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Review

Review about Clinical Application of the Use of Probiotics in Pediatric Age

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Introduction

A probiotic is defined as a living microbial species that may have a positive effect on intestinal flora and improve health condition. Probiotics are used in the treatment of several gastrointestinal conditions such as Helicobacter pylori infection, functional abdominal pain, diarrhea associated with antibiotics, celiac disease, food allergy, acute infectious diarrhea, infantile colic, irritable bowel syndrome, lactose intolerance, but also in extraintestinal alterations such as infantile eczema, atopic dermatitis, autism spectrum disorders, asthma and recurrent respiratory tract infection (Table 1). The intestinal microbial flora may contribute to the pathogenesis of allergic diseases. Genetic, environmental and dietary factors could modulate the gut microbiome-immune system axis [1]. The future role of probiotics could be the prevention of some recurrent infections such as bacterial vaginosis, urinary tract infections, recurrence after surgery in Crohn's disease and maybe Helicobacter pylori. More studies are needed to investigate optimal strain, dosage, bioavailability of drops and tablets, duration of treatment and safety. Infact the future could be the central role of human bacterial gastrointestinal flora (gut microbiota) and the response to immunotherapy in oncology. Probiotics and recombinant probiotic strain represent a promising source of molecules for the development of novel anti-infectious therapy [2]. An alteration of intestinal microbiota (dysbiosis) could be implicated in several pathologic conditions such us: cancer, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, obesity, diabetes mellitus, autism spectrum disorder [3].

Table 1. Species of Probiotics bacteria more commonly used in clinical practice.

Bifidobacterium	**Lactobacillus**	**Saccaromices**
longum reuter longum infantis breve lactis UABLA-12	rhamnosus GG rhamnosus LC705 fermentum VRI-033 paracasei plantarum salivarius acidophilus	boulardii

Some Gastrointestinal Conditions

Helicobacter pylori infections

Helicobacter pylori (Hp) infection has been recognized as a cause of chronic gastritis, peptic ulcer, atrophic gastritis and gastric cancer. Its acquisition is related with poor socioeconomic conditions, hygiene and living conditions, while the relationship of nutrition and Hp is still a question. There are several problems about Hp eradication therapy: triple therapy with frequent resistances and collaterals effects during antibiotics and proton pump inhibitor therapy. Several studies showed the possibility of probiotics to inhibit Hp growth in vitro [4] and to decrease the risk of Hp re-infection. The use of probiotics during Hp therapy is important and helpful to improve the eradication and to reduce collaterals effects. Also the high incidence of side effects with triple therapy can contribute to poor compliance with treatment regimens, which in turn may further contribute to failures in Hp treatment. The intake of high dose of broad spectrum antibiotics may cause serious side effects including the alteration of intestinal flora but it is possible the use of probiotics during this therapy to reduce the effects, improving tolerability and compliance of multiple antibiotic regimens [5]. Several studies demonstrated that probiotics in Hp eradication has been used additionally for the protection of physiological intestinal flora with high patient compliance, higher side effects and maintain lower levels of Hp in the stomach, infact some probiotics and/or their metabolites are also known to exert a bacteriostatic or bactericidal effect on H. pylori [6,7].

Functional abdominal pain

The clinical abdominal symptoms with pain, vomiting and nausea in children can vary considerably according their age and in general have an insidious clinical course, alternating between symptomatic and asymptomatic periods. Abdominal pain is usually epigastric or periombelical, but can also be present in the right lower quadrant. It can be intermittent or, more rarely, continuous; it can also be cyclic, with remission periods that last week or months. There is no correlation with food intake and it often occurs early in the morning. According to Rome IV criteria [8], the functional gastrointestinal disorders (FGIDs) are classified into three main classes based on the prime symptoms: functional nausea and vomiting disorders, functional abdominal pain disorders and functional defecation disorders.Different mechanisms have been suggest for the pathophysiology of FGIDs including gut microbiome composition and recent studies [9-13] suggest that FGIDs is associated with changes in the gut

