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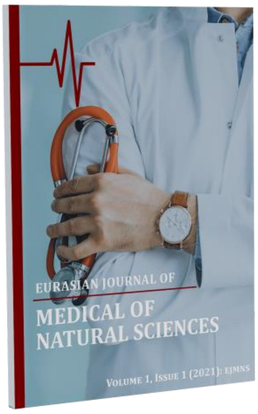

DYSBACTERIOSIS

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ABSTRACT

This comprehensive essay explores the intricate world of dysbacteriosis, a condition characterized by an imbalance in the gut microbiota. It delves into the fundamental role of bacteria in the gut and how dysbacteriosis disrupts this delicate balance. The essay covers the causes and contributing factors, consequences on digestive and overall health, diagnostic approaches, and potential interventions. By examining the complex interplay between the gut and various influencing factors, this essay provides valuable insights into the implications of dysbacteriosis and strategies for maintaining gut health.

Dysbacteriosis: Unraveling the Complexities of Microbial Imbalance in the Gut.

The human gut, a vibrant ecosystem hosting trillions of microorganisms, plays a pivotal role in maintaining health and well-being. However, disturbances in this delicate balance can lead to dysbacteriosis, a condition characterized by an altered composition of gut microbiota. This essay delves into the intricacies of dysbacteriosis, exploring its causes, manifestations, impact on health, diagnostic approaches, and potential avenues for intervention.

Introduction: Understanding Dysbacteriosis. Dysbacteriosis, often interchangeably referred to as dysbiosis, signifies an imbalance in the gut microbiota. This complex community of bacteria, viruses, fungi, and other microorganisms coexists harmoniously, contributing to digestion, nutrient absorption, immune function, and overall gastrointestinal health.

Signs and consequences of dysbacteriosis Dysbacteriosis can have profound effects on the host. Dysbacteriosis alters the GIT environment and favors the growth of pathogenic bacteria. Pathogenic bacteria produce toxins that increase intestinal motility or cause alterations in the amounts of mucus produced or in its composition. They also result in modifications of gastric acidity, reduction in the production of bacteriostatic peptides in the pancreas, and reduced immunoglobulin (IgA) secretion. Toxins released by entero-pathogens damage intestinal villi, resulting in focal ulcerations of the mucosa, tissue necrosis, and shifts in gut microorganism numbers and metabolism. The costliest condition for animal production is the chronic inflammatory response of the animal to constant minor dysbacteriosis. These chronic responses can reduce weight gain and cause low feed conversion efficiency. Coccidiosis infections and any other enteric disease can be aggravated when dysbacteriosis is prevalent. Generally, animals with dysbacteriosis have high concentrations of Clostridium that generate more toxins, leading to necrotic enteritis. In broilers, the syndrome is generally seen between 20 and 30 days of age . Clinically, the main signs are: pale, glistening or orange droppings with undigested food particles wet and greasy droppings and hence dirty feathers sometimes foamy caecal droppings reduced physical activity increased water intake decrease in feed intake with a check in weight or reduced gain rates increased feed conversion . Wet litter is also a general outcome of dysbacteriosis that may affect the air quality of the house, leading to a higher incidence of respiratory problems. Additionally, foodborne pathogens such as Salmonella spp. and E.coli proliferate more in the dysbiotic intestine and can become persistent residents of the hindgut. At necropsy, the main observations are a thin, fragile, often translucent intestinal wall watery or foamy intestinal contents frequent orange mucus and undigested particles in the intestines ballooning of the gut intestinal inflammation.

