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Microbial colonization of the gastrointestinal tract of dairy calves – a review of its importance and relationship to health and performance

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Review

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Abstract

This review aims to explain how microbial colonization of the gastrointestinal tract (GIT) in young dairy calves is related to health and, consequently, to the performance of these animals. The review addresses everything from the fundamental aspects of microbial colonization to the current understanding about the microbiota manipulation to improve performance in adult animals. The ruminal microbiota is the most studied, mainly due to the high interest in the fermentative aspects, the production of short-chain fatty acids, and microbial proteins, and its effects on animal production. However, in recent years, the intestinal microbiota has gained space between studies, mainly due to the relationship to the host health and how it affects performance. Understanding how the GIT's microbiota looks like and how it is colonized may allow future studies to predict the best timing for dietary interventions as a way to manipulate it and, consequently, improve the health and performance of young ruminants.

Introduction

Initial microbial colonization of the gastrointestinal tract (GIT) plays an essential role in the maturation of the endocrine, immune system of the mucosa, and central nervous system, strongly influencing and supporting the health and well-being of young animals (Badman *et al.*, 2019; Wijdeveld *et al.*, 2020; Williams *et al.*, 2020). Most studies describing the host-microbiota interaction are in the human gut. In ruminants, the major focus of studies has been on the rumen, due to the pre-gastric compartment symbiosis with microorganisms, allowing the ruminant to obtain energy in the form of short-chain fatty acids (SCFA) from fermentation of different feeds.

The importance of colostrum feeding, volume and quality of the liquid diet, levels of fiber in the concentrate, or providing hay to dairy calves has been extensively discussed. Also, the introduction of different molecular techniques, such as omics, have proven essential in microbiology studies, as well as the introduction of concepts, such as diversity and richness, making it possible to understand how different feed practices can affect the GIT microbiota of calves.

The nutrition offered to young calves affects the structure of the gastrointestinal microbiota by providing different substrates to the microbial communities (Li *et al.*, 2012; Rey *et al.*, 2014; Guzman *et al.*, 2015). Thus, the type of substrate available for growth affects the colonization and establishment of different microorganisms. So, understanding the microbial colonization process throughout the GIT is highly significant for the comprehension of host–microbiota interactions during the pre-weaning period and their impact on health and production in the animal's productive life. Furthermore, knowledge about these interactions is essential for gastrointestinal microbiota manipulation, either by replacing diets, by adding additives, or even by supplementing probiotics or prebiotics.

Therefore, this review aims to explore the colonization and maintenance of the gastrointestinal microbiota in dairy calves and to understand how they relate to health and performance. The primary focus will be on bacteria, followed by archaea, as few studies have examined colonization by fungi and protozoa.

Overview of gastrointestinal microbiota

In recent years, several studies have shown how the gastrointestinal microbiota is closely related to host health and performance, either through metabolic function or protection against pathogens (Maranduba *et al.*, 2015; Pascale *et al.*, 2018). The gastrointestinal microbiota is genetically complex, represented by various species of bacteria, protozoa, fungi, methanogenic archaea, and bacteriophages (Chaucheyras-Durand and Ossa, 2014; Dill-McFarland *et al.*, 2017; Dias *et al.*, 2018), with many functional and phylogenetic differences. The ruminal microbial ecosystem is more diverse and responsible for several functional niches, including

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proteolytic, fibrolytic, and lipolytic functions (Clemmons *et al.*, 2019). The counts are in the order of 10^{10} CFU ml^{-1} of ruminal fluid for bacteria, 10^8 for protozoa, 10^7 for archaea, and 10^3 for fungal spores (Deusch *et al.*, 2015).

Among all microorganisms, bacteria are the most studied for their functional and phylogenetic diversity, reproducibility, and accessibility to genetic material (Clemmons *et al.*, 2019). The bacteria are responsible for approximately half of the microbial genetic material in the rumen (Nagaraja, 2016), and may represent even more in other GIT compartments.

In general, the most abundant bacterial phyla in the GIT are Firmicutes (41.22%), Bacteroidota (33.51%), and Proteobacteria (12.15%), but these proportions are variable depending on the age and the GIT compartment (de Oliveira *et al.*, 2013; Myer *et al.*, 2015). In beef steers, Firmicutes were more abundant in the small and large intestines, while Bacteroidota were more abundant in the reticulum-rumen, omasum, and abomasum (de Oliveira *et al.*, 2013). Coincidentally, rumen, omasum, and abomasum had the highest bacterial diversity, and the jejunum was the lowest in bacterial diversity and richness.

In dairy calves, some results are similar. Dias *et al.* (2018) also observed higher diversity in the rumen, cecum, and colon compared to the jejunum, and also had fewer taxa shared with other groups, and a higher abundance of the Proteobacteria phylum. As calves aged, the bacterial community became more homogeneous. In newborn calves, Yeoman *et al.* (2018) observed higher abundance of Proteobacteria (41%), Firmicutes (29%), and Bacteroidota (23%), with significant differences between the lumen and mucosal-attached microorganisms. This higher abundance of Proteobacteria was associated to colostrum intake and had a bacterial composition of 42% Proteobacteria, 22% Firmicutes, and 21% Bacteroidota, similar values to gut microbiota. This age-related difference in the composition may be mainly associated to dietary changes occurring throughout the pre-weaning period.

The differences in composition affect the diversity indices (de Oliveira *et al.*, 2013; Dias *et al.*, 2018). Understanding the concept of these indices, as well as the distinction between indigenous (autochthonous) and transient (allochthonous) microorganisms in the GIT microbiota is fundamental to the ecological understanding of colonization, succession, and interaction mechanisms between intestinal microorganisms and hosts (Mackie *et al.*, 1999). This distinction is difficult, especially in neonates, as their microbiota is not yet well established, with many microorganisms being transient. Some of these concepts, as well as their definitions, are shown in Table 1.

