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Changes in the gut microbiome and colic in horses: Are they causes or consequences?

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Abstract

The gut microbiome is a compound for millions of microorganisms that coexist in an organized way and contribute to the fermentation of different types of indigestible fibers by the small intestine. Some techniques, such as the massive sequencing of the 16S ribosomal RNA gene, have made it possible to obtain information about the abundance and functionality of the microorganisms that compose the equine gut microbiome and the interaction with their environment. Recent studies have identified the change in the composition of the intestinal microbiome during and after a colic episode, although is not clear if it is a cause or a consequence. The objective of this review was to elucidate whether there is a direct relationship between the changes that occur in the gut microbiome and colic in the equine. A systematized search in Embase, Web of Science, and PubMed was realized. Although there is good evidence that horses with colic have a change in their gut microbiome, it is not fully understood whether these changes are causes or effects. It is necessary to delve into this topic, considering studying larger population sizes. In addition, it would be of great value to previously know the normal intestinal microbiome of a group of healthy horses, which in the future could develop an episode of colic, to compare the before and after in the same individual.

Keywords: Colic, Equine, Gut, Microbiome.

Introduction

In equine veterinary medicine, colic is the general term to refer to visceral abdominal pain and acute abdominal disease (Worku *et al*., 2017; Marshall and Blikslager, 2019). This pain is considered a symptom that may be reflecting various disorders of different magnitudes and severity at the digestive level, such as a simple obstruction, strangulating obstruction, or severe inflammatory processes, among others (Cook and Hassel, 2014; Marshall and Blikslager, 2019; Bowden *et al*., 2020). Despite the treatments and surgical interventions to address these episodes, there is a high morbidity and mortality associated with economic losses for the owners (Tinker *et al*., 1997; Proudman *et al*., 2002; Cook and Hassel, 2014; Tannahill *et al*., 2019). Therefore, identifying and understanding the variables that act as predisposing or determining factors have been key to suggesting management practices that reduce the prevalence of colic (Scantlebury *et al*., 2015; Blikslager, 2019; Kaufman *et al*., 2020; Vitale *et al*., 2020). In a 2019 report, these risk factors were evaluated and classified into three large areas: horse-related factors, management-related factors, and environment-related factors. It was concluded that the most common risk factors are related to diet, either due to changes in the concentrate or hay consumed by the animal and/or due to a decrease in water intake (Mehdi and Mohammad., 2006; Curtis *et al*., 2019).

The equine gut microbiome is a complex and diverse ecosystem composed primarily of bacteria, which cohabit with viruses, archaea, and fungi (Rodriguez *et al*., 2015; Arroyo *et al*., 2018; Nishida *et al*., 2018). As in other mammals, the intestinal microbiome of horses generates a complex and symbiotic environment, which in addition to its role in the digestion of food, fulfills metabolic functions of protection against pathogens and stimulation of the immune system, directly or indirectly affecting different physiological processes of the host (Icaza-Chavez, 2013; Shirazi-Beechey, 2008; Barko *et al*., 2018).

Modifications in the composition of the microbiome, known as dysbiosis (Blackmore *et al*., 2013; Venable *et al*., 2016; Salem *et al*., 2019), have been related to diets high in concentrate, poor quality forage, confinement, stress, fasting, and age, among other causes. Interestingly, in recent years, some authors have associated alterations in the gut microbiome of horses with colic, since changes in the abundance of certain bacterial groups that have an important role in maintaining a healthy gastrointestinal tract have been observed (Costa and Weese, 2018; Blikslager, 2019; Salem *et al*., 2018, 2019). The objective of this review

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was to elucidate whether there is a direct relationship between the changes that occur in the intestinal microbiome and colic in equines.

Gut microbiome

The equine gastrointestinal tract is made up of a complex consortium of microorganisms called the microbiome, which plays an important role in both health and disease. It is estimated that there are about 10^{15} microorganisms that compose it, with about 160 described species (Stewart *et al*., 2018, 2019).

The equine gut microbiome colonization process begins at birth, where the neonates acquire the first microorganisms occurring through the birth canal, for the direct contact with the mother and later for the contact with the environment (Barko *et al*., 2018). In humans and horses, it has been shown that the assembly and establishment of the gut microbiome are essential for proper growth and development (Mueller *et al*., 2015; Matsuki *et al*., 2016). The first colonizers are facultative anaerobic bacteria, such as Enterobacteriales, *Enterococcus*, and *Streptococcus*; these bacteria will consume the oxygen present in the intestinal lumen, creating an anaerobic environment that will allow the growth of strict anaerobes, such as *Bacteroides* and *Clostridium* (Dougal *et al*., 2014; Lindenberg *et al*., 2019).

