbon sources, increase with age (DEUSCH et al., 2015).

Another study found that the fecal microbiome of kittens changed only slightly between 8 and 16 weeks of age (DEUSCH et al., 2014). These results suggest that, as in humans, the developing gut microbiome converges to a temporally stable configuration as kittens mature. The same temporal instability and substantial interindividual variability were found in a study on puppies using DNA sequencing methods (BURTON et al., 2016). However, it is worth mentioning that the fecal microbiomes of geneti+1cally related dogs are more similar to each other than unrelated dogs (HAND et al., 2013). This indicates genetics and environmental factors and their influence (HAND et al., 2013). VILSON et al. (2018) studied the environment effect on early gut microbiota and found a strong impact (VILSON et al., 2018). In a study comparing dogs and their owners, significant sharing of skin microbiota and even fecal microbiota between dog-owners and their pets was observed (SONG et al., 2013). Despite individual variability in the healthy human microbiota, it has been reported that the microbiota

of a given individual remains stable over time, and that more than 60% of strains in humans remained stable over a 5-year period (FAITH et al., 2013). When studying the microbiome of neonatal dogs, the fecal microbiota of puppies was found to change between 2 and 56 days after birth. Significant phylogenetic changes were noted at all taxonomic levels, with the most profound changes being a shift from primarily *Firmicutes* in puppies at 2 days of age to a co-dominance of *Bacteroidetes*, *Fusobacteria,* and *Firmicutes* at 21 days of age. These shifts were characterized by increased microbial diversity and species richness. It was suggested that the increase in species richness indicated that the gastrointestinal tract of the puppies was gaining strength and resistance to environmental pathogens. By day 42, the microbial communities appeared to have reached relative stability (GUARD et al., 2017). In order to change the microbiota of an adult dog, maintenance on a specified diet is required, rather than feeding transitional diets (ALLAWAY et al., 2020).

Dogs and cats have several hundred bacterial phylotypes in the gastrointestinal tract. However, both dogs and cats have distinct bacterial species that differ from each other, and vary in different dog and cat species, and geographical areas. The microbial differences between dogs and cats are demonstrated in the microbial groups and species levels. Molecular fingerprinting has also revealed that each individual has a unique intestinal microbiota, and its composition is determined by management, diet, genetics, antibiotic exposure, and environmental factors. The composition of the microbiota also changes along the gastrointestinal tract under the influence of nutrient availability and the local microenvironment (SUCHODOLSKI, 2011). Microbial diversity and concentration increase along the length of the gastrointestinal tract (WERNIMONT et al., 2020). For example, the small intestine harbors a mixture of aerobic and facultative anaerobic bacteria, while the colon is colonized almost exclusively by anaerobes (SUCHODOLSKI, 2011; WERNIMONT et al., 2020). The predominant bacterial phyla in the duodenum are represented by *Protobacteria* in both dogs and cats, versus *Firmicutes, Bacteroidetes, Proteobacteria*, and *Fusobacteria* in the colon and feces of both dogs and cats, as well as *Eubacterium* in cats (PILLA and SUCHODOLSKI, 2020).