microbiome. Generally, the gut microbiota is composed of beneficial (Bifidobacterium) and potentially pathogenic bacteria (Enterobacteriaceae). The healthy balance in the gut microbiota is important for a normal gut function, while any dysbiosis may produce gut symptoms. The gut microbiota plays a significant role in the development and maintenance of barrier function and the effects of probiotics improve intestinal permeability and motility because they are important in immune regulation and reduce inflammatory response [14]. Many studies and trials have been conducted by several authors about the role of probiotics in the management of functional abdominal pain disorders. Generally, in these studies children treated with probiotics have more days without pain compared to placebo group and reduced pain intensity and frequency, but there are no significant differences between two groups. Maybe in the future a mixture of probiotics could be a key of resolution about the management of functional gastrointestinal disorders. Giannetti et al. studied a mixture of probiotics and referred a reduction of abdominal pain more often in the probiotic than in placebo group in patients with irritable bowel syndrome but not in those with functional dyspepsia [15-23].

Diarrhea associated with antibiotics

In pediatric age the use of antibiotics is most widespread than in adult population and simultaneous administration of probiotics has been used to alleviate the side effects of drug therapy such us nausea, abdominal distension and diarrhea improving patient and family compliance. With the extensive use of therapy with antibiotics a trend is being seen towards increased bacterial resistance to the agents. The effects of antibiotics on intestinal microbes depends on the antibiotic spectrum, the route of drug administration and the pharmacokinetic characteristics of the drugs. In recent years probiotics have been used additionally for the protection of the physiological microbial balance while lowering the severity of antibiotic side effects and improving patient compliance, reducing resistances that are the main cause of treatment failure [24].

Celiac disease

Several evidences shown that the gut microbiome could be important in the pathogenesis of celiac disease. Infact the composition of microbiota changes substantially from infancy to adulthood and plays a significant role in the development and maintenance of barrier function. Early microbial colonization is important for both the innate and the adaptive immune systems. Several studies demonstrated the presence of proinflammatory bacteria in intestinal microbiota of celiac patients and persistent dysbiosis during correct gluten-free diet with important gastrointestinal symptoms. It is possible a role of probiotics in celiac disease. Several studies showed beneficial effect of probiotic to reduce the frequency and severity of inflammatory response, maybe because improves the gut barrier function. There are also trials about multispecies probiotics treatment for six weeks that improved the severity of irritable bowel syndrome, in celiac patients on a strict gluten free diet [25-27].

Food allergy

The modulation of the intestinal microbiota seems a promising strategy for the control of allergic reactions. Food allergy is a common problem in pediatric age and derives from a defect of immune tolerance mechanism. Immune tolerance is modulated by gut microbiota function and structure, and dysbiosis could have an important role in the development of food allergy. There has been an increased interest in the role of probiotics for the prevention and treatment of allergic disorders. Future studies about microbiota- host interaction and gut immunity could be established the appropriate use of probiotics as a standard treatment regimen for food allergies [28].

Other Extraintestinal Alterations

Infantile eczema

The intestinal microbial flora may contribute to the pathogenesis of allergic diseases. Allergic disorders are an increased problem worldwide and it is a condition important in quality of life of people. The etiology remains unknown. Recently some studies demonstrated that dysbiosis of the gut microbiome can be associated with an increased risk of atopy. Several studies demonstrated that probiotics significantly reduces the frequency and severity of infantile eczema and maybe because improves the gut barrier function and reduce the inflammatory response [29]. There was no standardized probiotics regimen, with multiple different strains and concentrations of probiotics and variable duration of treatments. I recruited 41 children with infantile eczema treated with Lactobacillus GG or placebo for 6 weeks and entered follow up for 4 weeks. Children entered a randomized, double-blind, placebo-controlled trial. Lactobacillus GG, but not placebo, caused a significant reduction of both frequency ($P < .01$) and severity ($P < .01$) of eczema. These differences still were significant at the end of follow-up ($P < .02$ and $P < .001$, respectively). Lactobacillus GG was superior to placebo in the treatment of eczema in children (30). The potential association between gut microbiota perturbations and childhood with allergic disease opens interesting therapeutic possibilities with probiotics, but several studies are needed.