Prevention of dysbacteriosis The most important factors to prevent dysbacteriosis are Minimizing environmental stress Maintaining good water quality Improving feed digestibility Avoiding antinutritional factors, mycotoxins, and rancidity Feed additives that could modulate microbial component and avoid dysbacteriosis Growth-promoting antibiotics are well known for the inhibition of undesired microbiota and the negative effects of their metabolites, and selection for beneficial bacteria. However, the adverse result is that they diminish the natural diversity of the gut microbiota. Antibiotics can also result in animals developing bacterial resistance. Other products have been proposed as alternatives to growth promotion, taking into consideration the increasing bacterial resistance to some antibiotic categories. Alternate feed additive technologies that have a promising role in controlling dysbacteriosis are: Probiotics Prebiotics Enzymes Organic acids Essential oils and phytomolecules Probiotics The post-hatch period is very critical for the chicks' intestine development. Exposure to the environment in hatchery and farm affects microbial colonization in the intestine tract. The use of selective probiotics in day-old chicks at the hatchery and on the farm immediately after placement in broiler house reduces the risk of dysbacteriosis. Probiotics work by competitive exclusion, thereby prevent the colonization of potentially pathogenic bacteria. Probiotics prevent enteric diseases, improves intestine development and digestion process. The benefits include enhanced growth and laying performance, improved gut histomorphology, immunity, and an increase in beneficial microbiota.

Intestinal homeostasis and intestinal dysbiosis. The intestinal homeostasis (or eubiosis), is “the natural tendency to achieve a relative stability, both of internal chemical-physical properties and behavioral, which is common to all living organisms, for which this dynamic regime must be maintained over time, even when external conditions vary, through precise self-regulatory mechanisms”. The purpose of the intestinal microbiota is to maintain this balance, as it regulates the integrity of the epithelium, the motility of the intestine (peristalsis) and the formation of the immune system (innate and adaptive immune responses). The immune system, in the maintenance of intestinal homeostasis is called into play for the presence of good and bad luminal bacteria, food antigens, so it is continuously stimulated. In homeostasis (condition of balance), therefore, the microbiota performs effi ciently and effectively; on the contrary, in the hypothesis of "dysbiosis", which is a perturbation of the normal homeostatic balance, the intestine loses its natural permeability and the organism falls ill more easily, firstly going through a series of acute and temporary imbalances, such as colitis, diarrhea, constipation and digestive disorders, up to a whole series (if the dysbiotic cause should persist) of digestive disorders, constipation and digestive disorders, up to a whole series (if the dysbiotic cause should persist or become chronic) of chronic Infl ammatory Bowel Diseases (IBD or MICI), including Crohn's disease and ulcerative colitis and necrotizing enterocolitis in premature infants.

In addition to chronic infl ammatory diseases, directly caused and fed by the intestinal dysbiotic state, recent studies have shown a direct correlation between dysbiosis and other

extraintestinal pathologies, including diabetes, atherosclerosis, metabolic syndrome, autoimmune and neurodegenerative diseases, cardiac and circulatory disorders, atopic dermatitis, psoriasis, asthma and food allergies and intolerances . But also other conditions, at fi rst unlikely hypothesis, are actually directly correlated with intestinal dysbiosis, to the point of being concauses or even elements favoring or aggravating the pathology itself: we are talking about autism, epilepsy, sleep disorders, neurodegenerative diseases, eating disorders and obesity , psychotic disorders, bipolarity and personality disorders. The correlation between gut dysbiosis and severe forms of Covid-19 has also recently been demonstrated .

The target of clinical treatment must therefore be the "intestinal dysbiosis", in order to promote a new homeostasis (eubiosis). In the clinic, four forms of dysbiosis are recognized, each of them with a precise etiopathological and symptomatic mechanism, caused in any case by a reduction in the diversity of bacterial species, reduction of benefi cial species

and/or proliferation (increase) of harmful species :"putrefactive", which originate from an increase in the share of Bacteroides at the expense of Bifi dobacteria, is caused by an excessive intake of meat and saturated fats associated with a poor introduction of insoluble vegetable fi bers."fermentative", which originate from a poor acid secretion by the stomach associated with an overproduction of bacteria and yeasts in the stomach and small intestine, often motivated by an intolerance to gluten and carbohydrates."defi ciency" and "sensitization", often diffi cult to differentiate between them. Both forms are caused and maintained by excessive intake of toxic pollutants, antibiotic therapies and more generally by conditions that cause a decrease in the quotas of probiotic bacteria and an alteration of intestinal motility.