The equine gut microbiome is totally different in the first months of life from that existing or established in adulthood, which related to the intake of colostrum, milk, coprophagia, and/or the incorporation of fiber in the diet (Costa and Weese, 2018). In a study conducted in foals and their mothers, a marked stabilization of the gut microbiome was observed around day 50 postpartum, which was associated with the gradual introduction of the adult diet well before weaning. The early microbiome was characterized by bacteria previously identified in the milk and birth canal, while from day 50 there was a significant increase in certain anaerobic species capable of fermenting fiber (Lindenberg *et al*., 2019). Apparently, the diversity of species decreases with age, determined by a study concluding that horses between 19 and 28 years have lower bacterial richness compared to younger horses (Dougal *et al*., 2014). Venable *et al*. (2016) support the idea that the aging process in the horse generates a reduction in microbial diversity. Another study conducted on fecal samples found that the group made up of old horses had a higher relative abundance of the Proteobacteria phylum compared to the control group (Morrison *et al*., 2018).

The use of culture-independent identification methods, such as the massive sequencing of 16S ribosomal RNA gene, allowed obtaining information about the abundance and functionality of the microorganisms that compose the equine gut microbiome and the interaction with their environment (Costa and Weese, 2012). Most of these studies have been carried out from stool samples, being representative of the microbiome present in the large intestine, mainly in the caecum (Venable *et al*., 2016; Salem *et al*., 2019). In healthy adult horses, the microbial profiles that have been found are mostly represented by bacteria from the phyla Firmicutes (44%) and Bacteroidetes (38%), followed by Spirochaetes (2.5%), Fibrobacter (2.0%), Proteobacteria (0.8%), and Tenericutes (0.5%) (Stewart *et al*., 2019). On the contrary, other studies indicate that the most abundant phylum in healthy horses is Bacteroidetes, followed by Firmicutes, Verrucomicrobia, and methanogenic archeas (Costa and Weese, 2018; Kauter *et al*., 2019; Stewart *et al*., 2019). However, some studies have concluded that bacteria belonging to the phylum Firmicutes outnumber Bacteroidetes in a ratio of 4:1, in contrast to current data reporting that this ratio is 1: 1. Indeed, these differences may be influenced by factors such as geographic location, race, diet, intestinal segment, methodological differences in the DNA extraction technique, and even the sequencing platform used (Costa *et al*., 2012; Dougal *et al*., 2013; Ericsson *et al*., 2016; Kauter *et al*., 2019) (Table 1).

Additionally, some reports indicate that the microbiome is diverse and multifunctional throughout the gastrointestinal tract, which is related to the physiology of each segment. In general, the richness and diversity are much greater in the large intestine than in the stomach and small intestine. At the edge level, the Proteobacteria is dominant in the ileum, while Firmicutes and Bacteroides are abundant in the large intestine (Dougal *et al*., 2013; Abreu and Taga, 2016; Liu *et al*., 2019).

One of the main activities of the gut microbiome is to contribute to the fermentation of various types of indigestible fibers by the small intestine. Horses, as nonruminant herbivores, depend largely on the colon and the caecum to carry out fermentation processes where fibrolytic bacteria, mainly anaerobic, are capable of depolymerizing pectin, starch, cellulose, and hemicellulose to their respective monosaccharides through the Embden Meyerhoff pathway (Jassmin and Andrews, 2009). This activity results in the release of short-chain fatty acids (SCFA), such as butyrate, propionate, and acetate (Tazoe *et al*., 2008; Carpuso, 2016; Cerqueira *et al*., 2020). Butyrate has been shown to affect the growth and differentiation of colonocytes and has a positive role in reducing inflammation at the intestinal level (Zimmerman *et al*., 2012; Louis *et al*., 2014; Chung *et al*., 2017, Thomson *et al*., 2018; Chen *et al*., 2020). In addition, it has a direct impact on the development and activity of the immune system, considering that the intestinal epithelium represents a stable barrier between the lymphoid tissue and the microbiome itself (Janssen and Kersten, 2015; Tamburini *et al*., 2016; Thaiss *et al*., 2016). It is important to understand that microbial interactions are key to shaping the composition of the gut microbiome, where competition for nutrients is commonly observed (Rakoff-Nahoum *et al*., 2014; Abreu and Taga, 2016;

Table 1. Relative abundance of the main intestinal bacterial phyla reported for healthy equines (HE) and intestinal disease equines (IDE).