Study tools for assessment of the gut microbiota

Many ruminant studies have investigated the ruminal microbiota since the 1950s, and these studies focused more on the effects of nutritional factors on the diet than on the host relationship. In addition, studies have used culture-based methods for a long time (Hungate, 1966). However, any method that favors the growth of microorganisms over others is biased (Allaband *et al.*, 2019)

Genome sequencing by whole-genome shotgun and later by next-generation sequencing techniques allowed a great evolution and deepening of metagenomics (Koonin *et al.*, 2021), as well as in studies and definitions of other ‘omics’ (Table 1). Such techniques have allowed unculturable, and previously unknown, microorganisms to be discovered, and have their function and metabolites analyzed. Some estimates indicate that less than 0.1% of the prokaryotes represented in most environments can grow in culture (Fraser-Liggett, 2005; Koonin *et al.*, 2021).

Table 1. Concepts, definitions and techniques used in microbial ecology

Concepts	Definition
Microbiota	Set of microorganisms in a specific environment
Microbiome	Microbiota genes set
Diversity	Measure of richness and evenness
Richness	Total number of unique microbial taxa
Evenness	Measure of how evenly taxon abundance is distributed
α-Diversity	Microbial diversity within a local community, and measured by either the richness or by diversity indices, such as Shannon or Simpson
β-Diversity	Measurement of diversity between two or more local assemblages; higher β-diversity, more differences in species identities between the communities.
Autochthonous microorganism	A microbe that originated from the local/compartiment/biome it is identified in
Allochthonous microorganism	A microbe that did not originate from the local/compartiment/biome it is identified in
Techniques	
Amplicon-based sequencing	Study of the taxonomic composition and microbial abundance by sequencing the targeted gene products
Metagenomic	Study of taxonomic and functional composition, and gene abundance in microbiome
Transcriptomic	Study of expression of genes from a microbiome
Proteomic	Study of protein profile and expression from a microbiome
Metabolomic	Study of metabolite profile from a microbiome

Adapted from Yeoman and White (2014); Malmuthuge and Guan (2016); Thomas *et al.* (2017) and Allaband *et al.* (2019).

Bioinformatics is essential to support the microbiome analysis, applying methodologies from computer science, advanced mathematics, and statistics to the study of biological phenomena (Carriço *et al.*, 2018; Allaband *et al.*, 2019). Furthermore, the use of popular phylogenetic marker genes such as 16S ribosomal RNA (rRNA; bacteria and archaea), 18S rRNA (protozoa), and the internal transcribed spacer region (ITS; fungi) have aided in the investigation of microbial communities (Smith *et al.*, 2020).

Furthermore, especially for taxonomic classification of the 16S rRNA gene, reference databases are widely available, such as the Ribosomal Database Project (RDP), SILVA, GreenGenes, RefSeq, and the Genome Taxonomy Database (GTDB; Smith *et al.*, 2020). For classifying methanogens there are specific databases such as the Rumen and Intestinal Methanogen Database (RIM-DB; Seedorf *et al.*, 2014) and the Neocallimastigomycota, and more recently the GlobalFungi for fungi (Větrovský *et al.*, 2020). According to Allaband *et al.* (2019), metagenomic approaches lose many rare bacteria not well represented in reference databases. This could be a problem, as the reference database can interfere in the interpretation of microbiota analysis (Pollock *et al.*, 2018). As shown by Sanford *et al.* (2021), SILVA and GTDB are both well-updated databases; however, Greengenes and RDP became outdated since few years ago. In the study by Smith *et al.* (2020), considering different databases in conducting 16S rRNA amplicon sequencing taxonomic classification of ruminal microbiota, it was concluded that RefSeq + RDP and SILVA were the most appropriate reference databases due to superior classification at the genus level, even with limitations.

Even with several limitations, such as financial limitations and microbiome analysis, we cannot deny that this did not slow down the publication of studies in the area, both for humans and ruminants. Using the search data cited by Malmuthuge *et al.* (2015a), and comparing publications over the interval 2010–2020, we observed an increase of more than six times in the number of studies published for humans and more than 10 times for ruminants, depending on the search term used. Despite this higher publication rate for ruminants, the numbers of studies are well below those for humans. These increased publication numbers suggest that there is still a significant amount of research to be conducted on the microbiota.

Microbial colonization of the GIT

Microbial colonization is influenced by a series of factors associated with the host, the microbiota, and external factors. The external factors are the most diverse, such as maternal microbiota, birth type, environment, colostrum source and feeding time, liquid and solid diets, and antibiotic treatment during early life (Malmuthuge *et al.*, 2015a). Host-related factors have been cited as luminal pH, feeding retention time, and immune defense mechanisms, as well as microbiota-related factors such as adhesion, survival mechanisms under an oxygen gradient, and mechanisms to obtain nutrients from the host (Adlerberth and Wold, 2009). Some authors have suggested that prepartum events may influence newborn GIT colonization (Ley *et al.*, 2005; Dominguez-Bello *et al.*, 2010; Elolimy *et al.*, 2019).