A recent study comparing the gut microbiome of 46 cats and 192 dogs using fecal samples found that cats had higher bacterial phyla diversity than dogs. Compared to cats, the bacterial phyla *Enterococcus, Fusobacterium, Megamonas*, and SMB53 were higher in dogs, whereas several phyla were more abundant in cats, including *Adlercreutzia, Alistipes, Bifidobacterium, Carnobacterium, Collinsella, Coprococcus, Desulfovibrio, Faecalibacterium, Oscillospira, Parabacteroides, Peptococcus, Peptostreptococcus, Ruminococcus, Slackia,* and *Sutterella* (JHA et al., 2020). The same was also observed in a previous study (HAND et al., 2013). Moreover, cat feces contain high numbers of obligate anaerobes, and such levels are considered abnormal in dogs and humans (JOHNSTON et al., 2001). Using 16S rRNA analysis, it has been reported that the feline colon is commonly represented by five phyla, with *Firmicutes* dominating (68%), followed by *Proteobacteria* (14%), *Bacteroidetes* (10%), *Fusobacteria* (5%) and *Actinobacteria* (4%) (RITCHIE et al., 2008). However, a recent study using the metagenomic approach showed that the gut microbiota of cats is dominated by the bacterial strain of the Bacteroidetes/Chlorobi group, which comprises about 2/3 of the total classified diversity, followed by *Firmicutes* and *Proteobacteria* (TUN et al., 2012). Similar findings were also found in a recent study conducted by ALESSANDRI et al. (2020). This high diversity in cats compared to dogs could be due to the fact that dogs are more omnivorous than cats, and can digest a significant amount of carbohydrates. In contrast, cats are obligate carnivores and require foods high in protein to meet their nutritional needs, and consume smaller amounts of glucose (DENG and SWANSON, 2015; TIZARD and JONES, 2018).

There is also evidence that members of the microbiome from other parts of the gastrointestinal tract are important reservoirs for the communities found in the gut. Members of the oral microbiome colonize lower sections of the gastrointestinal tract. In addition, their presence has been associated with disease (LIRA-JUNIOR and BOSTRÖM, 2018).

Altogether, the gastrointestinal microbiome is now known to have a major impact on pet health, both directly and through its influence on dietary response (SUEZ and ELINAV, 2017).

Development of the immune response

Immune system development in newborn puppies and kittens is determined by the organisms that colonize the skin and the gastrointestinal and respiratory tracts. The presence of high numbers of microbes provides a rich source of signals to the immune system (TIZARD and JONES, 2018). This early microbial exposure determines how the immune system develops. The microbiota generates a complex mixture of microbially associated molecular patterns that act through enterocytic Toll-like receptors (TLRs) to promote the functional development of the immune system (GENSOLLEN et al., 2016). The gut and skin microbiota also contribute to this process as newborns are nursed and cared for by their mother (BROWN and CLARKE, 2017). The establishment of the gut microbiota is therefore essential for normal immune system development, and can be potentially disrupted by prematurity, different types of parturition, diet and use of antibiotics (TIZARD and JONES, 2018).

The microbiota also modifies the intestinal environment by maintaining a low pH and oxygen tension. There is more immune system activity in the intestine than in all other lymphoid tissues combined. It has been estimated that more than 80% of the body's activated B cells are found in the intestine. Their function is to defend against possible invasion by the microbiota. However, the key to successful accommodation with the intestinal microbiota also depends on the body's ability to regulate inflammation in the gut wall (KAMADA et al., 2013; DENG and SWANSON, 2015). This is achieved by maintaining a balance between proinflammatory Th17 cells and anti-inflammatory Treg cells (TIZARD and JONES, 2018).

In mice, it was shown that the maternal microbiota shapes the immune system of the offspring. Maternal colonization reprograms the intestinal transcriptional profiles of the offspring, including increased expression of genes encoding epithelial antibacterial peptides and metabolism of microbial molecules. Some of these effects are dependent on maternal antibodies that potentially retain microbial molecules and transmit them to the offspring during pregnancy and in milk. Puppies born to mothers transiently colonized in pregnancy are better able to avoid inflammatory responses to microbial molecules and penetration of intestinal microbes (GOMEZ DE AGÜERO et al., 2016).