Study group	HE	IDE	N° of equines evaluated (HE/IDE)	Reference
Donkeys	*Firmicutes, Bacteroidetes*	Uninformed	5/ 0	Liu *et al*., 2019
Sport horses	*Spirochaetes, Tenericutes, Firmicutes*	Uninformed	185/ 0	Mach *et al*., 2020
Sport horses without or with diarrhea	*Bacteoidetes, Verrucomicrobia, Firmicutes*	*Bacteroidetes, Proteobacterias, Firmicutes*	45/ 5	McKinney *et al*., 2020
Thoroughbred horses without or with colic	*Bacteoidetes Firmicutes*	*Firmicutes* *Bacteroidetes*	24/ 28	Park *et al*., 2021
Horses managed at pasture	*Bacteoidetes, Firmicutes, Spirochaetes*	Uninformed	7/ 0	Salem *et al*., 2018
Sport horses without or with colic	*Bacteoidetes Firmicutes, Fibrobacteres*	*Firmicutes* *Bacteroidetes, Fibrobacteres*	5/ 9	Salem *et al*., 2019
Horses without or with colic	*Bacteoidetes Firmicutes, Fibrobacteres*	*Firmicutes* *Bacteroidetes, Fibrobacteres*	30/ 17	Stewart *et al*., 2018
Horses with colic	Uninformed	*Firmicutes, Bacteroidetes, Spirochaetes*	0/ 17	Stewart *et al*., 2020
Horses without or with colic	*Firmicutes* *Bacteroidetes, Proteobacteria*	*Bacteoidetes Firmicutes, Proteobacteria*	6/ 10	Costa *et al*., 2012

Sung *et al*., 2017). These interactions are dependent on the chemical nature of dietary compounds and could influence health, according to the different SCFA profiles that each individual manifests (Medina *et al*., 2017; Adamberg *et al*., 2018; Thomson *et al*., 2018). The diet is the main factor that contributes to gut microbiome modification in horses (Willing *et al*., 2009; Daly *et al*., 2012; Steelman *et al*., 2012; Destrez *et al*., 2015, 2019; Hansen *et al*., 2015; Harlow *et al*., 2015; Venable *et al*., 2017; Barko *et al*., 2018).

Alterations of gut microbiome

In human and animal patients, it has been observed that losses of microbiome homeostasis, or dysbiosis, are associated with some diseases, which are explained by the imbalance and loss of some bacterial species (Núñez *et al*., 2021). An example of this is inflammatory bowel disease, which contains Crohn's disease and ulcerative colitis, in addition to metabolic syndrome and irritable bowel disease and chronic relapsing *Clostridium difficile* infection (Icaza-Chavez, 2013; Zhou *et al*., 2017; Costa and Wesse, 2018; Barko *et al*., 2018). One of the strongest links between irritable bowel syndrome (IBS) and intestinal microbiome was indicated in a study where fecal matter was transplanted from human subjects with IBS to healthy mice, observing that the mice showed changes associated with the disease, such as impaired intestinal motility, increased permeability of the intestine, and visceral hypersensitivity (Crouzet *et al*., 2013).

Currently, there is little research evaluating the relationship between the intestinal microbiome and colic in horses; one of them was carried out by Venable *et al*. (2013), where they analyzed fecal samples obtained from thoroughbred horses during the colic episode, and compared them with those obtained 30 and 90 days later; they reported an increase in the relative abundance of *Clostridium phytofermentans* and *Bacteroides* sp. in all samples obtained during colic, compared to samples collected at 30 and 90 days after the episode. Other studies mention that colicky horses have a significantly higher percentage of *Clostridioides difficile* compared to healthy horses (Niwa *et al*., 2013; Schoster *et al*., 2019). In this regard, Nomura *et al*. (2020) relate the administration of antimicrobials in hospitalized horses with diarrhea caused by *C. difficile*, where a clear increase in this species has been observed. Undoubtedly, among all the external factors that generate changes in the gut microbiome, the administration of antibiotics could have the most serious consequences (Jalanka-Tuovinen *et al*., 2011) since it favors the rapid proliferation of pathogenic bacteria (Britton and Young, 2014; Theriot *et al*., 2016).

In equine clinical practice, the oral administration of antibiotics can induce dysbiosis, which often results in diarrhea and colitis (Barr *et al*., 2012; Diab *et al*., 2013; Liepman, 2015). Indirectly, the administration of the fecal transplantation from a healthy donor horse to a patient with diarrhea has made it possible to generate a causal relationship between the composition of the microbiome and disease (McKinney *et al*., 2020, 2021) situation that has been reported in human patients (Coignard *et al*., 2006; Kachrimanidou and Tsintarakis 2020; Núñez *et al*., 2021; Thomson *et al*., 2021).