Until recently, newborn ruminants were commonly believed to have been born with sterile GITs (Taschuk and Griebel, 2012; Malmuthuge *et al.*, 2015a), and that these animals had the first contact with microorganisms during birth because, on fetal development, the placental barrier prevented them from having contact with the fetus. However, meconium samples collected immediately or shortly after birth showed diverse and low-abundant microbiota (Alipour *et al.*, 2018; Elolimy *et al.*, 2019), suggesting microbial colonization in the intestinal tract during the fetal period. Recently, a pioneering bovine study by Guzman *et al.* (2020) found a high density of bacterial genetic material in the fetal GIT and amniotic fluid between 5 and 7 months of gestation, indicating a possible pre-natal cow-to-fetus transmission across the placental barrier. Bi *et al.* (2021) also observed a low diversity microbiome in the intestine of goat fetus, composed of bacteriophages, viruses, and bacteria carrying antibiotic resistance genes. Despite these results, both human and rodent studies are still inconclusive and create considerable discussion, indicating no presence of bacterial genetic material during fetal development (Collado *et al.*, 2016; Hornef and Penders, 2017; Theis *et al.*, 2020).

At birth, colonization rapidly continues by an abundant and diverse microbial community (Jami *et al.*, 2013). The GIT colonization is a dynamic process and has a considerable fluctuation in the animal's early life. The processes related to the microbe establishment are complex, involving microbial succession and interactions between microorganisms and the animal, resulting in dense and stable populations inhabiting specific regions in the GIT. Colonization can continue until weaning because the microbial diversity, richness, structure, and composition of the GIT throughout the pre-weaning period are often constantly changing (Oikonomou *et al.*, 2013; Klein-Jöbstl *et al.*, 2014a; Dias *et al.*, 2017; Virgínio Júnior *et al.*, 2021). After this period, the microbiota become stabilized and resilient to change, being altered only by temporary changes in diet but possibly returning to the previous condition (Weimer, 2015).

From an ecological point of view, gastrointestinal colonization represents the assembly of a new microbial community (Costello *et al.*, 2012). Some older studies and reviews describe the colonization as occurring in stages (Rey *et al.*, 2014; Malmuthuge *et al.*, 2015a), however more recent studies show colonization to be much more dynamic from birth to weaning.

The inoculum sources of microorganisms are the most diverse. However, diet and frequency of supply are the most critical factors for establishing and maintaining the stability of microbial populations (Fonty *et al.*, 1987), as inoculation pathways of microorganisms and also serving as substrates for growth. However, it is not clear how microbiota–host interactions occur during the early life of ruminants, and if these interactions have any influence on the performance and health of the animal.

A recent study showed what are the main sources of microorganisms in the gut of lambs, comparing to animals that suckled directly to their dams to those that were bottle-fed (Bi *et al.*, 2019). The study showed that in lambs suckling their dam, the initial intestinal microbiota were more similar to that present in the teats (43%) and the environment (28%). In comparison, bottle-fed lambs were more similar to microorganisms in the vagina (46%), in the ambient air (31%), and the floor of the pen (12%).

The first contact extra-uterine with microorganisms occurs as the animal passes through the vaginal canal. Klein-Jöbstl *et al.* (2019) have observed some variation in the fecal microbiota of neonatal calves at 48 h, but closer to the vaginal microbiota of the dam than to the microbiota of the dam's mouth and feces, or even colostrum. Although the authors did not assess environmental influence, an important factor in post-natal colonization. Yeoman *et al.* (2018) also observed greater proximity of the vaginal microbiota to the ruminal microbiota 72 h after birth, including fibrolytic ruminal bacteria, as well as methanogenic archaea, potentially indicating a role for the vagina in populating the developing reticulum-rumen with microbes important to the nutrition of the adult animal. Less than 20 min after birth, archaea (*Methanobrevibacter* spp., *M. mobile*, and *M. votae*), fibrolytic bacteria (*F. succinogenes*, *Ruminococcus flavefaciens,* and *P. ruminicola*), and *Geobacter* spp. (phylum Proteobacteria) were detected in GITs and calf feces (Guzman *et al.*, 2015). Barden *et al.* (2020) compared the fecal and oral microbiota of beef and dairy cows and calves, and up to 4 weeks, the calves' fecal microbiota were closer to the cows' oral microbiota. Overall, no marked differences were observed in the calves' microbiota, indicating that vertical transmission through feces may be low.

While studies do not indicate colostrum as a major source for gut microbiota colonization, it is important to remember that colostrum represents an important substrate for the growth of commensal bacteria, accelerating bacterial colonization in the calf's small intestine. Calves that received fresh colostrum reached a total bacterial density of 10^{10} copies of the 16S rRNA gene g^{-1}

at 12 h of life, while calves that did not receive colostrum reached only 10^8 copies of the 16S rRNA gene g^{-1}, and have abundant *E. coli* both in the lumen and mucosal (Malmuthuge *et al*., 2015b), and this can have serious consequences in the calves' performance. Besides, colostrum feeding may result in a higher prevalence of *Bifidobacterium* in the small intestine during the first 12 h of life (Malmuthuge *et al*., 2015b). However, Fischer *et al.* (2018) observed a higher abundance of this genus with colostrum supply soon after birth. This increased prevalence may explain the reduced incidence of enteric infections (Godden *et al*., 2012), indicating that colostrum plays a crucial role in establishing a healthy GIT.

According to age and feeding rate, among other variables, 5–20% of the dry matter (DM) intake of whole milk is not digested (Guilloteau *et al*., 1986; Hill *et al*., 2010). In the case of milk replacers, these quantities may be even higher. Although this is presumably a higher flow of fermentable nutrients in the posterior intestine of the pre-ruminant calf, limited information is available about how early microbial activity can affect gut development and health (Oikonomou *et al*., 2013) compared to ruminal development. Therefore, during the calf pre-ruminant phase, the increased supply of fermentable substrate may result in bacterial colonization and establishment of fermentation in the posterior intestine, which is equally or more relevant than in the anterior intestine for the health and survival of the newborn (Castro *et al*., 2016).