Immune system development is both preprogrammed in neonatal tissues and later driven by exposure to pathogenic and nonpathogenic microbes. The composition of the gut microbiota also has significant effects on immune function, and regulates local production of antibodies. Although intestinal microbes are separated from direct contact with enterocytes by the inner mucus layer and glycocalyx, intestinal dendritic cells can extend their dendrites into the intestinal lumen and sample the microbiota (KOREN et al., 2012). These invading bacteria are usually killed by macrophages, and some are also presented to B cells. The B cells produce IgA that is secreted into the lumen, binds to the bacteria, and activates the targeted destruction of the bacteria (TIZARD and JONES, 2018). Intestinal helper T (Th) cell progenitors can differentiate into either Treg or Th17 cells, depending on the signals received from the microbiota (TIZARD and JONES, 2018). In homeostasis, Treg cell production is favored and Th17 cell production is suppressed, resulting in minimal inflammation within the intestinal wall. In the absence of Treg cells, uncontrolled effector T cells respond to microbial antigens and trigger inflammation (TIZARD and JONES, 2018). Gut dysbiosis can affect this process. Gut dysbiosis is defined as changes in the composition of the gut microbiota that result in functional changes in the microbial transcriptome, proteome, or metabolome (RIVERA-CHÁVEZ et al., 2017). An increase in the abundance of facultative anaerobic bacteria of the family Enterobacteriaceae is a common marker of dysbiosis (RIVERA-CHÁVEZ et al., 2017), which is also observed in dogs (VÁZQUEZ-BAEZA et al., 2016). Dysbiosis is seen in many pathologies, both local, within the gastrointestinal tract, and systemic (ZAPATA and QUAGLIARELLO, 2015), and is associated with

obesity (KIELER et al., 2017), metabolic diseases (MONTOYA-ALONSO et al., 2017), cancer (v et al., 2017), neurological disorders (WU et al., 2016) and many others, in both dogs and humans. Furthermore, the gut microbiome is altered in both acute and chronic diarrhea. As in healthy dogs, studies in dogs with gastrointestinal disease report different proportions of taxa abundance, or increased or decreased taxa within the same disease phenotype (PILLA and SUCHODOLSKI, 2020). Dysbiosis should always be considered when pathologies of the gastrointestinal tract are present. However, restoration of microbiome composition does not necessarily correlate with clinical recovery, and the long-term consequences of such residual alterations have yet to be discovered. The identification of the bacterial compounds involved in disease pathogenesis may aid the development of new diagnostic and therapeutic tools, and should be investigated (PILLA and SUCHODOLSKI, 2020).

Conclusion

The acquisition, colonization, and maintenance of the microbiota in early life, as well as subsequent interactions with the host, is a rapidly evolving area of research. Dogs and cats are considered the most valued companion animals of humans, and concern for their health is very important. Since the gut microbiota plays a crucial role in the development of the immune response and the health of the animal, more attention should be paid to its influence.

In this review, we discuss the microbiome in newborn cats and dogs, changes in the gut microbiota during early life, and the importance of a healthy microbiome in the early development of the immune response. While the human microbiome has been studied over the past two decades, limited data are available to assess the development of the fecal microbiota of puppies and kittens during the early stages of life, and the true impact of microbial changes on host development and overall health remains unknown. Recent advances in DNA sequencing technology, including 16S rRNA analysis, have improved our understanding of the neonatal microbiome and its impact on health in the early months. Metagenomic studies are extremely helpful for providing information about the healthy vaginal, oral, placental, and gut microbiome. However, further studies are needed to elucidate the relationship between puppy and kitten microbiota development, physiological growth, neonatal survival and morbidity, to gain clinical relevance for diagnostic, predictive and therapeutic options and achieve better neonatal survival.

Author contributions
MZP and reviewed the literature and wrote the manuscript.

Conflict of interest
The authors of this review declare no conflicts of interest.

Ethical statement
For this study ethical approval was not required.

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SAŽETAK

Nedavno je ustanovljeno da se štenad i mačići ne kote u sterilnom okruženju. Stjecanje, kolonizacija i održavanje mikrobiota u ranom životu područje je istraživanja koje se brzo razvija. U ljudi je ustanovljeno da je mikrobiota novorođenčeta ključan za ljudsko zdravlje, a njegov sastav određuje razmjena mikrobiota između majke i potomstva. Iako je i u pasa i mačaka to područje sve važnije, točna uloga neonatalnog mikrobiota još nije poznata. U ovom su radu prikazane dosadašnje spoznaje o neonatalnom mikrobiotu štenadi i mačića.

Ključne riječi: neonatologija; koćenje; štenad; mačići; mikrobiom

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