Bacteriocins. The prevalent competition for nutrients in the colon drives the development of strategies enabling bacteria to outcompete or eliminate their competitors. One of these strategies is illustrated by the secretion of bacteriocins, which are toxic proteins and peptides targeting related taxa competing for the same resources. The family of bacteriocin covers colicins in E. coli, pyocins in Pseudomonas, pesticins in Pasteurella pestis and Yersinia pestis among others . Bacteriocins also include microcins, which are short antimicrobial peptides . The bacterial strains producing bacteriocins also express immunity proteins that protect them against the toxic effect of their own bacteriocins. Most bacteriocins kill by forming pores in membranes or by cleaving nucleic acids. Stress conditions such as oxidative and genotoxic stress induce the expression of bacteriocins, thus underlining the significance of bacteriocins in the mechanisms amplifying shifts in bacterial composition during inflammation-related oxidative stress. The expression of microcins in Enterobacteriaceae is also induced in conditions of nutrient shortage. For example, E. coli Nissle 1917 secrete microcins preventing the growth of other E. coli strains when iron availability is limited, for example during inflammation. In fact, supplementation of mice with iron during intestinal inflammation decreases the production of microcins, which results in the proliferation of competing E. coli thereby restricting the growth of E. coli Nissle 1917 . Of note, E. coli Nissle 1917 is the only probiotic recommended by the European Crohn's and Colitis Organization as an alternative to the non-steroid anti inflammatory drug mesalazine in the treatment of ulcerative colitis, as underlined in recent metaanalyses . Niche competition in the intestine has also been described for Gram-positive bacteria, such as members of the Enterococcus genus. Enterococcus faecalis produces a bacteriocin transmitted through plasmid conjugation, which disrupts the proliferation of other enterococci. Beyond their contribution in the development of dysbiosis during inflammation, bacteriocins represent interesting candidate drugs aiming at the selective inhibition of pathogenic bacteria resistant to conventional antibiotics, such as C. difficile and methicillin-resistant Staphylococcus aureus. Dysbiosis and disease As outlined in the previous sections of this review, the mechanisms destabilizing the gut microbiota are plentiful. Equally numerous are the diseases, which intestinal dysbiosis influences the course and severity. Typical examples including IBD , type 1 diabetes , celiac disease , and cardiovascular disorders have been covered extensively in other reviews. We here focus our discussion on three diseases affecting human beings at different stages of life, namely necrotizing enterocolitis in newborns, colorectal cancer in adults, and C. difficile-associated diarrhea in elderly people. Necrotizing enterocolitis Necrotizing enterocolitis is a fulminant gut inflammation that is most frequent in premature newborns, affecting up to 10% of infants with a birthweight below 1500 g. Mortality can be as high as 30% . The first signs of necrotizing enterocolitis are usually a distended abdomen and bloody stool. As reflected by these unspecific symptoms, the pathogenesis of necrotizing enterocolitis is unclear. Several risk factors, including enteral feeding, bottle-feeding, immature immunity, and altered microbiota increase the incidence of necrotizing enterocolitis. Conversely, breastfeeding decreases the occurrence of necrotizing enterocolitis by at least six fold in comparison with bottlefeeding . This large impact has led the American Academy of Pediatrics to recommend feeding premature babies with breast milk immediately after birth . The molecular nature of the protection conferred by breast milk remains however elusive. Breast milk lactoferrin and immunoglobulins have been investigated as possible protective compounds but found to be ineffective at decreasing the incidence and severity of necrotizing enterocolitis. Given that pasteurized breast milk is as protective as fresh milk, heat-resistant compounds such as milk oligosaccharides are likely to contribute to the protective effect. Oral supplementation with the prebiotics galacto-oligosaccharide, fructo-oligosaccharide and lactulose nevertheless did not influence the course of necrotizing enterocolitis, although they mediated a relative increase of bifidobacteria and lactobacilli levels in the treated newborns . Supplementation with the probiotic Bifidobacterium breve BBG-001 also failed to improve the survival rate of infants with necrotizing enterocolitis.