Bacterial colonization has been the focus of different studies in recent years. Facultative anaerobes, such as *Streptococcus* and *Enterococcus*, are known as early colonizers and convert the GIT into a completely anaerobic environment (Adlerberth and Wold, 2009; Jami *et al*., 2013). These changes in the gastrointestinal microbiota are dynamic in the first 12 weeks of life, increasing diversity, richness, and evenness over the pre-weaning period (Li *et al*., 2012; Rey *et al*., 2014), including the appearance of new species such as *R. flavefaciens* and *Fibrobacter* species and reducing the abundance of *Bifidobacterium*, *Enterobacteriaceae*, *Streptococcus,* and *Lactobacillus* species (Uyeno *et al*., 2010; Li *et al*., 2012).

Archaea are difficult to detect in calf feces until week 4 of age, and fungi appear 1 week after birth but below detection until weaning (Dill-McFarland *et al*., 2017). In a microscopic evaluation, Virgínio Júnior *et al.* (2016) also observed no fungi attached to the fiber in calves at 60 days of age. Dias *et al.* (2017) have identified fungi and archaea in calves at 7 days of age, even before the starter concentrate supply. The absence of starter concentrate does not seem to be a limiting factor to the archaea. Zhou *et al.* (2014) have observed an abundance of *Methanobrevibacter* in the dairy calf GIT, and the higher diversity in the rumen. Malmuthuge *et al.* (2019) have found less than 0.1% of fungi in the ruminal environment of newborn calves. Archaea were not detected.

The colonization of ciliated protozoa depends on contact with other adult ruminants and can be detected in the first weeks of calf life (Dehority, 1998). If contact with adult ruminants occurs, protozoa populations develop between 15 and 20 days of age (Fonty *et al*., 1988). Malmuthuge *et al.* (2019) also did not detect protozoa in the rumen of newborn calves. Virgínio Júnior *et al.* (2016) have found no protozoa in dairy calves weaned at 60 days and attributed it to out of contact to other ruminants. Minato *et al.* (1992) found some genera such as *Entodinium* in calves at 8–10 weeks. Relatively limited information is available on the colonization of protozoa in the rumen of calves, and even a relatively recent review (Newbold *et al*., 2015), has no mention of colonization in dairy and beef calves. In the only study in beef calves at 6–8 months of age, Duarte *et al.* (2018) found a diversity of protozoal genera in the rumen of Nelore calves, but these calves are too old for comparisons to calves up to 60 days. Protozoa colonization may be delayed compared to bacteria because protozoa are sensitive to the lower ruminal pH characteristics of pre-weaning calves possibly to milk escape and subsequent lactic fermentation, as mentioned by Dias *et al.* (2017). The rapid establishment of protozoa requires a well-structured bacterial population. Bacteria promote physico−chemical characteristics in the ruminal environment (Fonty *et al*., 1988), and are a nitrogen source for growth of protozoa (Williams and Coleman, 1997).

The gastrointestinal microbiota are continually changing as calves increase the intake of a solid diet and are weaned, with the eventual establishment of a mature microbial community (Meale *et al*., 2016; Dill-McFarland *et al*., 2017). The development of diverse microbiota in young ruminants sets the ecosystem and initiates fermentative digestion in these animals (Fonty *et al*., 1991). The flaw in establishing healthy microbiota can result in bowel disorders and immune function impairment (Czarnecki-Maulden, 2008).

Importance of microbiota to the physiology of young ruminants

Ruminants have established symbiotic relationships with different microorganisms, and which degrade and metabolize different nutrients such as fibrous and non-fibrous carbohydrates and proteins. This symbiosis occurs because mainly the ruminal environment is suitable to allow microorganisms to establish and develop, and to provide ammonia, amino acids, vitamins, and SCFA to the animal through the fermentation of diet components (Hungate, 1966; Rey *et al*., 2014).

Ruminal microorganisms produce glycogenic, lipogenic, and aminogenic precursors that contribute to regulating energy and protein metabolism in cattle (Hungate, 1975), and provide the host approximately 70 and 60% of its daily energy and protein needs, respectively, through fermentation (Flint and Bayer, 2008; Yeoman and White, 2014). Therefore, studies on microbiota in ruminants have always focused on ruminal microbiota to understand the effects on meat and milk production (Malmuthuge *et al*., 2015a).

However, in the last few years, the topic of microbiota has gained importance in studies with ruminants, with the main focus on the effect of different diets. The gut microbiota also provide crucial physiological characteristics that the host organism would not be able to develop by itself (Gill *et al*., 2006; Neish, 2009).

Although numerous studies in humans and rats report the importance of early intestinal microbiota in the host's future health, few studies try to understand the role of intestinal colonization in the development of GIT and the health of neonatal ruminants. Moreover, ruminal and intestinal development and the establishment of microbiota have always been studied as separate aspects of ruminant biology. Only a few reports aimed to understand possible interactions between these two compartments (Malmuthuge *et al*., 2015a).

The gut microbial colonization at the beginning of life is essential to the development of metabolic functions, maturation of the immune system, and health of calves (Gomez *et al*., 2017; Kouritzin and Guan, 2017), and may have long-term health effects (Conroy *et al*., 2009). A stable commensal community protects the host from invasive pathogens (Kamada *et al.*, 2013), and expands the biosynthetic capacity of the host by improving nutrient uptake (Karasov *et al.*, 2011).

The simple provision of starter concentrate during the pre-weaning period increased the abundance of *Methanosphaera* spp., an archaea efficient in producing enteric methane (Dias *et al.*, 2017), and has a marked effect, not only by providing bacterial growth substrate, but also by altering the cecal microbiota, increasing the abundance of *Allistipes*, *Parabacteroides*, *Parassutterella* and *Butyricimonas*. Those microorganisms associated with digestion of fiber and other carbohydrates and butyrate production, and decreased the gene expression related to inflammatory factors, such as IL-12, TNF-α (Sun *et al.*, 2019). In the review by Steele *et al.* (2016), the authors have shown how important butyrate produced by microorganisms is for barrier protection, stimulating the growth of both ruminal and intestinal epithelium.