It has been shown that the diversity of species decreases in horses with colic, showing significant differences in 46 of 304 identified operational taxonomic units. Likewise, they point out that the relative abundance of bacteria such as *Prevotella*, *Clostridia*, and *Lachnospiraceae* is reduced while *Christenellaceae*, *Streptococcus*, and *Sphaerochaeta* increase in horses with colic compared to elective cases (Stewart *et al*., 2019). The decrease in the relative abundance of members of the family Lachnospiraceae producers of butyrate bacteria has been previously mentioned (Costa *et al*., 2012; Weese *et al*., 2015). Interestingly, Stewart *et al*. (2019) found an association between Firmicutes: Proteobacteria ratio and the appearance of colic with an odds ratio of 0.95, indicating that the higher this proportion, the lower the probability of developing a colic episode, information you can use to predict and prevent these types of events. However, other study could not find this relationship and found an overgrowth of lactic acid-producing bacteria, such as Lachnospiraceae and Lactobacillaceae, and a decrease of methanogenic bacteria (Park *et al*., 2021). Weese *et al*. (2015) found in postpartum mare that developed colic a higher relative abundance in Proteobacteria 1–76 days (mean 17.5) before the onset of the colic episode (Table 1). However, neither significant differences in community membership, structure, diversity, or evenness were found. Likewise, several studies carried out in humans support the idea of considering the Proteobacteria phylum as a marker of the alteration of the intestinal microbiome, and an increase in the relative abundance of this group of microorganisms associated with various gastrointestinal diseases has been observed (Van Nood *et al*., 2013; Cammarota *et al*., 2017; Chamorro *et al*., 2021).

Epidemiological studies have established an increased risk of colic associated with sudden changes in diet, which result from an alteration of fermentation patterns and a metabolic disorder within 4–6 days after a dietary change (Shirazi-Beechey, 2008; Salem *et al*., 2018; Stewart *et al*., 2019). Some authors explain that when horses are exposed to the sudden incorporation of high levels of soluble carbohydrates in the diet, the normal enzymatic degradation in the small intestine is overloaded and large amounts of starch pass to the large intestine, where the microbial fermentation occurs (Beuvink and Spolestra, 1992; Hansen *et al*., 2015; Warzecha *et al*., 2017). As a result of this fermentation, an accumulation of lactic acid and gas occurs by bacteria such as *Lactobacillus* and *Streptococcus* (Milinovich, 2006, 2010; Hansen *et al*., 2015), causing a rapid drop in the pH of the hindgut and consequently a loss in fibrolytic bacteria. Using culture-independent techniques, it was possible to confirm a lower abundance of the Lachnospiraceae, Ruminococcaceae and Fibrobacter families (Dougal *et al*., 2013; Hansen *et al*., 2015; Julliand and Grimm, 2017; Warzecha *et al*., 2017). It is also known that grass-fed horses have a higher relative abundance of bacteria belonging to the Clostridiaceae, Eubacterium, and Spirochataceae families in the hindgut (Daly *et al*., 2001; Daly and Shirazi-Beechey, 2003). On the other hand, those fed grain show a decrease in the relative abundance of Fibrobacter (Blackmore *et al*., 2013; Hansen *et al*., 2015). In addition, pregnant mares are at greater risk to have colic because of changes in their feeding management during the peripartum period that produce significant alterations in the pH of the colon, which can cause variations in the hindgut microbiota, leading to a significant increase in the phylum Proteobacteria (Salem *et al*., 2019).

Conclusion

Different factors can alter the composition of the intestinal microbiome in equines, modifying the relative abundance of the main bacterial phyla. The bacterial community composition in horses with colic is different from healthy horses, characterized by a less diverse population and changes in the relative abundance of some phyla and bacteria species.

In healthy animals, a predominance of the phyla Firmicutes and Bacteroidetes has been identified, while in horses with colic these phyla decrease and Proteobacteria increases. However, more studies are required to establish a causal relationship between these alterations and the presentation of colic in horses.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Authors' contributions

Felipe Lara: conception of the study, wrote the first draft of the manuscript, and critically revised the manuscript. Rodrigo Castro: wrote the first draft of the manuscript and critically revised the manuscript. Pamela Thomson: conception and design of the study, wrote the first draft of the manuscript, critically revised the manuscript, and funding acquisition.

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