Despite the unclear etiology, several findings converge towards a central role of the gut microbiota in triggering necrotizing enterocolitis. A sudden rise of Proteobacteria and a concomitant fall of Firmicutes levels has been found to precede the onset of the disease. Enterobacteriaceae, which are prominent members of the Proteobacteria phylum, express hexacylated LPS that are strong pyrogens and induce a robust inflammatory response mediated through TLR4 signaling. The mechanisms underlying the increase in Proteobacteria remain unclear. Is the proliferation of facultative anaerobic bacteria such as Enterobacteriaceae facilitated by the presence of oxygen in the newborn colon? As outlined in the present review, multiple mechanisms account for the development of dysbiosis. Given the resilience of the gut microbiota in response to changes, the occurrence of dysbiosis in necrotizing enterocolitis is likely the result of a chain of events combining an inadequate supply of protective nutrients and prebiotics, an immature immune system and an insufficient secretion of intestinal mucus.

Causes of Dysbacteriosis: Unraveling Triggers

Various factors can disturb the equilibrium of gut microorganisms, leading to dysbacteriosis:

Antibiotic Use: Broad-spectrum antibiotics can disrupt the natural balance by affecting both harmful and beneficial bacteria.

Dietary Choices: Imbalanced diets rich in processed foods and low in fiber can alter microbial diversity.

Stress: Psychological stress may influence the gut-brain axis, impacting microbial composition.

Infections: Viral, bacterial, or parasitic infections can disturb the microbiota.

Manifestations of Dysbacteriosis: From Digestive Distress to Systemic Effects.

Dysbacteriosis can manifest in various ways:

Digestive Issues: Bloating, gas, constipation, or diarrhea may occur.

Immune System Dysfunction: Altered microbiota can affect immune response and increase susceptibility to infections.

Metabolic Disturbances: Dysbiosis has been linked to conditions such as obesity and metabolic syndrome.

Mood Disorders: Emerging research suggests a connection between gut health and mental well-being.

Impact on Health: Beyond the Gut. The repercussions of dysbacteriosis extend beyond gastrointestinal discomfort:

Nutrient Absorption: Altered microbial balance may impact the absorption of essential nutrients.

Inflammation: Dysbiosis can contribute to chronic inflammation, implicated in various diseases.

Autoimmune Disorders: Some autoimmune conditions are linked to disturbances in gut microbiota.

Diagnostic Approaches: Decoding Dysbacteriosis.

Accurate diagnosis is crucial for targeted intervention:

Microbiome Analysis: Advanced sequencing technologies allow profiling of gut microbial communities.

Interventions and Treatment: Restoring Microbial Harmony.

Managing dysbacteriosis involves multifaceted approaches:

Probiotics: Beneficial bacteria supplements can restore microbial balance.

Prebiotics: Foods promoting the growth of beneficial microorganisms, such as fiber-rich foods.

Dietary Modifications: Adopting a balanced and diverse diet to support gut health.

Lifestyle Changes: Stress management and regular physical activity contribute to gut well-being.

Emerging Research and Future Perspectives. Ongoing research explores the intricate connections between gut health and various aspects of well-being. Understanding the nuances of dysbacteriosis opens avenues for innovative interventions and personalized medicine approaches.

Conclusion: Nurturing Gut Harmony. Dysbacteriosis underscores the importance of maintaining a balanced and diverse gut microbiome for overall health. By comprehending the causes, manifestations, and potential interventions for dysbacteriosis, individuals can proactively support their gut health, paving the way for enhanced well-being and resilience against various health challenges.

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