The resident microbiota represent a barrier to the invasion and proliferation of exogenous and opportunistic pathogenic microorganisms (Hooper *et al.*, 1998). This effect occurs by the production of antagonist substances (bacteriocins), production of metabolites and toxic products (SCFA and H_2S), maintenance of low oxide reduction potential, and depletion of nutrients necessary for the maintenance of pathogens (Savage, 1977; Bezirtzoglou, 1997).

Most of the intestinal bacterial species are probiotic species such as *Lactobacillus*, *Bifidobacterium*, *Enterococcus faecium*, and *Bacillus* species (Ballou, 2011). Dias *et al.* (2018) have shown a very peculiar distribution in the GIT. *Bifidobacterium* had a similar abundance in the rumen, jejunum, and cecum, without differing in age, while *Lactobacillus* was abundant in the jejunum and *Faecalibacterium* in the cecum and colon, both decreasing over age. These species play a beneficial role in the production of vitamins, essential amino acids, and other favorable metabolic substrates (Leahy *et al.*, 2005), in addition to supporting nutrient metabolism (Sommer *et al.*, 2016; Wu *et al.*, 2016), and assisting the host's immune system (Lukens *et al.*, 2014). *Lactobacillus* and *Bifidobacterium*, as well as *Faecalibacterium* species, can modulate the immune system and inflammatory response (De Simone *et al.*, 1992; Oikonomou *et al.*, 2013). These bacteria can prevent the binding of pathogens to intestinal epithelial cells (Duffy *et al.*, 1994), and stimulate the production of IgA (Fukushima *et al.*, 1998).

The GIT development and homeostasis depend on the dynamics between gut microorganisms and the immune system (Sansonetti and Medzhitov, 2009). The immune system 'learns' from the microbiota to recognize beneficial and pathogenic microorganisms, and thus quickly sends a response against harmful pathogens (Candela *et al.*, 2010).

On the other hand, other microorganisms are defined as causing pathology and virulence to the host, but all can cause endotoxemia under certain circumstances (Mackie *et al.*, 1999; Brooks *et al.*, 2007). As a consequence, beneficial microorganisms, such as species *Bifidobacterium* species limit the pathogenic agents' growth, e.g. *E. coli*, *Clostridium perfringens*, *Campylobacter*, *Listeria*, *Shigella*, and *Vibrio cholerae* (Gibson and Wang, 1994).

The gut microbiota's protective potential is reduced in stressful events, such as changes in diet, weaning, transportation, environmental changes, and contact with multiple infectious agents, causing dysbiosis and, consequently, the high incidence of bowel diseases in calves (Fleige *et al.*, 2007). In addition to affecting the ruminal and fecal microbiota, weaning decreased bacteria, such as *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, and *Blautia*, and reduced permeability in the rumen, duodenum, and jejunum (Wood *et al.*, 2015; Meale *et al.*, 2017). Changes in intestinal permeability may be the cause of diarrhea incidence in dairy calves (Araujo *et al.*, 2015).

Microbiota and ruminal development in dairy calves

The ruminal microbiome regulates the fermentation processes and, consequently, the diversity and functional capacity to support the digestive efficiency of ruminants (Abecia *et al.*, 2014). However, the rumen-reticulum of neonatal ruminants is small and non-functional, and will only develop during the pre-weaning period as the animal starts feeding on starter concentrate of adequate quantity and quality (Davis and Drackley, 1998; Baldwin *et al.*, 2004).

Stater concentrate composition for dairy calves should be between 20 and 22% CP, 80% TDN, 15–25% NDF, and 6–20% ADF (Davis and Drackley, 1998). Minimum levels of NDF and ADF ensure healthy ruminal epithelium, and maximum levels ensure the inclusion of highly digestible ingredients. The inclusion of higher levels of NDF does not depress the intake, animal performance, or ruminal development using a high-quality fiber source, such as soybean hulls (Poczynek *et al.*, 2020).

The solid diets intake increases microbial populations' development, resulting in higher production of SCFA (Baldwin *et al.*, 2004). Depending on the type and quality of the diet fed to the calves, the GIT's morphophysiology may be altered (Li *et al.*, 2011; Toledo *et al.*, 2020). In addition, the provision of drinking water is essential to maintain ruminal activity. Wickramasinghe *et al.* (2019) have reported the highest digestibility of NDF, ADF, and were more efficient than calves receiving water at day 17 or later.

Bacteria are the most significant ruminal microorganisms, mainly producing SCFA and microbial proteins, as well as some other metabolites such as biohydrogenated lipids (Clemmons *et al.*, 2019). Bacteria are key to mature ruminal function and can be detected one day after birth, before the rumen is mature, or even before the solid diet is consumed (Jami *et al.*, 2013; Dias *et al.*, 2017). The bacterial population increases with animal age and intake of solid diet (Dill-McFarland *et al.*, 2017; Dias *et al.*, 2017). Thus, as soon as calves consume solid feed, the faster the microbial composition and gastrointestinal function become similar to those seen in adult animals (Pitta *et al.*, 2010; Li *et al.*, 2012; Dill-McFarland *et al.*, 2017).

The increase in ruminal development is associated to starter intake resulting in the production of SCFA, especially butyric and propionic acids (Baldwin *et al.*, 2004). Acetate, which is not related to the changes observed in ruminal development, has a low molar ratio for the first 2 months and increases until 9 months of age as forage intake increases (Davis and Drackley, 1998; Suarez-Mena *et al.*, 2016), and is not related to the changes observed in ruminal development.