Atopic dermatitis

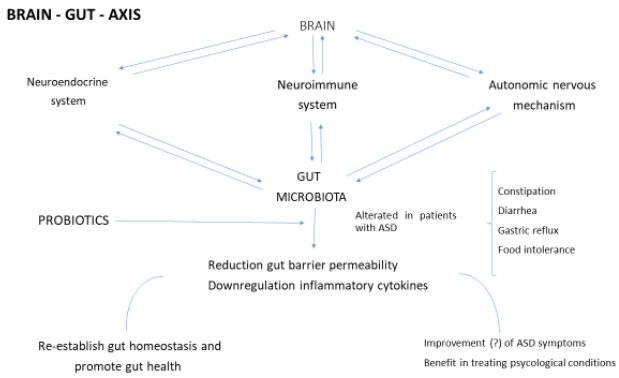
The human intestine is a large bacterial reservoir, it has been estimated that it is populated with up to 100 trillion microbes. Urbanization, hygiene and living conditions, change of dietary and low socioeconomics factors are assessing an alteration of the human gut microbiota. The intestinal microbial flora is a complex and dynamic populations of microrganism and plays a very important role in the host's life. Environmental factors that contribute most to interindividual diversity include diet, lifestyle and antibiotic use. Host genotype, age and sex also contribute to gut microbiota diversity. The colonization of infant gut is useful for the correct development of immune and metabolic homeostasis. The gut microbiota can interact with the host and perform multiple physiologic functions. A principal role of the gut microbiota is participating in food digestion and nutrient uptake. In addition the gut microbiota plays a role in regulating intestinal barriers and modulating the host immune system to prevent inappropriate inflammation; assists with the maturation of immunologic tissues by stimulating gut lymphatic tissue and can participate in neurologic development. The dysbiosis (alterations in gut microbial composition) cause an altered homeostatic process and disease. In these conditions of dysbiosis the gut microbiota biomodulators (probiotics) could be an important preventive avenue for several disease (31-33). Probiotics are microbiota-management tools for improving host health, infact

they are defined as live bacteria utilized to re-establish an appropriate intestinal balance. Potential mechanism of probiotics includes mainly pH modulation, antibacterial substance production and competition with pathogens. Actually, little is known about the role of the gut microbiota in the pathogenesis of atopic dermatitis (34). This condition is a chronic inflammatory skin disease with multifactorial pathogenesis (genetic factors, environmental factors and immunological factors) with a worldwide prevalence of 10-20% in children (35). Some conditions such as caesarean section, premature delivery, use of perinatal antibiotics, maternal diet and antibiotic treatment during pregnancy could cause dysbiosis and increase the risk of atopic dermatitis. The role of the gut microbiome in atopic dermatitis remains controversial and further studies are needed to clarify the role of microbiota in the aetiopathogenesis of atopic dermatitis. Probiotics modulate the intestinal microbiome and immune status by improving the intestinal barrier and these effects are responsible for reducing allergic phenomenon and atopic dermatitis severity [36-40].

Autism spectrum disorders

A brain-gut interaction through neuroendocrine, neuroimmune and autonomic nervous mechanism have been demonstrated, but the role of this bidirectional interaction (microbiota-gut-brain axis) in psychiatric disorders have not been systematically clarified yet [41]. One of these disorders is autism spectrum disorders (ASD). This is a neurodevelopmental psychiatric disorder of early childhood with symptoms beginning before the age of 36 months. It is characterized by deficits in social communication and interaction, stereotypical behaviours and restricted and/or circumscribed interests (American Psychiatric Association 2013). The cause is unknown, and the pathogenesis remains understood (genetic, epigenetic and environmental factors). ASD patients have an increased incidence of gastrointestinal (GI) symptoms such as constipation, diarrhea, gastric reflux and food intolerance. Considering that the symptoms start in early childhood, it is important to investigate the effect of microbiota on the brain during infancy. Probiotics, prebiotics and dietary exclusions have been investigated in the management of ASD symptoms [42-43]. Gut microbiota play and important role in modulating this gut-brain axis and dysbiosis can have negative effects on not only the GI tract, but also psychological symptoms. The dose and duration in the long term of the treatment designed to change the microbiota are not yet clear; presumably patients with ASD have significantly altered gut microbiota and probiotics reduce gut inflammation reducing gut barrier permeability, downregulating inflammatory cytokines and other immunomodulatory effects. Several studies show probiotics benefit in treating psychological conditions such as depression and axiety. Although the cause-effect relationship between ASD and gut microbiota is not yet well established (Figure 1), the consumption of specific probiotics may represent a side-effect free tool re-establish gut homeostasis and promote gut health [44-45].

Figure 1. Brain Gut Axis.



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