The concentration and absorption of butyrate and propionate in the rumen provide chemical stimulation necessary for ruminal epithelium proliferation (Khan *et al.*, 2008, 2016; Suarez-Mena *et al.*, 2016). Some studies suggest that ruminal papillae proliferation is associated with the direct effect of butyrate and propionate on gene expression (Gálfi *et al.*, 1991; Steele *et al.*, 2016).

Besides anatomical changes, changes in the site of digestion and absorption occur, which shift from the intestine to the rumen. The calf's energy metabolism is altered, beginning to use more SCFA and less glucose. The development of other digestive compartments also occurs with changes in intestinal enzyme activity, reduction in lactase activity, and increase in maltase as well as in the development of the salivary system and rumination behavior (Baldwin *et al*., 2004; Khan *et al*., 2016).

Feeding a high-starch starter, despite the fermentative benefit for ruminal development, can cause metabolic disorders such as acidosis (Daneshvar *et al*., 2015). The high production and low absorption/clearance of SCFA reduce the ruminal pH, resulting in reduced fiber digestibility by reducing fibrolytic bacteria (Russell and Wilson, 1996). This disorder, affecting developing calves, can change the establishment of the microbiota. However, the use of ingredients rich in non-starch polysaccharides (NSP), such as soybean hulls, which do not increase lactic acid concentration and, consequently, do not decrease pH, would be an alternative for inclusion in diets.

Forage or rougher feed promotes the development of ruminal muscle, maintains the integrity of the ruminal epithelium (Baldwin *et al*., 2004), and keeps the ruminal pH higher due to the larger particle size and fermentation profile (Terré *et al*., 2013). Maintaining a higher ruminal pH benefits microbial populations typically associated with forage, which in turn alter the production of butyrate and propionate to acetate.

Many recent studies have demonstrated that access to chopped hay promotes starter concentrate intake in calves, contrary to traditional recommendations (Jiao *et al*., 2016; Toledo *et al*., 2020). Castells *et al*. (2013) have conducted a meta-analysis and concluded that no difference in the intestinal filling was found between calves not consuming forage and those consuming forage up to 5% of total solid feed intake. However, the effect of forage feeding on the long-term microbial ruminal ecosystem has not yet been determined.

Despite all this discussion, relatively limited information about the relationship of the early microbiota to ruminal development is still available. Recently, Pan *et al*. (2021) have analyzed ventral sac rumen wall gene expression and the ruminal microbiome of goats until 56 d (weaning). The animals were fed only whole milk until 24 d, receiving the solid diet at 25 d. The analysis showed that the differentially expressed genes of the ruminal transcriptome related to two distinct phases, immune phase (1–14 d) and metabolic phase (21–56 d). In addition, they observed changes in the ruminal microbiome (at 42 d), with increased abundance of *Selenomonas* spp., *Prevotella* spp. and *Ruminococcus*, and increased expression of bacterial genes related to biosynthesis and glycolysis/glyconeogenesis activities. Based on this, the authors understood that ruminal development in the first phase is more likely a programmed process than continuously stimulated by the solid diet and the microbiome, but can be activated by microbial colonization at birth. The intense functional correlations between rumen genes and the microbiome are related to ruminal pH homeostasis, nitrogen metabolism, and immune response during early ruminal development. This study brings a new insight into the interactions between host and microbiota, however, there are some questions about the possible effect of the microbiota in activating the immune phase, and the expression of these genes to the animal has earlier access to a solid diet. Or if there is any effect of the liquid diet in this period.

Gut microbiota and health of dairy calves

Commensal bacteria in the intestine protect against the invasion of pathogenic microorganisms (Kamada *et al*., 2013; Kouritzin and Guan, 2017), stimulate and maintain the integrity of the gut mucosal barrier, and produce a variety of beneficial metabolic substrates (Leahy *et al*., 2005; O'Connell Motherway *et al*., 2011). Change in microbial composition leading to shifts in the proportion of commensal and pathogenic bacteria is called dysbiosis and is often related to gastrointestinal disorders, metabolic and immunological alterations, and generalized effects on the organism (Maynard *et al*., 2012; Zeineldin *et al*., 2018).

Nutrition is critical in maintaining and modifying the gut microbial composition. Besides the previously comments about supplying colostrum (Malmuthuge *et al*., 2015b; Fischer *et al*., 2018), the liquid diet plays a very important role during the pre-weaning period. The feeding of a liquid diet to the newborn has considerable implications on the development of gut microbiota. Several of its constituents, such as oligosaccharides, select for highly adapted intestinal microbiota dominated by *Bifidobacterium* species (Pacheco *et al*., 2015). However, the type and availability of nutrients in the milk replacers are different from those observed in whole milk, and can significantly impact the colonization of the animal's intestine.

Whole milk is the best feed for pre-weaning calves, both nutritionally and to stimulate the microbiota (Zou *et al*., 2017; Virgínio Júnior *et al*., 2021); however, many dairy herds still insist on feeding waste milk to calves. Deng *et al*. (2017), Zou *et al*. (2017), and Pereira *et al*. (2018) have already demonstrated that in addition to altering the intestinal microbiota, animals fed waste milk had a higher abundance of pathogenic microorganisms such as *Odoribacter* and *Fusobacterium*, and antibiotic residues in the feces. Pasteurization and acidification can be an alternative in reducing the bacterial load (Deng *et al*., 2017; Zou *et al*., 2017), but there are no ways to reduce antibiotic residues after milking.

Also, bacterial genera *Bifidobacterium*, *Faecalibacterium*, and *Megamonas* were associated with healthy calves and more weight gain (Oikonomou *et al*., 2013; Gomez *et al*., 2017; Virgínio Júnior *et al*., 2021), whereas unhealthy calves were associated to *Escherichia*, *Shigella* and *Fusobacterium* genera (Gomez *et al*., 2017; Virgínio Júnior *et al*., 2021) and had lower microbial diversity on the gut (Oikonomou *et al*., 2013; Ma *et al*., 2020).

According to Klein-Jöbstl *et al*. (2014b), diarrhea is a complex multifactorial disease with numerous infectious and noninfectious factors, and diarrhea is cited in several studies worldwide as the leading cause of morbidity and mortality in calves during the pre-weaning period (Lanz Uhde *et al*., 2008; Bartels *et al*., 2010; dos Santos and Bittar, 2015; Mohammed *et al*., 2019; Fruscalso *et al*., 2020). Among the pathogens commonly associated with diarrhea are *E. coli* and *Salmonella spp*. (Izzo *et al*., 2011), such as bovine rotavirus group A (BRV-A), bovine coronavirus (BCoV), bovine viral diarrhea virus (BVDV), *Clostridium perfringens* type C, and *Cryptosporidium parvum* (Saif and Smith, 1985; Singh *et al*., 2006; Gulliksen *et al*., 2009; Cho *et al*., 2013; Cruvinel *et al*., 2020). Farm management can also be responsible for the frequency and spreading of these pathogens, such as poor hygiene in milking equipment, buckets, feeding bottles, shelters, or even poor water quality, or related to the number of animals on the farm and the presence of other animal species (Klein-Jöbstl *et al*., 2014b; Mohammed *et al*., 2019).

To decrease the use of antimicrobials in the farms, alternative treatments have grown in recent years. The use of natural products, such as probiotics, prebiotics, herbal extracts, enzyme blends, among others, has been commonly used in studies to treat diarrhea. Signorini *et al*. (2012) reviewed the results of different studies using lactic acid bacteria (LAB) in calf feed, and only in studies using whole milk the LAB were effective in reducing the diarrheal incidence and increasing the ratio of LAB to coliforms. Probably the lack of effect on milk replacer feeding may be related to the different compositions among commercial products, and would make it difficult to provide a more specific response to the effects of LAB.

Cangiano *et al.* (2020) reviewed the strategic use of prebiotics in calf nutrition such as fructooligosaccharides, galactosaccharides, mannanooligosaccharides (MOS), and have showed that prebiotics have been little used in ruminant nutrition, compared to probiotics. Most of the prebiotic's studies have been on calves, primarily MOS, and have been effective in improving performance and gut health. However, some studies with beta-glucans have also shown promise (Ma *et al.*, 2015; Kido *et al.*, 2019). However, there is still a lack of studies to show further results or to indicate the best time to administer this prebiotics.

Other studies using compounds containing different microorganisms and enzyme blends, (Renaud *et al.*, 2019), red propolis (Slanzon *et al.*, 2019), and lysolecithin (Reis *et al.*, 2021) have shown potential effect in reducing diarrhea incidence in dairy calves. However, the effect on microbiota has not been reported. Fecal microbiota transplantation has also been shown to be a technique with beneficial effects, such as reduced fecal amino acid concentration, improved weight gain, and growth (Kim *et al.*, 2021). Ruminal transfaunation is also a similar technique, using ruminal contents from healthy cows to cows with ruminal disorders, and in addition to repopulating the rumen, it also provides various nutrients and energy to the microbiome (DePeters and George, 2014). However, the study by Yu *et al.* (2020) was the most promising, using freeze-dried ruminal fluid, they have observed in goats a higher digestibility of DM, crude protein during pre-weaning, and after weaning, improved starch digestibility. Bu *et al.* (2020) have observed a reduction in the overall incidence of diarrhea (91 vs 69 d) in animals receiving fresh ruminal fluid compared to those receiving autoclaved ruminal fluid.

Despite there is an increasing number of microbiota studies, there is still limited knowledge about the gut microbiota in dairy calves, and the mechanisms of influence of these microbiota on development and gut health are still unclear and undefined.

Diet as a factor in the manipulation of the gastrointestinal microbiota

The composition of the GIT microbial community is influenced by both the diet and the animal's age. Age is a factor in increasing diversity and uniformity (Jami *et al.*, 2013). On the other hand, diet plays a significant role in defining the structure of the ruminant microbiota and the general health of the GIT (Kreikemeier *et al.*, 1990). Diet is an influential contributing factor in establishing GIT microbiota and can serve as a tool to change the microbiota in early life (Dill-McFarland *et al.*, 2019). The manipulation of GIT microbiota in the pre-weaning period may result in the effective establishment of the desired microbiota that remains stable until maturity (Malmuthuge and Guan, 2016). According to Dias *et al.* (2017), manipulation of the ruminal microbiota at the pre-weaning period may be possible with dietary interventions, besides being useful to design strategies to promote colonization of specific microorganisms associated to better development of the calf. This allows for the selection of beneficial microorganisms, supporting their increased growth, and reducing pathogenic microorganisms that cause various diseases in calves, such as diarrhea.

The mature rumen is well known to be resilient to dietary changes. Any changes in the microbiota composition may be temporary, only occurring in the period of supplementation (Weimer, 2015). This fact suggests that microbiota manipulations can be challenging as they it is resilient (Abecia *et al.*, 2018). In contrast, neonatal microbiota are more sensitive to external pressures, such as antibiotics \ and changes in the composition of the liquid or solid diet (Mulder *et al.*, 2011; Malmuthuge *et al.*, 2015a). Thus, it is necessary to evaluate the GIT microbiota in the same individual during its entire development from calf to cow, to determine the best moment to the microbiota manipulation would be more efficient in improving future milk production.

External factors in early life cause changes in the composition of the gastrointestinal microbiota and this effect may persist into adulthood, in addition to causing an effect on the animal phenotype (Russell *et al.*, 2012; Abecia *et al.*, 2013). Thus, manipulating the gastrointestinal microbial community in neonates can allow a desirable microbial composition to establish itself in adult animals. This manipulation can in the future obtain animals producing less methane, having greater efficiency in milk production, or weight gain rates.

Recent, studies have shown how effective different diets can be on the microbiota. Malmuthuge *et al.* (2015b) and Fischer *et al.* (2018) have already shown how crucial is colostrum feeding or the timing of feeding influences the gut microbiome in early life. However, the effect of early management on the microbiome is still understudied. Colostrum powder, frozen colostrum, and colostrum enrichment are all routinely used on farms, but the impact on the microbiota is not well understood.

The liquid diet also has a significant impact on the intestinal microbiota. Whole milk should be the first choice to feed calves, and its composition has proven ideal to limit the growth of pathogenic microorganisms (Pacheco *et al.*, 2015). Acidification or pasteurization of whole or waste milk have proven to be good alternatives, with good results in performance, besides stimulating the growth of commensal and probiotic bacteria, and decreasing the incidence of diarrhea (Deng *et al.*, 2017; Coelho *et al.*, 2020; Virgínio Júnior *et al.*, 2021).

Milk replacers are the main liquid diet in many dairy herds, however, with a wide range of ingredients, such as dairy products and vegetable sources (Bittar *et al.*, 2018), that can affect the gastrointestinal microbiota. Virgínio Júnior *et al.* (2021) noted that the milk replacer composition used in one study may have negatively affected the initial microbiota, predisposing these animals to be more susceptible to diarrhea. Badman *et al.* (2019) also observed that the different composition impacts the initial microbiota up to 7 d.

The addition of prebiotics, probiotics, and additives to liquid diets is a beneficial alternative in modulating the rumenal and intestinal microbiomes, decreasing diarrhea incidence, modulating the immune response, promoting higher performance and gut health. O'Hara *et al.* (2018) adding sodium-butyrate to whole milk, observed higher SCFA concentration in the colon, as well as a higher abundance of *Phascolarctobacterium*, considered a probiotic bacteria. Other studies, even if not evaluating the microbiome, have high expectations in modulating the gut microbiota (Slanzon *et al.*, 2019; Reis *et al.*, 2021).

The concentrate supply also modulated the ruminal microbiota (Dias *et al.*, 2017). Changes in the solid diet, such as the forage/concentrate ratio, can cause changes in the ruminal bacterial community at the beginning of life and persist for up to 4 months

(Yáñez-Ruiz *et al*., 2010), as diets probably have higher NDF contents or even the supplementation of hay or whole-grain corn.

A recent study by Dill-McFarland *et al.* (2019) evaluated the fecal microbiota at 2, 4, and 8 weeks, and at 1 and 2 years, and the rumen at week 8 (from males that were slaughtered) and cannulated females at 1 and 2 years. A calf starter, corn silage, and a diet containing 25/75 concentrate and corn silage were fed to calves in the pre-weaning period. This study has shown off early intervention does not have as guaranteed long-term effects on the microbiota or milk production. However, some authors have reported that there is great inter-individual variability even in groups receiving the same diet (Klein-Jöbstl *et al*., 2014a; Zhou *et al*., 2014; Virgínio Júnior *et al*., 2021), so the differences in the ruminal microbiome may not be so accurate. Another question may be regarding the Greengenes database, as shown in the second topic, which has not been updated for a long time. So far, the Dill-Mcfarland study is the only study that has been up to 2 years old, but its results deserve to be discussed with more care and attention.

Another study that found similar results, Virgínio Júnior *et al.* (2021) evaluating the fecal microbiota of calves receiving different liquid diets (milk replacer, whole milke, and acidified whole milk), observed at weaning (week 8), that the bacterial community structure has similarities among treatments, and after the animals were housed in a pasture at week 10, this similarity was more evident, with few differences in composition after weaning. Thus, indicating that perhaps the environment is a factor to be considered as a modulator or leveler of the gastrointestinal microbiome, as well as the starter intake.

However, we cannot deny the fact that dietary modulation associated with management practices may affect the GIT microbial composition in neonatal calves. Thus, it can improve health status, prevent colonization by pathogenic microorganisms, and reduce inflammatory reactions. It is not yet clear if the effects of modulation are can persist in the microbiota of mature animals. Perhaps future studies on dietary modulation in the GIT microbiota should consider the effect of the environment. In addition, should also make use of integrating different molecular techniques, such as metabolomics, transcriptomics, and proteomics, which, also correlating microbiome data with performance, intake, metabolism, health, and behavior data. Only then, will we be able to make more strategic decisions regarding gut microbiota modulation.

Conclusion

In humans, studies in the microbiome are far ahead, with the identification of several microbial groups that are related to different bowel disorders as well as mental illnesses, with the intestinal health and healthy growth of the human being. Compared to the human microbiome, the gastrointestinal microbiome of ruminants is still 'unknown'. The studies focus on a cause-and-effect relationship. Studies still need to advance and relate the microbiota to the general physiology of the host, and should also include different molecular techniques.

An increasing number of studies on the ruminants microbial colonization have been ongoing, focusing mostly on bacteria, studying mainly their relevance to the rumen and newborn feces, but relatively limited attention has been dedicated to the microbiota within different compartments (e.g. colon and colon), or to the host interactions with different groups (e.g. protozoa and fungi).

In addition, we need to know the microbiome as a whole. Too little is understood about the presence of fungi and protozoa in the gastrointestinal environment, their distribution and function in each compartment. Although this review focuses on bacteria, it also highlights how poorly we know about other groups within the intestinal tract. The microbiota of young ruminants, especially calves, is a path that is still unknown and full of opportunities for future research.

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